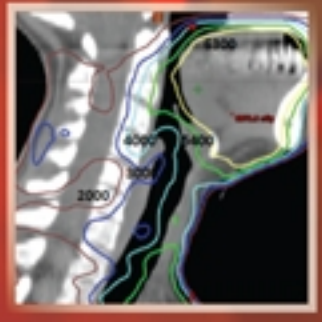
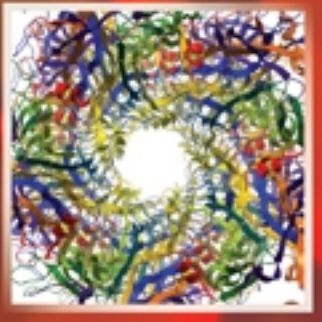
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FOURTH EDITION

# HEAD AND NECK CANCER

## A MULTIDISCIPLINARY APPROACH





Louis B. Harrison
Roy B. Sessions
Merrill S. Kies

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# Head and Neck Cancer

## A Multidisciplinary Approach

**FOURTH EDITION**

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# Head and Neck Cancer

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*With great love, I dedicate this book to my wife, Ilene. I am so grateful for all that she has done to support me in our lives together. Without her, this book, and most everything else that I have accomplished, would not exist.*

*LBH*

*In each of the three previous editions of this book, I mentioned my family in the dedication ritual—those members alive and those who are but fond memories. My thoughts were reflective of affection and respect, those very emotions implicit in the current endeavor. I am confident, then, that all—past and present—will or would have conceded that my professional accomplishment are to a great extent related to the thousands of my patients who have made the journey through the anguish of cancer, some successfully, others not; and the ultimate dedication should be to them. Their plight has been the essence of my mission in life, and my admiration of their courage is at the very core of my contribution to this book. I thank them for trusting me in the hour of their misfortune.*

*RBS*

*With love and affection, my contribution to this book is dedicated to Diana, my wife and partner.*

*MSK*

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# SPECIAL DEDICATION

## Dr. Waun Ki Hong, MD, FACP, DMSc

We are honored to gratefully acknowledge Dr. Waun Ki Hong, who, with Lou Harrison and Roy Sessions, conceived and was a founding editor of *Head and Neck Cancer: A Multidisciplinary Approach*. In many ways, this textbook is a literary projection and reflection of Dr. Hong. He has been and continues to be devoted to learning, scholarship, and the comprehensive evaluation and care of the broad spectrum of cancer patients. He has been a keen innovator and a leader paving the way to multidisciplinary thinking, utilizing physical examination skills, new imaging technologies, and creative colleagues from other specialties to develop and test new treatment strategies. He has long been engaged in blending the skills and talents of clinicians and clinical investigators to foster advances in patient care, constantly challenging the status quo.

Dr. Hong is Professor and Head of the Division of Cancer Medicine and Vice Provost for Clinical Research at The University of Texas MD Anderson Cancer Center. He obtained his medical degree from the Yonsei University School of Medicine, Korea, a medical residency at the Boston Veterans Affairs (VA) Medical Center, and fellowship in medical oncology at Memorial Sloan-Kettering Cancer Center of New York. He is an American Cancer Society professor and the Samsung Distinguished University Chair in cancer medicine. As the elected president of the AACR in 2001, he was influential in expanding the organization's international membership, and he has played an immense role in promoting multidisciplinary translational cancer research among physician-scientists worldwide. He has also played a pivotal role in shaping national public policy for cancer care and research in his commitment to the work of the National Cancer Institute. He has been the lead editor for numerous books, authored major treatises, and published 700 articles in scientific journals.

One story illustrates Dr. Hong's innovative thinking. As a young medical oncologist at the Boston VA, in 1979, he was one day called to the operating room by Stuart Strong, who was about to perform a total laryngectomy on a patient with clinical stage T4 squamous cancer. Dr. Hong had administered induction chemotherapy, and a wondrous, complete tumor response had occurred—so, now what to do? Of course, this led to formal clinical trials and, ultimately, the VA Cooperative Group study that showed the curative potential for chemotherapy and radiation, a nonsurgical and organ-preserving strategy that continues to be practiced in various platforms and, with many modifications later, throughout the world to benefit thousands of patients. He is renowned for seminal research in the role of retinoids in normal tissue biology and carcinogenesis, the broad area of chemoprevention of cancer, and importantly in the development of the methodology for cancer-prevention trials. His work has impacted the conduct of medical care for patients at risk of upper aerodigestive tract, breast, gastrointestinal, and genitourinary malignancies. Most recently, he spearheaded a remarkable new strategy for the systemic treatment of patients with advanced solid cancers. In the setting of progressive non–small cell lung cancer, in patients previously exposed to conventional therapies, he developed a platform for a fresh tumor biopsy at the time of enrollment and then an assignment to experimental therapies based on molecular assessments. He demonstrated that the approach is workable and has provided a blueprint for the conduct of future trials of molecular-targeted therapy across several solid tumors.

A centerpiece of current work is devotion to and mentoring of junior colleagues and fellows. Dr. Hong works vigorously within the MD Anderson fellowship program, with physician leaders and the fellows and students. Still directly caring for patients, he always has time to put his hand on young shoulders and show them the way. He sincerely cares about the future of both patients and the doctors who treat them.

To Dr. Hong, we offer our deepest appreciation for your devotion to and study of cancer medicine and for being a role model for the young and not-so-young, for all of us.

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# PREFACE

We take considerable pride in the fact that the integrity of *Head and Neck Cancer: A Multidisciplinary Approach (HNC)* has been retained through four consecutive editions. HNC I (1999) started a crescendo of learning for all of us, and with each subsequent book, we sought and found ways to do a better job. The planners have always been keenly in tune with the concept that a continuance of book quality must never be based on previous laurels and accolades. As a means of separating this statement from the theoretical, we cite the example of the first edition of HNC that won a prestigious international literary award, by which we were certainly humbled and honored. To assume that to be the apogee of quality, however, would almost certainly have been followed in subsequent editions by a diminution of substance and book vitality. Unlike dated works of literature, such as fiction and history, a book like HNC is a relentlessly moving target, and failure to continually address the rapidly evolving science within the relevant body of knowledge would invite obsolescence. Accordingly, we have launched every new edition with this attitude and these realizations. Each time, the challenges were substantial, but were surmounted.

We set out to create the standard of excellence in the head and neck oncology literature, but subsequently came to realize that it is as much of a challenge to sustain the high level achieved as to create it. Our retrospective analysis of the elusive reasons for the achievement invariably led us back to several key axioms: First, literary vitality and dynamism are best achieved by a formula of staggered rotations of authors; that is to say, partial change for a given edition. This practice injects new thinking into a text while fostering continuity from edition to edition, and additionally, generates an important byproduct by incorporating fresh young academics from the rich talent pool available. Properly energized, these new contributors approach their task with a serious sense of responsibility to the book, to the profession, and ultimately to cancer patients. Another key to the formula is the avoidance of repeating the same book that seems to result from merely tweaking old data, only to have repeated the same chapter, rather than critically reading and rethinking each that was in the previous edition—not necessarily always starting from scratch, but at a minimum, divesting treasured thoughts and words that are better captured by change. Noted authors are often loath to do this, and finding an appropriate compromise with the editors represents the sine qua non of literary collaboration. Thus, each edition has been a fresh, new book. However, although new, each is largely grounded in our long-held philosophy that continues to recognize and emphasize scholarship and academic integrity, places equal importance on "why" and "how to," and embraces the notion that in the contemporary world of oncology, the overall goal should be to maximize the chance for cure, but not at any cost; that is to say, quality of life and death issues must take center stage in all cancer management decisions and strategies. Treatment that was once based almost solely on mechanical audacity and elegance has matured to include intellectual creativity. That is not meant to suggest that surgery, radiation, medical treatments, and other standard methods are no longer important, but instead, it is the recognition that science—molecular and genetic—is the critical part of the present and the future canon. In this, the fourth edition of *HNC*, the reader will note that there are several key chapters that go well beyond their respective predecessor chapters in addressing the scientifically relevant material of the particular subject discussed. That being said, in this edition of *HNC*, we have also significantly increased and improved the technique sections. We believe, then, that throughout multiple editions, we have adapted and have embraced change, brevity, and efficiency, the combination of which makes this latest work a readable and imminently practical companion for all students of head and neck oncology.

As in the last edition, we have made extensive use of algorithms and guidelines in the quest for standardization of workup and management strategies. While doing so, we have attempted to incorporate flexibility in order to accommodate the substantial variability between patients. And finally, as proof that the book's title is more than a catchy marketing ploy, the reader will easily discover that the multidisciplinary philosophy of dealing with this dreaded complex of diseases is embedded throughout the corpus of the work.

Collaborating with a world-class publishing organization improves the entire working environment in undertaking such a substantial endeavor, and as it relates to the team at Lippincott Williams & Wilkins, this is most assuredly an understatement.

Finally, we feel that words alone fail to describe the heartfelt gratitude of the editors for the time commitment and other sacrifices of the authors who have labored to finalize this project. As usual, the busiest of scholars have somehow found time to hammer out yet another project despite their already saturated agendas—we thank them and their families for paying the substantial personal price to thus enrich the scientific literature.



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The editors want to express their deep appreciation and respect to Mr. John Battis, who has been an indispensable partner in the last three editions of this textbook. His commitment to perfection and professionalism is a hallmark that all of us should aspire to achieve.



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# PERSONAL THOUGHTS ON BEING AN ONCOLOGIST

This fourth edition of our textbook will be my last as an editor. My regret in stepping down relates mainly to the loss of the association with my co-editors and the publisher. Our professional chemistry will be a fond memory throughout the balance of my life. However, the inexorability of life's accrual and retirement are real, and my pathway is clear. In signing off, however, I have asked for the indulgence of my co-editors by allowing me to write a personalized essay of sorts. I thank them for graciously accepting this departure from the norm in which I expound on matters thus far only slightly addressed in our literature.

For appropriate reasons, psychosocial and ethical matters that are relevant to the moral foundation and behavior of oncologists have been infrequently mentioned in the literature. Mainstream cancer textbooks have always been devoted to the disease—its biology, pathology, pathogenesis, treatment, etc., without dwelling on the transcendental matters that relate to interaction with and care of cancer patients. Such a statement is in no way intended as an indictment of what has been written; instead, it is merely an acknowledgment of fact. In this discussion, therefore, I have attempted to touch on some of the more important of these issues, and in doing so I seek to create an imperative for oncologists that includes sensitivity and intuitiveness, in addition to intellectualism and technical skills. These thoughts are not limited to a particular oncology specialty; instead, they apply consistently to the entire cancer playbook. Unquestionably, esoteric thoroughness is beyond the capacity of this overview, but it is my hope that the reader will be stimulated to pursue further studies and deeper consideration of these matters.

Especially as it pertains to the medical profession, the desire to serve fellow humans is vocational, and the inherently strong and consuming passion required to function at this level goes well beyond routine ambition. This intensity is even more relevant to the life of an oncologist—whether focused on radiation, surgery, medical, or psycho-oncology; all are tethered to potentially insatiable emotional demands of a very needy patient population. While potentially appealing to one's vanity, these demands—unique in medicine—can consume an idealistic oncologist who is incapable of compartmentalization of life's priorities.

Being a *physician* is a privilege, and sober responsibilities go with the title. Caring for cancer victims magnifies this sobriety because the typical patient—frightened, vulnerable, and threatened to the core—justifiably expects compassion, a commitment to excellence, a seriousness of purpose, and an ethos of integrity and humanity from the cancer team in general, and especially from the cancer physician.[1] Whether justified or not, when responsible for cancer patients, the stakes are generally perceived to be higher than those associated with other maladies. Not surprisingly, being an oncologist involves a life with little room for frivolity or casualness, and at a minimum, dilettantish physicians who value style over substance should avoid the oncology specialties. Obviously, style and substance are not mutually exclusive, but in the personality of oncologists, the former must be substantially subordinated to the latter. Aspirants to these specialties must realize that to perform in this arena is neither an ordinary responsibility nor a casual commitment; none in medicine should be, but with cancer, there is usually heightened passion and drama. What is euphemistically labeled *the cancer experience* is can be an extraordinary test for physician and patient alike.

It is essential, then, for those on this career path to understand that oncologists are required to function with a heightened emotional capability—often in an atmosphere of sadness and fear. At a minimum, it's challenging to care for patients whose dependence, vulnerability, and psychological fragilities are extraordinary. Acceptance of this fact is fundamental to "Oncology 101." With that said, given the correct physician motivation, the experience can be deeply rewarding and the lifestyle very workable.

Even though most sophisticated cancer teams include psychiatric and other support colleagues, their participation, no matter how effective, should not preclude the involvement of the whole team; said another way, the emotional responsibilities of the oncologist are in no way mutually exclusive from those of the psycho-oncologist or social worker. Essentially, the psychological support from the cancer team should be circumferential.

The psychic issues at play between the oncologist and the patient are inextricably intertwined—and by the physician understanding the patient better, and by the patient understanding what is faced by the physician, *the cancer experience* is enhanced.

For starters, the repeated witnessing of agony and death can be emotionally erosive, and the personal price paid by oncologists can be substantial. That said, many of the contemporary treatment strategies are successful, and the rewards seem to consistently replenish our spirit. It is important, however, to recognize a consistent human characteristic present in the scenario just described; dealing with the travails associated with cancer can lead to an involuntary response of self-protection in which oncologists unintentionally shield themselves emotionally by being remote from their patients. This is similar to other human behavior in which barriers are erected out of fear of emotional pain. It is my observation that young physicians are more prone to such emotional defensiveness, but with maturation and self-analysis, many come to realize that the real rewards for a doctor come from the bonding and the affection that they sought to avoid in their younger years.

With emotional maturation, the oncologist hopefully begins to appreciate the rewards of success—not by always conquering the disease mind you, because unfortunately such is not the case—but by finding the human connection that helps guide and support patients in their time of extreme need. It has always amazed me how much genuine affection and gratitude cancer patients are capable of doling out. So when others remark that it must be discouraging to be an oncologist, my response is that while emotional and sometimes even depressing, quite the opposite from discouragement is the norm. On the contrary, gratification and satisfaction are abundant.

Absent an emotional commitment on the part of the oncologist—that is, failing to lower those self-imposed protective barriers—both the patient and the physician suffer. In fact, it is my unscientific observation that the latter's failure to commit can lead to crippling professional unhappiness. Those considering oncology as an avenue of study should, therefore, be self-analytical in this regard; if one is unwilling to commit emotionally, a psychologically less demanding specialty should be considered.

From the patient's standpoint, the psychic plight cannot be overstated. Admittedly, the intensity of fear—that most primordial of emotions—varies with the degree of seriousness of the malignancy and also from patient to patient. With some exceptions, however, these instinctive feelings are consistent and



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strong. How various patients handle and respond to these feelings is a subject of study that the emotionally astute oncologist must address. Most have no special training in psychology, and the level of perceptiveness and concern for the more spiritual aspects of doctor–patient interactions is largely inherent to the physician's persona.

The fears of these patients vary from simple to complex and range from low grade to paralytic. Whether cured or not, the cancer victim often dwells on a kaleidoscope of perceived threats—financial matters, family well-being, loss of dignity, pain, deformity, dependency with lose of autonomy, being abandoned and alone, and obviously death itself—all of which can be catalyzed by an emotionally uninvolved cancer team that minimizes these deeply rooted concerns. The take-home message of this general subject is as with raising children, needs differ from one individual to the other—some patients require more attention, some less; and if a physician does not have the flexibility to cater to this diverse emotional appetite, they should work in another specialty of medicine.

In addition to compromising their own chance of achieving professional fulfillment, the unwillingness of an oncologist to contribute to the emotional equation between doctor and patient often stymies the latter's ability to develop hope. This is no small consideration because, in the practical world of cancer medicine, there is nothing psychologically more valuable for a patient than hope—but only when it is realistic and honest. Better for the doctor to be noncommittal than to encourage false hope, which is deceptive, and perhaps even a betrayal of sorts.

The importance of the relationship between hope and trust of one's physician is extraordinary, especially when discussing cancer—the two are closely linked. To trust is to have faith and confidence not only in the integrity and unselfishness, but especially the beneficence of the person in charge; bottom line, "Will my doctor do and advise what is best for me, and not because of curiosity or a result of stubbornness." For the oncologist to find a balance between empathy and guidance throughout the cancer journey is the sine qua non of good leadership—a quality that should be practiced by those who have accepted the responsibility for cancer victims. The paradigm is straightforward: good doctor/patient relations come out of honest and forthright dialog that is based on realism rather than paternalistic avoidance of unpleasant news. Such a relationship begets trust, which in turn begets acceptance of the inevitable as the patient is led to the conclusion of care, whether it is improvement or death. In order to accommodate this paradigm, however, hope must be redefined. Let me explain just what I mean.

Too often, physicians misunderstand hope by thinking only in terms of cure or remission. This flawed concept is common in the ever-optimistic oncology community—surgical, radiation, and medical alike. Hope can also be for a good death; for time to mend interpersonal bonds that are in disrepair; for resolution of feelings about divinity and a life after death; and, yes, for comforting loved ones who will be left behind. Never mind what the medical team deems important, the patient should be the author of the new standard, and it is the job of the physician to incorporate that into the dialog and the relationship. As a result of trust and creditable dialogue, a patient should be able to completely rely on unselfish guidance in making practical choices, especially at the end of life. In this state of mind, one is better able to find closure in life and an acceptance of death, both of which add tranquility to the final stage of existence.

Oncologists—even those with the best of intentions—too often fight *the battle* to excess, and in an effort to do something, use up valuable end-of-life time and resources. It is my belief that this desperate behavior in a sense reflects our society's refusal to admit the existence of death's power, and perhaps even death itself, and in this high-tech biomedical era, when the tantalizing possibility of miraculous cure is dangled before patient and family, the temptation to see therapeutic hope is great, even in those situations when common sense would suggest otherwise.[2]

So as to take this out of the realm of speculation, I point to a study reported in the *Annals of Internal Medicine*[3] that used patients from California and Massachusetts as a study cohort. All were 65 and older, and had died as a result of their cancer. In more than 20% of the study group, chemotherapy had been administered within 3 months prior to their death, and significantly, the cancer's likelihood of responsiveness to chemotherapy did not seem to influence whether dying patients received chemotherapy at the end of life. Use of chemotherapeutic agents was similar for patients with breast, colon, and ovarian malignancies and even for those with cancers that are generally considered unresponsive to chemotherapy, such as melanomas and those of the pancreas, liver, and kidney.[4] Circumstantial data from another study[5] showed that 20% of the Medicare cancer patients with metastasis who were analyzed had been started on a new chemotherapy regimen within two weeks of death. The implications of this are far reaching and profound and among cynics surely suggest monetary motives. One is left to speculate how these data would differ in a population of uninsured patients. In evaluating what seems like a system's error, the obvious question is that if there are incentives for oncologists to try more treatment despite minimal odds for success, why can't the reverse be implemented; that is to say, why can't there be disincentives to go for that long shot.

In deciding how much treatment is enough, the cancer physician must repeatedly address the question of what is in the best interest of the patient—that is to say, he/she should act with beneficence. Even if what is done turns out to be the wrong strategy, if the motive was in quest of the patient's benefit, it is morally defensible. This sounds simplistic, but in fact, pride, vanity, and other unresolved or perhaps even unrecognized psychic forces within a physician can complicate a patient's life and death. Physicians, like other talented and intelligent people, are not immune to the insecurity that seeks reassurance of their abilities, and whether realized or not, part of their self-image depends on success and failure in patient care. Additionally, many physicians are extraordinarily competitive, and the instinct to fight on can be strong. Some oncologists seem to feel obligated to explore every avenue of treatment, no matter how unlikely the benefit. Aside from this being void of beneficence, it is financially an unsupportable strategy. My plea in this regard is for an early reality check, since the treatment decisions made near the end of life are prone to propel a dying person in a senseless direction. That being said, it is important to concede the need for certain palliative surgical techniques that are humanely applicable to those approaching death. For example, in selective circumstances, operations such as a gastrostomy, a colostomy, or a tracheostomy can diminish the misery associated with intestinal and airway compromise. Active palliative care—surgery and occasionally targeted radiation therapy included—has an important role, provided implementation is based on humaneness and beneficence.

A vulnerable cancer patient's reliance on their oncologist can be extraordinary, and it is not unusual for the patient to look to that physician for advice and counsel on a variety of health-related matters—psychiatric, nutritional, and some unrelated to the primary disease of concern. This role of the "perceived expert" on all medical matters must be handled with tact, realism, humility, and always with graciousness and generosity. It's a simple thing to disavowal expertise, but while doing that, to show obvious interest by offering suggestions on some questions and by promoting appropriate referrals when indicated. In this day and age of subspecialization, it is important to remind ourselves that we are still physicians and we should still attempt to look after and care for the "whole patient."

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It should always be remembered that during the final approach to death, the oncologist is often the go-to person for a variety of matters. While much of patient concerns can and will be handled by the supporting team, many of the questions asked are well within the purview of a mature and receptive oncologist. The patient and family should feel as if their physician is involved with and overseeing almost everything that's happening, and importantly, the oncologist especially should welcome discussing death with a cancer victim. From a patient's perspective, who is better to talk to about death? With a well-crafted discussion, there often follows an element of surrender to the reality of death, understandably sometimes accompanied by anxiety, but usually without terror. More often, the surrender is followed by acceptance and a sense of calm—in the vernacular of the hospice philosophy, a tranquil comfort, rather than turbulence and rampant fear of the unknown. This passage from realization to acceptance is essential to the willingness of a patient to cease trying to hold their mortality at bay.

This whole general subject provides much material for contemplation and reflection, and I suggest the following intellectual itinerary for the reader who's emotional and intellectual maturation should ideally be a dynamic process: what ought a cancer patient reasonably expect of the system, the cancer team, and especially, the cancer physician? What ought a cancer physician be able to expect of the patient? What are the physician's responsibilities to the patient—to the family? How much information about the disease is enough; how much is too much; and importantly, how much is too little? Where do optimism and encouragement end and the gravitas of realism begin? How specific and how graphic should the doctor be? Is pessimism allowed, and if so, should it be shared with the patient? How forcefully should the case be made for the recommended treatment; that is to say, should the physician attempt to alter the patient's search for autonomy when they are disinclined to follow physician recommendations? What is the cancer physician's role when treatment fails, or because of the advanced state of the disease, when no treatment is given? How important are quality of life and quality of death; and specifically what is the cancer physician's role in the dying process? Is death solely within the dominion of spiritual forces, or is there a place for the physician as a taker of life—that is to say, the catalyst to death; and, if not an active player, should a physician even introduce the possibility of induced patient death, that is, suicide? The Oath[6] that we have lived by clearly says "No" to the taking of life by the physician; but should this part of the Oath be adapted in search of modern relevance? That certainly has happened in several European countries, and in three states in America (Washington, Oregon, and Montana), in which there are laws condoning varying degrees of physician involvement with induced patient death, a high percentage of which are related to uncured cancer. Finally, because of the natural instinct for self-protection, is it justified for the cancer physician to remain emotionally detached, and in doing that, fail to provide an intensity of feeling that might be more helpful to the patient during treatment and even on into the dying process?

These questions and many others randomly flow through the lexicology of cancer management. The answers often cannot be rigid because so much of human nature varies from individual to individual—patient and physician alike—and there should be a somewhat tailored approach for the individual patient. With that said, however, a consistent pattern ideally should underlie it all, and the standards by which these questions are answered should be established by a medical profession that understands and advocates what is right as opposed to what is wrong.

*Roy B. Sessions, MD, FACS*

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SECTION 1

# General Principles of Management of Head and Neck Cancer

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CHAPTER 1

Bruce M. Wenig and Jean-Marc Cohen

# General Principles of Head and Neck Pathology

The surgical pathologist is an integral member of the clinical team that administers to the head and neck cancer patient. The pathologist's role is multifactorial. In the simplest of terms, it is his/her job to render the correct diagnosis. However, that "final" goal is not an isolated achievement, nor is the diagnosis the sole responsibility placed on the surgical pathologist. There are numerous factors that go into the diagnosis of cancer, not the least important of which are what type of cancer is it, how invasive is the tumor, are the surgical margins free of involvement, is there metastatic disease, and are there any pathologic features that may allow for predicting the biologic behavior for a given tumor.

This chapter will be an overview of the pathologic issues relative to head and neck cancer. The chapter will be divided into two sections. Section I will be an overview of the general principles of the pathology of head and neck neoplasms. Section II will focus primarily on head and neck squamous cell carcinoma (HNSCC), including the parthologic findings of precursor lesions of HNSCC, invasive squamous cell carcinoma (SCC), and variants of SCC. Due to limitations of space, the pathology of salivary gland neoplasms, neuroendocrine neoplasms, thyroid and parathyroid lesions, and mesenchymal and hematolymphoid neoplasms will not be included in this chapter. The reader is referred to other chapters in this textbook discussing these subjects.

## THE SURGICAL PATHOLOGY REPORT AND THE TISSUE SPECIMEN

The pathology report is the document that contains the pathologist's diagnosis for a given surgical or cytologic specimen. The pathology report not only contains the diagnosis of the tumor but may also include the type, differentiation, and histologic grade of the tumor, the extent of disease, including whether the tumor is invasive (*in situ* vs. submucosal invasion), whether the surgical margins are involved by tumor, whether there is neural or lymphvascular space invasion, and whether nodal metastases and extranodal extension is present. In addition, the pathology report may contain the results of any adjunct studies that assist in establishing the diagnosis. Therefore, the pathology report includes information of prognostic and therapeutic import. Further, the pathology report is a legal document that becomes a part of the patient's medical record. The College of American Pathologists (CAP) has established guidelines (referred to as checklists) for the reporting of human cancers. These guidelines include cancers of all body sites. The most recent guidelines for the reporting of cancers of the head and neck, including the thyroid gland, are detailed in Tables 1.1 through 1.6.

The final histologic diagnosis is not an isolated achievement or the sole responsibility of the pathologist. In addition to the final diagnosis, the pathology report contains the gross and microscopic description of the specimen. For small specimens such as a biopsy, the gross description is relatively simple and straightforward. For larger surgical resections, like those often required for the head and neck cancer patient, the surgical specimen may be large and complex in its details. The complexity of the surgical specimen necessitates that the pathologist has a good functional understanding of the surgical anatomy of the region. It is the responsibility of the pathologist to properly evaluate the gross specimen and to describe in detail the gross characteristics of the tumor to include its relationship to the surrounding structures. Equally important is the proper sectioning of the specimen. Improper sectioning will result in erroneous evaluation of the specimen. To this end, the surgeon and pathologist must work in unison, especially in appropriately orienting a large resection specimen and determining the key aspects of the specimen (e.g., surgical margins) that require special attention. The sections that are taken by the pathologist will ultimately indicate whether the tumor involves the surgical margins or whether the surgical margins are free of tumor. The issue of surgical margin involvement will impact on the necessity for additional surgical intervention and/or the utilization of adjuvant therapy. Therefore, the proper gross evaluation of the specimen, including the sectioning for histologic evaluation, is a critical component in the overall management of the head and neck cancer patient.

It should be obvious that the pathologist's role as a member of the clinical team goes beyond the histologic evaluation of a tumor and the assigning of a name (i.e., a diagnosis). Certainly, the diagnosis of the tumor is important, but there are multiple additional factors that are equally important, perhaps even more important to the overall management and prognosis of the head and neck cancer patient. These issues will be discussed in detail later in this chapter.

The pathologist is entirely dependent on the tissue sampling that is received from the surgeon.

Without the appropriate material, a diagnosis cannot be rendered. This is true for neoplastic, as well as nonneoplastic lesions. In general, necrotic or ulcerated tissue should be avoided as the diagnostic yield from this material, at best, is low. The viable tissue surrounding or deep to the ulcerated or necrotic tissue should be sampled. The most common types of neoplastic proliferations



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**TABLE 1.1 College of American Pathologists (CAP) Check Lists for Cancers of the Larynx**

**Surgical Pathology Cancer Case Summary (Checklist)**
**Protocol web posting date: June 2012**
LARYNX (SUPRAGLOTTIS, GLOTTIS, SUBGLOTTIS): Incisional and Excisional Biopsy, Resection
Select a single response unless otherwise indicated.

Specimen (select all that apply)
- Larynx, supraglottis
- Larynx, glottis
- Larynx, subglottis
- Other (specify): _____
- Not specified

Received
___ Fresh
___ In formalin
___ Other (specify): _____

Procedure (select all that apply)
___ Incisional biopsy
___ Excisional biopsy
___ Resection
- ___ Endolaryngeal excision
- ___ Transoral laser excision (glottis)

___ Supraglottic laryngectomy
___ Supracricoid laryngectomy
___ Vertical hemilaryngectomy (specify side): _____
___ Partial laryngectomy (specify type): _____
___ Total laryngectomy
___ Neck (lymph node) dissection (specify): _____
___ Other (specify): _____
___ Not specified

***Specimen Integrity**
*___ Intact
*___ Fragmented

**Laryngectomy (required only if applicable)**
___ Open
___ Unopened

Specimen Size
Greatest dimensions: ___ × ___ × ___ cm
*Additional dimensions (if more than one part): ___ × ___ × ___ cm

Tumor Laterality (select all that apply)
___ Right
___ Left
___ Bilateral
___ Midline
___ Not specified

*(continued)*

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**TABLE 1.1 College of American Pathologists (CAP) Check Lists for Cancers of the Larynx (Continued)**

Tumor Site (select all that apply)
___ Larynx, supraglottis
    ___ Epiglottis
        ___ Lingual aspect
        ___ Laryngeal aspect
    ___ Aryepiglottic folds
    ___ Arytenoid(s)
    ___ False vocal cord
    ___ Ventricle
___ Larynx, glottis
    ___ True vocal cord
    ___ Anterior commissure
    ___ Posterior commissure
___ Larynx, subglottis
___ Other (specify): _____
___ Not specified

Transglottic
___ Yes
___ No

Tumor Focality
___ Single focus
___ Bilateral
___ Multifocal (specify): _____

Tumor Size
Greatest dimension: ___ cm
*Additional dimensions: ___ × ___ cm
___ Cannot be determined (see Comment)

*Tumor Description (select all that apply)
*Gross subtype:
* ___ Polypoid
* ___ Exophytic
* ___ Endophytic
* ___ Ulcerated
* ___ Sessile
*___ Other (specify): _____

***Macroscopic Extent of Tumor**

*Specify: _____

**Histologic Type (select all that apply)**
___ Squamous cell carcinoma, conventional

*Variants of Squamous Cell Carcinoma*
___ Acantholytic squamous cell carcinoma
___ Adenosquamous carcinoma
___ Basaloid squamous cell carcinoma
___ Papillary squamous cell carcinoma
___ Spindle cell squamous cell carcinoma
___ Verrucous carcinoma
___ Giant cell carcinoma
___ Lymphoepithelial carcinoma (nonnasopharyngeal)

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**TABLE 1.1 College of American Pathologists (CAP) Check Lists for Cancers of the Larynx (Continued)**

*Neuroendocrine Carcinoma*
___ Typical carcinoid tumor (well-differentiated neuroendocrine carcinoma)
___ Atypical carcinoid tumor (moderately differentiated neuroendocrine carcinoma)
___ Small cell carcinoma, neuroendocrine type (poorly differentiated neuroendocrine carcinoma)
___ Combined (or composite) small cell carcinoma, neuroendocrine type
___ Mucosal malignant melanoma

*Carcinomas of Minor Salivary Glands*
___ Adenoid cystic carcinoma
___ Mucoepidermoid carcinoma
    ___ Low grade
    ___ Intermediate grade
    ___ High grade
___ Other (specify): _____
___ Other carcinoma (specify): _____
___ Carcinoma, type cannot be determined

Histologic Grade
___ Not applicable
___ GX: Cannot be assessed
___ G1: Well differentiated
___ G2: Moderately differentiated
___ G3: Poorly differentiated
___ Other (specify): _____

***Microscopic Tumor Extension**
Specify: _____

Margins (select all that apply)
___ Cannot be assessed
___ Margins uninvolved by invasive carcinoma
    Distance from closest margin: ___ mm *or* ___ cm
    Specify margin(s), per orientation, if possible: _____
___ Margins involved by invasive carcinoma
    Specify margin(s), per orientation, if possible: _____
___ Margins uninvolved by carcinoma *in situ* (includes moderate and severe dysplasia[#])
    Distance from closest margin: ___ mm *or* ___ cm
    Specify margin(s), per orientation, if possible: _____
___ Margins involved by carcinoma *in situ* (includes moderate and severe dysplasia[#])
    Specify margin(s), per orientation, if possible: _____
___ Not applicable

***[#]Applicable only to squamous cell carcinoma and histologic variants.***

*Treatment Effect (applicable to carcinomas treated with neoadjuvant therapy)
* ___ Not identified
* ___ Present (specify): _____
* ___ Indeterminate

Lymph-Vascular Invasion
___ Not identified
___ Present
___ Indeterminate

Perineural Invasion
___ Not identified

*(continued)*

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**TABLE 1.1 College of American Pathologists (CAP) Check Lists for Cancers of the Larynx (Continued)**

___ Present
___ Indeterminate

Lymph Nodes, Extranodal Extension
___ Not identified
___ Present
___ Indeterminate

Pathologic Staging (pTNM)
*Note: The phrases in italics include clinical findings required for AJCC staging. This clinical information may not be available to the pathologist. However, if known, these findings should be incorporated into the pathologic staging.*

*TNM Descriptors* (required only if applicable) (select all that apply)
___ m (multiple primary tumors)
___ r (recurrent)
___ y (posttreatment)

Primary Tumor (pT)
___ pTX: Cannot be assessed
___ pT0: No evidence of primary tumor
___ pTis: Carcinoma *in situ*

**For All Carcinomas Excluding Mucosal Malignant Melanoma**

*Primary Tumor (pT): Supraglottis*
___ pT1: Tumor limited to one subsite of supraglottis *with normal vocal cord mobility*
___ pT2: Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) *without fixation of the larynx*
___ pT3: Tumor limited to larynx *with vocal cord fixation* and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage
___ pT4a: Moderately advanced local disease. Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscle of tongue, strap muscles, thyroid, or esophagus)
___ pT4b: Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

*Primary Tumor (pT): Glottis*
___ pT1: Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) *with normal mobility*
___ pT1a: Tumor limited to one vocal cord
___ pT1b: Tumor involves both vocal cords
___ pT2: Tumor extends to supraglottis and/or subglottis *and/or with impaired vocal cord mobility*
___ pT3: Tumor limited to the larynx *with vocal cord fixation* and/or invades paraglottic space and/or minor thyroid cartilage erosion (eg, inner cortex) (Note H)
___ pT4a: Moderately advanced local disease. Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus) (Note H)
___ pT4b: Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

*Primary Tumor (pT): Subglottis*
___ pT1: Tumor limited to subglottis
___ pT2: Tumor extends to vocal cord(s) *with normal or impaired mobility*
___ pT3: Tumor limited to larynx *with vocal cord fixation*
___ pT4a: Moderately advanced local disease. Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
___ pT4b: Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

*Regional Lymph Nodes (pN)#*
___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension

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**TABLE 1.1 College of American Pathologists (CAP) Check Lists for Cancers of the Larynx (Continued)**

___ pN2: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
___ pN2a: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
___ pN2b: Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
___ pN2c: Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
___ pN3: Metastasis in a lymph node more than 6 cm in greatest dimension
___ No nodes submitted or found

*Number of Lymph Nodes Examined*
Specify: _____
___ Number cannot be determined (explain): _____

*Number of Lymph Nodes Involved*
Specify: _____
___ Number cannot be determined (explain): _____
* Size (greatest dimension) of the largest positive lymph node: _____

[#]*Superior mediastinal lymph nodes are considered regional lymph nodes (level VII). Midline nodes are considered ipsilateral nodes.*

Distant Metastasis (pM)
___ Not applicable
___ pM1: Distant metastasis
* Specify site(s), if known: _____
* Source of pathologic metastatic specimen (specify): _____

**For Mucosal Malignant Melanoma**

*Primary Tumor (pT)*
___ pT3: Mucosal disease
___ pT4a: Moderately advanced disease. Tumor involving deep soft tissue, cartilage, bone, or overlying skin
___ pT4b: Very advanced disease. Tumor involving brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space, or mediastinal structures

*Regional Lymph Nodes (pN)*
___ pNX: Regional lymph nodes cannot be assessed
___ pN0: No regional lymph node metastases
___ pN1: Regional lymph node metastases present

*Distant Metastasis (pM)*
___ Not applicable
___ pM1: Distant metastasis present
* Specify site(s), if known: _____
* Source of pathologic metastatic specimen (specify): _____

* Additional Pathologic Findings (select all that apply)
* ___ None identified
* ___ Keratinizing dysplasia (Note M)
  * ___ Mild
  * ___ Moderate
  * ___ Severe (carcinoma *in situ*)
* ___ Nonkeratinizing dysplasia (Note M)
  * ___ Mild
  * ___ Moderate
  * ___ Severe (carcinoma *in situ*)
* ___ Inflammation (specify type): _____
* ___ Squamous metaplasia

*(continued)*

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**TABLE 1.1 College of American Pathologists (CAP) Check Lists for Cancers of the Larynx (Continued)**

* ___ Epithelial hyperplasia
* ___ Colonization
    * ___ Fungal
    * ___ Bacterial
* ___ Other (specify): _____
* Ancillary Studies (Note N)
* Specify type(s): _____
* Specify result(s): _____

*** Clinical History (select all that apply)**

* ___ Neoadjuvant therapy
    * ___ Yes (specify type): _____
    * ___ No
    * ___ Indeterminate
* ___ Other (specify): _____

*Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

**TABLE 1.2 College of American Pathologists (CAP) Check Lists for Cancers of the Lip and Oral Cavity**

**Surgical Pathology Cancer Case Summary (Checklist)**
**Protocol web posting date: June 2012**

**Lip and Oral Cavity: Incisional Biopsy, Excisional Biopsy, Resection**

**Select a single response unless otherwise indicated.**

Specimen (select all that apply)
___ Vermilion border upper lip
___ Vermilion border lower lip
___ Mucosa of upper lip
___ Mucosa of lower lip
___ Commissure of lip
___ Lateral border of tongue
___ Ventral surface of tongue, not otherwise specified (NOS)
___ Dorsal surface of tongue, NOS
___ Anterior two-thirds of tongue, NOS
___ Upper gingiva (gum)
___ Lower gingiva (gum)
___ Anterior floor of mouth
___ Floor of mouth, NOS
___ Hard palate
___ Buccal mucosa (inner cheek)
___ Vestibule of mouth
    ___ Upper
    ___ Lower
___ Alveolar process
    ___ Upper
    ___ Lower

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**TABLE 1.2 College of American Pathologists (CAP) Check Lists for Cancers of the Lip and Oral Cavity (Continued)**

___ Mandible
___ Maxilla
___ Other (specify): _____
___ Not specified

Received
___ Fresh
___ In formalin
___ Other (specify): _____

Procedure (select all that apply)
___ Incisional biopsy
___ Excisional biopsy
___ Resection
    ___ Glossectomy (specify): _____
    ___ Mandibulectomy (specify): _____
    ___ Maxillectomy (specify): _____
    ___ Palatectomy
___ Neck (lymph node) dissection (specify): _____
___ Other (specify): _____
___ Not specified

*** Specimen Integrity**
* ___Intact
* ___Fragmented

**Specimen Size**
Greatest dimensions: _____ × _____ × _____ cm
* Additional dimensions (if more than 1 part): _____ × _____ × _____ cm

**Specimen Laterality**
___ Right
___ Left
___ Bilateral
___ Midline
___ Not specified

Tumor Site (select all that apply)
___ Vermilion border upper lip
___ Vermilion border lower lip
___ Mucosa of upper lip
___ Mucosa of lower lip
___ Commissure of lip
___ Lateral border of tongue
___ Ventral surface of tongue, NOS
___ Dorsal surface of tongue, NOS
___ Anterior two-thirds of tongue, NOS
___ Upper gingiva (gum)
___ Lower gingiva (gum)
___ Anterior floor of mouth
___ Floor of mouth, NOS
___ Hard palate
___ Buccal mucosa (inner cheek)

*(continued)*

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**TABLE 1.2 College of American Pathologists (CAP) Check Lists for Cancers of the Lip and Oral Cavity (Continued)**

___ Vestibule of mouth
___ Upper
___ Lower
___ Alveolar process
___ Upper
___ Lower
___ Mandible
___ Maxilla
___ Other (specify): _____
___ Not specified

Tumor Focality
___ Single focus
___ Multifocal (specify): _____

Tumor Size
Greatest dimension: ___ cm
* Additional dimensions: ___ × ___ cm
___ Cannot be determined (see Comment)

*** Tumor Thickness (pT1 and pT2 tumors)**

* Tumor thickness: ___ mm
* Intact surface mucosa: _____; or ulcerated surface: _____
* Tumor Description (select all that apply)
* Gross subtype
* ___ Polypoid
* ___ Exophytic
* ___ Endophytic
* ___ Ulcerated
* ___ Sessile
* ___ Other (specify): _____

*** Macroscopic Extent of Tumor**
* Specify: _____

Histologic Type (select all that apply)
___ Squamous cell carcinoma, conventional

*Variants of Squamous Cell Carcinoma*
___ Acantholytic squamous cell carcinoma
___ Adenosquamous carcinoma
___ Basaloid squamous cell carcinoma
___ Carcinoma cuniculatum
___ Papillary squamous cell carcinoma
___ Spindle cell squamous carcinoma
___ Verrucous carcinoma

___ Lymphoepithelial carcinoma (nonnasopharyngeal)

Carcinomas of Minor Salivary Glands
___ Acinic cell carcinoma
___ Adenoid cystic carcinoma
___ Adenocarcinoma, not otherwise specified (NOS)
___ Low grade
___ Intermediate grade

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**TABLE 1.2 College of American Pathologists (CAP) Check Lists for Cancers of the Lip and Oral Cavity (Continued)**

___ High grade
___ Basal cell adenocarcinoma
___ Carcinoma ex pleomorphic adenoma (malignant mixed tumor)
    ___ Low grade
    ___ High grade
    ___ Invasive
        ___ Minimally invasive
        ___ Invasive
    ___ Intracapsular (noninvasive)
___ Carcinoma, type cannot be determined
___ Carcinosarcoma
___ Clear cell adenocarcinoma
___ Cystadenocarcinoma
___ Epithelial-myoepithelial carcinoma
___ Mucoepidermoid carcinoma
    ___ Low grade
    ___ Intermediate grade
    ___ High grade
___ Mucinous adenocarcinoma (colloid carcinoma)
___ Myoepithelial carcinoma (malignant myoepithelioma)
___ Oncocytic carcinoma
___ Polymorphous low-grade adenocarcinoma
___ Salivary duct carcinoma
___ Other (specify): _____

*Adenocarcinoma, Non–Salivary Gland Type*
___ Adenocarcinoma, not otherwise specified (NOS)
    ___ Low grade
    ___ Intermediate grade
    ___ High grade
___ Other (specify): _____

*Neuroendocrine Carcinoma*
___ Typical carcinoid tumor (well-differentiated neuroendocrine carcinoma)
___ Atypical carcinoid tumor (moderately differentiated neuroendocrine carcinoma)
___ Small cell carcinoma (poorly differentiated neuroendocrine carcinoma)
___ Combined (or composite) small cell carcinoma, neuroendocrine type
___ Other (specify): _____
___ Carcinoma, type cannot be determined
___ Mucosal malignant melanoma

Histologic Grade
___ Not applicable
___ GX: Cannot be assessed
___ G1: Well differentiated
___ G2: Moderately differentiated
___ G3: Poorly differentiated
___ Other (specify): _____

* Microscopic Tumor Extension
* Specify: _____

*(continued)*

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**TABLE 1.2 College of American Pathologists (CAP) Check Lists for Cancers of the Lip and Oral Cavity (Continued)**

Margins (select all that apply)
___ Cannot be assessed
___ Margins uninvolved by invasive carcinoma
Distance from closest margin: ___ mm or ___ cm
Specify margin(s), per orientation, if possible: _____
___ Margins involved by invasive carcinoma
Specify margin(s), per orientation, if possible: _____
___ Margins uninvolved by carcinoma *in situ* (includes moderate and severe dysplasia#) (Note E)
Distance from closest margin: ___ mm or ___ cm
Specify margin(s), per orientation, if possible: _____
___ Margins involved by carcinoma *in situ* (includes moderate and severe dysplasia#) (Note E)
Specify margin(s), per orientation, if possible: _____
___ Not applicable

***#Applicable only to squamous cell carcinoma and histologic variants.***
* Treatment Effect (applicable to carcinomas treated with neoadjuvant therapy)
* ___ Not identified
* ___ Present (specify): _____
* ___ Indeterminate

Lymph-Vascular Invasion
___ Not identified
___ Present
___ Indeterminate

Perineural Invasion
___ Not identified
___ Present
___ Indeterminate

Lymph Nodes, Extranodal Extension
___ Not identified
___ Present
___ Indeterminate

Pathologic Staging (pTNM)

TNM Descriptors (required only if applicable) (select all that apply)
___ m (multiple primary tumors)
___ r (recurrent)
___ y (posttreatment)

**For All Carcinomas Excluding Mucosal Malignant Melanoma**

Primary Tumor (pT)
___ pTX: Cannot be assessed
___ pT0: No evidence of primary tumor
___ pTis: Carcinoma *in situ*
___ pT1: Tumor 2 cm or less in greatest dimension
___ pT2: Tumor more than 2 cm but not more than 4 cm in greatest dimension
___ pT3: Tumor more than 4 cm in greatest dimension
___ pT4a: Moderately advanced local disease.

Lip: Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, i.e., chin or nose
Oral cavity: Tumor invades adjacent structures only (e.g., through cortical bone [mandible, maxilla], into deep [extrinsic] muscle of tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, skin of face)

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**TABLE 1.2 College of American Pathologists (CAP) Check Lists for Cancers of the Lip and Oral Cavity (Continued)**

___ pT4b: Very advanced local disease. Tumor invades masticator space, pterygoid plates, or skull base, and/or encases internal carotid artery

*Note: Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumor as T4.*

Regional Lymph Nodes (pN)[#] (Notes J through M)
___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
___ pN2a: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
___ pN2b: Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
___ pN2c: Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
___ pN3: Metastasis in a lymph node more than 6 cm in greatest dimension
___ No nodes submitted or found

*Number of Lymph Nodes Examined*
Specify: _____
___ Number cannot be determined (explain): _____

*Number of Lymph Nodes Involved*
Specify: _____
___ Number cannot be determined (explain): _____
* Size (greatest dimension) of the largest positive lymph node: _____

[#]*Superior mediastinal lymph nodes are considered regional lymph nodes (level VII). Midline nodes are considered ipsilateral nodes.*

Distant Metastasis (pM)
___ Not Applicable
___ pM1: Distant metastasis
* Specify site(s), if known: _____
* Source of pathologic metastatic specimen (specify): _____

**For Mucosal Malignant Melanoma**

*Primary Tumor (pT)*
___ pT3: Mucosal disease
___ pT4a: Moderately advanced disease. Tumor involving deep soft tissue, cartilage, bone, or overlying skin
___ pT4b: Very advanced disease. Tumor involving brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space, or mediastinal structures

*Regional Lymph Nodes (pN)*
___ pNX: Regional lymph nodes cannot be assessed
___ pN0: No regional lymph node metastases
___ pN1: Regional lymph node metastases present

*Distant Metastasis (pM)*
___ Not applicable
___ pM1: Distant metastasis present
* Specify site(s), if known: _____
* Source of pathologic metastatic specimen (specify): _____

* Additional Pathologic Findings (select all that apply)
* ___ None identified
* ___ Keratinizing dysplasia (Note N)
* ___ Mild
* ___ Moderate
* ___ Severe (carcinoma *in situ*)

*(continued)*

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**TABLE 1.2 College of American Pathologists (CAP) Check Lists for Cancers of the Lip and Oral Cavity (Continued)**

* ___ Nonkeratinizing dysplasia (Note N)
    * ___ Mild
    * ___ Moderate
    * ___ Severe (carcinoma *in situ*)
* ___ Inflammation (specify type): _____
* ___ Epithelial hyperplasia
* ___ Colonization
    * ___ Fungal
    * ___ Bacterial
* ___ Other (specify): _____

* Ancillary Studies
* Specify type(s): _____
* Specify result(s): _____

*** Clinical History (select all that apply)**

* ___ Neoadjuvant therapy
    * ___ Yes (specify type): _____
    * ___ No
    * ___ Indeterminate
* ___ Other (specify): _____

*Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

**TABLE 1.3 College of American Pathologists (CAP) Check Lists for Cancers of the Nasal Cavity and Paranasal Sinuses**

**Surgical Pathology Cancer Case Summary (Checklist)**
**Protocol web posting date: June 2012**

**Nasal Cavity and Paranasal Sinuses: Incisional Biopsy, Excisional Biopsy, Resection**

**Select a single response unless otherwise indicated.**

**Specimen (select all that apply)**

___ Nasal cavity
    ___ Septum
    ___ Floor
    ___ Lateral wall
    ___ Vestibule
___ Paranasal sinus(es), maxillary
___ Paranasal sinus(es), ethmoid
___ Paranasal sinus(es), frontal
___ Paranasal sinus(es), sphenoid
___ Other (specify): _____
___ Not specified

Received
___ Fresh
___ In formalin
___ Other (specify): _____

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**TABLE 1.3 College of American Pathologists (CAP) Check Lists for Cancers of the Nasal Cavity and Paranasal Sinuses (Continued)**

**Procedure (select all that apply)**
___ Incisional Biopsy
___ Excisional Biopsy
___ Resection (specify type)
    ___ Partial maxillectomy
    ___ Radical maxillectomy
___ Neck (lymph node) Dissection (specify): _____
___ Other (specify): _____
___ Not Specified

* Specimen Integrity
* ___ Intact
* ___ Fragmented

Specimen Size
Greatest dimensions: ___ × ___ × ___ cm
* Additional dimensions (if more than one part): ___ × ___ × ___ cm

Specimen Laterality (select all that apply)
___ Right
___ Left
___ Bilateral
___ Midline
___ Not specified

**Tumor Site (select all that apply)**
___ Nasal cavity
    ___ Septum
    ___ Floor
    ___ Lateral wall
    ___ Vestibule
___ Paranasal sinus(es), maxillary
___ Paranasal sinus(es), ethmoid
___ Paranasal sinus(es), frontal
___ Paranasal sinus(es), sphenoid
___ Other (specify): _____
___ Not specified

**Tumor Focality (select all that apply)**
___ Single focus
___ Bilateral
___ Multifocal (specify): _____

**Tumor Size**
Greatest dimension: ___ cm
* Additional dimensions: ___ × ___ cm
___ Cannot be determined (see Comment)

*** Tumor Description (select all that apply)**
* Gross subtype
* ___ Polypoid
* ___ Exophytic
* ___ Endophytic

*(continued)*

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**TABLE 1.3 College of American Pathologists (CAP) Check Lists for Cancers of the Nasal Cavity and Paranasal Sinuses (Continued)**

* ___ Ulcerated
* ___ Sessile
* ___ Other (specify): _____

*** Macroscopic Extent of Tumor**

* Specify: _____

**Histologic Type (select all that apply)**

*Carcinomas of the Nasal Cavity and Paranasal Sinuses*

___ Squamous cell carcinoma, conventional
- ___ Keratinizing
- ___ Nonkeratinizing (formerly cylindrical cell, transitional cell)

*Variants of Squamous Cell Carcinoma*

___ Acantholytic squamous cell carcinoma
___ Adenosquamous carcinoma
___ Basaloid squamous cell carcinoma
___ Papillary squamous cell carcinoma
___ Spindle cell squamous cell carcinoma
___ Verrucous carcinoma

___ Giant cell carcinoma
___ Lymphoepithelial carcinoma (nonnasopharyngeal)
___ Sinonasal undifferentiated carcinoma (SNUC)

*Adenocarcinoma, Non–Salivary Gland Type*

___ Intestinal type
- ___ Papillary type
- ___ Colonic type
- ___ Solid type
- ___ Mucinous type
- ___ Mixed type

___ Nonintestinal type
- ___ Low grade
- ___ Intermediate grade
- ___ High grade

*Carcinomas of Minor Salivary Glands*

___ Acinic cell carcinoma
___ Adenoid cystic carcinoma
___ Adenocarcinoma, not otherwise specified (NOS)
- ___ Low grade
- ___ Intermediate grade
- ___ High grade

___ Carcinoma ex pleomorphic adenoma (malignant mixed tumor)
___ Clear cell adenocarcinoma
___ Epithelial-myoepithelial carcinoma
___ Mucoepidermoid carcinoma
- ___ Low grade
- ___ Intermediate grade
- ___ High grade

___ Myoepithelial carcinoma (malignant myoepithelioma)
___ Oncocytic carcinoma
___ Polymorphous low-grade adenocarcinoma

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**TABLE 1.3 College of American Pathologists (CAP) Check Lists for Cancers of the Nasal Cavity and Paranasal Sinuses (Continued)**

___ Salivary duct carcinoma
___ Other (specify): _____

*Neuroendocrine Carcinoma*
___ Typical carcinoid tumor (well-differentiated neuroendocrine carcinoma)
___ Atypical carcinoid tumor (moderately differentiated neuroendocrine carcinoma)
___ Small cell carcinoma (poorly differentiated neuroendocrine carcinoma)
___ Combined (or composite) small cell carcinoma, neuroendocrine type
___ Mucosal malignant melanoma
___ Other (specify): _____
___ Carcinoma, type cannot be determined

**Histologic Grade**
___ Not applicable
___ GX: Cannot be assessed
___ G1: Well differentiated
___ G2: Moderately differentiated
___ G3: Poorly differentiated
___ Other (specify): _____

*** Microscopic Tumor Extension**
* Specify: _____

**Margins (select all that apply)**
___ Cannot be assessed
___ Margins uninvolved by invasive carcinoma
Distance from closest margin: ___ mm or ___ cm
Specify margin(s), per orientation, if possible: _____
___ Margins involved by invasive carcinoma
Specify margin(s), per orientation, if possible: _____
___ Margins uninvolved by carcinoma *in situ* (includes moderate and severe dysplasia[#]) (Note D)
Distance from closest margin: ___ mm or ___ cm
Specify margin(s), per orientation, if possible: _____
___ Margins involved by carcinoma *in situ* (includes moderate and severe dysplasia[#]) (Note D)
Specify margin(s), per orientation, if possible: _____
___ Not applicable

***[#]Applicable only to squamous cell carcinoma and histologic variants.***

* Treatment Effect (applicable to carcinomas treated with neoadjuvant therapy)
* ___ Not identified
* ___ Present (specify): _____
***** ___ Indeterminate

**Lymph-Vascular Invasion**
___ Not Identified
___ Present
___ Indeterminate

Perineural Invasion (Note F)
___ Not identified
___ Present
___ Indeterminate

Lymph Nodes, Extranodal Extension (Note G)
___ Not identified

*(continued)*

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**TABLE 1.3 College of American Pathologists (CAP) Check Lists for Cancers of the Nasal Cavity and Paranasal Sinuses (Continued)**

___ Present
___ Indeterminate

**Pathologic Staging (pTNM)**

**TNM Descriptors (required only if applicable) (select all that apply)**
___ m (multiple primary tumors)
___ r (recurrent)
___ y ( posttreatment)

**Primary Tumor (pT)**
___ pTX: Cannot be assessed
___ pT0: No evidence of primary tumor
___ pTis: Carcinoma *in situ*

**For All Carcinomas Excluding Mucosal Malignant Melanoma**
**Primary Tumor (pT): Maxillary Sinus**
___ pT1: Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone
___ pT2: Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates
___ pT3: Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
___ pT4a: Moderately advanced local disease. Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
___ pT4b: Very advanced local disease. Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve ($V_2$), nasopharynx, or clivus

**Primary Tumor (pT): Nasal Cavity and Ethmoid Sinus**
___ pT1: Tumor restricted to any one subsite, with our without bone invasion
___ pT2: Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with our without bone invasion
___ pT3: Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
___ pT4a: Moderately advanced local disease Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
___ pT4b: Very advanced local disease. Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve ($V_2$), nasopharynx, or clivus

*Regional Lymph Nodes (pN)#*
___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
___ pN2: Metastasis in a single ipsilateral lymph node, more than 3cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral nodes, none more than 6 cm in greatest dimension
___ pN2a: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
___ pN2b: Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
___ pN2c: Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
___ pN3: Metastasis in a lymph node more than 6 cm in greatest dimension

___ No nodes submitted or found

*Number of Lymph Nodes Examined*
Specify: ____
___ Number cannot be determined (explain): _____

*Number of Positive Lymph Nodes*
Specify: ____

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**TABLE 1.3 College of American Pathologists (CAP) Check Lists for Cancers of the Nasal Cavity and Paranasal Sinuses (Continued)**

___ Number cannot be determined (explain): _____
* Size of the largest positive lymph node: _____
* Size of the associated metastatic focus: _____
* Position of the involved node (level): _____

[#]*Metastases at level VII are considered regional lymph node metastases. Midline nodes are considered ipsilateral nodes.*

*Distant Metastasis (pM)*
___ Not applicable
___ pM1: Distant metastasis
* Specify site(s) if known: _____
* Source of pathologic metastatic specimen (specify): _____

**For Mucosal Malignant Melanoma**

*Primary Tumor (pT)*
___ pT3: Mucosal disease
___ pT4a: Moderately advanced disease. Tumor involving deep soft tissue, cartilage, bone, or overlying skin
___ pT4b: Very advanced disease. Tumor involving brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space, or mediastinal structures

*Regional Lymph Nodes (pN)*
___ pNX: Regional lymph nodes cannot be assessed
___ pN0: No regional lymph node metastases
___ pN1: Regional lymph node metastases present

*Distant Metastasis (pM)*
___ Not applicable
___ pM1: Distant metastasis present
* Specify site(s), if known: _____
* Source of pathologic metastatic specimen (specify): _____

*** Additional Pathologic Findings (select all that apply)**
* ___ None identified
* ___ Carcinoma *in situ* (Note M)
* ___ Epithelial dysplasia (Note M)
* Specify: _____
* ___ Inflammation (specify type): _____
* ___ Squamous metaplasia
* ___ Epithelial hyperplasia
* ___ Colonization
* ___ Fungal
* ___ Bacterial
* ___ Other (specify): _____

*** Ancillary Studies (Note N)**
* Specify type(s): _____
* Specify result(s): _____

*** Clinical History (select all that apply)**
* ___ Neoadjuvant therapy
* ___ Yes (specify type): _____
* ___ No
* ___Indeterminate
* ___ Other (specify): _____

*Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

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**TABLE 1.4 College of American Pathologists (CAP) Check Lists for Cancers of the Pharynx**

**Surgical Pathology Cancer Case Summary (Checklist)**
**Protocol web posting date: June 2012**

**Pharynx (Oropharynx, Hypopharynx, Nasopharynx): Incisional Biopsy, Excisional Biopsy, Resection**

**Select a single response unless otherwise indicated.**

Specimen (select all that apply)
___ Oropharynx
___ Nasopharynx
___ Hypopharynx
___ Other (specify): _____
___ Not specified

Received
___ Fresh
___ In formalin
___ Other (specify): _____

Procedure (select all that apply)
___ Incisional biopsy
___ Excisional biopsy
___ Resection
    ___ Tonsillectomy
    ___ Laryngopharyngectomy
    ___ Other (specify): _____
___ Neck (lymph node) dissection (specify): _____
___ Other (specify): _____
___ Not specified

*** Specimen Integrity**
* ___Intact
* ___Fragmented

Specimen Size
Greatest dimensions: ___ × ___ × ___ cm
* Additional dimensions (if more than one part): ___ × ___ × ___ cm

Specimen Laterality (select all that apply)
___ Left
___ Right
___ Bilateral
___ Midline
___ Not specified

Tumor Site (select all that apply)
___Oropharynx
    ___ Palatine tonsil
    ___ Base of tongue, including lingual tonsil
    ___ Soft palate
    ___ Uvula
    ___ Pharyngeal wall (posterior)
    ___ Other
___ Nasopharynx
    ___ Nasopharyngeal tonsils (adenoids)
___ Hypopharynx
    ___ Piriform sinus
    ___ Postcricoid

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**TABLE 1.4 College of American Pathologists (CAP) Check Lists for Cancers of the Pharynx (Continued)**

___ Pharyngeal wall (posterior and/or lateral)
___ Other
___ Other (specify): _____
___ Not specified

Tumor Laterality (select all that apply)
___ Left
___ Right
___ Bilateral
___ Midline
___ Not specified

Tumor Focality
___ Single focus
___ Bilateral
___ Multifocal (specify): _____

Tumor Size
Greatest dimension: ___ cm
* Additional dimensions: ___ × ___ cm
___ Cannot be determined (see Comment)

* Tumor Description (select all that apply)
* Gross subtype:
* ___ Polypoid
* ___ Exophytic
* ___ Endophytic
* ___ Ulcerated
* ___ Sessile
* ___ Other (specify): _____

*** Macroscopic Extent of Tumor**
* Specify: _____

Histologic Type (select all that apply)

Carcinomas of the Oropharynx and Hypopharynx
___ Squamous cell carcinoma, conventional

*Variants of Squamous Cell Carcinoma*
___ Acantholytic squamous cell carcinoma
___ Adenosquamous carcinoma
___ Basaloid squamous cell carcinoma
___ Papillary squamous cell carcinoma
___ Spindle cell squamous carcinoma
___ Verrucous carcinoma

___ Lymphoepithelial carcinoma (nonnasopharyngeal)

*Carcinomas of the Nasopharynx*
___ Keratinizing squamous cell carcinoma (formerly WHO-1)
___ Nonkeratinizing carcinoma
___ Differentiated carcinoma (formerly WHO-2; transitional carcinoma)
___ Undifferentiated carcinoma (formerly WHO-3; lymphoepithelioma)
___ Basaloid squamous cell carcinoma

*(continued)*

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**TABLE 1.4 College of American Pathologists (CAP) Check Lists for Cancers of the Pharynx (Continued)**

*Adenocarcinomas (Non–Salivary Gland Type)*
___ Nasopharyngeal papillary adenocarcinoma
___ Adenocarcinoma, not otherwise specified (NOS)
    ___ Low grade
    ___ Intermediate grade
    ___ High grade
___ Other (specify): _____

Carcinomas of Minor Salivary Glands
___ Acinic cell carcinoma
___ Adenoid cystic carcinoma
___ Adenocarcinoma, not otherwise specified (NOS)
___ Low grade
___ Intermediate grade
___ High grade
___ Basal cell adenocarcinoma
___ Carcinoma ex pleomorphic adenoma (malignant mixed tumor)
___ Carcinoma, type cannot be determined
___ Clear cell adenocarcinoma
___ Cystadenocarcinoma
___ Epithelial-myoepithelial carcinoma
___ Mucoepidermoid carcinoma
    ___ Low grade
    ___ Intermediate grade
    ___ High grade
___ Mucinous adenocarcinoma (colloid carcinoma)
___ Myoepithelial carcinoma (malignant myoepithelioma)
___ Oncocytic carcinoma
___ Polymorphous low-grade adenocarcinoma
___ Salivary duct carcinoma
___ Other (specify): _____

*Neuroendocrine Carcinoma*
___ Typical carcinoid tumor (well-differentiated neuroendocrine carcinoma)
___ Atypical carcinoid tumor (moderately differentiated neuroendocrine carcinoma)
___ Small cell carcinoma (poorly differentiated neuroendocrine carcinoma)
___ Combined (or composite) small cell carcinoma, neuroendocrine type

___ Mucosal malignant melanoma

___ Other carcinoma (specify): _____
___ Carcinoma, type cannot be determined

Histologic Grade
___ Not applicable
___ GX: Cannot be assessed
___ G1: Well differentiated
___ G2: Moderately differentiated
___ G3: Poorly differentiated
___ Other (specify): _____

***** Microscopic Tumor Extension
* ___ Specify: _____

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**TABLE 1.4 College of American Pathologists (CAP) Check Lists for Cancers of the Pharynx (Continued)**

Margins (select all that apply)
___ Cannot be assessed
___ Margins uninvolved by invasive carcinoma
Distance from closest margin: ___ mm or ___ cm
Specify margin(s), per orientation, if possible: _____
___ Margins involved by invasive carcinoma
Specify margin(s), per orientation, if possible: _____
___ Margins uninvolved by carcinoma *in situ* (includes moderate and severe dysplasia[#]) (Note D)
Distance from closest margin: ___ mm or ___ cm
Specify margin(s), per orientation, if possible: _____
___ Margins involved by carcinoma *in situ* (includes moderate and severe dysplasia[#]) (Note D)
Specify margin(s), per orientation, if possible: _____
___ Not applicable

[#]Applicable only to squamous cell carcinoma and histologic variants

* Treatment Effect (applicable to carcinomas treated with neoadjuvant therapy)
* ___ Not identified
* ___ Present (specify): _____
* ___ Indeterminate

Lymph-Vascular Invasion
___ Not identified
___ Present
___ Indeterminate

Perineural Invasion
___ Not identified
___ Present
___ Indeterminate

Lymph Nodes, Extranodal Extension
___ Not identified
___ Present
___ Indeterminate

Pathologic Staging (pTNM)
*Note: The phrases in italics include clinical findings required for AJCC staging. This clinical information may not be available to the pathologist. However, if known, these findings should be incorporated into the pathologic staging.*
TNM Descriptors (required only if applicable) (select all that apply)
___ m (multiple primary tumors)
___ r (recurrent)
___ y (posttreatment)

Primary Tumor (pT)
___ pTX: Cannot be assessed
___ pT0: No evidence of primary tumor
___ pTis: Carcinoma *in situ*

**For All Carcinomas Excluding Mucosal Malignant Melanoma**

*Primary Tumor (pT): Oropharynx*
___ pT1: Tumor 2 cm or less in greatest dimension
___ pT2: Tumor more than 2 cm but not more than 4 cm in greatest dimension *without fixation of hemilarynx*
___ pT3: Tumor more than 4 cm in greatest dimension *or with fixation of hemilarynx* or extension to lingual surface of epiglottis

*(continued)*

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**TABLE 1.4 College of American Pathologists (CAP) Check Lists for Cancers of the Pharynx (Continued)**

___ pT4a: Moderately advanced local disease. Tumor invades larynx, deep/extrinsic muscle of tongue, medial pterygoid muscles, hard palate, or mandible[#]
___ pT4b: Very advanced local disease. Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base, or encases carotid artery
[#]*Note: Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of larynx.*

*Primary Tumor (pT): Nasopharynx*
___ pT1: Tumor confined to nasopharynx, or tumor extends to oropharynx and/or nasal cavity without parapharyngeal extension[#]
___ pT2: Tumor with parapharyngeal extension[#]
___ pT3: Tumor invades bony structures of skull base and/or paranasal sinuses
___ pT4: Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space
[#]*Parapharyngeal extension denotes posterolateral infiltration of tumor.*

Primary Tumor (pT): Hypopharynx
___ pT1: Tumor limited to one subsite of hypopharynx and/or 2 cm or less in greatest dimension
___ pT2: Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest dimension without fixation of hemilarynx
___ pT3: Tumor measures more than 4 cm in greatest dimension *or* with fixation of hemilarynx or extension to esophagus
___ pT4a: Moderately advanced local disease. Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, or central compartment soft tissue[#]
___ pT4b: Very advanced local disease. Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures
[#]*Note: Central compartment soft tissue includes prelarnygeal strap muscles and subcutaneous fat.*

Regional Lymph Nodes (pN)
___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis

Regional Lymph Nodes (pN): Oropharynx and Hypopharynx[#]
___ pN1: Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
___ pN2: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
___ pN2a: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
___ pN2b: Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
___ pN2c: Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
___ pN3: Metastasis in a lymph node more than 6 cm in greatest dimension

___ No nodes submitted or found

*Number of Lymph Nodes Examined*
Specify: _____
___ Number cannot be determined (explain): _____

*Number of Lymph Nodes Involved*
Specify: _____
___ Number cannot be determined (explain): _____
* Size (greatest dimension) of the largest positive lymph node: _____

[#]*Note: Metastases at level VII are considered regional lymph node metastases. Midline nodes are considered ipsilateral nodes.*

*Regional Lymph Nodes (pN): Nasopharynx*[#]
___ pN1: Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa[##]
___ pN2: Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa[##]
___ pN3: Metastasis in a lymph node greater than 6 cm and/or to supraclavicular fossa[##]
___ pN3a: Greater than 6 cm in dimension
___ pN3b: Extension to the supraclavicular fossa[##]

___ No nodes submitted or found

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**TABLE 1.4 College of American Pathologists (CAP) Check Lists for Cancers of the Pharynx (Continued)**

*Number of Lymph Nodes Examined*
Specify: ____
___ Number cannot be determined (explain): _____

*Number of Lymph Nodes Involved*
Specify: ____
___ Number cannot be determined (explain): _____
* Size (greatest dimension) of the largest positive lymph node: ____

#*Metastases at level VII are considered regional lymph node metastases. Midline nodes are considered ipsilateral nodes.*
##*Supraclavicular zone or fossa is relevant to the staging of nasopharyngeal carcinoma and is the triangular region defined by three points: (1) the superior margin of the sternal end of the clavicle, (2) the superior margin of the lateral end of the clavicle, (3) the point where the neck meets the shoulder (see Figure 1-3, no. 2). Note that this would include caudal portions of Levels IV and VB. All cases with lymph nodes (whole or part) in the fossa are considered N3b.*

Distant Metastasis (pM)
___ Not applicable
___ pM1: Distant metastasis
* Specify site(s), if known: _____
* Source of pathologic metastatic specimen (specify): _____

**For Mucosal Malignant Melanoma**

*Primary Tumor (pT)*
___pT3: Mucosal disease
___pT4a: Moderately advanced disease. Tumor involving deep soft tissue, cartilage, bone, or overlying skin.
___pT4b: Very advanced disease. Tumor involving brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space, or mediastinal structures.

*Regional Lymph Nodes (pN)*
___pNX: Regional lymph nodes cannot be assessed
___pN0: No regional lymph node metastases
___pN1: Regional lymph node metastases present

*Distant Metastasis (pM)*
___ Not applicable
___ pM1: Distant metastasis present
* Specify site(s), if known: _____
* Source of pathologic metastatic specimen (specify): _____

* Additional Pathologic Findings (select all that apply)
* ___ None identified
* ___ Keratinizing dysplasia
  * ___ Mild
  * ___ Moderate
  * ___ Severe (carcinoma *in situ*)
* ___ Nonkeratinizing dysplasia
  * ___ Mild
  * ___ Moderate
  * ___ Severe (carcinoma *in situ*)
* ___ Inflammation (specify type): _____
* ___ Squamous metaplasia
* ___ Epithelial hyperplasia
* ___ Colonization
  * ___ Fungal
  * ___ Bacterial
* ___ Other (specify): _____

*(continued)*

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## TABLE 1.4 College of American Pathologists (CAP) Check Lists for Cancers of the Pharynx (Continued)

Ancillary Studies (required only for oropharynx [p16, HPV] and nasopharynx [EBV] if available at time of report completion) (select all that apply) (Notes M and O)

___ p16
- ___ Positive
- ___ Negative

___ Human papillomavirus (HPV), *in situ* hybridization (ISH)
- Type (specify): _____
- ___ Positive
  - Pattern
    - ___ Punctate
    - ___ Diffuse
    - ___ Mixed
- ___ Negative
- ___ Indeterminate (explain): _____

___ HPV, polymerase chain reaction (PCR)
- Type (specify): _____
- ___ Positive
- ___ Negative

___ Epstein-Barr virus (Epstein-Barr virus–encoded RNA [EBER], other)
- ___ Positive
- ___ Negative

___ Other (specify): _____

___ Not specified

*** Clinical History (select all that apply)**

* ___ Neoadjuvant therapy
- * ___ Yes (specify type): _____
- * ___ No
- * ___ Indeterminate

* ___ Other (specify): _____

*Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

## TABLE 1.5 College of American Pathologists (CAP) Check Lists for Cancers of the Salivary Glands

**Surgical Pathology Cancer Case Summary (Checklist)**
**Protocol web posting date: June 2012**

**Major Salivary Glands: Incisional Biopsy, Excisional Biopsy, Resection**

Select a single response unless otherwise indicated.

Specimen (select all that apply)

___ Parotid gland
- ___ Superficial lobe only
- ___ Deep lobe only
- ___ Total parotid gland

___ Submandibular gland

___ Sublingual gland

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**TABLE 1.5 College of American Pathologists (CAP) Check Lists for Cancers of the Salivary Glands (Continued)**

___ Other (specify): _____
___ Not specified

Received
___ Fresh
___ In formalin
___ Other (specify): _____

**Procedure (select all that apply)**
___ Incisional biopsy
___ Excisional biopsy
___ Resection, parotid gland
    ___ Superficial parotidectomy
    ___ Total parotidectomy
___ Resection, submandibular gland
___ Resection, sublingual gland
___ Neck (lymph node) dissection (specify): _____
___ Other (specify): _____
___ Not specified

*** Specimen Integrity**
* ___ Intact
* ___ Fragmented

**Specimen Size**
Greatest dimensions: _____ × _____ × _____cm
* Additional dimensions (if more than 1 part): ___ × ___ × ___ cm

**Specimen Laterality**
___ Right
___ Left
___ Bilateral
___ Not specified

Tumor Site (select all that apply)
___ Parotid gland
    ___ Superficial lobe
    ___ Deep lobe
    ___ Entire parotid gland
___ Submandibular gland
___ Sublingual gland
___ Other (specify): _____
___ Not specified

Tumor Focality
___ Single focus
___ Bilateral
___ Multifocal (specify): _____

**Tumor Size**
Greatest dimension: ___ cm
* Additional dimensions: ___ × ___ cm
___ Cannot be determined (see Comment)

*(continued)*

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**TABLE 1.5 College of American Pathologists (CAP) Check Lists for Cancers of the Salivary Glands (Continued)**

* Tumor Description (select all that apply)
* ___ Encapsulated/circumscribed
* ___ Invasive
* ___ Solid
* ___ Cystic
* ___ Other (specify): _____

*** Macroscopic Extent of Tumor (extent of invasion)**

* Specify: _____

**Histologic Type (select all that apply)**

___ Acinic cell carcinoma
___ Adenoid cystic carcinoma
___ Adenocarcinoma, not otherwise specified (NOS)
___ Low grade
___ Intermediate grade
___ High grade
___ Basal cell adenocarcinoma
___ Carcinoma ex pleomorphic adenoma (malignant mixed tumor)
    ___ Low grade
    ___ High grade
    ___ Invasive
        ___ Minimally invasive
        ___ Invasive
    ___ Intracapsular (noninvasive)
___ Carcinosarcoma (true malignant mixed tumor)
___ Clear cell adenocarcinoma
___ Cystadenocarcinoma
___ Epithelial-myoepithelial carcinoma
___ Large cell carcinoma
___ Low-grade cribriform cystadenocarcinoma
___ Lymphoepithelial carcinoma
___ Metastasizing pleomorphic adenoma
___ Mucoepidermoid carcinoma
    ___ Low grade
    ___ Intermediate grade
    ___ High grade
___ Mucinous adenocarcinoma (colloid carcinoma)
___ Myoepithelial carcinoma (malignant myoepithelioma)
___ Oncocytic carcinoma
___ Polymorphous low-grade adenocarcinoma
___ Salivary duct carcinoma
___ Sebaceous adenocarcinomas
___ Sebaceous lymphadenocarcinoma
___ Sialoblastoma
___ Small cell (neuroendocrine) carcinoma
___ Squamous cell carcinoma, primary
___ Undifferentiated carcinoma, large cell type

___ Other (specify): _____
___ Carcinoma, type cannot be determined

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**TABLE 1.5 College of American Pathologists (CAP) Check Lists for Cancers of the Salivary Glands (Continued)**

Histologic Grade
___ Not applicable
___ GX: Cannot be assessed
___ G1: Well differentiated
___ G2: Moderately differentiated
___ G3: Poorly differentiated
___ Other (specify): _____

*** Microscopic Tumor Extension**
* Specify: _____

Margins (Notes D and E)
___ Cannot be assessed
___ Margins uninvolved by carcinoma
Distance of tumor from closest margin: ___ mm *or* ___ cm
Specify margin, if possible: _____
___ Margin(s) involved by carcinoma
Specify margin(s), if possible: _____

* Treatment Effect (applicable to carcinomas treated with neoadjuvant therapy)
* ___ Not identified
* ___ Present (specify): _____
* ___ Indeterminate

Lymph-Vascular Invasion
___ Not identified
___ Present
___ Indeterminate

Perineural Invasion
___ Not identified
___ Present
___ Indeterminate

**Lymph Nodes, Extranodal Extension**
___ Not identified
___ Present
___ Indeterminate

**Pathologic Staging (pTNM)**
*Note: The phrases in italics include clinical findings required for AJCC staging. This clinical information may not be available to the pathologist. However, if known, these findings should be incorporated into the pathologic staging.*

TNM Descriptors (required only if applicable) (select all that apply)
___ m (multiple primary tumors)
___ r (recurrent)
___ y (posttreatment)

Primary Tumor (pT)
___ pTX: Cannot be assessed

*(continued)*

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**TABLE 1.5 College of American Pathologists (CAP) Check Lists for Cancers of the Salivary Glands (Continued)**

___ pT0: No evidence of primary tumor
___ pT1: Tumor 2 cm or less in greatest dimension *without extraparenchymal extension*
___ pT2: Tumor more than 2 cm but not more than 4 cm in greatest dimension *without extraparenchymal extension* (Note l)
___ pT3: Tumor more than 4 cm and/or tumor *having extraparenchymal extension*
___ pT4a: Moderately advanced disease. Tumor invades skin, mandible, ear canal, and/or facial nerve.
___ pT4b: Very advanced local disease. Tumor invades skull base and/or pterygoid plates and/or encases carotid artery

*Note: There is no category of carcinoma in situ (pTis) relative to carcinomas of salivary glands (major, minor).*

*Regional Lymph Nodes (pN)#*
___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
___ pN2a: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
___ pN2b: Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
___ pN2c: Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
___ pN3: Metastasis in a lymph node, more than 6 cm in greatest dimension

___ No nodes submitted or found

*Number of Lymph Nodes Examined*
Specify: ____
___ Number cannot be determined (explain): _____

*Number of Lymph Nodes Involved*
Specify: ____
___ Number cannot be determined (explain): _____

* Size (greatest dimension) of the largest positive lymph node: _____ cm

*#Superior mediastinal lymph nodes are considered regional lymph nodes (level VII). Midline nodes are considered ipsilateral nodes.*

*Distant Metastasis (pM)*
___ Not Applicable
___ pM1: Distant metastasis
    * Specify site(s), if known: _____

*** Additional Pathologic Findings (select all that apply)**
* ___ Sialadenitis
* ___ Tumor associated lymphoid proliferation (TALP)
* ___ Other (specify): _____
* Ancillary Studies
* Specify type(s): _____
* Specify result(s): _____

*** Clinical History (select all that apply)**
* ___ Neoadjuvant therapy
    * ___ Yes (specify type): _____
    * ___ No
    * ___ Indeterminate
* ___ Other (specify): _____

*Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

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**TABLE 1.6 College of American Pathologists (CAP) Check Lists for Cancers of the Thyroid Gland**

**Surgical Pathology Cancer Case Summary (Checklist)**
**Protocol web posting date: June 2012**

**Thyroid Gland: Resection**

**Select a single response unless otherwise indicated.**

**Procedure (select all that apply)**
___ Thyroid lobectomy
    ___ Right
    ___ Left
___ Partial thyroidectomy (anything less than a lobectomy)
    ___ Right
    ___ Left
___ Hemithyroidectomy (lobe and part or all of isthmus)
    ___ Right
    ___ Left
___ Total thyroidectomy
___ Total thyroidectomy with central compartment dissection
___ Total thyroidectomy with right neck dissection
___ Total thyroidectomy with left neck dissection
___ Total thyroidectomy with bilateral neck dissection
___ Other (specify): _____
___ Not specified

* Received
* ___ Fresh
* ___ In formalin
* ___ Other

**Specimen Integrity**
___ Intact
___ Fragmented

**Specimen Size**
Right lobe: ___ × ___ × ___ cm
Left lobe: ___ × ___ × ___ cm
Isthmus ± pyramidal lobe: ___× ____× ____ cm
Central compartment: ___ × ___ × ___ cm
Right neck dissection: ___ × ___ × ___ cm
Left neck dissection: ___ × ___ × ___ cm
* Additional dimensions (specify): ___ × ___ × ___ cm

*** Specimen Weight**
* Specify: ____ g

**Tumor Focality (select all that apply)**
___ Unifocal
___ Multifocal (specify):
    ___ Ipsilateral
    ___ Bilateral
    ___ Midline (isthmus)

**Dominant Tumor**
*Tumor Laterality* (select all that apply)
___ Right lobe

*(continued)*

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**TABLE 1.6 College of American Pathologists (CAP) Check Lists for Cancers of the Thyroid Gland (Continued)**

___ Left lobe
___ Isthmus
___ Not specified

*Tumor Size*
Greatest dimension: ___ cm
* Additional dimensions: ___ × ___ cm
___ Cannot be determined

*Histologic Type* (select all that apply)
___ Papillary carcinoma
Variant, specify
___ Classical (usual)
___ Clear cell variant
___ Columnar cell variant
___ Cribriform-morular variant
___ Diffuse sclerosing variant
___ Follicular variant
___ Macrofollicular variant
___ Microcarcinoma (occult, latent, small, papillary microtumor)
___ Oncocytic or oxyphilic variant
___ Solid variant
___ Tall cell variant
___ Warthin-like variant
___ Other, specify: _____
Architecture
___ Classical (papillary)
___ Cribriform-morular
___ Diffuse sclerosing
___ Follicular
___ Macrofollicular
___ Solid
___ Other, specify: _____
Cytomorphology
___ Classical
___ Clear cell
___ Columnar cell
___ Oncocytic or oxyphilic
___ Tall cell
___ Follicular carcinoma
Variant, specify
___ Clear cell
___ Oncocytic (Hürthle cell)
___ Other, specify: _____
___ Poorly differentiated thyroid carcinomas, including insular carcinoma
___ Medullary carcinoma
___ Undifferentiated (anaplastic) carcinoma
___ Other (specify): _____
___ Carcinoma, type cannot be determined

* *Histologic Grade*
* ___ Not applicable

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**TABLE 1.6 College of American Pathologists (CAP) Check Lists for Cancers of the Thyroid Gland (Continued)**

* ___ GX: Cannot be assessed
* ___ G1: Well differentiated
* ___ G2: Moderately differentiated
* ___ G3: Poorly differentiated
* ___ G4: Undifferentiated
* ___ Other (specify): _____

*Margins*
___ Cannot be assessed
___ Margins uninvolved by carcinoma
    * Distance of invasive carcinoma to closest margin: ___ mm
___ Margin(s) involved by carcinoma
* Site(s) of involvement: _____

*Tumor Capsule*
___ Cannot be assessed
___ Totally encapsulated
___ Partially encapsulated
___ None

*Tumor Capsular Invasion* (select all that apply)
___ Cannot be assessed
___ Not identified
___ Present
    Extent
    ___ Minimal
    ___ Widely invasive
___ Indeterminate

*Lymph-Vascular Invasion* (select all that apply)
___ Cannot be assessed
___ Not identified
___ Present
    Extent
    ___ Focal (<4 vessels)
    ___ Extensive (4 or more vessels)
___ Indeterminate

* *Perineural Invasion*
* ___ Not identified
* ___ Present
* ___ Indeterminate

*Extrathyroidal Extension* (select all that apply)
___ Cannot be assessed
___ Not identified
___ Present
    Extent
    ___ Minimal
    ___ Extensive

**Second Tumor (for multifocal tumors only)**

*Tumor Laterality* (select all that apply)
___ Right lobe

*(continued)*

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**TABLE 1.6 College of American Pathologists (CAP) Check Lists for Cancers of the Thyroid Gland (Continued)**

___ Left lobe
___ Isthmus
___ Not specified

*Tumor Size*
Greatest dimension: ___ cm
* Additional dimensions: ___ × ___ cm
___ Cannot be determined

*Histologic Type* (select all that apply)
___ Papillary carcinoma
Variant, specify
___ Classical (usual)
___ Clear cell variant
___ Columnar cell variant
___ Cribriform-morular variant
___ Diffuse sclerosing variant
___ Follicular variant
___ Macrofollicular variant
___ Microcarcinoma (occult, latent, small, papillary microtumor)
___ Oncocytic or oxyphilic variant
___ Solid variant
___ Tall cell variant
___ Warthin-like variant
___ Other, specify: _____
Architecture
___ Classical (papillary)
___ Cribriform-morular
___ Diffuse sclerosing
___ Follicular
___ Macrofollicular
___ Solid
___ Other, specify: _____
Cytomorphology
___ Classical
___ Clear cell
___ Columnar cell
___ Oncocytic or oxyphilic
___ Tall cell
___ Follicular carcinoma
Variant, specify
___ Clear cell
___ Oncocytic (Hürthle cell)
___ Other, specify: _____
___ Poorly differentiated thyroid carcinomas, including insular carcinoma
___ Medullary carcinoma
___ Undifferentiated (anaplastic) carcinoma
___ Other (specify): _____
___ Carcinoma, type cannot be determined

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**TABLE 1.6 College of American Pathologists (CAP) Check Lists for Cancers of the Thyroid Gland (Continued)**

* *Histologic Grade*
* ___ Not applicable
* ___ GX: Cannot be assessed
* ___ G1: Well differentiated
* ___ G2: Moderately differentiated
* ___ G3: Poorly differentiated
* ___ G4: Undifferentiated
* ___ Other (specify): _____

*Margins*
___ Cannot be assessed
___ Margins uninvolved by carcinoma
    * Distance of invasive carcinoma to closest margin: ___ mm
___ Margin(s) involved by carcinoma
* Site(s) of involvement: _____

*Tumor Capsule*
___ Cannot be assessed
___ Totally encapsulated
___ Partially encapsulated
___ None

*Tumor Capsular Invasion* (select all that apply)
___ Cannot be assessed
___ Not identified
___ Present
    Extent
    ___ Minimal
    ___ Widely invasive
___ Indeterminate

*Lymph-Vascular Invasion* (select all that apply)
___ Cannot be assessed
___ Not identified
___ Present
    Extent
    ___ Focal (< 4 vessels)
    ___ Extensive (4 or more vessels)
___ Indeterminate

* *Perineural Invasion*
* ___ Not identified
* ___ Present
* ___ Indeterminate

*Extrathyroidal Extension* (select all that apply)
___ Cannot be assessed
___ Not identified
___ Present
    Extent
    ___ Minimal
    ___ Extensive

*(continued)*

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**TABLE 1.6 College of American Pathologists (CAP) Check Lists for Cancers of the Thyroid Gland (Continued)**

**Pathologic Staging (pTNM)**

*TNM Descriptors (required only if applicable) (select all that apply)*

___ m (multiple primary tumors)
___ r (recurrent)
___ y (posttreatment)

*Primary Tumor (pT)*

___ pTX: Cannot be assessed
___ pT0: No evidence of primary tumor
___ pT1: Tumor size 2 cm or less, limited to thyroid
___ pT1a: Tumor 1 cm or less in greatest dimension limited to the thyroid
___ pT1b: Tumor more than 1 cm but not more than 2 cm in greatest dimension, limited to the thyroid
___ pT2: Tumor more than 2 cm, but not more than 4 cm, limited to thyroid
___ pT3: Tumor more than 4 cm limited to thyroid or any tumor with minimal extrathyroid extension (e.g., extension to sternothyroid muscle or perithyroid soft tissues)
___ pT4a: Moderately advanced disease. Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus or recurrent laryngeal nerve
___ pT4b: Very advanced disease. Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels

*Note: There is no category of carcinoma in situ (pTis) relative to carcinomas of thyroid gland.*

**Anaplastic Carcinoma**

___ pT4a: Intrathyroidal anaplastic carcinoma
___ pT4b: Anaplastic carcinoma with gross extrathyroid extension

*Regional Lymph Nodes (pN)[#]*

___ pNX: Regional lymph nodes cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1a: Metastasis to Level VI (pretracheal, paratracheal and prelaryngeal/Delphian) lymph nodes
___ pN1b: Metastasis to unilateral, bilateral or contralateral cervical (Levels I, II, III, IV, V) or retropharyngeal or superior mediastinal lymph nodes (Level VII)
Specify: Number examined: ___
Number involved: ___

[#]*Superior mediastinal lymph nodes are considered regional lymph nodes (level VII). Midline nodes are considered ipsilateral nodes.*

* *Lymph Node, Extranodal Extension*
* ___ Not identified
* ___ Present
* ___ Indeterminate

*Distant Metastasis (pM)*

___ Not applicable
___ pM1: Distant metastasis
* Specify site(s), if known: _____
* Source of pathologic metastatic specimen (specify): _____

*** Additional Pathologic Findings (select all that apply)**

* ___ Adenoma
* ___ Adenomatoid nodule(s) or Nodular follicular disease (eg, nodular hyperplasia, goitrous thyroid)
* ___ Diffuse hyperplasia (Graves' disease)
* ___ Thyroiditis
* ___ Advanced
* ___ Focal (nonspecific)

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**TABLE 1.6 College of American Pathologists (CAP) Check Lists for Cancers of the Thyroid Gland (Continued)**

* ___ Palpation
* ___ Other (specify): _____
* ___ Parathyroid gland(s)
* ___ Within normal limits
* ___ Hypercellular
* ___ Other (specify): _____
* ___ C-cell hyperplasia
* ___ None identified
* ___ Other (specify): _____

*** Ancillary Studies (Note O)**

* Specify type (e.g., histochemistry, immunohistochemistry, DNA analysis): _____
* Specify results: _____

*** Clinical History (select all that apply)**

* ___ Radiation exposure
* ___ Yes (specify type): _____
* ___ No
* ___ Indeterminate
* ___ Family history
* ___ Other (specify): _____

*Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

of the upper aerodigestive tract (UADT) originate from the surface epithelium. A critical parameter utilized by the pathologist in differentiating a reactive or benign surface epithelial lesion from a malignant neoplasm is the presence or absence of stromal invasion. Adequate sampling should therefore include the depth of the tissue so that the pathologist can evaluate the epithelial-to-stromal interface, and an assessment for the presence or absence of stromal invasion can be made. Without an adequate epithelial-to-stromal interface, a diagnosis cannot be made, resulting in frustration for the pathologist, surgeon, and, most importantly, the patient. The deficiency of proper sampling leads to diagnostic and therapeutic delays. Further, tissue sampling of any anatomic site results in secondary pathologic changes that may cause diagnostic dilemmas for the pathologist.

The sampling of lymph nodes should include the largest node available as the diagnostic yield will be greatest as compared to a more accessible but smaller lymph node. Another issue in tissue sampling is the proper fixation of a specimen. Once a surgical specimen is removed, the surgeon should not delay in placing the specimen in the appropriate fixative. Excessive delay in placing the surgical specimen in fixative will result in autolytic and other artifactual alterations in the tissue. In general, the fixative that is most used by pathologists is formaldehyde. However, some specimens, especially lymph nodes removed for a possible diagnosis of lymphoma, may require special fixation. Some lymphoid-related antigens are lost by prior fixation so that in certain situations, the pathologist will want unfixed or fresh tissue in order to perform specific immunohistochemical, flow cytometric, or molecular biologic studies. The pathologist should be notified and consulted relative to the proper handling of the surgical material. Similarly, if it is anticipated that electron microscopy or cytogenetic evaluation will be required to assist in the diagnosis, then special fixatives, such as gluteraldehyde for electron microscopy and tissue culture medium (e.g., RPMI media, an acronym for Roswell Park Memorial Institute, where it was developed), will be required. When such circumstances are anticipated, the pathologist should be notified prior to the procedure that the specimen may require special handling.

The surgeon or any member of the surgical team should not bisect or section a tumor once it is excised from the patient. This may cause problems for the pathologist in the gross evaluation of the specimen, in appropriate tissue sectioning, and in appropriate tissue fixation. Such improper handling of the excised tissues may compromise the excised specimen. The gross evaluation, sectioning, and histologic examination of the surgical specimen falls under the purview of the pathologist. The surgeon should sample or remove sufficient tissue for diagnosis and send it to the pathologist intact, properly labeled, and with any specific requirements or requests that may be needed (e.g., specific surgical margins). The relationship of the surgeon and the pathologist is not adversarial, but should be collegial, with both specialists working in unison. Only in this way will the primary goal be achieved (i.e., optimal patient care).

# SECTION I
# General Principles of Head and Neck Neoplasms

## CLASSIFICATION OF HEAD AND NECK CANCERS

The general classification of malignant tumors of the head and neck are detailed in Tables 1.7 through 1.11.

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**TABLE 1.7 Classification of Epithelial Malignancies of the Head and Neck**

- Cutaneous epithelial malignant tumors
  - Squamous cell carcinoma
  - Basal cell carcinoma
  - Verrucous carcinoma
  - Malignant cutaneous adnexal tumors
- Mucosal epithelial malignant tumors
  - Squamous cell carcinoma
    - Keratinizing type
    - Nonkeratinizing type
  - Variants of squamous cell carcinoma including
    - Papillary squamous cell carcinoma
    - Verrucous carcinoma
    - Spindle cell squamous carcinoma
    - Basaloid squamous cell carcinoma
    - Oropharyngeal (HPV-associated) squamous cell carcinoma
    - Nasopharyngeal carcinoma
      - Keratinizing
      - Nonkeratinizing
        - Differentiated type
        - Undifferentiated type
    - Adenosquamous carcinoma
    - "Lymphoepithelial" or undifferentiated carcinoma
    - Others
  - Adenocarcinomas
    - Surface mucosal origin
    - Mucoserous gland origin

**TABLE 1.8 Classification of Neuroectodermal Tumors of the Head and Neck**

- Tumors of the dispersed neuroendocrine cell system (DNES) (as it applies to the head and neck)
- Central DNES
  - Olfactory neuroblastoma
- Peripheral DNES
  - Malignant melanoma
  - Neuroendocrine carcinomas
    - Carcinoid tumor (well-differentiated neuroendocrine carcinoma)
    - Atypical carcinoid (moderately differentiated neuroendocrine carcinoma)
    - Small-cell carcinoma undifferentiated neuroendocrine carcinoma (poorly differentiated neuroendocrine carcinoma)
    - Large-cell neuroendocrine carcinoma
  - Merkel cell carcinoma
  - Peripheral nerve sheath tumors (schwannoma, neurilemoma, and malignant peripheral nerve sheath tumors)
  - Paragangliomas
  - Others

**TABLE 1.9 Classification of Mesenchymal Malignancies of the Head and Neck**

- Soft tissue
- Lymphoproliferative
  - Malignant lymphomas (Non-Hodgkin and Hodgkin)
- Skeletal muscle
  - Rhabdomyosarcoma
- Nerve
  - Malignant peripheral nerve sheath tumors
- Vascular/lymphatic
  - Angiosarcoma
  - Malignant hemangioendothelioma
  - Kaposi sarcoma
- Pericytic
  - Hemagiopericytoma
- Smooth muscle
  - Leiomyosarcoma
- Fibrous tissue
  - Fibrosarcoma
  - Malignant fibrous histiocytoma
- Notochord cell remnant
  - Chordoma
- Undefined mesenchymal cell
  - Synovial sarcoma
  - Alveolar soft part sarcoma
- Matrix-producing malignacies
- Bone
  - Osteosarcoma
- Cartilage
  - Chondrosarcoma
  - Odontogenic

## TERMINOLOGY

The cell of origin for a given neoplasm (benign or malignant) is its histogenesis. In head and neck malignancies, the most common type of malignant tumor is one that arises from the surface squamous epithelium. Squamous epithelial malignant tumors are carcinomas. However, the head and neck is rich in nonsquamous epithelial–derived structures, so that epithelial malignancies (carcinomas) may originate from salivary glands (major and minor), cutaneous adnexae, thyroid follicular epithelium, as well as parathyroid glands. Gland-forming tumors are termed adenocarcinomas. In addition to being rich in epithelial structures, the head and neck also contains abundant nonepithelial structures. These nonepithelial components include bone, cartilage, muscle (skeletal and smooth), nerves, vascular channels, and lymphoid structures. Any one of these nonepithelial or mesenchymal structures may give rise to a malignant tumor. Malignant neoplasms of mesenchymal structures are sarcomas, whereas malignant lymphoproliferative neoplasms are (malignant) lymphomas. Finally, the head and neck contains neuroectodermal (peripheral and central) elements, including melanocytes, neuroendocrine cells, Schwann cells, paraganglia, and olfactory neuroepithelial cells, any one of which may give rise to malignant tumors, such as malignant melanomas, neuroendocrine carcinomas, malignant

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**TABLE 1.10 Classification of Salivary Gland Malignancies**

- Epithelial
  - Mucoepidermoid carcinoma
  - Adenocarcinoma, not otherwise specified
    - Low-grade
    - Intermeidate grade
    - High-grade
  - Acinic cell adenocarcinoma and mammary analogue secretory carcinoma
  - Adenoid cystic carcinoma
  - Polymorphous low-grade adenocarcinoma
  - Malignant mixed tumors
    - Carcinoma ex pleomorphic adenoma (invasive and noninvasive)
    - Carcinosarcoma
    - Metastasizing pleomorphic adenoma
  - Basal cell adenocarcinoma
  - Epithelial-myoepithelial carcinoma
  - Salivary duct carcinoma
  - Low-grade cribriform cystadenocarcinoma
  - Mammary analogue secretory carcinoma
  - Clear cell adenocarcinoma
  - Cystadenocarcinoma
  - Undifferentiated carcinoma
  - Oncocytic carcinoma
  - Sebaceous adenocarcinoma/lympadenocarcinoma
  - Myoepithelial carcinoma
  - Squamous cell carcinoma
  - Adenosquamous carcinoma
  - Mucinous adenocarcinoma
- Mesenchymal
  - Sarcomas
- Malignant lymphomas
  - Non-Hodgkin lymphomas and Hodgkin lymphomas

**TABLE 1.11 Classification of Thyroid Gland and Parathyroid Gland Malignancies**

- Thyroid gland
  - Epithelial (follicular cell origin)
    - Follicular carcinoma and variants
    - Papillary carcinoma and variants
    - Anaplastic carcinoma
    - Mucoepidermoid carcinoma
    - Squamous cell carcinoma
  - Neuroectodermal (C cell origin)
    - Medullary carcinoma
  - Lymphoproliferative
- Non-Hodgkin lymphomas and Hodgkin lymphomas
  - Mesenchymal
    - Angiosarcoma
    - Leiomyosarcoma
    - Malignant peripheral nerve sheath tumors
    - Others
  - Parathyroid gland
    - Parathyroid carcinoma

peripheral nerve sheath tumors, malignant paragangliomas, and olfactory neuroblastomas.

The discussion on terminology would not be complete without detailing the alterations of the surface epithelium that may represent the precursor change(s) heralding the malignant transformation of that epithelial structure. The reader is referred to the appropriate section in part II of this chapter that discusses this subject.

## HISTOLOGIC DIFFERENTIATION AND GRADE

The more a tumor recapitulates the appearance of the cell and/or tissue layer from which it arises, the better differentiated it is. This definition applies to virtually all malignant tumors, and perhaps it is most applicable to squamous epithelial tumors. A well-differentiated squamous carcinoma is one that has obvious keratinization and intercellular bridges. The keratinization appears as layered acellular eosinophilic material or appears within the cytoplasm of the cell as "glassy" eosinophilic deposits. Intercellular bridges are best viewed under oil-immersion magnification but can be seen on high magnification as very thin lines lying in between (outside) the cells and connecting these cells to each other (Fig. 1-1). As a tumor becomes less differentiated, it "loses" its histologic similarities to its cell of origin. A poorly differentiated squamous carcinoma has little, if any, keratinization, and the presence of intercellular bridges becomes less distinct or absent (Fig. 1-2). In this setting, direct derivation from the surface epithelium and/or the overall growth pattern assist in defining this tumor as an SCC. The same definitions of differentiation apply to gland-forming malignant tumors (adenocarcinomas) and to mesenchymal malignant tumors.

The phenotypic extreme on the poorly differentiated end of the spectrum may result in a "dedifferentiated" or "undifferentiated" tumor that loses its light microscopic similarities to its cell of origin. It is this type of neoplasm that often necessitates special pathologic studies (e.g., immunohistochemistry) to determine its histogenesis. A common example of this in head and neck sites is the spindle cell squamous carcinoma (SCSC). This high-grade variant of squamous carcinoma is characterized by the presence of a malignant spindle cell neoplastic infiltrate. The malignant spindle cells are devoid of keratinization and intercellular bridges. The histologic appearance of the spindle-shaped cells, the growth pattern including interconnecting and ramifying fascicles, and the absence of squamous epithelial features, simulate the appearance of several malignant mesenchymal neoplasms; hence, earlier terminology of these tumors as carcinosarcomas and sarcomatoid carcinomas. Immunohistochemistry plays an important role in defining this tumor and assisting in the final diagnosis. In the majority of cases, SCSCs will be cytokeratin positive. However, in addition to losing its phenotypic characteristics, tumors that are poorly differentiated may also lose their genotypic markers (i.e., epitopes), resulting in (false) negative immunohistochemical findings. In the situation of SCSCs, immunohistochemical markers of epithelial differentiation may not be present, yet this tumor is still epithelial in origin (see Section II under Spindle Cell Squamous Carcinoma).

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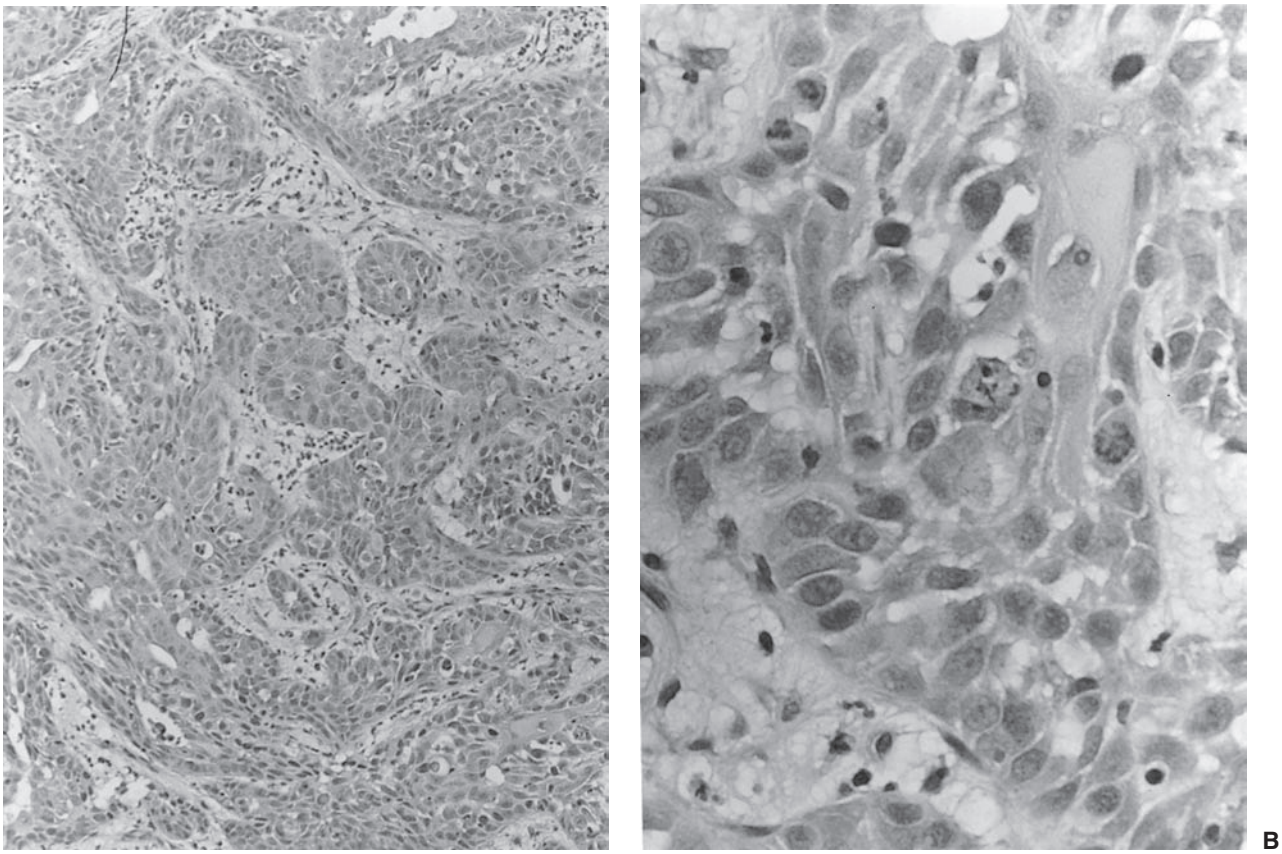



**FIGURE 1-1.** Well-differentiated squamous cell carcinoma. This tumor is invasive and is associated foci of individual cell keratinization **(A)** and intercellular bridges **(B)**.

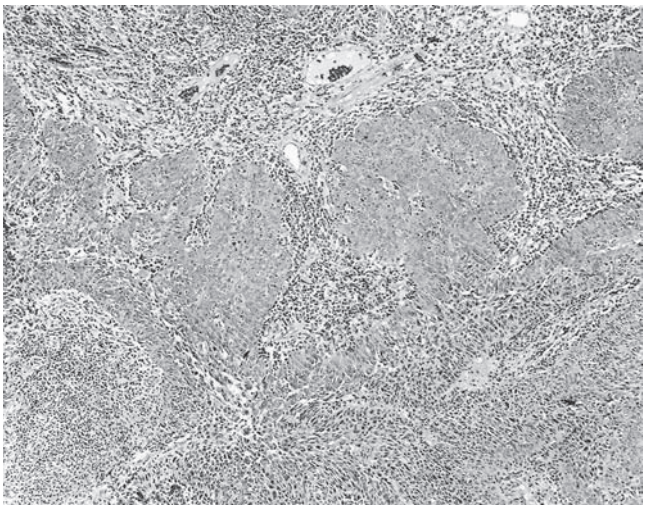


**FIGURE 1-2.** Poorly differentiated squamous cell carcinoma. In contrast to the previous illustration, the invasive neoplasm seen here lacks evidence of squamous differentiation (e.g., keratinization or intercellular bridges). However, the overall growth pattern is one that is seen in association with squamous cell carcinomas. Although not shown in this illustration, this neoplasm was identified as arising from the surface epithelium establishing its diagnosis as a squamous cell carcinoma.

The histologic grade of a tumor is dependent on its differentiation. The better differentiated a tumor is, the lower its histologic grade. A well-differentiated SCC is considered grade I, whereas a poorly differentiated SCC is a grade III. It stands to reason that better differentiated tumors tend to be DNA diploid or near DNA diploid with a lower cell proliferation rate (doubling time) and the less likelihood to have aggressive behavior (locoregional recurrence or metastasis) in comparison to less differentiated and/or anaplastic tumors.[1] This is not universally true. The extent and depth of invasion, and perhaps metastatic potential, may have no bearing on the histologic grade of a tumor so that a histologic grade I SCC can be a high clinical-stage cancer, while a histologic grade III SCC may be a low clinical-stage cancer. Nevertheless, prognostic correlation has been shown between histologic grade and clinical stage of SCCs of the UADT.[2–8] In a multivariate analysis, Wiernik et al.[1] showed that tumor grading was an independent significant factor in the prediction of prognosis. These authors evaluated 1,315 patients with laryngeal SCC followed for a 10-year period and showed a highly significant difference between the survival and tumor-free rates for those with well-differentiated laryngeal SCC versus patients with anaplastic cancers, with the former having a better outcome than the latter.[1]

## ADJUNCT TOOLS IN THE DIAGNOSIS OF HEAD AND NECK TUMORS

As described in the preceding section, the more a tumor recapitulates the appearance of its cell of origin, the better differentiated that tumor will be. Specific phenotypic characteristics for a given

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tumor, as seen by light microscopy, may immediately define that tumor type. For the pathologist, the light microscopic features of a malignant tumor that includes origin from the surface epithelium with the formation of keratin and intercellular bridges define an SCC. Given these features, the pathologist does not need to employ additional studies in determining the histogenesis of that tumor. Other examples may include a gland-forming tumor (adenocarcinoma), a melanin-rich malignant tumor (malignant melanoma), a tumor that is forming bone (osteosarcoma), and so on. However, not infrequently, the histogenesis of a malignant neoplasm is not readily apparent by light microscopy. The fact that the tumor is malignant may not be in dispute, but due to the absence of differentiation (undifferentiation), the histogenesis of the tumor becomes a guessing game. This is problematic to the pathologist who wishes to categorize a tumor by its cell of origin. More importantly, the exact tumor type may require specific treatment protocols and have specific prognostic import. It is under these circumstances that the pathologist will use additional studies to determine the histogenesis of a given tumor and therefore establish the correct diagnosis. Included among these studies are relatively simple tools such as histochemistry, immunohistochemistry, and electron microscopy, to more sophisticated molecular biologic and cytogenetic testing.

## Histochemistry and Immunohistochemistry

There are numerous histochemical stains that the pathologist can use in the identification of various chemicals, including stains for epithelial mucins (e.g., mucicarmine, periodic acid Schiff with and without diastase, others), stains for pigments and minerals (e.g., melanin, iron, lipofuscin, argentaffin, and argyrophil), stains for microorgansisms (e.g., acid fast bacilli, Grocott methenamine silver, periodic acid Schiff, Gram, Warthin-Starry, and others) and stains for connective tissue components (e.g., reticulin, elastic, alcian blue, phosphotungstic acid hematoxylin, and others). The results of these stains can be of critical importance in the diagnosis and differential diagnosis of nonneoplastic and neoplastic lesions, including benign and malignant neoplasms. The reader is referred to texts on diagnostic histochemistry for a more in-depth discussion.[9]

Immunohistochemistry is the application of an immunologic procedure (antigen–antibody reaction) allowing for the recognition of intracellular molecular components (antigens) by light microscopic evaluation. Fresh tissue is optimal for immunohistochemical studies. However, in most instances immunohistochemistry can be performed on formalin-fixed, paraffin-embedded tissue (FFPE), including archival material.

Based on the light microscopic appearance of a tumor, a panel of antibodies is used and algorithms followed in the differential diagnosis of a given neoplasm. It should be noted that there are very few tumor-specific markers. Examples of such tumor-specific markers include thyroglobulin for lesions of thyroid follicular cell origin and prostein for lesions of prostatic origin. As such, immunohistohemical reactivity alone is often not diagnostic but requires correlation with the clinical history, light microscopic features, and histochemical findings in order to arrive at the correct diagnosis. The list of imunohistochemical markers and their diagnostic utility is too numerous to be included. For a discussion on the use of immunohistochemistry in head and neck lesions and in endocrine organ lesions, the reader is referred to other texts.[10,11]

## Electron Microscopy

The role of electron microscopy in diagnostic surgical pathology has waned over the decade since the advent of immunohistochemistry. Presently, ultrastructural evaluation plays a limited role in tumor diagnosis, but is still used in those cases where light microscopy and immunohistochemistry may not provide the definitive answer as to the tumor type. More recently, the techniques of immunohistochemistry and electron microscopy have been wed to offer the best of both worlds.

## Flow Cytometry

Flow cytometry attempts to quantitate relative DNA content distributions in tumors and, thereby, attempt to assess at the cellular level the potential biologic behavior of a given tumor.[12]

For flow cytometric measurement of DNA content (DNA ploidy), cell suspensions made by disaggregating solid tissue or paraffin-embedded tissue sections, fine-needle aspirates, or body fluids are used and are passed ("flowed") in a linear stream through a laser beam for analysis. This analysis, resulting from the evaluation of thousands of cells per minute and consisting of up to 20,000 cell events, includes DNA histograms that relate to three phases of the cell cycle. Flow cytometry is extensively used for hematopoietic malignancies. Less often, flow cytometry has been used for solid tumors, including head and neck malignancies.[13–20] In general, these studies showed that increased recurrence rates, shorter relapse times, distant metastasis, and shorter survival rates were present in those HNSCC with high DNA indices, high-percent S-phase fraction, high proliferation rates, and DNA aneuploid tumors. The flow cytometric analysis of HNSCC needs to be viewed with caution as results do not always correlate with outcome.[21–23]

## Molecular Biology

***Cytogenetics.*** Cytogenetic analysis allows for the detection of clonal chromosomal aberrations, many of which may be diagnostic for a particular tumor type. The value of cytogenetic evaluation in head and neck epithelial malignancies is of questionable utility. However, evaluation of specific chromosomal abnormalities may be extremely valuable in the diagnosis of hematologic malignancies,[24] in undifferentiated small round cell malignancies and in soft-tissue tumors.[25]

Molecular techniques used in evaluating for chromosomal aberrations include polymerase chain reaction (PCR), comparative genomic hybridization (CGH), *in situ* hybridization (ISH), and DNA microarrays.[26] PCR is used for isolating and exponentially amplifying a fragment or sequence of interest of DNA via enzymatic replication. PCR is an *in vitro* technique, it can be performed without restrictions on the form of DNA, and it can be extensively modified to perform a wide array of genetic manipulations. PCR is used to amplify specific regions of a DNA strand; this can be a single gene, just a part of a gene, or a noncoding sequence. Most PCR methods typically amplify DNA fragments of up to 10 kilo base pairs (kb), although some techniques allow for amplification of fragments up to 40 kb in size.

CGH is a technique used to visualize losses and gains of chromosomal segments using DNA extracted from tumor tissue.[26] CGH is a powerful tool for screening tumors for genetic changes. The principles of ISH include the use of DNA probes complementary to genomic sequences of interest that are generated, labeled, and then hybridized to target tissue.[26] The different modalities of ISH include fluorescent *in situ* hybridization (FISH) and chromogenic *in situ* hybridization (CISH).[26,27] FISH or CISH signals can be identified in the nuclear compartment of cells. Aside from genes mapping to the sex chromosomes (ie, X and Y) in men, two copies of each gene are present in normal cells (ie, diploid genome) FISH/CISH generate two signals for any given probe.[27] As such, ISH can be used to identify aneusomy or numerical aberrations (i.e., gain or loss of a chromosome, gene gains, amplifications, and deletions) and structural chromosomal aberrations

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(i.e., chromosomal translocations).[27] The advantages of FISH/CISH over conventional cytogenetics include that they can be applied directly to interphase nuclei rather than requiring tissue culturing or mitotic cells and can be applied to many samples, including fresh samples, frozen samples, cytologic specimens, formalin-fixed material, and paraffin-embedded material, including archival material and tissue microarray sections.[27] Arguably, the greatest utility of ISH relative to head and neck cancers is in the identification of Epstein-Barr virus–encoded RNA (EBER) in nasopharyngeal carcinomas (NPCs), differentiated types and nasal-type NK/T cell lymphomas, and in the detection of high-risk human papilloma virus in the setting of oropharyngeal carcinomas. Further, since NPC, differentiated types, and oropharyngeal carcinomas may metastasize as occult primary tumors, the utility of ISH for EBER and HPV16 has expanded to include metastatic carcinomas to the cervical neck from occult primary cancers (see later in this chapter).

DBNA microarrays can be used to determine expression of multiple genes in a single reaction. DNA microarrays utilize a multiplex-spotted microarray technology where thousands of oligonucleoltide probes corresponding to human genes are spotted on a solid surface (gene chip) or on microscopic beads.[26] The intensity of the signals is proportional to the abundance of specific cDNA in a given specimen.[26]

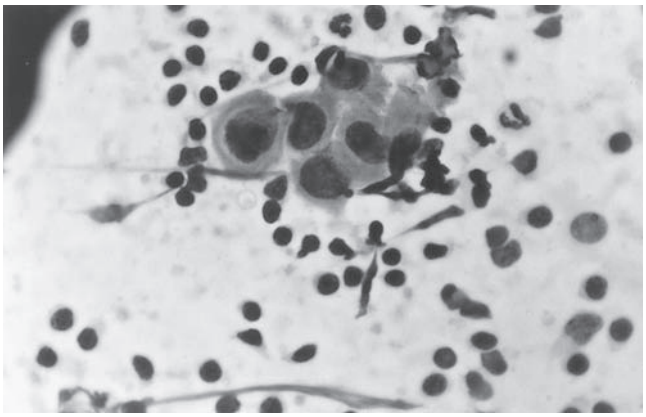


**FIGURE 1-3.** Fine-needle aspiration biopsy of a neck mass (lateral cervical lymph node) showing malignant cells with squamous features diagnostic for metastatic squamous cell carcinoma. Panendoscopic evaluation and biopsy identified the primary cancer to be of (ipsilateral) tonsillar origin.

## FINE-NEEDLE ASPIRATION BIOPSY

Fine-needle aspiration biopsy (FNAB) is a safe, inexpensive, rapid, and accurate procedure in the evaluation of almost any mass lesion. In the head and neck, FNAB is extensively utilized. The accessibility of the neck, salivary glands, thyroid gland, and orbit makes FNAB of lesions of these structures very practical. As such, FNAB is often the initial diagnostic procedure used in the assessment of a head and neck mass, but it should not be the sole determinant by which a major operative resection is performed. FNAB is an invaluable diagnostic modality in the evaluation of a mass in the head and neck providing cytologic diagnosis that assists the clinician in the appropriate management of the patient. Touch-imprint cytology represents the pressing or "touching" of a microscopic slide against the cut surface of a tissue specimen followed by immediate fixation and staining. Imprint cytology may be especially helpful in the diagnosis of hematolymphoid lesions, in the evaluation of small biopsy specimens, or in biopsy material that is distorted and/or crushed. Several studies have found that touch-imprint cytology is as sensitive as, and perhaps more reliable than, frozen section in the detection of micrometastases, especially in fatty lymph nodes that may be difficult to cut.[28–30] Further, on-site assessment by a pathologist or in the frame of a FNAB clinic reduces the false negative diagnosis and inadequacy rates and increases the cost-effectiveness of fine-needle aspiration (FNA).[31,32]

For details on the technique of FNAB, the reader is referred to more comprehensive texts of cytopathology. This section will be a brief overview of FNAB of the specific anatomic sites of the head and neck.

### Neck Mass

FNAB is a useful tool in the evaluation of a neck mass. The causes of neck masses and/or enlarged cervical lymph nodes are many, including reactive lymphadenopathies, infectious and granulomatous lymphadenitis, primary neoplasms (non-Hodgkin and Hodgkin lymphomas), and metastatic tumors (Fig. 1-3). In several reported studies that included a large number of cases, 25% to 60% of the aspirated enlarged lymph nodes showed reactive changes that were subsequently confirmed to be benign by either excisional biopsy or by close clinical follow-up of the patients who had benign clinical outcomes.[33–37] In patients with known primary malignancies originating elsewhere or suspected of metastatic disease to cervical lymph nodes, FNAB is an extremely useful diagnostic tool, as the presence of nonlymphoid neoplastic cells is readily identifiable.[38] In several series of FNAB of lymph nodes, metastatic cancer represented approximately 50% of the reported cases.[32–37]

The diagnostic accuracy rate for FNAB diagnosis of non-Hodgkin malignant lymphoma ranges from 83% to 94%[38,39] while that for Hodgkin disease is from 83% to 98%.[40,41] FNAB findings in conjunction with flow cytometry and/or immunohistochemistry enables the subclassification of many non-Hodgkin lymphomas.[42,43] FNAB can also be used in separating low-grade from high-grade non-Hodgkin malignant lymphoma. In a study by Russell and colleagues,[44] the authors had difficulty distinguishing among the low-grade malignant lymphomas, but had no difficulty separating the low-grade from the high-grade malignant lymphomas by FNAB. Although the diagnostic accuracy for Hodgkin disease is high, the accuracy for subtyping the Hodgkin lymphoma is not, reported in one study to be 58%.[43] A cytologic specimen cannot provide certain details relative to malignant lymphomas, including the architectural growth (i.e., follicular vs. diffuse), and it is very difficult to subtype Hodgkin disease by FNAB.[43] Therefore, a presumptive diagnosis in an enlarged lymph node of malignant lymphoma made by FNAB should be followed by excisional biopsy with histopathologic evaluation. The excised lymph node should include the largest identifiable node to allow for histopathologic evaluation, as well as for immunohistochemical and molecular biologic studies. In general, the diagnostic accuracy for the presence of a tumor (sensitivity) and for the absence of a tumor (specificity) in lymph nodes is high, ranging from 87% to 100% and 88% to 98%, respectively.[37,39,45]

### Salivary Glands

There are innumerable causes for enlargement of a salivary gland, including many nonneoplastic and neoplastic (benign and malignant) proliferations. By far, the most common salivary gland tumor is a benign mixed tumor (pleomorphic adenoma). Therefore, the diagnostic accuracy of a salivary gland tumor is usually high. The diagnostic accuracy of FNAB of salivary gland

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tumors has been reported to include a sensitivity of 92%, specificity of 100%, and accuracy of 98%.[46]

In general, the diagnosis of most salivary gland tumors by FNAB can be readily accomplished. However, a diagnosis by FNAB of certain specific salivary gland tumors, such as adenoid cystic carcinoma (ACC), low-grade polymorphous adenocarcinomas, and others, should be made with extreme caution. The cytologic features seen in these tumors can also be identified in benign mixed tumors. Further, it should be noted that when the differentiation of a benign from a malignant salivary gland tumor is based on the presence or absence of invasive growth, and not on the cytologic appearance, that FNAB will not generate this information. It could be argued that any mass lesion of the salivary gland will ultimately require surgical intervention, obviating the need for FNAB. Nevertheless, FNAB remains an excellent screening tool for salivary gland tumors, more often than not yielding enough information to guide the surgeon in his/her therapeutic approach. Despite the potential limitations of FNAB in the diagnosis of salivary gland tumors, it still remains an accurate diagnostic tool, quite comparable to frozen section diagnosis.[47,48]

## Thyroid Gland

As with salivary gland tumors, the thyroid gland is readily accessible so that there is much practical utility in the FNAB of thyroid gland lesions. FNAB of the thyroid represents the first-line diagnostic procedure in the evaluation of a patient with a thyroid mass. The main purpose of thyroid gland FNAB is to distinguish between patients with benign thyroid nodules that can be followed clinically from patients with neoplastic (benign or malignant) proliferations that require surgical intervention.[49] Not all solitary lesions of the thyroid require surgical intervention. FNAB may then offer the necessary diagnostic information for those lesions that can be nonsurgically monitored as compared to those thyroid lesions that do require surgical removal.[50] The diagnostic accuracy of thyroid FNAB is well established. The ability of thyroid FNAB to yield a positive aspirate in the presence of a neoplasm (sensitivity) (Fig. 1-4) and to be negative in the absence of a neoplasm (specificity) is high, reported in several large series to be over 90%.[50–53] Ultrasound guided FNAB with on-site evaluation can increase the sensitivity and specificity of thyroid FNAB in lesions that are difficult to palpate.[54] Of note, approximately 2% to 15% of smears are unsatisfactory for evaluation.[55] In satisfactory smears, a thyroid tumor is diagnosed as benign in greater than 60% of cases, malignant in approximately 5%, and suspicious in the remainder of cases.[49] Of the suspicious cases, approximately 20% prove to be malignant following surgical resection.[55] The accuracy of thyroid FNAB compares favorably to that of frozen section diagnosis.[56–58] In a study of 359 patients with thyroid nodules evaluated by FNAB and frozen section, Hamburger and Hamburger[59] report that in <1% of patients (3 cases) did frozen section influence the surgical procedure.

Similar to the challenges faced by the cytopathologist with FNAB of salivary glands, there are diagnostic limitations of thyroid gland FNAB, including those thyroid lesions in which the differentiation of a benign from a malignant tumor is not predicated on the cytologic appearance but requires the identification of capsular or vascular invasion (i.e., follicular adenomas vs. follicular carcinomas). In this situation, cytology alone is not diagnostic and FNAB does not allow for this determination. It should be noted that oxyphilic changes (so-called Hürthle cells) represent a descriptive term and are not diagnostic for any specific thyroid lesion. Numerous thyroid lesions contain Hürthle cells, including lymphocytic thyroiditis, adenomatoid nodules, follicular adenomas, follicular carcinomas, papillary carcinoma, and medullary carcinoma. Therefore, the presence of Hürthle cells on the FNAB of a thyroid lesion is not, in and of itself, diagnostic.

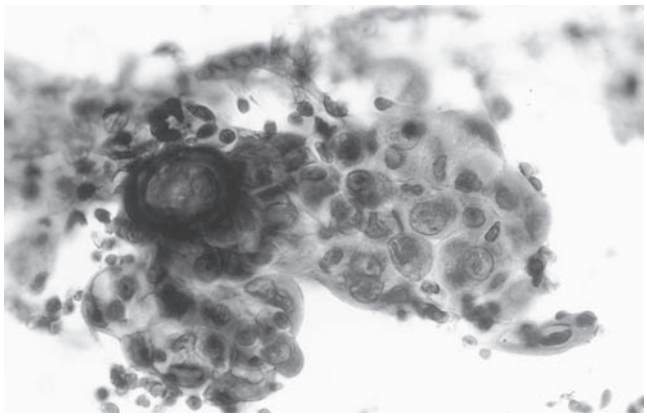


**FIGURE 1-4.** Fine-needle aspiration biopsy of a thyroid mass diagnostic for thyroid papillary carcinoma.

Despite these potential limitations, FNAB is accurate in the diagnosis of thyroid tumors. Pathologic alterations seen in permanent sections of resected thyroid lesions following FNAB may result in worrisome histologic features that may be mistaken for malignant neoplasm.[60,61] The post-FNA histologic changes occur in numerous lesions such as adenomatoid nodules, follicular adenoma and its variants, follicular carcinoma and its variants, papillary carcinoma and its variants, and hyperplastic lesions. Based on the type of reaction seen, post-FNA alterations may include acute or chronic type changes.[62] Acute changes are usually identified within 3 weeks from the FNA to surgical removal and may include hemorrhage with hemosiderin-laden macrophages and granulation tissue (these represent the most common findings), localized follicular destruction, capsular alterations, atypical cytologic features with necrosis and mitoses, and nuclear atypia that typically occurs near the needle tract and includes nuclear enlargement with clearing of the nuclear chromatin. Chronic changes are usually identified more than 3 weeks from the FNA to surgical removal and may include squamous or oxyphilic metaplasia, infarction, capsular alterations with foci of pseudoinvasive growth, vascular alterations, including artifactual implantation or "invasion" of tumor cells, dilated vascular spaces with thrombosis, organization and papillary endothelial hyperplasia and endothelial cell atypia.[62,63] Additional changes may include cyst formation with papillary growth, fibrosis, calcifications, and cholesterol granulomas. Oxyphilic cells occurring in all settings (metaplasia, follicular adenoma, follicular carcinoma, or papillary carcinoma) may be more sensitive to trauma due to the oxygen-sensitive mitochondria that predominate in these cells. Any compromise to the oxygen supply of the oxyphilic cells may result in degenerative changes, including hemorrhage, infarction, and papillary degeneration.

## Orbital Lesions

Orbital FNAB is an accurate and beneficial procedure in the evaluation of orbital lesions, obviating the need for extensive surgery to arrive at a diagnosis. Orbital FNAB allows for the evaluation of deeply situated unresectable tumors that in the past required extensive surgery in order to generate material for diagnosis. Kennerdell et al.[64] evaluated 156 orbital lesions by FNAB and reported that 80% contained diagnostic material, 18% were insufficient for evaluation, and 2% were either false positive or false negative. These authors indicate that insufficient aspirates were the result of a fibrous lesion, a lymphoproliferative process in which there were insufficient cells for diagnosis or an orbital

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apical location. According to Kennerdell et al.[64] the most common orbital lesions reported in their series were carcinomas (primary and metastatic), lymphoproliferative lesions, and inflammatory diseases. The accuracy of orbital FNAB is high. Char et al.[65] in a study of uveal melanomas, report an 89% positive identification rate. Shields, in a series of 159 cases of FNA of intraocular lesions, obtained an adequacy rate of 88%, a sensitivity rate of 100%, and a specificity rate of 98%.[66] Complications of orbital FNAB may include diffuse retrobulbar hemorrhage, blindness (transient or permanent), globe perforation, and brain-related complications.[64] All serious complications occurred due to faulty techniques, reaffirming the importance of experience in FNAB.

## FROZEN SECTIONS

Frozen section analysis plays an important part in the treatment of the head and neck cancer patient. The appropriate use of intraoperative consultations (frozen sections) usually results in a definitive diagnosis with immediate therapeutic impact while the patient is in the operating room. The accuracy of frozen sections has been analyzed for general surgical cases,[67–73] as well as specifically for head and neck surgery.[74–80] The studies on general surgical cases and otolaryngologic cases show similar findings with a 95% to 98% diagnostic accuracy rate, a 2% to 4% error rate (including <2% false negative and <1% false positive), and less than 4% of cases being deferred for permanent section evaluation. Diagnostic errors may occur due to improper sampling, technical flaws, interpretive inaccuracies, and faulty communication.[67,72,75,78,79]

Among the determinations made by frozen section analysis are (a) the evaluation of adequacy of surgical margins of resection, (b) the differentiation between nonneoplastic, benign, and malignant proliferations, (c) the evaluation of lymph nodes for the presence of metastatic disease, (d) the determination of specimen identification and specimen adequacy, including the verification of such organs as the parathyroid glands, and (e) the determination of whether a given case requires special diagnostic testing best performed on frozen material, such as for lymphomas.

Arguably, the most common request of the pathologist by the head and neck surgeon at the time of intraoperative consultation is the assessment of the surgical margins. Successful local control of a malignant tumor depends on complete surgical excision of all the disease. There are many factors that impact on the assessment of the surgical margins, including the type of surgical specimen, proper orientation of the specimen, proper sectioning of the specimen, and, obviously, the correct interpretation of the histopathologic changes. Unfortunately, even in the best situations an intraoperative report of negative margins may be followed a few days later by a permanent section diagnosis of positive margins. Byers et al.[81] reported on the results of frozen section in 216 patients with neoplasms of the oral cavity, oropharynx, and hypopharynx. Three groups were identified, including 68% of the patients in whom the tumors were initially adequately resected on the basis of negative surgical margins, 23% of the patients who had positive surgical margins that necessitated additional surgical resection to assure the presence of negative surgical margins, and the remaining 9% of patients in whom negative free margins by frozen section could not be obtained.[81] The follow-up of these three groups included local recurrence rates of 14.4%, 20%, and 80%, respectively, with the third group having the worst survival rates. Byers and colleagues concluded that the probability of local recurrence in head and neck cancer is reduced when the resection margins are determined by intraoperative frozen section consultation.[81] The use of intraoperative frozen sections will also allow the surgeon to extend the surgical resection without loss of orientation of the operative field, a potential problem when additional surgery is required in a second operation.[81] Further, carcinoma remnants that have not been completely removed in the initial operation are often difficult to identify macroscopically, making their removal in a second operation more difficult.[82] Spiro and colleagues[80] reported an intraoperative frozen section diagnostic accuracy of 89% for oral tongue cancer. These authors found that the diagnostic accuracy was the same whether the sample was taken from the patient or from the surgical specimen.

It must be noted that a diagnosis of margin(s) negative for carcinoma by frozen section analysis does not guarantee complete tumor removal. Limitations include the choice of biopsy sampling sites and the fact that frozen section results are not always confirmed by permanent sections.[82] Ord and Aisner[83] evaluated the accuracy of frozen section in assessing margins in 49 patients with oral cancer resections. These authors found a frozen section accuracy rate of 99%; however, 7 patients had final margins that were positive but had not been diagnosed as such at the time of the frozen section. Errors in interpretation and in sampling accounted for these discrepancies. Cooley et al.[84] found five discrepancies in 249 frozen sections of laryngeal SCC in which the frozen diagnosis was negative but the permanent sections revealed dysplasia or carcinoma *in situ* (CIS). These authors found that insufficient leveling of the frozen block resulted in these discrepancies. Their recommendation was that in examining margins for laryngeal SCC the frozen section tissue should be completely sampled by examining several levels at the time of frozen section. Spiro et al.[80] reported that of the 131 samples taken intraoperatively whose margins were reported as negative, 13 were later reported to be positive following permanent sections. Although the frozen section diagnosis of surgical margins are extremely accurate, they are not entirely reliable in eliminating positive margins in the final diagnostic report.

Frozen section consultations on mucosal surface lesions can be useful, especially in differentiating inflammatory and neoplastic lesions. Histologic grading of a mucosal malignancy (i.e., SCC) may be problematic and is not advocated by frozen section. Artifactual distortion and sampling limitations may lead to erroneous conclusions relative to the histologic differentiation of the carcinoma. Postirradiation alterations may lead to false-positive diagnosis due to the presence of bizarre cytologic alterations in the epithelium, minor salivary glands, fibroblasts, skeletal muscle, and endothelial cells.[85,86]

A mass lesion of virtually every head and neck anatomic site may initially be viewed by the surgical pathologist at the time of frozen section consultation. Among the head and neck sites, salivary gland lesions, thyroid gland lesions, parathyroid gland lesions, cervical neck masses, and mucosal-based lesions are often assessed by frozen section. As discussed in the previous section on FNAB, with the increased use of FNAB, the utilization of frozen sections, particularly for salivary gland and thyroid gland tumors, has diminished. For frozen section consultation of head and neck lesions, the reliability in the diagnostic accuracy of salivary gland tumors has been the most questioned.[87–91] However, Gnepp et al.,[92] in a review of 301 salivary gland lesions evaluated by frozen section, reported a diagnostic accuracy rate of 98% with an adjusted accuracy rate of 95.7% when deferred diagnoses were included. These authors report that this overall accuracy was comparable to that for other regions of the body.[92] Further, Luna indicates that the frozen section diagnoses of salivary gland tumors "present no more serious problems than do frozen section diagnoses elsewhere in the body."[93]

Frozen section evaluation has also been extensively utilized for thyroid lesions. The lesions that are usually identifiable at frozen section include thyroid papillary carcinoma, widely invasive follicular carcinoma, anaplastic carcinoma, and medullary carcinoma. Problems arise in the frozen section diagnosis of a

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single encapsulated thyroid mass that has a follicular growth pattern. The differential diagnosis in this setting would include a follicular adenoma, follicular carcinoma, and the follicular variant of thyroid papillary carcinoma. The differentiation of a follicular adenoma from a follicular carcinoma is predicated on the presence or absence of capsular and/or vascular space invasion. This finding may be present only in a very limited aspect of the tumor. Sampling this area at frozen section would be purely fortuitous as, macroscopically, the invasive foci are not discernible. Thyroid papillary carcinomas in permanent sections often display characteristic ground-glass appearing nuclei, which is a function of tissue fixation in formalin. As such, ground-glass nuclear changes are not present in frozen sections as frozen section tissue is performed on fresh tissue and not on tissue that has been formalin fixed.[94] Rosen et al.[95] point out that the relatively low sensitivity of frozen section diagnosis of thyroid carcinomas relates to these issues. Kingston et al.[96] reported on the role of frozen section in distinguishing benign from malignant thyroid follicular neoplasms. Using the final histologic diagnosis as seen in permanent sections as the gold standard, these authors report that frozen section was accurate in 79% of the cases in differentiating follicular adenoma from follicular carcinoma with a sensitivity of 52% and a specificity of 100%; an incorrect diagnosis of a benign lesion was reported in 21% of the patients.[96] Kingston et al.[96] compared the accuracy of frozen section diagnosis to the accuracy of using clinical factors alone to predict malignancy, including age >50 years, tumor size >3 cm, and a history of previous neck irradiation. These three clinical features were shown by Davis et al.[97] to be strong predictors of malignancy in thyroid follicular neoplasms. Kingston et al.[96] found an equally low sensitivity between frozen section and clinical parameters, ranging from 38% to 53%, in predicting malignancy, but that frozen section resulted in a much higher specificity and positive predictive value than any of the clinical parameters. These authors recommended the continued use of frozen section for thyroid follicular lesions as a guide to the required extent of surgery.[96] At present, there are major academic centers that do not routinely perform intraoperative consultations on thyroid lesions. However, the use of cytologic evaluation coupled with tissue sectioning in the intraoperative consultation of thyroid lesions greatly assists in the diagnosis of thyroid lesions, especially for thyroid papillary carcinoma.

The frozen section diagnosis of lymph nodes is considered to be extremely accurate. Gnepp, in a review of the literature, reported an accuracy rate of 98.9%, excluding deferred diagnoses, with a 0.1% false-positive rate and a 1% false-negative rate.[98] It should be noted that the lymph nodes represent the most frequently deferred specimen in frozen section diagnosis, especially in the diagnosis of a lymphoma. In general, the diagnosis of a carcinoma in a lymph node is not problematic at frozen section. Lymph node frozen section has also been utilized for accurate staging of the head and neck patient. Rassekh et al.[99] compared intraoperative node examination (palpation and inspection) to frozen section diagnosis in the identification of metastatic disease to cervical lymph nodes, thereby evaluating the surgeon's ability to predict nodal stage. These authors prospectively studied 108 necks in 79 patients and reported that the overall reliability for intraoperative staging (palpation and inspection) was 59.3% (64 of 108) as compared to 92.3% (24 of 26) for frozen section biopsy, representing a highly significant difference ($p < 0.005$).[99] Although frozen section biopsy was not performed on all cases, Rassekh et al.[99] concluded that upstaging the neck without frozen section biopsy is much less reliable and that frozen section biopsy is needed prior to converting a selective node dissection to a radical or modified radical neck dissection. Manni and van den Hoogan[100] reached a similar conclusion.

As with any surgical procedure, there are contraindications for the utilization of frozen sections. Frozen section consultation should not be used (a) when the frozen section diagnosis will not have any impact on surgery such as satisfying the curiosity of the surgical team; (b) if the tissue specimen is small and additional sampling is not planned (in which situation, frozen sections may be equivocal and/or the material is artifactually distorted by the frozen section technique hampering histologic evaluation following permanent sections); (c) for heavily calcified or ossified tissue; (d) for certain lesions such as small cutaneous melanocytic lesions and lymphoproliferative lesions requiring special handling or extensive histologic evaluation for diagnosis.

## HISTOPATHOLOGIC PARAMETERS IN THE ASSESSMENT OF HEAD AND NECK TUMORS

### Surgical Resection Margins

The evaluation of surgical margins of resection for the presence or absence of lesional tissue falls under the purview of the surgical pathologists. However, how the specimen is removed and the orientation of the specimen is the responsibility of the surgeon. This is particularly true for those cases in which the tumor is initially excised and the designated margins are separately removed, the tumor is removed in multiple parts or the specimen is a complex *en bloc* excision requiring proper orientation by the surgeon for those margins that are of critical concern. Once removed and properly oriented, the specimen becomes the responsibility of the surgical pathologist.

In brief, the designated margins are painted with India ink or other similar colored pigments, and then sections are submitted for histologic examination. Despite the stringent environment that goes into the processing of tissue, the dye is retained and the pathologist, by microscopic examination, can evaluate the relationship of the tumor to all surgical margins of the resection. Specimens in which no tumor or dysplasia is present at the surgical margins of resection are considered as completely excised. "At the margin of resection" means that the neoplastic cells are seen in contact with or lie within millimeters of the pigment that was painted along the margin prior to sectioning (Fig. 1-5). In

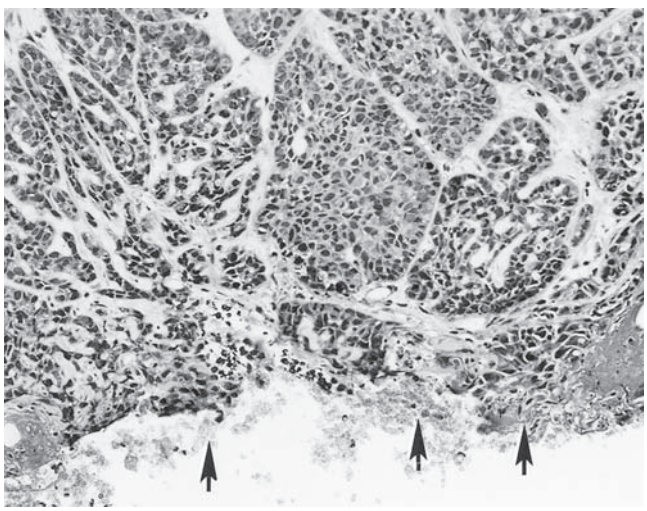


**FIGURE 1-5.** The malignant neoplasm shown in this illustration is identified in continuity with the edge of the resection margin. The latter, seen at the bottom of the illustration, is delineated by the presence of pigment (*arrowheads*). As such, this tumor is "at the margin of resection" and is incompletely excised.

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this situation, the specimen is considered incompletely excised, requiring a wider excision in order to be assured that all viable tumor cells have been adequately removed.

There is some discrepancy in the literature as to what constitutes a positive or negative resection margin. Although some authors only include invasive carcinoma at the margin as positive, excluding CIS, dysplasia, and gross residual disease,[101] most pathologists would agree with the classification of positive margins set forth by Loree and Strong.[102] In their review of 398 patients with primary oral cavity carcinoma, Loree and Strong[102] classified positive margins into four categories, including lesional tissue was within 0.5 cm of the surgical margin (so-called close margins), dysplastic epithelium at the margin, CIS at the margin, and invasive carcinoma at the margin. Suffice it to say that the evaluation of dysplasia under optimal circumstances can be subjective, let alone at the time of frozen section where tissue distortion and artifact create additional diagnostic difficulties potentially resulting in misdiagnoses, including overdiagnosis and underdiagnosis.

The presence of lesional tissue within 0.5 cm of the inked surgical margin irrespective of whether it is invasive carcinoma or CIS/severe dysplasia places a patient at a nearly equal risk for local recurrence.[103] The question of how wide a tumor should be excised is the responsibility of the surgeon. However, for some specimens such as the laryngeal SCC, free margins up to 2 mm may be sufficient (Fig. 1-6), whereas a similar tumor at another site, such as the hypopharynx, where submucosal spread may be more of a problem, and the oral cavity, wider margins (5–10 mm) are optimal. The incidence of positive surgical margins is quite variable, ranging from as low as 3%[104] in some studies to as high as 60% in other studies.[105] Certainly, this variability in "positive surgical margins" is dependent on multiple factors, not the least important of which may be the definition of what constitutes a positive margin.

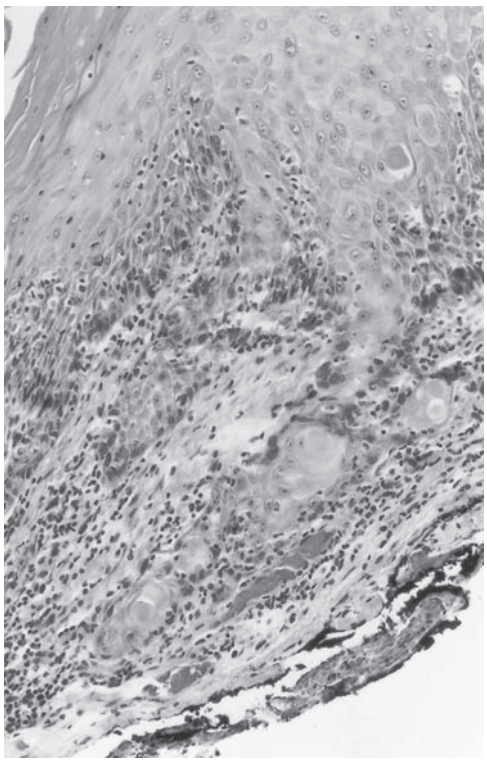


**FIGURE 1-6.** Laryngeal squamous cell carcinoma measuring approximately 2 mm from the inked surgical resection margin **(bottom)**.

Jacobs et al.[106] found that of the entry population of 696 patients in their study, 112 patients (16%) with stage III and IV resectable tumors had positive surgical margins. These authors indicate that the 16% represented a national average rather than an institutional incidence.[106] In comparison to patients with negative margins, patients with positive margins had a significantly higher rate of local failure (21% vs. 9%, $p = 0.0003$) and distant failure (20% vs. 12%, $p = 0.42$), but a similar incidence of regional (nodal) failure.[106] Patients with positive surgical margins were most often seen in nonglottic primary cancers and with increasing incidence as the N stage increased. The positive-margin patients of higher N stage had a higher rate of distant metastasis and died more rapidly than positive-margin patients with lower nodal status.[106] The survival of the positive-margin patients was approximately one half of the negative-margin patients. The addition of chemotherapy did not significantly alter the survival of positive-margin patients.[106] These authors reported a median survival of 19 months in patients with positive margins essentially equating to the expected outcome for patients with inoperable cancer.

Scholl et al.[107] reported that in 54 of 268 patients (20.1%) with lingual SCC, the carcinoma was not initially completely removed (i.e., positive margins at frozen section). When additional surgery resulted in negative margins, the local recurrence rate was worse than if the initial margin was negative. Scholl et al.[107] also found that positive mucosal margins were more often present in T1 and T2 tumors, and soft-tissue margins were more common in T3 and T4 lesions. Looser et al.[104] reported that 71% of patients with positive margins had recurrent disease at the primary site in comparison with 32% of patients with the tumor-negative margins. Spiro and colleagues[80] reported an intraoperative frozen section diagnostic accuracy of 89% for oral tongue cancer. These authors reported that the diagnostic accuracy was the same whether the sample was taken from the patient or from the surgical specimen. Positive or close margins (within one high-power field) was associated with a significant increase in local recurrence ($p < 0.003$).[80] Other studies have shown that implications of a positive surgical margin for SCC of the head and neck are associated with increased local failure and decreased survival rates.[102,108]

An additional factor that impacts on local recurrence is tumor size. The lower the clinical stage and/or pathologic class, the better the ability to achieve local control and the overall better survival rates.[81,104] Loree and Strong found that the incidence of positive margins was directly proportional to the increasing tumor size.[102] Scholl and colleagues, in their evaluation of oral tongue SCC, indicate in the presence of complete surgical removal of all disease to include macroscopic disease and histologically negative margins without neural invasion (NI) that adjunctive therapy does not improve local control as compared to surgery alone.[107] van Es and colleagues[109] reported that for T1 and T2 carcinomas of the mobile tongue and the floor of mouth, the single most important parameter in determining local recurrence is the histopathologic evaluation of margin status and that other histopathologic parameters were essentially irrelevant in predicting recurrence.

The presence of positive margins does not always translate into failure of local control; however, the overwhelming majority of patients with recurrent disease at the primary site have positive margins. The ability to completely resect a squamous carcinoma of the head and neck weighs heavily in the surgeon's decision to utilize surgery in the attempt to eradicate the cancer, and the presence of disease (gross or microscopic) at the surgical margins represents a key prognostic feature for patient survival. Batsakis notes that 5% to 10% of carcinomas resist the surgical goal of clear margins regardless of T stage.[110] He further notes that the survival of patients with free margins is related to the

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T stage of their carcinoma.[110] The identification of negative margins is not a guarantee for the absence of local recurrence. The larynx perhaps is an outlier in regard to positive-margins and local recurrence. As compared to extralaryngeal mucosal sites, patients with primary laryngeal SCC with positive surgical margins have a significantly lower incidence of local recurrence. Bauer et al.[111] reported that of a total population of 111 patients with laryngeal SCC, 39 (35%) had positive surgical margins. Of these 39 patients, 7 (18%) developed local recurrence, whereas 4 of the remaining 72 patients (6%) with negative margins developed local recurrence.[111] These findings suggest that margin status and local recurrence are site dependent and assists in explaining why surgeons are more apt to accept nearer margins for laryngeal carcinoma (free margins up to 2 mm), but require wider margins (5–10 mm) for carcinomas of extralaryngeal mucosal sites. Among the extralaryngeal sites with significant recurrence rates following negative surgical margin determination are the oral cavity and pharynx, including the hypopharynx.[81,104] Intraoral sites with negative margins but significant recurrence rates include the palate, the tonsil, the buccal mucosa, the tongue, the gingiva, the floor of the mouth, and the lip.[104]

## Factors Impacting on Margin Status and Prognosis

Certainly, this variability in "positive surgical margins" is dependent on multiple factors, not the least important of which may be the definition of what constitutes a positive margin. The factors that may impact on whether a margin is positive or negative, and on prognosis (control of disease) include the following:

- Clinical stage
- Tumor size
- Pattern of invasion
- Adjuvant therapy
- Histopathologic evaluation
- Site dependency
- Soft-tissue margins

More recently, Brandwein-Gensler et al.[112] suggest that resection margin status alone is not an independent predictor of local recurrence nor should resection margin status alone be used as the sole variable in deciding whether adjunctive radiation therapy is required; rather, the need to give adjunctive radiation is suggested to be based on the following parameters:

- Positive margins
- Perineural invasion
- Osseous invasion
- Histologic risk assessment that includes score based on worst pattern of invasion:
  - Patterns of invasion include
    - 1 = invasion in broad pushing front
    - 2 = invasion in "finger-like" broad pushing pattern or separate large tumor islands
    - 3 = invasive tumor islands of tumor at periphery greater than 15 cells/island
    - 4 = invasive tumor islands of tumor at periphery smaller than 15 cells/island or strands of tumor cells in single cell filing pattern regardless of island size
    - 5 = satellites of dispersed tumor infiltrates of any size with 1 mm or greater distance of intervening normal (nonfibrotic) tissue at the tumor–host interface
  - Perineural invasion
  - Lymphocytic response

According to Brandwein-Gensler et al.,[112] histologic assessment results in stratification of patients into low-risk, intermediate-risk, and high-risk categories that define recommendations for adjuvant radiotherapy (Table 1.12). To date, this classification scheme has not been universally accepted or applied.

Mucosal margins are not the only tissue margins. Surgical margins of resection may include all soft-tissue components, including adipose tissue, skeletal muscle, bone, and neural structures. The latter are of particular concern in those tumors that have a propensity for neurotropism, such as ACC of salivary glands. Bone, in particular the osseous margins of resection of the mandibular region, pose an especially significant issue in

**TABLE 1.12 Risk Assessment for Oral Squamous Cell Carcinoma**

| Histologic Variable | 0 | 1 | 3 |
|---|---|---|---|
| Perineural invasion | None | Small nerves | Large nerves |
| Lymphocytic response | Continuous band | Large patches | Little to none |
| Worst pattern of invasion at interface[a] | 1, 2 or 3 | 4 | 5 |

| Risk Score[b] | Risk for LR | Overall Survival Probability | Adjuvant Treatment with RT |
|---|---|---|---|
| 0 | Low | Good | No benefit |
| 1 or 2 | Intermediate | Intermediate | No benefit |
| 3–9 | High | Poor | Beneficial regardless of 5-mm margins |

Source: Adapted from Brandwein-Gensler M, Teixeira MS, Lewis CM, et al. Oral squamous cell carcinoma: histologic risk assessment, but not margin status, is strongly predictive of local disease-free and overall survival. *Am J Surg Pathol.* 2005;29:167–178, with permission.

[a]Patterns of invasion: 1 = invasion in broad pushing front; 2 = invasion in "finger-like" broad pushing pattern or separate large tumor islands; 3 = invasive tumor islands of tumor at periphery greater than 15 cells/island; 4 = invasive tumor islands of tumor at periphery smaller than 15 cells/island or strands of tumor cells in single cell filing pattern regardless of island size; 5 = satellites of dispered tumor infiltrates of any size with 1mm or greater distance of intervening normal (nonfibrotic) tissue at the tumor–host interface.

[b]Risk score, sum of all points; LR, local recurrence; RT, radiotherapy.

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regard to carcinomas of the alveolar ridge, the floor of mouth, the lower buccal sulcus, and the lower retromolar region. Carcinomas of these sites are among those with the highest rate of recurrence. As such, the evaluation of the mandibular bone for the presence and extent of involvement is a key determinant in patient management.[113] The clinical determination of mandibular involvement is not reliable since one third of histologically proven carcinomatous invasion of the mandible showed no clinical indication of (preoperative) bone involvement.[114] Spread of oral carcinoma to the mandible typically occurs by direct invasion rather than by metastasis, by lymph-vascular space spread, or via nerves. The frozen section assessment is difficult given the inherent difficulties in performing frozen section on bone. Touch preparations or imprints of the osseous stump can be performed. Evaluation of the nonosseous soft tissue is not a reliable indicator vis-à-vis osseous involvement. In their evaluation of local control of oral and oropharyngeal carcinomas with clinically determined mandibular bone involvement, Dubner and Heller[115] found a 19% recurrence rate following marginal mandibulectomy and 6% following segmental mandibulectomy. In this study, local recurrence was not dependent on tumor size, N stage, invasion of the mandible, or radiotherapy. In those patients who recurred following segmental mandibulectomy, the recurrent disease was present within extraosseous soft tissues.

## Tissue Shrinkage and Surgical Margins

The reliability of measuring the resection margins is impacted by postremoval changes, especially related to tissue shrinkage. It is obvious that obtaining adequate tumor-free surgical margins is critical for the successful management of the cancer patient. Any discussion on surgical resection margins would not be complete without a discussion on tissue shrinkage in the pathologic processing of resected tissues. Disparate surgical margin lengths of resected specimens between the *in vivo* measurements by the surgeon and the *in vitro* measurements by the pathologist have been reported for head and neck resection specimens[116,17] and non–head and neck resection specimens.[118–121] Johnson et al.[116] found a mean tissue shrinkage of 31% ($p < 0.0001$) from the initial *in situ* measurement by the surgeon to the final microscopic assessment of oral cavity and lingual surface mucosal margins by the pathologist. These authors reported that to obtain 5 mm of histopathologically clear margin, an *in situ* margin of resection of at least 8 to 10 mm needs to be taken. In their evaluation of oral SCCs, Beaumont and Hains[117] found a reduction of 46% from the planned surgical margin before resection to the microscopically measured margin following pathologic preparation (minimum of 10 mm measured *in situ* surgical margin and average of 5.8 mm margin following fixation). These authors reported significant differences in the longitudinal diameter of the whole specimen from *in situ* to fresh states ($p < 0.0004$) and in the diameter of the tumor from the fresh state to fixed states ($p < 0.0000$), with the most significant shrinkage reported from the fresh state to the fixed state with a mean shrinkage of 4.82 mm. Goldstein et al.,[119] in their evaluation of colorectal resection specimens, found that bowel segments shrank to a median length of 3 cm or 40% of their original *in vivo* length after being removed from the patient and left in an unfixed state for 10 to 20 minutes. After formalin fixation, the free-floating ends shrank an additional 0.85 cm. Overall, after fixation, colon segments shrank 57% of their original *in vivo* length. However, the majority of the tissue shrinkage occurred within the first few minutes after removal of the specimen, and only 30% of the tissue shrinkage was attributed to formalin fixation. Similarly, Johnson et al.[116] found that the greatest proportion of shrinkage occurred immediately upon resection. Although there are very few studies assessing the shrinkage of tissue margins, it is apparent that a significant amount of tissue shrinkage occurs from the moment the tissue is excised to the time the pathologist reviews the histologic preparation of the excised tissues. Such tissue shrinkage should be taken into account and accommodated for by the surgeon at the time of the operation.

# PATHOLOGIC TNM SYSTEM FOR THE CLASSIFICATION OF MALIGNANT TUMORS

The American Joint Committee on Cancer (AJCC) utilizes a staging system to describe the anatomical extent of a malignant tumor.[122] This assessment of tumor includes three components: T for the extent of the primary tumor; N for the presence or absence of regional lymph node metastasis; and M for the presence or absence of distant metastasis. This classification system includes both clinical and pathologic parameters, and often these parameters will coincide. The following section will include the pathologic parameters utilized in the TNM staging system for malignant tumors supplemented by pathologic features not necessarily part of the TNM system but which may impact on prognosis and treatment.

## Tumor Size, Thickness, and Location

The TNM system utilized tumor size (T) to indicate the extent of disease. Lower T-staged tumors measure less than 2 cm; intermediate-staged tumors measure between 2 and 4 cm; higher staged tumors measure more than 4 cm.[122] It is generally considered that the size of a tumor represents an independent variable in its prognosis. Larger tumors (T3 and T4) have been reported to correlate with increased local recurrence as well as with decreased 2- and 5-year survival rates.[81] However, larger tumors are not necessarily indicative of a worse prognosis, and smaller tumors do not necessarily confer an indolent biologic behavior. Some head and neck tumors, such as in the oral cavity, may have a large surface component (high T stage), but these tumors are only superficially invasive and have a favorable prognosis. Similarly, large tumors of the thyroid gland measuring more than 5 cm may be entirely encapsulated with an associated favorable outcome. Conversely, small head and neck tumors may be deeply invasive and have a poor prognosis despite their small size. Some examples of this phenomenon occur with small cell (oat cell) neuroendocrine carcinomas of the head and neck, extranodal angiocentric T-cell malignant lymphomas of the sinonasal tract, and mucosal malignant melanomas. Therefore, while there is some validity to a larger malignant tumor conveying a worse prognosis, this is not universally true and should not unequivocally be utilized as an independent variable of prognosis.

The predictive value of tumor thickness and/or quantitative measurement of depth of invasion has been utilized for cutaneous malignant melanomas.[123,124] A similar quantitation does not apply for mucosal malignant melanomas.[125] Studies of SCCs of the UADT have attempted to correlate the extent of invasive cancer with the likelihood of cervical lymph node metastasis and/or prognosis.[126–130] The findings in these studies vary in predicting at what depth of infiltration an SCC is more apt to metastasize. Spiro et al.[126] retrospectively evaluated the predictive value of tumor thickness in T1, T2, and T3 N0 SCCs of the oral tongue and the floor of the mouth. Tumor thickness >2 mm correlated best with treatment failure, manifested as the presence of regional node metastases in 38% of the patients with tumors >2 mm as compared to 7.5% for tumors ≤2 mm (minimal follow-up of 2 years). They concluded that in the N0 patient, tumor thickness of >2 mm, regardless of tumor size, merited elective neck

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dissection. Mohit-Tabatabai et al.[127] found a strong statistical correlation between tumor thickness and regional metastasis. In their study, patients with floor-of-mouth squamous cancers stage as T1 or T2 and N0 with thickness measuring ≤1.5 mm, 1.6 to 3.5 mm, and >3.5 mm had corresponding regional metastases in 2%, 33%, and 60%, respectively (mean follow-up of 69 months).[127] They concluded that floor-of-mouth cancers measuring more than 1.6 mm should have elective neck dissections.[127] Other studies of oral cancers have also shown a statistical correlation between the depth of invasion and the presence of regional metastasis although the depth of tumor varied in each study.[131–133] However, there are a number of studies in which a statistical correlation could not be found between tumor thickness and nodal metastasis or prognosis.[129,134,135] Karas et al.[130] examined the relationship of tumor thickness as determined in biopsy specimens with the tumor thickness in the final resected specimens in patients with floor-of-mouth cancers. They found that in biopsy specimens with tumor thickness of ≤1 mm that the tumor thickness in the final specimens would be <2 mm ($p = 0.055$) and that tumor thickness of >2 mm in the biopsy material measured >3.5 mm in the final specimen ($p = 0.0001$).[130] They suggested that the information from the biopsy samples could be extrapolated and correlated with the findings of other investigators who correlated tumor thickness in oral cavity cancers with likelihood of regional metastasis, to suggest the possible needs for prophylactic neck dissection. In the study by Karas et al.,[130] tumor thickness measuring between 1 and 2 mm were too variable to be of predictive value.

In regard to other sites, Baredes et al.[136] found that in 44 patients with variably staged soft-palate SCCs (7 as T1, 14 as T2, 16 as T3, and 7 as T4), none of the patients with a tumor thickness of <2.86 mm had nodal metastasis, 60% of patients with tumor thickness >2.86 mm but <3.12 mm had metastatic disease, and all patients with tumors >3.12 mm had nodal metastasis. They concluded that there was a significant correlation between tumor thickness and the presence of nodal disease and that this association was more direct than that between T stage and nodal disease.[136] Baredes et al. also reported that thicker lesions had poorer survival.[136] Frierson and Cooper[128] evaluated 187 SCCs of the lower lip and found that the tumor thickness strongly correlated with nodal metastasis. For Frierson and Cooper,[128] nodal metastasis occurred in 74% of patients with cancers measuring ≥6 mm, suggesting that lip squamous cancers of that thickness need elective neck dissections. Moore et al.[137] and Urist et al.[138] also identified depth of invasion and tumor thickness as important prognostic parameters in upper aerodigesive tract cancers. More recently, Zitsch et al.[8] reviewed a series of 1,252 patients with lip cancer over a 47-year period. These authors did not measure tumor thickness, but among multiple parameters available in 1,036 patients, they found tumor size impacted on prognosis, with those lip cancers measuring >3 cm (T2 or greater) having a higher rate of nodal metastases (16%) than patients whose tumors measured <3 cm (6%).[8] Further, the range of 5-year survival rate for patients whose tumors measured >3 cm was 30% to 50%, in contrast to 90% 5-year survival rates for patients whose tumors measured <3 cm.[8] Based on their findings, they suggested aggressive management for lip cancer ≥3 cm.

The location of a tumor in the UADT may have an impact on the depth of invasion and potential for metastatic disease. As an example, the glottic area of the larynx quantitatively has less vascular spaces than other anatomic sites of the larynx. Therefore, for histologically similar carcinomas of equal invasive growth, those arising in the glottic area may be less likely to metastasize as compared to supraglottic or subglottic cancers due to less availability of vascular spaces in this anatomic site. This may also apply to other mucosal sites of the head and neck. However, tumor location does play an extremely important factor in tumor identification and in prognosis. Cancers that present earlier in the course of disease will have a better prognosis than those cancers that remain undetectable until they present at a more advanced stage of disease. Some examples of the former include tumors that present in areas that are visible to the patient (e.g., cutaneous sites of the head and neck) or result in symptomatology in the earlier stages of disease (e.g., true vocal cord). Patients with cancers of these sites may be diagnosed and treated while their tumors are still of a lower clinical stage and/or in areas that are readily accessible to complete surgical resection or radiation therapy without functional compromise or involvement of vital structures. In contrast, patients who have cancers that arise in areas in which symptoms may not develop early or whose symptomatology simulates nonspecific pathologic processes, such as cancers of the hypopharynx, the paranasal sinuses, and the middle ear, may only be detected in the advanced stages of disease with large tumors, extensive invasive growth, involvement of vital structures, difficult localization for complete removal, portending a poor outcome. Cerezo et al. found strong statistical correlation between the site of the primary tumor and prognosis.[139] In a multivariate analysis of 492 patients with squamous carcinoma of the head and neck, these authors found that patients with primary tumors of the larynx and the nasopharynx had higher survival rates than patients with carcinoma of the oropharynx, the mobile tongue, the floor of mouth, the retromolar trigone, and the hypopharynx.[139] They correctly attributed this discrepancy to the ability to control locoregional disease and/or better tumor response to therapy (surgery, radiation, or chemotherapy). Dworek and collegues[140] evaluated 250 patients with advanced head and neck cancer and found that patients with hypopharyngeal carcinoma were at greater risk of developing distant metastasis than were patients with carcinoma of the oral cavity, the oropharynx, and the larynx.

## Lymph-Vascular Space Invasion, Neurotropism, and Soft-Tissue Invasion

The presence of tumor within lymphatic spaces and/or blood vessels (Fig. 1-7) does not necessarily indicate that metastatic disease is present or will develop. However, several studies have

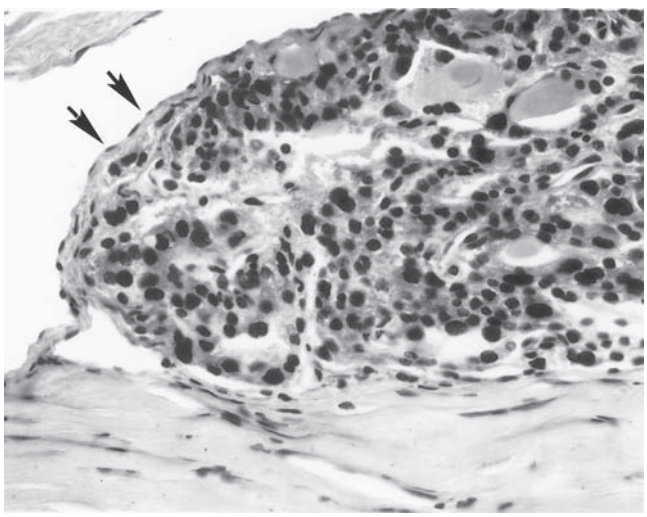


**FIGURE 1-7.** Parathyroid carcinoma showing vascular space invasion. Toward the left side of the illustration the endothelial cells lining this vascular space are seen (*arrowheads*) but become attenuated or lost due to the intravascular invasion of this tumor.

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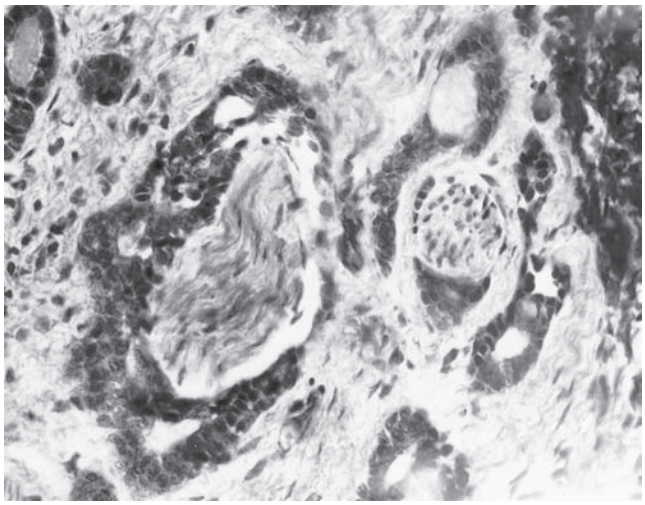


**FIGURE 1-8.** Adenoid cystic carcinoma of the parotid gland showing perineural invasion.

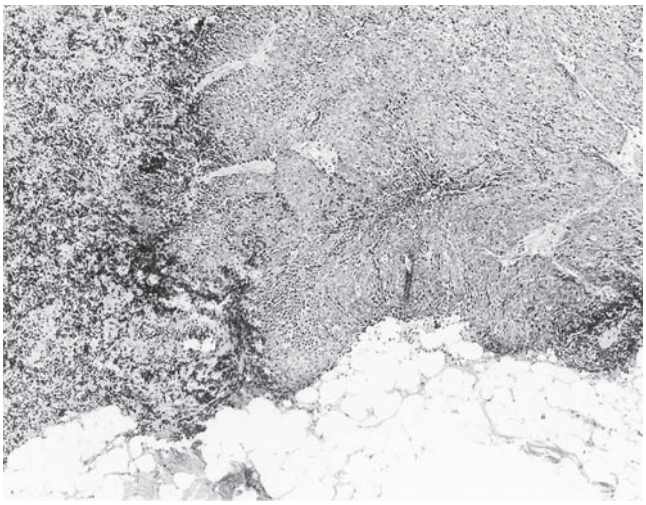


**FIGURE 1-9.** Metastatic carcinoma to a cervical neck lymph node with extracapsular extension. The remnant of the lymph node is seen at the left. Most of the lymph node has been replaced by metastatic carcinoma, which shows extension into perinodal adipose tissue (lower portion of illustration). Extracapsular spread is considered an adverse prognostic finding.

demonstrated a statistical correlation between the identification of vascular space invasion and nodal metastasis.[129,141–143] Sarbia and coworkers[144] evaluated the incidence and prognostic significance of blood-vessel invasion (BVI), lymph-vessel invasion (LVI), and neural invasion (NI) in SCC of the esophagus. These authors found a higher incidence of all three variables in higher pathologic and clinical-stage tumors than in patients with lower pathologic and clinical-stage tumors. Further, 5-year survival rates were significantly lower in patients with BVI and LVI than in patients without these findings.[144] These authors report no prognostic significance with the presence of NI (Fig. 1-8). Nevertheless, the presence of neurotropism in SCC of various UADT sites should be considered an adverse finding in head and neck malignancies indicative of a tumor's biologic aggressiveness as determined by an increased incidence of local recurrence, nodal metastasis, and/or decreased patient survival.[128,135,145–147] Similarly, extension into soft-tissue structures such as fat and muscle, or cartilaginous and osseous invasion by SCC of the head and neck generally indicates a higher clinical-stage tumor associated with a higher incidence of nodal metastasis.[143,148] It has been felt that hyaline cartilage is resistant to invasive cancer[149] and that in the larynx, there is preferential invasion of squamous carcinoma into ossified cartilage as compared to nonossified cartilage. However, Michaels has not found this to be true.[150] Michaels identified extensive invasion of laryngeal squamous carcinoma into nonossified cricoid and thyroid cartilage.[150] The invasion and destruction of bone by cancer is thought to be performed by osteoclasts mediated by prostaglandins[151] rather than by the direct action of the invasive cancer.

## Lymph Nodes

The presence of lymph node and/or distant metastasis is correlated with increased morbidity and mortality in association with most malignancies. For head and neck metastatic carcinoma to lymph nodes, several factors may have prognostic significance, including the presence of extracapsular extension by the tumor, site of nodal metastasis, number of lymph nodes with metastatic disease, node fixation, and tissue response to metastatic tumor. The presence of nodal metastasis with extension of the tumor outside the capsular confines of the lymph node and into perinodal soft tissues (extracapsular spread or ECS) (Fig. 1-9) is generally considered an adverse finding associated with increased risk of recurrent disease, increased risk of distant metastasis, and a reduction in long-term survival by up to 50%.[139,143,152–162] ECS is further subdivided based on whether the extracapsular spread was found microscopically or whether this feature was evident by gross examination. Macroscopic ECS is associated with an even greater risk of recurrent disease than by microscopic determination alone.[43,163] Further, lymph nodes measuring more than 3 cm demonstrate a >75% incidence of ECS.[152,156,158,159] Johnson et al.[164] advocate the use of postoperative adjuvant therapy (radiation and/or chemotherapy) in the presence of transcapsular extension. Similarly, Leemans and colleagues in two separate studies advocate the use of adjuvant systemic therapy in patients with ECS.[160,161] Myers et al.[162] reaffirm that ECS is the most significant predictor of both regional recurrence and the development of distant metastasis, accounting for decreased survival of patients with SCC of the oral tongue. Of the 260 patients in their study, 146 patients (55%) were pathologically node negative (pN0), 75 patients (28%) were pathologically node positive without ECS (pN+/ECS–), and 45 patients (17%) were node positive with ECS (pN+/ECS+). Following the order of pN0, pN+/ECS–, and pN+/ECS+, the 5-year disease-specific and overall survival rates for the pN0 patients were 88% and 75%; pN+/ECS– were 65% and 50%; and pN+/ECS+ were 48% and 30%. The overall recurrence rates were 19.8%, 34.2%, and 51.1%, respectively; the regional failure rates were 11.5%, 19.2%, and 28.9%, respectively; and the distant metastases rates were 3.3%, 8.2%, and 24.4%, respectively. Based on their findings, the authors advocate the use of intensive regional and systemic adjuvant therapy for patients with ECS.

The role of ECS as a prognosticator and adjuvant therapy determinant in human papilloma virus–related oropharyngeal squamous cell carcinoma (OPSCC) was recently reported by Sinha et al.[165] These authors evaluated 152 p16-positive primary OPSCC patients with pathologically positive necks. At a median follow-up of 43 months, the presence of ECS was not associated with poorer disease-free survival in multivariate analyses. Overall and in the presence of ECS or even soft-tissue metastasis,

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adjuvant CRT was not associated with better disease-free survival over radiotherapy alone. In addition, matched analyses in patients with and without ECS for T-stage, surgical margins, and adjuvant therapy showed no significant reduction in disease-free survival for the presence of ECS versus the absence of ECS or reduced disease-free survival for the administration of adjuvant radiotherapy alone versus CRT in ECS-positive patients. In conclusion, Sinha et al. concluded that ECS was not prognostic. Adjuvant CRT versus radiotherapy alone produced no improvement in disease-free survival for ECS-positive patients. The authors propose that de-escalated adjuvant therapy should be considered for patients with p16-positive OPSCC who undergo surgery and that routinely reported ECS should not be used to justify adjuvant chemotherapy.[165]

The site of metastatic disease may impact on overall prognosis. Patients with a nodal metastasis to the lower neck area have a worse prognosis than patients in whom the metastatic deposits are limited to the upper neck.[153,166,167] McLaughlin et al.[168] found that abnormal retropharyngeal adenopathy, as determined by radiographic assessment (CT scan, MRI), was a predictor of outcome in SCC of the head and neck. Patients with squamous carcinoma of the head and neck of varying T stages (I–IV) and varying N stages (N0–N3), followed for a minimum of 2 years, had rates of neck relapse and distant metastasis that were significantly higher with retropharyngeal adenopathy[168]; the rates of 5-year relapse-free survival and absolute survival were significantly lower.[168]

The prognostic implication of whether metastatic tumor is found in a single lymph node or whether multiple nodes harbor disease has been debated. A number of studies have found that there is no prognostic significance in the absolute number of positive lymph nodes.[169,170] However, other studies have found prognostic significance in the number of lymph nodes containing metastatic cancer, showing an inverse relationship between the absolute number of lymph nodes containing metastatic cancer and survival.[139,140,152,156,157,160,161,171] Doweck et al.[140] in their study on 250 patients with advanced head and neck cancer reported that the most accurate predictor of distant metastasis was the number of neck levels with clinical evidence of disease. Patients with more than one level of nodal metastases had an odds ratio of 3.17 for having distant metastasis. Of these patients, 36% had distant metastasis compared with 17.9% if only one level of the neck was involved and 10.2% if the neck was negative. There is no specific cut-off in the number of positive lymph nodes associated with decreased survival. In a number of studies, the involvement by metastatic tumor in 3 or more lymph nodes appeared to be a predictor of distant metastasis and decreased survival.[139,160,161] Olsen et al.[143] found no significance when the number of lymph nodes involved was between 1 and 3, but when 4 or more lymph nodes were positive for metastatic tumor, there was a significant statistical correlation with 2-year recurrence-free survival (51% with at least 4 lymph nodes compared with 79% with 1–3 positive lymph nodes). Spiro et al.[171] reported that the presence of bilateral nodal metastases is an adverse prognostic finding associated with a worse prognosis in comparison to patients with unilateral metastatic disease. Mamelle et al.[172] retrospectively evaluated 914 patients with SCC of various head and neck sites who underwent lymph node dissection, in an attempt to determine prognostic factors relative to nodal disease. These authors reported that in a multivariate analysis, the most significant prognostic factors were the site of the positive node in or out of the sentinel node area ($p < 0.001$) and the number of positive nodes ($p < 0.001$), and that a more accurate approach was obtained by combining both factors.[172] The presence of nodal metastasis in 4 or more lymph nodes located out of the sentinel node area was associated with decreased 5-year survival rates and increased likelihood of metastatic disease.[172] These authors reported that in the multivariate analysis, extracapsular spread was a nonsignificant risk factor in survival or distant metastatic spread ($p = 0.09$), but was significant in their univariate analysis ($p < 0.001$).[172]

## Distant Metastasis

Distant metastasis by hematogenous spread to visceral sites from a head and neck squamous carcinoma most commonly includes spread to the lungs, the liver, and bone.[173] Distant metastatic tumor from a head and neck squamous carcinoma carries ominous clinical import generally heralding the demise of the patient over relatively short periods of time despite all attempts at controlling disease.[174] Among the factors that may be associated with distant metastatic tumor are the histologic type of cancer, tumor size, and the status of cervical lymph node involvement. Several of the high-grade variants of squamous carcinoma, including the basaloid SCC and adenosquamous carcinoma, often present as large tumors that are deeply invasive associated with nodal and distant metastasis. The reason for this aggressive behavior at presentation is not completely understood.

Both the tumor size (T stage) and the cervical node involvement (N stage) have been shown to have a high incidence of distant metastases.[139,161,175–177] In addition to N stage, the number of lymph nodes involved, the number of lymphatic chains involved, and the presence of extracapsular spread have all been shown to be associated with an increased incidence of distant metastasis.[139,140,157,160,161] Cerezo et al.,[139] in a multivariate analysis of 492 patients with metastatic neck disease from squamous cell carcinoma of the head and neck, found that when 3 or more lymph nodes had metastatic disease the distant recurrence-free survival was reduced to 41% as compared to 84% when 1 lymph node was involved and 57% when 2 lymph nodes were involved. These same authors also found that when 2 or more lymphatic chains contained metastatic tumor, the distant recurrence-free survival was reduced to 40% as compared to 74% when 1 lymphatic chain was involved.[139] In an autopsy study of 112 patients who had SCC of the head and neck, Nishjima et al.[173] found that nodal status was a significant prognostic factor in the presence of distant metastases. Of the 41 patients (37%) in their study who were found to have distant metastases at the time of death, 26 patients (63%) had evidence of cervical lymph node metastases, which represent a positive correlation between nodal status and development of distant metastases ($p < 0.01$). Nishijima et al. further combined their patients into those who had tumor at the primary site with those who had tumor in cervical lymph nodes (classified as cancerous lesions above the clavicle), and found that of these 82 patients 43% had distant metastases ($p < 0.05$). These authors concluded that distant metastasis occurred most frequently in patients with residual or recurrent disease in the neck. Nishijima et al. reported no correlation between the T and N stages, anatomic site of the primary tumor, presence or absence at controlling disease at the primary site with the frequency of developing distant metastases. The authors indicate that in their patients, the T and N stages were determined at the time of the initial examination (when the patients were alive). Irrespective of the T or N stage, these patients ultimately died of their tumors, and so it was felt that the initial T and N stages may not have played a significant role in the analysis of patients who died of advanced disease.[173]

Skin involvement by mucosal SCC of the head and neck is uncommon and is usually an indication of advanced or recurrent disease.[178] Cole and McGuirt[179] have shown that cutaneous involvement from a primary mucosal SCC has adverse prognostic implications. These authors found that the presence of direct cutaneous extension from a mucosal SCC was associated with a mean survival of 7 months while intradermal lymphatic spread carried

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a mean survival of 3 months; involvement of facial skin had an overall better prognosis than when there was involvement of neck skin with 12-month and 3-month median survival, respectively.[179]

## Second Malignancy

As compared to the standard population, the head and neck cancer patient is at greater risk (10–30 times) of developing a second primary malignancy[180] with the frequency varying from <5%[181] to as high as 36%[182] with many studies in the 15%-to-25% range.[183–185] Criteria used in defining multiple primary carcinomas include that the tumors be separate and distinct (at least 2 cm apart) without any dysplasia in the intervening mucosa and that the second primary tumor does not represent a metastasis or recurrent tumor.[181] The diagnosis of a second primary tumor such as in the lung includes the presence of a solitary lesion that is histologically distinct from the primary tumor.[185] Second primary malignancies occurring within a 6-month period from the discovery of the primary cancer are termed synchronous tumors, whereas second primary malignancy that occurs after the 6-month period from the discovery of the first tumor are referred to as metachronous tumors. Most of the second malignancies develop in other upper aerodigestive tract mucosal sites.[183,184,186] Non–head and neck sites in which second malignancies develop include the lungs,[184–186] the esophagus,[148,185,187] and the bowel.[184,186] Most often, the histology of the second primary malignant neoplasm is a squamous carcinoma,[185,187] but other histologic types such as adenocarcinomas may occur.[186] Some of the high-grade variants of SCC, including the basaloid cell squamous carcinoma and adenosquamous carcinoma, are notorious for the presence of multiple concurrent primary tumors in mucosal sites of the head and neck at the time of initial presentation.

Factors that may play a significant role in the development of a second malignancy include the site of the original primary cancer, the age of the patient, the size of the primary tumor, the status of regional lymph nodes, and the use of tobacco and alcohol. Head and neck second malignancies are more likely to develop when the primary cancer is in the oral cavity, the hypopharynx, or the oropharynx than if the index tumor is of laryngeal origin.[184–186] Patients who developed their tumors prior to 60 years of age may be at greater risk of developing a second primary malignancy.[185,186] Jones et al.[186] showed that patients with lower stage index tumors (T1 and T2) and patients who had no nodal metastasis (N0) at the presentation of their index tumor were more likely to develop a second malignancy than patients with higher stage index tumors and patients who did have nodal metastasis at the presentation of their index tumor ($p$-values of $< 0.0001$ and 0.0003, respectively). Lippman and Hong[188] also identify the threat of a second malignancy in early stage head and neck index cancer patients. Patients with index tumors of the head and neck who smoke tobacco (>20 pack years) and consume alcohol were at significant increased risk of developing a second malignancy than head and neck cancer patients who did not.[185] Survival rates after the second cancer are influenced by the site of the second malignancy and persistent use and abuse of tobacco and alcohol.[185] Second malignancies of the lung and the esophagus portend a significantly worse prognosis than second malignancies of other head and neck sites with 5-year survival rates from the diagnosis of the second malignancy of 2% (for lung) and 3% (for esophagus) versus 20% for second head and neck malignancies.[185] Continued use of tobacco and alcohol also adversely affected survival rates with 5-year survival rates of 5% for smokers versus 20% for nonsmokers, and 6% for drinkers versus 27% for nondrinkers.[185]

The site of the second malignancy differs for different index tumors. Head and neck, and esophageal second primary malignancies are more prevalent after oral cavity and pharyngeal index tumors, whereas the development of a second primary tumor of the lung was most common after a laryngeal index tumor.[184,186] Haughey et al.[184] suggest a shared mucosal susceptibility between the index tumor and the second malignancy to account for this phenomenon. A common "digestive tract axis" is shared between the oral cavity, the pharynx and the esophagus, whereas the larynx and the lung share a common "respiratory tract axis." This shared mucosal susceptibility is a variation on the "field cancerization" concept, which highlights the importance of carcinogen activation of an entire exposed mucosa.[189–197]

The critical issue for the clinicians in the evaluation and planned treatment of the head and neck cancer patient is to be acutely aware of the possibility that the patient has or will develop a second primary malignancy. The diagnosis of a primary head and neck cancer should initiate panendoscopic evaluation of the entire UADT, as well as the lower aerodigestive tract and esophagus to exclude the possibility of a synchronous second primary cancer, with vigilant follow-up care given the possibility of developing a metachronous cancer. The results of these findings may ultimately impact on the diagnostic approach, treatment protocol, and prognostic impact for that patient. The development of a second primary malignancy is in all likelihood a multifactorial process combining genetic and environmental risks.

# SECTION II
# Squamous Cell Carcinoma

In the head and neck region, the most common lesion encountered by the otolaryngologist and the pathologist relate to alterations of the surface squamous epithelium. This section will focus on the squamous epithelial alterations of the UADT, including precursor lesions, SCC, and selected variants of SCC.

## DYSPLASIA AND INTRAEPITHELIAL NEOPLASIA

Dysplastic or intraepithelial neoplastic changes represent a spectrum of abnormal epithelial maturation and cellular aberrations that may or may not precede an invasive carcinoma. Dysplasia is synonymous with atypia. The uterine cervix represents the paradigm for the histologic grading of dysplastic changes. Typically, uterine cervical dysplasias are nonkeratinizing lesions. Similar to the uterine cervix, the grading of UADT intraepithelial dysplasia includes mild, moderate, and severe depending on the extent of involvement of the surface epithelium although the most common type of dysplastic lesions are keratinizing ones. In general, the lower the degree of dysplasia, the less likely the transformation to an invasive carcinoma, whereas higher-grade dysplasias are more likely to progress to invasive carcinoma. In the UADT, particularly in the larynx and the oral cavity, severe dysplasia as defined histologically by the presence of full-thickness intraepithelial dysplasia (i.e., CIS) is not a prerequisite for the development of an invasive SCC.[198,199] In the UADT, where keratinizing dysplasias are more common than "classic" or nonkeratinizing dysplasia, invasive carcinoma may develop in the presence of dysplastic changes limited to the basal zone without full-thickness intraepithelial dysplasia.[199]

## CARCINOMA *IN SITU*

As classically defined, CIS represents full-thickness mucosal intraepithelial dysplastic change without violation of the basement membrane. For all intents and purposes, severe

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dysplasia is synonymous with CIS. As previously noted, in the upper airways, CIS (as classically defined) is not a requirement prior to the development of an invasive SCC. The latter may arise from the basal epithelial layer in the absence of overlying dysplastic changes. Therefore, in this setting, the definition of CIS can be expanded to include those lesions in which the mucosal alterations are so severe that there would be a high probability for the progression to an invasive carcinoma if left untreated. Extension of the dysplastic process to involve the mucoserous glands is still considered as CIS and not invasive carcinoma.

## EARLY, SUPERFICIALLY, OR MICROSCOPIC INVASIVE SCC

Microinvasive carcinoma (MIC) represents squamous carcinoma in which there is penetration of the basement membrane with invasion of the carcinoma into the underlying submucosal compartment. There is no uniformity among pathologists as to how to histologically define MIC.[198] The various histologic definitions of MIC include small number of cells below the basement membrane, invasion through the basement membrane, invasion through the basement membrane limited to 1 to 2 mm of the basement membrane without angioinvasion, and invasion no more than 0.5 mm from the basement membrane with no angioinvasion. The identification of superficial or MIC is significant given the presence of vascular spaces high in the lamina propria and the potential, even in the presence of "early" invasive cancer, for metastatic disease. Relative to HNSCC, invasive carcinoma may develop in the setting of nonkeratinizing dysplasia as a continuum from CIS or more often develops in the setting of keratinizing dysplasia in which CIS is not a prerequisite for the development of invasive carcinoma with invasive carcinoma arising from a surface epithelium in which there may be dysplastic alterations limited to the basal zone area (so-called "drop off" carcinoma) (see subsequent text).[199]

## PRECURSOR LESIONS

Precursor lesions to squamous epithelial lesions of the UADT present diagnostic challenges in that the majority of dysplastic epithelial changes are of the keratinizing type to which the continuum of mild to moderate to severe dysplasia to invasive carcinoma that characterizes the nonkeratinizing dysplasias does not consistently apply. This results in problems in the histologic grading of these changes and raises questions about what constitutes a diagnosis of severe dysplasia. In this context, the justification of using the designation CIS relative to keratinizing dysplasia becomes questionable.

Leukoplakia, erythroplakia, and speckled leukoplakia are not histopathologic terms. The qualitative intraepithelial alteration in a malignant direction is referred to as dysplasia. Dysplasia is for all intents and purposes synonymous with atypia although dysplasia has been used in relation to architectural abnormalities, while atypia has been used for cytomorphologic changes.

Histologic criteria for the diagnosis of intraepithelial neoplasia of the UADT include both cytomorphologic and maturation abnormalities. These alterations include the proliferation of immature or "uncommitted" cells characterized by a loss of cellular organization or polarity, nuclear pleomorphism (variations in the size and shape of the nuclei), increase in nuclear size relative to the cytoplasm, increase in the nuclear chromatin (hyperchromasia) with irregularity of distribution, and increased mitoses, including atypical forms in all epithelial layers. The dysplastic changes may or may not be associated with keratosis and/or dyskeratosis. The location of the architectural and cytomorphologic changes within the epithelium represents key diagnostic parameters in the assessment of UADT epithelial dysplasia.

The paradigm for grading epithelial dysplasia is the one used for the uterine cervix. In the uterine cervix, the "classic" or nonkeratinizing form of dysplasia commonly occurs. The increasing gradations of cervical dysplasia include mild (CIN I), moderate (CIN II), and severe (CIN III), with the latter representing full-thickness replacement of the squamous epithelium by atypical, small, immature basaloid cells and is referred to as carcinoma *in situ* (CIS) (Fig. 1-10). This grading scheme is reproducible and is clinically useful. However, the "classic" or nonkeratinizing dysplasia of the uterine cervix is uncommon in the UADT, especially in the glottic larynx. In contrast, most of the intraepithelial neoplasias of the UADT are keratinizing dysplasias. Using the definition of CIS of the uterine cervix that requires loss of maturation of squamous epithelium, a keratotic lesion cannot be CIS because keratosis requires maturation of the squamous epithelium. Therefore, the use of the specific term CIS in keratinizing dysplasias has been questioned and is likely inappropriate in this setting. A more appropriate designation is of severe keratinizing dysplasia.[199]

The criteria for evaluating keratinizing dysplasias are less defined, and the diagnosis of severe keratinizing intraepithelial dysplasia remains controversial. The definition of severe dysplasia in the UADT, especially in the glottic larynx, is broader than the highly reproducible pattern seen in the uterine cervix and includes a microscopically heterogeneous group of lesions. In the setting of keratinizing dysplasia where surface maturation is retained with only partial replacement of the epithelium by atypical cells, severe dysplasia includes those lesions in which the epithelial alterations are so severe that there would be a high probability for the progression to an invasive carcinoma if left untreated (Fig. 1-11). Severe dysplasia shows the presence of aberrant cell maturation with dyskeratotic cells and mitotic figures with or without atypical forms above the basal zone. These alterations often occur in the presence of surface keratinization (Fig. 1-12). In the evaluation of UADT dysplasia, the presence

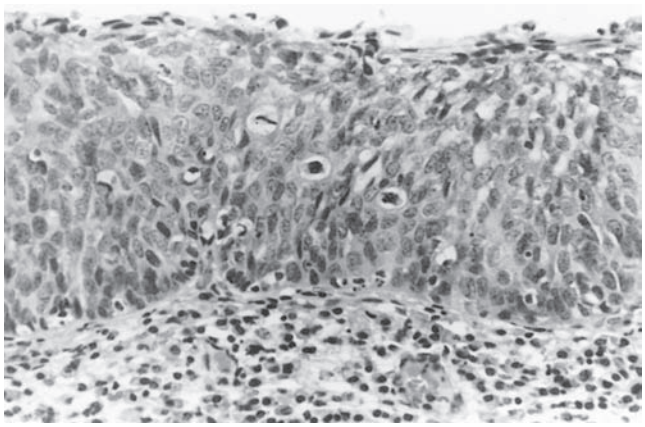


**FIGURE 1-10.** Laryngeal (glottic) carcinoma *in situ* "classic" or nonkeratinizing type. There is full-thickness dysplasia with replacement of the squamous epithelium by atypical, small, immature basaloid cells, including numerous mitotic figures in the absence of surface keratinization. The dysplastic cells are confined to within the surface epithelium and do not penetrate the basement membrane into the submucosa.

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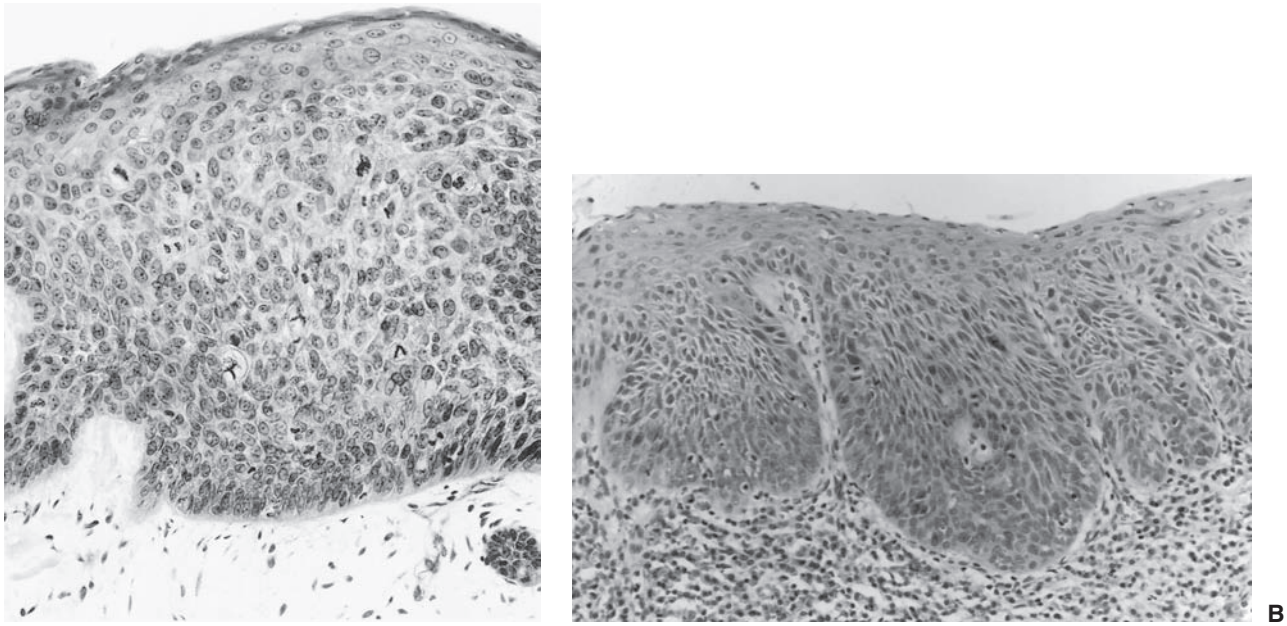



**FIGURE 1-11.** **A:** Laryngeal (glottic) keratinizing dysplasia. Surface maturation is retained with replacement of the squamous epithelium by atypical cells, including numerous suprabasal mitotic figures. Although there is no full-thickness dysplasia, the lesion is considered as severe dysplasia given that the epithelial alterations are so severe that there is a high probability for the progression to an invasive carcinoma if left untreated. **B:** Similar alterations as those seen in **(A)**, but the downward growth of the bulbous adds concern for the evolution to invasive carcinoma.



**FIGURE 1-12.** Laryngeal biopsy showing keratosis and severe dysplasia with superficial invasion. This epithelium does not show full-thickness dysplasia (i.e., carcinoma *in situ*). The dysplastic alterations are limited to the lower portion of the epithelium but is still considered severe, and the angulated downward extension of this severely dysplastic epithelium is sufficient to consider this as superficially invasive.

of surface keratinization is not significant; however, finding dyskeratotic cells represents an important clue to the presence of significant dysplasia.

## GRADING EPITHELIAL DYSPLASIA OF THE UADT

The histopathologic interpretation and grading of epithelial dysplastic changes in the UADT are imprecise and subjective. Given the complexities in the issues relative to UADT intraepithelial lesions, confusion and misunderstandings may occur between the clinician and the pathologist that may result in inappropriate management of the patient. Uniformity in terminology is desirable so that there is a correlation between the pathologic diagnosis and the clinical import of that diagnosis. In an attempt to standardize the terminology of UADT intraepithelial lesions using a grading system akin to that of the cervical mucosa, Crissman and Zarbo[200] used the terminology of squamous intraepithelial neoplasia (SIN) with SIN I equivalent to mild dysplasia, SIN II to moderate dysplasia, and SIN III to severe dysplasia. Similar gradations but using the terminology of laryngeal intraepithelial neoplasia (LIN) have been proposed.[201] More recently, the Ljubljana classification of laryngeal precancerous lesions was proposed.[202] In this system, the terms used include simple hyperplasia (i.e., keratosis without atypia), abnormal hyperplasia (i.e., keratosis with atypia), atypical hyperplasia (i.e., severe dysplasia), and CIS. These systems have conceptual validity, but may not be entirely applicable from a practical standpoint in the UADT. At present, the WHO recommends grading dysplastic epithelial alterations of the UADT as mild, moderate, and severe dysplasia depending on the degree and extent of cellular and maturation alterations that are present.[203]

Regardless of the terminology employed, close interaction between the pathologist and the clinician is required so that each

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individual understands the impact of their respective findings and the import to the patient in therapy and prognosis.

## Risk of Progression

The end point for the grading of dysplasia is to convey to the clinician what the potential biologic behavior of a given epithelial lesion is. Keratotic epithelium without dysplasia carries a very low risk of developing subsequent carcinoma with reported incidences of 1% to 5%.[198,203] In contrast, keratotic epithelium with dysplasia is associated with an increased risk for the subsequent progression or development of premalignant or overtly carcinomatous changes varying from 11% to 18% of cases.[198,203] This risk of malignant transformation represents an increase of three to five times as compared to carcinoma arising in keratotic lesions without atypia. Bouquot and Gnepp[204] found greater variability relative to risk progression of keratosis with and without atypia in their review of the literature. Nevertheless, the potential value in grading keratotic dysplasias is apparent from Barnes's review of the literature[198] in which the risk for developing invasive carcinoma in mild, moderate, and severe dysplasia was 5.7%, 22.5%, and 28.4%, respectively. Bauer and McGavran[205] indicated that if enough sections are taken, MIC will be found in laryngeal lesions that have keratosis with cytologically atypical cells.

Another important point to recognize is the clinical concern attached to a diagnosis of severe keratinizing dysplasia. This clinical concern is due to the fact that severe dysplasia is often multifocal and frequently occurs adjacent to or near synchronous foci of invasive carcinoma. Further, this form of dysplasia has a rate of progression to invasive carcinoma that is greater than that of "classic" CIS.[206–208] A diagnosis of severe dysplasia requires therapaeutic intervention, as well as clinical evaluation of the entire UADT to exclude the possible presence of additional foci of dysplasia or carcinoma.

In general, mild dysplasia is felt to be reversible alterations. Circumstantial evidence supports the idea that preinvasive dysplasias are potentially reversible following cessation or removal of an instigating factor such as tobacco use. The problem of predicting the malignant potential of a dysplastic lesion is greatest in cases of moderate dysplasia. It is virtually impossible to differentiate the moderately dysplastic lesions that are reversible from those that represent the earliest forms of neoplastic transformation. Therefore, a diagnosis of moderate dysplasia should engender enough concern to the clinician to warrant close patient follow-up. Recurrence or persistence of this dysplasia may be indicative of malignant transformation. Further, there are no significant differences in the progression to invasive carcinoma between keratinizing moderate dysplasia and keratinizing severe dysplasia so that treatments for these dysplasias are essentially similar.[198] As such, it may be prudent to adopt a similar approach to the two-tier histologic classification scheme used in the grading of uterine cervical dysplasia to dysplasias of the UADT including:

1. Low-grade squamous intraepithelial lesion for mild dysplasia
2. High-grade squamous intraepithelial lesion for moderate and severe dysplasias

The determination of whether a mild to moderate dysplasia is reactive or neoplastic, although a desirable goal, is not always achievable. The clinically abnormal lesions that show limited cytologic and maturation abnormalities falling under the designation of reactive atypias or hyperplastic lesions represent reversible changes that rarely, if ever, progress to carcinoma. These lesions are responsive to conservative management. Epithelial hyperplasia (acanthosis) is a common finding and can be seen without atypia or in association with atypia. In hyperplasia, there usually is an irregular contour to the basal zone, and there may be protrusion of the epithelium below adjacent epithelium, possibly suggesting an MIC. A diagnosis of MIC should be reserved for those examples in which there is definitive evidence of dissociated squamous cells at the epithelial-to-stromal interface. Epithelial hyperplasias may be caused by an infectious agent (e.g., fungi), and fungal stains may be useful to identify the causative microorganism.

## MICROINVASIVE, SUPERFICIAL, OR "EARLY" INVASIVE SCC

Microinvasive SCC is a cancer that infiltrates into the superficial compartment of the lamina propria. As simple as this may appear, the diagnosis of superficially invasive SCC can be subjective, with no unanimous definition among pathologists. For laryngeal lesions, some authors consider microinvasive cancer to include the presence of scattered malignant cells within the submucosa just below the basement membrane[209] or within 1 to 2 mm of the basement membrane,[200,210,211] whereas other authors feel that MIC is present when tongues or discrete foci of malignant epithelium invades through the basement membrane.[212] Barnes defines MIC as invasive SCC that extends into the stroma no more than 0.5 mm as measured from the adjacent (nonneoplastic) epithelial basement membrane.[198] Irrespective of its specific definition, a diagnosis of MIC excludes those lesions that are restricted to the surface epithelium or carcinoma *in situ* (Tis) and those carcinomas that are deeply invasive into muscle and cartilage, and extralaryngeal structures (T2 or greater tumors). Also, the presence of lymph-vascular space invasion would exclude a diagnosis of MIC. Of note, extension of the dysplastic process to involve the seromucinous glands is still considered as CIS and not invasive carcinoma (Fig. 1-13). The clinical manifestations

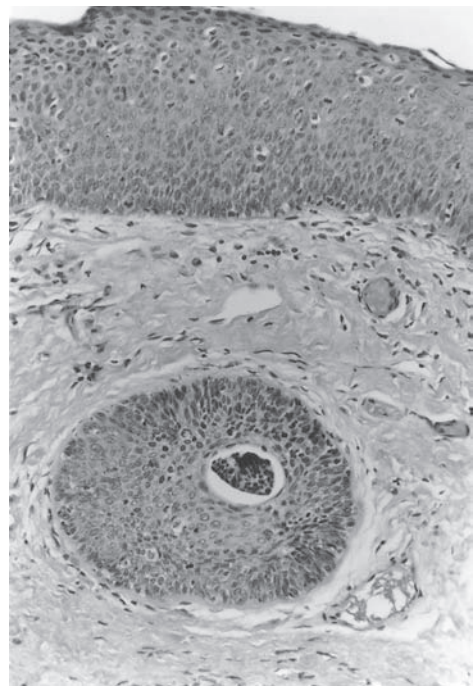


**FIGURE 1-13.** Laryngeal (glottic) carcinoma *in situ* of the surface epithelium with extension of the dysplastic process to involve the seromucinous glands. The extension to seromucinous glands is still considered as carcinoma *in situ* and not invasive carcinoma.

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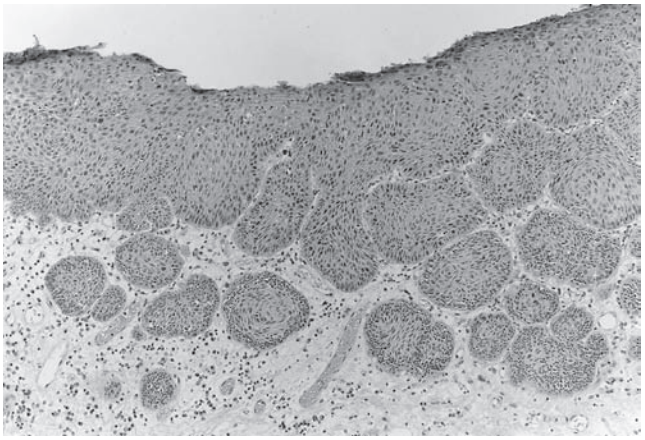


**FIGURE 1-14.** Laryngeal (glottic) microinvasive squamous cell carcinoma developing as a continuum from carcinoma *in situ*.

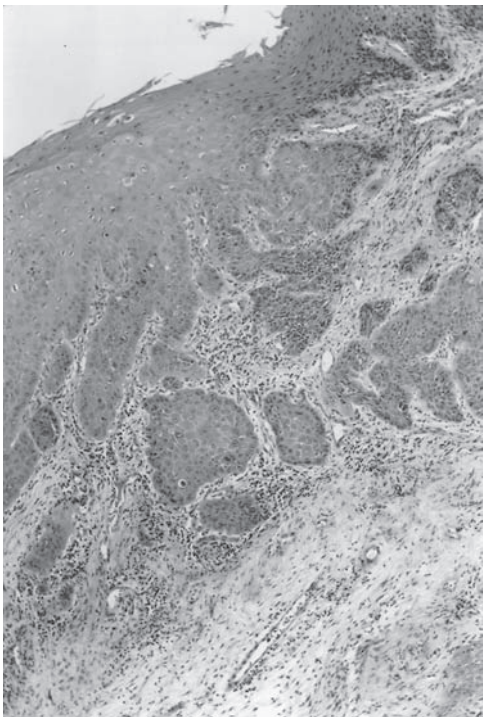


**FIGURE 1-15.** Laryngeal (glottic) invasive squamous cell carcinoma developing from the basal zone of the surface epithelium in which most of the epithelium is free of dysplastic changes (so-called drop-off carcinoma).

and appearance of microinvasive SCC are similar to those of CIS. In the larynx, full-cord mobility is present. Any dysfunction in vocal cord mobility (fixation), by definition, means muscle invasion, which excludes a diagnosis of microinvasive cancer.

Histologically, MIC can occur in two unrelated phases. The first is the development from and as a continuum of CIS (Fig. 1-14). The second is invasion from an epithelium demonstrating no evidence of CIS. In the UADT, particularly in the larynx, severe dysplasia (i.e., CIS) is not a prerequisite for the development of an invasive SCC. Such invasive carcinomas "drop off" or "drop down" from the basal cell layer, with the overlying mucosa showing no evidence of dysplasia (Fig. 1-15). In all examples of invasive carcinoma, the invasive nests must be cytologically malignant with dysplastic changes, dyskeratosis, and mitotic figures, including atypical forms. The tumor nests have an irregular outline with infiltrative borders. The presence of invasive cancer generally results in stromal induction or a desmoplastic host response that includes edematous change immediately around the tumor nests with granulation tissue and fibrosis.

Microinvasive cancer is a biologically malignant lesion potentially capable of gaining access to lymphatic or vascular channels in the lamina propria that may result in metastatic disease. For MIC of the laryngeal glottis, several studies have shown that the clinical significance is similar to CIS/severe dysplasia and that with appropriate therapy, progression of disease from a microinvasive to a more invasive carcinoma does not occur.[207,209–212] This may be due to the earlier clinical manifestations produced by glottic cancers leading to an earlier diagnosis of cancer before it has invaded into deeper aspects of the larynx. Glottic microinvasive cancers are generally not associated with metastatic disease due to the fact that the glottic portion of the larynx has quantitatively less lymph-vascular spaces as compared to the supra- and subglottis. In contrast to the laryngeal glottis, supraglottic MICs are associated with metastatic disease in approximately 20% of patients.[213]

## INVASIVE SCC

The clinical (gross) appearance of invasive SCC is quite variable and includes ulcerated, flat, exophytic, verrucoid or papillary growths. The histologic appearance of invasive SCC may be as variable as the gross appearance without specific correlation between the gross appearance and the histopathologic findings. Invasive SCC of the UADT includes keratinizing and nonkeratinizing carcinomas varying from well to poorly differentiated. Severe dysplasia/CIS of the surface epithelium may be a common component found in association with invasive SCC; this component need not be present. For all types of SCC, the presence of invasion is diagnostic of a malignancy. Invasion can be as single (dyscohesive) cells or small irregular aggregates or can appear as large cords or cohesive aggregates. In addition, a desmoplastic stromal response and foreign body reaction to keratin in the stroma may assist in identifying invasion. Invasive cancer will efface the normal architecture and may be associated with lymph-vascular space invasion, neurotropism, and invasion into muscle, bone, and cartilage. Once the cancer invades beyond a few millimeters or extends into muscle, cartilage, or other soft-tissue components outside the anatomic structure from which it originates, the tumor is a higher clinical-stage neoplasm with the potential for a more aggressive behavior. Immunohistochemical studies have shown that the presence or absence of basement membrane components around invasive cancer correlated with the pattern of tumor invasion.[214] The pattern of tumor invasion (single cell vs. large cords) represents an inherent biologic parameter of tumor aggressiveness.[200,214]

### Pitfalls in the Diagnosis of Invasive SCC

Sampling is a major issue in the evaluation of SCC of the UADT. In the absence of adequate representative tissue, including epithelial-to-stroma interface, one should be circumspect relative to a diagnosis of SCC. Pitfalls in the diagnosis of SCC include pseudoepitheliomatous hyperplasia,[199,215] necrotizing sialometaplasia,[199,216] juxtaoral organ of Chievitz,[199,216] and radiation atypia.[199]

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***Histologic Prognostic Indicators.*** The histologic findings that may impact on the prognosis in HNSCC include (a) status of the surgical resection margins, (b) tumor size, thickness, and location of the lesion, (c) pattern of invasion, (d) involvement of lymphvascular spaces, (e) invasion of soft-tissue structures, including nerves, bone, and cartilage, (f) nodal metastasis with or without extranodal extension of tumor, (g) distant metastasis, (h) host response, (i) neovascularization, and (j) presence of multiple malignancies.

## MORPHOLOGIC SUBTYPES OF SCC

There are numerous variants of HNSCC (Table 1.13). The diagnostic criteria and diagnostic problems associated with some of these specific subtypes of HNSCC will be discussed.

### Papillary (Exophytic) SCC

Papillary (exophytic) SCC represents an uncommon but distinct subtype of head and neck SCC.[217–219] The demographics for this subtype of SCC are similar to those of conventional SCC with the tendency to affect men more than women and occurring in adults with a mean age in the seventh decade of life. Papillary SCCs predilect to the larynx, the oral cavity, the oro- and the hypopharynx, and the sinonasal tract.[217–219] The larynx is the most common site of occurrence. Symptoms vary according to the site of involvement. Papillary SCC usually arise de novo without identification of coexisting benign lesion such as a papilloma, although association with precursor papilloma or occurrence in patients with previous history of a papilloma at the site of the papillary SCC have been reported.[219] Human papillomavirus (HPV) by ISH and PCR have been detected in papillary SCC.[219]

Papillary SCC is most often seen as a solitary lesion with an exophytic or papillary growth. Tumor size may range from 2 mm up to 4 cm. Histologically, papillary SCC has filiform growth with finger-like projections and identifiable fibrovascular cores or a broad-based bulbous to exophytic growth with rounded projections resembling a cauliflower-like growth pattern in which fibrovascular cores can be seen but tend to be limited to absent (Fig. 1-16). The squamous epithelium is cytologically malignant, and this malignant epithelium identifies these tumors as carcinomas separating them from papillomas. Surface keratinization is generally limited and often absent. Definitive invasion may be difficult to demonstrate in biopsy specimens, with the carcinomatous epithelium suggesting an *in situ* process rather than invasive carcinoma. However, the extent of growth with the formation of a clinically appreciable exophytic mass goes beyond the general concept of an *in situ* carcinoma. These tumors should be considered as being invasive even in the absence of definitive stromal invasion.

**TABLE 1.13 Head and Neck Squamous Cell Carcinoma (SCC) and Variants**

| |
|---|
| Conventional SCC |
| Papillary SCC |
| Verrucous carcinoma |
| Spindle cell squamous carcinoma |
| Basaloid SCC |
| Nasopharyngeal carcinoma |
| Adenoid SCC |
| Adenosquamous carcinoma |
| Others |

### Verrucous Carcinoma

Verrucous carcinoma (VC) is a highly differentiated variant of SCC with locally destructive but not metastatic capabilities. VC affects men more than women and generally occurs in the sixth and seventh decades of life. VC can occur anywhere in the UADT. The most common sites of occurrence in descending order include the oral cavity, the larynx, the nasal fossa, the sinonasal tract, and the nasopharynx.[220–222] Symptoms vary according to site: larynx—hoarseness is the most common complaint, less frequent symptoms include airway obstruction, hemoptysis, dysphagia; oral cavity—mass with or without pain; sinonasal tract—airway obstruction; nasopharynx—dysphagia. The most common site of occurrence in the larynx is the glottic area. Oral cavity VCs most commonly arise on the buccal mucosa and the gingiva.

The etiology of VC remains speculative and includes tobacco smoking or chewing. Viral-induction appears to be a legitimate etiologic factor in the development of VC, but a causal relationship has not been clearly identified. The active role of HPV is

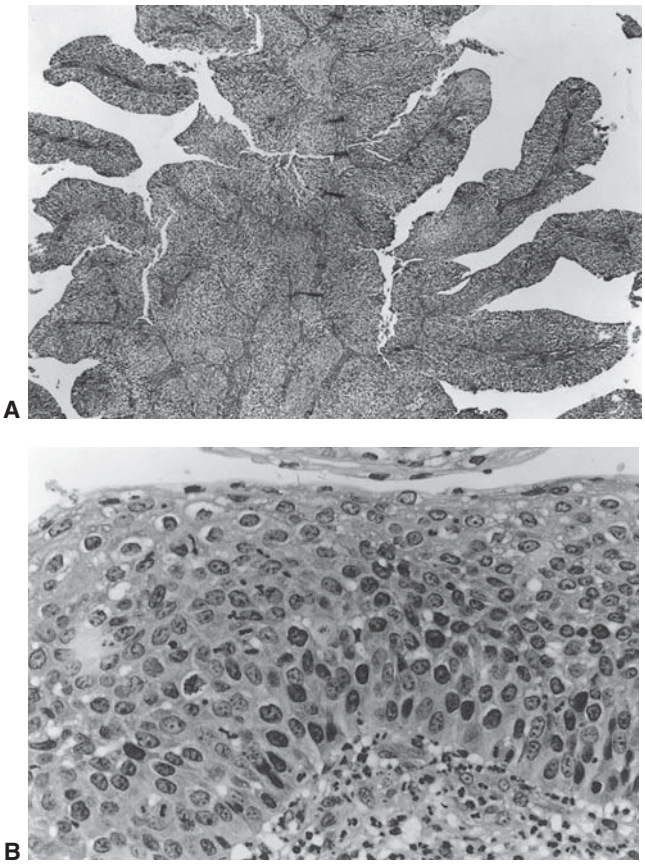



**FIGURE 1-16.** Papillary squamous cell carcinoma. **A:** Papillary epithelial neoplasm with fibrovascular cores devoid of surface keratinization. **B:** Higher magnification shows the presence of cytologically malignant epithelial cells.

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more likely as a promoter in the multistep process of carcinogenesis in squamous cells of the UADT.[223–225]

VC appear as tan or white, warty, fungating or exophytic, firm to hard masses of varying size measuring up to 9 to 10 cm in diameter. In general, the tumors are attached by a broad base. The histologic appearance of VC is that of a benign-appearing squamous cell proliferation requiring the following characteristics for diagnosis: (a) uniform cells without dysplastic features or mitoses; (b) marked surface (ortho)keratinization ("church-spire" keratosis); (c) broad or bulbous rete pegs with a pushing but not an infiltrative margin (Fig. 1-17). A mixed chronic inflammatory cell infiltrate composed of lymphocytes, plasma cells, and histiocytes may be prominent along the adjacent stroma. The pathologic diagnosis of VC may be extremely difficult, requiring multiple biopsies over several years prior to identification of diagnostic features supporting appropriate interpretation. Both clinicians and pathologists should be aware of this fact. To this end, adequate biopsy material is critical to interpretation and should include a good epithelial–stromal interface. The pathologist should not over interpret a verrucoid lesion as a carcinoma without seeing the relationship of the more superficial aspects of the lesion to the underlying stroma.

## Spindle Cell Squamous Carcinoma

Spindle cell squamous carcinoma (SCSC) is defined as a tumor composed of conventional SCC (*in situ* or invasive carcinoma) associated with a malignant spindle cell stromal component. Synonyms have included "sarcomatoid" carcinoma, carcinosarcoma, pleomorphic carcinoma, metaplastic carcinoma, collision tumor, pseudosarcoma, and Lane tumor. The preferred terminology is spindle cell squamous carcinoma.

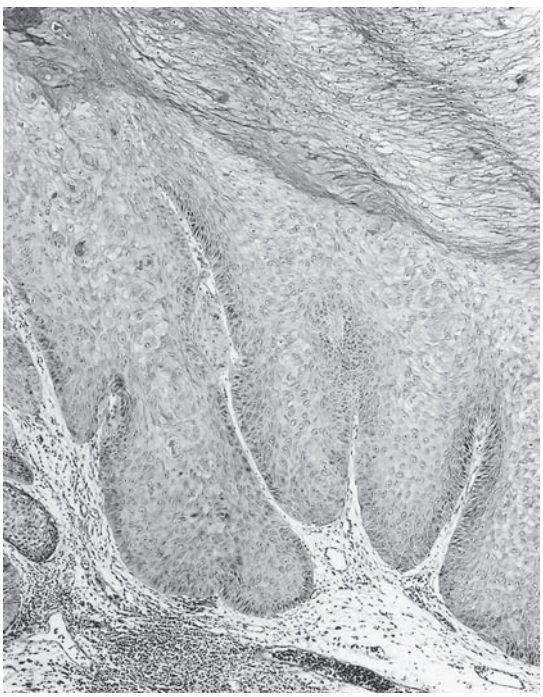


**FIGURE 1-17.** Verrucous carcinoma of the larynx characterized by an epithelial proliferation of uniform cells without dysplastic features or mitoses, marked surface keratinization, and broad or bulbous rete pegs pushing downward into the submucosa.

The overwhelming majority of SCSC occur in men (85%) most frequently in the sixth to eighth decades of life.[198] SCSC can occur anywhere in the UADT. The most common sites in descending order of occurrence include the larynx (true vocal cords > false vocal cords and supraglottis), the oral cavity (lips, tongue, gingiva, floor of mouth, buccal mucosa), the skin, the tonsil, and the pharynx. Symptoms vary according to site: larynx—hoarseness, voice changes, airway obstruction, dysphagia; oral cavity or skin—mass or nonhealing sore with or without pain; sinonasal tract and nasopharynx—airway obstruction, pain, epistaxis, discharge, facial deformity, unilateral otitis media, orbital symptoms. There is no specific correlation with known risk factors (alcohol, tobacco, or environment/occupation). SCSC has been reported in areas of prior irradiation.

SCSC is often a grossly polypoid or fungating mass commonly found in the larynx, the hypopharynx, the oral cavity, and the sinonasal tract. Variations in the gross appearance may correlate with the primary site of occurrence: larynx—polypoid or exophytic; sinonasal/nasopharynx—fungating and/or ulcerative. SCSC are firm, tan-white, gray or pink mass varying in size from 1 to 6 cm.

The histologic features that define SCSC include the identification of a malignant undifferentiated spindle cell proliferation and the presence of a conventional squamous cell component (Fig. 1-18). The latter includes either *in situ* squamous carcinoma or frankly invasive differentiated squamous carcinoma. The spindle cell component generally is the dominant cell type. The spindle cell proliferation is usually hypercellular and pleomorphic with large, hyperchromatic nuclei, prominent nucleoli, and many mitoses (typical and atypical). Necrosis is not uncommon. The spindle cell proliferation may be sparsely cellular (hypocellular) with marked stromal collagenization (so-called collagenized SCSC), but nuclear pleomorphism and mitotic figures are still present. The growth pattern varies and includes fascicular, storiform, or palisading; an associated myxomatous stroma may be present. Heterologous elements, including bone and cartilage, may be present and may even be malignant (chondrosarcomatous or osteosarcomatous foci).

The spindle cells are cytokeratin immunoreactive in the majority of cases,[227–231] but in up to 40% of cases may be cytokeratin negative.[229] Cytokeratin staining may vary from focal to diffuse. p63, a marker for squamous cells (as well as myoepithelial cells), may be a useful adjunct to cytokeratin staining in

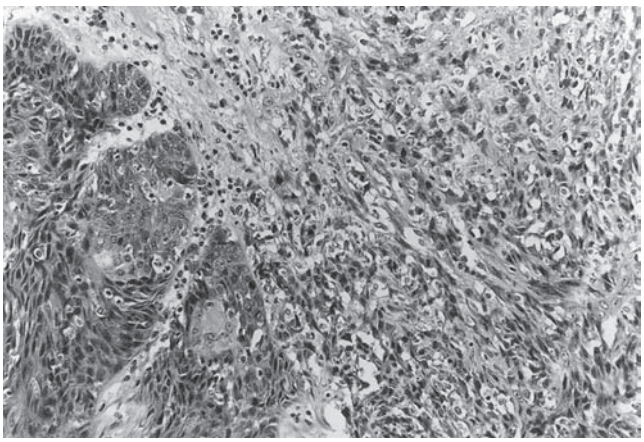


**FIGURE 1-18.** Laryngeal (glottic) spindle cell squamous cell carcinoma. The neoplastic infiltrate includes differentiated squamous cell carcinoma **(left)** intimately associated with a malignant spindle-shaped and pleomorphic cellular component.

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identifying the spindle cells as being of epithelial (ie, squamous cell) origin. Expression of vimentin and various myogenic markers (desmin, actins) have been reported.[229–232]

## Basaloid SCC

Basaloid squamous cell carcinoma (BSCC) is a high-grade variant of SCC with a predilection to the supraglottic larynx, the hypopharynx, the base of the tongue, and the palatine tonsil.[233,234] BSCC is histologically characterized by an invasive neoplasm composed of basaloid cells intimately associated with either a dysplastic squamous epithelium, *in situ* SCC, and/or invasive SCC.

BSCC occurs more commonly in men than in women and predominantly occurs in the sixth to seventh decades of life. These tumors have a predilection for the hypopharynx (pyriform sinus), the larynx (supraglottis), and the tongue. Symptoms depend on the site of occurrence and include hoarseness, dysphagia, pain, or a neck mass. Etiologic factors include excessive alcohol and/or tobacco use. The cell of origin has not definitively been identified, but in all probability is a single totipotential cell capable of divergent differentiation and located either in the basal cell layer of the surface epithelium or within seromucous glands. BSCC of nonoropharyngeal sites are typically not associated with human papillomavirus 16 (HPV16), but BSCC of the oropharynx (i.e., base of tongue and tonsil) are associated with HPV16 (see later).

Grossly, these tumors are described as firm to hard, tan-white mass often with associated central necrosis, measuring up to 6.0 cm in greatest dimension. Infrequently, they may be exophytic in appearance. Histologically, BSCC is often a deeply invasive neoplasm, although shallow biopsies may belie the depth and extent of invasion and may not be representative of the lesion leading to erroneous classification. BSCC is composed of basaloid cells with an associated squamous component and demonstrating a variety of growth patterns, including solid, lobular, cribriform, cords, trabeculae, and gland-like or cystic growth (Fig. 1-19). The basaloid cell component is the predominant cell type and consists of cells with pleomorphic, hyperchromatic nuclei, scanty cytoplasm, and increased mitotic activity (Fig. 1-19). Peripheral nuclear palisading may be present. Comedonecrosis is seen in the center of the neoplastic lobules. Intercellular deposition of a hyalin or mucohyalin material can be seen similar in appearance to the reduplicated basement membrane material that is seen in some salivary gland tumors. Infrequently, a spindle cell component may be identified and true neural-type rosettes may rarely be present.[235] The squamous component includes dysplastic squamous epithelium, foci of abrupt keratinization, *in situ* SCC, or invasive SCC. The squamous foci typically are a minor component (Fig. 1-19), may be focally present, and may be absent in biopsies. Continuity with the surface epithelium may be seen.

Immunoreactivity is consistently present with epithelial markers, including cytokeratins (AE1/3, 34$\beta$E12, CAM5.2), EMA, and

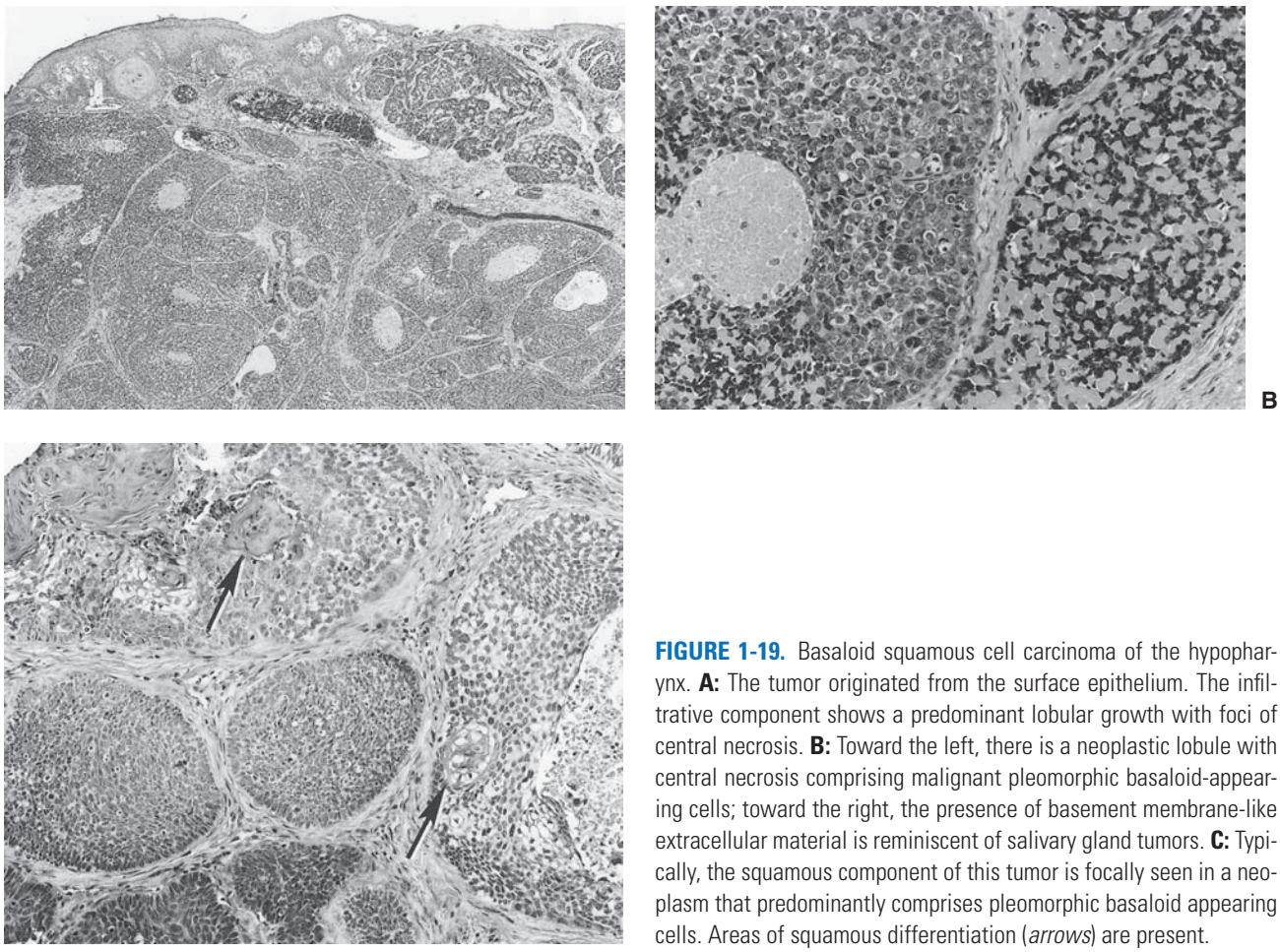



**FIGURE 1-19.** Basaloid squamous cell carcinoma of the hypopharynx. **A:** The tumor originated from the surface epithelium. The infiltrative component shows a predominant lobular growth with foci of central necrosis. **B:** Toward the left, there is a neoplastic lobule with central necrosis comprising malignant pleomorphic basaloid-appearing cells; toward the right, the presence of basement membrane-like extracellular material is reminiscent of salivary gland tumors. **C:** Typically, the squamous component of this tumor is focally seen in a neoplasm that predominantly comprises pleomorphic basaloid appearing cells. Areas of squamous differentiation (*arrows*) are present.

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CEA. Neuroendocrine markers (i.e., chromogranin and synaptophysin) are typically negative, but may rarely be present.[236]

## Sinonasal Undifferentiated Carcinoma

The original definition for SNUC was reported by Frierson et al.[237] as a high-grade malignant epithelial neoplasm of the nasal cavity and paranasal sinuses of uncertain histogenesis with or without neuroendocrine differentiation but without evidence of squamous or glandular differentiation. Subsequently, the WHO classification defines SNUC as a highly aggressive and clinicopathologically distinctive carcinoma of uncertain histogenesis that typically presents with locally extensive disease; it is composed of pleomorphic tumor cells with frequent necrosis and should be differentiated from lymphoepithelial (and other) carcinomas or olfactory neuroblastoma.[238]

There is a male predominance (2-3:1).[238,239] SNUCs occur over a wide age range, from the third to the ninth decades of life, with a median at presentation in the sixth decade.[237,239] Generally, SNUC are extensive at presentation and involve multiple sites, including the nasal cavity, one or more paranasal sinuses, the orbit, the skull base, and the brain.[237,240] Most patients have unilateral disease, but bilateral disease may occur. Typically, patients present with multiple symptoms that include nasal obstruction, epistaxis, proptosis, visual disturbances (e.g., diplopia), facial pain, and symptoms of cranial nerve involvement. A rather characteristic clinical phenomenon is that patients with SNUC develop symptoms usually of relatively short duration (weeks to months). Radiographic studies (CT scan, MRI) often demonstrate a large (sinonasal) mass typically with local invasive growth extending beyond its bony confines with involvement of orbital and/or cranial bones.[239] Intracranial extension may occur.

SNUC is a tumor of uncertain histogenesis. It seems likely that SNUC arises from the Schneiderian epithelium and, therefore, is of ectodermal derivation. However, although speculative, given overlapping clinical, light microscopic, immunohistochemical, and ultrastructural features with olfactory neuroblastoma and neuroendocrine carcinoma, the cell of origin may be related to both the Schneiderian membrane and the olfactory epithelia. On the basis of finding neuroendocrine features by immunohistochemistry and electron microscopy, Mills[241] suggested that SNUC may be a neuroendocrine carcinoma with classification essentially equivalent to the pulmonary large cell (neuroendocrine) carcinoma.

There are no known etiologic agents. SNUCs are typically negative for Epstein-Barr virus (EBV)[242,243] even though there are reports of EBV RNA identified in Asian and Italian patients with SNUC, but not in other Western patients with SNUC.[244,245] p16 immunoreactivity has been reported in SNUCs, suggesting a possible link to HPV, but in these cases HPV DNA was not detected.[246] Although no specific etiology is linked to the development of SNUC, cigarette smoking and nickel exposure have been identified in patients with SNUC.[247] Deletion of the retinoblastoma gene has been implicated in the development of SNUC.[247]

SNUCs are usually large tumors typically measuring >4 cm in greatest dimension and tend to be fungating with poorly defined margins and with invasion into adjacent structures and/or anatomic compartments, including bone destruction. The histologic appearance is characterized by a hypercellular proliferation with varied growth, including trabecular, sheet-like, ribbons, solid, lobular, and organoid patterns (Fig. 1-20). Surface involvement may be seen in the form of severe dysplasia/CIS, but often there is ulceration, which precludes evidence of surface epithelial derivation. The cellular infiltrate consists of polygonal cells composed of medium- to large-sized, round to oval, hyperchromatic to vesicular nuclei, inconspicuous to prominent nucleoli, and a varying amount of eosinophilic appearing cytoplasm with poorly defined cell membranes, although in some examples distinct cell borders may be present; occasionally, cells with clear cytoplasm can be identified. The nuclear-to-cytoplasmic ratio is high. Increased mitotic activity is present, including atypical mitoses, and there is often prominent tumor necrosis (confluent areas and individual cells) and apoptosis (Fig. 1-20). Lymph-vascular

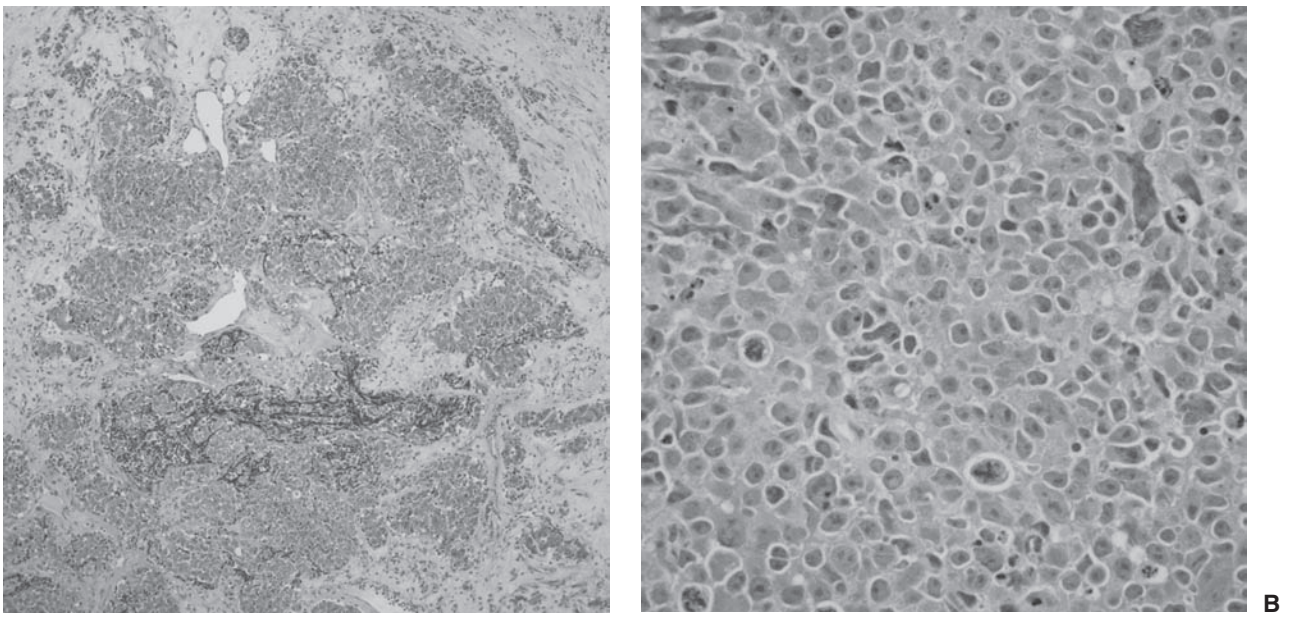



**FIGURE 1-20.** Sinonasal undifferentiated carcinoma. **A:** Hypercellular and infiltrative neoplasm showing trabecular and lobular growth. **B:** At higher magnification, the cellular infiltrate includes pleomorphic round to oval, hyperchromatic and pleomorphic nuclei, prominent nucleoli, increased mitotic activity, and individual cell necrosis. These tumors lack any evidence of cellular differentiation by light microscopy and are consistently immunoreactive (diffusely and intensely reactive) with cytokeratin (not shown).

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invasion and neurotropism are often present. Squamous or glandular differentiation is not present. Neurofibrillary material and true neural rosettes are not identified.

The immunohistochemical antigenic profile may vary from case to case, but SNUCs are consistently immunoreactive with epithelial markers, including pankeratins and simple keratins. Variable reactivity can be identified for p63.

## Viral-Related HNSCC

There is increasing evidence that HPV and EBV play a pathogenic role in a subset of head and neck squamous cell carcinomas (HNSCC). HPV, in particular the high-risk type 16 (HPV-16), is present in most oropharyngeal carcinomas (i.e., base of tongue, tonsils), and for those oropharyngeal cancers positive for high-risk HPV, HPV16 is detected in greater than 90% of cases.[248,249]

For NPCs, EBV is associated with the nonkeratinizing types of NPCs, including both differentiated and undifferentiated subtypes in practically 100% of cases irrespective of the ethnic background of the patient. The most reliable detection method for EBV is ISH for EBV-encoded early RNA (EBER) present in cells latently infected by EBV and can facilitate the diagnosis of NPC.

The viral-related HNSCCs may be termed HPV–head and neck squamous cell carcinoma (HPV-HNSCC) and EBV-associated head and neck squamous cell carcinoma (EBV-HNSCC). Such designations are not as yet universally accepted, but have merit given their unique clinical, pathologic, therapeutic, and prognostic implications associated with these cancers.

## Oropharyngeal Nonkeratinizing SCC (HPV-associated SCC)

Approximately 20% to 25% of SCCs of the UADT are related to HPV infection, and the incidence of HPV-associated HNSCC is rising.[248] In contrast, the incidence of HPV-unrelated HNSCC has stabilized or is decreasing with the decreasing use of tobacco products. The majority of HPV-associated SCC of the UADT occur in the oropharynx predominantly arising at the base of the tongue or palatine tonsil.[250] The propensity for HPV to infect the base of tongue and the tonsil might be due to greater accessibility of the virus to the basal and proliferating squamous cells in these locations possibly secondary to epithelial disruption.[251]

HPV-associated oropharyngeal SCC represents a unique subtype of HNSCC frequently occurring in patients with no known risk factors for HNSCC (i.e., nonsmokers and nondrinkers), in younger aged patients, and associated with a better outcome (better overall and disease-specific survival) than non-HPV-associated HNSCCs (Table 1.14). Further, these carcinomas are highly curable even in the presence of advanced disease. Symptoms associated with HPV-associated oropharyngeal SCC often relate to a mass. However, these cancers may be small and clinically/radiographically difficult to detect. Further, HPV-associated oropharyngeal SCC frequently develop early neck metastasis and may present as metastatic cancer to a cervical neck lymph node from an unknown primary site. PET/CT scan plays an important role in the imaging evaluation of these cancers, in particular in trying to localize/identify the primary oropharyngeal carcinoma.

The HPV-associated HNSCC are nonkeratinizing carcinomas characterized by basaloid cell morphology (Fig. 1-21). The carcinoma often grows in solid sheets, trabecula, cords, and nests, but individual infiltrative cells can be seen. These carcinomas are often cystic with central areas of necrosis and frequently metastasize as cystic metastatic carcinomas (Fig. 1-21). In the absence of a known primary carcinoma, such cystic neck masses may be considered branchial cleft cysts with malignant transformation, a diagnosis of questionable existence. The neoplastic cells include marked nuclear pleomorphism with increased mitotic activity, including atypical mitoses. Focal keratinization may present. Typically, the extent of keratinization is limited but in some cases more extensive keratinization may be present. Given their basaloid morphology including features of a histologic higher grade carcinoma, such carcinomas (whether on FNA or biopsy) have been erroneously designated as poorly differentiated. In fact, these nonkeratinizing carcinomas are considered better differentiated carcinomas recapitulating the crypt epithelium from which they may arise. It should be noted that the initial designation of these cancers as "basaloid"[253] may result in confusion with basaloid SCC, which is a high-grade variant of conventional SCC predilecting to the hypopharynx (i.e., piriform sinus) and the supraglottic larynx not associated with HPV (or EBV). The oropharyngeal nonkeratinizing carcinomas are often associated with a dense benign lymphocytic cell infiltrate. These cancers

**TABLE 1.14 Comparison between Human Papilloma Virus–Positive and Human Papilloma Virus–Negative Squamous Cell Carcinoma**

| | HPV-Positive SCC | HPV-Negative SCC |
|---|---|---|
| Age | Younger | Older |
| Gender | M = F | M > F |
| Race | Caucasian >>>> African American | Caucasian = African American |
| Risk factors (Tobacco/alcohol) | No known risk factors (usually nonsmokers, nondrinkers) | Associated with tobacco and/or alcohol use/abuse |
| Primary location | Oropharynx (base of tongue; tonsil) | All mucosal sites of the UADT |
| Histology | Nonkeratinizing carcinoma predominantly composed of basaloid cells | Keratinizing squamous cell carcinoma |
| p16 | Positive | Negative |
| Prognosis | Better disease-free and overall survival | Worse disease-free and overall survival |
| Tumor stage at presentation | Often higher (more nodal metastasis) | Often lower |

SCC, squamous cell carcinoma; HPV, human papillomavirus; UADT, upper aerodigestive tract.

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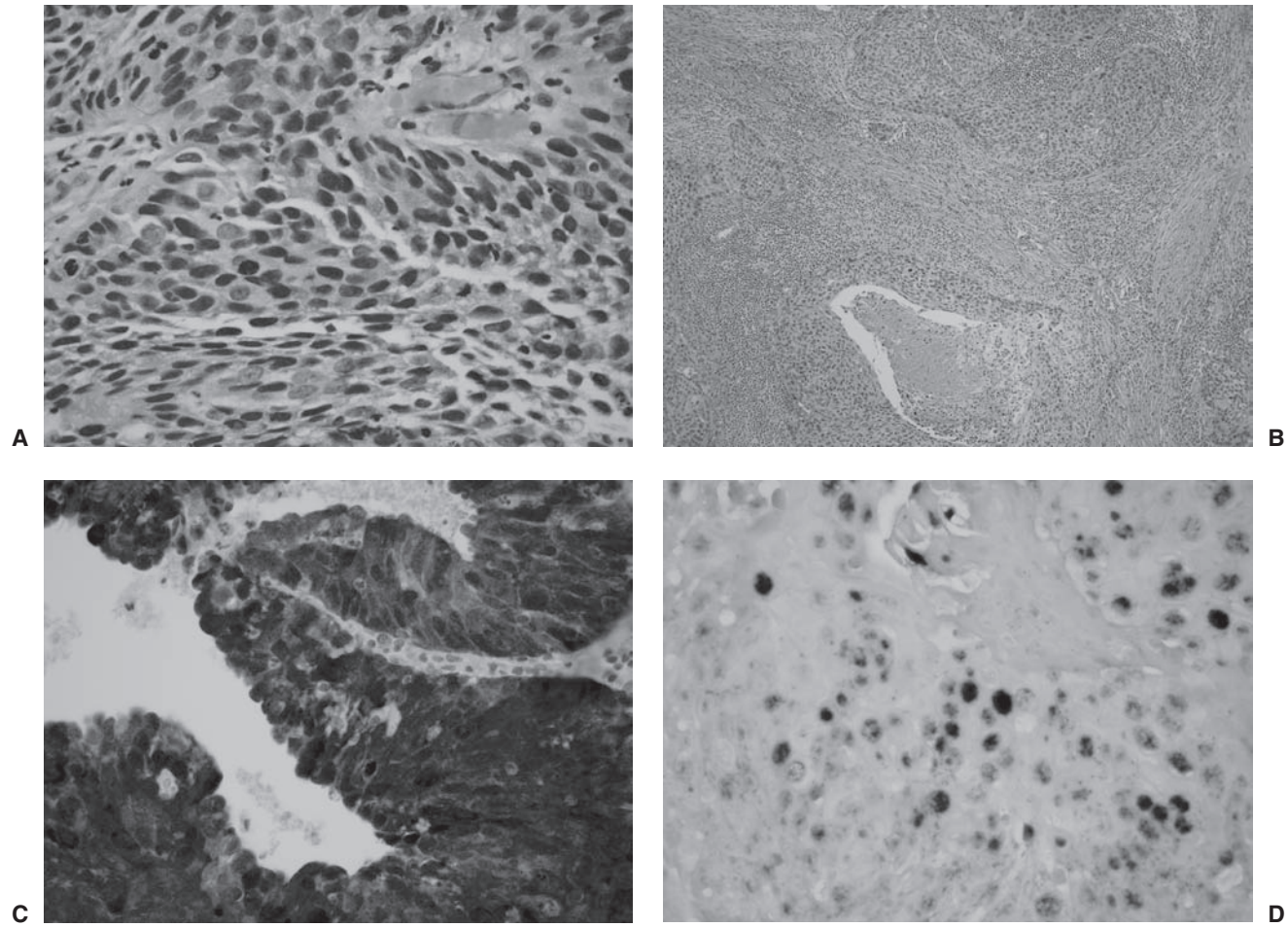



**FIGURE 1-21.** HPV-associated SCCs are predominantly/exclusively nonkeratinizing carcinomas characterized by: **A:** basaloid cell morphology; **B:** solid and solid growth central areas of necrosis; **C:** p16 immunoreactivity (nuclear and cytoplasmic); and **D:** HPV *in situ* hybridization.

may invade without associated desmoplasia and, as such, the neoplastic cells may be obscured by the associated lymphocytic cell infiltrate. Oropharyngeal HPV-associated SCCs may include papillary growth. Alternatively, these carcinomas may show growth patterns and cytomorphologic characteristics similar to nasopharyngeal nonkeratinizing carcinoma undifferentiated type carcinoma including syncytial growth and cells with enlarged vesicular nuclei and prominent nucleoli.[255] Although this morphology overlaps with the EBV-associated NPCs, this subset of oropharyngeal carcinomas are associated with HPV rather than EBV.[255]

The neoplastic cells of oropharyngeal nonkeratinizing carcinomas are immunoreactive for cytokeratins, including AE1/AE3, CAM5.2, and CK5/6. Such cytokeratin immunoreactivity may be extremely helpful in identifying the malignant cells in the presence of obscuring benign lymphoid infiltrate. Oropharyngeal nonkeratinizing carcinomas are positive for HPV16 and the presence of HPV16 represents a reliable predictor of origin from the oropharynx.[256] At present, there is no standard assay for HPV detection. Detection methods include immunohistochemical staining of surrogate biomarkers (i.e., p16 protein) (Fig. 1-21), DNA ISH (Fig. 1-21), and PCR-based (consensus and type-specific; real-time assays to quantify viral load). The presence of p16 immunostaining correlates with the presence of HPV16. The reactivity pattern for p16 includes nuclear and cytoplasmic staining and is usually diffuse and strongly reactive. P16 IHC can be performed on aspiration material and on tissue sampling.[256,257] In a comparison of detection methods, Singhi and Westra found that in comparison to PCR-based methods, ISH is more practical and they recommended combined IHC and ISH testing.[258] Using the combined strengths of HPV ISH and p16 IHC, these authors reported that (a) given the sensitivity approaching 100%, negative p16 staining serves to identify HPV-16 negative cases that would not benefit from additional analysis; (b) given specificity approaching 100%, positive HPV-16 ISH reduces number of false-positive cases by p16 staining alone; (c) p16+/HPV-16 singles out a subset of tumors requiring more rigorous analysis for other HPV types (consensus hybridization probe) and detects extended panel of HPV types. Using a combined approach including IHC and ISH, Singhi and Westra found HPV detected in a remarkably high percentage of oropharyngeal SCC (82%), which was greater than reported prevalence ranging from 19% to 72%.[258]

Guidelines for p16 and/or HPV testing in head and neck carcinomas may include the following:

- In an oropharyngeal biopsy showing atypical basaloid cells, the presence of p16 confirms the diagnosis of HPV-associated HNSCC;

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**TABLE 1.15 World Health Organization (WHO) Classification of Nasopharyngeal Carcinoma**

| |
|---|
| WHO Type I |
| Keratinizing squamous cell carcinoma |
| WHO Type II |
| Nonkeratinizing differentiated |
| Nonkeratinizing undifferentiated |
| Basaloid squamous cell carcinoma |

- In tumors with overlapping morphology (e.g., basaloid SCC), the presence of p16 helps confirm the diagnosis of HPV-associated HNSCC;
- In the presence of cervical nodal metastatic disease p16 staining would confirm the diagnosis of metastatic cystic SCC, localize the primary site of origin (i.e., oropharynx), and establish the tumor classification.

HPV-associated HNSCC have unique therapeutic and prognostic parameters. HPV-HNSCC are radioresponsive tumors associated with a better outcome (better overall and disease-specific survival) and are highly curable even in the presence of advanced disease.[259,260] Factors that may be in play relative to their better outcome include the possibility of absence of field cancerization and presence of enhanced radiation sensitivity.

## Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma (NPC) is a SCC arising from the surface epithelium and subtyped according to the World Health Organization (WHO) into two histologic variants: keratinizing and nonkeratinizing (Tables 1.15 and 1.16).[261] The nonkeratinizing type is further subdivided as being "differentiated" and "undifferentiated." The current WHO classification retains the terminology of the 1991 classification and adds the category of basaloid SCC to this classification.[262] NPC, by definition, takes origin from the nasopharyngeal mucosa and shows evidence of squamous differentiation by light microscopy, immunohistochemistry, or electron microscopy. Therefore, the use of this term is to the exclusion of all other malignant tumors that may arise in this region, including adenocarcinomas (minor salivary gland origin and nonsalivary gland origin). Synonyms for NPC include lymphoepithelioma, Rigaud and Schmincke types of lymphoepithelioma, and transitional carcinoma. The designation *lymphoepithelioma* is a misnomer. This is a tumor entirely of epithelial origin with a secondary associated benign lymphoid component. Use of the term lymphoepithelioma may result in confusion with a diagnosis of malignant lymphoma. The prior numerical designations of WHO types 1 (SCC), 2 (nonkeratinizing carcinoma), and 3 (undifferentiated carcinoma) are no longer used. It should be noted that, although they share the unfortunate designation of "undifferentiated," there is no relationship between the sinonasal undifferentiated carcinoma (see subsequent text) and the nasopharyngeal undifferentiated carcinoma. These tumors are anatomically distinct with differing therapeutic approaches and biologic outcome. The terms should not be used synonymously, nor should the tumors be confused clinically and pathologically. Basaloid SCC also occurs in the nasopharynx, representing another histologic subtype of NPC.[262]

Overall, NPC is an uncommon neoplasm in the United States, accounting for approximately 0.25% of all cancers.[263,264] In China, it accounts for 18% of all cancers,[265] and 1 in 40 men develop NPC before the age of 72.[266] NPC affects men more than women and occurs over a wide age range, but is most common in the fourth to sixth decades of life. Less than 20% of cases occur in pediatric age groups. Pediatric NPC is most common in northern and central Africa, accounting for 10% to 20% of all cases, whereas only approximately 2% of NPC in China occur in children.[267–270] Irrespective of the histologic type, the clinical presentation is similar and includes the presence of an asymptomatic cervical neck mass typically localized to the posterior cervical triangle or the superior jugular nodal chain, with additional clinical signs and symptoms that include nasal obstruction, nasal

**TABLE 1.16 Nasopharyngeal Carcinoma**

| | Keratinizing Squamous Cell Carcinoma | Nonkeratinizing, Differentiated Type | Nonkeratinizing, Undifferentiated Type |
|---|---|---|---|
| Percentage | Approximately 25% | Least common <15% | Most common >60% |
| Sex/age | M > F; 4th–6th decades | M > F; 4th–6th decades | M > F; 4th–6th decades; may occur in children |
| Histology | Keratinization, intercellular bridges; conventional squamous carcinoma graded as well, moderately, or poorly differentiated; desmoplastic response to invasion | Little to absent keratinization, growth pattern interconnecting cords (similar to transitional urothelial carcinoma); typically, limited to absent desmoplastic response to invasion | Absence of keratinization, syncytial growth, cohesive or noncohesive cells with round nuclei, prominent eosinophilic nucleoli, scant cytoplasm and limited mitoses; prominent nonneoplastic lymphoid component; typically, absence of desmoplastic response to invasion |
| EBV | Weak association | Strong association | Strong association |
| Treatment | Radio-responsiveness is not good | Radioresponsive | Radioresponsive |
| Prognosis | 20%–40% 5-y survival | 65% 5-y survival | 65% 5-y survival |

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discharge, epistaxis, pain, serous otitis media, otalgia, hearing loss, and headache.[271] The signs and symptoms are often subtle and nonspecific, and thereby may cause a delay in the diagnosis, often resulting in clinical presentation at an advanced stage of disease. Up to 25% of patients may experience cranial nerve involvement.[272] The lateral wall of the nasopharynx (fossa of Rosenmüller) is the most common site of occurrence followed by the superior posterior wall.[270]

Multiple interactive etiologic factors have been linked to the development of NPC. Genetic and geographic factors play an important role in the genesis of NPC. There is an increased incidence of NPC in China, especially in southern (Kwantung province) and northern provinces and Taiwan.[265] Although the incidence among Chinese people decreases after emigration to low-incidence areas, it still remains higher than in non-Chinese populations.[265,273]

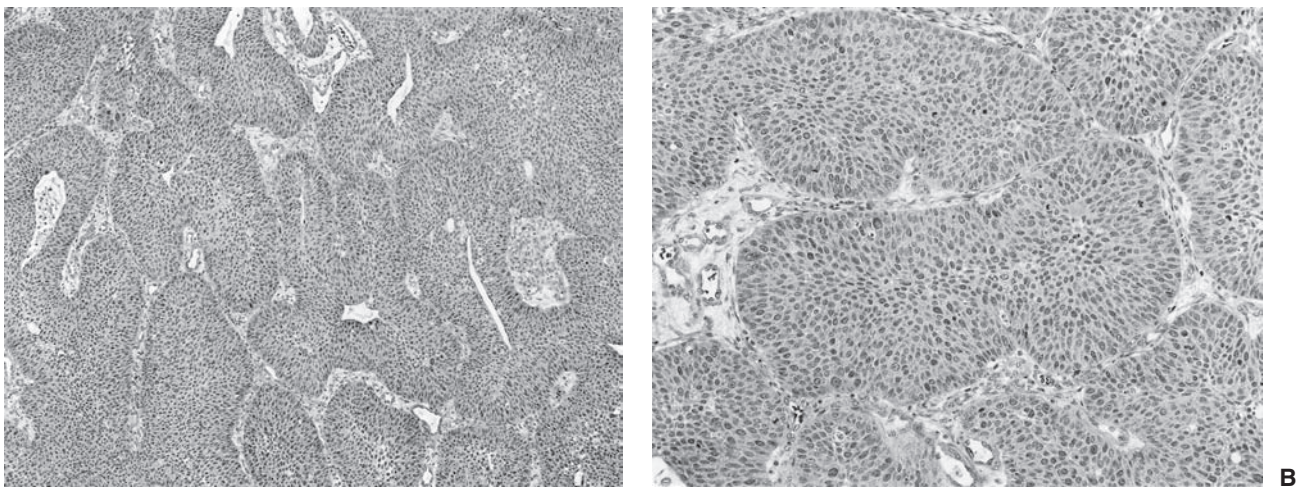
Perhaps the most important link to the development of NPC is the EBV.[265,274,275] There is a strong association between certain NPCs and the presence of EBV, indicating a probable oncogenic role of EBV in the development of NPC.[275] Both the nonkeratinizing and undifferentiated types of nasopharyngeal squamous carcinoma are linked with the presence of EBV DNA. Molecular biologic analysis of NPC by either ISH for EBER or PCR detects EBV DNA or RNA in 75% to 100% of NPC.[276,277] This is not true of the keratinizing subtype, in which the detection of EBV genomes is variable and, if present, is generally limited to scattered dysplastic intraepithelial cells.

Three histologic types are recognized based on the predominant appearance.[278] The keratinizing conventional squamous carcinoma is characterized by the presence of keratinization and intercellular bridges and graded as well, moderately, or poorly differentiated. A desmoplastic response is typically found in response to invasive growth by this histologic type of NPC. The keratinizing NPC represents approximately 25% of all NPC and rarely occurs in patients below 40 years of age.[279]

The nonkeratinizing carcinomas show little to no keratinization and have a growth pattern similar to transitional cell carcinoma of the bladder, including stratified cells with sharp delineation from the surrounding stroma (Fig. 1-22). Well-defined cell borders and vague intercellular bridges may be present; rarely, an occasional keratinized cell may be identified. Typically, there is an absence of a desmoplastic response to invasive growth. These tumors may undergo cyst formation with associated necrosis and may metastasize as such to the cervical neck region. Further, the primary carcinomatous focus may be small and lie within the submucosa (e.g., in crypt epithelium) with an overlying intact, nondescript surface epithelium representing an occult primary carcinoma. This type of NPC is the least common, representing approximately 12% of all NPC.[279]

The undifferentiated type of NPC represents approximately 60% of all NPC[279] and is the most frequent tumor type seen in pediatric age groups.[268] The neoplastic cells are characterized by the presence of round nuclei, prominent eosinophilic nucleoli, dispersed nuclear chromatin, and scant eosinophilic to amphophilic cytoplasm (Fig. 1-23). Keratinization is absent. Increased mitoses, including atypical forms, are present. A prominent nonneoplastic lymphoid component composed of mature lymphocytes and plasma cells is seen in association with the malignant epithelial cellular infiltrate, although in any given example there may be a relative absence of an associated lymphoplasmacytic cell infiltrate. This tumor type may have a syncytial growth with cohesive or nested cells or has a diffuse cellular infiltrate composed of noncohesive cells. The diffuse pattern is the one that is difficult to differentiate from a malignant lymphoma by light microscopy (Fig. 1-23). The Regaud and Schmincke types of NPC refer to those neoplasms with a syncytial versus individual cell growth pattern, respectively. These designations and their correlated growth have no bearing on the biology of the disease. The infiltrative growth of this tumor generally does not produce a host desmoplastic response. This may be problematic in biopsy samples as the tumor may be overrun by the benign lymphohistiocytic cell infiltrate and thus is easily overlooked. Similarly, metastasis to cervical lymph nodes may not elicit a desmoplastic response in the involved lymph node.

Since the distinction between the nonkeratizing differentiated and the nonkeratinizing undifferentiated is of no clinical or prognostic significance, subclassification into differentiated and undifferentiated subtypes is optional.[262] Shanmugaratnam et al.[280] reported that in their study, 26% of the NPC had features of more than one tumor type. In such a situation, classification is according to the dominant component. It should be noted that the histologic distinction among the three types of NPC may not always be clear, with overlapping histology in any given tumor.



**A** **B**

**FIGURE 1-22.** Nasopharyngeal nonkeratinizing carcinoma, differentiated type. **A:** The neoplasm invades in broad anastomosing cords and trabeculae. **B:** The neoplastic cells have pleomorphic nuclei with increased mitotic activity lacking keratinization.

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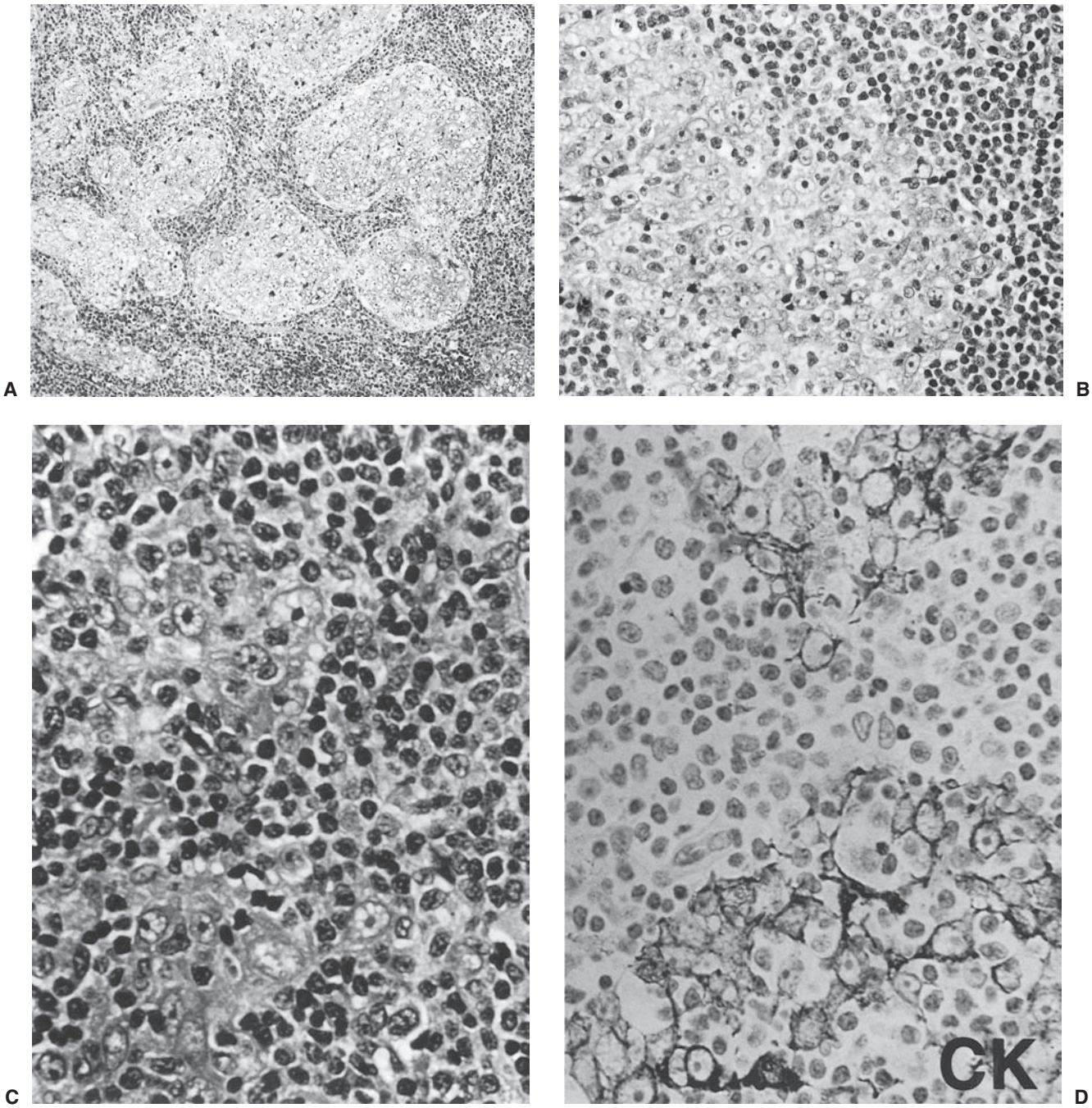
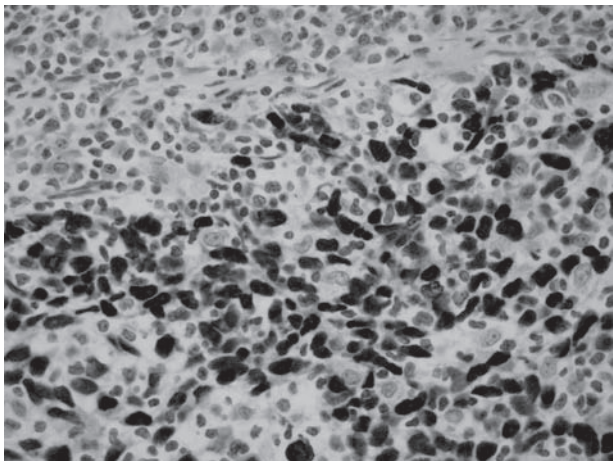



**FIGURE 1-23.** Nasopharyngeal nonkeratinizing carcinoma, undifferentiated type. **A:** Tumor nests are readily apparent and are clearly delineated from surrounding nonneoplastic lymphocytic cell infiltrate. **B:** The neoplastic cells are characterized by the presence of enlarged round nuclei, vesicular chromatin, prominent eosinophilic nucleoli, and scant eosinophilic to amphophilic cytoplasm. A nonneoplastic lymphoid component is present. **C:** The carcinoma may show a diffuse (noncohesive) growth and raise suspicion for a diffuse large cell B-cell lymphoma. **D:** Irrespective of the growth characteristics, the neoplastic cells are cytokeratin positive and **E:** consistently positive for EBER.

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E

**FIGURE 1-23.** *Continued*

All three histologic types of NPC are immunoreactive with cytokeratin, including pan-cytokeratins and high-molecular-weight cytokeratins; weak immunoreactivity is present for low-molecular-weight cytokeratins (Fig. 1-23). The nonkeratinizing carcinomas, differentiated and undifferentiated, are highly associated with EBV as detected by ISH for EBER (Fig. 1-23).

## Metastatic Cervical Carcinoma to the Neck with an Unknown Primary

MCCUP is the histologic diagnosis of metastatic carcinoma without a diagnosis of a primary tumor.[281] Aside from oropharynx and nasopharynx, metastatic SCC to neck lymph nodes may originate from any mucosal site in head and neck. MCCUP is most frequently diagnosed between the fifth and seventh decades with a peak incidence in the sixth decade of life.[282] However, HPV-associated MCCUP occurs in younger patients than does non-HPV-associated SCC. MCCUP can present anywhere within the neck, but the jugulodigastric lymph node group is the most common location. Specifically, level II is most commonly followed by levels I and III.[282] An isolated nodal mass in the submental triangle is rarely carcinoma. Patients typically present with a painless neck mass that has enlarged over recent months. The mass is often fixed and usually present for <6 months in duration. MCCUP may be bilateral enlargement in 10% of patients.

Once a metastasis is diagnosed, the primary carcinoma can be sought and the workup attempting to find the primary carcinoma. Approximately 30% of patients never have the primary carcinoma identified.[282] About 30% of patients with metastatic SCC show exclusively cystic metastases. It should be noted that a primary carcinoma in the tonsil or the base of the tongue may be very small (<0.1 cm), making detection difficult. Further, there is no correlation with the size of the primary carcinoma, which may be very small (1–2 mm), and the metastasis, which may be large (>1 cm).

The histologic features for metastatic keratinizing SCC include the presence of keratinization in the majority of carcinoma. The histologic grades include well, moderately, and poorly differentiated. In poorly differentiated SCC, evidence of keratinization may be minimal. This type of carcinoma is typically associated with desmoplastic tissue response. The pattern of carcinoma and presence of desmoplasia contrast with features seen in nonkeratinizing and undifferentiated SCC.

Metastatic nonkeratinizing SCC often appears as cystic metastasis with central necrotic material (Fig. 1-24). The carcinoma shows ribbon-like or band-like, uniformly thick epithelium lining cystic spaces, frequently thrown into papillary folds or projections. An endophytic pattern can be seen with budding into lymphoid stroma. There is an absence of maturation toward the cyst lumen with a loss of cellular polarity, disorganization, and enlarged cells showing a high nuclear to cytoplasmic ratio. Significant nuclear pleomorphism focally or diffusely can be found. Limited keratinization may be present, and the presence of keratinization does not exclude a diagnosis of nonkeratinizing SCC. Transitional-like epithelium with limited atypia may be present, showing remarkably bland-appearing epithelium. Such benign-appearing epithelium suggests a possible diagnosis of a branchial cleft cyst.

Metastatic undifferentiated carcinoma may appear as cystic metastasis with central necrotic material. Syncytial growth in the form of cohesive nests can be identified. The neoplastic cells are characterized by enlarged nuclei with vesicular chromatin and prominent nucleoli. Limited keratinization may be present, and the presence of keratinization does not exclude diagnosis of undifferentiated carcinoma. A desmoplastic response may be absent, and the neoplastic cells may be overrun and obscured by benign lymphocytes.

The immunohistochemical staining of these carcinomas include consistent positive reactivity for cytokeratins as well as p63 (nuclear) staining. HPV-associated SCCs are p16 positive (nuclear and cytoplasmic staining) (Fig. 1-24). P16 immunoreactivity represents a reliable predictor of origin from the oropharynx (i.e., tonsil, base of tongue). P16 immunostaining can be performed on cytologic and/or surgical resection material.[256,257] Oropharyngeal carcinomas with morphology of nasopharyngeal-type undifferentiated carcinoma may be p16-positive and EBER negative.[255] Such carcinomas may metastasize as MCCUP so workup should include both p16 and EBER staining. EBV-associated SCC are EBER-positive (nuclear staining) and p16 negative.

Controversy exists between the diagnosis of metastatic cystic SCC versus a carcinoma arising in a branchial cleft cyst (branchiogenic carcinoma). Martin et al.[283] established the criteria for the diagnosis of a branchiogenic carcinoma, including the following: (a) the metastatic tumor occurs along the line extending from a point anterior to the tragus along the anterior border of the sternocleidomastoid muscle to the clavicle; (b) the histology supports origin from a branchial cleft-derived structure; (c) the histology supports carcinoma arising in the wall of an epithelium-lined cyst; (d) a minimum of 5-year follow-up demonstrates no evidence of a primary source for this neoplasm. Despite the fulfillment of these criteria, it is highly unlikely that carcinoma arises in a branchial cleft cyst.[284–286] Rather, all these cystic nodal lesions represent metastatic SCC most often originating from a primary tumor in the oropharynx (i.e., Waldeyer tonsillar ring).[286] The primary oropharyngeal carcinoma may be so small as to defy clinical detection, but nevertheless is capable of metastasizing. It should be noted that unlike oropharyngeal carcinomas, branchial cleft cysts have been p16 negative in a limited number of cases evaluated to date.[287] The histology of branchial cleft cysts includes the presence of benign epithelium lining cystic spaces, usually showing intimate admixture of epithelium with stroma. Maturation is noted without atypia or mitotic figures. Branchial cleft cysts lack associated desmoplasia or thickened fibrous capsule and are typically p16 and EBER negative.[250,287] The existence of primary branchiogenic carcinoma has sufficiently been challenged as to render it nonexistent.

# SALIVARY GLAND MALIGNANT NEOPLASMS

The classification of malignant salivary gland tumors is listed in Table 1.10. A discussion of the full spectrum of malignant salivary gland tumors is beyond the scope of this chapter. A select group of malignant salivary gland tumors will be discussed.

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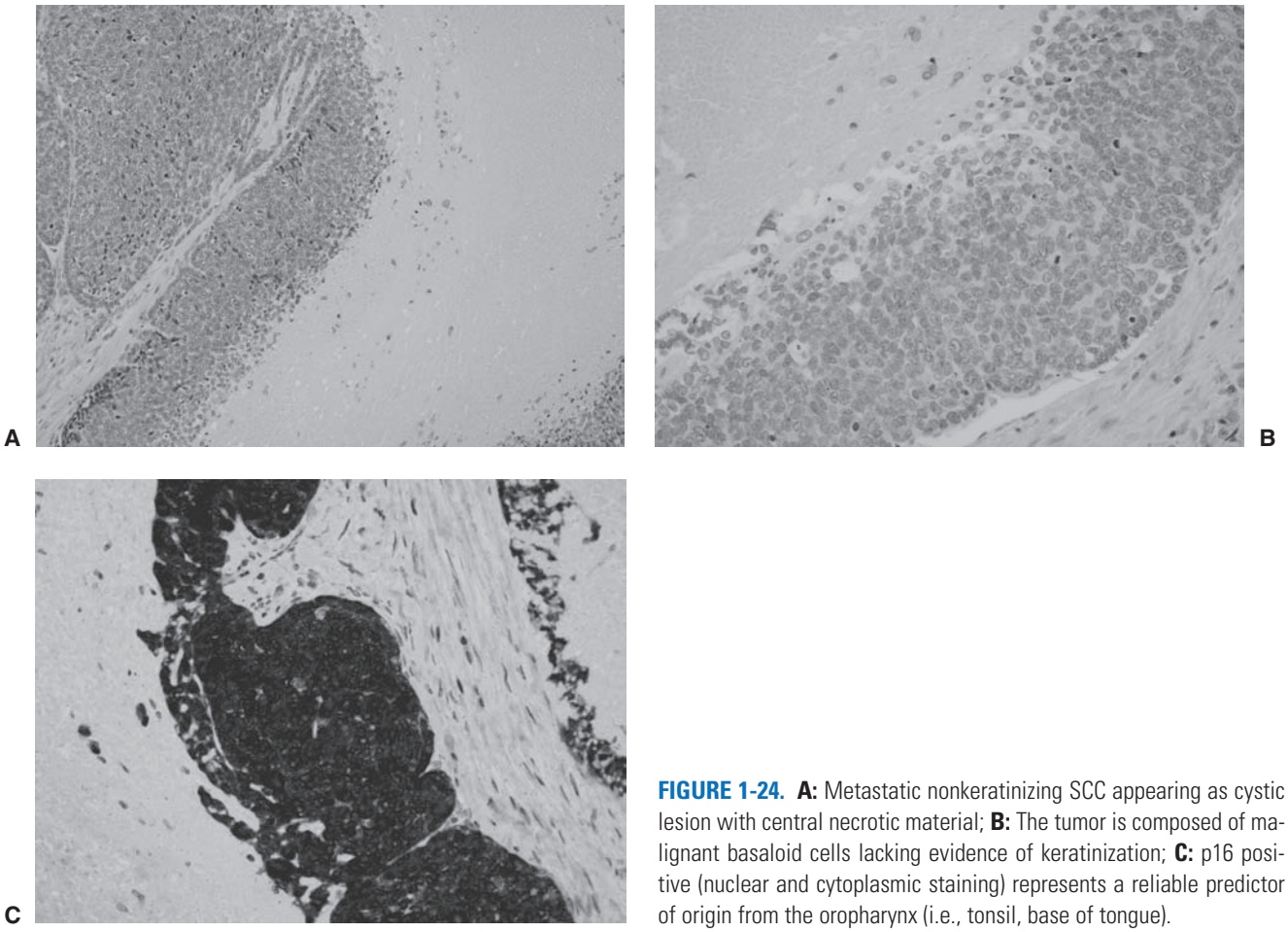


**FIGURE 1-24.** **A:** Metastatic nonkeratinizing SCC appearing as cystic lesion with central necrotic material; **B:** The tumor is composed of malignant basaloid cells lacking evidence of keratinization; **C:** p16 positive (nuclear and cytoplasmic staining) represents a reliable predictor of origin from the oropharynx (i.e., tonsil, base of tongue).

## Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma (MEC) is a malignant epithelial salivary gland neoplasm composed of a variable admixture of epidermoid, mucous, and other types of cells, including intermediate, columnar, and clear cells. MEC is the most common malignant salivary gland tumor and is second to pleomorphic adenoma as the most frequently occurring neoplasm among all salivary gland tumors. MEC represents approximately 30% of all malignant salivary gland tumors of both major and minor salivary glands and approximately 10% to 15% of all salivary gland neoplasms.[288,289] In the pediatric age group, MEC represents the most common malignant salivary gland neoplasm. MEC occurs in both the major and the minor salivary glands. Among the major glands, MEC is most common in the parotid gland; the most common minor salivary gland involvement occurs in the palate. MEC are uncommon primary tumors of the sinonasal tract and nasopharynx.

Grossly, MEC are unencapsulated or incompletely encapsulated, round to oval, predominantly solid, tan-white to pink mass measuring from <1 up to 12 cm in greatest dimension. Cysts of variable size and prominence can be seen on sectioning of the tumor. The basis for histologic grading of MEC into low, intermediate, and high categories is dependent on the architectural growth pattern, the cellular components, and the cytomorphology in a given tumor (see below). The characteristic histologic features for all grades of MEC include the presence mucous cells, epidermoid cells, and intermediate cells. The mucous cells are identified lining cystic spaces or admixed within nests or solid areas with epidermoid cells, and are large or balloon-shaped with distinct cell borders composed of pale-staining or foamy appearing cytoplasm with peripherally placed, small, dark-staining nuclei. The epidermoid cells form nests and/or solid areas in conjunction with the mucous cells, have a pavement-like arrangement, and are polygonal-shaped with vesicular nuclei and abundant eosinophilic cytoplasm. Individual cell keratinization may be seen; however, keratin (squamous) pearls, extensive keratinization, and intercellular bridges do not predominate. The absence of keratin (squamous) pearls, extensive keratinization, and intercellular bridges assists in separating MEC from such tumors as adenosquamous carcinoma. Extracellular mucous pools or "cysts" may be seen, which may infiltrate adjacent salivary gland and/or connective tissue. The intermediate cells are round to oval, contain small, dark-staining nuclei, and have scanty, eosinophilic cytoplasm. Cellular pleomorphism, mitoses, necrosis, and hemorrhage are generally absent. A variable degree of local invasion may be seen; however, NI is not normally a component of the low-grade MEC. Clear cells composed of round to oval cells with distinct cell borders, peripherally placed, small, dark nuclei and their hallmark clear cytoplasm may be seen and infrequently may predominate.

The microscopic grading of MEC remains a debatable subject. Suggested criteria for the histologic grading of MEC have included (single or in combination) the proportion of the tumor

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composed of cystic spaces relative to solid growth, proportion of cell types, degree of maturation of cell types, mitotic rate, extent of invasiveness, including pattern of invasion, neurotropism and vascular space invasion, and the presence of necrosis.[290]

Brandwein et al.[291] devised an alternative grading scheme that included an intracystic component less than 25%, tumor front invades in small nests and islands, pronounced nuclear atypia, lymph-vascular invasion, bony invasion, 4 or more mitoses, perineural invasion, and necrosis assigning numerical values for each feature. In a retrospective study, Auclair et al.[290] analyzed the grading criteria for 143 minor salivary gland MEC. These authors found that the most useful features for histologic grading, particularly in predicting high-grade tumors, were an intracystic component of <20% (predominantly solid growth), 4 or more mitotic figures per 10 high-power fields, cellular anaplasia, necrosis, and NI.[290] The low-grade tumors had numerous cystic spaces formed by a variety of cell types with rare mitoses and bland cytomorphology. The intermediate grade tumors had cellular anaplasia, with either cystic spaces comprising <20% of the tumor or NI.[290] The percentage of cell types did not correlate with behavior. Auclair et al.[290] suggested a quantitative grading system based on the specific histologic features such that tumors with a total point score of 0 to 4 were considered low grade, 5 to 6 were intermediate grade, and 7 or more were high grade. The results of their published study as well as an ongoing study of major salivary glands[289] show that microscopic grade was influential in prognosis. Combining the results of their research, Ellis and Auclair[289] report that of 305 patients with low-grade MEC of major and minor salivary gland, 10 (3.3%) died of disease; of 31 patients with intermediate-grade MEC, 3 (9.7%) died of tumor; and of 41 patients with high-grade MEC, 9 (46.4%) died of tumor. It is noteworthy that the grade of MEC in the submandibular gland is not felt to be as reliable a predictor of behavior as compared to other salivary gland sites[292]; Ellis and Auclair[289] report that metastatic disease or patient death occurred in 6 of 23 patients (26%) with low-grade MEC of submandibular gland origin.

Histochemical studies demonstrate the presence of intracytoplasmic mucin (diastase-resistant, PAS-positive, and mucicarmine positivity) in the mucous cells. The epidermoid cells may be faintly PAS positive but are mucicarmine negative. The intermediate cells and clear cells show no staining with either PAS or mucicarmine. The immunohistochemical staining includes cytokeratin, epithelial membrane antigen (EMA), and p63 positivity but S-100 protein, glial fibrillary acidic protein (GFAP), and muscle-specific actin and carcinoembryonic antigen (CEA) are at best variably positive and more often negative.

Recently, the MECT1/MAML2 translocation has been identified in a large proportion of MECs of the salivary gland.[293] MECT1/MAML2 has emerged as a favorable prognosticator. MECT1/MAML2 translocation is present in 66% of MECs and is negative in 100% of non-MEC and is negative for translocation. Low- to intermediate-grade MEC have a higher frequency of translocation (75%) than high-grade MEC (46%) ($p = 0.039$). Translocation-positive cases have a better disease-specific survival (log rank $p = 0.026$), although 2 patients still died of disease. Within high-grade MEC, MECT1/MAML2 positive tumors had lower rates of anaplasia ($p = 0.001$) and mitotic counts ($p = 0.012$). MECT1/MAML2 translocation is considered highly specific for MEC and imparts a better prognosis. This translocation is frequent even within high-grade MEC (seen in lethal cases, suggesting that translocation status should not supersede conventional parameters). Two distinct subgroups within high-grade MEC have been identified, including translocation-positive tumors and translocation-negative tumors, and the latter may actually be more appropriately categorized as another tumor type (e.g., adenosquamous carcinoma).

## Acinic Cell Adenocarcinoma

Acinic cell adenocarcinoma (ACA) is a low-grade malignant epithelial salivary gland neoplasm characterized by a variety of histologic growth patterns and the tendency for at least some of the neoplastic cells to recapitulate the appearance of normal serous acinous cells characterized by the presence of cytoplasmic (zymogen type) secretory granules. In the Armed Forces Institute of Pathology (AFIP) experience, ACA represents approximately 18% of all primary malignant salivary gland neoplasms and 6.5% of all salivary gland neoplasms.[294] In the pediatric age group, ACA represents the second most common malignant salivary gland neoplasm next to MEC, representing 12% of all cases of ACA in the AFIP files.[294] Given the fact that the parotid gland is entirely composed of serous-type acini, the most common site of occurrence is the parotid gland, in which >80% of all cases are found.[294] ACA may also be identified in the submandibular in up to 4% of cases. The remaining sites of occurrence include intraoral minor salivary glands and, less frequently, in minor salivary glands in other sites of the upper respiratory tract. Sublingual gland involvement is rare.

ACA are well-demarcated and/or encapsulated tumors, round or multilobulated, soft to rubbery, tan-gray to yellow or pink mass usually measuring <3.0 cm in greatest diameter, but occasionally may reach sizes up to 13 cm. Most neoplasms have a homogeneous appearance but may be cystic and hemorrhagic. Recurrent neoplasms are less well demarcated and tend to be multinodular in appearance. Histologically, ACA are circumscribed tumors characterized by a variety of growth patterns, including solid, microcystic, papillary-cystic, and follicular. The solid and microcystic type is the most common pattern consisting of either sheets of tumor cells in an organoid arrangement or numerous small cystic spaces. The papillary-cystic and follicular are the least common patterns consisting of variable-sized cystic spaces associated with papillary projections supported by a fibrovascular core or follicular spaces resembling thyroid parenchyma containing eosinophilic proteinaceous material lined by cuboidal to columnar cells. ACA are also noteworthy for their cytologic variations, including acinar, intercalated ductal, vacuolated, clear, and nonspecific glandular. Acinic cells are characterized by a polyhedral shape with small, dark, eccentrically placed nuclei and abundant basophilic granular cytoplasm characteristic of serous acinar cell differentiation. This production of cytoplasmic zymogen-like secretory granules readily identifies acinar differentiation, and these cells predominate in well-differentiated tumors. In contrast to normal acinar cells, neoplastic acinar cells are polygonal rather than triangular or trapezoidal, have greater cellular and nuclear variability, and have hyperchromatic to vesicular-appearing nuclei. Further, there are no striated ducts or retention of the normal lobular architecture seen in nonneoplastic acini. More than 40% of ACA acinar cells are of the predominant cell type[293]. The intercalated duct cells are cuboidal or columnar with centrally placed, small, dark nuclei and eosinophilic to amphophilic cytoplasm. Vacuolated cells contain cytoplasmic vacuoles that may be numerous and small, or few and large, distending the cell membranes. The clear cells are round to oval with distinct cell borders, peripherally placed, small, dark nuclei and the hallmark clear cytoplasm, the result from fixation and/or tissue processing. Nonspecific glandular cells are round to polygonal with round basophilic to vesicular nuclei and have amphophilic to eosinophilic cytoplasm. For all cell types, cellular pleomorphism and mitotic activity are limited, and, typically, the stroma is scant, but occasionally may be dense and hyalinized. A prominent lymphoid component composed of mature lymphocytes, including lymphoid follicles, can be seen.

Acinar cells and intercalated duct cells show diastase-resistant, PAS-positive intracytoplasmic granules; mucicarmine and alcian

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blue are typically negative but may be weakly positive. The presence of some intracytoplasmic mucicarminophilic material can be seen in acinic cell adenocarcinoma and does not exclude the diagnosis. Vacuolated cells, clear cells, and nonspecific glandular cells are PAS, mucicarmine, and alcian blue negative. Intraluminal and extracellular PAS positive and mucicarmine positive material may be present. Immunostaining is nonspecific and include cytokeratins reactivity, variable immunoreactivity for S-100 protein, and vimentin; p63, calponin, and actins are negative. A low proliferation rate is seen by Ki-67 (MIB1) staining.

## Mammary Analogue Secretory Carcinoma

Mammary analogue secretory carcinoma (MASC) is a recently described distinctive low-grade salivary gland malignant neoplasm with features resembling acinic cell adenocarcinoma and low-grade cystadenocarcinoma and displaying strong similarities to secretory carcinoma of the breast.[295] It is more common in men than women and primarily arises in the parotid gland; less commonly, MASC may arise in minor salivary glands. Microscopically, the tumors have a lobulated growth pattern and are composed of microcystic and glandular spaces with abundant eosinophilic homogeneous or bubbly secretory material. The intratubular secretory material is diastase-resistant, PAS-positive and mucicarmine negative. The immunohistochemical staining profile includes consistent immunoreactivity for mammaglobin, BRST-2, S100 protein, vimentin, CK7, CK19, STAT 5a, and MUC1. The t(12;15) (p13;q25) ETV6-NTRK3 translocation is identified.[296] In contrast, acinic cell carcinomas are generally not reactive for mammaglobin, BRST-2, S100 protein (4/12), and vimentin although STAT 5a and MUC1 staining can be seen in a majority of cases. There is an absence of t(12;15) (p13;q25) ETV6-NTRK3 translocation.

## Adenoid Cystic Carcinoma

ACC is a malignant epithelial salivary gland neoplasm characterized by its histologic appearance, tendency to invade nerves, and its protracted but nonetheless relentless clinical course. In major salivary glands, ACC primarily involve the parotid and submandibular glands. ACC is the most frequently encountered malignant neoplasm of the submandibular gland. Minor salivary gland involvement may occur throughout the upper respiratory tract, where it most frequently involves the palate; other intraoral sites of involvement include the tongue, the lower lip, the retromolar-tonsillar pillar region, and the sublingual gland. ACC may also occur in the ceruminal glands of the external auditory canal as well as representing 50% of all lacrimal gland neoplasms.

Grossly, ACC may be circumscribed, unencapsulated or partly encapsulated, solid, rubbery to firm, tan-white to gray-pink mass measuring from 2 to 4 cm in its greatest dimension. The histologic appearance of ACC is that of an unencapsulated, infiltrating neoplasm with varied growth patterns consisting of cribriform, tubular/ductular, and solid. Individual neoplasms may have a single growth but are characteristically composed of multiple patterns, any one of which may predominate. The most common pattern is the cribriform type, considered the "classic" pattern, demonstrating arrangement of cells in a "Swiss cheese" configuration with many oval or circular spaces. These spaces contain basophilic mucinous substance or hyalinized eosinophilic material. The tubular type has cells arranged in ducts or tubules. The ducts or tubules contain faintly eosinophilic mucinous material. Cribriform and tubular patterns often occur together. The least common pattern is the solid type, composed of neoplastic cells arranged in sheets or nests of varying size and shape. There is little tendency to form cystic spaces, tubules, or ducts.

Irrespective of the growth pattern, the neoplastic components are the same, consisting of fairly uniform-sized cells with small, hyperchromatic round to oval to angulated nuclei, scant amphophilic to clear cytoplasm, and indistinct cell borders. The nuclear-to-cytoplasmic ratio is about 1:1. The majority of the neoplastic cells are abluminal-type cells of myoepithelial differentiation. The cystic spaces seen in the cribriform or classic type are pseudocysts, which are extracellular and lined by replicated basement membrane. Scattered among these abluminal cells are ductal cells which surround small true lumens (glands). True duct-like lumens are an infrequent feature of ACC, but are most frequently seen in the ACC with a tubular growth. In the solid pattern, the cell population is dominated by the basaloid myoepithelial cells. The interstitial stroma, from which the epithelial component is sharply demarcated, varies in appearance from myxoid to hyalinized. Cellular and nuclear pleomorphism, necrosis, and mitotic activity are limited in the cribriform and tubular patterns. However, these features are more frequently seen in the solid pattern. Common to all histologic variants is the proclivity for nerve invasion (neurotropism), including peri- and intraneural invasion. However, ACC are not the only salivary gland tumor with neurotropism. Invasion of adjacent issue structures can also be seen.

Histochemical features of ACC include the presence of diastase-resistant, PAS-positive, and mucicarmine-positive material within the pseudocysts. Alcian blue staining is also present within the pseudocysts. Immunohistochemistry of ACC varies depending on the cellular component, with the myoepithelial cells showing cytokeratin, vimentin, p63, S-100 protein, and actin (muscle-specific) positivity with variable and GFAP reactivity. The ductal cells show cytokeratins, EMA, and CEA positivity. C-kit immunoreactivity is present in ACC, but it is not a unique marker for ACC and can be seen in other malignant salivary gland neoplasms, including (but not limited to) polymorphous low-grade adenocarcinoma (PLGA).

## PLGA of Minor Salivary Gland Origin

PLGA is a low-grade malignant epithelial neoplasm arising from the minor salivary glands, characterized by a varied architecture (polymorphous), bland cytomorphology, infiltrative growth, and indolent biologic behavior.

The tumors are polypoid or raised, round to oval, mucosal-covered masses ranging in size from 1.0 to 6.0 cm in their greatest dimension. In general, the mucosa remains intact; however, scattered surface ulceration may occur. The histologic appearance is that of a well-circumscribed but unencapsulated tumor characterized by morphologic diversity, cytologic uniformity, and infiltrative growth. The polymorphic nature of these lesions refers to the variety of growth patterns that include solid, trabecular, glandular, ductular, and tubular; cribriform and cystic patterns can be seen, but generally do not predominate. These patterns may be identified within the same lesion and from lesion to lesion. The presence of small tubular structures with a distinct central lumen lined by a single layer of cuboidal cells is a characteristic feature. A pattern of cell growth in which the cells are arranged in a single row termed "Indian file" can be seen and is often located at the periphery of the tumor. A focal papillary pattern can be identified. PLGA is composed of cuboidal to columnar isomorphic cells with indistinct cell borders that have uniform ovoid to spindle-shaped nuclei and small and inconspicuous nucleoli. The nuclear chromatin pattern varies from vesicular to stippled, but basophilic nuclei can also be identified. Scant to moderate amounts of eosinophilic to amphophilic cytoplasm can be seen, and occasionally clear cytoplasmic changes predominate. The tumor stroma varies from mucoid to hyaline to mucohyaline, and in some cases tumor nests are separated by a fibrovascular stroma. Neurotropism (peri- and intraneural) is found in the majority of

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tumors; perivascular invasion can also be seen with tumor nests often arranged in concentric fashion around these structures. In addition, the tumor may infiltrate the surface epithelium, residual minor salivary glands, and/or connective tissue components (bone, cartilage, muscle, and adipose tissue). Mitotic figures are rare and necrosis is not seen. Other histologic changes that may be identified include intratubular calcifications (psammoma-like bodies), pseudoepitheliomatous hyperplasia of the surface epithelium, and squamous metaplasia within the tumor. Squamous metaplasia can be identified following FNAB.

Intraluminal mucin can be identified by diastase-resistant, PAS-positive material; however, only focal intracytoplasmic mucin is seen. The immunohistochemical reactive pattern for PLGA may include reactivity for cytokeratins, EMA, CEA, p63, calponin, S100 protein, vimentin, muscle-specific action, GFAP, and C-kit. PLGA show a low proliferative index by Ki-67 (MIB1) staining.

## Salivary Duct Carcinoma

SDC is a high-grade malignant epithelial salivary gland neoplasm arising from the excretory ducts, histologically resembling ductal carcinoma of the breast. SDC may occur as a *de novo* neoplasm unrelated to any other salivary gland neoplasms, or, not infrequently, it is the malignant component identified in a carcinoma ex pleomorphic adenoma.

The majority of SDCs are poorly circumscribed and infiltrative, but may occasionally appear circumscribed. Cut section reveals a tan-white to gray-yellow solid mass ranging in size from 1 to 10 cm in its greatest dimension; on average, these tumors measure 3.5 cm. Cystic spaces filled with necrotic material may be identified.

The histologic features of SDC include the presence of an intraductal and infiltrating neoplasm with a variety of growth patterns, including cell nests, nodules, or lobules with central comedo-type necrosis, cribriform, solid, cystic, and papillary; multiple growth patterns can be seen in any given tumor. Comedo-type necrosis is a characteristic but not pathognomonic finding. Larger nodules tend to be cystic and irregular in shape. The appearance may suggest growth confined to within ducts (intraductal), but features of invasive growth include much larger size of the cystic foci as compared to normal ducts (intralobular and interlobular), presence of stromal fibrosis, and absence of normal (nonneoplastic) salivary gland parenchyma within the neoplastic foci.

The neoplastic cells of SDC are large, cuboidal to polygonal, with round, often centrally situated hyperchromatic nuclei and eosinophilic cytoplasm; eosinophilic nucleoli may be prominent, and oncocytic cytoplasmic changes may be present. Nuclear pleomorphism is present, and increased mitotic activity and necrosis are commonly seen. Cribriform pattern is reminiscent of intraductal mammary carcinoma and includes so-called "Roman bridge" pattern characterized by bands of neoplastic carcinoma demonstrating an admixture of abluminal cells lining pseudocysts and scattered epithelial cells lining small duct-like spaces, a pattern not seen in salivary duct carcinoma. The papillary pattern includes projections of neoplastic epithelium with fibrovascular cores; apocrine-like apical globules may be present. Psammoma-like bodies may be present. Squamous metaplasia may be identified. Stromal changes include the presence of fibrosis, often dense or sclerotic, as well as a mixed lymphoplasmacytic cell infiltrate. Invasive growth includes angioinvasion, NI, and invasion of adjacent salivary gland parenchyma and surrounding soft-tissue structures, including adipose tissue, skeletal muscle, and overlying skin.

Histologic variants include sarcomatoid, micropapillary, mucin rich, osteoclast-type giant cell and low grade (see subsequent text under low-grade cribriform cystadenocarcinoma). The sarcomatoid variant is characterized by a salivary duct carcinoma with associated malignant spindle-shaped and pleomorphic cell infiltrate; heterologous elements such as osteosarcomatous foci may be present. Similar findings can be seen in SCSC and are not indicative of a mixed carcinoma and sarcoma (i.e., carcinosarcoma). The micropapillary variant is characterized by a salivary duct carcinoma with associated clusters of morula-like epithelial cells with fibrovascular cores, reported to be more aggressive than "conventional" salivary duct carcinoma. The mucin-rich variant is characterized by conventional salivary duct carcinoma with associated lakes of extracellular mucin within which are nests or islands of neoplastic epithelium. The osteoclast-like giant cell variant is characterized by conventional salivary duct carcinoma with associated osteoclast-like giant cells, the latter resembling the cells seen in giant cell tumor of bone. In contrast to the cells in a giant cell tumor, the osteoclast-like giant cells in salivary duct carcinoma are immunoreactive for epithelial markers and androgen receptor.

Histochemical staining may include the presence of intracytoplasmic diastase-sensitive, PAS-positive material. Intracytoplasmic mucicarmine staining is usually negative, but intraluminal mucicarminophilic material may be present. Immunohistochemical reactivity includes the following: the presence of staining for cytokeratins (low and high molecular weight), CK7, EMA, and CEA positive; the presence of androgen receptor, which represents a very helpful diagnostic finding for SDC; HER-2/neu (c-erbB-2) being positive (membranous staining) in a majority of cases; chances of BRST2 being positive; estrogen and progesterone receptor markers being positive in a minority of cases; S100 protein and markers indicative of myoepithelial differentiation, including calponin, p63, smooth muscle actin and vimentin, typically being negative. Similar to its use in ductal carcinomas of the breast, myoepithelial markers have been used to identify a peripheral nonneoplastic myoepithelial layer that, if identified, may indicate a tumor to be confined to within a duct (intraductal carcinoma) as opposed to absent staining that may indicate an infiltrative process; however, reactivity with stromal myofibroblasts may suggest myoepithelial layering and, therefore, an intraductal process when in fact the carcinoma is invasive. Rare documentation of neuroendocrine differentiation, as evidenced by the presence of chromogranin and synaptophysin reactivity, may be identified. Prostate-specific antigen and prostatic acid phosphatase may be reactive. SDC shows a high proliferative index ranging from 25% to 80% by Ki-67 (MIB1) staining.

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CHAPTER 2

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# Clinical Evaluation of the Head and Neck Cancer Patient

## GENERAL APPROACH TO THE HEAD AND NECK CANCER PATIENT

Clinical evaluation of the patient with head and neck cancer entails multiple challenges for the physician. In the context of an initial clinical encounter, the caregiver needs to collect the findings that will guide diagnosis, while also establishing a constructive therapeutic relationship with the patient and family members, addressing acute intervention needs, and outlining and initiating a plan for further diagnostic workup and treatment. The imperatives that the physician must address in the evaluation of the head and neck cancer patient may be considered as 12 *Key Tasks*, as outlined in Table 2.1. An accurate and comprehensive examination must be performed. A complete medical history should be undertaken, with special attention paid to key risk factors, including prior cancer history, smoking history, alcohol intake, extent of sun exposure, reflux, industrial or occupational exposures, and immunosuppression. Cardinal signs and symptoms associated with head and neck cancer include lesions or masses, persistent hoarseness, mouth or throat pain, dysphagia, odynophagia, hoarseness or dysphonia, dyspnea, stridor, unilateral otalgia or hearing loss, aspiration, weight loss, or cranial nerve deficits. Assessment and documentation must be performed of the patient's overall medical and functional status, which may influence the suitability of specific treatments such as surgical resection or radiotherapy. Critical information regarding previous treatments must be collected, including previous oncologic surgeries, chemotherapy treatments, or prior radiotherapy. If the patient has had prior radiotherapy, key elements of therapy must be documented, including treatment portals, dosages, fractionation, treatment duration and compliance, and specifics regarding prior surgical or chemotherapeutic interventions obtained.

A provisional diagnosis or differential should be established with rapid formulation of a plan of care and clear delineation of the next steps required. At the same time, the treating physician must be vigilant in assessing areas in which immediate intervention may be necessary, such as treating pain, airway management, or addressing severe nutritional deficiencies. Assessment and treatment of pain is an important aspect of the clinical evaluation of the head and neck cancer patient, although insufficient attention is often paid to this aspect of care. In a recent meta-analysis of studies on pain among patients with cancer, den Beuken and colleagues found that >50% of patients had inadequately treated pain; when considered by cancer type, patients with head and neck cancer had the highest prevalence of insufficient pain management at 70%.[1]

A comprehensive evaluation of the head and neck cancer patient typically involves adjunctive measures such as radiographic imaging and cytopathologic tissue analysis. However, physical examination of the head and neck and history-taking by the evaluating clinician retain a central role in shaping further assessment and treatment. For example, patient age is a key factor to be considered in evaluating the patient with a solitary neck mass. Whereas the overwhelming majority of neck masses in young patients are either infectious or inflammatory in origin, most neck masses in adults involve neoplasia. Although benign pathologies are common in young patients with cystic neck masses, >80% of patients over the age of 40 who present with such findings are ultimately found to have carcinoma.[2] The clinician should be highly suspicious of the diagnosis of branchial cleft cyst or thyroglossal duct cyst in patients older than 40 with no prior history of symptoms; >30% of patients over 40 initially diagnosed with branchial cleft cyst subsequently prove to have cystic metastases of squamous cell carcinoma.[3]

As part of the initial visit, head and neck cancer patients should be engaged with a team of professionals dedicated to providing guidance and support through their course of care, including an oncology nurse, nurse practitioner or physician assistant, and patient navigator. Such multilayered staffing in the management of head and neck cancer patients improves treatment compliance and overall satisfaction with care.[4] If the patient is a smoker, provision of smoking counseling and offering treatment or referral to smoking cessation resources is necessary at the initial visit, as persistent smoking during treatment is an independent risk factor for poor treatment outcome.[5]

In many cases, patients will present having already been told that they have a head and neck cancer or they may have a strong suspicion of such a diagnosis. There is wide variation regarding patients' desires regarding the detail in which they want cancer diagnoses described and the degree of specificity with which they want prognostic information delivered.[6] Although legal and ethical standards in the United States regarding informed consent demand full disclosure, it is incumbent upon the clinician to attempt to furnish such information in an optimal manner for individual patients. The obligation to full disclosure does not obviate the responsibility of the provider to attempt to tailor the delivery in accordance with patient preferences and sensitivities.[7,8]



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**TABLE 2.1 12 Key Tasks in the Initial Evaluation of the Head and Neck Cancer Patient**

- Perform comprehensive head and neck examination; additional physical examination as indicated.
- Elicit complete HPI and symptom description.
- Delineate risk-factor profile (e.g., smoking history, sun exposure, radiation exposure, etc.).
- Assess overall medical and functional status in the context of possible treatment options.
- Engage a care team (cancer nurse, cancer nurse practitioner, and cancer patient navigator) to provide patient support and guidance.
- Ascertain critical information regarding prior therapies and start process to obtain such data if not available at the time of initial consultation.
- Recognize and address needs for urgent intervention: airway compromise, aspiration risk, inadequately treated pain, severe malnutrition, and hemorrhage risk.
- Obtain biopsy specimens, as indicated and feasible in office setting.
- Express recognition of the patient's concerns regarding diagnosis and acknowledgment of the impact regarding stress, anxiety, fear, and grief on patients and their loved ones.
- Initiate multidisciplinary board review and key referrals as indicated: medical oncology, radiation oncology, speech and swallow therapy, maxillofacial surgery/prosthodontics, pain management, anesthesiology/medicine, social work, financial/benefits counseling, smoking cessation resources.
- Order directed imaging and laboratory studies.
- Clearly identify and explain next steps in diagnosis and treatment in terms appropriate for the individual patient.

## PHYSICAL EXAMINATION

Thorough physical examination is critical in the evaluation of the patient with possible head and neck cancer. A complete physical examination of the entire head and neck is essential, regardless of suspected primary site. Appropriate steps should be taken prior to the initiation of the physical exam in order to develop and enhance patient comfort and rapport. Appropriate hand washing should precede examination, and adherence to universal precautions should be maintained. These actions promote trust between patient and physician. Physical examination should begin with attention to the general appearance of the patient. Information regarding a patient's overall health, mood and affect, hygiene, and smoke exposure may be gained with simple observation.

In addition to visualization of anatomic structures of the head and neck, manual palpation is a critical tool for assessment of the head and neck. Palpation should routinely be performed of the neck and oral cavity. Bimanual palpation is necessary for comprehensive evaluation of the floor of mouth and submandibular areas. Palpation techniques can yield critical information regarding submucosal extension, fixation, and tumor thickness. Any abnormal or concerning findings should be described in relation to key landmarks and anatomic subsites, so as to facilitate accurate communication with other providers and appropriately document changes over time.

### Examination of the Skin

Examination should begin with assessment of facial structures; any gross asymmetry or facial swelling should be noted. Thorough external inspection of the patient's skin for any suspicious lesions is performed. Particular attention should be given to sun-exposed areas, including the external auricles and the posterior neck. The scalp and other hair-bearing areas should be closely inspected, as lesions in these areas often escape notice. All pigmented lesions and nevi should be examined closely for color variation, border quality, asymmetry, and ulceration.

### Examination of the Ear

Examination of the ear and temporal bone is a required portion of the assessment. The skin overlying the external ear and mastoid region is inspected and palpated when appropriate. Following inspection of the external ear, otoscopic examination should be performed to assess the external auditory canal, tympanic membrane, and middle ear space. The presence and quality of any otorrhea or evidence of effusion is noted. Subjective pain associated with aural discharge is particularly concerning for underlying malignancy. In an adult presenting with unexplained unilateral or bilateral serous otitis media, fiberoptic endoscopic assessment should be performed to rule out obstruction of the Eustachian tube by a nasopharyngeal mass.

### Examination of the Nose

Anterior rhinoscopy is performed under direct visualization with a nasal speculum and a headlight or head mirror. With exposure enhanced by appropriate speculum technique, the anterior nasal cavity and its contents are visualized, including the vestibule, anterior septum, floor of the nasal cavity, inferior turbinate, middle turbinate, and middle meatus. The presence of secretions, masses, obstruction, scabbing, or active bleeding should raise suspicion for sinonasal pathology.

### Examination of the Oral Cavity

The oral cavity begins anteriorly at the skin/mucosal junction of the vermillion border of the lips. The hard/soft palate junction, the anterior tonsillar pillar, and circumvallate papillae form a plane posteriorly, which separates the oral cavity from the oropharynx. The oral cavity is divided into the following subsites: the lips, buccal mucosa, floor of mouth, retromolar trigone, oral tongue, hard palate, and alveoli. Oral cavity examination is best performed with two tongue blades and a head light or head mirror. The use of a handheld light source is discouraged, as it prevents the examiner from using both hands to manipulate oral cavity contents.

Examination should begin with external inspection of the lips and then proceed to thorough intraoral examination. When asking the patient to open their mouth, the presence of trismus should be noted, as it suggests pterygoid muscle involvement. The buccal mucosa, gingiva, gingivobuccal sulci, the retromolar trigone, and overall state of dentition are then assessed. The tongue is then grasped with a gauze pad and gently manipulated to allow full visualization of the ventral, dorsal, and lateral surfaces. The lateral surfaces should be inspected for lesions and palpated to assess for induration. With the tongue pulled superiorly, the floor of the mouth should be inspected and manually palpated; submucosal masses in the floor of the mouth should raise suspicion for minor salivary gland tumors. Midline protrusion and lateral excursion of the tongue should be tested; atrophy of one side or asymmetric protrusion raises suspicion for tongue invasion or cranial nerve XII involvement. Inspection and palpation of the hard palate is performed.

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Oral cavity examination requires assessment of all mucosal surface changes suggestive of potential or *premalignancy*: leukoplakia, erythroplakia, lichen planus, oral submucosal fibrosis, discoid lupus erythematosus, and dyskeratosis.[9] The most common sites for premalignant lesions include the buccal mucosa, lower gingiva, tongue, and floor of mouth.[10] Adjunctive screening methods including toludine blue application, fluorescence, and brush biopsy have not proven to be of unequivocal benefit in enhancing detection of oral malignancy,[11] but early findings regarding the potential application of optical coherence tomography in early detection are promising.

## Examination of the Oropharynx

The oropharynx extends from the level of the soft palate to the hyoid bone and has four distinct subsites: soft palate, tonsillar region, base of tongue, and posterior and lateral oropharyngeal wall. The soft palate should be examined for mucosal lesions and submucosal fullness or swelling. Elevation of the soft palate should be symmetric and can be assessed by asking the patient to say "ah"; asymmetric elevation should raise suspicion for CN X involvement. The tonsillar region consists of anterior and posterior tonsillar pillars encompassing the palatine tonsils. The anterior tonsillar pillar and tonsil represent the most common sites for primary tumors of the oropharynx. Asymmetrically hypertrophied lymphoid tissue, particularly in the palatine tonsils, should raise suspicion. The lateral and posterior pharyngeal walls are inspected; medialization of the lateral oropharynx may represent mass effect from an entity in the parapharyngeal space, which lies posterolateral to the tonsil. Palpation of the base of tongue is paramount as direct examination of this area is limited. Submucosal lesions may be missed on indirect visualization, but can often be palpated with good manual examination techniques. The base of tongue, pharyngoepiglottic folds, and vallecula should be inspected during indirect laryngoscopy with either mirror examination or fiberoptic endoscopy, as discussed below.

## Examination of the Neck and the Parotid Region

Examination of the neck is paramount in the evaluation of head and neck cancer. All levels of the neck, including the supraclavicular region, should be palpated to assess for the presence of lymphadenopathy. The anatomy of the neck is divided into six levels, as described in Table 2.2.[12] Size, mobility, and location of suspected malignant lymph nodes should be carefully documented in relation to these levels. The thyroid should be palpated for the presence of distinct nodules or gross enlargement. Standing behind the patient and having them swallow facilitates identification of irregularities of the thyroid lobes. The parotid glands, the preauricular lymph nodes, and the postauricular lymph nodes should be palpated. A mass in the parotid may represent primary neoplasm, metastatic lymph node, a cyst, or an inflammatory process. If the patient presents with a neck mass without an obvious primary, the index lesion can be identified in most cases on the basis of a comprehensive examination. In cases where the primary lesion is not discovered on initial physical exam, further workup with adjunctive imaging (CT, MRI, or PET/PET-CT), tissue sampling, operative endoscopy, and immunohistochemical or molecular studies as indicated will facilitate ultimate discovery of the primary lesion in 97% of patients.[13]

**TABLE 2.2 Anatomic Boundaries of the Levels of the Neck**

| | |
|---|---|
| Level IA (submental) | Bound by lateral edge of the anterior bellies of the digastric muscles and the hyoid bone. |
| Level IB (submandibular) | Bound by mandible, anterior belly of the digastric muscle, and the stylohyoid muscle. |
| Level IIA and Level IIB (upper jugular) | Bound by the skull base superiorly and hyoid bone inferiorly, the stylohyoid muscle medially, and the posterior border of the sternocleidomastoid muscle (SCM) laterally. Level IIA is anterioinferior to the spinal accessory nerve, while level IIB is posterosuperior to the spinal accessory nerve. |
| Level III (midjugular) | Bound by the hyoid superiorly, the inferior border of the cricoid cartilage inferiorly, the lateral border of the sternohyoid muscle medially, and the posterior border of the SCM laterally. |
| Level IV (lower jugular) | Bound by inferior border of the cricoid cartilage superiorly, the clavicle inferiorly, the lateral border of the sternohyoid muscle medially, and the posterior border of the SCM laterally. |
| Level VA and Level VB (posterior triangle) | Bound by the convergence of the SCM and trapezius muscle superiorly, the clavicle inferiorly, the posterior border of SCM medially, and the anterior border of the trapezius muscle laterally. Level VA is located superior to the level of the inferior aspect of cricoid cartilage; Level VB is located inferior to this horizontal plane. |
| Level VI (anterior or central compartment) | Bound by the hyoid bone superiorly, the suprasternal notch inferiorly, and the carotid arteries laterally. |

## Neurologic Examination

Complete neurologic examination should be performed with a focus on the cranial nerves (CN). Cranial nerve deficits may be indicators of underlying neoplastic processes and require further workup. Any paresis of the facial nerve (CN VII) must be characterized in accordance with the House-Brackmann grading scale. The House-Brackmann scale (Table 2.3) has been adopted by the American Academy of Otolaryngology–Head and Neck Surgery as the universal standard for the clinical assessment of facial nerve function.[14] Characterization of facial nerve deficits using the House-Brackmann scale facilitates accurate communication between providers and clear documentation of symptom progression. However, it should be noted that the House-Brackmann scale was developed and tested in neuro-otologic setting and has only limited usefulness in assessing tumors of the head and neck. Nevertheless, it is a common grading system that is now universally known and it does help with communication to other health professionals.

## Fiberoptic Endoscopy

The nasopharynx, portions of the oropharynx, larynx, and hypopharynx cannot be assessed by unaided physical examination. These areas can be visualized using either mirror techniques or

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**TABLE 2.3 House-Brackmann System of Grading Facial Nerve Paralysis**

| Grade | Description | Characteristics |
|---|---|---|
| I | Normal | Normal facial function |
| II | Mild dysfunction | Gross: weakness on close inspection, normal symmetry and tone at rest, may have slight synkinesis |
| | | Motor: moderate to good facial function, complete closure of the eye with minimal effort, slight asymmetry of the mouth |
| III | Moderate dysfunction | Gross: obvious but not disfiguring difference between the two sides of the face, normal symmetry and tone at rest, noticeable but not severe synkinesis, contracture, hemifacial spasm |
| | | Motor: slight to moderate forehead movement, complete eye closure with effort, weak mouth with medium effort |
| IV | Moderately severe dysfunction | Gross: disfiguring asymmetry and/or obvious weakness, normal symmetry and tone at rest |
| | | Motor: no forehead movement, incomplete eye closure, asymmetric mouth with maximal effort |
| V | Severe dysfunction | Gross: barely perceptible motion, asymmetry at rest |
| | | Motor: no forehead movement, incomplete eye closure, slight mouth movement |
| VI | Total paralysis | No movement |

Source: House-Brackmann System of Grading Facial Nerve Paralysis. Reprinted with permission from House J, Brackmann D. Facial nerve grading system. *Otolaryngology—Head and Neck Surgery,* 1985 Apr;93(2):146–147.

fiberoptic endoscopy. Fiberoptic endoscopy provides the most accurate visualization of these areas, allowing for assessment of primary lesions and evaluation of airway status. The nose is typically anesthesized with topical anesthetic spray and decongested with a vasoconstrictive spray. A flexible laryngoscope is passed through both nasal cavities and into the nasopharynx.

The nasopharynx extends from the skull base superiorly to the soft palate inferiorly and communicates with the nasal cavity through the choanae. Midline posterior pharyngeal mucosa and the nasopharyngeal lymphoid tissue should be assessed. Posterior pharyngeal wall fullness raises suspicion for retropharyngeal pathology. The scope is then angled to view the lateral wall and its contents including epithelial mucosa, the Eustachian tube orifice, the posterior lip of the opening of the Eustachian tube or *torus tubarius*, and the fossa of Rosenmüller lying behind the *torus tubarius*. The lateral wall must be carefully inspected with particular attention given to the fossa of Rosenmüller, as nasopharyngeal tumors have a predilection for this site.[15] The scope should then be angled inferiorly, and the base of tongue and the vallecula inspected. Protrusion of the tongue facilitates complete examination of the vallecula and the base of tongue. Advancing the tip of the scope until it is just above the epiglottis allows for visualization of the larynx and the hypopharynx.

The larynx is divided into three subsites: the supraglottis, glottis, and the subglottis. The supraglottic region includes the epiglottis, the false vocal cords, the ventricles, the arytenoid cartilages, and the aryepiglottic folds. The glottis consists of the true vocal cords and anterior commissure. The supraglottic and glottic larynx are examined for any mucosal lesions or submucosal masses. It is vital to fully visualize the anterior cords and anterior commissure. Bilateral cord involvement, cord mobility, and involvement of surrounding subsites should all be documented. True vocal fold mobility is assessed by having the patient phonate, pant, and breathe quietly. Although clinical staging is partially based on cord mobility, in the setting of impaired cord movement, it is critically important to attempt assessment of the cricoarytenoid unit, which may represent a more specific involvement, rather than a mass effect related to deep muscle invasion. The cricoarytenoid is the basic functional unit of the hemilarynx, and mobility of the cricoarytenoid is often the critical factor determining patient eligibility for organ-preserving laryngeal surgery.[16] Unfortunately, discrimination of vocal cord movement restriction due to paraglottic space involvement or mass effect of bulky lesions from true cricoarytenoid fixation based upon endoscopic examination is difficult, and evaluation in the operating room is often required.

The subglottis begins 5 to 10 mm below the free edge of the true vocal folds. Primary tumors of the subglottis are rare. However, transglottic extension of superior lesions has important staging and prognostic implications. Visualization of the subglottis may be obscured by glottic pathology, and comprehensive evaluation of the subglottis is not possible in the office examination.

The hypopharynx extends from the hyoid bone superiorly to the esophageal introitus inferiorly. It is continuous with the oropharnyx and sits just behind the larynx. The hypopharynx is divided into three distinct subsites: the piriform sinus, posterior pharyngeal wall, and postcricoid region. Adequate visualization of the hypopharynx in the office setting may be difficult. Having the patient perform a Valsalva maneuver may enhance visualization due to clearance of pooled secretions. The majority of tumors that arise in the hypopharynx are SCC or an SCC-variant.[17]

The larynx and hypopharynx may alternatively be visualized with rigid endoscopy. Patients with sensitive gag reflexes may need to be sprayed with topical anesthesic intraorally. Rigid nasal endoscopy with angled scopes allows for optimum visualization of the nasal cavity and should be performed in any patient with suspected skull-base or sinonasal tumors. Stroboscopic examination of the glottis allows for enhanced visualization of true vocal cords, and subtle changes in mucosal wave dynamics may be detected; it is especially valuable in judging the depth of glottic lesions.

Physical examination findings, considered in the context of patient's symptomatology and risk factor profile, form the basis for further workup. In most cases, comprehensive evaluation of suspicious findings will require adjunctive imaging. Prior to treatment, definitive tissue diagnosis must be obtained by fine needle aspiration (FNA), core needle biopsy, or open biopsy. Operative endoscopy with biopsy may also assist in securing definitive tissue diagnosis and achieving accurate staging.

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# IMAGING MODALITIES

Prior to therapeutic intervention, precise tumor staging is critical. Accurate staging is generally best achieved with a combination of clinical evaluation and radiologic imaging. Pretreatment imaging assists in staging by helping to delineate tumor origin, size, extension, and presence of locoregional metastases. Imaging facilitates preplanning by defining the relationship between masses and nearby vital structures such as blood vessels and cranial nerves, and may also detect possible signs of malignancy not readily appreciable by physical examination such as ill-defined tumor borders, cartilage invasion, bone erosion, perineural spread, and multifocality. Traditionally, computed tomography (CT) and magnetic resonance imaging (MRI) have been the standard imaging modalities employed in the workup of head and neck cancer patients. More recently, positron emission tomography (PET) has emerged as a powerful tool in the diagnosis and management of these patients. Ultrasound (US) is radiation sparing and useful in the performance of directed biopsies, and is currently the first-line imaging modality for most thyroid and salivary lesions. Scintigraphy currently has a limited role in the evaluation of thyroid nodules. Emerging technologies in biologic neuroimaging, such as proton MR spectroscopy, CT-perfusion, perfusion-weighted MRI, and diffusion-weighted imaging, utilize biologic behavior patterns such as tumor cellularity and perfusion to depict additional imaging dimensions.

## Chest X-Ray (CXR)

PA and lateral CXRs are indicated prior to any endoscopy or surgical intervention requiring general anesthesia. A CXR may assist in identifying cardiac pathology, chronic pulmonary disease, synchronous lung cancer, or distant metastases. However, CT and PET-CT are superior to CXR in ruling out second lung primaries and distant metastases.

## Computed Tomography (CT)

CT is often the initial study of choice in evaluation of head and neck masses. Advantages include relative availability and cost-effectiveness relative to MRI and PET scanning along with rapid image acquisition. CT is a powerful tool for depicting the deep tissue of the aerodigestive tract, and thus complements endoscopic evaluation of mucosal lesions.[18] CT is also a suitable means of radiologic staging of neck disease; however, modern CT and MRI scanners appear to have comparable effectiveness in staging the neck,[19] with CT and MRI demonstrating similar sensitivities (82% and 85%, respectively) and specificities (80% and 90%, respectively) in detecting cervical lymph node metastases.[20] CT is indicated in laryngeal and hypopharyngeal cancers and is particularly useful in determining the extent of bone involvement in oral cavity, oropharyngeal, and sinonasal tumors. Thoracic spiral CT is frequently used to assess early synchronous lung cancer or distant metastases.

## Magnetic Resonance Imaging (MRI)

MRI is the preferred imaging modality for evaluation of sinonasal and nasopharyngeal tumors. MRI is capable of differentiating inflammatory sinus disease from neoplasms and is superior to CT in detecting intraorbital and intracranial extension of nasopharyngeal cancers.[21] MRI is very accurate and far more sensitive than CT for detection of perineural tumor extension. MRI is limited in its ability to detect subtle skull-base erosion, while CT with bone algorithm is highly sensitive for detection of bony erosion of sinus walls and skull base.[22]

MRI is the most accurate imaging technique for assessment of salivary gland masses. MRI has superior soft-tissue resolution with the capacity to accurately reveal local extension of a tumor and demonstrate perineural tumor spread.[23] CT with bone algorithm is superior in determining the extent of bone destruction and thus may be of value if bony fixation or invasion is suspected. MRI can have important advantages in the depiction of oral cavity and oropharyngeal tumors. Tumors at these sites can be difficult to identify on CT because of the adjacent dense mandible and dental amalgam artifact. MRI is less affected by dense bone and dental artifact allowing for visualization of even small tumors. Furthermore, MRI is superior for assessment of tumor spread into the bone marrow. Disadvantages of MRI include the relatively long imaging time required to obtain high spatial resolution images. Prolonged imaging time often leads to significant motion artifact, making accurate interpretation of imaging difficult; this is particularly frequent at the laryngeal and hypopharyngeal levels.[21]

## Positron Emission Tomography (PET)

Positron emission tomography (PET) takes advantage of the increased metabolic rate of tumors and the resultant increased absorption of 18F-flourodeoxyglucose when compared to normal tissue. PET has become widely utilized in both initial staging and follow-up of patients with head and neck cancer. Recent evidence suggests that PET has a higher sensitivity and specificity for staging cancers of the head and neck when compared to CT and MRI. PET can provide additional information in roughly one-third of patients who have undergone previous CT or MRI with equivocal findings.[24–26] A prospective, histopathologically controlled study demonstrated that PET is superior to CT, MRI, and US in detecting cervical lymph node metastases.[4] PET imaging can identify synchronous primary neoplasms that may be missed with conventional imaging techniques. Whole-body scanning with PET-scanning has clear advantages in terms of ability to detect distant metastases. Lastly, patients with clinically evident nodal disease and unknown primaries despite application of conventional imaging techniques and clinical investigation should undergo PET imaging. In such cases, the PET scanning allows for identification of the primary site of tumor in 10% to 72% of cases.[27,28]

The role of PET in posttreatment surveillance of head and neck cancer has also expanded in recent years. Studies have demonstrated that PET is superior to CT and MRI in the detection of posttreatment persistence or recurrence of head and neck squamous cell carcinoma.[29] Positive posttreatment PET findings also provide important prognostic information regarding relapse-free and overall survival.[30] Terhaard et al. advocate PET as the initial step in evaluation of all patients with suspected local recurrence. Given that a negative PET is highly reliable for all sites, negative PET scan may preclude the need for biopsy in many cases.[31,32]

An important limitation of standard PET is limited resolution of anatomic detail. However, combined PET-CT techniques permit near-synchronous image acquisition and combine the anatomic detail of CT with the whole-body sensitivity of PET. Initial studies demonstrated that fused PET-CT improved anatomic localization of PET abnormalities and reduced the number of equivocal PET findings.[33] When the diagnostic accuracy of PET for detection of head and neck cancer is compared to that of PET-CT, PET-CT improves accuracy and alters treatment plans in 18% of cases.[24] In the initial diagnostic workup of head and neck cancer patients, utilization of PET-CT alters treatment plans in 30% of cases. In posttreatment surveillance, PET-CT reduces the fraction of false-positive studies compared to PET alone while maintaining a very

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high NPV.[34] By consolidating imaging acquisition, PET-CR also reduces overall scan time compared to independent application of imaging modalities. PET/CT is thus emerging as the optimal diagnostic modality in many cases based on evidence of its superiority to either modality alone for initial evaluation, radiologic staging, and surveillance for disease recurrence.[25,26]

## Ultrasound (US)

US is the preferred imaging modality for assessment of suspected benign salivary gland tumors and thyroid nodules. It is relatively inexpensive when compared to CT and MRI and spares the patient administration of radiation. Further it is safe, noninvasive, and readily available at most clinical sites for point-of-care evaluation and facilitation of fine-needle aspiration biopsy. US is the initial study of choice for suspected benign salivary gland tumors, as it can characterize tumor size, border regularity, vascularity patterns, multifocality, and adjacent lymphadenopathy. However, US is unsuitable for assessing perineural spread, extraglandular invasion of bone or soft tissue, and oropharyngeal or retropharyngeal nodal metastases, which should be evaluated with MRI if suspected.[35] A disadvantage of US is that its accuracy in assessment of salivary gland lesions is significantly operator-dependent, and interpretation of US images can be more challenging than corresponding MRI or CT images for those without extensive experience.

US is also the most useful imaging technique for assessment of thyroid nodules. High-resolution US can detect lesions as small as 3 mm. Sonographic features suggestive of thyroid nodule malignancy include microcalcifications, marked hypoechogenicity, poorly defined margins, direct invasion through the thyroid capsule, and central vascularity.[36,37] Microcalcifications have a reported PPV for carcinoma of up to 70% and are the most concerning sonographic finding.[37] The American Thyroid Association (ATA) recommends preoperative neck US on all patients undergoing thyroidectomy for biopsy-proven malignancy. The ATA also recommends surveillance cervical US 6 to 12 months posttreatment and periodically thereafter depending on risk factors and thyroglobulin status.[38]

US may be employed for diagnostic imaging and guidance of biopsy in both the radiology suite and the clinician's office. Although the utilization of portable US in evaluation of the head and neck in both outpatient and emergency settings is commonplace in Europe,[39] it is much less frequently utilized in the United States. It is, however, becoming increasingly available to clinicians as an adjunctive modality, which may be selectively utilized as part of the initial evaluation of the head and neck cancer patient. This trend has been encouraged recently by the introduction of smaller, less expensive high-resolution ultrasound machines into the marketplace. The selective application of US technology in the office setting is increasingly being viewed as "an important extension of the physical exam," which allows clinicians to further investigate concerning findings by "seeing pathology below the skin" in real time without irradiation.[40]

Portable US can be used in the office setting for evaluation of neck masses, cervical lymphadenopathy, salivary gland masses, parathyroid adenomas, and thyroid nodules. US can provide key information regarding a pathologic entity of the neck, including size, cystic quality, presence of solid elements, vascularity, and relationship to critical structures. US characteristics of cervical lymph nodes that are concerning for malignancy include size > 1 cm (except for the jugulodigastric node whose upper limit of normal size is 1.5 cm), round shape (nonpathologic lymph nodes tend to be oval with a 2:1 diameter ratio), irregular margins, focal necrosis, node clustering, loss of hilar architecture, anechoic echogenicity, peripheral nodal vascularity, focal vascularization defects, and microcalcification.[41,42]

The scope of use of US within the office setting is expected to increase as units become smaller and less expensive. Several manufactures now offer laptop-sized models suitable to head and neck applications, and handheld units, which are already in use in other clinical settings, are on the horizon.[43] At present, the primary barrier to increased usage of office-based US is adequate training and credentialing for nonradiologists.[44] However, performance of head and neck US by the treating physician in the office setting can have important benefits in terms of treatment planning and surveillance.[45] New US techniques, including elastography and sonoelastrography, are likely to improve the accuracy of office-based testing. Lyschik and colleagues recently reported a 98% sensitivity and 92% accuracy rate utilizing US sonoelastrography to determine malignancy in cervical lymph nodes.[46]

## Scintigraphy

Scintigraphy is a nuclear medicine technique in which uptake of radiotracers by select tissues can be measured. Its routine use in the evaluation of thyroid nodules has significantly decreased, and its utility in the workup of thyroid carcinoma is limited. Iodine-123 and technetium-99m pertechnetate are radiotracers commonly used to evaluate thyroid nodules. Hyperfunctioning nodules are more likely benign, while hypofunctioning nodules are more suspicious for malignancy. The reported risk of cancer is 1% to 4% for a hot nodule and 15% to 25% for a cold nodule.[47] However, since scintigraphy cannot reliably identify malignancy, it is of limited value in routine evaluation of the thyroid nodule. Whole body iodine-123 scanning can be performed as a posttreatment test and can provide information related to the presence of metastatic disease, completeness of surgical resection, and disease recurrence. Whole-body scanning is indicated for follow-up of patients at high or intermediate risk for persistent disease after radioactive iodine therapy.[38] Scintigraphy with Technetium-99m Sestamibi, a parathyroid tissue-localizing agent, is the imaging modality of choice for the initial localization of parathyroid lesions.[48]

## Fine-Needle Aspiration

Fine-needle aspiration (FNA) is the preferred tissue sampling method for initial evaluation of neck masses or thyroid nodules. FNA may be performed using either manual palpation techniques or under image guidance. Systematic review of FNA cytology from all head and neck sites, including pooled analysis of over 2,700 specimens, reported sensitivity, specificity, and accuracy levels of 89.5%, 98.5%, and 95.1%, respectively.[49] Addition of US guidance to FNA yields increased sensitivity, specificity, and accuracy, while decreasing nondiagnostic sampling rates by approximately 50%.[50,51] Multiple studies have suggested that the use of on-site adequacy assessment by cytopathologists improves the diagnostic yield of US-guided FNA.[52–54] However, recent evidence suggests FNA in the office setting under US guidance by surgeons with experience in US techniques may afford comparable results in terms of diagnostic yield and accuracy.[55]

Thyroid nodules detected by US should be selectively sampled via FNA on the basis of size and the presence of suspicious findings on US. Current guidelines mandate FNA of lesions >1 to 1.5 cm. Concerning findings on US include the following: microcalcifications, hypoechoic nodules, irregular or lobulated margins, intranodal vascularity, lymphadenopathy, or disruptions in the fascial sheath suggestive of extrathyroidal extension; FNA may be deferred at the physician's discretion if the nodule is purely cystic with no solid elements on US.[56] A multicenter study of 849 nodules revealed the following prognostic value for malignancy of sonographic criteria: hypoechogenicity

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(sensitivity = 87%; PPV = 61%); shape (sensitivity = 40%, PPV = 78%); spiculation (sensitivity = 49%; PPV = 82%); and microcalcification (sensitivity = 44%, PPV = 78%).[57] An oft-overlooked step is the submission of accompanying clinical information that can assist the cytopathologist in interpretation of findings and reduce the rate of nondiagnostic findings. The National Cancer Institute (NCI) guidelines mandate that office-based thyroid FNA specimens be submitted with the data listed in Table 2.4.[58]

## DIRECTED LABORATORY STUDIES

Routine laboratories include a complete metabolic panel (CMP) and complete blood cell count (CBC) for all patients undergoing workup for suspected head and neck cancer. Head and neck cancer patients are frequently anemic; thus documentation of CBC is important in the pretreatment period and should be periodically followed throughout treatment. Coagulation studies are indicated in anticipation of surgical intervention. Heavy alcohol use and malnutrition are relatively prevalent among patients with head and neck cancer. Assessment of nutritional markers such as albumin, prealbumin, and Fe studies may help identify at-risk patients and allows for pretreatment nutrition optimization planning.[59] Baseline thyroid function tests should be obtained prior to initiation of treatment. Liver function tests are sometimes used as part screening workup for metastatic disease, but have very poor PPV when used for screening purposes.[60] In patients with suspected nasopharyngeal carcinoma, antibody titers against Epstein-Barr virus antigens may be useful as an accessory diagnostic test.[61]

## DELIVERING DIFFICULT MESSAGES TO PATIENTS AND FAMILIES

A key element of the initial interaction with head and neck cancer patients is how the clinician addresses the fears and concerns of patents and their families. Although the physician may desire to defer discussion of diagnosis and possible treatment until after workup is complete and a firm diagnosis is determined, this is often not possible. Patients will often arrive having already received a diagnosis of cancer or may strongly suspect such a diagnosis. Moreover, a significant proportion of patients will have previously been afflicted with a head and neck cancer. Thus, the process of dealing with the possibility (or certainty) of a cancer diagnosis generally begins during the initial interaction with the patient. The potential consequences of the manner in which a cancer diagnosis or prognosis is communicated should not be underestimated. Studies have documented that the manner in which critical prognostic information is communicated to patients and families has a demonstrable impact on long-term patient outcomes.[62] A recent systematic review found that poor caregiver performance in terms of delivering bad news to cancer patients results in increased stress and anxiety levels, more severe adjustment difficulties, and worse overall disease outcomes.[63] Dunn has characterized the delivery of bad news to patients and families regarding head and neck disease as an *invasive procedure*,[64] regarding which clinicians should employ the same level of care and concern for adverse impact as they would use for other invasive interventions.

For patients who ultimately receive a diagnosis of the cancer, the impact of receiving such news is determined not just by the exchange in which they are specifically informed of their diagnosis and prognosis, but in the context of their overall relationship and experience with the cancer caregiver. Schaepe describes patients' experience of learning and accepting a cancer diagnosis as a clinical *process* that may unfold over the course of multiple clinical interactions starting with *first impressions* of the caregiver and culminating in a *realization event* for the patient.[65] Initial assessment and evaluation is the key initial step in the process that plays a determinative role in shaping patient experience, irrespective of whether a specific diagnosis is explicitly delivered at that time.

Loge and colleagues assessed factors determining patients' satisfaction regarding disclosure of a cancer diagnosis and found the factor with the most statistical impact to be patient perception that their physician was *engaged* and *personally interested* in their care. Perceived level of physician interest was significantly more impactful than the amount of time spent with the physician or whether patients completely understood their diagnosis.[66] Using an open-ended interview method, Back and colleagues found that the most important qualities perceived by cancer patients regarding the delivery of cancer diagnoses by providers was *recognition* and *guidance*: patients wanted their clinicians to recognize and acknowledge their experiences in receiving such news, to provide specific guidance regarding the next steps in treatment, and to repeatedly move back and forth between these modes as needed by the patient during the course of the clinical encounter.[67] Although the delivery of bad news must be calibrated to the needs of the individual patient, common themes have emerged in the literature on delivering cancer diagnoses that should inform the provider's approach; Baile and colleagues developed the 6-step SPIKES protocol to help caregivers deliver bad news in accordance with evidence-based standards (Table 2.5).[68]

In communicating the implications of a cancer diagnosis, the clinician should strive to treat the patient with the appropriate

**TABLE 2.4 NCI Guidelines Regarding Data Submitted with Thyroid FNA Specimens**

- Comprehensive patient identification information
- Location of the nodule
- History of hypothyroidism, autoimmune thyroiditis, or a positive test for antithyroid antibodies
- History of Graves disease
- History of $I^{131}$ or external radiation therapy
- Personal history of cancer
- Family history of thyroid cancer

**TABLE 2.5 The SPIKES Protocol for Delivering Bad News to Patients with Cancer**

| |
|---|
| Step 1: Setting up the interview |
| Step 2: Assessing the patient's perceptions |
| Step 3: Obtaining the patient's invitation |
| Step 4: Giving knowledge and information to the patient |
| Step 5: Addressing the patient's emotions with empathic responses |
| Step 6: Strategy and summary |

Source: Modified from Baile W, Buckman R, Lenzi R, et al. SPIKES—A six-step protocol for delivering bad news: application to the patient with cancer. *Oncologist*. 2000;5:302–311.

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cultural sensitivity and an appreciation of the culturally specific manner in which patients and their families may interpret and respond to a cancer diagnosis and how patients from different backgrounds may deal with issues such as pain and quality of life.[69] In non-Western cultures, cancer illness tends to be a more collective experience involving the entire family, and there is accordingly a more inclusive and consensus-oriented approach to receipt of prognostic information and medical decision making. A recent systematic review of published literature on breaking bad news of cancer found that the most significant differences in patient preferences across cultures involved degree of specificity regarding the involvement of family members in delivery of a cancer diagnosis; less than 30% of Asian patients desired detail regarding life expectancy as compared to >60% of non-Asians.[70] In some Asian societies, the diagnosis of cancer has extremely grave culturally specific implications, and patients and their families may be inclined to view a cancer diagnosis as inevitably terminal and thus view treatment measures as futile. It is thus critically important for providers to attempt to incorporate cultural factors in their approach both to communicating diagnostic and prognostic information and to formulating treatment plans.

## PRETREATMENT PLANNING

Head and neck cancer involves a heterogenous group of pathologic entities, with wide variation in terms of histopathogenesis, tumor biology, required pretreatment workup, optimal treatment modality, prognosis, and quality-of-life implications.[71] Given this complexity, successful management of this disease process requires a concerted multidisciplinary approach. Comprehensive treatment of head and neck cancer patients involves participation by an array of specialists: head and neck surgeons, radiation oncologists, medical oncologists, neuroradiologists, head and neck pathologists, oral pathologists, endocrinologists, facial plastic and microvascular reconstructive surgeons, oral surgeons, maxillofacial prosthodontists, dental pathologists, speech pathologists, social workers, nutritionists, occupational therapists, nursing coordinators, research coordinators, nurses, and others. Coordinating such interdisciplinary care can be challenging, but is necessary in order to furnish optimal patient care.

In most institutions, weekly head and neck tumor boards have emerged as the institutional structure for coordinating the interdisciplinary care of head and neck cancer patients, and recent studies have examined the impact of multidisciplinary tumor boards on the provision of head and neck cancer care. In addition to providing a structured, regular mechanism for interdisciplinary collaboration, tumor boards also provide a forum for reevaluation of outside radiology and pathology findings. A prospective study evaluated 120 consecutive patients presented at a multidisciplinary head and neck tumor board and compared "preconference" and "postconference" diagnosis, stage, and treatment plan. The diagnosis, stage, or treatment was changed in approximately one out of every four patients reviewed. Of these patients, 68% (roughly 18% of the total study population) had their treatment plan altered.[72] In regard to reinterpretation of radiographic studies, a retrospective review of 136 patients demonstrated that review of outside imaging studies by dedicated specialists led to changes in findings in 41% of cases; 34% of patients had a change in T, N, and/or M staging. Furthermore, changes in radiographic findings almost always altered treatment decisions and affected prognosis in 95% of patients.[73] A retrospective review of 213 patients with locally advanced head and neck cancer demonstrated that overall survival in patients managed with tumor board recommendations was comparable to that reported in randomized clinical trials.[74]

Multidisciplinary tumor board participation in evaluation and treatment planning is thus now the standard of care for management of head and neck cancer patients in most settings. Evidence from the literature demonstrates multiple benefits from routine engagement of multidisciplinary tumor boards, including improved staging accuracy, greater accordance with clinical practice guidelines, improved communication between providers, enhanced cost-effectiveness of care, shorter time lapse from diagnosis to initiation of treatment, and improved clinician and patient satisfaction.[74–77]

## CONCLUSIONS

This chapter outlines the required steps in the initial evaluation of head and neck cancer patients and describes the resources available to the clinician in planning further workup and treatment. However, it must be stressed that there is no such thing as a *routine* visit for the head and neck cancer patient. The complexity of the pathologic entities involved and the enormity of the potential impact on patients and their families precludes the adoption of a facile approach to evaluation, treatment, or patient interaction. Head and neck conditions have profound effects on patients because, in addition to the specter of cancer, fundamental qualities of life are often affected, including appearance, facial identity, and key functions of living including breathing, eating, and speaking.[78] Undertaking the treatment of patients with head and neck cancer demands that the clinician maintain both vigilance and vigor in providing the best possible care.

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CHAPTER 3

Sung Kim, Benjamin D. Smith, and Bruce G. Haffty

# Prognostic Factors in Patients with Head and Neck Cancer

## INTRODUCTION

Treatment of head and neck cancer requires accurate risk stratification in order to determine the type and extent of therapy and the expected clinical outcome. Physical exam, diagnostic imaging studies, and pathologic review enable the clinician to determine the size and extent of the primary tumor, the status of cervical lymph nodes, and the likelihood of distant metastatic disease, thus generating an accurate tumor, lymph node, metastasis (TNM) stage for each patient. In addition to TNM staging, other clinical and pathologic factors not routinely incorporated into the staging system have been shown to influence response to therapy and eventual outcome. These factors may be categorized as follows: (a) prognostic factors related to the primary tumor, (b) prognostic factors related to the cervical lymph nodes, (c) prognostic factors related to patient demographics, and (d) prognostic factors related to the patient's general medical condition.

In addition to clinical and pathologic factors, recent interest has focused on identifying molecular factors that may influence clinical outcome. These molecular markers not only provide useful prognostic information, but also serve as targets for novel pharmacotherapies that antagonize cellular proliferation by interfering with specific cellular processes. Molecular factors that influence tumor behavior fall into several broad categories, including proto-oncogenes, tumor suppressor genes, growth factors, immune-related factors, loss of heterozygosity at various genetic loci, total cellular DNA content, and parameters related to the kinetics of *in vivo* tumor growth. Finally, the correlation of human papilloma virus (HPV) has been crucial to furthering our understanding of this new and important subset of cancers. This will be discussed in detail in Chapter 12.

When considering prognostic factors in head and neck cancer, several specific outcomes merit attention. In addition to disease-free and overall survival, the relationship between a specific prognostic factor and local recurrence, regional recurrence, and distant metastatic disease must be considered. Factors specifically related to local recurrence may necessitate wider surgical resection, external beam radiotherapy dose escalation or altered fractionation, or the use of a brachytherapy boost to the primary tumor bed. Factors specifically related to regional recurrence may prompt prophylactic neck dissection or radiotherapy in the clinically N0 neck or determine the type of neck dissection selected in patients with clinically positive cervical lymph nodes. Finally, factors predictive of distant metastases may prompt more aggressive screening for concomitant distant metastases before local-regional treatment[1] and influence the decision to offer systemic therapy.

## FACTORS RELATED TO THE PRIMARY TUMOR

### Tumor Dimensions

Tumor size and extent of invasion determine clinical and pathologic T stage for head and neck squamous cell carcinomas (HNSCC). T stage is determined clinically by measuring the maximal surface diameter of a mucosal neoplasm or pathologically by measuring the maximal cross-sectional diameter of a resected tumor. Because tumors arising from mucosal surfaces do not conform to spherical geometry, the maximal tumor diameter does not perfectly correlate with either tumor depth or tumor volume.

As the primary determinant of T stage, maximum tumor diameter has traditionally been considered an important risk factor for the presence of concomitant nodal metastases, local recurrence, and poor survival. For example, in two studies conducted on a total of 603 patients with HNSCC, Magnano et al. found that T stage was a consistent, independent predictor of pathologically positive cervical lymph nodes.[2,3] In addition, pathologic maximal tumor diameter has been shown to predict local recurrence in tumors arising from the lower lip,[4] oral cavity and oropharynx,[5] and larynx.[6] Finally, most studies,[5,7–10] though not all,[11] have shown a univariate association between either clinical or pathologic tumor diameter and survival.

One limitation of using tumor size as a prognostic determinant was highlighted by Moore et al., who stratified 155 patients with oral SCC based on surface diameter of the primary tumor.[7] Eighty-four percent of patients with tumors ≤2 cm survived disease free for 3 years, compared with 52% of patients with tumors larger than 2 cm. However, no significant differences in survival existed between tumors with surface diameters in the following three groups: 2.1 to 3 cm, 3.1 to 4 cm, and >4 cm. Thus, although a gross trend exists between surface diameter and survival, this trend does not follow a simple dose–response relationship. In a follow-up study conducted on 151 patients with oral and oropharyngeal SCC, Moore et al. found that tumor thickness was a more consistent predictor of concomitant nodal metastasis and 3 year disease free survival than tumor surface diameter.[12]



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The correlation between tumor thickness and risk of concomitant cervical lymph node metastases has been confirmed in multiple studies.[4,13–20] The critical thickness, above which the risk of nodal metastasis increases substantially, varies depending upon the specific anatomic site involved, perhaps due to variation in density of lymphatic channels.[21] Nevertheless, for most anatomic subsites, the critical thickness ranges from 3 to 5 mm depending upon the specific study. For example, a recent study of 105 patients with clinically node negative oral cavity tumors reported that the risk of occult nodal metastasis was 10% if the tumor thickness was ≤5 mm, compared to 46% if the tumor thickness was >5 mm.[14] Furthermore, in a series of 76 patients with carcinoma of the tongue who all received neck dissection, Woolgar demonstrated that the mean reconstructed thickness of tumors with pathologically positive cervical lymph nodes was 19 mm, compared to 10 mm in patients without metastases.[22] Tumors with a large mucosal surface area but minimal invasion were not at increased risk of nodal metastases. In such cases, clinical and pathologic T stage may overestimate the likelihood of concomitant nodal disease.

In addition to consideration of maximal tumor diameter and thickness, utilization of computed tomography (CT) enables the calculation of total tumor volume. In a series of 63 patients with supraglottic primaries treated with primary irradiation, Mancuso et al. found that tumor volume calculated from pretreatment CT scans was an independent predictor of local control, with local control rates of 89% in tumors <6 $cm^3$ versus 52% for tumors ≥6 $cm^3$.[23] Furthermore, in a study of 103 patients with supraglottic SCC, tumor volume as calculated from pretreatment CT was a stronger predictor of local-regional failure than clinical T stage in multivariate analysis.[24] Hence, calculation of tumor volume using diagnostic imaging provides important prognostic information that can supplement traditional clinical staging for tumors of the larynx. In contrast, T stage, rather than tumor volume estimated from diagnostic imaging studies, appears to be a better predictor of local control for tumors of the oropharynx and hypopharynx treated with definitive radiation.[25]

## Margin Status

The presence of residual carcinoma at the margins of surgical resection is an important risk factor for local recurrence in HNSCC. Although the presence of positive margins may indicate an error in surgical judgment at the time of resection, it may also imply a more biologically aggressive tumor that extends microscopically through the muscle bundles, submucosal lymphatics, and perineural spaces.[26] The precise definition of "positive margins" varies depending on the study and may include invasive tumor involving the initial surgical margin, invasive tumor involving the final surgical margin, invasive tumor approaching within 5 mm of the final surgical margin, carcinoma *in situ* involving the final surgical margin, or dysplasia involving the final surgical margin. Guidelines used in the United Kingdom define "negative" margins as invasive tumor more than 5 mm away from the surgical margin, "close" margins as invasive tumor within 1 to 5 mm from the surgical margin, and "positive" margins as tumor <1 mm from the surgical margin.[21]

In a review of resections for head and neck cancer performed at Memorial-Sloan Kettering Cancer Center, Looser et al. classified 1,775 cases according to final margin status.[27] After excluding patients with gross residual disease, they identified 62 patients with microscopically positive margins, defined as either cancer within 0.5 cm of the margin, marked atypia or premalignant changes in the margin, carcinoma *in situ* in the margin, or invasive carcinoma in the margin. Interestingly, patients in all four of these groups experienced increased local recurrence rates, ranging from 64% in patients with invasive cancer at the margin to 85% for patients with carcinoma *in situ* at the margin, compared to a local recurrence rate of 32% in patients with negative margins.

Many other studies have confirmed the prognostic importance of margin status in HNSCC. The presence of positive margins has been shown to predict local or local-regional recurrence for the following sites: lower lip,[4] oral cavity,[28–30] buccal mucosa,[31] oral tongue,[13,32] oral and oropharyngeal tongue,[33,34] base of tongue,[35] oral cavity and oropharynx,[36] larynx,[37,38] and all sites combined.[39–43] Furthermore, the presence of positive margins predicts poor overall survival in univariate analysis for the following sites: oral cavity,[30] oral tongue,[44] oral and oropharyngeal tongue,[34] oral cavity and oropharynx,[45] base of tongue,[35] supraglottic larynx,[46] larynx,[8,38,47] and all sites combined.[39,40,48,49] Whether or not margin status is an independent predictor of survival remains somewhat controversial, with two studies confirming an independent association,[38,49] but six others failing to find an association.[5,8,9,39,46,50] Margin status has not been shown to predict regional or distant recurrent disease.

Given the negative prognostic implications of positive margins, Byers et al. demonstrated that use of intraoperative frozen sections can identify those patients with initially positive margins and thus allow resection of additional tissue to remove residual carcinoma and reduce the risk of local recurrence.[48] In this cohort of 216 patients with SCC arising from the oral cavity, oropharynx, and hypopharynx, patients with initially positive margins on frozen section received additional resection to achieve final negative margins. Local recurrence in this group was 13%, compared with a local recurrence rate of 12% in patients with negative margins on initial frozen section. Patients with positive final margins suffered from an 80% local recurrence rate. Hence, use of intraoperative frozen section analysis of surgical margins may result in a clinically significant reduction in local recurrence.

However, in a follow-up study of 268 patients with SCC of the tongue, those patients with initially positive margins that were ultimately rendered negative experienced an increased risk of local recurrence and death compared to patients with initially negative frozen section margins.[26] Thus, the authors recommended use of postoperative radiotherapy in all patients with initially positive frozen section margins. One additional concern regarding the use of intraoperative frozen sections to determine margin status is potential inaccuracy, with one study reporting a 14% (7/49) false negative rate for oral cancer.[51]

For those patients with persistently positive margins, postoperative external beam radiotherapy remains an important component of therapy. However, even with combined modality therapy, most investigators,[31,39,42,52] although not all,[53] report an increased incidence of local recurrence in those patients with positive margins. One important factor influencing local control in patients with positive margins is the dose of postoperative radiotherapy, as Zelefsky et al. noted a 7-year local control rate of 92% in patients who received ≥60 Gy, compared with 44% in patients receiving <60 Gy.[53] In addition, interest has grown in using postoperative brachytherapy, either alone or following postoperative external beam radiotherapy, to improve local control in patients with positive margins.[54–57] Beitler et al. reported 29 patients with microscopically close or positive margins after curative surgery treated with postoperative external beam radiotherapy to a median dose of 60 Gy followed by $^{125}$I permanent implant designed to deliver a cumulative lifetime dose of 120 to 160 Gy to the high-risk target volume.[57] This treatment strategy resulted in a 92% 2-year actuarial local control rate and clearly merits further study. Finally, growing evidence from two large randomized trials indicates that the addition of cisplatin (100 mg/$m^2$ on days 1, 22, and 43) to postoperative radiation improves local-regional control and perhaps overall survival for patients with positive surgical margins.[58–60]

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## Malignancy Grading

Pathologists have long recognized the potential prognostic significance of cellular morphology in squamous cell carcinoma. In 1920, Broders proposed a four-tiered grading system for carcinoma of the lip that was based on the proportion of the neoplasm resembling normal squamous epithelium.[61] This grading system provides an easily assessed scheme for assessing tumor differentiation and roughly correlates with prognosis, as poorly differentiated tumors are more likely to recur and reduce survival.[30,46,62–68] Broders' grading system has been criticized, however, for its subjectivity and for its failure to consistently predict survival in multivariate modeling.[9,30,46,69,70] The lack of independent significance of Broders' grading system may be due to the association between higher grade (more poorly differentiated) and advanced stage.[71]

In 1973, Jakobsson proposed a semiquantitative grading system that considered not only histologic parameters of the tumor cell population but also the host–tumor interface.[72] Parameters describing the tumor cell population included structure and growth of the neoplasm, degree of keratinization, nuclear pleomorphism, and the frequency of mitoses. The tumor–host interface was assessed for mode of invasion, degree or stage of invasion, vascular invasion, and lymphoplasmacytic cellular response. When this classification system was applied to a series of 42 laryngeal SCCs treated with radiotherapy, tumors with high malignancy grade were more likely to recur and result in death with disease. However, in a subsequent multivariate analysis conducted on 77 patients with oropharyngeal cancer, Crissman et al. found that invasion pattern was the only histologic parameter that independently predicted survival.[73] None of the other histologic parameters, either independently or as a composite score, were significant predictors of outcome.

In 1987, Anneroth et al. reviewed efforts to devise a malignancy grading system and proposed that grading consist of six morphologic features: degree of keratinization, nuclear polymorphism, number of mitoses, pattern of invasion, stage of invasion, and lymphoplasmacytic infiltration.[74] In 1989, Bryne et al. applied Anneroth's grading system to only the most anaplastic fields in the most invasive areas of the tumor (Table 3.1).[75] In two cohorts of 68 and 61 patients with oral SCC, Bryne's invasive cell grading was a highly significant, independent, and reproducible predictor of survival.[75–77] Those patients with a total malignancy score between 5 and 10 experienced a 57% 5-year survival, compared to a 19% 5-year survival in patients with malignancy scores >10. In contrast, Broders' grading system failed to correlate with survival in both cohorts. The authors concluded that histologically invasive regions might be responsible for the clinical behavior of HNSCC. Further study of invasive cell grading (ICG) conducted by other groups has shown that a high ICG score strongly predicts the presence of occult cervical metastases and extracapsular extension (ECE).[17,22,78] Due to the strong correlation between ICG and concomitant nodal metastases, this factor should be considered in decisions regarding elective treatment of the clinically negative neck.

In addition to assessment of malignancy grade, many studies have attempted to determine which individual histologic parameters contribute most strongly to prognosis. Several studies suggest that pattern of invasion may predict outcome independent of other histologic parameters. Tumors that infiltrate in small groups or cords of cells, or infiltrate with marked cellular dissociation, may behave more aggressively. For example, Spiro et al. found that oral tongue SCCs with a high-grade pattern of invasion were more likely to present with concomitant nodal metastases, develop distant metastases, and result in death.[32] In addition, for oral carcinoma that invades the mandible, high-grade invasion pattern increases the rate of mandibular margin positivity and local recurrence and results in a fourfold increased risk of death with disease in multivariate analysis.[79] The correlation of aggressive invasion pattern with poor local-regional control[4,33,80–83] and survival[10,45] has been noted in several other studies.

In addition to pattern of invasion, lymphoplasmacytic infiltration of the tumor bed has been considered as a potential independent marker of prognosis. In a study of 396 patients with HNSCC, multivariate analysis revealed that the presence of a lymphocytic tumor infiltrate decreased the risk of concomitant

**TABLE 3.1 Invasive Cell Grading System**

| | Score | | | |
|---|---|---|---|---|
| **Morphologic Feature** | **1** | **2** | **3** | **4** |
| Degree of keratinization | Highly keratinized (>50% of the cells) | Moderately keratinized (20%–50% of the cells) | Minimal keratinization (5%–20% of the cells) | No keratinization (0%–5% of the cells) |
| Nuclear polymorphism | Little nuclear polymorphism (>75% mature cells) | Moderately abundant nuclear polymorphism (50%–75% mature cells) | Abundant nuclear polymorphism (25%–50% mature cells) | Extreme nuclear polymorphism (0%–25% mature cells) |
| Number of mitoses (high-power field) | 0–1 | 2–3 | 4–5 | >5 |
| Pattern of invasion | Pushing, well-delineated infiltrating borders | Infiltrating, solid cords, bands, and/or strands | Small groups or cords of infiltrating cells | Marked and widespread cellular dissociation in small groups and/or in single cells ($n < 15$) |
| Lymphoplasmocytic infiltration | Marked | Moderate | Slight | None |

*Source:* From Bryne, M., Koppang HS, Lilleng R,et al., New malignancy grading is a better prognostic indicator than Broders' grading in oral squamous cell carcinomas. *J Oral Pathol Med.* 1989;18(8):432-437, with permission.

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cervical lymph node metastases, whereas a plasmacytic infiltrate increased the risk.[2] In addition, several studies have reported a correlation between lymphocyte infiltration and improved local-regional control.[81,84,85]

Basaloid SCC (BSCC) is a rare variant of SCC that has historically been thought to be chemo- and radiosensitive, with similar-to-better loco regional control than "typical" SCC, but with higher risk of distant metastases. Soriano reported a case control series of BSCC versus SCC treated with various modalities and reported that loco regional recurrence caused death in only 15% of the BSCC patients versus 51% of the SCC patients. Distant metastasis, however, occurred in 45% versus 7%, respectively.[86] Thariat reported a case control series of radiated patients with BSCC versus poorly differentiated (PSCC) or well-differentiated SCC (WSCC). The loco-regional control for BSCC, PSCC, and WSCC was similar at 81%, 86%, and 82%, respectively; distant metastases free survival was worse for BSCC at 71%, 86%, and 86%, respectively, but not significantly so.[87]

Why the seeming inconsistency that BSCC is considered an aggressive variant of SCC, yet HPV-associated SCC is more commonly BSCC but has a better prognosis? It may be that BSCC is a more heterogeneous disease than previously recognized. Certainly the demographics of the BSCC patient are evolving: whereas the typical BSCC patient has been thought to be in his 60s or 70s, with history of frequent, intense tobacco use and alcohol use, recent cases have also affected young women without a significant tobacco or alcohol history, suggesting a causal link between BSCC and HPV-associated SCC.[88] Therefore, BSCC may have a dual nature similar to SCC, depending on factors such as HPV status and tobacco and alcohol use.

## Perineural Invasion

Infiltration of perineural spaces occurs in up to 52%[89] of HNSCCs and was first noted to influence surgical and adjuvant treatment strategies by Ballantyne et al. in 1963.[90] Perineural invasion (PNI) may result in dysphagia secondary to involvement of the vagal trunk[91] or pain and paresthesias along the territories of the glossopharyngeal or trigeminal nerves.[91,92] CT findings suggestive of PNI include obliteration of the fat within the pterygopalatine fossa, enlargement of neural foramina, and increased enhancement in the region of Meckel's cave.[93] In addition, a study of 48 patients with oral tongue, base of tongue, or floor of mouth SCC utilized CT to identify the presence of vascular and/or PNI with a sensitivity of 88% and a specificity of 83% using criteria including "aggressive" tumor margins, invasion of the sublingual space, and direct adjacency to the lingual vasculature.[94]

PNI may be mediated by the presence of nerve cell adhesion molecule (N-CAM) on the surface of squamous carcinoma cells, which engages in homophilic binding with N-CAM expressed in neural and perineural tissues. In two studies of 76 and 66 patients with HNSCC, expression of N-CAM on the surface of neoplastic cells was significantly associated with PNI detected on review of pathologic sections.[95,96]

Numerous clinical studies have identified PNI as an important predictor of poor prognosis. In tumors arising from the lower lip,[4,97,98] oral tongue,[99] oral cavity,[20,89,100,101] larynx,[102] and all sites combined,[2,3] the presence of PNI is associated with a higher risk of metastasis to regional lymph nodes. Furthermore, following definitive treatment of HNSCC, the presence of PNI in the primary tumor is associated with poor local control,[4,89,103,104] regional control,[64] local-regional control,[81,84,105,106] cause-specific survival,[89,105] and overall survival.[44,105] PNI has been associated with an increased risk of distant metastasis in some,[107] though not all,[108] studies.

The association between PNI and local recurrence may result from either centrifugal or centripetal propagation of malignant cells along perineural spaces and away from the primary tumor. Most primary tumors will only disseminate up to 2 cm along the perineural space,[109] although PNI 12 cm from the primary tumor has been reported.[90] As a result, PNI may allow malignant cells to evade surgical excision or radiotherapy and result in local recurrence. In addition, the association between PNI and regional recurrence implies that these tumors may be more biologically aggressive. The association between *perineural* invasion and tumor aneuploidy, a known marker of poor prognosis, lends support to this hypothesis.[110]

Despite the clear importance of PNI, the percentage of mucosal HNSCCs positive for PNI varies widely in the literature, from 5%[104] to 52%.[89] This discrepancy may result from a tendency to identify PNI only when large, named nerves are involved. However, although PNI of small, unnamed nerves may not result in clinical symptoms, the relationship between PNI and prognosis appears to be independent of nerve diameter.[89] Hence, all HNSCC pathologic specimens should be closely examined for PNI, even in nerves <1 mm in diameter.

## Vascular Invasion

Vascular invasion, defined as the presence of neoplastic epithelium within an endothelial-lined channel, occurs in over 50% of HNSCCs.[5,22,111] As with tumor depth and pattern of invasion, the presence of vascular invasion may identify tumors with an aggressive biologic nature due to their ability to invade normal anatomic structures. Indeed, vascular invasion has been shown to correlate with the presence of concomitant cervical metastases in both univariate[20,22,45,103,111] and multivariate models.[2,3,99,112] In addition, the presence of vascular invasion in the primary tumor specimen has been noted to increase the risk for subsequent local regional recurrence in oral cavity, oropharyngeal, and laryngeal SCC treated surgically.[5,64,103] However, in a large series of 226 patients treated with surgery and postoperative radiotherapy, vascular invasion did not correlate with local-regional control, suggesting that postoperative radiotherapy may mitigate the poor prognosis associated with vascular invasion.[106] Vascular invasion has also been associated with increased risk of distant metastatic disease.[5,69]

## Imaging

$^{18}$F-fluorodeoxyglucose (FDG) PET scan is a functional test that combines a positron-emitting nuclide with a glucose molecule, thereby revealing areas of increased glucose metabolism. PET/CT scans are commonly performed prior to therapy to determine extent of disease, and afterward to assess response and need for further treatment.

The utility of a posttreatment PET has been well studied. Isles performed a meta-analysis of radiated patients who received posttreatment FDG PET scans. The weighted mean pooled sensitivity, specificity, PPV, and NPV of posttreatment PET for the primary site was 94%, 82%, 75%, and 95%, respectively. At the neck, the corresponding numbers were 74%, 88%, 49%, and 96%, respectively. They reported that sensitivity was greater for scans performed 10 weeks or longer after completion of therapy.[113] Gupta also performed a meta-analysis; his corresponding numbers for the primary site were 79.9%, 87.5%, 58.6%, and 95.1%, respectively, and for the neck 72.7%, 87.6%, 52.1%, and 94.5%, respectively. Scans performed ≥12 weeks after therapy had moderately higher diagnostic accuracy.[114]

Moeller prospectively compared posttreatment PET/CT with contrast-enhanced CT in radiated patients. Patients were imaged with PET/CT and CT prior to and 8 weeks after radiation.

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Though postradiation maximum SUVs were significantly higher in nonresponders compared with responders, the positive and negative predictive values for PET/CT were similar to CT alone. In order to improve the PPV of the postradiation scans, they stratified patients into high-risk (HPV negative, nonoropharynx primary, tobacco history) and low-risk categories. In the high-risk patients, PET/CT outperformed CT alone, especially in terms of accurately detecting residual nodal disease, where the PPV for PET/CT was twice that of CT alone (75% vs. 37.5%).[115]

Whether pretreatment PET/CT reveals loco-regional versus metastatic disease is clearly prognostic, but the predictive value of pretreatment SUV in localized disease is controversial. Moeller found no significant difference in the pretreatment SUVmax at the primary site or lymph nodes between responders and nonresponders.[115] Higgins came to a similar conclusion, but did report that increased pretreatment SUVmean at the primary site correlated with disease-free survival.[116] Imsande found that SUVmax at the primary site correlated with overall survival, whereas Demirci found that disease-free survival correlated with nodal (but not primary site) SUVmax.[117,118] Tang[119] evaluated metabolic tumor volume (MTV) on pretreatment PET-CT and concluded that MTV was an independent predictor of outcomes. Specifically, MTV $>17$ cm$^3$ was associated with a greater risk of both disease progression and death. Lim[120] also reported that primary tumor MTV was predictive of local failure, distant metastases, and overall survival.

In conclusion, a negative posttreatment PET/CT that is appropriately timed portends a favorable prognosis and may be especially helpful in higher-risk patients. A positive result is less reliable, probably due to the possibility of a false positive due to residual inflammation or infection.

# FACTORS RELATED TO THE CERVICAL LYMPH NODES

## Number of Positive Lymph Nodes

The number, size, and location of positive cervical lymph nodes define the N stage for HNSCC and provide important information regarding prognosis and selection of treatment. The number of cervical lymph nodes histologically positive for squamous cell carcinoma provides one of the simplest, and perhaps most important, prognostic markers in head and neck cancer. Mamelle et al. retrospectively reviewed 914 patients who received cervical lymph node dissection as a component of initial therapy for oral cavity, oropharyngeal, hypopharyngeal, and laryngeal SCC.[121] Patients with palpable lymph nodes >3 cm underwent radical lymph node dissection, and all other patients underwent selective neck dissection on sentinel nodes with immediate pathologic evaluation. Those patients with positive sentinel nodes then received ipsilateral modified radical neck dissection and contralateral selective neck dissection. Thus, all patients, regardless of their clinical N stage, received pathologic evaluation of their cervical lymph nodes. Those patients with positive cervical lymph nodes received 50 Gy to the neck with a 15 Gy boost in areas of extracapsular spread. In this study, lymph node number exhibited a strong dose–response correlation with distant metastasis and survival (Fig. 3-1). In multivariate analysis stratified by tumor site and patient age, number of positive nodes was a significant, independent predictor of survival. Furthermore, although extracapsular spread and node location (upper vs. middle vs. lower neck) were significant predictors of survival in univariate analysis, after controlling for number of positive lymph nodes,

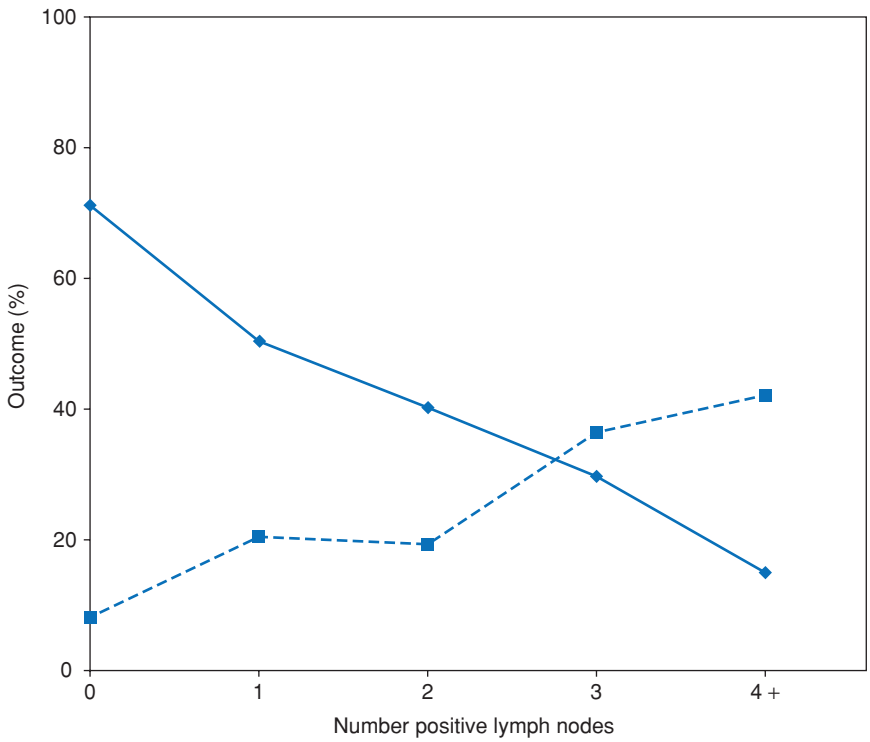



**FIGURE 3-1.** Number of positive cervical lymph nodes as a predictor of distant metastasis and 5-year overall survival in a cohort of 914 patients undergoing lymph node dissection for a primary head and neck squamous cell carcinoma.

*Source:* From Mamelle G, Pampurik J, Luboinski B, et al. Lymph node prognostic factors in head and neck squamous cell carcinomas. *Am J Surg.* 1994;168:494–498, with permission.

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they lost their prognostic significance. Thus, with this particular treatment algorithm, the number of positive nodes emerged as an important, independent predictor of prognosis.

The importance of positive cervical nodes has been noted in many other studies and appears to correlate with risk of regional recurrence and distant metastasis. Studies have demonstrated a correlation between increasing number of positive nodes and regional recurrence in patients with advanced SCC who receive postoperative radiotherapy,[122] patients who do not receive radiotherapy,[64] patients with oral cavity[30] and hypopharyngeal or lateral epilaryngeal primary tumors,[123] and patients who receive neck dissection for mucosal HNSCC from any site.[124,125] Furthermore, number of positive nodes clearly predicts risk of distant metastatic disease for all sites of HNSCC.[11,108,121,126–130] Number of positive nodes predicts both regional recurrence[64] and distant recurrence,[129] even after controlling for other prognostic variables in multivariate analysis.

Finally, the number of positive cervical lymph nodes consistently correlates with survival in univariate analysis for all major sites of HNSCC.[9,30,62,122,123,126,131–135] The relative importance of ECE versus number of positive nodes remains somewhat controversial. In addition to the Mamelle et al. study,[121] Moe et al. found the number of positive nodes to predict poor survival independent of ECE in 159 patients with advanced laryngeal cancer.[11] However, cohorts of 136 patients with clinically node positive oral cavity cancer[63] and 281 patients with supraglottic cancer[46] found that ECE, not number of positive nodes, was an independent predictor of poor survival. Differences in treatment modalities and stratification of pathologic variables may explain some of the differences noted in these studies. Regardless, patients with either multiple positive lymph nodes or ECE are at higher risk for recurrence and should be considered for aggressive therapy.

## Extracapsular Extension

ECE occurs in roughly 60% of patients with positive cervical nodes and is of paramount importance in predicting patient outcomes.[136,137] A recent study of 337 patients reported a strong association between the presence of ECE and clinical N stage, with ECE present in 10.5% (18/171) of clinical N0 patients, 35% (26/75) of clinical N1 patients, 55% (35/64) of clinical N2 patients, and 74% (20/27) of clinical N3 patients.[135] The extent of ECE can be stratified into the following three levels based on the morphology of the involved cervical lymph nodes: (a) macroscopic extracapsular spread with involvement of adjacent anatomic structures such as the internal jugular vein or skeletal muscle, (b) macroscopic extracapsular spread confined to the perinodal fibro-adipose tissue, and (c) microscopic extracapsular spread.[22] A recent study of 96 dissected cervical lymph nodes with ECE measured the maximum distance from the capsule border to the farthest extent of the tumor.[138] The mean extension was 2.2 mm, and in 96% of lymph nodes the maximum extension was <5 mm. Rarely, the extension measured up to 9 mm. These findings have important implications for target delineation in the setting of intensity modulated radiation therapy to treat lymph nodes at high risk for ECE.

As a general marker of tumor invasiveness and biologic aggressiveness, some authors have proposed that the presence of ECE in cervical lymph nodes may predict recurrence at the primary site. This hypothesis remains unresolved, as two studies conducted on a total of 207 patients with laryngeal cancer noted a significant association between ECE and local recurrence,[139,140] but two other studies conducted on a total of 392 HNSCC patients failed to confirm this association.[123,136]

Regardless of its relationship with local recurrence, ECE is a significant determinant of prognosis due to its association with increased risk of recurrence in the neck and distant metastatic disease. For example, in a review of 284 patients with HNSCC who received neck dissection as a component of initial therapy, the presence of gross or microscopic ECE tripled the risk of neck recurrence in multivariate modeling.[64] In addition, patients with gross ECE were 1.5 times more likely to develop regional recurrence when compared to patients with microscopic ECE, although this trend did not reach statistical significance. Many other series have confirmed this relationship for the following sites: oral tongue,[22] oral cavity and oropharynx,[5,29] hypopharynx and lateral epilarynx,[123] pyriform sinus,[9] supraglottic larynx,[139,141] larynx,[140,142,143] and all sites combined.[70,122,124,125,144] The association between ECE and regional recurrence is independent of other prognostic variables in HNSCC.[64,125,142]

The presence of ECE also increases the risk of distant metastatic disease. In a review of 281 patients who received a neck dissection as a component of initial therapy for HNSCC, the presence of ECE tripled the risk of distant metastasis as the first site of failure (19.1% in ECE positive patients vs. 6.7% in ECE negative patients).[127] These findings have been reproduced in several large studies.[108,126,128,135,145] Currently, it is unclear whether the relationship between ECE and distant metastatic disease is independent of the number, size, and location of positive cervical lymph nodes.

In addition, ECE is a significant predictor of poor disease-free, cause-specific, and overall survival. In a retrospective study of 281 patients with supraglottic SCC treated with surgery with or without postoperative radiotherapy, pathologic N0 patients experienced a 5-year overall survival of 65%, compared to 49% in node-positive patients without ECE and 20% in node-positive patients with ECE.[46] In a multivariate model, the presence of ECE conferred the highest risk of death, resulting in a sixfold increased risk of death when compared with node-negative patients. In contrast, patients with positive nodes but no ECE experienced a threefold increased risk of death. This independent association between ECE and poor cause-specific or overall survival has been confirmed for the following sites: oral cavity,[63] oral cavity and oropharynx,[5] supraglottic larynx,[62] larynx and hypopharynx,[143] and all sites combined.[49,125,142]

The importance of ECE as compared to other pathologic factors was underscored in a prospective randomized clinical trial conducted by Peters et al. that evaluated radiation dose in the postoperative setting.[146] In this trial, patients with ECE experienced significantly higher local-regional recurrence rates than patients without ECE. In addition, in the subset of patients without ECE, only those patients with four or more adverse risk factors experienced a local-regional recurrence rate comparable to those patients with ECE. Adverse factors examined included oral cavity primary, close or positive margins, PNI, two or more positive nodes, largest node >3 cm, Zubrod score ≥2, and delay in starting radiotherapy. As a result, the study authors concluded that ECE is the dominant pathologic risk factor in HNSCC. Furthermore, this study showed that, in patients with ECE, local-regional control increased from 52% to 74% as dose increased from 57.6 to 63 Gy. No such dose–response was evident for patients without ECE, suggesting that tumors with ECE require a higher dose of postoperative radiation to achieve adequate local-regional control.

Due to the poor prognosis associated with ECE, several investigators have explored the potential benefit of postoperative chemoradiation in this patient population. The first randomized data to support a benefit of chemoradiation was reported by Bachaud et al. in 1996.[147] This trial included 83 patients with histologically documented ECE treated with surgery and postoperative radiation with or without concurrent cisplatin (50 mg given weekly with radiation for seven to nine cycles). The addition of cisplatin lowered the risk of local-regional recurrence, from 41% in the radiation alone group down to 23% in the chemoradiation

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group. Subsequently, large multicenter trials conducted by the Radiation Therapy and Oncology Group (RTOG) and the European Organization for the Research and Treatment of Cancer (EORTC) randomized patients with high-risk, resected head and neck cancer to receive postoperative radiation or postoperative radiation with concurrent cisplatin (100 mg/m$^2$ given on days 1, 22, and 43).[58,59] A *post hoc* pooled analysis revealed that the addition of cisplatin was specifically beneficial for patients with ECE, lowering the relative risk of local-regional recurrence by 50% and also improving overall survival.[60] The updated data on the RTOG 9501 Intergroup Phase III trial has failed to show an overall benefit to the addition of chemotherapy, with a median follow-up of 9.4 years.[148] However, the subgroups with positive resection margins or extracapsular spread did have improved loco regional control with the addition of chemotherapy.

## Node Location

The anatomic location of positive cervical lymph nodes has been classically described by dividing the neck into five anatomic levels.[149] Level I refers to nodes within the submandibular and submental triangles. Levels II, III, and IV refer to the chain of nodes along the upper, middle, and lower third of the jugular vein, respectively. Level V refers to nodes along the spinal accessory nerve and within the posterior cervical triangle. Using these categories, Mamelle et al. defined sentinel nodes as those nodal groups that provide the primary lymphatic drainage for a particular site within the head and neck.[121] Thus, sentinel nodes for oral cavity tumors were defined as levels I, II, and III; and sentinel nodes for oropharyngeal, hypopharyngeal, and laryngeal tumors were defined as levels II and III. Applying this classification to cervical node pathologic specimens from 914 HNSCC patients, Mamelle et al. found that the presence of nodal metastases outside the sentinel node region independently decreased 5-year survival by more than 50% and nearly doubled the rate of distant metastasis. Furthermore, node location inside versus outside of the sentinel area predicted survival independent of number of positive nodes and extracapsular spread. The increased risk of regional recurrence, distant recurrence, and death associated with positive low cervical lymph nodes has been noted in several other studies of patients with HNSCC.[11,36,123,129,131,132,134,150,151] Setton[152] reported that low-lying cervical metastases (levels IV, VB) were independent predictors of distant metastasis. Finally, de Bree et al. found that 33% of HNSCC patients with low jugular lymph node metastases showed evidence of concomitant distant metastatic disease on preoperative CT of the thorax.[1] Clearly, patients with positive lymph nodes outside of the sentinel node regions merit aggressive preoperative screening for distant disease and are at increased risk of treatment failure and death following aggressive local-regional therapy.

## Node Size

The diameter of the largest metastatic cervical lymph node contributes to the assessment of N stage in HNSCC and may correspond with total tumor burden. In a review of 250 radical neck dissection specimens, Carter et al. found that pathologic nodal size >2 cm correlated with increased risk for regional recurrence.[125] However, several other studies have failed to determine a relationship between node size assessed clinically or pathologically and either regional recurrence or local-regional recurrence.[36,38,124] In contrast, Mamelle et al. found that nodal size increased the risk of distant metastases, with patients having nodal diameter <3 cm experiencing a distant metastasis rate of 22%, compared with 35% for patients with nodal diameter between 3 cm and 6 cm and 49% for patients with nodal diameter >6 cm.[121] Furthermore, in a multivariate analysis of clinical parameters only, node size was a significant predictor of poor overall survival. In contrast, other studies have not found an independent relationship between pathologically assessed nodal size and survival when other relevant pathologic variables are considered.[9,38,125,143] Thus, the diameter of the largest positive cervical lymph node may serve as a helpful clinical predictor of outcome, but may not exert an independent prognostic when other pathologic factors are considered.

## Pathologic Residual Disease on Neck Dissection After Chemotherapy

In Chapter 14, there is a comprehensive discussion of all aspects of neck management. In the current era of definitive, concomitant chemotherapy-radiation therapy, neck dissection is often used exclusively when there is suspicion of residual disease on PET-CT performed about 3 months after treatment. This is discussed at length in Chapter 14. For this subset of patients, the presence of pathologic residual disease in the neck after chemotherapy has prognostic value.[153] Hu also reported the prognostic value of pathologic residual neck disease in patients who have planned neck dissections after chemotherapy. In both subsets, there is an adverse impact on risk of distant metastasis and disease-free survival.

# DEMOGRAPHIC PARAMETERS

## Age

Age is a commonly considered covariate and is known to influence outcome in certain types of cancer. For example, patient age and attendant comorbidities may influence the vigor of the immune response directed against the tumor and the patient's ability to tolerate maximal therapy. In addition, head and neck cancers arising in patients at either extreme of the age continuum may result from different etiologic agents and thus manifest different clinical outcomes. For example, Schantz et al. found that cultured lymphocytes from nonsmoking young adults with HNSCC were more susceptible to bleomycin-induced chromosome damage than lymphocytes from older smokers with HNSCC and healthy controls, suggesting that genetic susceptibility to environmental carcinogens may influence the risk of HNSCC in young adults.[154] Recently, investigators have noted a striking increase in the incidence of tongue and tonsillar cancer in adults under 40 years of age, thus prompting additional interest in the risk factors, natural history, and optimal treatment of HNSCC in the young.[155] The relationship of HPV to these malignancies has become well established and is covered later in this chapter as well as in Chapter 12.

Risk factor profiles indicate that young adults with HNSCC are less likely to report prior exposure to tobacco or alcohol and more likely to be female.[156,157] With respect to clinical outcome, Siegelman-Danieli et al. examined a retrospective cohort of 87 oral tongue SCC patients, 30 of whom were 45 years of age or younger at the time of diagnosis.[157] In this study, age did not influence relapse rates, cancer-free survival, or overall survival in both univariate and multivariate analysis. Similarly, Verschuur et al. conducted a retrospective case-control study on 185 previously untreated HNSCC patients under the age of 40 who were matched to controls based on tumor site, sex, and date of presentation.[156] Age did not influence cause-specific survival in univariate or multivariate analysis. However, older patients were twice as likely to develop second primary SCCs of the upper aerodigestive tract (14% vs. 7%), possibly due to their increased use of tobacco products. The effect of young age remains controversial, however, as a recent report on 1,030 HNSCC patients found that the recurrence risk was 50% less for patients under the age of

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40 as compared to those over the age of 40, even after controlling for TNM stage, primary tumor site, and comorbidity.[158] Therefore, the current literature suggests that young patients experience a prognosis that is either similar to or slightly better than that experienced by older patients. Because HPV status was not known in most prior studies, its effect on this cohort is difficult to assess.

Head and neck cancers in elderly populations also present a different epidemiologic profile. In a study of 161 elderly patients with HNSCC, Leon et al. found that patients over the age of 70 were less likely to use tobacco and alcohol and more likely to be female.[159] The decreased consumption of tobacco and alcohol in elderly HNSCC patients correlates with a lower incidence of *p53* mutations in this population.[160] With respect to survival, Leon et al. demonstrated that although elderly laryngeal cancer patients experienced worse overall survival, cause-specific survival was not influenced by patient age. Furthermore, in a prospective study of 203 head and neck cancer patients, advanced age correlated with worsening 2-year overall survival in univariate analysis, but this association was not significant when adjusted for TNM stage and the presence of comorbid illness.[161] Finally, a population-based case-control study that included over 5,000 patients found that, after adjusting for stage, elderly patients age 70 years and older did not experience significantly worse cause-specific survival than their younger counterparts.[162] Thus, although elderly HNSCC patients may present with different risk factor profiles and are at increased risk of death from comorbid illness, they are not at an increased risk of death from cancer and should receive curative treatment if possible.

Though their cancers may not necessarily act worse stage for stage, the patients themselves may have difficulty withstanding the most toxic treatments. For example, chemoradiation is associated acutely with skin and hematologic toxicities, fatigue, mucositis, dysphagia, odynophagia, xerostomia, and change in taste. The meta-analysis of chemotherapy in head and neck cancer (MACH NC) reported that the benefit of adding concurrent chemotherapy to radiation decreased with advancing age. There was a significant OS advantage for patients up to 70 years old, but not for patients 71 and older.[163] In a more recent publication, MACH NC breaks down the benefit by primary site in addition to age.[164]

## Sex

Sex is not generally considered a significant determinant of survival in patients with head and neck cancer. Indeed, most large series have failed to find a significant difference in outcome with respect to sex.[66,165–170] In contrast, one relatively large study conducted on 278 patients with stage I to IV laryngeal cancer found an independent association between sex and survival.[38] In this study, female patients experienced a 76% 3-year overall survival, compared to 63% in male patients. However, the disease-free interval was nearly identical, 60.4 months in women and 59.7 months in men. Thus, it is likely that the survival benefit experienced by women was more likely due to sex-specific differences in the distribution of comorbid illness rather than sex-specific differences in tumor behavior.

## Race

Data from the National Cancer Institute's SEER registry indicate that both the incidence of HNSCC and its disease-specific mortality are higher in Black males than White males.[171] In contrast, such race-based differences are not apparent among females. Race-based differences in stage at presentation may account for the increased burden of HNSCC mortality among Black males. For example, in a cohort of 295,022 patients with HNSCC reported by the National Cancer Database, 40% of African Americans presented with stage IV disease, compared with 24% of Whites and 26.4% of Hispanics.[71] Other factors that may contribute to increased disease-specific mortality in Black males may include a higher prevalence of alcohol abuse and lack of health insurance.[172] In studies that have adjusted for both disease-related and socioeconomic-related factors, Black race does not appear to be associated with increased disease-specific mortality, suggesting that the biologic aggressiveness of HNSCC does not fundamentally differ between White and Black patients.[161,172] However, one study has shown that Black race is associated with a higher risk of distant metastatic disease even after adjusting for relevant covariates,[173] and this finding merits further study.

Recently, Settle et al. proposed an alternative reason for Black HNSCC patients' worse prognosis. They looked retrospectively at data from the phase 3, multicenter TAX 324 trial of induction chemotherapy followed by concurrent chemoradiation in HNSCC patients. The racial disparity in overall survival was due entirely to the subgroup of patients with oropharyngeal cancer, in which the OS for Whites versus Blacks was 69.4 months and 25.2 months, respectively ($p = 0.0006$). OS was not reached in the HPV-positive patients versus 26.6 months in the HPV-negative patients (hazard ratio [HR] 5.1; $p < 0.0001$). Whites were significantly more often HPV-16 positive than Blacks, 34% versus 4% ($p = 0.0004$). Furthermore, survival was similar for Whites versus Blacks in nonoropharyngeal sites and in HPV-negative patients.[174] This study represents one of the very first biologic rather than socioeconomic rationales for difference in racial outcomes in HNSCC.

## Alcohol and Tobacco Exposure

Tobacco and alcohol use have long been recognized as important risk factors for the development of HNSCC. Exposure to these carcinogens results in specific molecular insults that promote neoplasia. For example, cigarette smoking has been associated with overexpression of the proto-oncogene bcl-2, a protein known to inhibit apoptosis.[175] In addition, concurrent use of alcohol and tobacco has been associated with a high rate of nonspecific mutations in the tumor suppressor gene *p53*.[176] Perhaps as a result of these deleterious mutations, prior or continued use of alcohol and tobacco in patients with head and neck cancer is a risk factor for poor outcome. Furthermore, use of these substances has been associated with immunosuppression, malnutrition, and impaired tissue oxygenation resulting in hypoxic radioresistance.

The most rigorous exploration of the relationship between alcohol consumption and outcome in head and neck cancer patients resulted from a prospective study of 649 patients who received in-depth questioning near the time of diagnosis regarding alcohol consumption, treatment for alcoholism, abstinence from alcohol prior to the diagnosis of cancer, and alcohol-related health problems.[66] The authors utilized the Michigan Alcoholism Screening Test (MAST) to devise a three-tier alcohol severity staging system to allow rapid risk stratification of head and neck cancer patients. Stage A included nonalcoholics and abstinent (less than one drink per week) alcoholics without a history of alcohol-related systemic health problems. Stage B included abstinent alcoholics with a history of alcohol-related systemic health problems and alcoholics currently drinking without a history of alcohol-related systemic health problems. Stage C included alcoholics currently drinking with a history of alcohol-related systemic health problems. Patients in stages B and C were more likely to die from any cause following treatment for HNSCC. In addition, after adjusting for other potential predictors of survival, stage C patients were two times more likely than stage A patients to die from HNSCC. The authors speculated that alcohol intake may influence outcomes by contributing to immunosuppression and malnutrition.

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Of note, this study provided indirect evidence that interventions to eliminate alcohol intake may help to improve outcomes. After controlling for relevant covariates, alcoholics abstinent at the time of diagnosis were half as likely to die as alcoholics who were currently drinking. Eighty percent of abstinent alcoholics had received formal treatment for their alcoholism, either through inpatient programs or Alcoholics Anonymous.

The interaction between cigarette smoking and response to radiotherapy was demonstrated in a prospective study of stage III to IV HNSCC patients treated with primary irradiation with or without concomitant 5-fluorouracil.[177] Any smoking during the 6½-week course of radiotherapy decreased the complete response rate from 74% to 45%, the 2-year survival rate from 66% to 39%, and the median survival from 30 to 16 months. In addition, mortality was influenced by the length of time between smoking cessation and initiation of treatment, with a risk reduction of 40% for those patients who quit <12 weeks prior to diagnosis and of 70% for patients who quit more than 1 year prior to diagnosis. In multivariate analysis, smoking was the only significant predictor of survival, with those who abstained 2.5 times more likely to survive. The authors speculated that the deleterious impact of smoking may be related to lower levels of natural-killer-cell activity, reduced cell-mediated immunity, and increased blood carboxyhemoglobin concentrations, resulting in tissue hypoxia and increased radioresistance.[178] The adverse effect of continued smoking during radiotherapy has also been noted in two studies conducted on patients with T1 and T2 glottic carcinomas treated with primary radiation.[179,180] In addition to mortality, continued smoking doubles the risk of long-term complications in patients with T1 glottic cancer treated with primary radiation.[181]

To evaluate the effect of alcohol and tobacco consumption on the risk of second primary malignancies, Day et al. conducted a nested case-control study composed of 80 case patients with second cancers and 189 sex- and survival-matched oral cancer patients free of second cancers.[182] The risk of a second primary tumor of the aerodigestive tract (oral cavity, pharynx, larynx, esophagus, and lung) increased with both number of cigarettes smoked per day and years of cigarette smoking, peaking at odds ratio of 4.7 for those patients who smoked 40 or more cigarettes per day for 20 or more years. Similarly, consumers of 15 or more beers per week experienced a 3.8-fold increased risk of aerodigestive tract second primary tumors when compared to nondrinkers or light drinkers (0–4 drinks per week). There was little or no excess risk for hard liquor and wine drinking.

Day et al. also investigated the relationship between cessation of smoking or drinking at the time of diagnosis and risk of second primary tumor. Cessation of smoking at the time of diagnosis did not decrease the risk of second primary tumors within the first 5 years after diagnosis. However, risk was significantly reduced 5 years after smoking cessation. Thus, smoking cessation at the time of diagnosis may reduce the long-term risk of second primary tumors. No clear trend existed between cessation of alcohol consumption and risk.

Due to the well-documented deleterious effects of tobacco and alcohol use, in addition to data suggesting that abstinence from these substances may improve outcomes, substance abuse counseling and cessation programs should be integrated into the care of head and neck cancer patients.

# FACTORS RELATED TO THE PATIENT'S GENERAL MEDICAL CONDITION

## Comorbidity

Comorbidity refers to the presence of other diseases, illnesses, or conditions not directly related to the index cancer. Although not included in TNM staging, comorbidity directly influences the care of cancer patients, selection of treatment modalities, and evaluation of treatment effectiveness. Multiple instruments have been utilized to characterize comorbidity in head and neck cancer patients, and no single instrument has been consistently shown to be superior.[183] Using a four-tiered classification (none, mild, moderate, and severe), Piccirillo found that 24% of head and neck cancer patients suffer from moderate or severe comorbidity.[184] Examples of moderate comorbidity include poorly controlled hypertension, old stroke with residua, and history of an alcoholic seizure. Examples of severe comorbidity include congestive heart failure or myocardial infarction within the last 6 months, recent stroke, and severely decompensated alcoholism. In a prospective study of 1,086 patients with primary head and neck cancer, the presence of comorbidity was a significant, independent predictor of 2-year survival, even after controlling for age, sex, race, and stage.[184] As compared to patients without comorbidity, the mortality HR was 1.9 for patients with moderate comorbidity and 2.5 for patients with severe comorbidity. Similar results were reported in a study of 9,386 elderly Medicare beneficiaries with HNSCC.[185]

Given the importance of comorbidity as a predictor of survival, efforts have been made to develop new systems for staging head and neck cancer that combine TNM staging with symptom-severity and comorbidity indices. The general scheme for such a staging system of oral cavity cancer is presented in Figure 3-2. Of note, the most advanced stage, stage D, is determined solely by the presence of severe comorbidity or moderate or severe symptom severity. Hence, advanced TNM stage alone is not sufficient to merit placement in the worse prognostic category. Utilizing multivariate modeling, the investigators convincingly demonstrated that this model was more strongly predictive of disease-free and overall survival than TNM staging alone in a retrospective cohort of 277 patients with oral cavity SCC.[186] Similar results were obtained in other retrospective studies conducted on oral cavity,[187] oropharyngeal,[188] and laryngeal[189] cancers. Clearly, the combination of comorbidity, symptom severity, and TNM stage holds promise for more accurate prognostication in head and neck cancer and merits prospective validation.

## Nutritional Status

Malnutrition is common in patients with head and neck cancer and attributable to a number of causes including poor dietary habits, excessive alcohol consumption, local tumor effects, tumor-induced cachexia, and the effects of various therapies.[190] In 1984, Goodwin and Torres applied a prognostic nutritional index to a retrospective cohort of 50 consecutive patients with advanced head and neck cancer to determine whether nutritional status influenced postoperative complications and survival.[191] The prognostic nutritional index considers serum albumin, serum transferrin, triceps skin-fold thickness, and cutaneous delayed hypersensitivity to mumps, streptokinase-streptodornase, or candida. This index was generated from retrospective review of 161 patients undergoing gastrointestinal surgery and then prospectively validated in 100 patients as an indicator of risk for postoperative complications.[192] Goodwin and Torres found that 89% (8/9) of patients with prognostic nutritional index >39% suffered major postoperative complications, compared to 14% (4/29) of patients with prognostic nutritional index ≤39%. In addition, 64% (9/14) of the patients with prognostic nutritional index >39% died of their disease within 1 year, compared to 28% (10/36) of patients with prognostic nutritional index ≤39%.

The relationship between nutritional status, postoperative complications, and survival has been further explored in several prospective studies. In an analysis of six different nutritional parameters, 10% weight loss in the 6 months preceding surgery was the only significant, independent predictor of major

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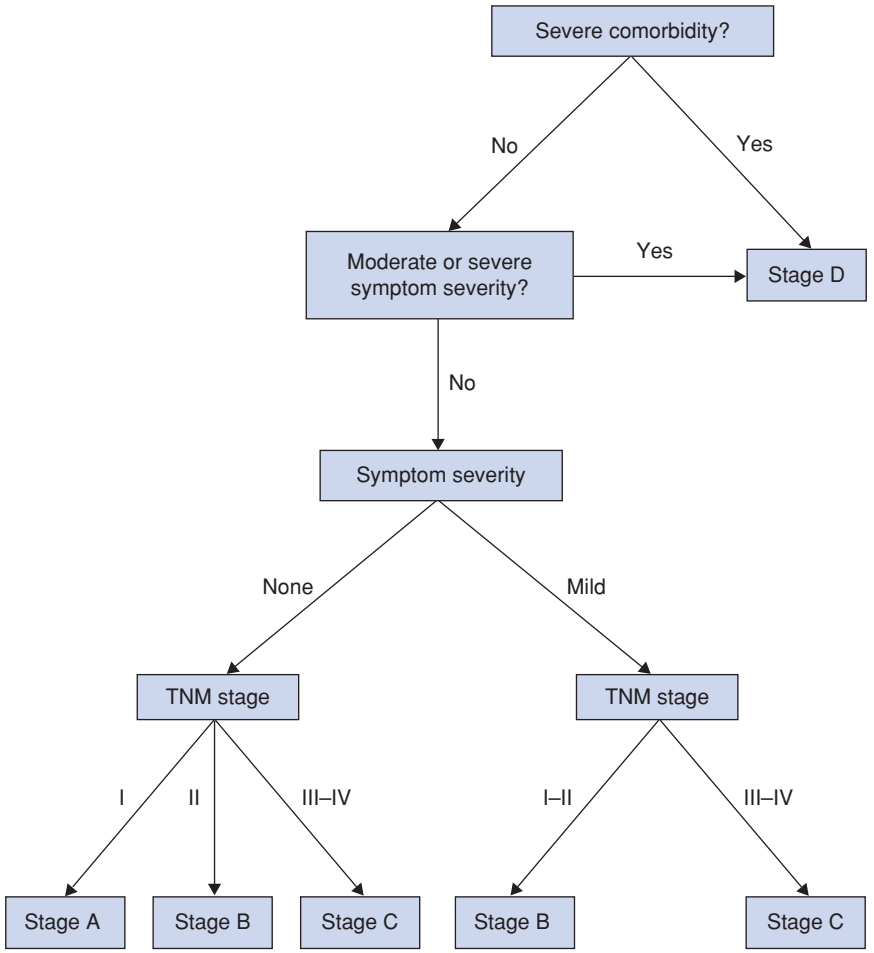



**FIGURE 3-2.** Decision tree for clinical-severity staging of oral cavity cancer.

*Source:* From Pugliano FA, Piccirillo JF, Zequeira MR, et al. Clinical-severity staging system for oral cavity cancer: five-year survival rates. *Otolaryngol Head Neck Surg.* 1999;120:38–45, with permission.

postoperative complications in a cohort of 64 patients with T2-4 carcinomas of the oral cavity, oropharynx, hypopharynx, and larynx.[193] In a subsequent study, 5% weight loss in the 6 months preceding initial treatment for advanced HSNCC was identified as an independent predictor of poor disease-specific survival in men but not women.[194]

Given the strong evidence for an association between malnutrition and an increased risk of postoperative complications, interest has grown in evaluating the benefits of nutritional support. A meta-analysis of 28 trials revealed that preoperative parenteral nutrition lowers the risk of major surgical complications and surgical mortality for patients with gastrointestinal cancers,[195] yet a small randomized trial of preoperative tube feeding in 49 severely malnourished head and neck cancer failed to show a similar benefit.[196] An observational study of 1,073 patients treated with definitive radiation therapy on RTOG 90-03 examined the correlation between baseline nutritional support (BNS), radiation toxicity, and survival.[197] BNS was defined as either oral supplements, enteral feedings, or parenteral nutrition used by the patient prior to beginning radiation. BNS was associated with a slightly lower risk of grade 3 or 4 radiation-induced mucositis: 34% with BNS versus 40% without BNS. However, even after adjusting for potential confounders, BNS was associated with a highly significant 1.5-fold increased risk of local-regional failure. This finding generated the hypothesis that nutritional support of head and neck cancer patients, though beneficial for their general medical condition and for minimizing toxicity of therapy, may actually exert a deleterious effect on cancer outcomes by providing the cancer with nutrients needed to resist the effects of radiation therapy. This hypothesis clearly merits further prospective study.

## Anemia

Anemia commonly occurs in patients with head and neck cancer and may be due to a number of causes, including comorbid illness, intraoperative blood loss, toxicity from chemotherapy and/or radiation, and malignancy-associated anemia of chronic disease. Anemia is commonly thought to enhance radioresistance via enhancing tumor hypoxia. Numerous retrospective studies have suggested a strong association between anemia and inferior local-regional control and survival among patients treated for HNSCC (Table 3.2).[198–217] This association has been reported for patients with both early and advanced disease treated with a variety of treatment modalities, including radiation alone, chemoradiation, surgery and postoperative radiation, and surgery alone. The finding that anemia correlates with inferior local-regional control among patients treated with

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**TABLE 3.2 Prognostic Significance of Anemia in Head and Neck Cancer**

| Author | Description of Patients | Treatment Given | MVT | Local/Regional Recurrence | Survival | Measure of Anemia |
|---|---|---|---|---|---|---|
| Overgaard et al.[198] | 950 Larynx or pharynx SCC | RT | No | Yes ($p < 0.01$) | OS ($p < 0.01$) | Hemoglobin <14.5 g/dL for men and <13.0 g/dL for women pretreatment |
| van Acht et al.[199] | 357 T1-4 N0-2 glottic or supraglottic SCC | RT | Yes | NR | DFS ($p < 0.05$)<br>OS ($p > 0.05$) | Hemoglobin <11.0 mmol/L for men and <10.0 mmol/L for women at day 35 of RT<br>Decrease in hemoglobin ≥1.0 from before treatment to day 35 of RT |
| Dubray et al.[200] | 217 T1-4 N0-3 oral cavity and oropharynx SCC | RT and surgical salvage | Yes | Trend ($p = 0.06$) | OS ($p = 0.04$) | Hemoglobin <13.5 g/dL for men and <12.0 g/dL for women pretreatment |
| Tarnawski et al.[201] | 847 T1-4 N0-2 laryngeal supraglottic SCC | RT | Yes | Yes ($p < 0.0001$) | NR | Hemoglobin as continuous variable and change in hemoglobin during treatment period |
| Lee et al.[202] | 451 Stage III or IV HNSCC | RT | Yes | Yes ($p = 0.003$) | OS ($p = 0.0007$) | Hemoglobin <14.5 g/dL for men and <13.0 g/dL for women pretreatment |
| Overgaard et al.[203] | 422 (414 eligible) T1-4 N0-3 pharynx and supraglottic larynx SCC | RT and surgical salvage | Yes | Yes ($p = 0.001$) | Trend DFS and recurrence ($p = 0.09$) | Hemoglobin <9.0 mmol/L for men and <8.0 mmol/L for women pretreatment |
| Warde et al.[204] | 735 T1-2 glottic SCC | RT | Yes | Yes ($p < 0.05$) | NR | Hemoglobin <10.0 g/dL to <14.0 g/dL |
| Lutterbach et al.[205] | 258 T1-4 glottic SCC | Surgery | Yes | Yes ($p < 0.05$) | NR | Hemoglobin <13.0 g/dL for men and <12.0 g/dL for women pretreatment |
| Glaser et al.[206] | 191 T2-4 N0-3 M0 oral cavity or oropharynx SCC | RT, CTX, surgery | No | Yes ($p < 0.05$) | OS ($p < 0.05$) | Hemoglobin <14.5 g/dL with or without exogenous erythropoetin treatment |
| Nguyen-Tan et al.[207] | 223 T3-4 larynx SCC | Any | Yes | Yes ($p = 0.01$) univariate only | OS ($p < 0.001$) | Hemoglobin nadir during RT as continuous variable |
| Jin et al.[208] | 238 T1 N0 glottic SCC | RT | Yes | Yes ($p = 0.03$) | No | Hemoglobin drop >1 g/dL during treatment |
| Daly et al.[209] | 238 Stage III–IV HNSCC | RT | Yes | Yes ($p = 0.009$) | CSS ($p = .009$) | Hemoglobin <13 g/dL in men and <12 g/dL in females pretreatment |
| Grau et al.[210] | 478 Stage III–IV HNSCC | RT +/– mitomycin C | No | Yes ($p = 0.02$) | No | Hemoglobin drop >1.3 g/dL during treatment |
| Reichel et al.[211] | 120 Stage I–IV HNSCC | surgery + postoperative chemoradiation | Yes | Yes ($p = 0.02$) | OS ($p = 0.008$) | Hemoglobin <13 g/dL in men and <12 g/dL in females postoperatively |
| Schafer et al.[212] | 214 Stage I–IV HNSCC | RT +/– surgery +/– chemotherapy | Yes | NR | OS ($p = 0.01$)<br>DFS ($p = 0.05$) | Hemoglobin stratified into quartiles pretreatment |
| Cho et al.[213] | 246 T1-2 N0 larynx SCC | RT | Yes | Yes ($p = 0.03$) | OS ($p < 0.001$) | Hemoglobin stratified into quartiles pretreatment |

*(continued)*

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**TABLE 3.2 Prognostic Significance of Anemia in Head and Neck Cancer (Continued)**

| Author | Description of Patients | Treatment Given | MVT | Local/Regional Recurrence | Survival | Measure of Anemia |
|---|---|---|---|---|---|---|
| Chua et al.[214] | 334 Ho Stage III–IV nasopharyngeal SCC | RT +/– induction chemotherapy | Yes | Yes ($p = 0.001$) | CSS ($p = 0.01$) | Midradiation hemoglobin ≤11 g/dL |
| Denis et al.[215] | 226 Stage III–IV oropharynx SCC | RT +/– concurrent chemotherapy | Yes | Yes ($p < 0.05$) | OS ($p < 0.05$)<br>CSS ($p < 0.05$) | Hemoglobin <12.5 g/dL pretreatment |
| Haugen et al.[216] | 214 Stage I–IV larynx SCC | RT | Yes | Yes ($p = 0.02$) | DFS ($p = 0.004$)<br>OS ($p = 0.003$) | Hemoglobin <13.75 g/dL pretreatment |
| Prosnitz et al.[217] | 159 Stage III–IV HNSCC | RT + concurrent chemotherapy | Yes | Yes ($p = 0.05$) | OS ($p = 0.05$)<br>DFS ($p = 0.05$) | Hemoglobin <13.5 g/dL pretreatment |

CSS, cause-specific survival; CTX, chemotherapy; DFS, disease-free survival; HNSCC, head and neck squamous cell carcinoma; MVT, multivariate; NR, not reported; OS, overall survival; SCC, squamous cell carcinoma.

surgery alone suggests that anemia may influence outcome in head and neck cancer patients independent of its influence on hypoxic radioresistance.[205]

The optimal timepoint to assess anemia for the purposes of prognostication is unclear and varies widely throughout the literature (Table 3.2). Options include pretreatment hemoglobin, midradiation hemoglobin, postoperative hemoglobin, and drop in hemoglobin concentration during radiation. Due to colinearity in these measures, they all likely confer some degree of prognostic significance. The optimal hemoglobin cutpoint for defining anemia is also unclear, ranging from 10 to 14 g/dL, depending on the study (Table 3.2). Denis et al. used an ROC curve to conclude that 12.5 g/dL is the best cutpoint for predicting mortality.[215] In addition, at least two studies have shown a strong dose-response relationship when hemoglobin is divided into quartiles,[212,213] suggesting that a single cutpoint for defining anemia may be inadequate.

Given the strong association between anemia and adverse outcomes, two randomized trials were launched to assess the benefit of treating anemic patients with recombinant erythropoietin (EPO) during radiotherapy. The first study, a double-blind, placebo-controlled randomized trial reported by Henke et al. in 2003, found that administration of epoetin-$\beta$ increased the median hemoglobin concentration from 11.7 g/dL pretreatment to 14.8 g/dL posttreatment.[218] However, patients who received epoetin-$\beta$ experienced inferior local-regional control (HR, 1.62; 95% confidence interval [CI], 1.22–2.14) and inferior overall survival (HR, 1.39; 95% CI, 1.05–1.84). This study has been criticized due to unequal distribution of certain covariates among the study arms. RTOG 99-03 similarly found that taking epoetin increased hemoglobin concentration, by 1.66 g/dL in the experimental arm compared with 0.24 g/dL decrease in the control arm ($p = 0.0001$). However, there was no statistically significant difference in the primary endpoint of local-regional failure (LRF) or overall survival.[219]

The possibility that exogenous EPO could exert a deleterious effect on control of HNSCC has prompted research into possible mechanisms. Winter et al. demonstrated that 99% of HNSCCs express the EPO receptor,[220] and Lai et al. reported that treatment of HNSCC cell lines with EPO increased invasion and proliferation.[221] Further, a secondary analysis of the trial reported by Henke et al. examined the interaction of EPO administration with EPO receptor expression among 154 patients treated at a single institution.[222] In this study, 67% of tumors had moderate or strong expression of the EPO receptor and were considered EPO receptor positive. Among EPO receptor positive tumors, administration of EPO was associated with an increased risk of local-regional failure (relative risk, 2.07; 95% CI, 1.27–3.36). In contrast, among EPO receptor negative tumors, administration of EPO did not affect local-regional control (relative risk, 0.94; 95% CI, 0.47–1.90). The *p*-value for the interaction of EPO administration with EPO receptor expression was 0.08, suggesting that EPO administration exerts a deleterious effect only among tumors that are EPO receptor positive.

In summary, although there is a strong association between anemia and adverse outcomes, there is little evidence to suggest that modification of anemia through administration of growth factors produces a clinical benefit. Clinicians should be cognizant that administration of EPO may stimulate tumor growth and should therefore utilize extreme caution when considering this medication.

## MOLECULAR PROGNOSTIC FACTORS

The vast array of molecular factors studied in head and neck cancer can be divided into several broad categories. Proto-oncogenes code for proteins that promote cellular proliferation. A proto-oncogene is transformed into an oncogene when its protein product becomes unresponsive to the normal regulatory processes that control cell division. Activation of proto-oncogenes occurs by point mutations, chromosomal translocations, or gene amplification. At the cellular level, an oncogene exerts a dominant phenotype over its proto-oncogene counterpart because only one copy of an oncogene is necessary to promote neoplasia. In contrast, tumor suppressor genes (antioncogenes) inhibit cellular proliferation. At the cellular level, both copies of a tumor suppressor gene must be disabled to promote neoplasia. Another class of markers includes proteins and growth factors that mediate the interaction between neoplastic cells and their local microenvironment. In addition to these specific molecular markers expressed in neoplastic cells, other factors such as tumor ploidy and the rate of tumor cell proliferation may yield important prognostic information. This chapter will focus on molecular markers that may become important targets for new pharmacotherapies.

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***p53.*** *p53* is a transcription factor with tumor suppressor function that negatively regulates the cell cycle and serves to protect the integrity of the genome. Its gene resides on chromosome 17p13 and is composed of 11 exons spanning 20 kb in length.[223] Activation of *p53* occurs in response to a variety of cellular stressors, such as DNA damage, hypoxia, and cell cycle aberrations.[224] Such stressors lead to $p^{14ARF}$-mediated increases in *p53* protein levels, which can result in several different cellular events, including G1 arrest, apoptosis, or senescence. *p53* mediates G1 arrest through transactivation of at least two genes: $p21^{WAF1/CIP1}$, an inhibitor of the G1 cyclin-dependent kinases essential for the G1/S transition, and GADD45, a gene implicated in growth arrest and DNA excision repair.[225–227] *p53* induction also results in apoptosis, presumably when the extent of DNA damage exceeds the capacity of cellular repair mechanisms.[228] Thus, *p53* protects the cell from propagating mutations to subsequent generations and is considered the "guardian of the genome."[229]

Loss of *p53* function may contribute to tumor aggressiveness by promoting resistance to radiation and chemotherapy, accelerated growth in hypoxic conditions, and tumor neovascularization. When compared to cells with wild-type *p53*, *p53* mutant cell lines exhibit more resistance to ionizing radiation and certain chemotherapeutic agents.[230–232] This evidence led to the hypothesis that tumors lacking a functional *p53* gene will exhibit a radioresistant and chemotherapy-resistant phenotype due to a deficiency in DNA damage-induced apoptosis.[227] This hypothesis has been strengthened by experiments conducted in *p53* mutant cell lines derived from HNSCCs. Transfection with an adenoviral vector or a liposomal system containing a functional *p53* gene resulted in a dose-dependent increase in radiation sensitivity, restoration of the G1 checkpoint, and induction of apoptosis.[233–236] *p53* may also mediate hypoxia-induced apoptosis. Graeber et al. demonstrated that mutations in *p53* reduce hypoxic cell death and confer a competitive advantage to cells growing in a hypoxic environment.[237] Thus, mutations in *p53* may increase the number of hypoxic cells, conferring hypoxia-mediated radioresistance. Finally, loss of *p53* function results in the down-regulation of thrombospondin-1, an inhibitor of angiogenesis.[238] Indeed, a strong correlation between *p53* overexpression, a surrogate marker for *p53* gene mutation, and both elevated tumor microvessel density and vascular endothelial growth factor (VEGF) expression has been reported in HNSCC.[239,240] As a whole, the data from basic science studies support the hypothesis that *p53* mutations contribute to biologically aggressive tumor behavior by conferring resistance to radiotherapy and chemotherapy and by promoting angiogenesis.

Inactivation of *p53* is a common event in HNSCC and may result from spontaneous or tobacco-induced mutations[176] or from sequestration by cellular proteins such as mdm2[241] or the E6 viral oncoprotein of HPV.[242] Detection of *p53* mutations has been attempted through both protein-based and DNA-based techniques. Many studies have utilized immunohistochemistry (IHC), capitalizing on the differential expression of wild type and mutant *p53*. Wild-type *p53* has a half-life of 20 minutes, whereas many *p53* mutations confer stability to the protein and thus result in higher intracellular levels detectable via IHC.[223] Unfortunately, this technique often fails to detect nonsense or frameshift mutations that result in *p53* protein truncation.[243] Furthermore, induction of wild-type *p53* in response to DNA damage can result in sufficient quantities for IHC detection. Saunders et al. sequenced all coding exons of the *p53* gene from 39 laryngeal SCCs and found that *p53* IHC resulted in a 64% concordance, 42% false positive rate, and 23% false negative rate.[244] Larger studies that examined only the conserved regions of the *p53* gene reported 59% to 71% concordance with IHC.[243,245] Thus, although relatively simple and inexpensive, IHC is not an accurate method for detecting *p53* mutations.

DNA-based techniques for detection of *p53* mutations have focused on exons 5 to 8, a highly conserved region that codes for a DNA-binding domain.[223] However, recent studies have found that 20% to 25% of *p53* gene mutations lie outside the conserved region,[244,246] although these mutations may not influence *in vivo* *p53* function. Finally, loss of heterozygosity at the *p53* gene locus has been examined using polymorphic markers and fluorescent *in situ* hybridization (FISH).[247–249]

Recent studies correlating *p53* mutation with outcome in HNSCC have suggested that *p53* mutations, as assessed via direct sequencing, are associated clinically with resistance to radiotherapy and chemotherapy (Table 3.3).[160,244,246,250–255] In the largest study to employ direct sequencing, Koch et al. evaluated the prognostic significance of *p53* mutations in exons 5 to 9 in 110 HNSCCs treated with either primary or postoperative radiotherapy.[160] These tumors spanned all major sites for HNSCC and included all clinical stages. In multivariate analysis, patients with *p53* mutations were 2.4 times more likely to develop local-regional recurrence, equal to the risk of local-regional recurrence conferred by the presence of positive cervical lymph nodes. In contrast, *p53* expression as assessed via IHC failed to correlate with any outcome variable.[243] Similarly, two other studies showed that *p53* mutation, but not protein overexpression, predicted poor local-regional control and survival in cohorts composed of 58 and 68 patients with HNSCC, most of whom received radiotherapy.[250,253] Furthermore, a study conducted on 22 recurrent HNSCCs previously treated with radiation found that 21 of the 22 recurrences had evidence for *p53* inactivation by either gene mutation, mdm2 overexpression, or HPV infection.[256]

In addition to the relationship between *p53* mutation and response to radiotherapy, several groups have considered the relationship between directly sequenced *p53* mutations and response to chemotherapy. In a cohort of 105 patients with HNSCC treated with platinum- and fluorouracil-based induction chemotherapy, Temam et al. directly sequenced all coding regions of the *p53* gene from biopsy specimens taken prior to the initiation of chemotherapy. Multivariate modeling revealed that tumors with a mutant *p53* gene were 70% less likely to experience major response to chemotherapy and, independently, tumors with high levels of *p53* protein expression were 60% less likely to experience a major response.[246] The correlation between *p53* overexpression and resistance to chemotherapy persisted in the subset of patients with wild-type *p53*, suggesting that *p53* IHC conveys independent prognostic information in patients treated with chemotherapy. An additional study conducted on 106 HNSCC patients treated with cisplatin and 5-fluorouracil neoadjuvant chemotherapy screened for *p53* mutations using denaturing gradient gel electrophoresis (DGGE) on PCR products from exons 4 to 9 of the *p53* gene followed by direct sequencing of those exons that demonstrated a variant DGGE pattern.[254] In agreement with Temam et al. this study found that *p53* mutation was the only significant predictor of response to chemotherapy in multivariate analysis, with *p53* mutant tumors 63% less likely to respond to chemotherapy. At least three other studies have reported a correlation between *p53* overexpression and poor survival in HNSCC patients who receive chemotherapy.[255,257,258] Thus, strong evidence supports a role for *p53* alterations in predicting poor initial response and long-term survival following treatment with chemotherapy.

At least one group has considered whether the location of *p53* mutations influences the clinical phenotype of HNSCC. Erber et al. sequenced exons 5 to 8 and assessed for loss of heterozygosity at the *p53* allele in 86 oral cavity, oropharyngeal, hypopharyngeal, and laryngeal SCCs, stage I to IV.[252] All patients received surgical resection, and 79% (68/86) received postoperative radiotherapy. Twenty-eight percent (24/86) of tumors

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**TABLE 3.3 Prognostic Significance of *p53* in Head and Neck Cancer**

| Author | Description of Patients | Treatment Given | MVT | Detection of *p53* Abnormality | % Positive | Local/ Regional Recurrence | Survival | Notes |
|---|---|---|---|---|---|---|---|---|
| ***p53* sequencing in primary radiotherapy series** | | | | | | | | |
| Overgaard et al.[250] | 68 HNSCC (stage not specified) | RT + Nimorazole | Yes | IHC<br>DGGE + sequencing exons 5–9 | 67%<br>47% | No<br>Yes (HR = 4.1) | No | *p53* mutants at risk for LR recurrence |
| Saunders et al.[244] | 35 Laryngeal SCC (mainly T1-2) | Primary RT | No | IHC<br>Sequenced exons 2–11 | 67%<br>48% | No<br>No | NR<br>NR | *p53* status not correlated with local failure |
| Gallo et al.[251] | 85 HNSCC (mostly T1-2 N0) | Primary RT | Yes | SSCP + sequencing exons 5–8 | 45% | No | No | *p53* mutants trended to LR failure in univariate analysis only ($p = 0.10$) |
| ***p53* sequencing in heterogeneous series** | | | | | | | | |
| Koch et al.[160] | 110 Stage I–IV HNSCC | 68 Surgery + RT 42 primary RT | Yes | Sequenced Exons 5–9 | 44% | Yes (RR = 2.4) | No | *p53* mutants more likely to develop LR recurrence |
| Erber et al.[252] | 86 Stage I–IV HNSCC | Surgery (68 received post-op RT) | No | sequenced exons 5–8 | 15% (DNA contact mutations) | NR | DFS ($p = 0.05$)<br>OS ($p = 0.01$) | Only DNA contact mutations conferred poor prognosis |
| Mineta et al.[253] | 58 Stage I–IV oral and oropharyngeal SCC | Mostly primary or preoperative RT | Yes | IHC<br>SSCP + sequencing exons 5–8 | 74%<br>18% | NR<br>NR | No<br>CSS (RR = 9.9) | |
| ***p53* assessment in chemotherapy series** | | | | | | | | |
| Etienne et al.[255] | 82 Stage II–IV HNSCC | 61 Induction cisplatin/5-FU, 21 concurrent chemoRT | Yes | Immuno-luminometric assay | NA | Trend for chemoRT group only | No | *p53* status correlated with poor CSS in univariate but not MVT analysis |
| Temam et al.[246] | 105 Stage III–IV HNSCC | Induction cisplatin and 5-FU | Yes | IHC<br>Sequenced exons 2–11 | 61%<br>37% | Yes ($p = 0.05$)<br>Yes ($p = 0.01$) | NR<br>NR | Both *p53* IHC and mutation were independent predictors of response |
| Cabelguenne et al.[254] | 106 Stage I–IV HNSCC | Induction cisplatin and 5-FU | Yes | *p53* LOH<br>DGGE + sequencing exons 4–9 | 54%<br>68% | Trend<br>Yes (RR = 2.7) | NR | Presence of *p53* mutation or anti-*p53* serum antibodies conferred highest risk of not responding (RR = 4.9) |

CSS, cause-specific survival; CTX, chemotherapy; DFS, disease-free survival; DGGE, denaturing gradient gel electrophoresis; HNSCC, head and neck squamous cell carcinoma; HR, hazard ratio; IHC, immunohistochemistry; LOH, loss of heterozygosity; LR, local-regional; MVT, multivariate analysis; NR, not reported; OS, overall survival; RT, radiotherapy; RR, relative risk; SCC, squamous cell carcinoma; SSCP, single-strand conformation polymorphism.

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exhibited a mutation within structural components of the *p53* gene, and 15% (13/86) of tumors exhibited mutations within regions critical for DNA binding of the *p53* protein. DNA contact mutations were associated with nodal positivity, advanced stage, and poor recurrence-free and overall survival in univariate analysis. Furthermore, in the subset of stage IV patients, the presence of contact mutations correlated with poor overall survival. No such correlation between structural mutations and stage at presentation or outcome was observed. These results imply that *p53* mutations resulting in the specific loss of DNA binding and thus transcriptional regulation result in radioresistance and particularly poor survival. Clearly, the clinical significance of specific *p53* mutations merits further study.

Given the association between *p53* mutation and adverse outcomes, multiple groups have investigated the potential benefit of *p53* gene therapy, and phase III clinical trials are currently ongoing in the United States.[259] In China, a recombinant human adenovirus in which the E1 region has been replaced by the *p53* expression cassette has been trademarked Gendicine and approved for clinical use.[260] To date, approximately 3,500 patients have received this gene therapy in China.[261] However, data on the effectiveness of this intervention in the English literature is sparse.

## Angiogenesis-Related Markers

Angiogenesis, the sprouting of new blood vessels from a preexisting endothelium, enables the growth of tumors beyond microscopic size.[262,263] Many growth factors and cytokines, including the VEGF family, basic and acidic fibroblast growth factor (bFGF, aFGF), interleukin-8 (IL-8) and platelet-derived endothelial cell growth factor (PD-ECGF) have been shown to promote angiogenesis.[264] The VEGF family consists of five members including VEGF, P1GF, VEGF-B, VEGF-C, VEGF-D, and the Orf virus VEGFs (VEGF-E).[265] Of these factors, VEGF plays a pivotal role in vasculogenesis and angiogenesis, and VEGF-C is a potent inducer of lymphangiogenesis.[266] Receptors for the VEGF family include VEGFR-1, VEGFR-2, and VEGFR-3, also known as *flt*, KDR/*flk-1*, and *flt4*, respectively.[265] VEGFR-1 and VEGFR-2 are expressed on vascular endothelium, whereas VEGFR-3 is expressed in the lymphatic endothelium.[265]

VEGF, a 34-50 kDa dimer composed of two identical disulfide-linked subunits that arise from differential splicing of a single gene,[267] is frequently expressed in HNSCC[268] and has received the most study as a potential mediator of angiogenesis. Overexpression of VEGF may result from hypoxia-induced upregulation of transcription and eIF4E-mediated upregulation of translation.[269–271] Because hypoxic tumors display increased radioresistance, VEGF protein levels may serve as a surrogate marker for hypoxic radioresistance. Furthermore, angiogenic activity may influence a tumor's metastatic potential by exposing it to a greater endothelial surface area, thus increasing the likelihood of hematogenous or lymphatic dissemination.[272] In addition, once a tumor has formed a distant micrometastasis, it must recruit a vascular supply in order to proliferate to a clinically relevant size.

Angiogenic activity can be assessed in archival tumor tissue directly by staining with antibodies targeted against proteins that reside on endothelial cells, such as Factor VIII, CD-31, CD-34, and CD-105, in order to calculate the density of microvessels in the tumor bed. In addition, expression of angiogenesis-promoting factors has been assessed via IHC and ELISA. Expression of both VEGF and PD-ECGF has been reported to correlate with microvessel density (MVD) in HNSCC.[239,240,273]

Elevated tumor MVD as assessed via IHC has been shown to correlate with risk for concomitant cervical lymph node metastasis in oral cavity[274–276] and nasopharyngeal carcinomas.[277,278] Furthermore, elevated MVD has been shown to correlate with risk of regional relapse in clinically N0 oral cavity carcinomas treated with surgery.[279,280] These studies strongly suggest that the finding of high MVD in the primary tumor suggests a higher risk of concomitant nodal metastasis. In contrast, studies are mixed regarding the potential correlation of elevated MVD with either local-regional control or survival.[281–283] However, a recent study of 127 HNSCC patients suggested that endothelial expression of CD-105 (endoglin), which is a marker of neovascularization, was strongly correlated with poor disease-free and overall survival.[284] In contrast, expression of CD34, which is commonly expressed on both quiescent and proliferating endothelial cells, was not associated with outcome, suggesting that the proliferating endothelial component is the primary determinant of tumor behavior.

Direct assessment of angiogenic factor expression offers another approach to the study of tumor angiogenesis. High levels of VEGF and PD-ECGF have been shown to correlate with the presence of concomitant nodal metastases in both nasopharyngeal and oral cavity carcinomas.[276–278,285] Furthermore, expression of VEGF-C in the primary tumor and VEGFR3 on lymphatic endothelium both correlate with risk of nodal metastasis, suggesting that lymphangiogenesis may increase the likelihood of spread to the cervical lymph nodes.[285,286]

Expression of VEGF has also been shown to correlate with local-regional recurrence, distant metastasis, and poor survival.[287] A critical meta-analysis of 12 studies including 1,002 patients concluded that high levels of VEGF expression assessed via IHC correlated with a highly significant 1.88-fold increased risk of 2-year mortality.[288] Given the strong, reproducible association between elevated expression of VEGF and adverse outcomes, phase I/II clinical trials are now ongoing to assess the possible therapeutic benefit of anti-VEGF therapy, such as bevacizumab.

## Cyclin D1

Cyclin D1, also known as PRAD1, is a proto-oncogene located on chromosome 11q13[289] that serves as the rate-limiting controller of G1-phase progression through the cell cycle.[290] In response to extracellular mitogens, cyclin D1 levels increase and complex with the cyclin-dependent kinases cdk4 or cdk6 in order to mediate progression through G1 by phosphorylation of the retinoblastoma protein. Cyclin D1 is the most commonly amplified oncogene in HNSCC, with approximately 35% of tumors revealing increased gene copy number in FISH analysis.[291] Overexpression of cyclin D1 shortens the G1 interval and reduces the cell's dependence on mitogens for proliferation. For example, overexpression of cyclin D1 in a human epithelial breast cancer cell line reduced the fraction of cells entering quiescence under conditions where growth factors were limited, resulting in accelerated growth.[292] Such observations suggest that overexpression of cyclin D1 may increase the aggressiveness of certain cancers by desensitizing cellular proliferation to inhibitory signals.

Although the literature remains somewhat mixed, a growing body of evidence suggests a relationship between cyclin D1 amplification and poor prognosis (Table 3.4).[293–299] In patients with clinically negative cervical lymph nodes, expression or amplification of cyclin D1 in the primary tumor increases the risk of cervical nodal metastasis by four- to eightfold.[300,301] Bova et al. found cyclin D1 overexpression to predict increased risk for poor disease-free and overall survival in 148 patients with stage I to IV oral tongue SCC treated with surgery (52 patients received postoperative radiotherapy).[296] Similarly, Michalides et al. found that cyclin D1 overexpression was an independent predictor of shortened disease-free interval in 115 stage I to IV HNSCCs treated with surgery (73 received postoperative radiotherapy).[293]

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**TABLE 3.4 Prognostic Significance of Cyclin D1 in Head and Neck Cancer**

| Author | Description of Patients | Treatment Given | Marker | % Positive | Multivariate Analysis | Local Control | Survival | Notes |
|---|---|---|---|---|---|---|---|---|
| Michalides et al.[293] | 115 Stage I–IV HNSCC | Primary surgery (72 received post-op RT) | IHC | 50% | Yes | No | DFS ($p = 0.05$) | Overexpression correlates with recurrence when all sites considered |
| Muller et al.[294] | 280 Stage I–IV HNSCC | 201 Surgery + post-op RT | 11q13 amplification | 57% | Yes | NR | No | |
| | | 79 Surgery alone | | 35% | | NR | No | |
| Pignataro et al.[295] | 149 Stage I–IV laryngeal SCC | Surgery (63 received post-op RT) | IHC | 32% | Yes | NR | DFS ($p = 0.02$) OS ($p = 0.06$) | Cyclin D1 expression associated with alcohol and tobacco consumption |
| Bova et al.[296] | 148 Stage I–IV oral tongue SCC | Surgery (53 received post-op RT) | IHC | 68% | Yes | NR | DFS ($p = 0.05$) OS ($p = 0.02$) | Cyclin D1 expression plus loss of *p16* expression associated with worst prognosis |
| Mineta et al.[297] | 94 Stage I–IV tongue SCC | Surgery (not otherwise specified) | IHC | 19% | No | NR | OS ($p = 0.04$) | |
| Yoo et al.[298] | 30 T1-2, N0 laryngeal SCC, nonrecurrent | Radiotherapy | IHC | 67% | No | Yes ($p = 0.02$) | NR | Low cyclin D1 levels predicted local recurrence |
| | 30 T1-2, N0 laryngeal SCC, recurrent | | | 37% | | | | |
| Hwang et al.[299] | 65 Stage I–IV nasopharynx cancer | Radiotherapy | IHC | 66% | Yes | Yes ($p = 0.01$) | NR | Low cyclin D1 levels predicted local recurrence |

CSS, cause-specific survival; CTX, chemotherapy; DFS, disease-free survival; HP, hypopharynx; HNSCC, head and neck squamous cell carcinoma; IHC, immunohistochemistry; NR, not reported; OC, oral cavity; OP, oropharynx; OS, overall survival; RT, radiotherapy; SCC, squamous cell carcinoma.

In addition, Pignataro et al. demonstrated that cyclin D1 overexpression independently doubled the risk of tumor relapse in 149 stage I to IV laryngeal SCCs treated with surgery (63 received postoperative radiation).[295]

In contrast, some evidence suggests that cyclin D1 overexpression may actually increase the sensitivity of tumors treated with definitive radiation. For example, Yoo et al. and Hwang et al. reported that high cyclin D1 protein levels were associated with a threefold reduction in the risk of local-regional recurrence among patients with laryngeal[298] and nasopharyngeal[299] cancers treated with definitive radiation. In summary, for patients treated with surgery with or without postoperative radiation, strong evidence suggests that cyclin D1 upregulation correlates with poor disease-free and overall survival in HNSCC. In contrast, for patients treated with primary radiation, upregulation of cyclin D1 may be correlated with improved local-regional control, and further study is needed to characterize the effect of cyclin D1 levels on radiosensitivity.

## EGFR and TGF-α

The receptor tyrosine kinase epidermal growth factor receptor (EGFR) and its ligand transforming growth factor-alpha (TGF-$\alpha$) are frequently overexpressed in HNSCC.[302,303] Activation of EGFR induces autophosphorylation, resulting in activation of several signaling pathways including Ras-MAP kinase, phospholipase C$\gamma$, phosphatidylinositol 3-kinase, and STATs (signal transducers and activators of transcription).[304–306] In HNSCC, autocrine activation of EGFR by TGF-$\alpha$ functions to promote cellular proliferation and inhibit apoptosis. For example, *in vitro* experiments

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conducted on HNSCC-derived cell lines demonstrated that inhibition of TGF-$\alpha$ with antisense oligonucleotides and inhibition of EGFR with antisense oligonucleotides, monoclonal antibodies, or specific inhibitors of EGFR kinase activity resulted in reduced cellular proliferation.[307,308] Furthermore, *in vivo* transfection of a vector expressing EGFR antisense oligonucleotides resulted in growth inhibition and induction of apoptosis in nude mice tumor xenografts.[309]

EGFR expression may also modulate tumor radioresistance. In murine tumors, Akimoto et al. found that the magnitude of EGFR expression positively correlated with increased radioresistance and inversely correlated with radiation-induced apoptosis.[310] Blockade of EGFR with the monoclonal antibody C225 enhances radiosensitivity of SCCs both *in vitro* and *in vivo*. In cell lines derived from HNSCC patients, concomitant C225 administration and radiotherapy enhances of radiosensitivity, in part because inhibition of EGFR results in down-regulation of antiapoptotic proteins such as Stat3 and thus promotes radiation-induced apoptosis.[311,312] Furthermore, *in vivo* experiments suggest that C225 inhibits repair of radiation-induced DNA damage and promotes tumor necrosis.[313,314]

In agreement with laboratory data, clinical studies have established a correlation of EGFR overexpression with poor prognosis and radioresistance (Table 3.5).[315–323] Initial evidence for the prognostic utility of EGFR levels was derived from Dassonville et al. who found that EGFR expression independently predicted poor relapse-free survival in 109 stage I to IV HNSCC patients treated primarily with either chemotherapy or surgery.[315] Maurizi et al. reported an independent relationship between EGFR protein expression and poor disease-free and overall survival in 140 stage I to IV laryngeal SCCs treated primarily with surgery.[316] Similarly, Grandis et al. utilized quantitative IHC to show that increasing levels of both TGF-$\alpha$ and EGFR predicted poor disease-free and cause-specific survival in a cohort of 91 stage I to IV HNSCCs[318] treated with surgery (56 received postoperative radiotherapy). Finally, Chung et al. used FISH in 75 patients with stage I to IV HNSCC to determine that patients with more than two copies per cell of the EGFR gene experienced a higher risk of progression and death.[322] Thus, the cumulative evidence suggests that EGFR protein overexpression or gene amplification is associated with poor prognosis.

Overexpression of EGFR has also been shown to correlate with radioresistance. For example, Ang et al. reported that, in a cohort of 155 patients with stage II to IV HNSCC treated with conventional radiotherapy on RTOG study 90-03, overexpression of EGFR was associated with poor local-regional control, disease-free survival, and overall survival in multivariate analysis.[319] In addition, growing evidence suggests that accelerating the course of radiotherapy may mitigate the adverse effect of EGFR overexpression on local-regional control. For example, Bentzen et al. reported a cohort of 304 patients with stage II to IV HNSCC randomized to receive either conventional daily radiation to a total dose of 66 Gy in 33 fractions over 45 days or continuous hyperfractionated accelerated radiation therapy (CHART) to a total dose of 54 Gy in 36 fractions over 12 days.[321] Patients with high EGFR expression derived a significant local-regional control benefit from CHART, whereas patients with low EGFR expression experienced similar local-regional control regardless of whether they received conventional radiation or CHART. Two other recent studies also suggest that a short overall treatment time may compensate for the adverse effects of EGFR.[320,323] One potential explanation for this observation is that EGFR may mediate accelerated repopulation late in the course of conventional radiotherapy, thus allowing EGFR-positive tumors to become increasingly resistant to radiation during the last few weeks of conventional treatment.

Emerging evidence suggests that targeting the EGFR receptor with either small molecule tyrosine kinase inhibitors such as erlotinib or monoclonal antibodies such as cetuximab results in clinical gains. In the locally advanced setting, a recent randomized trial of 424 patients with stage III to IV HNSCC revealed that median overall survival for patients treated with cetuximab and radiotherapy was 49.0 months versus 29.3 months in the radiotherapy-alone arm (HR, 0.73; 95% CI, 0.56–0.95; $p = 0.018$).[324] In the first-line recurrent/metastatic setting, the EXTREME trial found that adding cetuximab to platinum-fluorouracil significantly prolonged median OS from 7.4 months to 10.1 months (HR for death, 0.80; 95% CI, 0.64–0.99; $p = 0.04$) and median progression-free survival from 3.3 to 5.6 months (HR, 0.54; $p < 0.001$).[325] In addition, for patients with recurrent or metastatic disease that is refractory to first-line chemotherapy, cetuximab monotherapy has been shown to produce response rates ranging from 5% to 15%,[326] and the addition of platinum agents to cetuximab further improves response rates from approximately 18% to 26%.[327] These trials have provided the first conclusive evidence that molecularly targeted therapies can produce meaningful gains in the treatment of head and neck cancer.

## Human Papillomavirus

HPV is a small, circular DNA virus that infects basal cells in the squamous epithelium. HPV is transmitted through sexual contact and the recent rise in HPV-related HNSCC is thought to be due to increased oral sexual practices. D'Souza found that a high lifetime number of vaginal-sex partners (26 or more) was associated with oropharyngeal SCC (OR 3.1; 95% CI, 1.5–6.5), as was a high lifetime number of oral-sex partners (6 or more) (OR 3.4; 95% CI, 1.3–8.8).[328] HPV causes cancer by means of viral oncoproteins E6 and E7, which inactivate two human tumor suppressor genes, *p53* and *RB*. Though there are over 100 different subtypes of HPV, the vast majority of HPV-related HNSCC is related to HPV16, which is found in up to 90% of these cases. HPV-associated HNSCC patients are typically younger, more often white, nonsmokers, nonalcohol abusers, have higher socioeconomic status, with primary tumors more commonly in the oropharynx.[329,330]

Ang looked at patients treated on RTOG 0129, which randomized patients with advanced HNSCC treated with cisplatinum to either standard versus accelerated fractionation radiation therapy. While the radiation fractionation scheme made no significant difference in OS, subgroup analysis of the oropharyngeal SCCs revealed that the HPV-positive patients had better outcomes compared to HPV-negative patients (3-year OS, 82.4% vs. 57.1%; $p < 0.001$). Using recursive-partitioning analysis, they subdivided these patients into low, intermediate, or high risk of death on the basis of four factors: HPV status, greater or less than 10 pack-years of tobacco use, T stage, and N stage.[331] The improved prognosis of HPV-related HNSCC does not appear confined to patients treated with primary radiation, but extends to surgical patients as well.[332–334] How to take advantage of the improved prognosis of HPV-related HNSCC will be a major area of research in the coming years, specifically whether it is possible to de-escalate radiation dose or systemic therapy and maintain these patients' favorable prognosis. RTOG 1016 is a phase III trial randomizing patients with HPV-positive oropharyngeal SCC to concurrent cisplatinum radiation versus cetuximab radiation, the rationale being that if concurrent cetuximab can offer similarly excellent outcomes in this population, the toxicity of concurrent cetuximab is much less than concurrent cisplatinum.[335] HPV and its implications in head and neck cancer is also discussed in detail in Chapter 12.

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**TABLE 3.5 Prognostic Significance of Epidermal Growth Factor Receptor in Head and Neck Cancer**

| Author | Description of Patients | Treatment Given | MVT | Marker | Method (% Positive) | Local/Regional Recurrence | Survival | Notes |
|---|---|---|---|---|---|---|---|---|
| Dassonville et al.[315] | 109 Stage I–IV HNSCC | 73 CTX, 29 surgery, 6 RT, 1 none | Yes | EGFR | RRA | NR | DFS ($p = 0.03$) | EGFR status correlated with overall survival in univariate but not mvt model |
| Maurizi et al.[316] | 140 Stage I–IV laryngeal SCC | Surgery (post-op RT not mentioned) | Yes | EGFR | RRA: 20% | NR | OS ($p = 0.0001$)<br>DFS ($p = 0.01$) | |
| Almadori et al.[317] | 140 Stage I–IV laryngeal SCC | Surgery (post-op RT not mentioned) | Yes | EGFR | RRA: 20% | Yes ($p = 0.001$) | NR | EGFR status independently predicts regional recurrence |
| Grandis et al.[318] | 91 Stage I–IV HNSCC | Surgery (56 received post-op RT) | Yes | TGF-$\alpha$ | IHC | NR | CSS ($p = 0.0001$) | EGFR status divided into tertiles using computerized image analysis |
| | | | | EGFR | | NR | CSS ($p = 0.0001$) | |
| Ang et al.[319] | 155 Stage II–IV HNSCC | Conventional RT | Yes | EGFR | IHC | Yes ($p = 0.002$) | DFS ($p = 0.003$)<br>OS ($p = 0.006$) | EGFR status dichotomized at median staining intensity measured used quantitative image analysis |
| Eriksen et al.[320] | 336 T1-4 HNSCC | Conventional RT + misonidazole or nimorazole | No | EGFR | IHC: 65% | Yes ($p < .05$)<br>see notes | NR | EGFR was associated with poor local-regional control only for patients who received RT over 9.5 weeks, and not for patients who received RT over 5.5–6.5 weeks |
| Bentzen et al.[321] | 304 Stage II–IV HNSCC | 120 Conventional RT, 184 CHART | No | EGFR | IHC | NR | No | For tumor with high EGFR expression, CHART, but not conventional RT, improved local-regional control |
| Chung et al.[322] | 75 Stage I–IV HNSCC | 51 Surgery, 24 not surgery | Yes | EGFR | FISH: 58% | NR | PFS ($p < 0.02$)<br>OS ($p < 0.01$) | EGFR amplification only significant predictor of outcome in MVT model |
| Smid et al.[323] | 165 Stage I–IV oral SCC | Surgery and post-operative radiation | Yes | EGFR | IHC: 80% | No<br>see notes | No | For patients with EGFR positive tumors only, long overall treatment time >42 days was associated with poor local-regional control |

CHART, continuous hyperfractionated accelerated radiation therapy; FISH, fluorescent *in situ* hybridization; HNSCC, head and neck squamous cell carcinoma; IHC, immunohistochemistry; MVT, multivariate model; NR, not reported; PFS, progression-free survival; RT, radiotherapy; RRA, radioligand receptor assay; SCC, squamous cell carcinoma; TGF-$\alpha$ transforming growth factor–alpha.

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## SUMMARY

Understanding the vast array of factors that contribute to the prognosis of patients with HNSCC enables an accurate assessment of patient risk and promotes the development of optimal treatment strategies. In addition, novel targeted therapies are emerging, which enable clinicians to mitigate the risk associated with adverse molecular factors.

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CHAPTER 4

Jeffrey A. Bennett

# Radiologic Evaluation of the Head and Neck Cancer Patient

## INTRODUCTION

Cross-sectional imaging studies are an essential part of the care of the head and neck cancer patient, from initial diagnosis and staging to surveillance for cancer recurrence. This chapter will begin with a general discussion of normal imaging anatomy because this knowledge is very important for interpretation of the images. The appearance of pathology will then be addressed with emphasis on what needs to be in the radiology report. This includes a description of the full extent of the primary tumor, including which anatomic spaces of the head and neck are involved, whether or not there is bone or cartilage invasion, and whether there is perineural or perivascular spread of disease. What makes a lymph node positive or suspicious for cancer will be addressed, including extracapsular spread of disease and involvement of the dermal lymphatics. Finally, the identification of distant metastatic disease will be discussed. This approach to imaging is fundamental to the accurate staging of cancer and appropriate treatment, so that there will be no surprises at surgery and so that radiation portals can be optimally created. The pros and cons of the available imaging techniques, primarily computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), will be discussed throughout the chapter. The reader is referred to the site-specific chapters in Section 2 for suggested CT and MRI protocols and imaging concerns specific to disease in those locations.

## IMAGING ANATOMIC CONSIDERATIONS

### Nasopharynx

The nasopharynx (Fig. 4-1) is the epithelium-lined most superior aspect of the pharynx and is supported and held open by the rigid and strong pharyngobasilar fascia. The superior boundary is the skull base at the floor of the sphenoid sinus and the upper portion of the clivus (Fig. 4-2). Anterolaterally are the medial pterygoid plates. The inferior boundary of the nasopharynx is at the level of the hard palate where it merges with the oropharynx. Anteriorly the nasopharynx is continuous with the nasal cavity by way of the posterior choanae. Posteriorly the nasopharynx is bordered by the retropharyngeal space, and posterior to that is the prevertebral space. Laterally the nasopharynx is separated from the fat-filled parapharyngeal space by the superior pharyngeal constrictor muscle and palatal muscles. The pharyngobasilar fascia is medial to the superior pharyngeal constrictor muscle and tensor veli palatini muscle. The levator veli palatini muscle is medial to the pharyngobasilar fascia and attaches to the Eustachian tube.

The torus tubarius is seen on axial sections at the level of the mid- and upper nasopharynx. It is made up of the distalmost part of the cartilaginous portion of the Eustachian tube, whose orifice

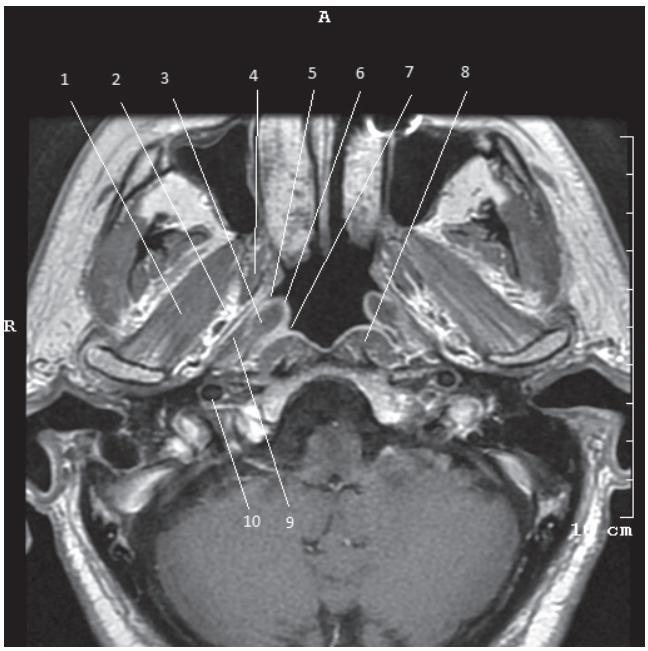



**FIGURE 4-1.** Axial T1-weighted postcontrast MRI through the nasopharynx demonstrating normal anatomy. *1*, lateral pterygoid muscle; *2*, fat in the prestyloid parapharyngeal space; *3*, torus tubarius made up of the cartilaginous end of the Eustachian tube; *4*, tensor veli palatini muscle; *5*, Eustachian tube orifice; *6*, mucosa over the torus tubarius; *7*, fossa of Rosenmüller; *8*, prevertebral flexor muscles; *9*, levator veli palatini muscle; *10*, carotid artery.



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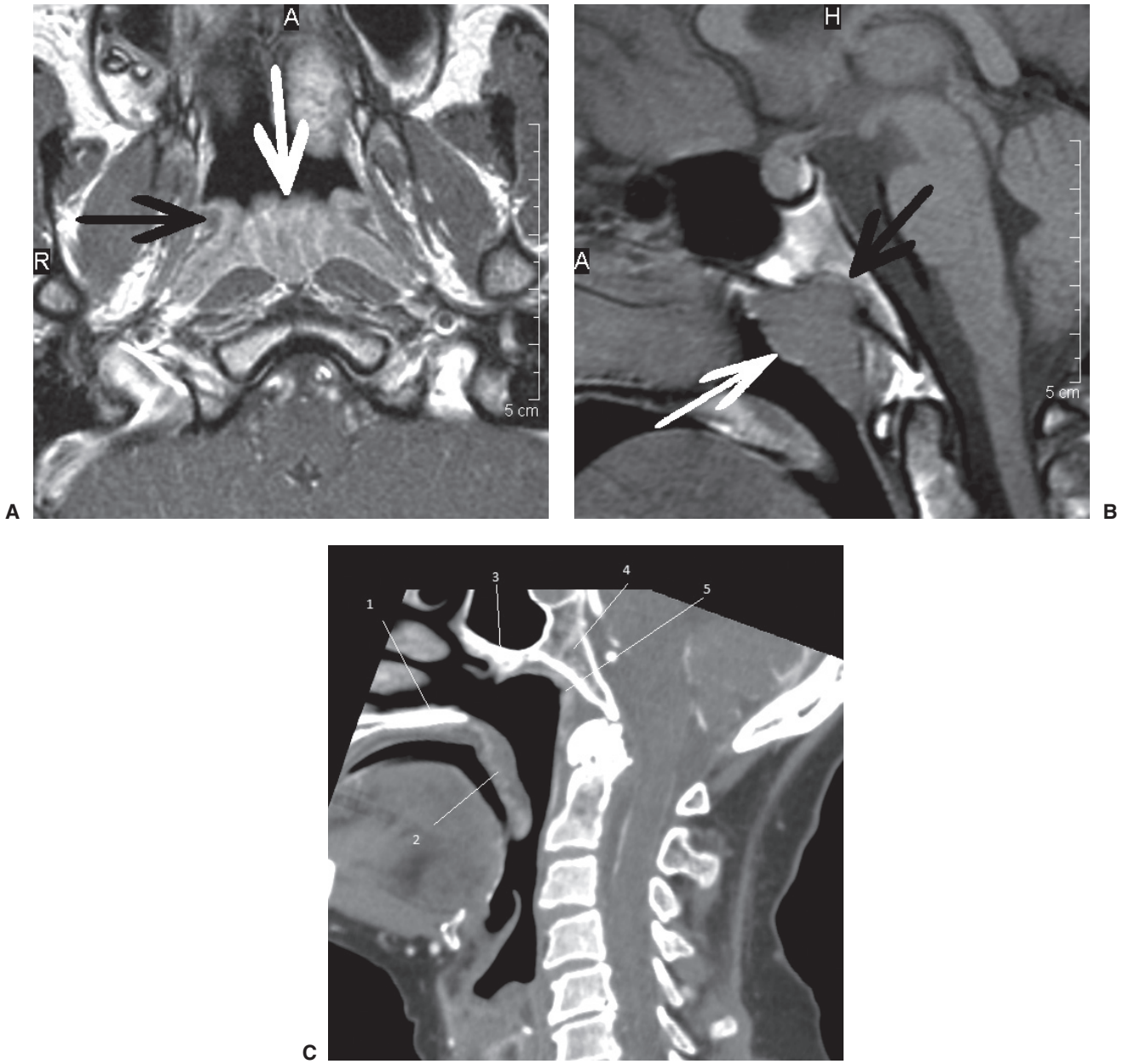



**FIGURE 4-2.** Axial T1-weighted contrast-enhanced MRI (**A**) at the level of the nasopharynx shows abundant lymphoid tissue (*white arrow*) lining the mucosa. This is normal in this 13-year-old patient. Notice the torus tubarius (*black arrow*). Sagittal noncontrast T1-weighted image in the same patient (**B**) shows the abundant adenoids (*white arrow*). The apparent scalloping of the cortex of the clivus (*black arrow*) is a normal variation. Midline sagittal postcontrast CT reformation (**C**) in a 75-year-old patient shows that the adenoids have atrophied. *1*, hard palate; *2*, soft palate; *3*, floor of the sphenoid sinus; *4*, clivus; *5*, nasopharyngeal mucosa with atrophied lymphoid tissue. MRI, magnetic resonance imaging; CT, computed tomography.

is just anterior to the torus tubarius. The Eustachian tube and the levator veli palatini muscle pass through an opening in the pharyngobasilar fascia called the sinus of Morgagni. This opening in the fascia provides a potential conduit for spread of nasopharyngeal carcinoma into the parapharyngeal space and to the central skull base.[1] The Eustachian tube connects the nasopharynx to the middle ear. In close to 50% of patients with a nasopharyngeal mass, the Eustachian tube becomes obstructed, leading to serous otitis media.[2] Thus, a finding of middle ear and mastoid opacification should prompt a search for a nasopharyngeal obstructive mass (Fig. 4-3).

The fossa of Rosenmüller is a mucosal recess located posterior to the tori and lateral to the flexor muscles of the neck, the longus coli and longus captitus muscles, which lie in the prevertebral space. Tumors that originate in the fossa of Rosenmüller are often clinically occult.

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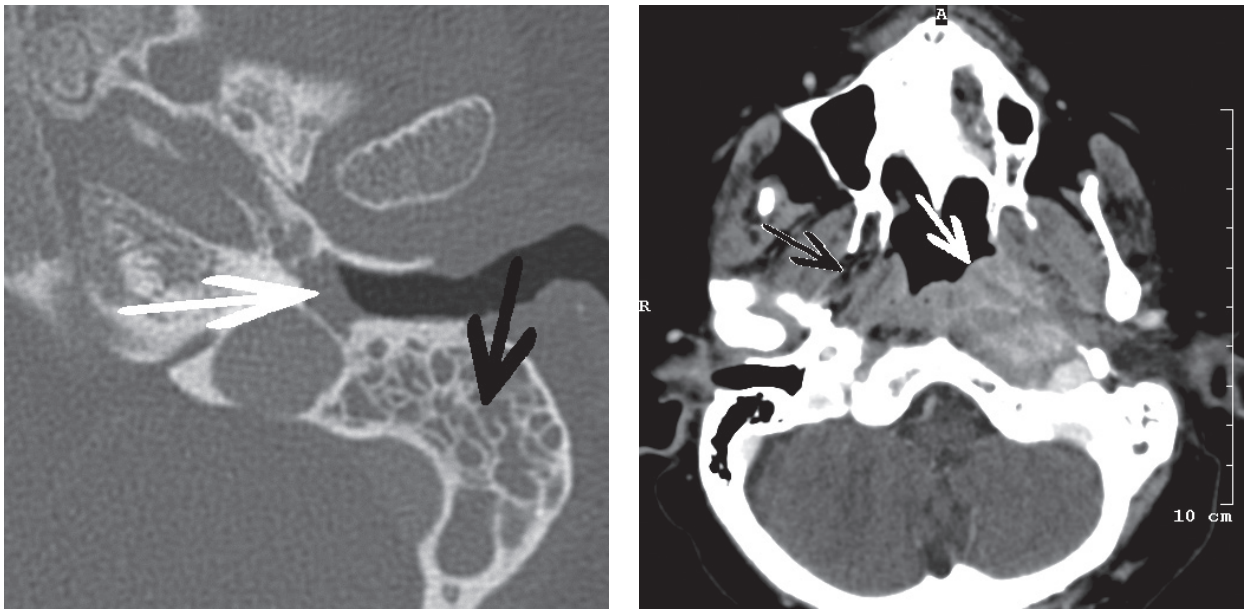



**FIGURE 4-3.** Axial CT scan with bone algorithm through the temporal bone (**A**) shows a serous otitis media (*white arrow*) and opacification of the mastoid air cells (*black arrow*). This unilateral finding in an older patient should prompt a search for a lesion causing obstruction of the Eustachian tube. Axial contrast-enhanced CT (**B**) in the same patient shows an aggressive nasopharyngeal mass (*white arrow*) which proved to be squamous cell carcinoma. Notice how the mass has extended into the prestyloid and retrostyloid parapharyngeal spaces causing obliteration of fat planes. The normal parapharyngeal space fat is seen on the opposite side (*black arrow*). CT, computed tomography.

Along the roof of the nasopharynx are the adenoids, or nasopharyngeal tonsil. This lymphoid tissue varies in appearance with age (Fig. 4-2), normally involuting by age 30, but can remain prominent in smokers and in patients with HIV.[3] As it appears similar in density to carcinoma on CT, when the finding is made of apparent lymphoid tissue infiltrating into the adjacent deeper tissue planes, a tumor should be suspected, as normal lymphoid tissue does not do this.

There is an extensive submucosal capillary lymphatic plexus in the nasopharynx, which explains the high incidence of positive lymph nodes in cases of nasopharyngeal squamous cell carcinoma.[4] Primary drainage is to the retropharyngeal lymph nodes and level 2 nodes.

The lateral retropharyngeal nodes of Rouviere lie in the retropharyngeal space medial to the carotid sheath and lateral to the flexor muscles of the neck. One to three nodes can normally be present on each side, usually at the level of C1, but they can be seen as low as the level of C3. The retropharyngeal nodes atrophy with age, possibly because of frequent upper airway infections in childhood. Normal retropharyngeal nodes in children measure 10 mm ± 2 mm and in adults measure 5 mm ± 2 mm (Fig. 4-4).

## Oropharynx

The oropharynx (Fig. 4-5) is bounded anterolaterally by the anterior tonsillar pillars, inferiorly by the pharyngoepiglottic folds, and superiorly by the soft palate, which is considered part of the oropharynx. The palatine tonsils are contained in the oropharynx as are the glossotonsillar sulci, which connect the lateral oropharyngeal wall with the tongue base. The anterior tonsillar pillar is made up of mucosa covering the palatoglossus muscle, whereas the posterior tonsillar pillar is made up of mucosa covering the palatopharyngeus muscle. In between these pillars is the tonsillar fossa containing the partially encapsulated palatine tonsil. This contains a variable amount of lymphoid tissue from side to side as well as with age. Lateral to the palatine tonsil is the fat-filled parapharyngeal space. This space gets smaller in its more inferior aspect where it communicates freely with the submandibular space.

The posterior third of the tongue, referred to as the tongue base, is also contained in the oropharynx. It extends from the circumvallate papillae to the vallecula. The mucosa of the vallecula and the anterior surface of the free margin of the epiglottis is part of the oropharynx, whereas the mucosa over the posterior surface of the free margin of the epiglottis is included in the supraglottic larynx (Fig. 4-6).

The lingual tonsil is incorporated into the mucosa of the tongue base. Like the adenoids and palatine tonsils, this lymphatic tissue has increased prominence with younger age and in smokers.

## The Oral Cavity and Floor of the Mouth

The oral cavity consists of the lips, anterior two-thirds of the tongue, and the hard palate. The hard palate and soft palate are best evaluated with imaging in the coronal plane. Also best evaluated in the coronal plane is the floor of the mouth, which lies between and includes the mucosa of the floor of the mouth and the mylohyoid muscle (Fig. 4-7). The mylohyoid muscle attaches to the mylohyoid line of the mandible and posteriorly to the hyoid bone. It is a U-shaped muscle with a median raphe in the midline and creates an opening posteriorly.

The submandibular space, actually part of the suprahyoid neck, is located below the mylohyoid muscle, although the submandibular gland itself extends around the posterior edge of the mylohyoid to enter the sublingual space in the floor of the mouth.

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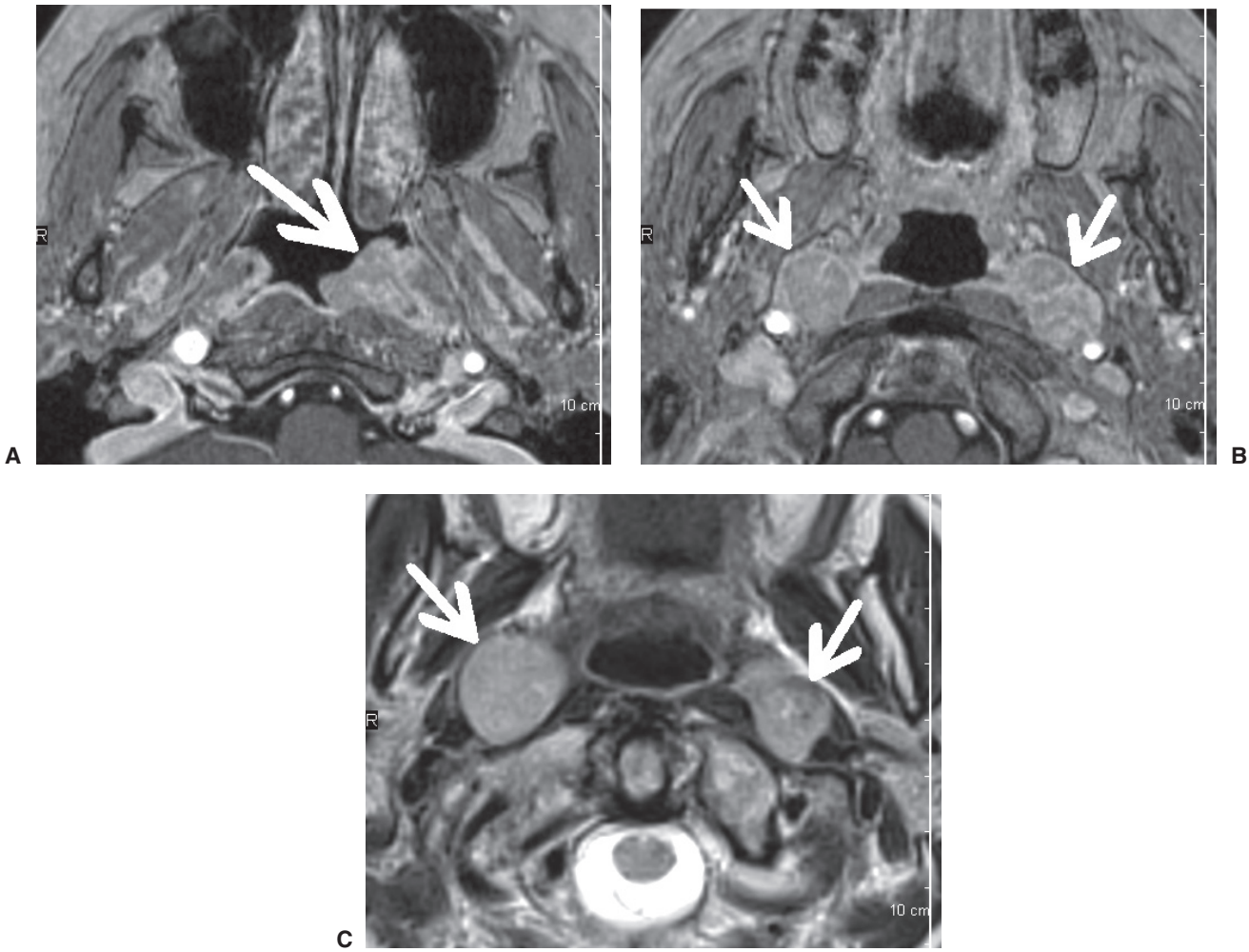



**FIGURE 4-4.** Axial T1-weighted contrast enhanced MRI (**A**) shows a left nasopharyngeal mass (*arrow*), which on biopsy proved to be squamous cell carcinoma. In the same patient, axial T1-weighted postcontrast MRI (**B**) and axial T2-weighted MRI at a slightly lower level (**C**) show bilateral bulky positive lateral retropharyngeal lymph nodes (*arrows*). MRI, magnetic resonance imaging.

The genioglossus muscles, which are extrinsic muscles of the tongue, and the geniohyoid muscles attach to the genial tubercles on the lingual surface of the mandible. Between these paired muscles is the midline septum of the tongue. The sublingual space containing the sublingual gland is located between these muscles and the mylohyoid. The submandibular duct, lingual nerve, and hypoglossal nerve all course through the sublingual space. The sublingual gland and lingual nerve, which is a branch of V3, course lateral to the hyoglossus muscle, whereas the lingual artery and vein and the hypoglossal nerve are medial to the hyoglossus muscle (Fig. 4-8). The lingual artery supplies blood to the tongue, with the lingual septum preventing much anastomosis across the midline.

The buccal mucosa is the mucosa of the cheek. The buccinator muscle lies deep to the mucosa and attaches to the maxillary alveolar ridge, the body of the mandible, and posteriorly inserts on the pterygomandibular raphe. The pterygomandibular raphe is a thick, vertically oriented fibrous band that also serves as the insertion of the orbicularis oris and superior constrictor muscles. It serves as a relative barrier to the spread of cancer. It lies deep to the mucosa of the retromolar trigone, which is the triangular mucosal surface behind the third mandibular molars and covers the ascending ramus of the mandible (Fig. 4-9). A surgical landmark superior to this region is the maxillary tuberosity, which is a bony bulge behind the third maxillary molar.

The mucosa covering the lingual alveolar surface and buccal alveolar surface of the maxilla and mandible is called the gingiva. The junction between the gingiva and buccal mucosa is called the upper and lower gingivobuccal sulcus, respectively, and is a common location in the oral cavity for squamous cell carcinoma to arise (Fig. 4-10).

## The Suprahyoid Neck

The compartmental organization of the neck is based on the superficial and deep fascial layers. On imaging studies, the fascia itself usually blends in with the structures it surrounds such as muscles and blood vessels.[5] However, fat contained in the spaces created between fascial boundaries is of low attenuation on CT scans and high signal compared to muscle on T1-weighted and fast spin echo T2-weighted images, and thus provides contrast that is very helpful for the localization of masses. The prestyloid parapharyngeal space, for example, contains mostly fat, although it also contains the ascending pharyngeal neurovascular bundle

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**FIGURE 4-5.** Axial T2-weighted MRI shows the normal anatomy of the oropharynx. *1*, stylopharyngeus muscle; *2*, styloglossus muscle; *3*, medial pterygoid muscle; *4*, palatine tonsil; *5*, tongue base; *6*, masseter muscle; *7*, middle pharyngeal constrictor muscle; *8*, palatopharyngeus muscle; *9*, fat in the parapharyngeal space. MRI, magnetic resonance imaging.

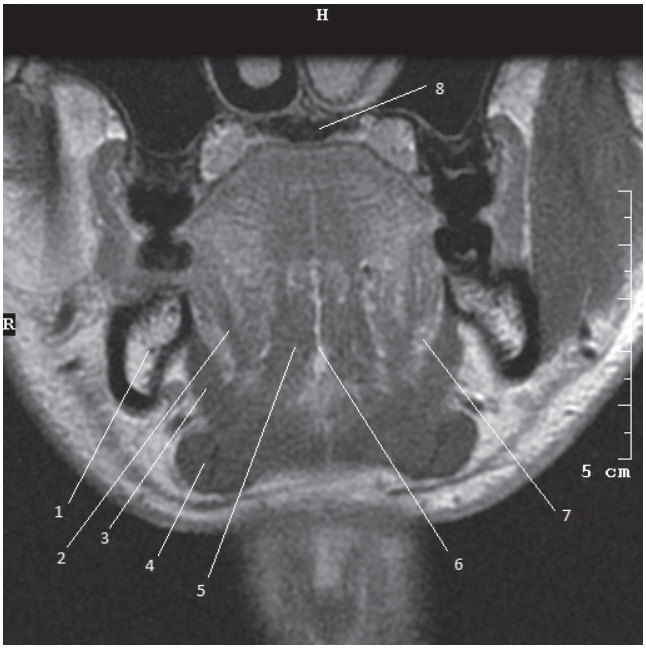



**FIGURE 4-7.** Coronal T1-weighted MRI with contrast through the oral cavity. *1*, mandible; *2*, hyoglossus muscle; *3*, mylohyoid muscle; *4*, anterior belly of the digastric muscle; *5*, genioglossus muscle; *6*, fatty midline septum of the tongue; *7*, sublingual space; *8*, hard palate. MRI, magnetic resonance imaging.




**FIGURE 4-6.** Axial contrast-enhanced CT scan at the level of the hyoid bone demonstrates a squamous cell carcinoma of the suprahyoid epiglottis (*white arrow*) since the cancer arises from the posterior mucosa of the free margin of the epiglottis. Mucosa on the anterior surface of the free margin of the epiglottis is part of the oropharynx and is continuous with the mucosa of the vallecula (*black arrows*). CT, computed tomography.



**FIGURE 4-8.** Axial contrast-enhanced CT through the floor of the mouth shows an aggressive infiltrating squamous cell carcinoma (*black arrow*), which encases the lingual neurovascular bundle (*white arrow*). The contralateral normal lingual artery can be seen just lateral to the genioglossus muscle. The tumor extends to the midline fatty septum of the tongue. CT, computed tomography.

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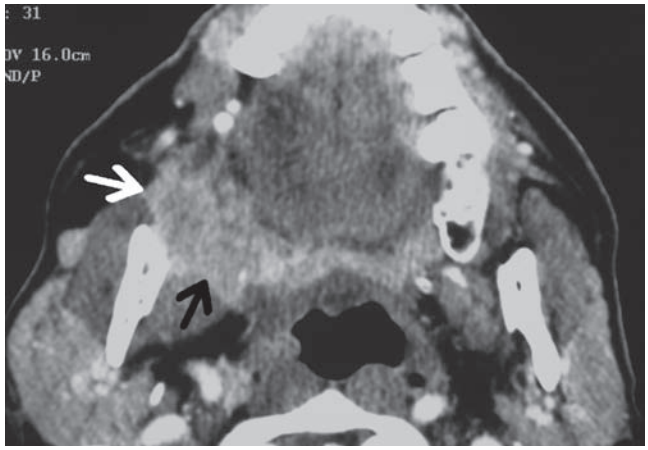


**FIGURE 4-9.** Axial contrast-enhanced CT scan shows a squamous cell cancer originating at the right retromolar trigone (*white arrow*) and extending along the glossotonsillar sulcus (*black arrow*) to the anterior tonsillar pillar. CT, computed tomography.

and the tensor muscle of the palate. This fat is easily visualized on imaging studies and will be displaced laterally by a nasopharyngeal or oropharyngeal mass, medially by a masticator space mass, and anteriorly by a retrostyloid parapharyngeal space mass (Fig. 4-11).

The medial boundary of the prestyloid parapharyngeal space is the buccopharyngeal fascia, which surrounds the superior

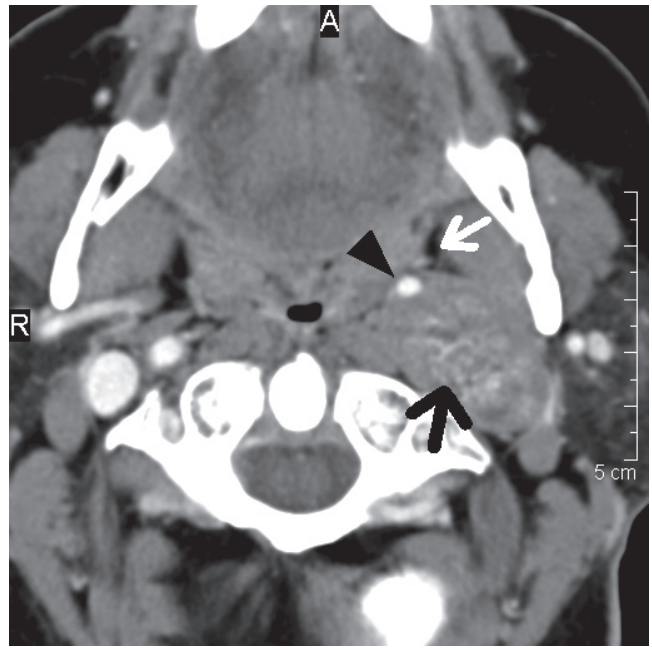



**FIGURE 4-11.** Axial contrast-enhanced CT scan shows a retrostyloid parapharyngeal space mass (*black arrow*), presumed to be a nerve sheath tumor. This has displaced the internal carotid artery (*black arrowhead*) anteriorly and has displaced the prestyloid parapharyngeal space fat anteriorly (*white arrow*). CT, computed tomography.

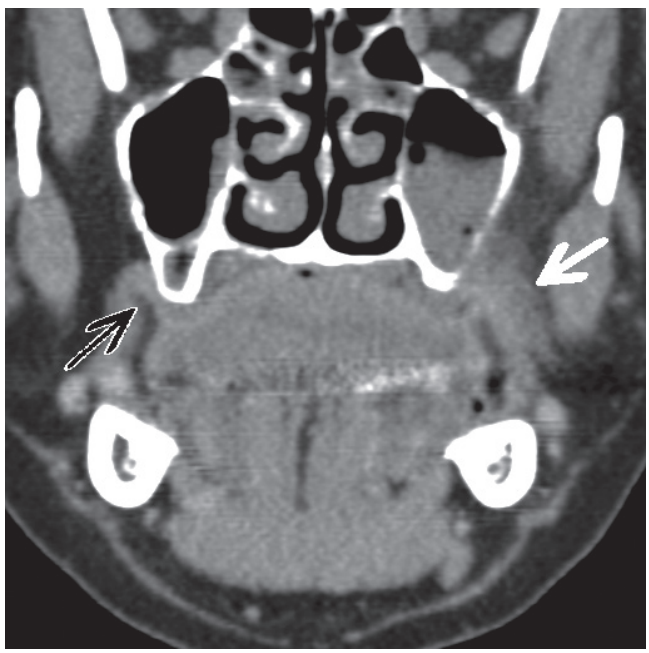


**FIGURE 4-10.** Coronal reformat of a contrast-enhanced CT shows a left glossotonsillar squamous cell carcinoma (*white arrow*), which has infiltrated the surrounding fat and eroded the lateral wall of the maxillary sinus. Compare the contralateral normal gingivobuccal sulcus (*black arrow*). CT, computed tomography.

constrictor muscle. Medial to this fascia superiorly is the previously described thick and strong pharyngobasilar fascia that encases the nasopharyngeal mucosa, lymphatic plexus, and some musculature. Deep to the buccopharyngeal fascia posteriorly is the prevertebral fascia, which encases the longus coli, longus capitus, and rectus capitus muscles contained in the prevertebral space. This space extends from the skull base to T3. Between the buccopharyngeal fascia and the prevertebral fascia is the retropharyngeal space.

The fascial layer that surrounds the styloglossus muscle, stylopharyngeus muscle, and stylohyoid muscle separates the prestyloid parapharyngeal space from the retrostyloid parapharyngeal space (see Fig. 4-5). The retrostyloid parapharyngeal space is sometimes called the carotid space, and is made up of several fascial layers. It contains the carotid sheath, in which resides the carotid artery, jugular vein, cranial nerves IX through XII, and the cervical sympathetic plexus, as well as lymph nodes along the vein.

The fascia covering the deep lobe of the parotid gland and the pterygoid muscles forms the boundary between the parapharyngeal space and the masticator space. The masticator space is essentially synonymous with the infratemporal fossa and is bounded laterally by the zygomatic arch and anteriorly by the posterior wall of the maxillary sinus. It contains the muscles of mastication, portions of the mandible, the internal maxillary artery, pterygoid venous plexus, and V3. The masticator space extends to the skull base where V3 passes through foramen ovale and the middle meningeal artery passes through foramen spinosum. There is a fat pad posterior to the maxillary sinus antrum, which is called the retroantral fat pad. This fat continues inferiorly as the buccal space, through which courses the parotid duct (Fig. 4-12).

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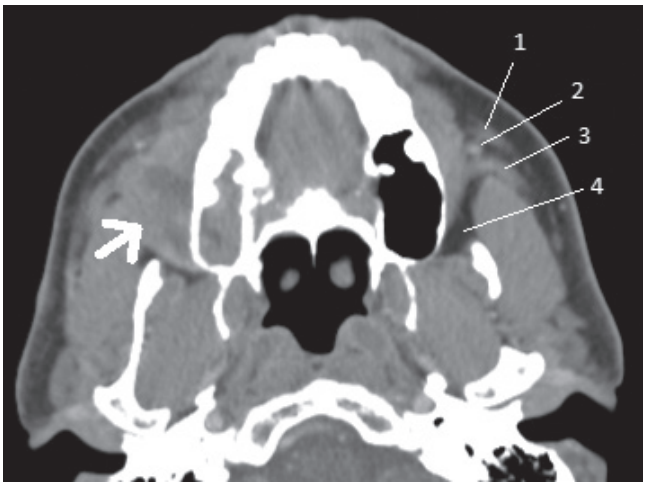



**FIGURE 4-12.** Axial contrast-enhanced CT scan shows a mass in the right buccal space (*arrow*), which was biopsied and proved to be lymphoma. The left buccal space is normal. *1*, superficial musculoaponeurotic system; *2*, facial vein; *3*, parotid duct; *4*, buccal space fat. CT, computed tomography.

## The Infrahyoid Neck

Central in the infrahyoid neck is the visceral compartment, which contains the larynx, hypopharynx, trachea, esophagus, thyroid, and parathyroid glands. Detailed imaging anatomy of the larynx will be discussed in the chapter dedicated to that organ.

The hypopharynx is continuous with the oropharynx superiorly, separated at the level of the hyoid bone and vallecula. It extends posterior to the larynx to end at the level of the cricopharyngeus muscle. On axial images, the postcricoid portion of the hypopharynx has a flattened ellipsoid shape (Fig. 4-13A,B). The inferior continuation of the hypopharynx is the esophagus, which has a more rounded shape posterior to the trachea (Fig. 4-13C).

The pyriform sinuses are paired lateral recesses of the hypopharynx, the anterior aspect of which abuts the paraglottic fat of the larynx (Fig. 4-13C). The most inferior extent, called the pyriform sinus apex, is at the level of the true vocal cords. Deep to the lateral mucosa of the pyriform sinuses is the thyroid membrane superiorly and the thyroid cartilage inferiorly. The medial wall of the pyriform sinus is the lateral surface of the aryepiglottic fold.

Posterior to the hypopharynx is the retropharyngeal space, which extends from the skull base to the mediastinum. Posterior to this is the thick prevertebral fascia, which surrounds the paraspinous muscles and forms a relatively strong barrier to the spread of disease.

The retropharyngeal space is in direct communication with the lateral compartments of the neck. The lateral compartments are also referred to as the vascular and paravisceral spaces and contain the carotid sheath containing the common and internal carotid arteries, the jugular vein and accompanying lymph nodes, and the vagus nerve, which runs in between the carotid artery and jugular vein. The lateral compartment of the neck also includes the sternocleidomastoid muscle.

The posterior compartment of the neck is made up of the cervical spine and paraspinal muscles.

## The Brachial Plexus

The brachial plexus is an area that is difficult to image with both CT and MRI because of the change in contour from a relatively thin neck to broad shoulders. Brachial plexopathies can occur following treatment of head and neck cancer and can present concern over whether the symptoms are from recurrent tumor or radiation neuritis. The brachial plexus can be seen in the region of the cervicothoracic junction as it courses between the anterior and middle scalene muscles (Fig. 4-14). When affected by radiation, the brachial plexus can enlarge, becoming edematous on T2-weighted images, and can enhance.

## CT VERSUS MR VERSUS PET-CT

Which imaging modality to choose depends on how pathology will appear compared to normal tissue and whether there is a contraindication to giving intravenous contrast. For example, a history of severe reaction such as anaphylaxis to iodinated contrast will limit the patient to a noncontrast CT scan or MRI. Severe renal insufficiency will limit the ability to give iodinated contrast for CT as it may worsen renal function, and gadolinium is typically not given when glomerular filtration rate is <30 because of the risk of nephrogenic systemic fibrosis.

Noncontrast CT is not optimal for head and neck cancer imaging because tumor often has the same density as muscle and lymphoid tissue. Inherent contrast between fat, which appears dark, and soft tissue is excellent, and visualization of cortical bone and cartilage erosion is excellent on thin-section CT (Fig. 4-15).

The addition of intravenous iodinated contrast is very helpful for CT because tumor usually enhances more than muscle, allowing differentiation. Many tumors incite an inflammatory reaction in the surrounding tissue, which will also enhance, allowing visualization of tumor compared to normal tissue. For practical purposes, the inflammatory reaction should be considered as tumor for treatment planning purposes, as it is impossible to differentiate the two on imaging studies. CT has advanced tremendously in terms of speed of imaging and coverage. Axial CT images can now be acquired in very thin sections, and software is commonly available to reconstruct these data in any plane, which was a former advantage of MRI.

MRI has the advantage over CT of being able to manipulate contrast by changing the imaging parameters. T1-weighted images give excellent inherent contrast between fat and soft tissue. This is particularly useful when looking for perineural tumor spread where the obliteration of fat at skull base foramina, for example, is a sign of tumor extension. Similar to CT, however, noncontrast T1-weighted images give poor contrast between tumor, muscle, and lymphoid tissue.

T2-weighted images tend to give good contrast between tumor and muscle, and fat suppression techniques can be very helpful for visualization of tumor. However, differentiation of tumor from lymphoid tissue may be difficult.

The administration of gadolinium shortens the T1 relaxation of enhancing tumor, and so is very helpful. T1-weighted images postgadolinium with fat suppression is a commonly used sequence for imaging the extent of tumor.

In general, the appearance of tumor compared to normal surrounding tissue depends on the tumor histology and its growth pattern. In terms of histology, the cellularity, nuclear to cytoplasm ratio, and stromal factors can affect the tumor's density on CT or signal intensity on MRI. Also affecting the tumor's appearance is the presence of microcysts, macrocysts, necrosis, hemorrhage, and calcification.

Tumors that are very cellular with large nuclei and little stroma, such as lymphoma, can be of higher attenuation than muscle on noncontrast CT and hyperintense to muscle on noncontrast T1-weighted images and hypointense on T2-weighted images. Squamous cell cancer tends to be slightly hyperintense

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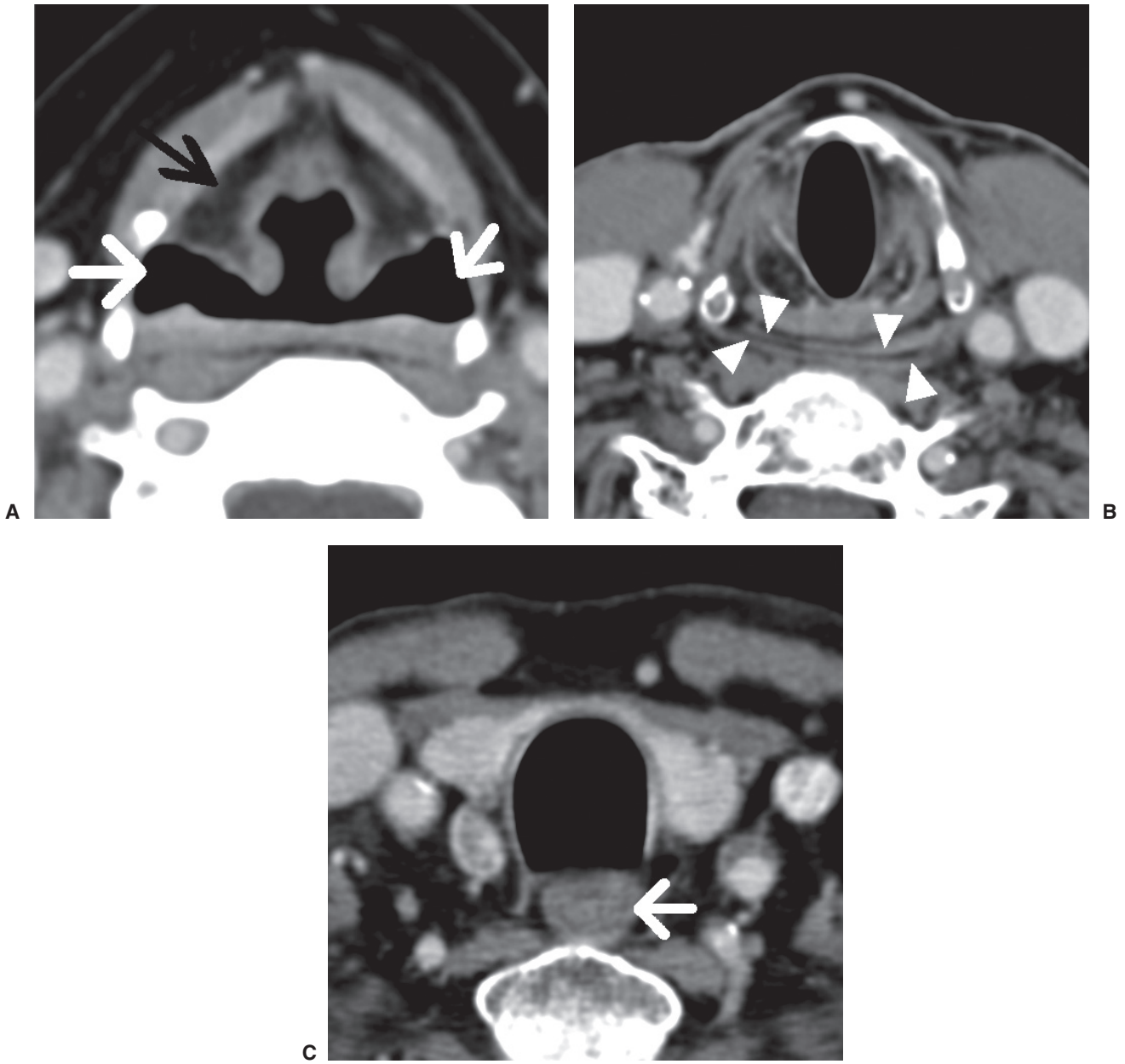



**FIGURE 4-13.** Axial postcontrast CT images of the hypopharynx. At the upper level of the hypopharynx (**A**) are the paired pyriform sinuses (*white arrows*). The paraglottic fat (*black arrow*) is well seen as a low attenuation region anterior to the aryepiglottic folds. **B:** At the postcricoid level, the hypopharynx appears as a thin ellipse (*arrowheads*). **C:** Posterior to the trachea the hypopharynx has merged into the esophagus, which appears as a rounded structure (*arrow*). CT, computed tomography.

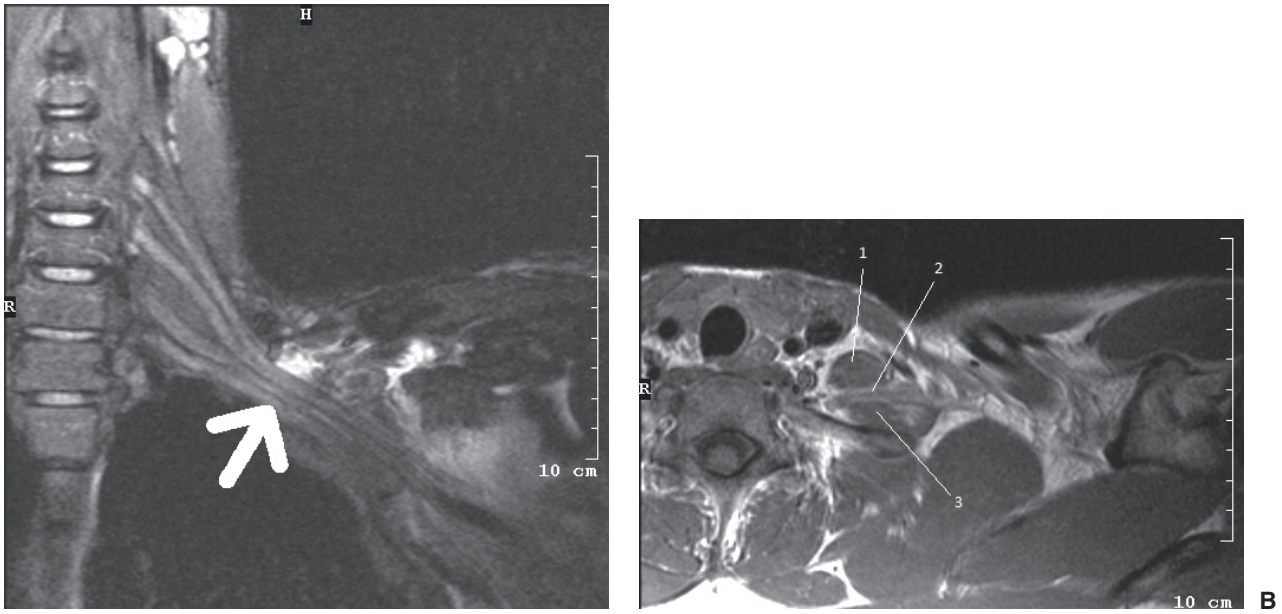
to muscle on T2-weighted images. The presence of microcysts or macrocysts can make the tumor hypointense to muscle on T1-weighted images and hyperintense on T2-weighted images. If the lesion is very dark on T2-weighted images, a fibrous matrix, hemorrhagic or calcified lesion, or lymphoma should be considered (Fig. 4-16).

FDG-PET has spatial resolution that does not allow for clear distinction of the full extent of the tumor, the presence of bone destruction, or perineural spread. It can be helpful in the workup of the unknown primary (Fig. 4-17), in determining positive lymph nodes, in determining the presence of distant metastatic disease (Fig. 4-18) and is especially useful in posttreatment surveillance scans. The use of PET-CT is described in more detail in the radiologic imaging concerns section of Chapter 10.

## PATTERNS OF TUMOR GROWTH

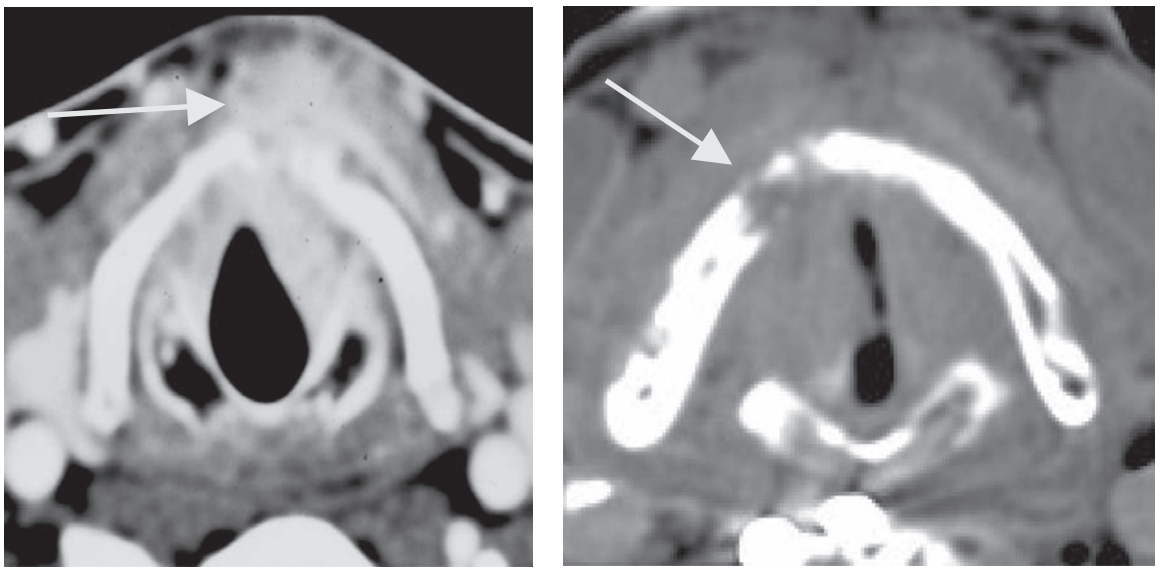
Tumors tend to grow as a sphere unless they are constrained by anatomic boundaries. When faced by boundaries, they grow along the path of least resistance. Hard tumors will remodel bone and push away vessels and nerves. Softer tumors can insinuate around structures such as vessels. Ultimately, malignant tumors will not respect boundaries and will directly invade structures.

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A B

**FIGURE 4-14.** Coronal short tau inversion recovery (STIR) MR image (**A**) shows the roots of the brachial plexus (*arrow*) extending inferiorly and laterally from the spinal neuroforamina to the throracic inlet. Axial T1-weighted MRI (**B**) shows the brachial plexus coursing between the anterior scalene and middle scalene muscles. *1*, anterior scalene muscle; *2*, brachial plexus; *3*, middle scalene muscle. MRI, magnetic resonance imaging.



A B

**FIGURE 4-15.** **A:** Axial CT obtained at the level of the true vocal cord demonstrates an anterior commissure eroding the anterior portion of the thyroid cartilage and extending into the adjacent soft tissue (*arrow*). **B:** Axial CT obtained in a different patient shows a left-sided true vocal cord carcinoma eroding both the inner and outer cortex of the thyroid cartilage without bulk involvement into the adjacent soft tissues. CT, computed tomography.

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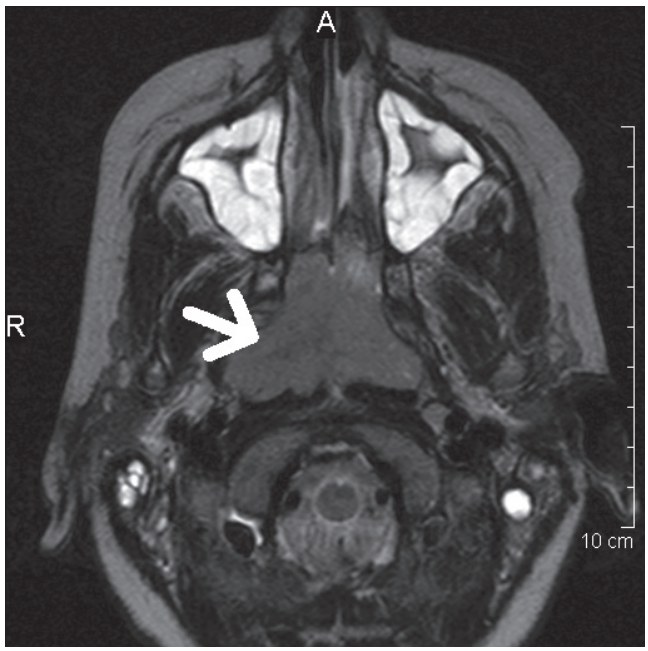



**FIGURE 4-16.** Axial T2-weighted MRI of a patient with nasopharyngeal lymphoma. Notice how low signal the tumor appears (*arrow*) compared to most pathology, which is usually bright on T2-weighted images. Compare the mucosal thickening in the maxillary sinuses. MRI, magnetic resonance imaging.

That being said, they prefer to grow along structures first, prior to invading them. For example, malignant squamous cell cancer can grow along fascial planes in the neck, including the fascia surrounding muscle bundles and along periosteal tissue, along neurovascular structures, and within the medullary spaces of bone. Therefore, when tissue fat planes between tumor and muscle, tumor and bone, or tumor and a vessel are obliterated on imaging, it does not necessarily mean that the muscle, bone, or vessel has been invaded. The tumor may just be growing along that structure's fascial lining. Fixation of a vessel can be assumed if tumor surrounds it by more than 270°.

Certain structures provide more of a boundary than others. For example, the pharyngobasilar fascia that holds the nasopharynx open is a thick structure and so is relatively resistant to tumor invasion compared to other thinner and weaker fascial planes such as the buccopharyngeal fascia. Cartilage is resistant to tumor invasion probably because it is hypovascular. When cartilage is invaded, it tends to happen at sites of ossification, where there are penetrating neurovascular bundles. Similarly, bone invasion tends to happen at sites of penetrating neurovascular bundles or at sites of muscle attachment.

Bone erosion is an important sign that invasion has occurred. CT is the best for detecting cortical erosions (Fig. 4-19). MR, particularly noncontrast T1-weighted images and fat-saturated postgadolinium T1-weighted images, is good for demonstrating tumor spread through bone marrow spaces. Increased bone density, or sclerosis, is indeterminate for tumor invasion.

## Perineural and Perivascular Spread of Tumor

Tumor can spread along the perineurium as well as along fascia surrounding vessels and muscles. For example, an oropharyngeal tumor can spread along the styloglossus and stylopharyngeus muscles to reach the carotid sheath. Superior growth of tumor can then reach the carotid canal and jugular fossa of the skull base.

Perineural spread is demonstrated on imaging by obliteration of fat planes, enlargement and enhancement of nerves, and erosion of bony foramina through which nerves pass. Certain structures are best imaged in the axial plane, such as the entrance of the mandibular nerve into the alveolar canal, the greater and lesser palatine foramina, and the pterygopalatine fossa. The connection between V3 and VII along the auriculotemporal nerve is also best seen in the axial plane (Fig. 4-20). Another connection between the fifth and seventh cranial nerves is along the greater superficial petrosal nerve from the pterygopalatine fossa (Fig. 4-21).

Spread of cancer along V3 to the trigeminal ganglion and cavernous sinus is better imaged in the coronal plane (Fig. 4-22). In general, MRI is superior to CT for imaging perineural spread of tumor.

## Lymphatic Spread of Tumor

The likelihood of tumor to spread along lymphatics is based on a number of factors. One is the location of the primary tumor. Certain sites are rich in lymphatic drainage such as the nasopharynx and so commonly present with positive nodes. Other sites, such as the true vocal cords, have relatively sparse lymphatic drainage. The overall size of the tumor and biological aggressiveness also affect the likelihood of finding positive lymph nodes.

The radiological features that define a positive lymph node are the enhancement pattern with presence of internal nonenhancing areas, and the periphery of the node, where indistinct borders are a sign of extracapsular spread of tumor. These features are more helpful than size of the node (Fig. 4-23). CT has been shown to be slightly superior to MR for the detection of small suspicious lymph nodes.[6] FDG-PET can also be very helpful. This topic is dealt with in greater detail in Chapter 10.

# POSTTREATMENT REACTIONS AND SCARRING VERSUS RECURRENT TUMOR

Posttreatment scans of head and neck cancer patients are among the most challenging imaging studies to interpret secondary to the distortion of normal anatomy from surgery and flaps and reactive tissue changes in response to surgery and radiation.

During radiation therapy tumor becomes edematous and necrotic, with the amount of peritumoral edema peaking at the end of treatment. Tissue then heals following the course of radiation but reactive mucosal edema and deep tissue space edema may persist for months. The inflammatory response is isodense to muscle on CT, isointense to hypointense in T1-weighted images, hyperintense on T2-weighted images, and enhances. In other words, this granulation tissue has imaging characteristics indistinguishable from tumor. The inflammatory response is FDG avid, so PET scanning generates too many false positives in the first 3 to 4 months following treatment.

The inflammatory response usually resolves in 3 to 12 months to form scar tissue, which is isodense to muscle and tumor on CT, but is low signal on both T1-weighted and T2-weighted images with slight enhancement.

General rules to follow in posttreatment imaging are that decreased size or disappearance of tumor indicates a good response to therapy. Focal residual masses are seen not infrequently on scans obtained >3 months posttherapy. Persistent enhancement

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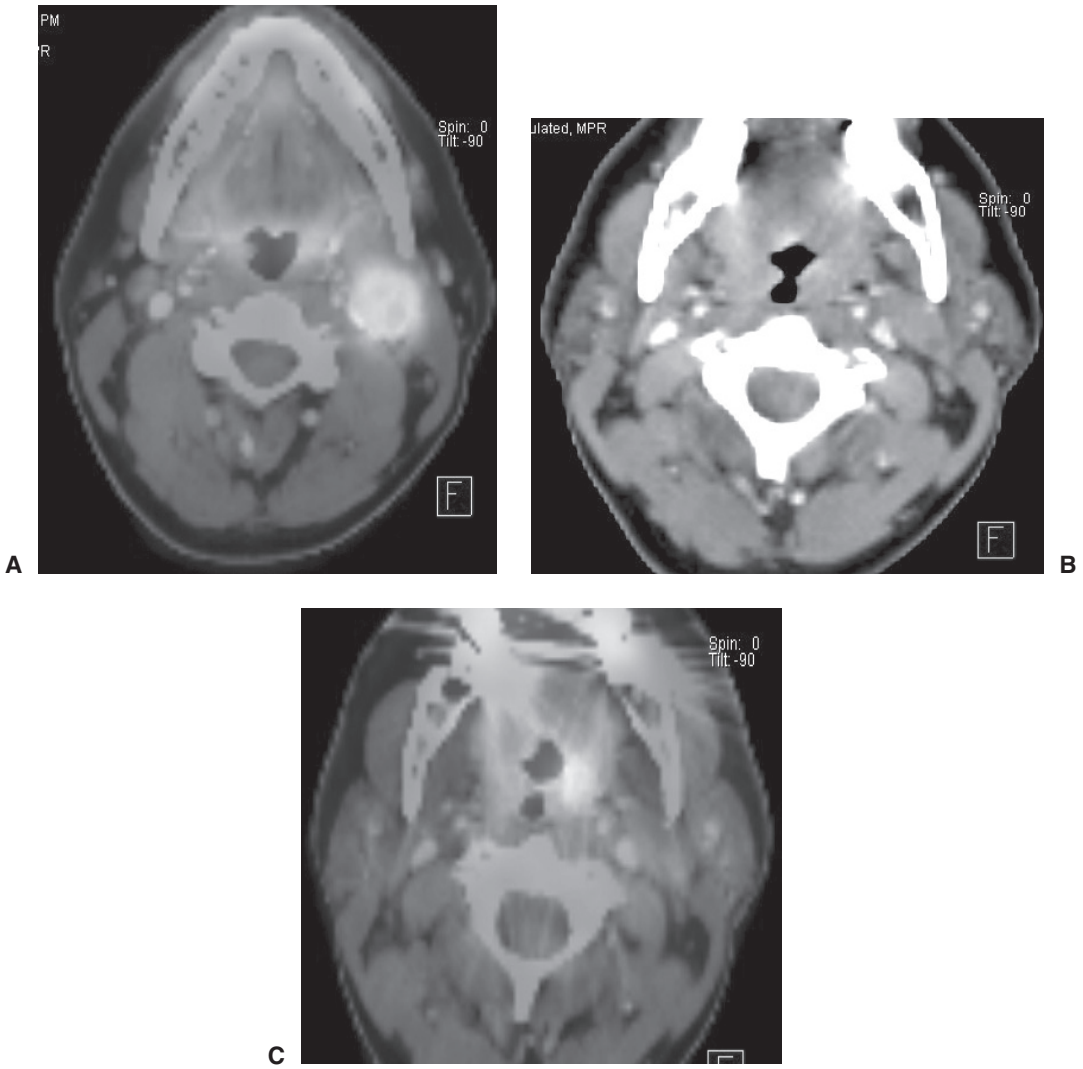



**FIGURE 4-17.** Axial PET-CT (**A**) performed in patient with a biopsy-proved nodal metastases shows uptake in the left level II lymph node. Contrast-enhanced CT (**B**) showed evidence of a primary site tumor. No mucosal disease was identified at endoscopy. On the basis of these findings, the patient was given the diagnosis of an unknown primary tumor. PET-CT (**C**) shows focal uptake in the left tonsil that was suspicious for a primary site. The patient underwent a left tonsillectomy, and pathology revealed squamous cell carcinoma. (See color insert.) PET, positron emission tomography; CT, computed tomography.

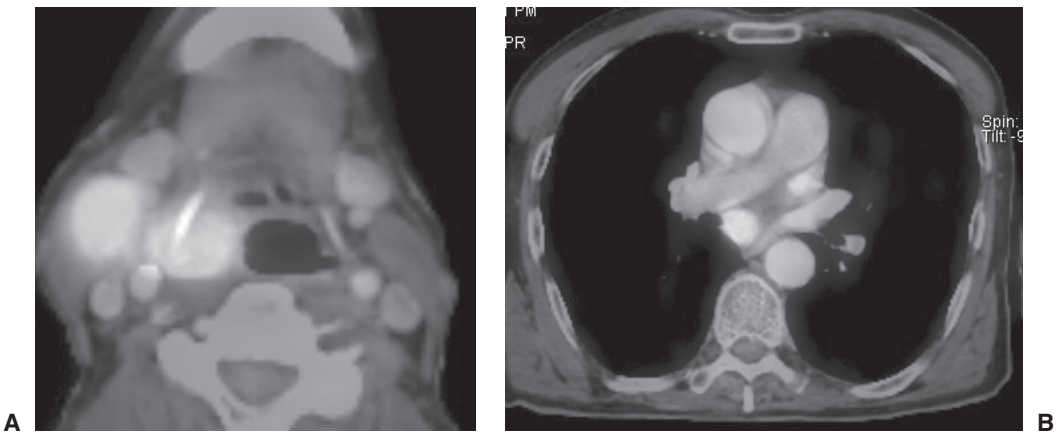



**FIGURE 4-18.** **A:** PET-CT performed in a patient with a known right pyriform simus carcinoma and level II nodal disease shows uptake at the primary site and lymph node. **B:** There is also abnormal uptake in a mediastinal lymph node, which is not detected in standard cross-sectional imaging. (See color insert.) PET, positron emission tomography; CT, computed tomography.



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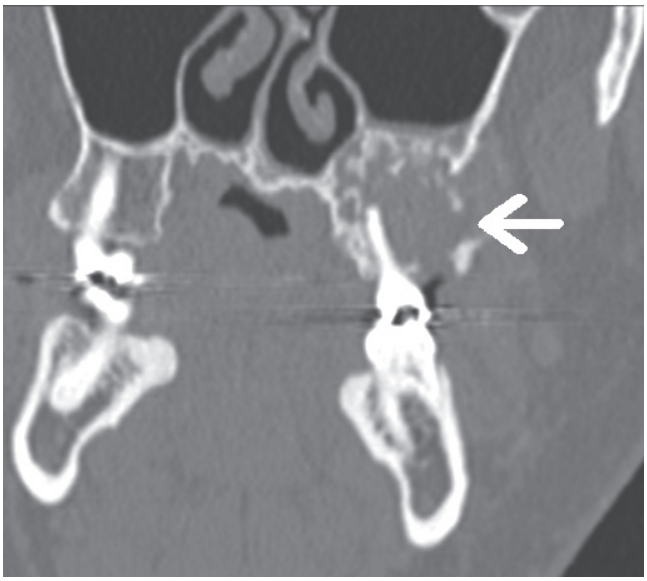


**FIGURE 4-19.** Coronal reformation of a noncontrast CT scan showing bony destructive changes (*arrow*) from a maxillary alveolar ridge mucoepidermoid carcinoma. CT, computed tomography.

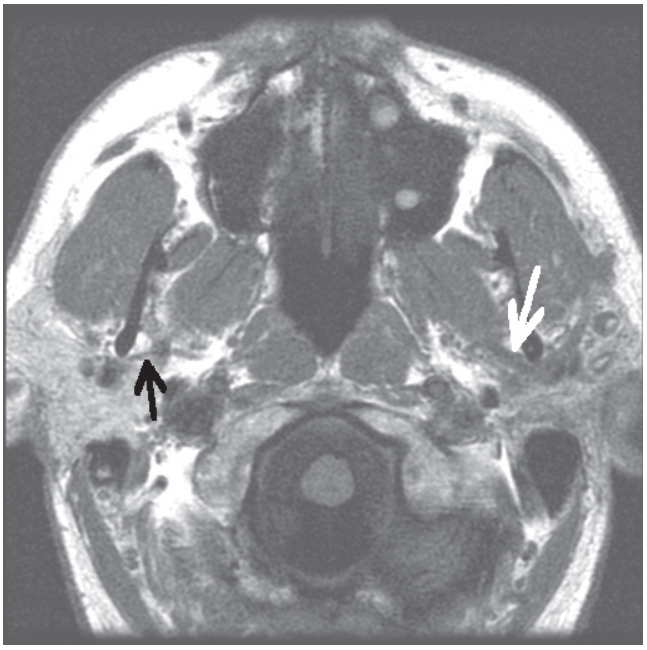
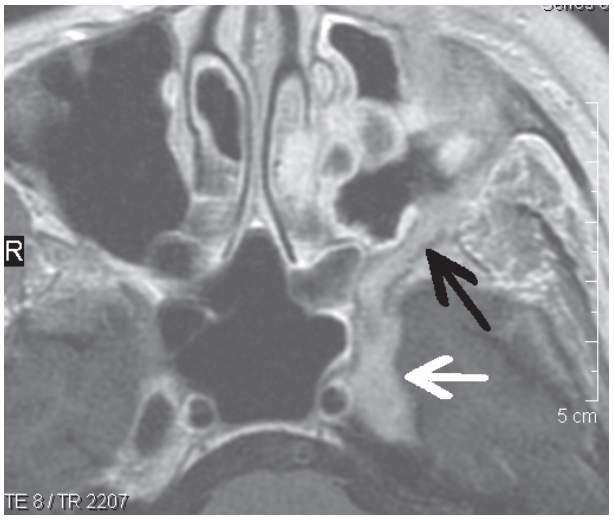
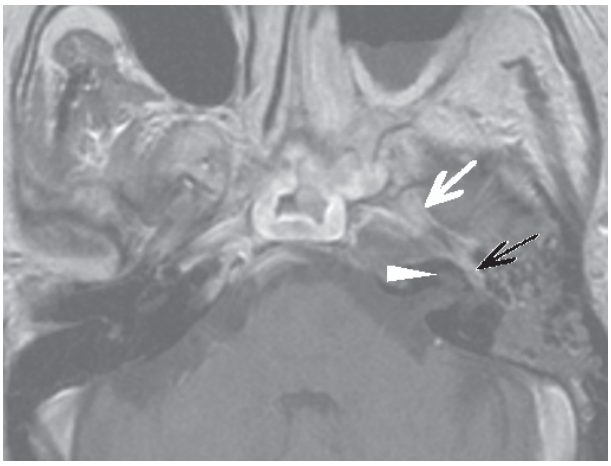


**FIGURE 4-20.** Axial noncontrast T1-weighted MRI shows perineural spread of skin cancer along the auriculotemporal nerve on the left (*white arrow*) connecting V3 with the facial nerve. The normal course of the auriculotemporal nerve is shown on the right side (*black arrow*). MRI, magnetic resonance imaging.




A



B

**FIGURE 4-21.** **A:** Axial postcontrast T1-weighted MRI shows perineural spread of skin cancer from Meckel cave (*white arrow*) through foramen rotundum to the pterygopalatine fossa (*black arrow*). In the same patient (**B**) the perineural spread of cancer can be seen extending through the vidian canal along the greater superficial petrosal nerve (*white arrow*) to reach the facial nerve (*black arrow*). Note the position of the cochlea (*white arrowhead*). MRI, magnetic resonance imaging.

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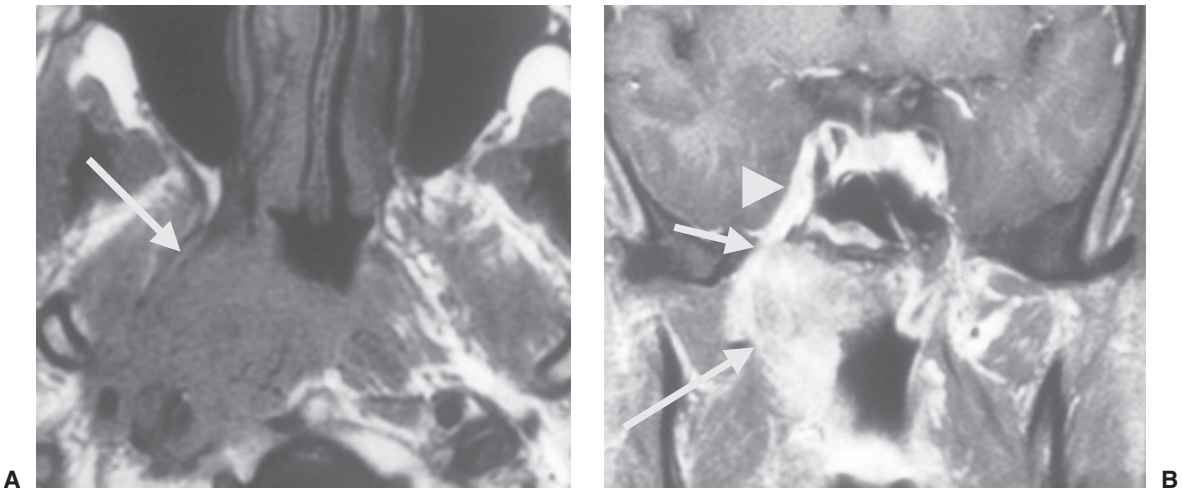



**FIGURE 4-22.** **A:** Axial noncontrast T1W image shows a right-sided nasopharyngeal carcinoma (*arrow*). **B:** Coronal contrast-enhanced T1W image shows the enhancing tumor (*long arrow*) extending superiorly along V3 through foramen ovale (*short arrow*) and into the cavernous sinus (*arrowhead*). T1W, T1-weighted.

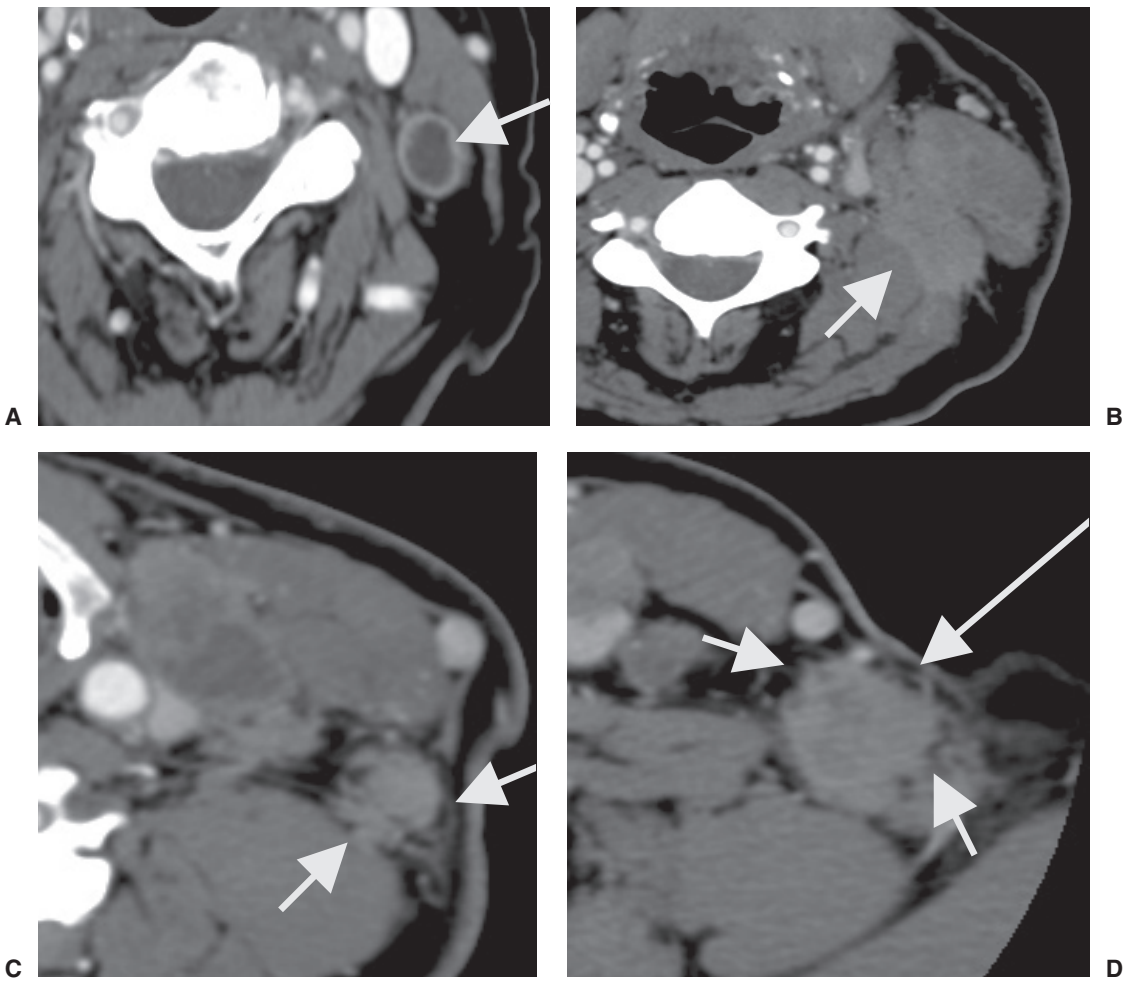



**FIGURE 4-23.** Imaging findings indicative of metastases. **A:** Central necrosis—axial CT shows the metastatic lymph node to contain a central area of decreased attenuation (*arrow*). **B:** Invasion of deep neck musculature—this metastatic lymph node has irregular margins that are indistinct from the paraspinal musculature (*arrow*). **C:** Extracapsular penetration—reticulated margins of suspicion or obviously metastatic lymph nodes are indicative of extracapsular penetration (*arrows*). **D:** Dermal lymphatic invasion—reticulation of the dermal fat is suggestive of dermal lymphatic invasion. This metastatic lymph node has both extracapsular penetration (*short arrows*) and dermal lymphatic invasion (*long arrow*). CT, computed tomography.



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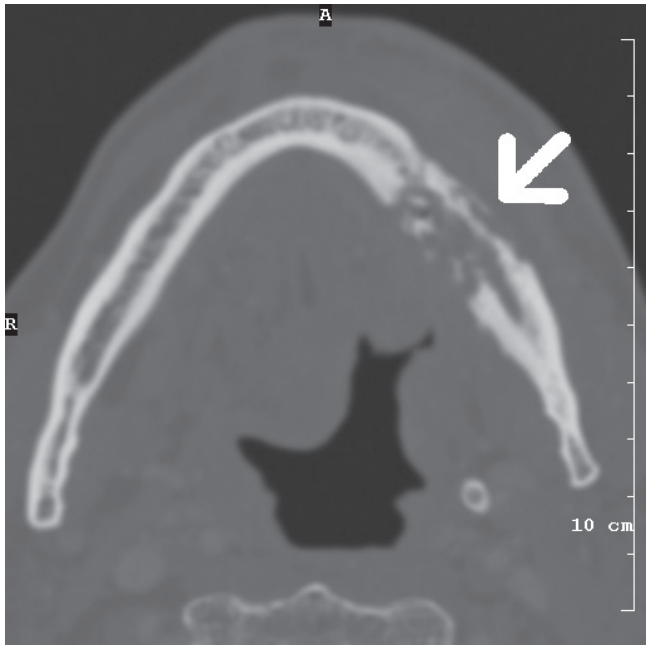



**FIGURE 4-24.** Axial CT scan with bone windowing shows typical findings of osteoradionecrosis (*arrow*) including fragmentation and tunneling. CT, computed tomography.

and T2 signal greater than muscle are suspicious findings for residual tumor, but nevertheless most of these masses still shrink or stabilize over time.[5] A negative PET scan is very encouraging in these cases.

Changes in nontumoral tissue are commonly encountered on the postradiation therapy scans. These include skin thickening and stranding in the fat from either lymphedema or perilymphatic fibrosis. Atrophy or fatty replacement of the major salivary glands, lacrimal glands, and lymph nodes that were in the radiation portal may be seen. Mucosal thickening in the paranasal sinuses and mastoid air cells in the radiation field is a common finding. These changes may all persist for years.

Bony changes on posttreatment scans also create diagnostic challenges. The surgical margins of partially resected bone usually heal in about 3 months with a smooth cortical margin. Osteoradionecrosis can occur months to years following radiation therapy. It typically can be distinguished from recurrent tumor by its fragmented nature with sloughing of cortical bone and endosteal tunneling (Fig. 4-24). Lucencies that develop between bone and hardware indicate loosening, but the cause may be osteonecrosis, infection, or tumor.

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CHAPTER 5

Avraham Eisbruch

# Novel Radiation Therapy Techniques in the Management of Head and Neck Cancer

In traditional irradiation of head and neck cancer, the placement of the radiation fields and their shapes are based on the bony anatomy acquired by the simulator diagnostic-quality films. During the late 1980s, advancements in computer technology and imaging introduced methods to identify the targets on computed tomographic (CT) scans and display the radiation beams in three dimensions relative to the anatomy. In addition, calculation and display of the radiation dose distributions and methods to evaluate and compare rival plans using dose–volume histograms (DVHs) became available. The introduction of multileaf collimators (MLCs) facilitated an increase in the number of beams that could be delivered without a large extension of treatment time. Treatment could now be delivered from multiple angles, including noncoplanar directions, when required. The result was the emergence of three-dimensional conformal radiotherapy (3DCRT), which allowed better precision of irradiation delivery to image-based targets, and some improvements in the sparing of uninvolved critical organs. Early studies of the utility of 3DCRT in head and neck cancer examined cancer of the larynx,[1] nasopharynx,[2,3] hypopharynx,[4] and paranasal sinuses.[5] These studies demonstrated a significant benefit from 3DCRT such as better coverage of the tumors and reduced doses to critical tissue compared with standard techniques. A step forward has been gained in the mid-1990s by intensity-modulated radiotherapy (IMRT), which facilitated a higher degree of dose conformality and offered opportunities for additional clinical gains. More recently, imaging-guided radiotherapy (IGRT) has emerged, providing opportunities for better precision of patient setup and for tracking tumor regression and anatomic changes in the noninvolved tissue during the course of radiation. Tracking these anatomic changes may facilitate future replanning during the course of therapy to address them, a concept referred to as adaptive radiation therapy (ART). Other emerging technologies include new imaging modalities that provide opportunities to study the customization of the radiation dose depending on the expected tumor biology, and the use of heavy particles like protons or carbon ions, which offer additional advantages in dose conformality. In addition, technical innovations in the delivery of IMRT, such as tomotherapy and volumetric-modulated arc therapy (VMAT), provide specific improvements and introduce specific trade-offs compared with beamlet-based IMRT. Some recent experience has been gained with stereotactic radiotherapy using a robotic radiosurgery system for recurrent cancers near the base of the skull. These advancements will be described in this chapter, emphasizing the role of IMRT, for which ample clinical experience has accumulated.

## IMRT: GENERAL ASPECTS

IMRT implies the use of radiation fields for which intensity varies across the field, depending on the thickness of the target and the existence of critical organs or critical noninvolved tissue in their path. Treating the targets with multiple beams of varying intensity allows a relatively uniform dose in an irregularly shaped target while avoiding a high dose to the surrounding structures. Two technologic developments made IMRT possible: the introduction of computer-controlled MLCs and the development of computerized optimization or "inverse planning," which determines the intensity of the beams required to satisfy a specified set of dose distributions.

Currently, most IMRT delivery systems use conventional MLCs. Delivering IMRT using a conventional MLC can be made in a "dynamic" or "static" form. In the "dynamic" form, the leaves at each gantry position are swept across the target while the beam is on and their speed determines the radiation fluence. In "static" or "segmental" multileaf IMRT, each field consists of multiple segments with different intensities. These forms of IMRT are currently offered by most manufacturers of linear accelerators. A helical tomotherapy design has been developed at the University of Wisconsin and is similar in its operation to the helical CT, delivering essentially an infinite number of beams while the gantry rotates around the patient. This design has been available commercially in recent years.

The complexity of IMRT plans cannot usually be achieved by the forward, iterative process alone used in 3DCRT plans. Instead a computer-based optimization process, called *inverse planning*, is used. Inverse planning demands that the physician and planning team state the treatment goals, usually in terms of the dose and/or dose–volume goals for the targets, and the constraints for the critical normal tissue (the objective, or cost function). The computer attempts to achieve the desired outcome by iteration through numerous possible beam intensities. The desired solution is the dose distribution that minimizes the variance of the delivered dose relative to the objective function. For each target and noninvolved organ or tissue, an importance factor or weight is assigned, and the objective function is the sum of the variance terms representing each structure of interest, multiplied by the importance factor. Because the variance is the sum of the squares of the differences between the prescribed and the delivered doses, this approach is called a *quadratic objective function* and is the one used in most current optimization systems. A publication by the Intensity Modulated Radiation Therapy Collaborative Working



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Group summarized the consensus regarding IMRT planning, delivery, commissioning, radiation safety and quality assurance, and detailed recommendations about target volume and dose specification.[6] This publication is recommended for readers interested in more detailed discussions about the general aspects of IMRT.

## IMRT FOR HEAD AND NECK CANCER

The anatomy of the neck is complex, with many critical and radiation-sensitive organs in close proximity to the targets. Tight dose gradients around the targets that limit the doses to the noninvolved tissue, features characteristic of IMRT, are desirable and offer the potential for therapeutic gains. The sparing of uninvolved normal organs can offer significant improvement in outcomes. This includes major salivary glands, minor salivary glands dispersed within the oral cavity, the mandible, and the pharyngeal musculature as well as other organs pertinent to specific anatomic tumor locations. In the cases of nasopharyngeal and paranasal sinus cancer, critical normal tissue that may be partly spared using IMRT include the inner and middle ears, the temporomandibular joints, temporal brain lobes, and the optic pathways.

In addition to noninvolved tissue sparing, IMRT offers a potential for improved tumor control by reducing the constraints on the tumor dose due to critical organs, for example, the spinal cord, brain stem, and the optic pathways, which occasionally limit the tumor boost doses in conventional radiation therapy (RT). This is achieved by specifying a maximal dose to the critical organs and a high penalty in the optimization process if that dose is exceeded. In addition, IMRT eliminates the need for posterior neck electron fields, commonly used in conventional RT, and their associated dose deficiencies. IMRT in the head and neck is more feasible than in other sites as breathing-related organ motion is practically absent. However, there are other factors that need to be taken into account such as patient setup uncertainties, swallowing-related organ movements, and changes in target and organ positions related to tumor shrinkage and patient weight loss during therapy, detailed in the subsequent text.

### Patient Selection

Head and neck IMRT is work intensive and lengthens treatment time. Not every patient is expected to benefit; those who would benefit most are patients with paranasal sinus cancer where the targets are near the optic pathways, patients with oropharyngeal or nasopharyngeal cancer in whom standard RT fields would encompass most of the salivary glands, and patients in whom standard techniques would require a compromise in the tumor dose, due to proximity of the tumor to the spinal cord or the brain stem. Patients with laryngeal cancer and clinically noninvolved neck, receiving treatment to the larynx alone or requiring irradiation of the neck encompassing the jugulodigastric nodes but not extending to the base of the skull, may not benefit from IMRT compared with simpler techniques. The same applies to patients requiring irradiation to the ipsilateral neck alone. In recent years, there have been suggestions to use IMRT when the glottic larynx alone is treated, to spare the carotid artery and reduce the risk of development of an atheromatous plaque and subsequent brain stroke.[7,8] However, the utility and value of this uproach is not known and it is not practiced by most centers.

### Immobilization

Head and neck immobilization is typically performed using a thermoplastic mask with several attachment points to the treatment table and a head support. Several commercial systems are available. Typically, immobilization with these systems results in average daily setup errors of few millimeters.[9] These errors require an extension of the targets to ensure adequate irradiation (see "The Planning Tumor Volumes" in the subsequent text). It is important to extend the mask to include the lower neck and shoulders, if targets in the lower neck and the supraclavicular nodes are included in the IMRT plans. An alternative is to treat the lower neck with an anterior field and match this field with the upper neck IMRT fields using a split-beam technique. This strategy reduces the doses to the glottic larynx and to the skin of the lower neck and reduces treatment complexity, compared with whole-neck RT.[10] Such a strategy is recommended in cases where the risk of disease in the lower neck is low. In these cases, the head and upper neck alone need to be immobilized.

### Defining the Target: Imaging

In most cases, the simulation contrast-enhanced CT is in most cases the only imaging modality required for the delineation of the targets. Magnetic resonance imaging (MRI) is limited by its sensitivity to artifacts, difficulty in interpretation, long examination time, and cost. MRI is a necessary adjunct to CT for tumors close to the base of the skull, such as nasopharyngeal and paranasal sinus cancer. In these situations, MRI provides better details of tumor extension and the parapharyngeal and retropharyngeal spaces, compared with CT.[11] Fluorodeoxyglucose-positron emission tomography (FDG-PET) has recently been found to add significantly to the information gained from CT regarding the tumor extent in lung cancer.[12] In contrast, early series of head and neck cancer where CT, MRI, and FDG-PET were obtained, and surgery was then performed to validate the primary tumor extent and lymph node involvement, reported a rather limited benefit of FDG-PET compared with CT/MRI.[13] More recent studies have better defined the role of FDG-PET as a tool for target delineation in IMRT of head and neck cancer. Daisne et al. performed pretreatment CT, MRI, and FDG-PET on 29 patients with stage II to IV laryngeal and oropharyngeal cancers.[14] Nine of these patients subsequently underwent total laryngectomy, and these specimens were compared with coregistered radiographic images. There was no difference between total CT and magnetic resonance (MR) volumes, but GTVs obtained from FDG-PET were smaller than these two, and surgical specimens were even smaller, indicating overestimation of GTVs with all three imaging modalities. However, when examined in detail, despite overestimating in most dimensions, all three imaging modalities actually underestimated the mucosal extent of disease, highlighting the importance of the physical examination in determining the mucosal extent of tumors for treatment planning purposes. Another study, from Emory University, did not have pathologic correlation, but imaged 40 patients with FDG-PET and CT.[15] In this report, the target according to PET was smaller than the CT-defined target in 75% of cases, but larger in 18%. When the PET images were registered on the treatment plan constructed with only CT volumes, the PET-defined target was noted to be underdosed in 25% of cases. It is possible that the difference in the results of these two studies can be attributed to different thresholds for determining PET positivity. Whereas fixed thresholds have been commonly used, the group from the Universite Catholique de Louvain in Brussels, Belgium, has published work suggesting that the correct threshold depends on the signal-to-background ratio of each study and is typically between 36% and 73%.[16] The practice at the University of Michigan has been to combine the information gained from FDG-PET and CT (and MRI for tumors near the base of the skull) for a composite gross target, as the information gained from any single imaging modality cannot be considered gold-standard taking into account current published studies. In all cases, the findings of a careful clinical examination

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form the basis for assessing the extent of the primary tumor. For example, palpation of oropharyngeal tumors can assess their extent in a way that is complementary to imaging, especially the mucosal extent which is poorly assessed by imaging.[14]

## Selection and Outlining of the Targets

A major potential pitfall of IMRT is the failure to select and delineate the targets accurately. This is especially relevant in head and neck cancer, where a high risk of subclinical local and nodal disease exists and where adequate irradiation of the lymph nodes at risk is crucial for local-regional control and survival. For example, in standard three-field head and neck RT, the first echelon and the retropharyngeal nodes are treated routinely when the primary tumor is targeted. In contrast, these nodes will not be adequately irradiated by IMRT if they are not specified on the planning CT.

## Target Definitions in the Head and Neck

The GTVs consist of the primary tumor and lymph nodes with apparent or suspected metastasis. The primary tumor GTV is defined using radiologic and clinical assessment. Lymph node GTVs include nodes with radiologic criteria of involvement: diameter >1 cm (in the case of the jugulodigastric nodes, >1.1–1.5 cm), smaller nodes with spherical rather than ellipsoid shape, nodes containing inhomogeneities suggestive of necrotic centers, or a cluster of three or more borderline nodes.[17] The clinical target volume (CTV) surrounding the primary tumor consists of tissue perceived to contain microscopic, subclinical tumor extension. In addition to the primary tumor CTV, the lymphatic CTVs consist of nodal areas that are at risk of metastatic disease but do not match the radiologic criteria of involved nodes.

## Delineation of the Primary Tumor Clinical Target Volume

Factors used for assessing the extent of the CTV margins in each case include tumor site, size, stage, differentiation, and morphology (exophytic vs. ulcerative, infiltrative vs. pushing front). Rather than assign or expand the GTV uniformly, outlining of the CTV is recommended on the planning CT on slice-by-slice basis. Knowledge of the anatomic and clinical patterns of tumor extension and clinical judgment, as well as a familiarity with head and neck imaging, are necessary for accurate estimation of the CTV margins around the tumor. Specific recommendations for each tumor site have been detailed elsewhere.[18]

## Selection and Delineation of the Lymphatic Clinical Target Volumes

Our knowledge of the pattern and risk of lymphatic drainage from different head and neck sites is based on the classical anatomic work of Rouviere,[19] reviewed recently,[20] the assessment of the location and prevalence of clinical neck metastasis by Lindberg et al.,[21] and the large experience with elective neck dissections providing information about microscopic metastases, reported by Byers and Shah.[22,23] A division of the neck to six levels has been developed by surgeons from Memorial Hospital and revised by Robbins et al.,[24,25] allowing standardized and improved reporting of the nodal involvement and the surgical therapy of the neck. Adoption of this system for identification and outlining of the nodal CTVs for IMRT is highly recommended. It should be emphasized that the retropharyngeal nodes, which are not routinely dissected surgically, are not considered in the surgical neck levels classification, but are important targets in the irradiation of nasopharyngeal and other advanced head and neck cancer.[26] Reviews of the risk of metastases to each neck level[27] and of the neck levels at risk for each tumor site and stage[18] have recently been published. Several publications are recommended for identifying the neck levels on the planning CT scans. An imaging-based nodal classification, using CT- or MRI-based criteria that correspond to the surgical anatomic landmarks, has been developed by head and neck radiologists.[28] In addition, several articles have been published by radiation oncologists demonstrating how to outline the lymph node neck levels as CTVs on the planning CT scans[18,27,29–32] or axial MRI.[27]

In the postoperative cases, the surgical specimens provide information which helps in determining the neck levels at risk. Neck dissection disrupts some anatomic landmarks used to define the borders between the levels. On the other hand, the surgical bed is apparent on the CT scan and should be encompassed entirely within the CTV.[32] It is often impossible to distinguish between the primary tumor resection and the adjacent neck dissection bed, and they are encompassed within a unified CTV. Neck levels in which microscopic extracapsular lymph node extension has been found are considered high-risk volumes and are assigned a higher dose (see subsequent text). At these levels, the target may be extended to include the subcutaneous tissue.[33]

## The Planning Tumor Volumes

Once the GTVs and CTVs are outlined on the axial CT images, a uniform expansion of these targets is performed to obtain the planning tumor volumes (PTVs) that accommodate setup uncertainties. Typically, the magnitude of the margin is 5 mm, which means that an extra 5-mm rind of normal tissue around the target receives full dose. In a region with targets and organs at risk (OARs) in close proximity, reducing this margin can potentially reduce treatment-related toxicity. Indeed, it has been estimated that each 1 mm of margin adds 1.3 Gy of dose to the parotid gland, which are particularly sensitive to low doses of radiation.[34] To reduce setup uncertainty, many groups have advocated daily imaging, with a position correction if the displacement from the original plan exceeds a threshold value. At the University of Michigan, daily imaging and setup correction before each treatment fraction has reduced the setup error to 1 ± 1 mm, enabling a reduction in PTV margins to 3 mm. The importance of daily imaging and correction has been evident in studies which examined setup uncertainties: daily imaging is required if PTV margins are 3 mm, and every other day if the margins are 5 mm.[35] Whether imaging is performed by CT or by orthogonal portal imaging seems to be less important than the frequency of imaging and correction.[36] It should be noted that while setup uncertainties are usually measured in the upper neck, near the targets, they are frequently larger in the lower neck even if the shoulders are included in the immobilization device.

Doses are prescribed to the PTVs or to comparable "growth" areas in some commercial planning systems. When the targets are close to the skin, as may occur in postoperative case, the PTV may extend beyond the surface. In such a case, the PTV should be edited back to the surface. If the PTV extends to the skin and the skin is not at high risk, the external body contour may be defined as a noninvolved organ for the optimization system. This facilitates avoiding excessive dose to the skin.[37]

Similar to the expansion of the targets to yield the PTVs, there is a need to accommodate uncertainties regarding the critical normal organs, especially the spinal cord, brain stem, and the optic pathways, that may lie in regions of steep dose fall-off near the targets. This can be accomplished by expanding these organs uniformly, yielding the planning-risk volumes (PRVs). At the University of Michigan, the spinal cord is expanded by 0.3 cm to yield the spinal cord PRV. The maximal accepted doses

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are 45 Gy to the spinal cord and 50 Gy to the PRV. Similarly, the optic nerves and chiasma are expanded for treatment plans of nasopharynx or paranasal sinus tumors.

An example of the delineation of the targets and noninvolved structures in a case of oropharyngeal cancer is provided in Figure 5-1.

## Dose Prescription and Specification and Normal Tissue Dose Constraints

The delivery of a single IMRT plan throughout the course of treatment provides better dose conformality compared with several consecutive plans, like the consecutive plans common in conventional radiotherapy, which consist of initial fields encompassing all targets followed with a boost to the gross tumor.[38] When a single plan is prescribed, the gross tumor PTV receives both a higher total dose and a higher dose per fraction compared with the PTVs of the subclinical disease. Owing to the differences in the daily fraction doses, a correction of the total dose to yield the normalized total dose (NTD) for a 2-Gy fraction regimen is required when the fraction dose is different from standard fractionation. An extensive discussion of this issue is provided by Mohan et al.[38] There are two general approaches to dose prescription. The first would be prescribing a total dose delivering standard fraction dose to the gross disease PTV, for example, 70 Gy over 35 fractions, and doses delivering low fraction doses to the subclinical disease PTVs: 63 Gy to the high-risk and 56 to 59 Gy to lesser-risk elective targets, which over 35 fractions would deliver fraction doses of 1.8 Gy and 1.6 to 1.7 Gy, yielding NTDs of 60 Gy and 50 to 54 Gy, respectively (the NTDs are calculated for late-reacting tissue, assuming an $\alpha/\beta$ of 3 Gy). When used for advanced disease, this schedule should be delivered concurrent with chemotherapy. The second strategy is to deliver a higher-than-standard fraction dose to the gross disease PTV, adjusting the total dose to yield NTD near 70 Gy, and standard fraction doses to the elective targets' PTVs. Such a strategy was adopted by the Radiation Therapy Oncology Group (RTOG) study of IMRT for oropharyngeal cancer (RTOG study H-0022). In this study, the gross disease PTV receives a total of 66 Gy in 30 fractions, 2.2 Gy/fraction. PTVs of high-risk subclinical disease receive 60 Gy, and low-risk PTVs receive 54 Gy, at 2.0 and 1.8 Gy/fraction, respectively. This results in the gross disease PTV receiving NTD of 70 Gy over 6 weeks, similar to the total time and dose delivered by accelerated RT regimen.[39] A more aggressive reported regimen delivers a total of 60 Gy in 25 fractions (2.4 Gy/fraction) to the gross disease and 50 Gy (2.0 Gy/fraction) to electively treated volumes, yielding an NTD of 66 Gy delivered over 5 weeks.[40] If we take into account the relatively large target dose inhomogeneity produced by IMRT, it would be apparent that large tissue volumes within the targets receive even higher fraction doses, and higher NTDs, than those calculated for the prescribed doses. A phase I dose escalation study was conducted at the Medical College of Virginia, in which the fraction size and the total dose

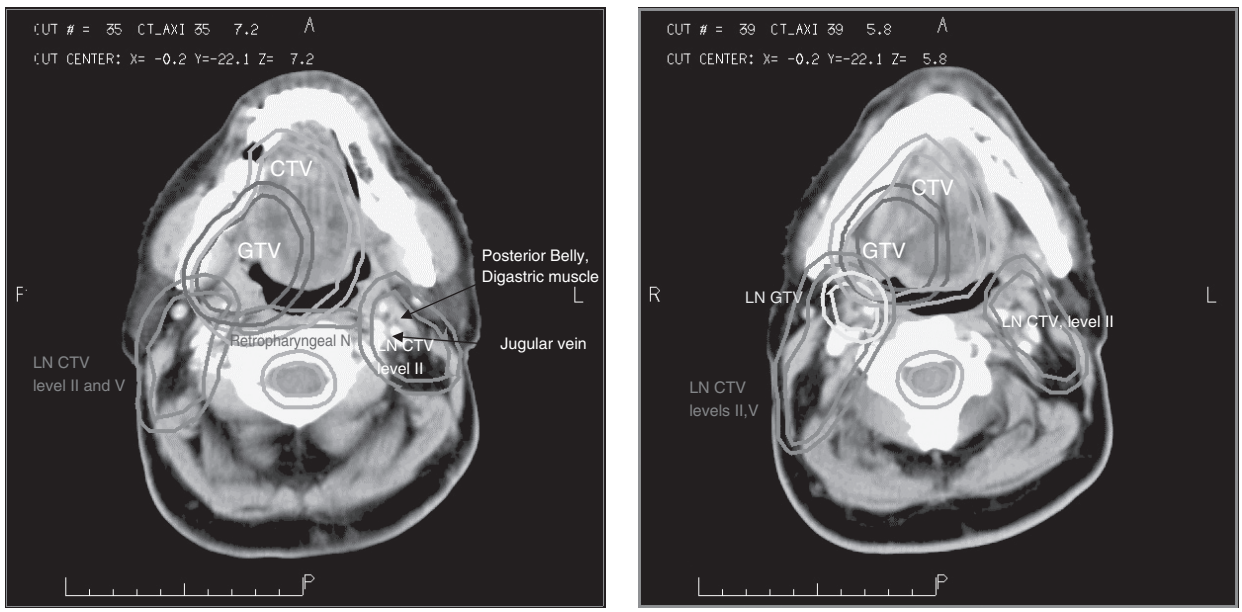
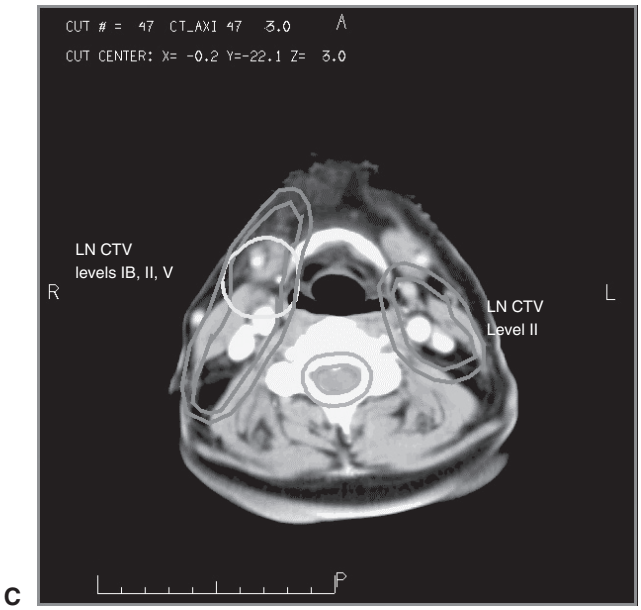
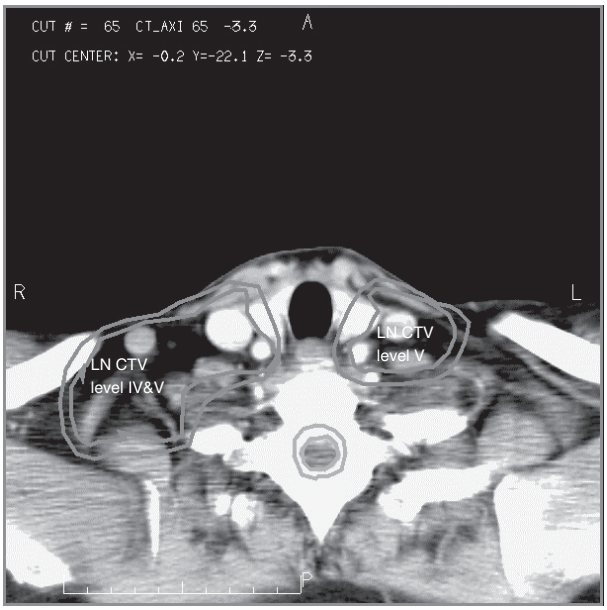



**FIGURE 5-1.** The targets outlined on planning CT in a case of stage T2, N1 carcinoma of the right tonsil, involving the lateral base of the tongue. The GTV, primary tumor CTV, and lymphatic GTV and CTVs are each expanded uniformly by 0.5 cm to yield the corresponding PTV. **A:** Level II nodal targets in the ipsilateral neck, and the retropharyngeal nodes bilaterally, are outlined through the base of the skull. Level II nodes in the contralateral neck are outlined up to the level in which the posterior belly of the digastric muscle crosses the jugular vein. Cephalad to this level, only the ipsilateral (LT) level II nodal CTVs and the retropharyngeal nodes are outlined. In cases where the contralateral neck contains clinical or radiologic evidence of metastasis, or in the case of nasopharyngeal cancer, level II is outlined through the base of the skull bilaterally. **B:** Nodal metastasis in the LT neck is outlined as a nodal GTV, expanded to yield its PTV. **C** and **D:** In the ipsilateral lower neck, nodal levels IV and V are included in the CTV. Only level IV is outlined in the contralateral lower neck (the contralateral neck did not have clinical evidence of metastasis). **E:** A sagittal reconstruction of the CT may help in the assessment of the extent of disease. On axial images, it is difficult to distinguish the soft palate from the base of tongue that contains the targets. The sagittal view facilitates the exclusion of the soft palate (*P*) from the targets. CT, computed tomography; GTV, gross tumor volume; CTV, clinical target volume; PTV, planning tumor volumes. (See color insert.)

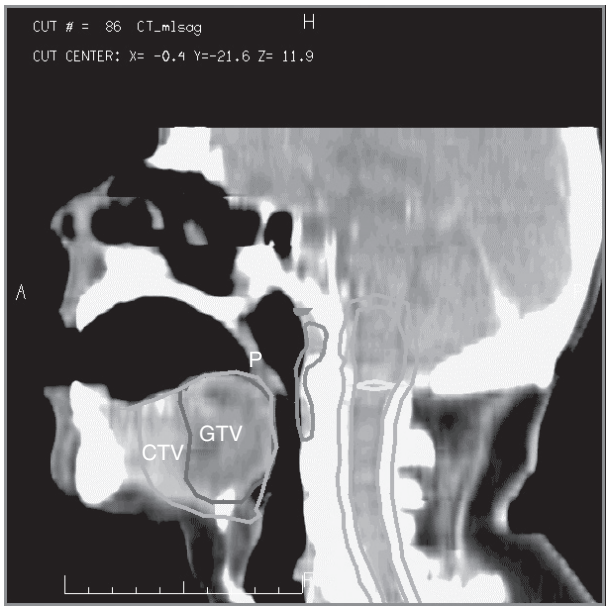
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C




D




E

**FIGURE 5-1.** *Continued*

to the gross disease PTVs were escalated.[41,42] It was postulated that limiting the high-dose treated volume to the target alone by IMRT may reduce the risk of late complications arising from large fraction doses.[40] However, critical normal tissues at risk in the head and neck, such as nerves, noninvolved mucosa, blood vessels, bone, and so on, are embedded within the targets and are at risk of late toxicity. In addition, these schemes may be associated with an excessive toxicity risk when they are combined with concurrent chemotherapy. As yet, the follow-up periods of published head and neck cancer IMRT series are not sufficient to assess the full risk of late complications arising from higher-than-standard fraction doses and total NTDs delivered to the targets. GTV dose escalation using IMRT should not, therefore, be practiced outside of careful and well-defined clinical trials.

Dose and dose–volume specifications are made to impose constraints on the DVHs of the targets, noninvolved tissue of interest, and nonspecified tissue outside the targets. RTOG protocol H-0022 specified the prescription dose as the dose that encompasses at least 95% of the PTV. No more than 20% of the PTV can receive >110% and no more than 1% of the PTV can receive <93% of the prescribed dose. To limit hot spots outside the targets, the protocol specifies that no more than 1% of the tissue outside the PTVs can receive >110% of the prescribed dose. This is done by adding a dose constraint for all nonspecified tissue (all tissue outside the targets and the specified organs) to prevent volumes of high dose outside the targets.

Dose constraints regarding critical organs are usually stated in terms of the maximal dose. Commonly applied constraints in the head and neck are maximal doses of 45 Gy to the spinal cord, 54 Gy to the brain stem, 70 Gy to the mandible, and 50 to 55 Gy to the optic pathway. These constraints were derived from standard irradiation, where the organ at risk receives irradiation at a

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standard daily fraction dose for part of the therapy course and is then fully shielded. In contrast, IMRT typically delivers lower daily fraction doses to these organs throughout therapy. In addition, the maximal dose derived from the DVH represents only a small organ volume, whereas standard RT delivers any specified dose homogeneously to relatively large volumes. In most instances, therefore, the same dose constraints are more conservative when applied to IMRT compared with standard RT. On the other hand, steep fall-off of doses near the critical organs may increase the risk of inadvertent overdosage to these organs due to motion and setup uncertainties. This issue can be addressed by a uniform expansion of the critical organs to yield the PRVs, as discussed in the preceding text. Organs with parallel functional architecture require specification of the mean dose or partial organ volume dose, rather than the maximal dose. Examples are the specification in RTOG protocol H-0022 of the maximal mean dose to the parotid salivary glands at 26 Gy, or limiting the dose to at least 50% of the gland volume to <30 Gy, and constraining the dose to two thirds of the larynx at <50 Gy.

Recommended dose constraints to specific organs are beyond the scope of this chapter. A recent effort by multiple clinicians and physicists, Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC), resulted in the publications of papers detailing normal tissue toxicity probabilities for critical organs based on actual data accumulated in the past decade.[43] These publications aimed specifically at guiding IMRT dose prescriptions and constraints for each critical organ.

## The Optimization Process

The PTVs and uninvolved organs lie in close proximity or overlap with each other. It is necessary to assign weighting factors (or penalty/importance factors) to each target and organ, which determine the relative importance of fulfilling their dose specifications or constraints. These weighting factors are derived following an iterative, trial-and-error process that requires refinement for each patient in order to produce an optimal plan. These factors differ among the various optimization systems. Examples of penalty factors for head and neck cancer plans were provided by several authors.[44,45] It was noted that because normal structure doses are penalized during optimization only if they exceed the limits set by the user, the constraints need to be more stringent than the clinical criteria.[45] At the University of Michigan, the optimization system uses a cost function that strives to minimize the dose to some noninvolved structures, in addition to setting a maximal dose constraint. This facilitates a reduction of the doses to these organs as much as possible, rather than settling at just below the maximal dose allowed.[46] Also, using a combination of linear and high-power objective functions (in addition to the quadratic objective function used in most commercial systems), strict head and neck target dose homogeneity can be achieved.[46]

In addition to the physical dose and dose–volume optimization criteria, several investigators examined the utility of biologic/clinical criteria as a basis for optimization in the head and neck. These investigations include optimization using the probability of uncomplicated tumor control,[47] tumor control probability (TCP) and normal tissue complication probability (NTCP),[48] and the equivalent uniform dose (EUD) concept, which is defined as the biologically equivalent dose that, if given uniformly, will lead to the same cell kill in the tumor volume as the actual nonuniform dose distribution.[49] The latter investigators found that optimization using EUD as the cost function is superior to optimization using dose or dose–volume. Biologic cost functions are expected to be superior to dose-based functions when the parameters of the biologic models, derived from clinical dose–response and dose-complication data, are known with greater confidence. An example is the optimization of advanced paranasal sinus cancer plans, where optic pathway NTCPs derived from patient complication data were used for the critical organ cost function.[50]

## The Number and Directions of The Beams

While tomotherapy uses arcs around the patient, IMRT using MLCs requires decisions regarding the number and orientation of the beams. It has been suggested early on that if the number of segments (or beamlets) is large enough, the direction of the beams is not important, and coplanar beams arranged at equidistance around the patient's head and neck would achieve satisfactory results. Most investigations of IMRT of head and neck with MLCs use this approach. The beam number should be odd, to prevent opposed beams which would increase hot spots near their entrance to the neck. Nine beams arranged at equidistance (40° apart) were found to be optimal: they provided better dose distributions than 5 or 7 beams, whereas 15 beams did not seem to improve the plans.[41] An optimization of the beam angles was found to be unnecessary by some authors,[41] whereas others reported an improvement in head and neck plans when optimized, noncoplanar beam angles were used.[51] This issue continues to be a subject of research. Current recommended field arrangement for IMRT of head and neck cancer with MLCs is nine equidistant, coplanar fields (Fig. 5-2), for patients with advanced tumors and complex anatomy like nasopharyngeal cancer. On the other hand, patients with prior tumors, or less complex anatomy, seven or even five coplanar nonopposed fields may achieve the planning objectives.

In patients without nodal disease in the lower neck, in whom the primary tumor resides in the nasopharynx, oropharynx, or oral cavity, treating the upper neck and primary tumor with IMRT while abutting the IMRT fields to an anterior–posterior low field containing a laryngeal block (split-field IMRT) reduces monitor units. It also reduces contouring and treatment time and can achieve better sparing of the larynx compared with whole-field IMRT.[52] However, if glottic larynx sparing is denoted by a higher weight (importance) in the optimization than full coverage of the

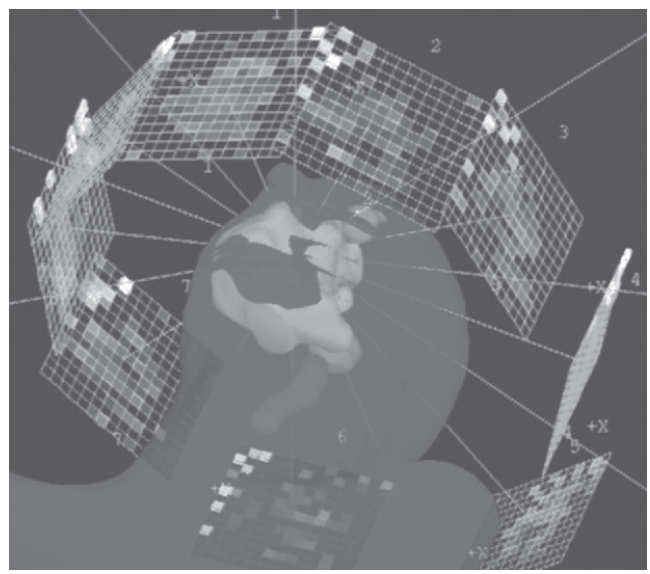



**FIGURE 5-2.** Beam arrangement for IMRT using an MLC. Nine coplanar, equidistant beams are used, each containing $1 \times 1$ cm or $0.5 \times 0.5$ cm pencil "beamlets." IMRT, intensity-modulated radiotherapy. (See color insert.)

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targets in the low neck, laryngeal avoidance can be as good.[53] The benefits of whole-field IMRT are mostly in cases with high-risk targets in the lower neck, where this method ensures adequate target coverage, while patients whose low-neck targets are at low risk are best treated with split-field IMRT.

## Clinical Results of IMRT Series: General

Most series reporting clinical results of tumor control rates following IMRT are still quite limited. They are either very heterogeneous regarding tumor sites and stages[26,31,33,54,55] have relatively small patient numbers or suffer from relatively short follow-up. Potential patient selection factors are probably the most important issues that should be considered in assessing the outcome in retrospective series of IMRT. IMRT is far more complex and time consuming compared with conventional radiotherapy. It also requires extensive skill and time commitment on the part of the radiation oncologist. It is likely that different selection factors play a role in each institution: patients who cannot tolerate lengthy treatment, those judged to be too sick to benefit from complex therapy, those requiring urgent start of therapy, and so on, may be selected to receive more simple, conventional treatment. These factors make any attempt to compare the results of different IMRT series, or even series of IMRT to series of conventional RT, futile. These issues have been demonstrated in a recent analysis from the University of Wisconsin, which assessed potential selection factors for patients treated with IMRT or conventional RT during the same time period.[56] They found that patients with T3–4 and N3 disease were less likely to be treated with IMRT. IMRT was found to be a significant prognostic factor improving tumor control rates; however, when the T stage was included in the model, the use of IMRT lost independent significance. Notably, although treatment results using IMRT were better than the results in the pre-IMRT era, there was also an improvement of tumor control rates in patients treated with conventional RT in recent years compared to those treated with conventional RT in the early 1990s.[56] Therefore, tumor control improvements in recent years may be related to factors like improvements in tumor imaging and chemotherapy, rather than solely to the introduction of IMRT. Because the use of IMRT becomes more common and the large majority, or all patients, at each institution are treated with IMRT, the potential bias due to patient selection factors in clinical series of IMRT is diminishing.

Another major clinical factor is the emergence of human papilloma virus (HPV)–related oropharyngeal cancers in the past decade, which have a better prognosis compared with the smoking-related oropharyngeal cancers that were prevalent in earlier decades. The modern series of IMRT which include oropharyngeal cancers are likely to report better oncologic results compared to previous series of conventional RT primarily due to this clinical factor, rather than due to any dosimetric superiority of the technique.

## Clinical Results of IMRT Series: Specific Sites

***Nasopharynx.*** IMRT of the nasopharynx represents opportunities in sparing many critical uninvolved structures and improved tumor coverage, as detailed in the preceding text. These improvements have been demonstrated in several treatment planning exercises in nasopharyngeal and oropharyngeal tumors, where IMRT plans were compared to "standard 3D" plans in the same patients.[45,55–57] However, in order to translate the advantage apparent in planning to a clinical benefit, it is crucial to outline the targets adequately. This may be more difficult in the case of nasopharyngeal cancer compared with other tumor sites. The GTV should be derived from an MRI that has been registered with the planning CT, as discussed previously. The CTV should encompass adequately potential subclinical tumor extension at the base of the skull. For example, the entire nasopharynx, the clivus, base of the skull, the pterygoid fossa, the parapharyngeal space, the inferior sphenoid sinus, and the posterior third of the nasal cavity and the maxillary sinuses (ensuring adequate margin to the pterygopalatine fossae) should be included. The CTV that encompasses the above regions can be modified according to the T stage. Lymph node CTVs should include level II nodes through the base of the skull, as well as levels III through V bilaterally, and the retropharyngeal nodes. Level IB should be included in the lymphatic CTV if level II is grossly involved (see references 18, 27, 29, 30 for details regarding the outlining of the neck lymph node levels on the planning CT). Specified critical tissue include the major salivary glands, the optic nerves and chiasm, the brain stem, the spinal cord, the inner ears, the temporomandibular joints, and the mandible. Options for the prescribed doses and constraints for noninvolved organs are detailed in a previous paragraph (see "Dose Prescription and Specification and Normal Tissue Dose Constraints"). An example of the targets and IMRT dose distributions in a case of nasopharyngeal cancer is provided in Figure 5-3.

A large clinical series of IMRT of nasopharyngeal cancer has been reported by investigators at the University of California in San Francisco (UCSF).[58] They reported 67 patients treated between 1995 and 2000. The GTV dose was 2.12 to 2.25 Gy/fraction to a total of 65 to 70 Gy and the CTV dose was 1.8 to 2.0 Gy/fraction to a total of 50 to 60 Gy. To prevent underdosing of the targets, the prescribed doses were typically the minimal doses encompassing the targets. The resulting delivered mean GTV dose was 74.5 Gy, at mean GTV fraction doses of 2.24 to 2.4 Gy. The resulting NTD (calculated for late-responding tissue) was 80 Gy. This regimen yielded excellent local-regional tumor control: 97% at median follow-up of 31 months, with reasonable acute toxicity. The authors stated that no excessive late effects were observed. However, longer follow-up is still required for adequate assessment of the late toxicity. These excellent tumor control rates have been preserved in a recent update of the UCSF data.[59] Excellent tumor control results have been reported by investigators conducting randomized studies of IMRT versus conventional RT for nasopharyngeal cancer.[60,61] Tumor-related outcomes of patients receiving IMRT or conventional RT were similar in these series, supporting our assumption that IMRT alone is not the only factor causing improved tumor control rates in recent years compared with previous eras. However, distant metastases remain a significant issue.[59,62] Efforts focused on decreasing the rates of distant metastases by using targeted biologic agents concurrent with chemotherapy and IMRT are under way at the RTOG.[63]

For reirradiation of nasopharyngeal cancer, IMRT offers dose distribution advantages as it significantly reduces the extent of irradiation of the previously irradiated tissue volume. Lu et al. has recently reported on the experience with reirradiation using IMRT for recurrent nasopharyngeal cancer.[64] Acute toxicity was acceptable and at a median follow-up of 9 months, the locoregional control rate was 100%. Although longer follow-up is necessary, the preliminary toxicity and local control data for these recurrent cases are promising.[64]

***Paranasal Sinuses.*** Similar to the nasopharynx, MRI is required for accurate delineation of the GTV when the tumor is near the base of the skull. Defining the extent of the CTV depends on the sinuses involved and tumor extent, discussed in detail elsewhere.[18] The main obstacle for adequate tumor irradiation is the proximity of the optic pathways to the target in advanced cases. In these cases, IMRT can provide adequate target coverage while sparing the optic pathways (Fig. 5-4). The group from Royal Marsden Hospital used MLC-based IMRT employing standard

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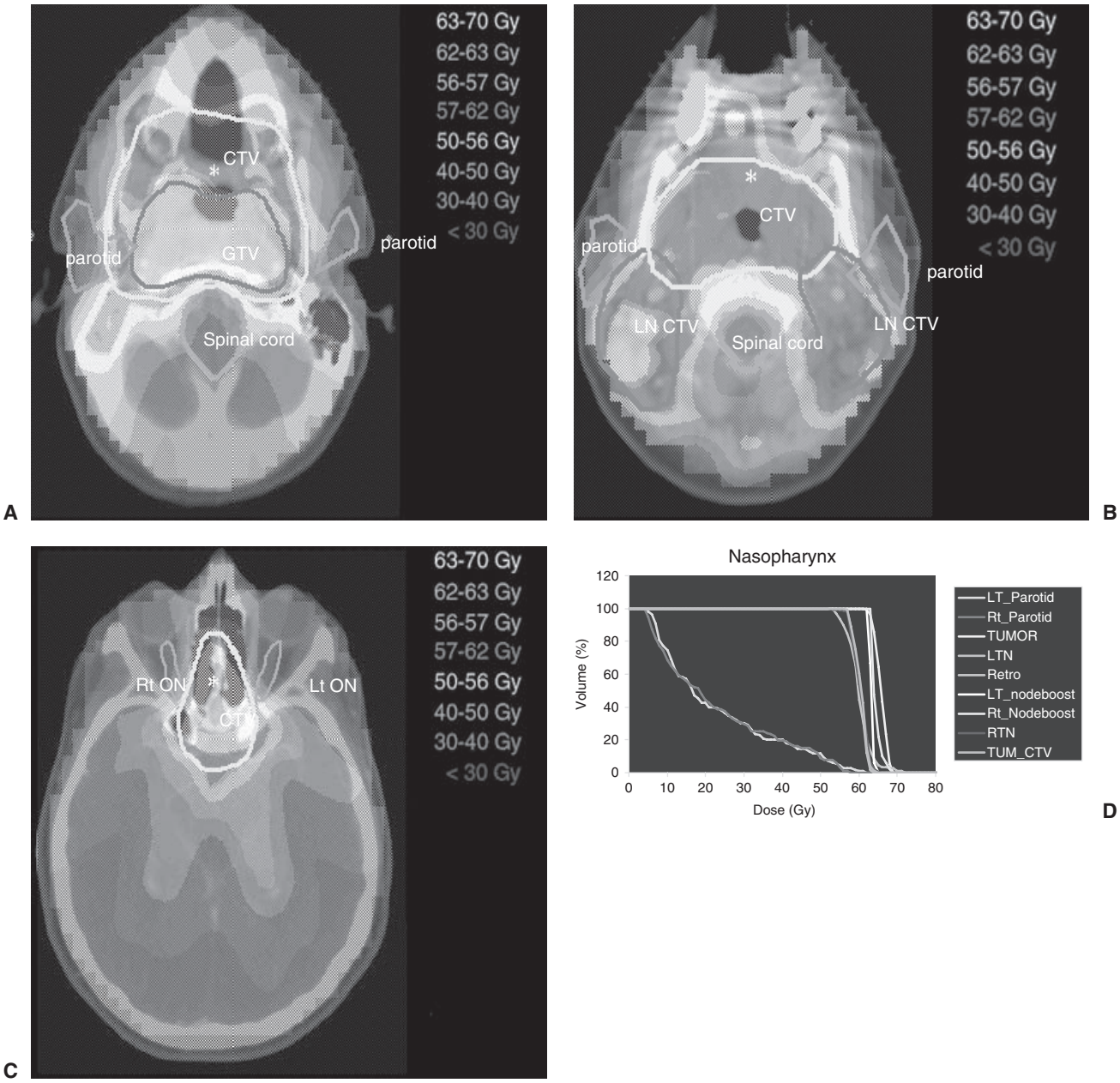



**FIGURE 5-3.** Targets and doses in IMRT of nasopharyngeal cancer. **A:** The GTV was outlined following registration of the planning CT with diagnostic MRI. The CTV includes the base of the skull, the posterior paranasal sinuses, the clivus, and the parapharyngeal space. **B:** Caudal to the GTV, the CTV contains the parapharyngeal and posterior pharyngeal space through midtonsils. Level II nodal CTV is outlined through the base of the skull bilaterally. **C:** The CTV encompasses the sphenoid and cavernous sinuses in locally advanced cases. Limiting the dose to the optic pathways is an important objective of planning. **D:** DVHs of the case described in Figure 5.3. Both parotid glands are spared while the targets are adequately irradiated. (See color insert for Parts **A**–**C**.) IMRT, intensity-modulated radiotherapy; GTV, gross targe volume; CT, computed tomography; CTV, clinical target volume; DVH, dose–volume histograms.

arrangement of beams: an anterior and two half-blocked lateral fields.[65] They found that compared with 3D conformal radiotherapy, using the same beam arrangement, IMRT reduced the dose to the optic nerves significantly and improved PTV coverage. MLC-based IMRT planning of patients with nonresectable maxillary sinus cancer at the University of Michigan revealed no substantial difference between plans using an anterior and two lateral fields, compared with nine equidistant beams arranged around the patient.[50] Therefore, the use of a field arrangement considered optimal in standard radiotherapy may provide benefits over IMRT by reducing beam numbers and reducing the complexity of treatment delivery. Significant improvement in the doses to the optic pathways, compared with 3D conformal RT plans, was noted. IMRT plans of 13 patients with unresectable paranasal sinus tumors demonstrated doses to the contralateral optic nerve and to the optic chiasm that were within known

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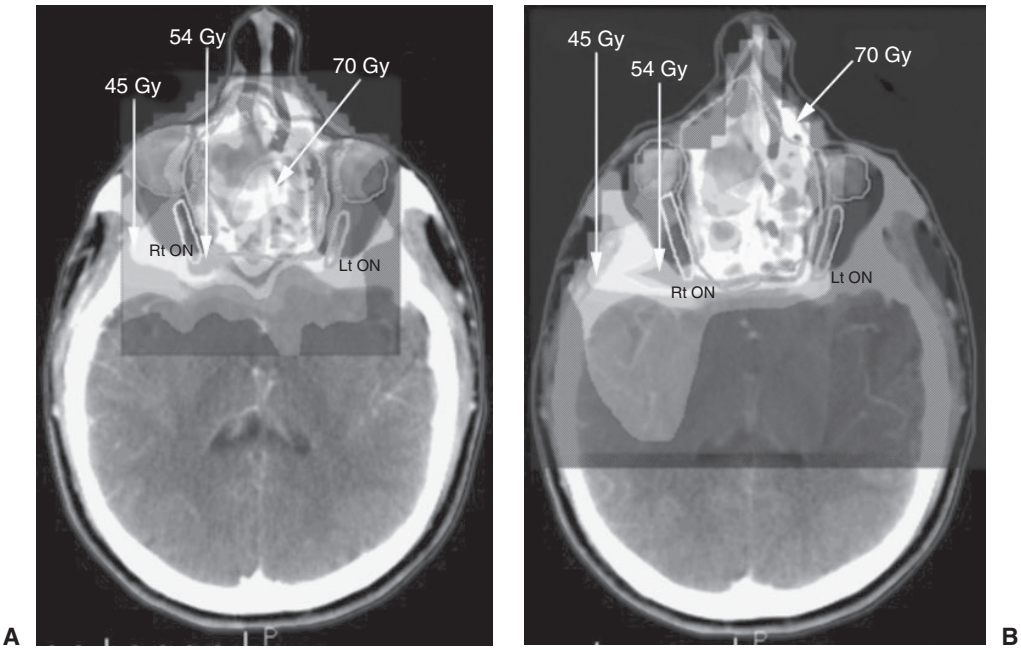



**FIGURE 5-4.** **A** and **B:** Isodoses of IMRT for advanced paranasal sinus cancer. Sparing the optic pathways was a major planning objective. IMRT, intensity-modulated radiotherapy. (See color insert.)

tolerance (<60 Gy), while the ability to spare the ipsilateral optic nerve depended on the anatomic relationships between the PTV and the nerve. Optimization using NTCP of the optic nerves as an objective function was found to facilitate planning and provide a basis for the assessment of the clinical trade-off between PTV coverage and ipsilateral optic nerve sparing.[50]

Large clinical series of IMRT for paranasal sinuses were reported from Ghent University in Belgium.[66] Thirty-nine patients were treated postoperatively and the 4-year actuarial local control after surgery and IMRT was >80% for patients with T1–4aN0M0 disease. Patients with adenocarcinoma of the ethmoid sinus who received IMRT were compared to historical control group of patients treated with two dimensional (2D)- or 3D-conformal noncoplanar techniques. Local recurrences occurred in all patients with cribriform plate invasion. The present IMRT implementation was clearly not able to reverse the dismal local control rates that are known to exist in stage T4b with cribriform plate invasion. By excluding patients with cribriform plate invasion, a patient group with good local control and survival could be selected; no conclusions should be drawn regarding the effect of IMRT on local control as compared to conventional techniques. However, in the IMRT group, there was a significant reduction in the incidence of severe dry-eye syndrome compared to previous techniques. Dose–effect analysis in the IMRT group showed that even at median doses of <30 Gy to the main lacrimal glands, mild forms of dry-eye syndrome could occur.[66]

***Oropharynx.*** Outlining of the primary tumor and lymph node CTVs and GTVs depend on tumor location and extent. In general, for lateralized tumors, the ipsilateral level II nodal CTV is outlined through the base of the skull. The contralateral nodes at highest risk are the jugulodigastric nodes in level II. On CT axial images, these nodes lie below the level in which the posterior belly of the digastric muscle crosses the jugular vein. This is also the uppermost extent of radical neck dissection. At the University of Michigan, the cephalad-most contralateral level II nodal CTV is outlined in these images. However, the contralateral nodal level II CTVs in patients with clinical evidence of nodal involvement in the contralateral neck, or in those with midline tumors, are outlined through the base of the skull. In all patients, if the retropharyngeal nodes are at risk they are outlined bilaterally through the base of the skull.[26] An example of the dose distributions obtained by IMRT in a case of oropharyngeal cancer is shown in Figure 5-5. Details of dose prescriptions, critical organ dose constraints, and quality assurance procedures for the treatment of early oropharyngeal cancer are provided in RTOG protocol H-0022, available at the website of RTOG.

Notwithstanding the limitations in interpretation of the results of published IMRT series, discussed earlier, all series of IMRT outcome of oropharyngeal cancer have reported outstanding local-regional control rates.[26,33,55,67] These series reported 2-year locoregional tumor control rates of 90% to 98% for patient populations consisting mainly of stage III to IV tumors. However, some of these series contain a mixture of definitively and postoperatively treated patients and variable ratios of patients treated with concurrent chemoirradiation or radiotherapy alone. The series from Michigan included patients with various nonnasopharyngeal tumor sites. Notably, having an oropharyngeal cancer site was the most significant favorable predictor of local-regional tumor control.[68] As detailed above (Clinical Results of IMRT Series: General), the emergence of HPV-related oropharyngeal cancer as the most common cancer in this anatomical site, and its improved prognosis compared to the smoking-related oropharyngeal cancer prevalent in previous decades, are the most likely explanation to the excellent tumor control results reported in IMRT series.

Some of the most reliable information gained from clinical series of IMRT for head and neck cancer in general, and oropharyngeal cancer in particular, relates to the pattern of tumor recurrences relative to the targets and the locally delivered doses. These data allow an assessment of the adequacy of target selection and delineation. In all reported cases, it seems that careful selection and delineation of the targets resulted in very few or no marginal or out-of-field recurrences. De Arruda et al. reported

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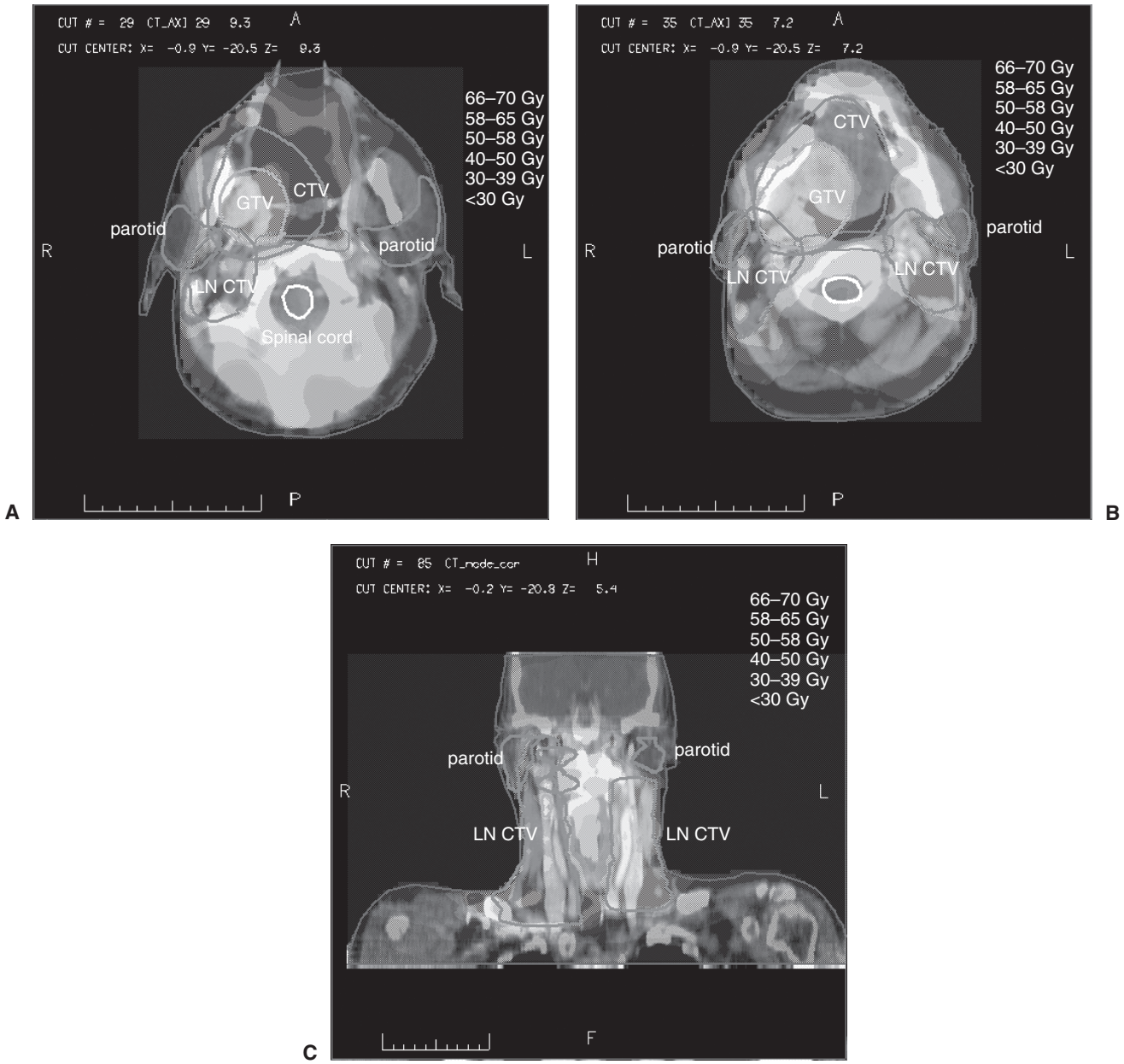



**FIGURE 5-5.** **A** to **C:** Isodoses of IMRT for the patient described in Figure 5.1. The contralateral parotid gland received a low dose (mean 17 Gy) and the ipsilateral gland a moderate dose (mean 32 Gy). (See color insert.) IMRT, intensity-modulated radiotherapy.

that all recurrences in their series were in-field.[67] Chao et al. reported that most marginal recurrences occurred in the lower neck, which was treated with an anterior field that was matched to the IMRT-treated upper neck.[33] At the University of Michigan, where most patients had oropharyngeal cancer, almost all recurrences occurred in-field, in high-risk volumes that had received the full prescribed doses.[26] At a median follow-up of 32 months, 21 local-regional failures (16%) occurred. Of these, 17 recurred in-field and 4 were marginal recurrences. After the first analysis of marginal recurrences, modifications in target delineation principles were made, following which no additional marginal recurrences were noted.[26] This demonstrates a learning curve, characteristic of complex therapies, and the likelihood that treatment outcome improves as the experience of the team using IMRT increases. Of note, no marginal recurrence occurred in the contralateral N0 neck where the cranial-most target included the subdigastric (jugulodigastric) nodes, confirming Rouviere's observations and the recent consensus recommendations.[19,69] Two marginal recurrences in the Michigan series were noted in the lateral retropharyngeal nodes (both occurred in patients with oropharyngeal cancer), in which the cranial-most extent of the retropharyngeal nodal targets was defined at the top of C1, according to Rouviere's observations of the locations of the lateral retropharyngeal nodes. Following these observations, we currently define the retropharyngeal nodes through the base of the skull. Interesting observations about marginal or out-of-field recurrences were reported by the series from the University of Iowa.[55] They found several cases of recurrences in the

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contralateral level I in patients with lateral oral cavity and oropharyngeal cancer, underscoring the need to include these nodes in locoregionally advanced oral cancer. As more data about marginal recurrences are accumulated, a better understanding and higher certainty are expected to be gained in defining the targets. This is expected to lead to improved tumor control and ability to spare noninvolved tissues even further.

***Larynx/Hypopharynx.*** IMRT can improve target dose homogeneity for laryngeal and hypopharyngeal squamous cell carcinoma (SCC) while reducing the dose to the normal tissues at risk[70–72] (Fig. 5-6). Clinical data on IMRT for laryngeal and hypopharyngeal SCC are, however, scarce and include limited numbers of patients within large heterogeneous series of multiple head and neck tumor sites.[26,33,55] In general, these series showed lower tumor control rates compared with oropharyngeal sites. Potential reason could be patient selection factors. For example, at the University of Michigan only laryngeal cancer patients with advanced nodal disease receive IMRT because for patients with nodal stage N0 to N1, the uppermost nodes at level II are the subdigastric nodes, which can be treated with conventional techniques while sparing most of the parotid glands and avoiding the oral cavity, as the retropharyngeal nodes or level II nodes near the base of the skull are not at risk in these patients.[26,68] A recent study reported the feasibility of a dose escalation trial in laryngeal SCCs using IMRT.[73] The potential perils associated with dose escalation of head and neck cancer using IMRT have been discussed earlier (see "Dose Prescription and Specification and Normal Tissue Dose Constraints").

## Noninvolved Organ Sparing with IMRT: Clinical Results

Most of the studies assessing clinical toxicity reduction using IMRT have concentrated on reduced xerostomia through the sparing of the parotid salivary glands. Data about dose response in the parotid glands are accumulating.[74–79] At the University of Michigan, it was initially found that the output related to the mean doses to the glands. The large majority of the glands receiving a mean dose of >26 Gy did not produce measurable saliva and did not recover, whereas glands receiving lower mean doses produced variable salivary output that increased over time.[74] One year after radiotherapy, parotid glands receiving a moderate dose (mean dose of 17–26 Gy) recovered, on average, to the pretreatment salivary production levels.[75] When the doses to the parotid glands were very low, as in cases of unilateral neck radiotherapy in which the contralateral glands received mean doses <10 Gy, an "overcompensation" of the damage to the ipsilateral glands was noted in the second year post therapy. In particular, the salivary flow rates from the contralateral glands exceeded, on average, their pretreatment flow rates. This finding motivates reducing the doses to the salivary glands to as low levels as possible. Data from other institutions suggest thresholds in the range of 20 to 40 Gy.[76–79] The common finding in all these data is that a relationship seems to exist between the mean doses to the glands and their residual salivary output. The reasons for this wide range include different methodologies in assessing the salivary flows as well as clinical factors, beyond the radiation dose, which affect the salivary output but have not been taken into account in most of these studies. These factors include dehydration, which is common in patients receiving head and neck radiotherapy, and various medicines found to affect the salivary flow rates significantly.[74,75] An additional important factor is one reported recently by investigators from the University Hospital in Groningen, the Netherlands.[80] They irradiated different parts of rat salivary glands using high-precision proton radiation and found regional differences in dose–salivary production relationships. Such regional differences are likely to exist in the human parotid glands, and they may be the reason for different results found by researchers using different radiotherapy techniques, which produce different dose distributions within the glands. Further research into intraparotid regional differences in sensitivity to radiation is required for better understanding of radiation limits. In addition, recent studies have demonstrated an anatomic shift of the parotid glands medially, correlated with weight loss during therapy, which may increase actual delivered doses compared with the planned ones (see "Tracking Anatomical Changes

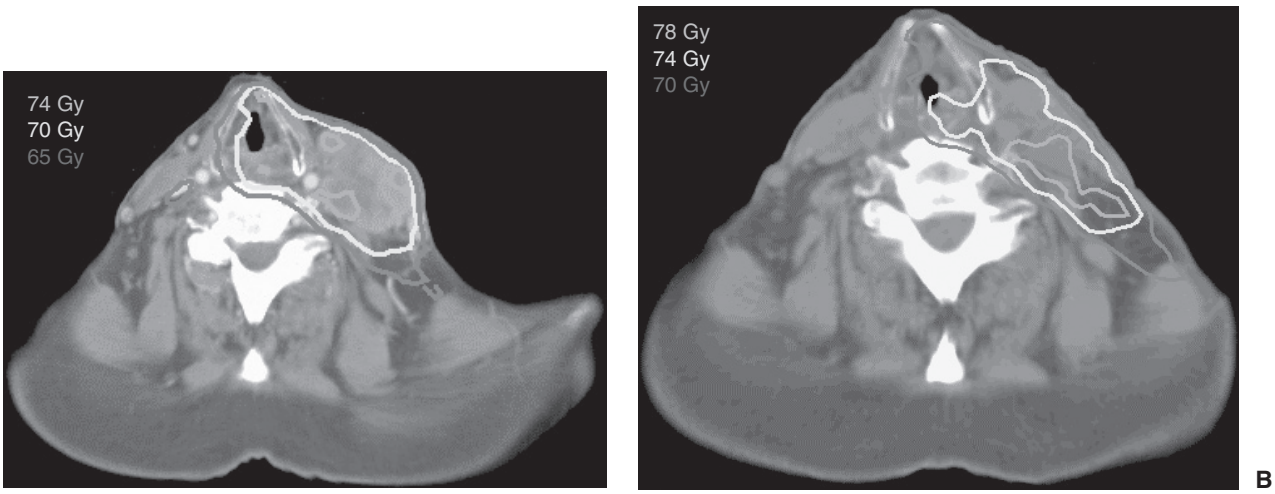



**FIGURE 5-6.** A case of laryngeal cancer stage T2N3 treated with IMRT concurrent with chemotherapy. Significant regression of the metastatic node was observed by week 4, in tandem with severe local skin toxicity. The doses produced by the original treatment plan **(A)** showed relative uniform dose distributions. Recalculating the dose distributions using the original IMRT plan for the new anatomy disclosed higher "hot spots" and skin doses than originally planned **(B)**. The case was replanned using the new CT, the hot spots were corrected, and the patient continued treatment using the new plan, resulting in improvement of the skin toxicity. IMRT, intensity-modulated radiotherapy.

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During Radiotherapy"). The initial data from the University of Michigan related to patients in whom only the contralateral parotid glands were spared. More recently, efforts are made to spare the ipsilateral parotid glands as well, resulting in intermediate doses delivered to these glands, in the range of 30 to 40 Gy. A recent study comparing the dosimetry of the parotid glands to their salivary output in patients treated with these methods found a high agreement between the results in two different institutions. Rather than a threshold, this study found continuous reduction in salivary output as the mean doses increased: the dose causing 50% probability of grade 4 toxicity was found to be 39 Gy, and the dose causing 25% probability was 25 Gy.[81] Regardless of the dose threshold, it is now apparent not only that spared glands partly retain the salivary output but also that the output increases over time through at least 2 years after radiotherapy. In comparison, there is generally no improvement over time following standard radiotherapy in which most of the parotid glands receive full radiotherapy doses.

Once preservation of the salivary output is achieved, there are questions related to similar improvements in patient-reported xerostomia symptoms. The correlation between the salivary output from the major salivary glands and xerostomia symptoms is significant, but is not very high. Part of the reason for this less-than-straightforward relationship lies in the contribution of the minor salivary glands. These glands are scattered throughout the oral cavity, notably on the surface of the palate, and produce much of the salivary mucin. It has been found that the dose delivered to the oral cavity, serving as a surrogate for the residual function of the minor salivary glands (whose output cannot be measured) was an independent factor in patients' reported xerostomia after radiotherapy, similar to the importance of the doses to the major salivary glands.[75] An optimal practice is to add the sparing of the oral cavity as an objective in radiotherapy planning, in addition to the sparing of the parotid glands. An analysis at the University of Michigan of a validated patient-reported xerostomia questionnaire demonstrated that xerostomia improved significantly over time, in tandem with the increase in saliva production.[82] Two years following irradiation, xerostomia reported by patients receiving parotid sparing bilateral neck radiation was only slightly worse than in patients receiving unilateral neck radiotherapy. Investigators at UCSF also reported an improvement to mild or no xerostomia during the second year after IMRT for nasopharyngeal cancer.[58] Small randomized studies of IMRT versus conventional RT have been reported for nasopharyngeal cancer. Kam et al. showed an advantage of IMRT in terms of improvement of salivary flow rates, but not in xerostomia symptoms.[60] Pow et al. demonstrated significant improvement of both salivary flow rates and xerostomia-related quality of life in patients with nasopharyngeal cancer randomized to IMRT compared with those randomized to conventional RT.[61] The differences between the two studies may be related to the validity of the instruments used to measure patient-reported xerostomia. It is apparent from all of these studies that the partial sparing of the salivary glands, made possible by IMRT, achieves tangible gains both in the retention of the salivary production and in the symptoms of xerostomia. A European randomized study in various head and neck cancer sites comparing IMRT, which spared the contralateral parotid glands, to conventional RT found that observer-rated xerostomia and salivary output were significantly better in the IMRT arm. Patient-reported xerostomia was also significantly better. However, during the first posttherapy year the difference in patient-reported xerostomia between the two arms was very small.[83]

Another issue in the efforts to reduce xerostomia by IMRT is the importance of the submandibular glands. These glands lie anterior to the level II lymph node targets in the neck and produce (together with the minor salivary glands in the oral cavity) a substantial amount of mucin, which is important in lubricating the mucosa and providing a sense of hydration. Commonly, it is difficult to spare a substantial amount of these glands while treating both sides of the neck (which is required for all advanced head and neck cancer), resulting in no measurable salivary output from most of these glands after radiation.[75] Canadian investigators who moved one submandibular gland to the submental space, away from the radiotherapy fields, reported impressive reduction in xerostomia.[84] However, this technique has not yet gained broad acceptance. Efforts to spare the contralateral submandibular gland in patients in whom the contralateral neck level I is not in the target have been reported by several investigators, resulting in higher salivary output and reduced xerostomia in patients with reduced doses to these glands.[85,86] Dose–effect relationships for the submandibular glands are emerging and can guide these efforts.[87] It is important to make sure that the jugulodigastric nodes, which are important nodes lying immediately posterior to the submandibular glands, will not be underdosed if the contralateral level II is judged to be at risk.

An additional potential functional gain from IMRT over conventional RT includes reduced long-term dysphagia. For example, IMRT strategies which spare the pharyngeal constrictor muscles, as well as the glottis and supraglottic larynx, have been helpful in reducing the risk of long-term dysphagia and aspiration.[88] Sparing the pharyngeal constrictors is made easier by realizing that the lateral retropharyngeal nodes, but not the medial ones, are at risk in head and neck cancer.[89] Clinical assessment of the clinical effect of these efforts demonstrated significant dose–response relationships for these swallowing/aspiration structures, which may serve as a basis for related optimization cost functions and motivate the efforts to reduce the doses to these structures as much as possible.[89,90]

***Investigational Tumor Imaging and "Dose Painting."*** Although glucose metabolism measured by FDG-PET is the functional modality most often used to aid in target delineation, researchers are developing and testing new agents to image hypoxia, protein synthesis, DNA synthesis, and receptor expression. Hypoxia is a predictor for poor local control and the second most developed area in PET imaging.[91] $^{18}$F-misonidazole (F-MISO) is a freely diffusible tracer, which binds to intracellular molecules under oxygen concentration <10 mm Hg such that 2 hours after injection, the tracer only remains in hypoxic viable cells. Static scans can identify areas of hypoxia, whereas dynamic scans can identify areas of poor blood flow.[92] Another compound, Cu-diacetyl-bis ($N^4$-methylthiosemicarbazone [Cu-ATSM]), is reduced in low oxygen conditions and is similarly trapped within viable hypoxic cells.[91] The correlation of uptake of these tracers and local control in head and neck cancer is currently being studied. Other types of tracers are being developed to image DNA synthesis through thymidine incorporation ($^{18}$F-fluorothymidine [FLT]), angiogenesis through $\alpha_v\beta_3$ receptor expression ($^{18}$F-Galacto-RGD), and EGFR expression in the head and neck.[93,94] In addition to helping to define the tumor, some of these new PET tracers may yield additional useful information about tumor subvolumes, which may not respond well to current therapies and should be targeted for intensification of treatment.

The terms *dose painting* and *dose sculpting* refer to customizing radiation plans to deliver nonuniform doses to different subvolumes within the tumor.[95] Whereas dose uniformity has traditionally been favored, it is possible that a benefit may be gained from intensifying the doses in certain volumes within traditional anatomic borders. By incorporating metabolic, functional, and phenotypic biologic information into IMRT planning, we can devise a boost volume of potentially more radioresistant areas of tumor, which may benefit from a higher dose. Theoretic planning studies have demonstrated this proof of principle using Cu-ATSM and F-MISO to increase the dose to hypoxic volumes

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within GTVs.[96,97] However, the clinical utility of these plans have not yet been determined. This issue seems to be much more complex than was originally thought. For example, the hypoxic subvolumes within tumors change during the course of therapy,[98] reducing the potential utility of pretherapy planning of hypoxia-driven "dose painting." It is possible that this utility is higher for imaging nearer the completion of therapy.[94] Using FDG-PET during therapy may be another method to evaluate tumor subvolumes, which retain PET activity and may be less responsive to radiotherapy.[99–101] Whether boosting these subvolumes during the rest of the treatment course to a higher dose will overcome their perceived resistance is not yet known.

## PROTON THERAPY

Currently, all centers utilize photons, or high-energy x-rays, for their IMRT treatments. However, due to their inherent physical characteristics, protons are better able to concentrate dose inside targets and minimize dose to surrounding normal tissues. Most of the energy of a proton beam is deposited near the end of the beam path ("Bragg peak"), the location of which is determined by the energy of the beam. Therefore, the target can be included in the tissue volume receiving the high dose while little is delivered before or after the beam passes through the target, and the integral dose delivered outside the targets is lower than delivered using IMRT. This is expected to reduce the risk of secondary malignancies, which is especially important in pediatric cancer patients.[102] Using inverse planning, intensity-modulated proton therapy (IMPT) can further improve the therapeutic index of radiotherapy. Several groups, including the University of Florida, Massachusetts General Hospital, University Hospital Vienna, and the Paul Scherrer Institute in Switzerland, have published treatment planning comparisons of photon IMRT with IMPT.[103–106] Using IMPT, mean doses to OARs, the parotid glands, in particular, have been reduced by as much as 50%. However, long-term clinical treatment results are not yet available. The areas in the head and neck likely to benefit from the added conformality achievable with protons are the paranasal sinuses and nasopharynx because they are often in close proximity to the optic nerves and chiasm, as well as brain.[107] Retrospective reviews of 3D conformal proton therapy from Massachusetts General Hospital and Loma Linda University suggest maintenance of local control rates with minimal toxicity, including preservation of vision in advanced sphenoid sinus cancers.[108] As more patients are treated with protons and with IMPT, we will be able to determine whether these dosimetric improvements lead to significant clinical gains.

## NEUTRON AND CARBON ION THERAPY

In addition to protons, other particles have been used to treat head and neck cancers. Neutrons have found a niche in treatment of salivary gland tumors, after a small trial randomizing patients to photon or neutron radiotherapy demonstrated a survival benefit to neutron therapy.[109] Other ions, including helium, neon, and carbon, have been investigated over the last 50 years. Currently, carbon ion therapy shows the most promise. Compared with photons, carbon ions have the conformality advantage of protons, with the additional advantage of a greater relative biologic efficacy (RBE): a smaller dose of carbon ions is required to achieve the same biologic effect as a reference dose of photons. This is due to a higher linear energy transfer, which theoretically causes more irreparable DNA damage, is more effective on hypoxic cells, and is less subject to variation in radiosensitivity with cell cycle. Currently, there are three centers worldwide that are able to treat with this modality. Initial results in adenoid cystic carcinoma, unresectable head and neck sarcoma, and locally advanced SCC of the head and neck are promising and demonstrate excellent local control rates with low toxicities.[110,111] However, long-term results are not yet available.

## IMAGING-GUIDED RADIOTHERAPY

The term *IGRT* relates to patient and tumor imaging using electronic portal imaging devices (EPIDs) or CT before each fraction or every few fractions of therapy to ensure tracking of the tumor by the treatment beams. In cancer of the head and neck, where breathing-related motion is nonconsequential, IGRT aims at two main goals: (a) minimizing setup uncertainties and enabling reduction of the PTV margins and (b) assessing anatomic changes in tumor and critical tissue during the course of therapy.

### Reduction of Setup Uncertainties

To reduce setup uncertainty, many groups have advocated daily imaging, with patient position correction if the displacement from the original plan exceeds a threshold value.[112,113] The systematic error can typically be observed and corrected after few initial daily imaging, following which it is only required to correct the small random errors. This can be done by imaging once weekly, if the PTV margins are set at 5 to 6 mm; however, more frequent imaging is required if PTV margins are smaller (see details in "The Planning Tumor Volumes" above). Using 2D EPIDs for this end, relying on orthogonal view of the bony anatomy before treatment in comparison with the bony anatomy observed at the planning CT may be sufficient. Using CT for this purpose may achieve a marginal benefit, allowing corrections of patient rotation (which is not efficiently detected by 2D imaging). However, lacking breathing-associated movements, it is questionable whether CT is required for head and neck cancer. At the University of Michigan, daily online imaging and setup correction before each treatment fraction has reduced the setup error to $1 \pm 1$ mm, enabling a reduction in PTV margins to 3 mm.

### Tracking Anatomic Changes during Therapy

During the 6- to 7-week course of radiotherapy, many anatomic changes can occur. As dose distributions achieved using IMRT have steep gradients, and PTV "safety" margins are becoming smaller, it is especially important to understand the consequences of anatomic changes during therapy on the dose to both targets and normal tissues. In definitive cases, the primary tumor and/or nodes can shrink, whereas in postoperative cases, inflammation and edema can resolve. Additionally, weight loss, a common consequence of acute treatment toxicity, can lead to muscle wasting and shifting of both normal tissue and tumor positions. Barker et al. recently conducted a detailed study of such anatomic changes during radiotherapy for head and neck cancer.[114] The primary tumors and nodes were noted to shrink at a median rate of 1.8% of the initial volume per treatment day, such that on the last day of treatment, the median overall volume loss was close to 70%. The tumor center of mass changed as well: while the median displacement of the GTVs was small (3.3 mm), it varied widely and was 17.3 mm in one case. The parotids moved medially during treatment such that the median displacement at the end of therapy was 3.1 mm, with a range of 0 to 9.9 mm, and the volume of the parotid glands decreased by a median of 28% by the end of treatment. These changes were highly correlated with patient weight loss and reflect significant changes in the position and size of both the gross tumor and OARs during therapy. Similar findings have recently been reported by additional

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investigators.[115,116] Taken together, these studies indicate that the mean dose to the parotid glands increases during radiotherapy as they move medially toward high-dose regions. Because parotid dose and resulting xerostomia have a significant impact on quality of life, several replanning studies have been undertaken to specifically address parotid sparing. By replanning half way through treatment, the volume of the parotids receiving 26 Gy or more was decreased by 15% to 20%.[115,116] However, significant change in parotid volumes and doses is only observed in a minority of patients who lose substantial weight, while on average the change is quite small. Although comparative objective salivary function tests and quality of life studies have not been performed to determine whether replanning results in clinical benefit, compared with no replanning, it seems that replanning at some point during treatment may be reasonable for patients who lose substantial weight or who have bulky tumors which shrink rapidly. However, it is unclear when and how often this should be performed. Strategies are being developed to deform treatment plans in near real time to account for differences in anatomy rather than replan the entire case.[117] This method closely approximates full IMRT replanning in a small fraction of the time required for full planning. Few replanning series showed improvements in parotid gland doses in the range of few percentage points, while target coverage is in general retained throughout treatment, such that the related benefit of replanning is marginal.[118,119] Also, current data suggest that for most patients, replanning is not likely to be beneficial more than once at midtherapy, and only few patients are likely to benefit from replanning twice during therapy. This topic is a subject of research performed in many institutions, and it is likely that significant additional related information will be available in the very near future.

***New Technologies to Deliver Highly Conformal Radiotherapy.*** While IMRT is usually delivered using multileaf collimators, new technologic innovations have provided some improvements in several aspects of the dose delivery, usually with some trade-offs, compared to the multileaf IMRT.

1. Tomotherapy delivers treatment through continually rotating around the patient in a slice-by-slice manner in combination with integrated image-guided abilities. In principle, the patient is treated continuously during the rotation of the radiotherapy source, practically increasing substantially the number of beams compared with the beams utilized by MLC-based IMRT. As expected, this substantially higher number of beams increased dose conformality and target dose homogeneity, allowing better sparing of critical tissues, at the expense of higher tissue volumes receiving low-to-moderate doses. However, the apparent dosimetric improvement, which is reported in studies which compare tomotherapy with IMRT, may not be enough to translate into clinically meaningful benefits.[120]
2. VMAT delivers modulated radiation in one or two arcs.[121] The main advantage is a marked reduction in overall treatment time, which increases the comfort of the immobilized patient, is expected to reduce intrafraction setup uncertainties, and has obvious benefits for a busy clinics. Planning exercises show that VMAT, if planned by experienced planners, can achieve similar dosimetric results as IMRT, especially if two arcs are used.[121] It delivers less monitor units and produces similar delivery accuracy compared with IMRT. However, VMAT planning time is longer, and it requires much more data for 3D dose storage and computing resources, which may interfere with adaptive replanning (if desired) during therapy.
3. Robotic radiosurgery, using Cyberknifec or other commercial systems, has been used for stereotactic hypofractionated RT in cranial and extracranial sites. Its main benefits are very sharp fall-off of doses and its ability to track respiration-related moving targets in the chest and abdomen. In the head and neck, few publications in recent years have suggested its use for reirradiation of recurrent tumors. Treatments are delivered as hypofractinated, high dose per fraction programs (typically 5 Gy or more), twice weekly to a total of 30 to 40 Gy. Clinical results published thus far using this method suggest that local tumor control is not superior to that expected after standard fractionated RT, while severe toxicity rate is high and is likely underdocumented given the short follow-up in these series.[122] Specifically, the rate of reported carotid blowout seems to be higher following stereotactic RT compared with standard fractionated RT.[123] At this time, the use of robotic radiosurgery for recurrent head and neck cancer, or for any other indication in head and neck cancer patients, is not recommended.

## Intraoperative Radiation Therapy

Intraoperative radiation therapy (IORT) is a novel approach to delivering high doses of radiation directly into a tumor bed, at the time of surgical resection. The intraoperative setting allows displacement of skin and other normal organs and permits the radiation oncologist to deliver radiation to very limited tissue volumes, encompassing the tumor bed with minimal normal tissue. The role of IORT in head and neck cancer has been recently reviewed.[124] Its major application has been in the management of recurrent disease in previously irradiated patients, or in patients who have developed a second primary cancer in a bed of prior treatment. Treatment can be delivered using either electron beam techniques or using high dose rate remote afterloading (HDR-IORT) in a shielded operating room. Often IORT is part of a strategic plan that includes postoperative external beam RT, in an effort to comprehensively re-irradiate a patient.[125] Free-flap reconstruction is an important complement to the surgical resection and IORT, both aiding the wound healing, and providing a fresh blood supply.[126] This allows additional external beam radiation to be added safely. Nowadays, with multidisciplinary approaches to salvage therapy, including surgical resection, IORT, flap reconstruction plus addition external beam RT, and biologic/chemotherapy, 2-year survival rates have been reported in 60%[125] of a patient population that was previously without good therapeutic options.

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CHAPTER 6

F. Christopher Holsinger

# New Approaches: Robotics and Endoscopic Head and Neck Surgery

## INTRODUCTION

Minimally invasive and endoscopic head and neck surgery[1] (eHNS) represents the natural evolution of the surgical disciplines within the multidisciplinary treatment paradigm. Yet, for years, head and neck surgery was virtually synonymous with "radical" transfacial and/or transcervical procedures. Although there were "conservation" or organ-preservation procedures in the larynx, such as the vertical partial laryngectomy or the open supraglottic laryngectomy, (Chapter 18), operative indications were often too narrow for surgery to play a significant role in treatment. Thus, multidisciplinary care for head and neck cancers gradually shifted toward a radiation-based approach. Multidisciplinary care was virtually synonymous with nonsurgical therapy.

However, an evolution in our understanding of transoral anatomy, the advent of computer-assisted surgery, and a host of new technologies has ushered in a new era for the head and neck surgeon. For tumors of the upper aerodigestive tract, especially the larynx and oropharynx, eHNS has naturally developed around transoral exposure, using either transoral laser microsurgery (TLM) or transoral robotic surgery (TORS) or a combination of the two (Table 6.1). With greater understanding of these minimally invasive approaches, surgeons have now begun to apply eHNS techniques to the neck systematically. Finally, using transaxillary and retroauricular approaches, surgeons have demonstrated the feasibility of operating on the neck for both thyroid and parathyroid surgery and even lymphadenectomy through small cervical incisions with video-assistance or through small inconspicuous incisions located some distance from the primary tumor site, hidden in the folds of the axillary or behind the ear.

Here, we review these developments, focusing on rationale, anatomy, and technical aspects, as well as indications and limitations of minimally invasive and eHNS. The term "eHNS" is preferred, since every approach described below from robotic surgery to TLM or minimally invasive video-assisted thyroid surgery (MIVAT) utilize an endoscope to provide unparalleled access and visualization of head and neck surgical anatomy. More importantly, eHNS is independent of a particular technology or medical device industry, and focuses on surgical technique and its evolution, unfettered by the bonds of commercial affiliations and sponsorship.

## TRANSORAL LASER MICROSURGERY

### Laser Physics and Choice of Technology

eHNS was born in 1972 within the field of laryngology using transoral exposure for the resection of benign and early limited cancers by Strong and Jako.[2] Since then, the technique of TLM has emerged as a standard of care for early laryngeal cancer (Chapter 18b) and also an important surgical approach for selected tumors of the oropharynx, supraglottis, and hypopharynx. TLM is performed via direct laryngoscopy, with an operating microscope, microsurgical instruments, and the surgical carbon dioxide ($CO_2$) (Fig. 6-1), pulsed potassium titanyl phosphate (KTP), or thulium laser.

Since a surgical laser serves as a scalpel, the surgeon must understand this tool and have a firm grasp of laser physics and the thermal and mechanical aspect unique to a particular laser's soft-tissue interactions. In TLM, the laser is used to cut, not to ablate or to simply cauterize tumors, delivering energy in the form of light directly to target tissue. Light energy is absorbed directly without mechanical or electrical trauma, but when absorbed by soft tissue is transformed into heat, producing a photothermolysis. As more laser energy is absorbed by a particular

**TABLE 6.1 Endoscopic Head and Neck Surgery**

| | Larynx | | Oropharynx | Hypopharynx |
|---|---|---|---|---|
| | Glottic | Supraglottic | | |
| Transoral laser microsurgery | ☑ | ☑ | ☑ | ☑ |
| Transoral robotic surgery | | ± | ☑☑☑ | ± |



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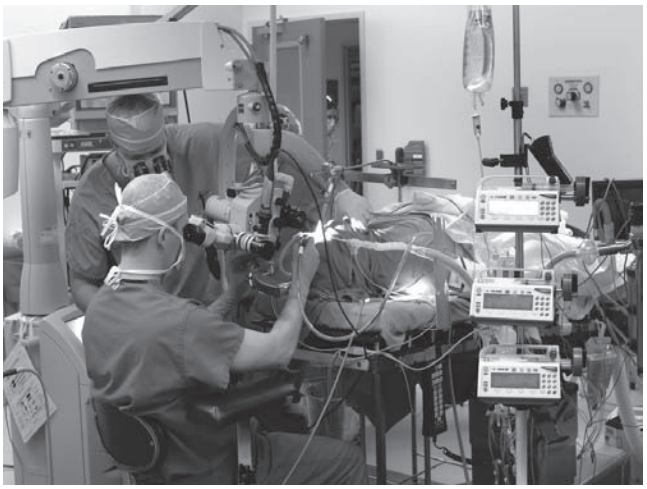


**FIGURE 6-1.** Intraoperative photograph demonstrating the technique of transoral laser microsurgery. A laryngoscope is fixed to a bedside stand and an operating microscope provides 4x to 10x magnification. A bedside assistant is seen providing external compression which assists the operating surgeon by providing exposure and countertraction to optimize the resection.

tissue, the laser's chromophore, covalent bonds are released and tissue is vaporized, usually at the boiling point. The physics of the $CO_2$ laser make it ideally suited for head and neck surgical applications. Water, as the primary component of most cells in the human body, serves as an efficient chromophore for light energy from the $CO_2$ laser, due to its frequency of 10,600 nm. As the cells absorb the light energy from the laser, the cells' temperature rises quickly and at 100°C the cells vaporize. This soft-tissue interaction allows the surgeon to cut and coagulate tissue without electrocautery, thus minimizing collateral damage to adjacent neurovascular, mucosal, and muscular structures.

If laser beam is not efficiently delivered, tissues are burned, not completely vaporized. Inefficiently denatured protein appears to the surgeon as carbon debris, or "char," which further interferes with the surgeon's visualization and obstructs the efficient delivery of laser energy to the target tissue resulting in greater subablative heat build-up. Using a pulsed laser is an important way to avoid thermal injury: that is, turning the laser on and off in microsecond bursts. In this pulsed mode, thermal relaxation time is reduced and target tissues can dissipate heat before char develops. Also, thermal injury can be diminished by reducing exposure time. That is, using a "repeat-delay" setting, a pulsed laser can be turned on every 0.1 to 0.3 seconds, further reducing thermal damage during TLM.

In addition to these general considerations, the long wavelength of the $CO_2$ laser carries with it some limitations. The beam itself is invisible. Thus, a visible and parallel **beam** of light from a **Helium–Neon** laser (wavelength of 656 nm) is used to identify the invisible 250 $\mu$m "spot" generated by the $CO_2$ laser. A mirror micromanipulator is connected to a microscope, and the laser beam can then be directed with a small surgical joystick. For many patients with tumors throughout the laryngopharynx, direct "line-of-sight" exposure is achieved, whether by direct transoral exposure to the oral cavity, tonsil, and palate or via endoscope for the deeper oropharynx, larynx, and hypopharynx. However, this line of sight restriction may limit the "working space" of the laser within which the surgeon can work and proves problematic as tumour size increases or patient anatomy restricts line-of-sight delivery. The Omni Guide System (Omni Guide, Inc., Cambridge, Massachusetts) introduced the first widely commercially available fiber-optic $CO_2$ laser.[3] With a fiber, the surgeon can wield and direct the fiber-optic laser almost as a scalpel. In so doing, the $CO_2$ laser can be used "around-corners" and into the difficult recesses of the head and neck, thus overcoming some of the limitations associated with line-of-sight exposure.[4] The flexibility of the $CO_2$ laser fiber delivery system permits either hand-held operation or even mounting to a specialized robotic manipulator. Yet, these hollow-core fibers can be fragile and fail when handled too aggressively or bent at extreme angles. Other teams are at work to deliver $CO_2$ laser energy through glass fibers that might provide greater durability.[5]

Further technical refinement for the $CO_2$ laser was first presented by Remacle et al.[6] with the introduction of the scanning robotic micromanipulator. The surgeon can use this robotically crafted, pulsed laser beam in several different shapes and spot sizes ranging from 0.4 to 5 mm, using a computer-assisted algorithm. These settings allow the surgeon a great deal of precision to customize the laser–soft tissue interaction, resulting in greater finesse, especially for instance when operating on lesions of the true vocal cord. Furthermore, the surgeon can choose from several patterns or cutting shapes, instead of just a 250 $\mu$m spot. Using this "digital acublade" on varying pulsed modes, Remacle et al.[6] showed significant reduction in thermal injury zone to 12.5 $\mu$m and increased operative precision, when compared to the traditional "dot-by-dot" joystick micromanipulator approach.

Finally, thulium-based fiber-optic lasers[7] have similar properties to $CO_2$ lasers and demonstrate promise for benign laryngeal and tracheal disease, as well as, for cancer. The 2,013-nm wave length of this laser allows its energy to be delivered by a small caliber glass fiber, yet it retains water as a chromophore. This laser appears to offer a smooth vaporization pattern and excellent hemostasis, similar to that realized with the pulsed KTP laser,[8] but with less risk of deep tissue penetration.

## Technique and Its Role in the Multidisciplinary Paradigm

Independent of the novel and emerging technologies in TLM, head and neck surgeons now routinely employ this transoral endoscopic approach for tumors of the upper aerodigestive tract. Traditionally, these techniques fell under the purview of laryngologists. Steiner and Ambrosch[9] first paved the way for broader use and greater acceptance of TLM through head and neck oncologic surgery. First and foremost, the laser is used as a precise endoscopic scalpel, to cut and to coagulate, not to ablate or cauterize. Furthermore, TLM, as espoused by Steiner and Ambrosch, challenged widely held belief in Halsted's fundamental surgical principle of en bloc resection.[10] With TLM, as a tumor is transected, precise visualization under the operating microscope reveals the full depth of tumor. By understanding this third dimension of the resection, the surgeon can optimize margin of resection. Oncologic outcomes from TLM are discussed in further detail in Chapter 18b, but by conserving the maximum amount of normal mucosa, crucial structures are preserved and function is optimized. Preservation of laryngopharyngeal function is accomplished through maintenance of at least one valve of the larynx for airway protection, swallowing, and native voice.[11] In fact, the promise of TLM and endoscopic head and neck surgical approaches to larynx cancer and that of other sites within the upper aerodigestive tract is this: patients who undergo these procedures, especially for T1-2 tumors, tend to fare remarkably better than was expected when these techniques were first introduced. Transoral endoscopic resection preserves the laryngeal

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cartilaginous and musculature framework in the neck. The end-terminal branches of the superior laryngeal nerve (Fig. 6-2) are preserved providing rapid return of laryngopharyngeal sensation and thus swallowing function. In an unradiated patient, the repeated and constant use and soft-tissue remodeling appears to restore anatomy to its near normal state, with a surprising degree of associated normal function. For instance, a surgical defect for a T1 verrucuous carcinoma, that requires a deep resection of the mucosa and even a portion of the vocal ligament, heals over time without significant deformity and good vocal outcomes (Fig. 6-3). For larger tumors of the larynx, with a more complex defect, from glottic larynx through the ventricle and into the false cord, the same postoperative healing appears to restore normal function (Fig. 6-4). Ultimately, the human body's remarkable restorative capacity lies at the heart of the opportunity and potential for eHNS within the multidisciplinary paradigm.

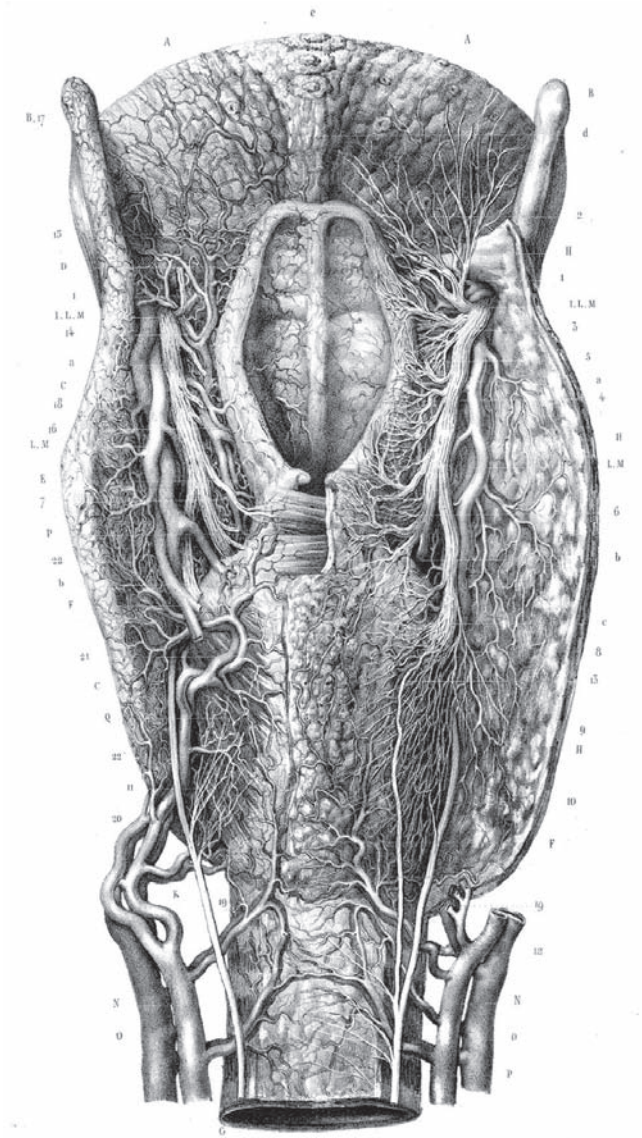


**FIGURE 6-2.** This monograph from 1831 to 1832 in the Bourgery and Jacob's *Atlas of Anatomy* shows the extensive network of the superior laryngeal neurovascular network.

*Source:* From Traité complet de l'anatomie de l'homme comprenant la medecine operatoire, par le docteur Marc Jean Bourgery. Illustrated by Nicolas Henri Jacob, 1831, with permission.

# TRANSORAL ROBOTIC APPROACHES

## Robotic Technology and Its Application in eHNS

Although the term "robot" dates back to a 1921 play *Rossum's Universal Robot*[12] by a Czech playwright,[12] the widespread use of robotics in surgery has debuted only in the last decade. In 2007, "robotic surgery" was defined as any "surgical procedure or technology that adds a computer technology–enhanced device to the interaction between a surgeon and a patient during a surgical operation and assumes some degree of control heretofore completely reserved for the surgeon."[13]

At present, there is only a single commercially available surgical robot. While the da Vinci Surgical System (Intuitive Surgical Inc., Sunnyvale, CA) is widely used to facilitate laparoscopic minimally invasive surgery in urological, abdominopelvic, thoracic, and cardiac surgery, its use for "transoral otolaryngology" procedures was approved by the FDA in December 2009.[14] The da Vinci is not a singular "robot" but rather a surgical system in three parts or, to be more precise, three surgical carts. At the operating room table, surgical instruments are deployed from a **"patient-side" cart** and are safely placed by the surgeon within the patient's body under direct and/or endoscopic guidance. A binocular 8.5- or 12-mm endoscope with dual 0- or 30-degree optics is used to visualize target anatomy. The three-dimensional surgical anatomy is then recreated using the "vision" cart, where computer processing links the camera's image and the real-world spatial relationships of the instruments in a virtual environment. The surgeon, sitting at a **remote console cart** (Fig. 6-5) can then operate within this virtual three-dimensional environment using "master-controllers" (Fig. 6-6) that control and direct movements of the robotic instruments. These master controllers bear a remarkable similarity to joysticks and other hand-held devices employed in video games and other virtual reality simulators. The surgeon has an unprecedented perspective on the surgical anatomy as well as the ability to operate with 540 degree of wristed instrumentation and at either 0- or 30-degree angle. Furthermore, motion scaling increases precision and reduces the larger hand movements required by humans while eliminating tremor and fatigue. This surgical system permits the surgeon to interact with surgical anatomy with a novel perspective, around corners, in otherwise accessable places, and in ways that would not otherwise be possible. In other words, robotic surgery represents a fundamental advance in the art and science of surgery. For the first time, the surgeon and his hands are physically separate from the patient (Fig. 6-7). Real surgery is performed in a virtual environment. With further technological refinement and innovation, as stereoscopic cameras and instruments become smaller and more miniature, the limitations in what can be achieved will become even fewer.

The first transoral robotic head and neck procedure was performed by McLeod and Melder[15] in 2003 at the Walter Reed Army Medical Center. Using a slotted and custom-modified Lindholm laryngoscope, the authors resected a vallecular cyst with the first-generation "standard" da Vinci robotic system. Their report was finally published in 2005; that same year, Hockstein et al. first demonstrated the feasibility of transoral robotics for more extensive laryngopharyngeal surgery. "Hockstein's leap" was to place robotic arms through oral and oropharyngeal retractors, rather than traditional laryngoscopes, to more reliably facilitate surgery and thus significantly reduce external collisions.[16,17] Using standard tubed laryngoscopes, this team documented limited mobility of the robotic instruments (either 8 or

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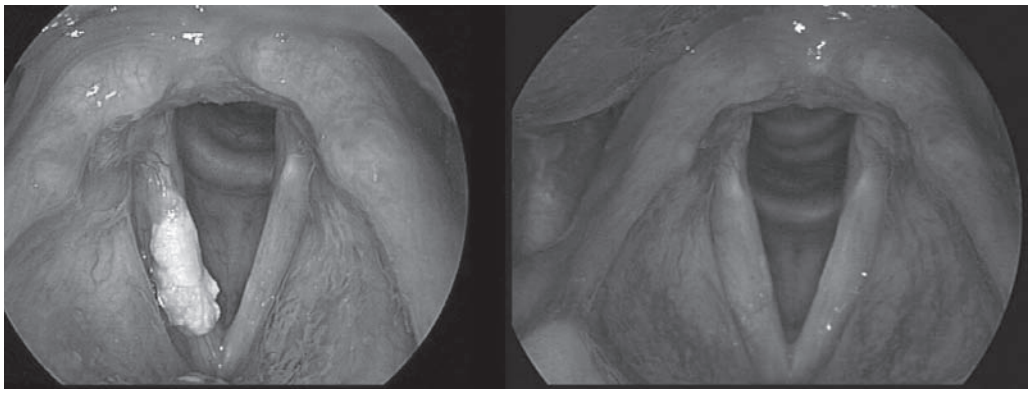


**FIGURE 6-3.** Preoperative **(left)** and postoperative **(right)** views of a T1 verrucous carcinoma resected via transoral laser microsurgery. The surgical defect is not evident, despite submucosal resection down to the vocal ligament. Adaptive remodeling of the larynx after transoral laser microsurgery may provide better functional outcomes that expected, when the proper lesion is choice. No radiation therapy was given. (See color insert.)

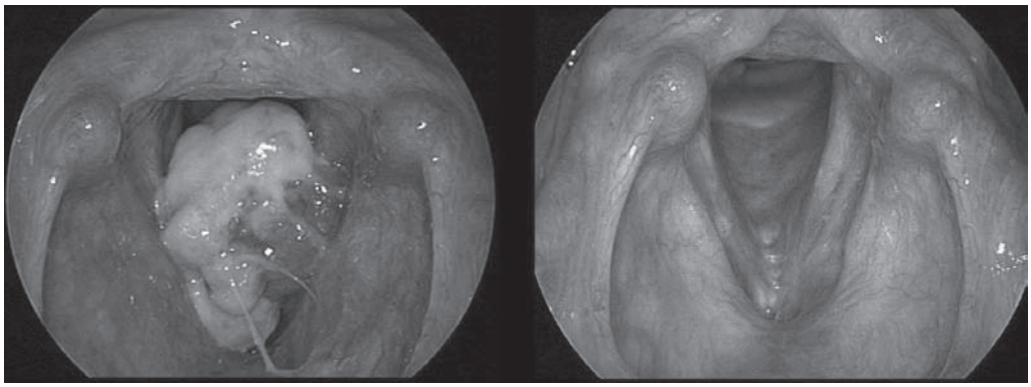


**FIGURE 6-4.** Preoperative **(left)** and 3-year postoperative **(right)** views of a squamous carcinoma of the larynx. CT imaging staged this as a T3 lesion, though the tumor was pedunculated from the undersurface of the left false cord. The tumor was resected via transoral laser microsurgery and no postoperative radiation therapy was given. (See color insert.)




**FIGURE 6-5.** The surgeon operates via remote surgical console during transoral robotic surgery, manipulating virtual three-dimensional environment that precisely representing the patient's actual surgical anatomy.



**FIGURE 6-6.** The surgeon uses "master controllers" which control and direct movements of the robotic instruments which have been placed within the patient.

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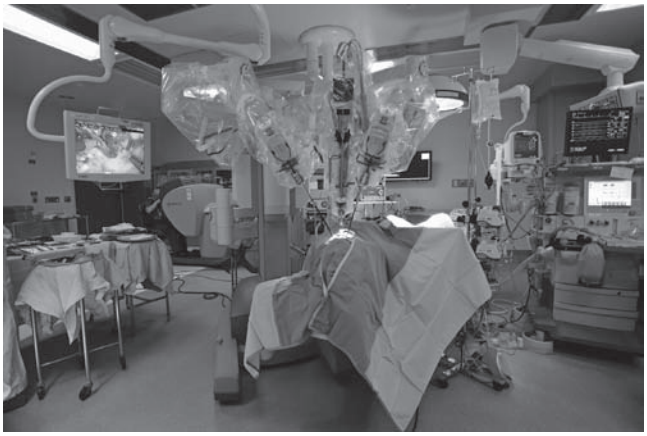


**FIGURE 6-7.** This intraoperative photograph demonstrates the relationships between the patient (foreground; covered in drapes), the patient-side robotic surgical cart, delivering the instruments into the oropharynx, and the remote surgical console **(back left)** where the surgeon operates. Robotic surgery incorporates real surgical maneuvers performed in a virtual environment.

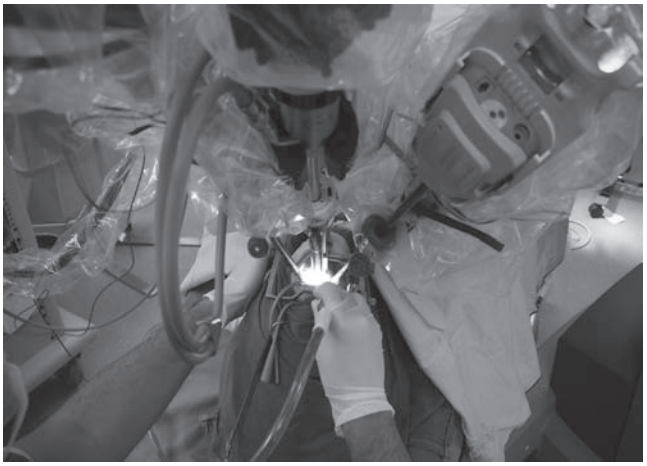


**FIGURE 6-8.** The Feyh-Kastenbauer retractor (Olympus) shown here provides several axes of exposure and retraction, first distracting the mandible from the maxilla. In addition, different "blade" can be inserted providing varying soft-tissue retraction. Finally, the blade can be angled to provide additional exposure and angulation during transoral endoscopic head and neck surgery.

5 mm) as well as the stereo-endoscopic camera. In fact, using this configuration, movement of the robotic arms tended to move the laryngoscope significantly, which suddenly and unpredictably changed visualization—a limitation that precluded safe simulated surgical procedures, even in a mannequin model. However, when the McIvor oropharyngoscope was utilized, instrument collisions were reduced or eliminated entirely in the oropharynx and was still possibly in both the hypopharynx and supraglottis. Difficulty in accessing the glottic larynx persisted using the da Vinci System.

Thus, the term "transoral robotic surgery" was proposed and a series of papers reported on robotic resection of oropharyngeal carcinoma (OPC) in the tongue base[18] and tonsil.[19] In TORS, three of the four da Vinci robotic arms are placed through the mouth using standard retractors such as the McIvor, Crowe-Davis, or Dingman oral retractor. Tumors of the tonsil (without glossopharyngeal sulcus extension) and soft palate are nicely exposed with these retractors. O'Malley reported on the superiority of the Feyh-Kastenbauer over standard oral/oropharyngeal retractors, such as the Dingman and Crowe-Davis,[18] especially for tongue-base carcinomas (Fig. 6-8). Once exposure is achieved, the surgeon introduces the binocular camera and on its side two instruments, using 5- or 8-mm dimensions. Typically, monopolar electrocautery is used for cutting and coagulation by means of a 5-mm spatulated cautery device (Fig. 6-9). While the hemostasis achieved with the spatula is excellent, the thermal burn associated 5-mm instrument may sacrifice excess normal tissue. For this reason, the $CO_2$[5,20,21] (Fig. 6-10A) has been used to increase the precision of mucosal incisions and to reduce collateral thermal damage. A 5-French introducer (Fig. 6-10B) has been developed to deliver a Thulium laser[22] through a robotic arm. A variety of tissue forceps, with teeth for gently grasping (Fig. 6-11), provide the ability for fine dissection as well as traction and counter-traction.

TORS simultaneously introduces two new aspects to traditional surgical techniques for many surgeons: transoral endoscopic surgery and robotics. Yet despite its novelty, several centers adopted the technique, which was associated with a clear learning curve and much of which surrounded, gaining initial transoral exposure and access. Genden[23] showed a precipitous decline in the setup time from over an hour to only 20 minutes, in his first series of 20 cases. Lawson[24] found a similar learning curve in a series of 24 patients from Mont-Godinne in Belgium. Setup time was 24 ± 14 minutes (range 10–60 minutes), with mean surgical time of 67 ± 46 minutes (range 12–180 minutes). Moore[25] found that operative times were significantly longer in the first 10 cases, then rapidly declining to an average of 71 minutes. Many of the initial surgeons who published earlier experience in TORS also had extensive published expertise in conventional transoral[26–28] or TLM,[24] suggesting that facility



**FIGURE 6-9.** A 5-mm spatulated cautery tip is the work-horse for transoral robotic surgery. Using the "cut" setting minimizes mucosal char when compared to "coagulate" mode.

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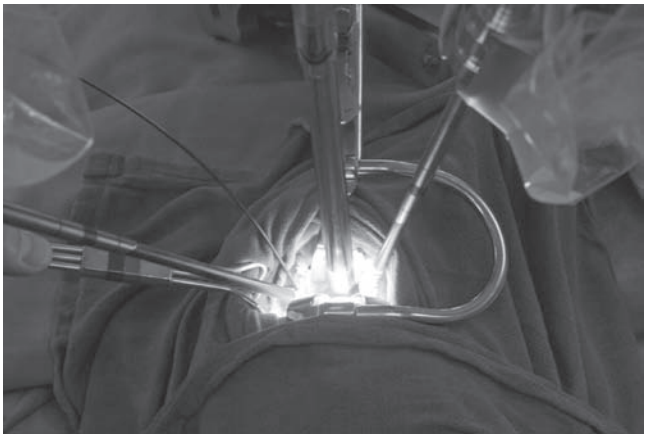




**FIGURE 6-10.** A 5-French introducer has been developed to permit the delivery of doped thulium or carbon dioxide fiber-optic laser as a more precise cutting instrument.

with transoral exposure and surgery might reduce these learning curves and possibly complications.

## TORS for Oropharyngeal Tumors: Surgical Technique

***Transoral Robotic Oropharyngectomy.*** Understanding the transoral surgical anatomy of the lateral oropharynx, which was well described prior to TORS, is likely paramount for adequate hemostasis and good outcomes.



**FIGURE 6-11.** A 5-mm Maryland forceps provides soft-tissue handling during the initial mucosal incisions. This instrument is well suited for tonsillar and soft-palatal tumors. For tongue-base and larger tumors, the Cadiere or ProGrasp forceps with larger open jaws provide better traction on surrounding normal tissues.

Transoral robotic oropharyngectomy is performed under general endotracheal anaesthesia. After adequate oropharyngeal exposure is obtained, the surgeon first palpates the tonsillar fossa, to confirm that the tumor and surrounding tonsillar fossa is mobile. Preoperative trismus (suggesting medial pterygoid [MP] involvement) and/or hypomobility or fixation of the tonsil is a clear contraindication to transoral surgery. An incision is made through the mucosa overlying submucosal raphé between the superior constrictor and buccinator muscles. Cuts are made superiorly through the intermaxillary mucosa and inferiorly through the glossotonsillar fold, and if need be, some of the posterior floor of mouth. The tumor and attached lateral oropharynx is then retracted medially, which opens a fascial plane just deep to the superior constrictor, from the cranial to caudal aspect of the lateral oropharyngeal resection (Fig. 6-12). The MP muscle can then be identified as the specimen is retracted laterally (Fig. 6-13). The surgeon can use the precise visualization of robotics to identify the parapharyngeal fat, which covers the plane of the internal carotid artery, which is located more posterolaterally. Depending on the location of the tumor, the anterior tonsillar pillar is then transected both above at the soft palatal margin and below at its junction with the tongue base, glossotonsillar fold, and posterior floor of the mouth. These maneuvers release the surgical specimen from the lateral oropharyngeal wall, both above and below, which then allow the surgeon to separate the specimen from its deep attachments from the parapharyngeal space (PPS). Located more cephalad, the stylopharyngeus muscle is divided from its attachment to the undersurface of the superior constrictor. Usually, a branch of the ascending pharyngeal artery and vein is found here and is ligated using a surgical clip for adequate long-term hemostasis. More caudally, the styloglossus muscle is identified and transected. Often a branch of the glossopharyngeal nerve is found between these two muscle bellies, as well as branches from the facial vascular system. Finally, a medial incision is made in the posterior oropharyngeal completing the resection. Most often, the surgical defect is left to heal by secondary intention.

***Transoral Robotic Resection of the Tongue Base.*** After the patient's tongue base is exposed with an FK retractor, a horizontal tongue-base incision is made just posterior to the circumvallate papillae, extending from the posterior- most aspect of the floor of the mouth, through the lateral-most aspect of the base of tongue

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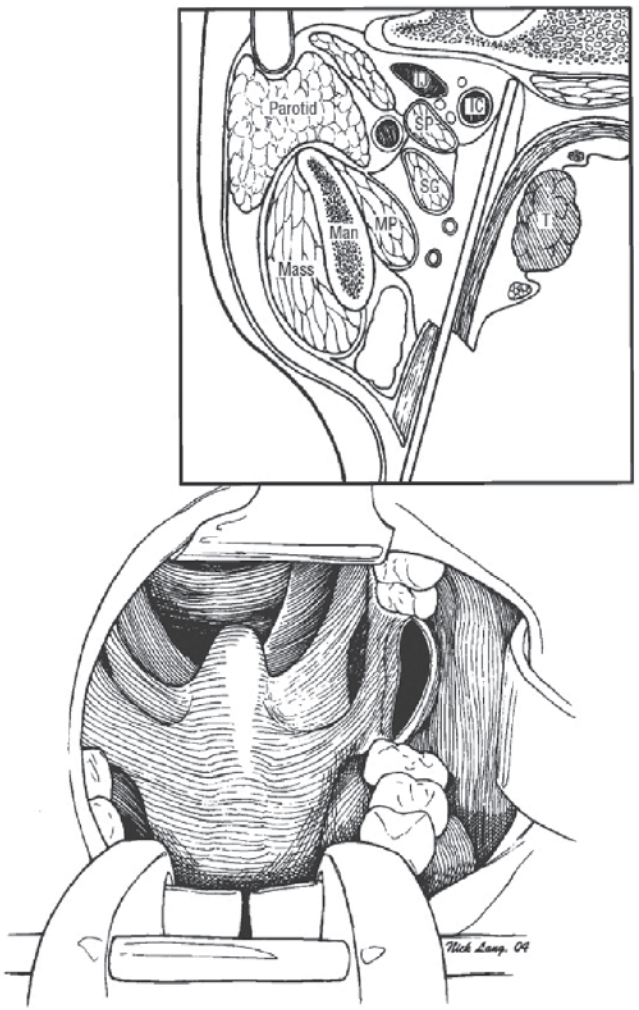



**FIGURE 6-12.** The secret to understanding transoral approach to the oropharynx is transposing and merging the endoscopic view of the mouth, with the better understood cross-sectional anatomy. The transoral anatomy is shown below with Huet's incision **(below)** is correlated with the underlying parapharyngeal anatomy. IJ, internal jugular vein; IC, internal carotid artery; SP, stylopharyngeus muscle; SG, styloglossus muscle; Mass, masseter muscle; MP, medial pterygoid muscle.

*Source:* From Holsinger FC, McWhorter AJ, Menard M, et al. Transoral lateral oropharyngectomy for squamous cell carcinoma of the tonsillar region: I. Technique, complications, and functional results. *Arch Otolaryngol Head Neck Surg.* 2005;131:583–591, with permission.

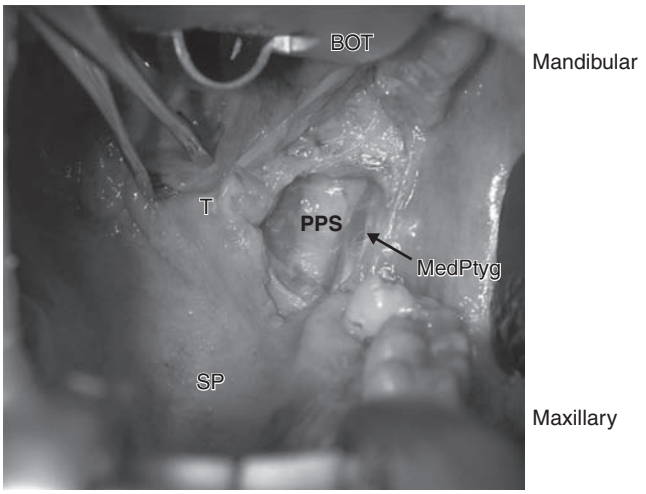



**FIGURE 6-13.** For orientation, the mandibular and maxillary dentition are labeled to the right. The base of tongue is shown above and the soft palate below. A submuscular plane of dissection deep to the superior constrictor is developed as the ipsilateral tonsil (T) is gently grasped with tenaculum and pulled medially. The right medial pterygoid muscle can then be identified as the specimen is retracted laterally. Then, the parapharyngeal space can be safely exposed without significant risk of vascular injury. Small venules from the ascending pharyngeal and dorsal facial vascular system must be clipped and precisely controlled to prevent hemorrhage on postoperative days 7 to 10.

(BOT) to nearly the midline (depending on tumor location and size). A sagittal incision is then made down into the substance of the tongue. This serves as our medial margin. From the lateral aspect of the incision, in the floor of mouth, an incision is made along the anterior tonsillar pillar and down through the remnant tonsillar fossa or superior margin into the glossopharyngeal sulcus, all the way to the posterior oropharyngeal wall. Returning to the substance of the tongue base, the muscle of the substance of the tongue is divided from lateral to medial, essentially aiming toward the hyoid bone. During every pass of the electrocautery spatula tip, tissue is retracted more posteriorly, to optimize the amount of tissue that is resected. This minimizes the chance for a positive deep margin. Once the hyoid is found (or an adequate cuff of muscle margin is obtained), an incision is made into the vallecula. From the previous sagittal incision in the midline, a deep plane of dissection then connects the medial aspect of resection toward the lateral oropharyngeal wall. This is done to safely approach and avoid injury to the hypoglossal nerve and lingual artery. Branches of the superior laryngeal system can be identified in the pharyngoepiglottic fold and then, a sagittal incision to the midline of the tongue connects all the way down to the base of the vallecula. The final incision follows through the base of the vallecula, thus avoiding thermal trauma to the epiglottis.

## Oncologic Outcomes and Functional Outcomes for TORS

The University of Pennsylvania's first extensive report on the role of TORS came in 2007. Weinstein performed "radical tonsillectomy" via TORS in 27 patients with previously untreated invasive squamous cell carcinoma of the tonsillar region, staged T1-3 N0-2, without free-flap reconstruction. A careful reading of the paper clarifies that a transoral lateral oropharyngectomy was actually performed; the term "radical tonsillectomy" is inadequate. This technique had been initially described in French by Huet[29] with wide mucosal margins and an underlying deep muscular margin of the superior constrictor muscle.[26] Nonetheless, with this novel use of robotics, negative margins were achieved in 25 of 27 patients (93%), which compared favorably with conventional technique.[27] Complications were limited to a single case of postoperative mucosal bleeding, delirium tremens, unplanned tracheotomy for temporary exacerbation of sleep apnea, and hypernasality and two cases of moderate trismus. Postoperative adjuvant therapy was required for most patients: 89% had radiation, and at least a third of these also had chemotherapy.

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Yet, at the completion of the study, 96% (26/27) were swallowing without the use of a gastrostomy. That same year, Weinstein reported on the University of Pennsylvania's TORS experience for the treatment of 3 patients with supraglottic laryngeal cancer as well.[30] Two patients had close or positive margins, but subsequent re-resection at the time of the initial surgery revealed no microscopic residual disease. One of these three patients had chemoradiation afterward for multiple metastatic lymph nodes found during staged neck dissection.

Adverse events following TORS appear to be limited. Most patients complain of a week or two of postoperative odynophagia and most return to normal swallowing within 30 days. Moore et al. reported a prospective study from Mayo with 45 patients treated with TORS and found that no patients required long-term feeding tubes nor tracheostomy.[25] However, for patients with advanced T stage 3 to 4 or location outside the oropharynx, functional outcomes following TORS may be associated with a higher risk for enterogastric feeding and poor swallowing outcomes.[31] This study from the University of Alabama–Birmingham showed that initially most patients resumed an oral diet before leaving the hospital (69%) and 83% within 2 weeks. However, longer term at a year, age >60 ($p = 0.017$), advanced T-stage classification ($p = 0.009$), and tumors within the larynx had higher rates of swallowing dysfunction using the MD Anderson Dysphagia Inventory (MDADI).[32] Assessment of functional outcomes using other quality-of-life instruments, including the Performance Status Scale (PSS) for Patients with Head and Neck Cancer,[33] showed similar results. For 38 patients treated with TORS and postoperative adjuvant therapy, PSS Eating and Diet domains demonstrated significant decreases occurred at 6 months, returning to postoperative baseline at 12 months.[34] This finding correlated with a decline in the SF-8 Global Health (QualityMetric Inc., Lincoln, RI) domain at 6 months, returning to normal at 1 year. Surprisingly, in this series of patients with oropharynx cancer, declines in the PSS Speech domain were seen at both endpoints, 6 and 12 months. Patient who had TORS only had rapid return of function on all indices and maintained this recovery.

In the largest functional outcomes study, Hurtuk et al.[35] reported on the TORS experience at The Ohio State University with 64 previously untreated patients: 57 patients had malignant tumors and 7 benign. The same decline from baseline in the speech, eating, aesthetic, social, and overall QOL domains was documented immediately after treatment. One year following treatment, the health-related quality-of-life (HRQOL) scores in the aesthetic, social, and overall QOL domains recovered. However, patients who underwent adjuvant radiation therapy or chemotherapy and radiation therapy had lower postoperative scores in the eating, social, and overall QOL domains ($p < 0.05$). Sinclair et al. found that postoperative chemotherapy was associated with reliance upon gastrostomy for longer than 3 months.[36]

In 2012, an extensive experience with TORS was published,[37] describing results from a US multicenter study on the feasibility, safety, and surgical margins for 177 patients undergoing TORS.[38] There was no intraoperative mortality or death in the immediate postoperative period. Postoperative hemorrhage following transoral surgery is always a concern.[39] In this series, there were no cases of catastrophic hemorrhage or emergent airway compromise: average blood loss was 83 mL and no patients required transfusion. A similar study in France[40] found higher rates of postoperative hemorrhage and reported two deaths, but nearly 65% of the patients had TORS for tumors of the supraglottic larynx, epilarynx,[41] or hypopharynx. These data suggest that robotics using the da Vinci Surgical System is best suited for tumors of the oropharynx.

Results are now emerging from several long-term experiences. Mayo Clinic recently presented a series of 66 patients with previously untreated squamous cell carcinoma (SCC) of the tonsil or the tongue base with a minimum follow-up of 24 months. The rate of gastrostomy dependence for nutrition was 4.5% and a single patient had tracheotomy. Local control and regional control at 3 years were estimated at 97.0% and 94.0%, respectively. Disease-specific and recurrence-free survival were 95.1% and 92.4% at 2 years, respectively.[42]

Furthermore, in contrast to the literature, outcomes following TORS may be independent of human papillomavirus (HPV) status. At the University of Pennsylvania,[43] 50 patients with OPC undergoing TORS as primary therapy had HPV status evaluated by real-time quantitative polymerase chain reaction (AttoSense HPV) for E6 proto-oncogenes for high-risk HPV. Thirty-seven patients were HPV positive (74.0%) with 34 of them (91.9%) being serotype-16. There was no difference in the ability to achieve negative margins: 92.3% for the HPV-negative cohort and 94.6% for the HPV-positive cohort. Neither group had local recurrence, but a single regional and distant recurrence was found in the HPV-negative cohort and two distant recurrences in the HPV-positive group. There were no statistically significant differences in survival between the two cohorts (overall survival, disease-specific survival, disease-free survival). In a follow-up paper, also from the University of Pennsylvania, Quon[44] evaluated the role of p16 immunohistochemistry (IHC) as well as polymerase chain reaction (PCR) for high-risk HPV subtypes to determine any association with HPV and oncologic outcomes. There was good concordance between p16 IHC and PCR, with p16 and HPV positivity in 73% and 74% of patients, respectively. Only a single local-regional relapse was seen in both p16-positive and p16-negative groups, and there were no differences in disease-free and overall survival differences. However, in both of these studies, HPV-negative patients represented a minority of the patients under evaluation. With this skewed population (with a favorable overall outcome in HPV-positive patients), further study is required to determine whether successful upfront treatment with TORS is truly independent of HPV status.

## Role of Robotic Surgery within the Multidisciplinary H&N Treatment Paradigm

While the safety and feasibility of TORS appears to be gaining acceptance, its role within the multidisciplinary paradigm is less certain. In many of the initial reports, well over half of patients undergoing TORS received some form of postoperative adjuvant therapy: radiation therapy with or without chemotherapy, ranging from 63% to 89%. Since the rate of positive margins in these series was low, the most common indication was neck disease. Skeptics suggest that TORS results in overtreatment, since most of the tumors amenable to TORS would be effectively treated with upfront chemoradiation.[45] Advocates, though, point to the superb functional results seen in these experiences, despite triple-modality therapy. In fact, in the largest published series to date, in which 89 patients had upfront surgical treatment with TORS, 63% received postoperative radiation therapy, with 49% of these patients also receiving concurrent chemoradiation.[46] Progression-free survival at 2 years was 86.5%, and no patient required a feeding tube for nutrition. In the multicenter trial, in patients undergoing TORS without previous therapy, the percutaneous endoscopic gastrostomy (PEG)-dependency rate was 5.0%.[37] Advocates interpret this and other series favorably and suggest the hypothesis of "deintensification."

That is, OPC patients treated upfront with TORS, even while needing postoperative chemoradiation, have similar oncologic outcomes, but do quite well functionally with "triple-modality" therapy because the overall dose to the pharynx is diminished.[47]

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This hypothesis will require further testing: ideally in the setting of a prospective clinical trial.

In the meantime, the changing epidemiology of oropharyngeal cancer will likely lead to a greater role for eHNS in the management of this disease. Reports from the United States[48,49] and abroad[50] have documented the precipitous rise in the incidence of OPC in individuals younger than typically expected for "traditional" head and neck cancer patients.[51] In a prospective case-control study, D'souza and Gillison[52] demonstrated an association between HPV and OPC, as well as the role of increasing oral sexual partners. This is explored in more detail in Chapter 12. Using the Surveillance, Epidemiology, and End Results (SEER) repository, Chaturvedi reported that the incidence of HPV-positive oropharyngeal cancers increased by 225% from 1988 to 2004.[49]

Fortunately, these tumors tend to respond favorably to standard organ-preservation approaches. In RTOG 0129, Ang et al. highlighted the significant impact HPV status has on the treatment of OPC,[53] after adjusting for demographics, T-stage, N-stage, smoking, and patients with HPV-positive. OPC had a 58% reduction in the risk of death and a 51% reduction in risk of progression or death. While these response rates are encouraging, young OPC survivors have the potential to live decades with the sequelae of their disease. Hutcheson et al.[54] have recently drawn attention to the long-term chronic severe dysphagia that may develop or progress years after radiation-based therapy for OPC. Given the potential long-term sequelae of radiation[54] in a rapidly enlarging population[49] of young patients with OPC, eHNS must play a greater role in their management.

## FUTURE DIRECTIONS: THE NECK AND BEYOND

A convergence of new techniques available in minimally invasive thyroid surgery[55,56] and the capabilities of the da Vinci Surgical System has ushered in a new era of opportunity in the neck for the endoscopic head and neck surgeon.[57] Minimally invasive endo-robotic and/or endoscopic neck surgery had been performed in human cadaver models.[58] Werner et al. demonstrated the feasibility of endoscopic sentinel lymph node biopsy for squamous carcinoma.[59] However, recent reports of robotic neck dissection for differentiated thyroid cancer from the Republic of South Korea have suggested the feasibility of routine endoscopic neck dissection for head and neck cancer.[60] Chung and colleagues performed robotic neck dissection via incisions in the axilla on 33 patients with lateral neck metastases from a differentiated papillary thyroid cancer. These patients had robot-assisted thyroidectomy and modified radical neck dissection using a gasless, transaxillary approach, yielding, on average, 6 nodes from the central compartment and 28 nodes in the lateral compartment. Koh et al. have demonstrated a similar technique for clinically N0 patients with oral tongue cancer, also using a robotic approach, but with transaxillary and retroauricular incisions.

Endoscopic approaches to the neck and the innovative techniques of robotic surgery may not have reached their full potential just yet. As access to robotic systems increases and as smaller robotic platforms are developed, TORS and robotic neck dissection may serve as a stepping stone to more complex operations of the neck, including tracheoesophageal resection and reconstruction, laryngeal framework surgery, and skull base surgery. Through the years, the radical neck dissection, as described by Crile in 1906,[61] has progressively been replaced by functional and selective neck dissections without compromising oncologic outcome. A similar thoughtful and clinical trial driven effort is required here, as well.

## SUMMARY

eHNS represents the natural evolution for the field of head and neck surgery. For tumors of the glottic larynx, TLM remains the gold standard. TORS has emerged as a safe, feasible, and effective approach for tumors of the oropharynx and selected tumors of the supraglottic larynx (Table 6.1). In the ensuing years, with robotic surgery and laser technology as a common platform, we foresee the development and widespread use of several new and innovative procedures for head and neck surgery, via transoral, retroauricular, and transaxillary approaches.

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CHAPTER 7

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# Targeted Agents in Squamous Cell Carcinoma of the Head and Neck

## INTRODUCTION

Squamous cell carcinoma of the head and neck (SCCHN) is a heterogeneous disease of cancers located in different anatomic subsites and made up of diverse molecular biology. As our understanding of the molecular biology of the disease evolves, so do therapy options. This chapter will further describe the main mechanisms of disease, important pathways, and newer agents under investigation in SCCHN.

Over the last several years, epidemiologic studies have revealed that HPV-related oropharynx cancers represent a distinct disease entity based on clinical and molecular characteristics. HPV-related SCCHN is primarily driven by silencing of critical tumor suppressor genes by viral proteins and will be discussed in detail in Chapter 13. Several other oncogenes and tumor suppressors are dysregulated in non-HPV SCCHN and, for the first time, comprehensive exome sequencing data are available to catalogue these changes.[1,2] Some important pathways are described in Figure 7-1. The full impact of these alterations on tumorigenesis, prognosis, and therapeutics has yet to be realized, but generalizations can be made regarding which pathways are most frequently disrupted in SCCHN.

### Epidermal Growth Factor Receptor and Its Ligands

Epidermal growth factor receptor (EGFR) is a transmembrane receptor tyrosine kinase that is almost universally expressed in SCCHN. It contains an extracellular ligand-binding domain, a hydrophobic transmembrane segment, and an intracellular tyrosine kinase domain that is autophosphorylated upon activation. The primary ligands in SCCHN appear to be amphiregulin and transforming growth factor alpha (TGF-$\alpha$), which induce homo- or hetero-dimerization with other receptors.[3] EGFR activation has been linked with proliferation, invasion, angiogenesis, and metastasis. Moreover, increased EGFR expression has been associated with worse outcome in patients treated with surgery, radiotherapy, or chemotherapy.[4–6]

EGFR expression is primarily driven by gene amplification or polysomy, which together are observed in 40% to 50% of SCCHN.[7] Increased EGFR expression appears even in preneoplastic lesions, and preclinical studies have demonstrated a reversal of SCCHN formation upon inhibition of EGFR.[8] Therefore, EGFR has been a rationale target in SCCHN although protein expression, gene copy number, or ligand expression have not been reliable predictive parameters in patients treated with EGFR inhibitors.[9]

### PI3K/AKT Pathway

The PI3K/AKT/mTOR pathway has been implicated in many cancers, and activation of this pathway contributes to formation and progression of SCCHN as well as resistance to chemotherapy and radiation. Constitutive AKT activation has been associated with amplification of the gene encoding the p110$\alpha$ catalytic subunit of PI3K (*PIK3CA*) or *AKT2*; activating mutations in *PIK3CA* or *AKT1*; and *PTEN* loss. In studies of SCCHN tumor specimens, *PIK3CA*, *AKT2*, or *PTEN* alterations were found in 30% to 50%.[10–12]

### *p53*

The *p53* gene product is a pleiotropic protein that is the most commonly mutated gene in SCCHN (50%–60%).[1,2] Functionally, *p53* is involved in the regulation of diverse cellular processes including cell cycle, apoptosis, autophagy, DNA repair, and metabolism. Mutations generally render the gene nonfunctional and provide growth advantage to cancer cells. Specific *p53* mutations have been linked with poor outcome in SCCHN and likely render tumors more resistant to therapy.[13] Interestingly, *p53* mutations are almost exclusively associated with HPV negative, tobacco-related SCCHN.[14]

### Cyclin D1

Entry into S phase of the cell cycle is dependent on phosphorylation of pRb by cyclin D1–cyclin-dependent kinase (CDK)-4, cyclin D1–CDK6 and cyclin E–CDK2 complexes. This leads to release of inhibition of key transcription factors that activate genes required for cell-cycle progression. Cyclin D1 itself is tightly regulated through transcriptional control (e.g., Myc), protein degradation (e.g., GSK3$\beta$), or inhibition of its partner CDKs by CDK inhibitors (e.g., p16). However, when cyclin D1 is amplified, which is detected in approximately 30% of SCCHN,[15–18] physiologic controls can be overridden driving rapid proliferation and tumor growth. Cyclin D1 amplification has been associated with early carcinogenesis and resistance to therapy including cisplatin, EGFR targeting agents, and other small molecule kinase inhibitors.

With these important pathways in mind, an extensive list of agents has been developed and grouped in the following sections by their mechanism of action.



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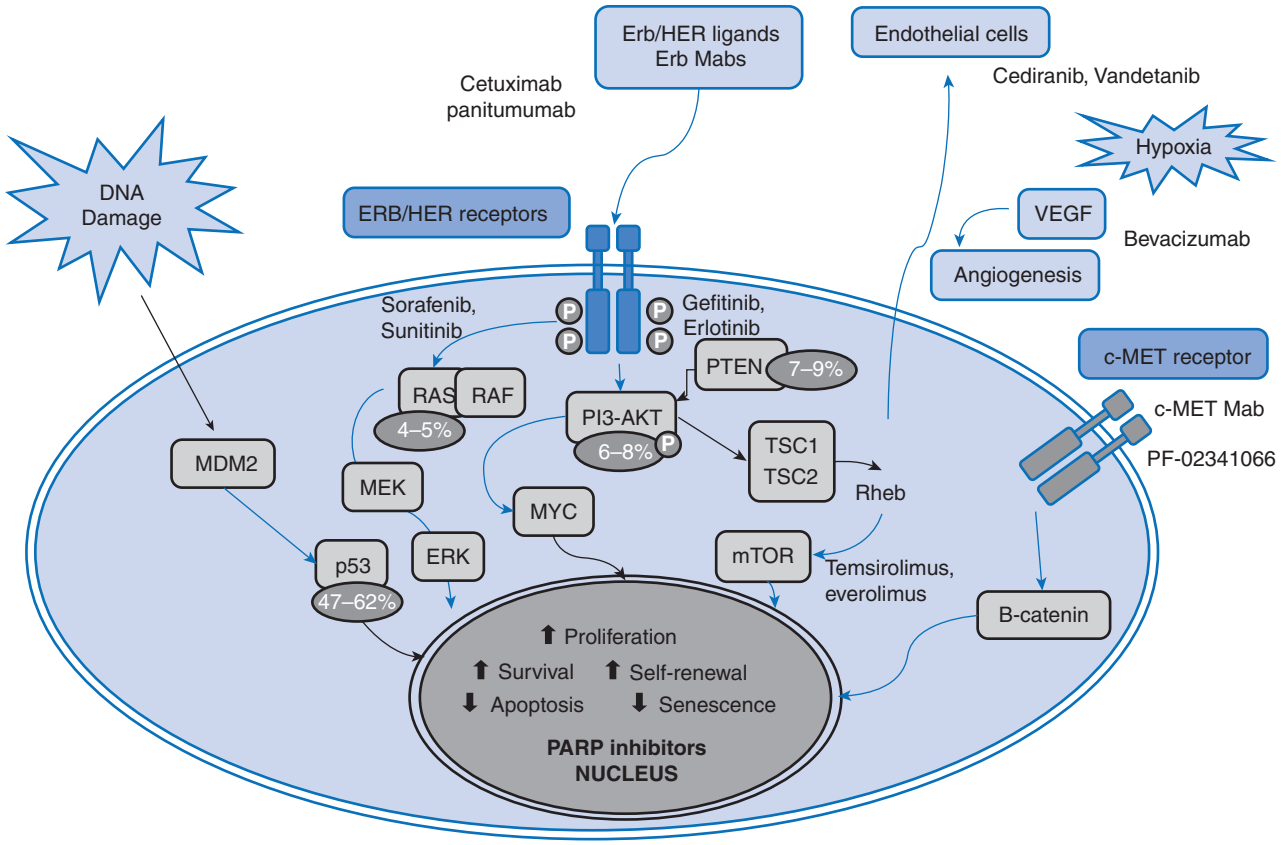



**FIGURE 7-1.** Selected pathways, targeted agents, and mutations important in squamous cell carcinoma of the head and neck. Red arrow, inhibitory activity; blue arrow, stimulatory activity; yellow circles; frequency of mutated genes; bold names, targeted drugs; PARP, poly(ADP-ribose)polymerases. (See color insert.)

## EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS

Cetuximab, a recombinant chimeric anti-EGFR monoclonal antibody, was the first drug approved by the FDA for SCCHN since cisplatin, and it remains the only targeted therapy to have an indication and be routinely used in clinical practice for this disease. It inhibits activation of the receptor tyrosine kinase in addition to inducing antibody-dependent cellular cytotoxicity.[19] Cetuximab is approved in combination with radiation therapy for locally advanced disease, in combination with platinum-based chemotherapy and 5-fluorouracil (5-FU) for the first-line treatment of recurrent/metastatic disease, and as a single agent for R/M disease after failure of platinum-based chemotherapy.

Vermorken et al.[20] investigated cetuximab monotherapy in a phase II trial enrolling 103 patients with R/M SCCHN who failed to respond to platinum-based therapy. Patients were allowed to receive platinum plus cetuximab as salvage treatment upon disease progression. The best overall response rate—the primary endpoint of the trial—was 13% (95% confidence interval [CI], 7%–21%) with no complete responses seen. Of the 53 patients (51%) who received platinum plus cetuximab at progression, no responses were seen. Two phase II trials[21,22] further tested the addition of cetuximab to cisplatin in patients who were refractory to platinum-based combination chemotherapy. In the first trial,[21] the addition of cetuximab to platinum chemotherapy, the latter administered at the same dose and schedule at which progressive disease (PD1) was documented, produced an overall response rate of 10% in 96 patients, compatible to single agent cetuximab and likely only exposing patients to added cisplatin toxicities. The second trial[22] enrolled 132 patients to receive two 3-week cycles with cisplatin/paclitaxel or cisplatin/5-FU. Patients ($n$ = 30) with a complete or partial response continued standard therapy and cetuximab was given with cisplatin to those with stable disease (SD), PD1 and progressive disease within 90 days after platinum-based therapy (PD2). In total, 9 out of 51 patients who had SD after the first 2 cycles, 5 out of 25 patients who had progressed after 2 cycles of chemotherapy (PD1), and 3 of 54 patients who had progressed beyond 2 cycles up to 90 days (PD2) achieved an objective response, with median duration of response of 4.2, 4.1, and 7.4 months for the PD1, PD2, and SD groups, respectively, with median overall survival times of 6.1, 4.3, and 11.7 months. The lessons learned from these early trials were twofold: (a) cetuximab in combination with these agents was safe and tolerable at full doses of the respective cytotoxic agents; (b) the response rates of cetuximab as a single agent in platinum-refractory patients-suggest that its activity can be attributed mostly to the addition of cetuximab and that the monoclonal agent alone may achieve the same results. These trials led to a phase III trial in the first-line treatment for R/M SCCHN, conducted by the Eastern Cooperative Oncology Group (E5397).[23] In a placebo-controlled randomized phase III trial of cisplatin (100 mg/m$^2$ on day 1 every 4 weeks) with or without cetuximab (400 mg/m$^2$) loading dose on week 1 followed by 250 mg/m$^2$ weekly, a total of 117 patients with SCCHN were randomized. The patients had newly diagnosed metastatic disease or locoregional recurrence/persistence after initial locoregional therapy. A significant improvement in the objective response rate was

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observed for the cetuximab plus cisplatin patient group, with 22.66% versus 9.3% ($p = 0.03$). Although the trial did not have the power to show significant differences in survival endpoints, the cisplatin-cetuximab arm had longer progression-free survival (4.2 vs. 2.7 months, hazard ratio [HR] for progression of 0.78; 95% CI, 0.54–1.12) and a trend for a longer median overall survival (9.2 vs. 8.0 months, $p = 0.21$).

The definite trial was the Erbitux in First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer (EXTREME), which confirmed the benefit of adding cetuximab to standard chemotherapy as a first-line treatment in the R/M setting.[24] In total, 442 patients with R/M SCCHN, who were not candidates to local therapy and had not received systemic therapy in this disease setting, were randomized to treatment with either cetuximab plus platinum-based chemotherapy (cisplatin or carboplatin plus 5-FU) or platinum-based chemotherapy alone. Patients received cetuximab at a loading dose of 400 mg/m$^2$ followed by 250 mg/m$^2$ weekly until progression or unacceptable toxicity and either carboplatin (AUC, 5; Day 1) or cisplatin (100 mg/m$^2$ intravenously; Day 1) plus 5-FU (1,000 mg/m$^2$ intravenously; Days 1–4) every 3 weeks for a maximum of 6 cycles or the same dose and schedules of platinum plus 5-FU without cetuximab. Crossover of patients after disease progression was not allowed. The primary endpoint was OS with secondary endpoints of PFS, best overall response, disease control (complete response + partial response + stable disease), time to treatment failure, duration of response, and safety. The most common primary site in both arms was oropharynx (36% in cetuximab arm, 31% in chemotherapy alone arm).

The addition of cetuximab to platinum-based chemotherapy with fluorouracil (platinum–fluorouracil) significantly prolonged the median overall survival from 7.4 months in the chemotherapy-alone group to 10.1 months in the group that received chemotherapy plus cetuximab (HR for death, 0.80; 95% CI, 0.64–0.99; $p = 0.04$). The addition of cetuximab further prolonged the median progression-free survival time from 3.3 to 5.6 months (HR for progression, 0.54; 95% CI, 0.43–0.67; $p < 0.001$). The addition of cetuximab improved the response rate from 20% with chemotherapy alone to 36% with chemotherapy plus cetuximab ($p < 0.001$), although the duration of response did not differ significantly (4.7 months in chemotherapy arm, 5.6 months with cetuximab).

These clinical benefits were achieved with no changes in quality of life associated with the addition of cetuximab to chemotherapy.[25] Of the 219 patients receiving cetuximab, 9% had grade 3 skin reactions and 3% had grade 3 or 4 infusion-related reactions. Patients in the cetuximab arm also had significantly more hypomagnesemia ($p = 0.05$) and sepsis ($p = 0.02$). Six patients in the cetuximab arm had grade 3 or 4 infusion reactions compared with none in the chemotherapy alone group. There were 10 treatment-related deaths, 3 on the cetuximab and 7 in the chemotherapy-alone arm, although there were no cetuximab-related deaths. In a subset analysis, there was a greater benefit for patients below 65 years of age, those with better performance status, and those who received cisplatin (as three quarters of study participants did, and also compatible with data that suggest that carboplatin is not as effective as high-dose cisplatin.[26] Based upon these data, cetuximab is approved for first-line use in combination with platinum-based chemotherapy in both Europe and the United States, and a triplet regimen consisting of platinum (preferably cisplatin), 5-FU and cetuximab should be strongly considered in symptomatic patients with a good performance status.

In the locally advanced setting, cetuximab is approved in combination with radiotherapy based on a multinational trial in which 424 patients with oropharynx, hypopharynx, or larynx locally advanced tumors were randomly assigned to radiotherapy with or without concurrent weekly cetuximab.[27] Cetuximab was initiated 1 week before radiotherapy with a loading dose of 400 mg per square meter, followed by 250 mg per square meter weekly throughout radiotherapy.

Median overall survival of patients treated with cetuximab and radiotherapy was 49.0 (95% CI, 32.8–69.5) versus 29.3 (95% CI, 20.6–41.4) months in the radiotherapy-alone group (hazard ratio [HR] 0.73; 95% CI, 0.56–0.95; $p = 0.018$). Five-year overall survival was 45.6% in the cetuximab-plus-radiotherapy group and 36.4% in the radiotherapy-alone group. The addition of cetuximab to radiotherapy was associated with similar rates of grade 3 or 4 toxic effects in both groups. The incidence of acneiform rash and related hypersensitivity reaction was significantly higher in the combination cetuximab–radiotherapy group than in the group receiving radiotherapy alone. Rash and nail changes appeared to be the most common side effects associated with cetuximab. A further unplanned and underpowered subset analysis-showed that this benefit was limited to patients below the age of 65 and with a Karnofsky performance score (KPS) 90 to 100, and those with oropharyngeal cancer, findings that have to be confirmed.

Further, the interpretation of this trial is challenging since chemotherapy was not part of the study, making it difficult to assess whether the combination of cetuximab and radiotherapy was as effective as concurrent chemoradiotherapy. RTOG 0522 further enrolled 940 patients with locally advanced squamous cell carcinoma of the oropharynx, hypopharynx, or larynx to answer this question.[28] Preliminary results from the clinical trial RTOG 0522 did not show benefits of concurrent cisplatin (100 mg/m$^2$ on days 1 and 22) plus accelerated radiotherapy (70 Gy in 42 fractions over 6 weeks) with cetuximab when compared to concurrent treatment without cetuximab. With a median follow-up of 2.4 years, neither was there any improvement in progression-free survival, the primary endpoint of the trial, nor was there a statistically significant improvement in overall survival (83% vs. 80%, HR 0.87, 95% CI, 0.66–1.15). The final analysis of this trial is eagerly awaited.

Other monoclonal EGFR receptor inhibitors have also been investigated. Panitumumab is a fully humanized IgG2 monoclonal antibody with high affinity to the extracellular domain of EGFR,[29] currently approved for use in metastatic colorectal cancer. Because of its structure (fully human antibody), infusion-related reactions are minimal. After promising early phase trials,[30] a trial similar in design to the EXTREME trial was performed. The SPECTRUM trial[31] assessed the addition of panitumumab to cisplatin and 5-FU chemotherapy had clinical activity with a significant increase in PFS and response rate, but failed to demonstrate a survival benefit. With median PFS of 5.8 months for patients in the panitumumab arm and 4.6 months for patients in the chemotherapy-alone arm (HR = 0.78; 95% CI, 0.66–0.92; $p = 0.004$), and overall response rate of 36% in the panitumumab arm, compared to 25% for patients who received only chemotherapy (descriptive $p = 0.007$), the median overall survival was 11.1 months in the panitumumab arm, compared to 9.0 months in the chemotherapy-alone arm (HR = 0.87; 95% CI, 0.73–1.05; $p = 0.14$). In a subsequently planned subanalysis, outcomes were analyzed by tumor HPV status. Of the 657 patients enrolled in the trial, 443 (67%) were evaluable for HPV testing by central review. There were 83 (22%) HPV-positive tumors and 294 (78%) HPV-negative tumors. In patients with HPV-negative disease, the addition of panitumumab was associated with significantly improved OS (11.7 vs. 8.6 months; HR = 0.73; 95% CI, 0.58–0.93; $p = 0.01$) and PFS (6.0 vs. 5.1 months; $p = 0.001$).[32] However, this result has yet to be confirmed in further studies, given the lack of data that define HPV as a prognostic factor in R/M SCCHN or predictive factor regarding anti-EGFR therapy, as well as limitations in this analysis,

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including its retrospective nature and missing HPV status in 35% of patients. Furthermore, similar findings were not seen in the phase II randomized CONCERT I trial of chemoradiotherapy with or without panitumumab in patients with unresected, locally advanced SCCHN.[33] In this trial, compared with the cisplatin and radiation with regard to PFS and OS, there was a trend favoring concurrent cisplatin and radiation without panitumumab, with the addition of panitumumab increasing the HR of death to 1.63 ($p = 0.1223$).

Zalutumumab, previously known as HuMax-EGFr, is a completely human IgG1 monoclonal antibody against human EGFR that also triggers Fc-mediated antibody-dependent cellular toxicity. Following a phase I/II study that included 28 patients with R/M SCCHN after failure to conventional treatments showed promising activity,[34,35] an open-label phase III study was conducted. A total of 286 patients with SCCHN who were regarded as incurable by standard therapy and had PD1 within 6 months of platinum-based therapy were randomized in a 2:1 ratio to receive zalutumumab plus best supportive care (191 patients) or best supportive care with optional methotrexate (95 patients). Zalutumumab was dose-escalated to achieve a grade 2 rash. Patients in the best supportive care arm had the option to receive weekly methotrexate up to 50 mg/m$^2$/week. Eligible patients were allowed up to two prior chemotherapy regimens in addition to treatment with platinum. There was a statistically nonsignificant increase in overall survival with zalutumumab compared with best supportive care (6.7 vs. 5.2 months; HR = 0.77; 95% CI, 0.57–1.05). The percentage of patients surviving at 12 months was longer with zalutumumab (22% vs. 12%). Zalutumumab significantly prolonged PFS from 8.4 weeks in the control group to 9.9 weeks (HR for progression or death, 0.63; 95% CI, 0.47–0.84; $p = 0.0012$). Response rate for zalutumumab was 6% including two complete responses. Grade 3 to 4 infection, hypomagnesemia, and cardiac events occurred more frequently in the zalutumumab group than in the control group. Given that methotrexate was utilized by 78% of patients in the control arm and that poststudy chemotherapy drugs other than methotrexate were given earlier and more frequently in the control group, the study essentially compared zalutumumab with an active treatment arm.

Small-molecule EGFR tyrosine kinase inhibitors have also been investigated in SCCHN. The most studied agents are erlotinib and gefitinib. Several trials assessed the single agent activity of gefitinib, an anilinoquinazoline reversible EGFR inhibitor that has been shown to be effective as a single agent in SCCHN cell lines and tumor xenografts as well as a radiosensitizer agent. Its promising early results have not translated into a survival benefit in a randomized trial. In the R/M setting, a randomized phase III trial of gefitinib versus standard methotrexate including 486 patients.[36] Patients were stratified by whether they had received prior platinum-based chemotherapy (group A) or were too ill to receive such treatment (group B). Patients in each group were randomized to three treatment arms: oral gefitinib (250 or 500 mg daily) or intravenous methotrexate (40 mg/m$^2$ weekly with dose escalation to 60 mg/m$^2$ weekly) until disease progression. The overall response rates were 2.7%, 7.6%, and 3.9% in the gefitinib (250 and 500 mg) and methotrexate arms, respectively. The median overall survival was similar in the three treatment groups: 5.6, 6.0, and 6.7 months in the gefitinib (250 and 500 mg) and methotrexate arms, respectively. However, patients who received gefitinib experienced higher rates of tumor-related hemorrhage than those who received methotrexate, and gefitinib was associated with skin rash in 29% to 39% of patients and with diarrhea in 26% to 39%. When combined with conventional chemotherapy, also in the R/M setting, a phase III randomized trial of docetaxel plus placebo or docetaxel plus gefitinib 250 mg orally until disease progression was also reported.[37] Although there was a statistically significant difference in time to progression from 2 months with docetaxel/placebo to 3.5 months with docetaxel/gefitinib ($p = 0.03$), there was no increased overall survival.

In the locally advanced setting, gefitinib was further incorporated into the chemoradiotherapy regimen in 67 patients.[7] Two cycles of induction therapy with carboplatin and paclitaxel followed by FHX (5-FU, hydroxyurea, and radiotherapy on days 1 through 5 every 2 weeks for 5 cycles) and concomitant gefitinib 250 mg daily were administered, and gefitinib was continued for 2 years after the start of chemoradiotherapy. Grade 3 and 4 toxicities included mucositis (76% grade 3, 10% grade 4), dermatitis (29% grade 3, 3% grade 4), and diarrhea (1% grade 3, 0% grade 4). The majority of patients ($n = 62$) received maintenance gefitinib, and the median number of weeks on gefitinib was 95. The estimated overall 2-year survival was 83%, with PFS of 77%. Disease-specific survival at 2 years was 86%. The overall clinical response rate was 91%. These data further suggested a potential role for EGFR inhibition in combination with standard chemoradiotherapy regimens. Furthermore, maintenance gefitinib was feasible and this finding may support future chemopreventive strategies with EGFR-inhibitors.

Erlotinib is an orally available, potent, reversible, and selective inhibitor of the EGFR tyrosine kinase. In a large phase II trial including 150 patients receiving erlotinib 150 mg daily,[38] an overall response of 4.3%, median OS of 6.0 months, and median PFS was 9.6 weeks were noted. Given these results, one can conclude that erlotinib as a single agent is marginally cytoreductive in this patient population. When combined with cisplatin in a phase I/II trial, erlotinib 100 mg daily and cisplatin 75 mg/m$^2$ every 21 days[39] showed a response rate of 21%, with one complete response, eight partial responses, and disease stabilization in 21 patients (49%; 95% CI, 33%–65%). Median progression-free survival was 3.3 months (95% CI, 2.7–4.8 months), and median overall survival was 7.9 months (95% CI, 5.6–9.5).

Another single arm phase II study assessed 60 previously untreated patients with stage III or IV locally advanced SCCHN (60% with oropharynx tumors).[40] Patients received induction chemotherapy with 6 weeks of paclitaxel, carboplatin, infusional 5-FU, and bevacizumab; followed by concurrent chemoradiotherapy that included weekly paclitaxel, bevacizumab, and erlotinib. Radiation therapy began on day 1, with 1.8-Gy single daily doses, Monday through Friday, to a total dose of 68.4 Gy. Paclitaxel 50 mg/m$^2$ was administered by 1-hour intravenous infusion on day 1 and weekly for six consecutive doses. Bevacizumab 15 mg/kg, intravenous infusion, was administered on days 1 and 22. Erlotinib 150 mg daily began concurrently with radiation therapy and continued daily during the 7-week course of radiation. At 2 and 3 years, the estimated progression-free survival rates were 83% and 71%, respectively, whereas the 2- and 3-year overall survival rates were 90% and 82%, respectively. The investigators reported significant toxicities, with treatment breaks in 72% of patients, treatment noncompletion in 18%, two treatment-related deaths, and one myocardial infarction. In addition, 46 patients (76%) required enteral or parenteral nutrition during treatment. There are currently several clinical trials in progress assessing erlotinib for head and neck cancer. An interesting use of this agent has been in the chemoprevention setting. A clinical trial assessing erlotinib versus placebo as chemopreventive agents in a patient at high risk of developing SCCHN has finished accrual.

Lapatinib is an oral, small-molecule, reversible inhibitor of both EGFR and ErbB2. In a phase II trial in R/M SCCHN, oral lapatinib 1,500 mg daily was given to two groups of patients, those with and without previous exposure to an EGFR inhibitor.[41] In all the evaluable patients, no objective responses were observed in either cohort, and lapatinib appeared to have no activity in this disease setting. In an intent-to-treat analysis, SD was observed in 37% of patients without prior exposure, and 20%

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of those who had previously received an EGFR inhibitor. Thus, lapatinib appeared to have little clinical activity as a single agent in patients with SCCHN who were EGFR inhibitor naive or who had refractory disease. In the locally advanced setting, a phase II study including 107 therapy-naive patients were randomized (2:1) to receive 1,500 mg of oral lapatinib or placebo.[42] During the short duration (14 days) of lapatinib treatment, there was a statistically significant reduction in mean tumor cell proliferation index in patients who had received lapatinib compared to the placebo arm (−6% vs. −1.7%, respectively, $p = 0.030$), and 17% had a complete or partial response, compared with no responders on the placebo arm. A further randomized phase II trial comparing lapatinib (1,500 mg/day) or placebo with concurrent chemoradiotherapy followed by maintenance therapy with lapatinib or placebo in unresected LAHNC[43] showed a complete response rate at 6 months postchemoradiotherapy of 53% with lapatinib versus 36% with placebo. Furthermore, a phase III study (NCT00424255) is in progress to assess the benefit of lapatinib (1,500 mg) or placebo once-daily with radiotherapy and cisplatin for 7 weeks in high-risk SCCHN patients.

Other agents able to simultaneously inhibit cooperative signaling, such as EGFR and ERBB2, have been developed. Afatinib or BIBW292, an anilinoquinazoline derivative, is a highly selective, irreversible inhibitor of EGFR/HER1 and ERBB2. The open-label, phase II trial randomized 124 patients (median age 58.0 years, 87.1% male) to afatinib 50 mg/day, or weekly cetuximab 400 mg/m$^2$ loading dose followed by 250 mg/m$^2$/week until disease progression or treatment-related adverse events (AEs) (stage 1), at which point they could opt to cross over treatment arms (stage 2). Following stage 1, mean tumor shrinkage, the primary end point, was comparable for afatinib and cetuximab by independent central review. Objective response rate was 8.1% for afatinib and 9.7% for cetuximab ($p = 0.78$) and median progression-free survival was 13 weeks and 15 weeks ($p = 0.99$). The most common treatment-related AEs were diarrhea, 78.7% for afatinib versus 20.2% for cetuximab, and rash/acne, 78.7% versus 76.6%, respectively.

Preliminary results of a phase II study of afatinib versus cetuximab in 124 patients with platinum-refractory R/M SCCHN showed that following stage 1, mean tumor shrinkage, the primary end point, was comparable for afatinib and cetuximab, −16.6% versus −10.1% by independent central review ($p = 0.30$). Objective response rate was 8.1% for afatinib and 9.7% for cetuximab ($p = 0.78$) and median progression-free survival was 13 and 15 weeks ($p = 0.99$). Median PFS was 16 versus 10 weeks for afatinib versus cetuximab, respectively. In stage 1, most common treatment-related AEs were diarrhea, 78.7% for afatinib versus 20.2% for cetuximab, and rash/acne, 78.7% versus 76.6%,-respectively. For Stage 2, in which 68 patients crossed over arms (32 from afatinib and 36 from cetuximab), disease control rate was 33.3% (afatinib as second treatment) versus 18.8% (cetuximab second); duration of disease control was 17.3 versus 16.6 weeks. In the afatinib and cetuximab arms, 29.5% and 3.3% of patients had AEs leading to dose reduction, and 37.7% and 16.7% leading to discontinuation. Giving these promising results, a phase III trial of afatinib versus methotrexate in patients with platinum-refractory R/M SCCHN (NCT01345682) is planned, and a phase III trial of afatinib versus placebo as adjuvant therapy after chemoradiotherapy in patients with unresected locoregional SCCHN (NCT01345669) is recruiting participants.

Dacomitinib or PF-00299804 is an irreversible TKI of HER1, ERBB2, and HER4 which has demonstrated single-agent activity in a phase II trial of 69 patients as a first-line treatment in the R/M SCCHN, reporting an objective response rate (ORR) of 12.7%, median progression-free survival of 12.1 weeks and median overall survival of 35.9 weeks.[45] The most common grade 3 events were (3% of patients) diarrhea, fatigue, dermatitis acneiform, and hand–foot skin reaction.

In summary, EGFR inhibition has been a landmark in SCCHN, monotherapy has had limited success, mainly with cetuximab, and several inhibitors are still under development. Moving forward, two issues become of paramount importance in further developing this class in SCCHN. Given that virtually all SCCHN cases express EGFR, the first challenge lies in a better understanding of mechanisms of resistance to EGFR inhibitors. Secondly, simultaneous inhibition of other pathways, such as detailed later in this chapter, has been actively investigated and may further inhibit the molecular crosstalk between pathways.

## Insulin Growth Factor Receptor Pathway

The insulin-like growth factor system is composed mainly of the circulating ligands, insulin-like growth factor I (IGF-I), IGF-II, insulin, multiple receptors, and their binding proteins. Both preclinical research and clinical investigations have implicated the IGF-1R and its ligands in the development and progression of human epithelial tumors.[46] It has been shown that IGF-1R expression is increased in SCCHN compared to normal mucosal epithelia[47,48] and that IGF-1R signaling significantly promotes S-phase transition in a phosphoinositide-3-kinase/AKT and mitogen-activated protein kinase-dependent of human head and neck cancer cell lines.[47] It has also been shown that erlotinib and gefitinib induce heterodimerization of EGFR/IGF-1R, resulting in the activation of IGF-1R and induction of AKT/mTOR-mediated synthesis of survivin protein,[49,50] suggesting that targeting both IGF-1R and EGFR may be an effective approach. A recent case report also suggested that AMG-479, an IGFR-I receptor inhibitor, may have sensitized a previously cetuximab resistant tumor to further cetuximab therapy, as shown by its gene expression profile.[51] However, a study of CP-751,871 as monotherapy in R/M SCCHN was terminated due to lack of efficacy. A study of IMC-A12 with or without cetuximab in R/M SCCHN finished accrual and results are awaited.

## Hepatocyte Growth Factor and the c-Met (HGF/Met) Pathway

The receptor tyrosine kinase c-Met and its only known ligand, hepatocyte growth factor (HGF), also known as scatter factor, have become promising targets for new therapies. c-Met and HGF have normal physiological functions in regulating the embryonic development of a variety of organs.[52,53] Upon HGF binding, c-Met autophosphorylates and activates downstream several pathways including RAS-RAF-ERK, phosphatidylinositol 3-kinase-AKT-mTOR, and the signal transducer and activator of transcription (STAT) 3 pathway.[54–56] The Ras-mitogen-activated protein kinase (MAPK) signaling cascade, which operates as downstream effectors for the activated MET receptor, particularly, plays an essential role in cancer cell invasion by inducing epithelial-to-mesenchymal transition as a result of loss of intracellular adhesion by cadherins.[55] Small molecule tyrosine kinase inhibitors as well as antagonistic antibodies to either HGF or c-Met are currently being evaluated in phase I and/or phase II clinical trials for patients with advanced cancers, including SCCHN[57–59] PF-02341066 is an orally available selective Met competitor that has been shown to inhibit tumor cell growth *in vitro* and *in vivo*.[58,60] In a preclinical model, invasion of SCCHN cells induced by HGF derived from tumor-associated fibroblasts was completely blocked by a HGF-neutralizing antibody.[61] Further work by Seiwert et al.[62] showed that Met inhibition by PF-02341066 in SCCHN tumors disrupted Met signaling, cell viability, motility/migration *in vitro*, and tumor angiogenesis *in vivo*. Further, inhibition-of PI3K/AKT

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and MAPK by blocking either EGFR or c-Met may be overcome by activation of the other pathway, which may advocate for dual EGFR and c-met targeting. Thus, the combination of PF2341066 with the EGFR inhibitor gefitinib was assessed in SCCHN cell lines and the expression levels of EGFR and c-Met further determined by Western analysis and correlated with antitumor responses.[63] The inhibition of both pathways resulted in maximum antitumorigenic effects compared with single-agent therapy both *in vitro* and in a preclinical xenograft model. Inhibition of cell growth was also observed when combining a Met inhibitor with cisplatin or erlotinib, and synergy was hypothesized to be related to EGFR-3 signaling.

## Ras/Raf/MEK/ERK Pathway

An important downstream pathway of the EGFR family is via the Ras/Raf/MEK/ERK pathway. Although mutations in *ras* or *BRAF* genes are rare, with only approximately 3.5% of patients with locally advanced SCCHN presenting K-Ras codon 12 mutations,[64] members of the *ras* family are overexpressed in SCCHN[65–69] and *in vitro* evidence suggests that the level of K-Ras expression is a determinant of proliferation of SCCHN cell lines.[65] Thus, the EGFR-Ras-Raf-MEK-ERK signaling pathway in SCCHN is an attractive therapeutic target. Further, when coupled with the high levels of VEGF observed in EGFR-inhibitor resistant tumors and as the upregulation of VEGF levels by EGFR activation, agents that simultaneously inhibit the Ras-Raf-MEK-ERK and vascular factors are very promising.[70,71] The further combination of erlotinib and bevacizumab, a recombinant monoclonal antibody to the VEGF is described further in this chapter.[72]

Among the multikinase inhibitors, sorafenib is a multiple tyrosine kinase inhibitor, targeting VEGFR-2 and 3, platelet-derived growth factor receptor (PDGFR)-$\beta$, c-Kit, and RET, as well as inhibiting downstream Raf kinase isoforms (wild-type Raf-1, and B-Raf and mutant b-raf V600E).[73] A phase II Southwest Oncology Group trial assessed sorafenib as a single agent in 44 chemotherapy naive patients with R/M SCCHN.[74] With a median overall survival of 9 months (95% CI, 7–14 months) and progression free survival of 4 months (95% CI, 2–4 months), one patient (2%) had a confirmed and two had unconfirmed partial responses.

Another agent, sunitinib, was assessed in other two phase II studies in R/M SCCHN, also with disappointing results in several trials.[75,76] In the largest phase II trial, 38 patients with SCCHN having evidence of PD1 were treated with sunitinib 37.5 mg/day monotherapy given continuously until progression or unacceptable toxicity. A partial response was observed in only one patient and SD in 18, and disease progression in 19.[77] In summary, sorafenib and sunitinib have shown poor activity as single agents in R/M SCCHN, and caution should be exercised when embarking on trials of these agents in this disease.

## Mammalian Target of Rapamycin (mTOR) Inhibitors

The mTOR is a conserved serine/threonine protein kinase, belonging to the phosphatidylinositol kinase-related kinase (PIKK) family. The phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mTOR pathway has been implicated in proliferation, survival, angiogenesis, invasion, and metastasis of several cancers including SCCHN. Dysregulation of the PI3K/AKT/mTOR pathway occurs frequently in SCCHN and has been linked with poor outcome. Furthermore, AKT activation, PI3K accumulation, and PTEN down-regulation detected in SCCHN could reflect the early biochemical effects of tobacco components such as nicotine.[78,79] Rapamycin is an FDA-approved macrolide antibiotic derived from the bacteria *Streptococcus hygroscopicus*, commonly used as an immunosuppressant. To illustrate the importance of this pathway, the combination of enzaustarin, an AKT inhibitor, with rapamycin has been shown to have efficacy in cell lines and cause tumor shrinkage *in vivo*.[80] The rapamycin analogues temsirolimus (CCI-779), everolimus (RAD-001), and deforolimus (AP-23573) have been developed as cancer drugs. Temsirolimus is an ester of rapamycin that is available as an intravenous or oral formulation. *In vivo* studies using a mouse model demonstrated that even at the lowest possible dose, temsirolimus inhibited 70% of growth in SCCHN cell lines by 7 days and 80% by 21 days.[81] Everolimus is an oral mTOR inhibitor that is approved in Europe as an immunosuppressive agent for solid organ transplantation. Nine patients with SCCHN received escalating doses of everolimus in combination with cisplatin in a phase I trial, with one partial response.[82] A third mTOR inhibitor, ridaforolimus, can be delivered orally or intravenously. In a phase I study with deforolimus and capecitabine, 1 patient with advanced SCCHN was reported to have SD for $>4$ months.[83]

# TUMOR VASCULATURE

Angiogenesis, the process of forming new blood vessels to support growth in both normal and tumor tissues, is a hallmark of tumor progression. Vascular endothelial growth factor A (VEGF-A) is the best known agent that induce angiogenesis, belonging to the platelet-derived growth factor (PDGF) superfamily, which also includes VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor (PlGF). Several cytokines are produced in SCCHN that induce angiogenesis.[84,85] VEGF expression is regulated by hypoxia-inducible factor-1$\alpha$ (HIF-1$\alpha$) dependent and independent mechanisms involving PI3-K and AKT. HIF-1$\alpha$ levels rise rapidly under hypoxic conditions and induce the transcription of multiple genes including VEGF, endothelin-1, and c-Met.[86] The vascular growth factor receptor (VGFR) tyrosine kinases VGFR-1, VGFR-2, and VGFR-3 also play an important role, and VEGFR-2 is the most important one through which VEGF exerts its vascular permeabilizing effects on endothelial cell.[4] In SCCHN, a meta-analysis of 12 studies including 1,002 patients affected by cancer of oral cavity (70.8% of patients), pharynx (15.2%), and larynx (14%), VEGF expression detected by immunohistochemistry was evaluated, and its positivity was associated with a 1.88-higher risk of death at 2 years.[87] In addition, resistance to EGFR inhibitors in preclinical models has been associated with upregulation of VEGF.[71]

The humanized recombinant monoclonal antibody to the VEGF bevacizumab has been the most studied antiangiogenic agent and several studies have been performed. The combination of bevacizumab and an EGFR inhibitor has been initially assessed in a phase I/II in R/M SCCHN.[72] The phase I study was designed to determine the maximum tolerated dose of bevacizumab when associated to erlotinib: erlotinib was given at dosage of 150 mg/daily, while bevacizumab was administered in escalating dose cohorts. In the phase II portion, 48 patients were assessed for response, the best observed response included complete or partial response in 7 patients (15%; 95% CI, 6–28) and SD in 15 patients. Four patients achieved a complete response with duration of response that lasted up to 17 months in one patient. The median overall survival was 7.1 months (95% CI, 5.7–9.0), with 15 patients surviving 1 year, and the median progression-free survival time was 4.1 months (2.8–4.4). The most common toxic effects of any grade were rash and diarrhea (41 and 16 of 48 patients, respectively). Three patients had serious bleeding events of grade 3 or higher, one of which was fatal, ascertained at autopsy to be laryngeal in origin, but not at a site of active disease. In an exploratory analysis, high phosphorylated

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VEGFR2/VEGFR2 and endothelial cells phosphorylated EGFR/EGFR ratios in baseline tumor specimen identified patients with the greatest probability of response to erlotinib and bevacizumab. Another trial evaluating bevacizumab and cetuximab revealed a partial response in 5 (20%) and SD in 14 (56%) of 25 evaluable patients.[88,89] In these two studies, patients were allowed up to one prior regimen for their R/M disease. When bevacizumab was combined with the antifolate pemetrexed in previously untreated R/M disease in a phase II trial, an interim analysis showed an overall response of 36%.[90] In 22 evaluable patients, 3 (14%) had complete response, 5 had (23%) partial response, and 13 (59%) SD. Two deaths were reported, one from sepsis in a neutropenic febrile patient and another from tracheal bleeding in a previously reirradiated area triggered by suctioning. Three hemorrhagic events were reported.

In the locally advanced setting, Seiwert et al.[91] performed a phase 1 study where bevacizumab was added to fluorouracil and hydroxyurea-based chemoradiotherapy (BFHX) in patients with relapsed previously irradiated SCCHN or with poor prognosis of newly diagnosed disease. Forty-three patients were treated: 29 patients (67.4%) were previously irradiated, while 14 patients (32.6%) were newly diagnosed. Dose-limiting toxicities were reached at level 3 (bevacizumab 5 mg/kg, FU 800 mg/m$^2$, HU 1,000 mg), with two grade 3 transaminase elevations and one grade 4 neutropenia, attributed to the combination of chemotherapy with bevacizumab. For level 4, chemotherapy doses were reduced (FU 600 mg/m$^2$, HU 500 mg), and bevacizumab escalation continued to 10 mg/kg. After chemotherapy dose de-escalation (level 4) no neutropenia occurred. The adverse events probably related to bevacizumab were grade 3 hypertension in 3 patients, 1 allergic rash reaction, 2 deep vein thrombosis, 1 stroke, and 2 fatal hemorrhages. The median OS of the patients enrolled was 10.7 months. Patients with no prior radiation had a significantly longer OS (40.1 months) than those with prior radiotherapy (9.2 months). Further, with the hypothesis that BFHX with twice-daily radiotherapy would be adequate for T4N0-1 and provide locoregional control rates similar to historical controls, a randomized phase 2 study of FHX with or without bevacizumab was performed.[92] This study was closed early due to an increased locoregional failure rate in the experimental (BFHX) arm, with all four locoregional progression cases occurring in T4 tumors randomized to BFHX. Two-year survival was 89% for those treated with FHX and 58% (95% CI, 33%–78%) treated with BFHX. Two patients receiving BFHX died during therapy, and one died shortly after therapy. No catastrophic bleeding events were seen. Further, the addition of bevacizumab to FHX required dose reductions on both 5-FU and hydroxyurea compared with standard FHX. The reduced doses of cytotoxic chemotherapy in the FHX plus bevacizumab regimen could be determinant with regard to the increased incidence of locoregional failure, although the small sample size (26 patients) in the phase 2 study precludes definitive conclusions. Alternatively, there is a possibility that the combination of bevacizumab with FHX decreased the efficacy of the regimen, given that prior FHX regimens including a third systemic agent demonstrated that T4 tumors had locoregional control rates of 71% to 75%.[93,94]

The combination of an EGFR inhibitor with bevacizumab has also been reported in the locally advanced setting.[95] In a single arm, nonrandomized study in newly diagnosed patients with stage III/IV, patients received a 2-week regimen consisting of bevacizumab 10 mg/kg and/or erlotinib 100 mg daily, followed by both agents with concurrent cisplatin and twice daily radiotherapy. Twenty-nine patients were enrolled on study, with 27 completing therapy. Common grade III toxicities were mucositis ($n$ = 14), dysphagia ($n$ = 8), dehydration ($n$ = 7), osteoradionecrosis ($n$ = 3), and soft tissue necrosis ($n$ = 2). Median follow-up was 46 months in survivors, with 3-year locoregional control and distant metastasis-free survival rates of 85% and 93%. Three-year estimated progression-free survival, disease-specific survival, and overall survival rates were 82%, 89%, and 86%, respectively.

Bevacizumab has also been added to the widely common regimen consisting of concurrent high-dose cisplatin and definitive intensity-modulated radiation therapy (IMRT) in patients with stage III through IV SCCHN.[96] Forty-two previously untreated patients (39 patients with oropharyngeal carcinoma and 3 with laryngeal carcinoma) were treated with IMRT (70 grays) with concurrent cisplatin (50 mg/m$^2$ on days 1, 2, 22, 23, 43, and 44) and bevacizumab (15 mg/kg on days 1, 22, and 43). Human papillomavirus (HPV) status was determined by *in situ* hybridization (HPV positive, 16 patients; HPV negative, 14 patients, unknown HPV status, 12 patients). The most common grade ≥3 adverse events were lymphopenia (100% of patients), mucositis (86% of patients), throat pain (74% of patients), and neutropenia (43% of patients). There were two treatment-related deaths, including 1 sudden death and 1 death from aspiration pneumonia. With a median follow-up of approximately 31.8 months (range, <3–51 months), the 2-year PFS rate was 75.9% (95% CI, 63.9%–90.1%), and the 2-year OS rate was 88% (95% CI, 78.6%–98.4%).

Vandetanib (ZD6474) has shown potent, selective activity against VEGF receptor-2 and has activity against EGFR and rearranged during transfection (RET) tyrosine kinases. Vandetanib has been shown to reduce invasion of SCCHN cell lines, where its antitumor effects seemed to be exerted via its EGFR inhibitory.[97] In cisplatin and radiation-resistant SCCHN cell lines, treatment with vandetanib, cisplatin, and radiation alone or in combination *in vitro* and *in vivo* showed that vandetanib plus cisplatin radiosensitized SCCHN cells *in vitro* and *in vivo*.[98] Further, the combination treatment with vandetanib, cisplatin, and radiation was superior to the rest of treatments (including the double combinations) in antitumoral effects, prolonging survival, decreasing cervical lymph node metastases *in vivo*. Clinical trials assessing vandetanib as monotherapy and in combination with chemotherapy are in progress. An interesting hypothesis currently being tested in a randomized placebo-controlled phase II study is that vandetanib will inhibit angiogenesis in preneoplatic tissues compared to placebo as a chemopreventive agent. Patients at high risk for oral squamous cell carcinoma are currently being enrolled in this trial.

In summary, the addition of angiogenesis inhibitors has been feasible in most studies, and encouraging efficacy has been found in comparison with historical controls. However, this comparison may prove difficult in view of the higher incidence of HPV-positive oropharyngeal tumors with a more favorable prognosis present in current studies. Thus, the potential benefit of these drugs, mainly bevacizumab, as either a radio or chemosensitizer is still unknown. Active ongoing research has been done in identifying predictive biomarkers, such as functional imaging techniques, which may allow the selection of patients who may benefit from this approach.

## PARP-Inhibitors: the Chemo/Radiosensitizers

With respect to chemotherapy and radiotherapy modifiers, a promising new area investigation is the use of poly (ADP-ribose) polymerases (PARP) inhibitors (PARPi) to improve both cytotoxic modalities. PARP is involved in several forms of DNA repair including single and double strand break (DSB) repair as well as base excision repair. PARP-1 is the principal isoform involved in the cellular process,[99] whereas PARP-2 and other PARP members constitute the residual activities (10%) when PARP-1 is inhibited. The concept of "synthetic lethality" is applied when targeting

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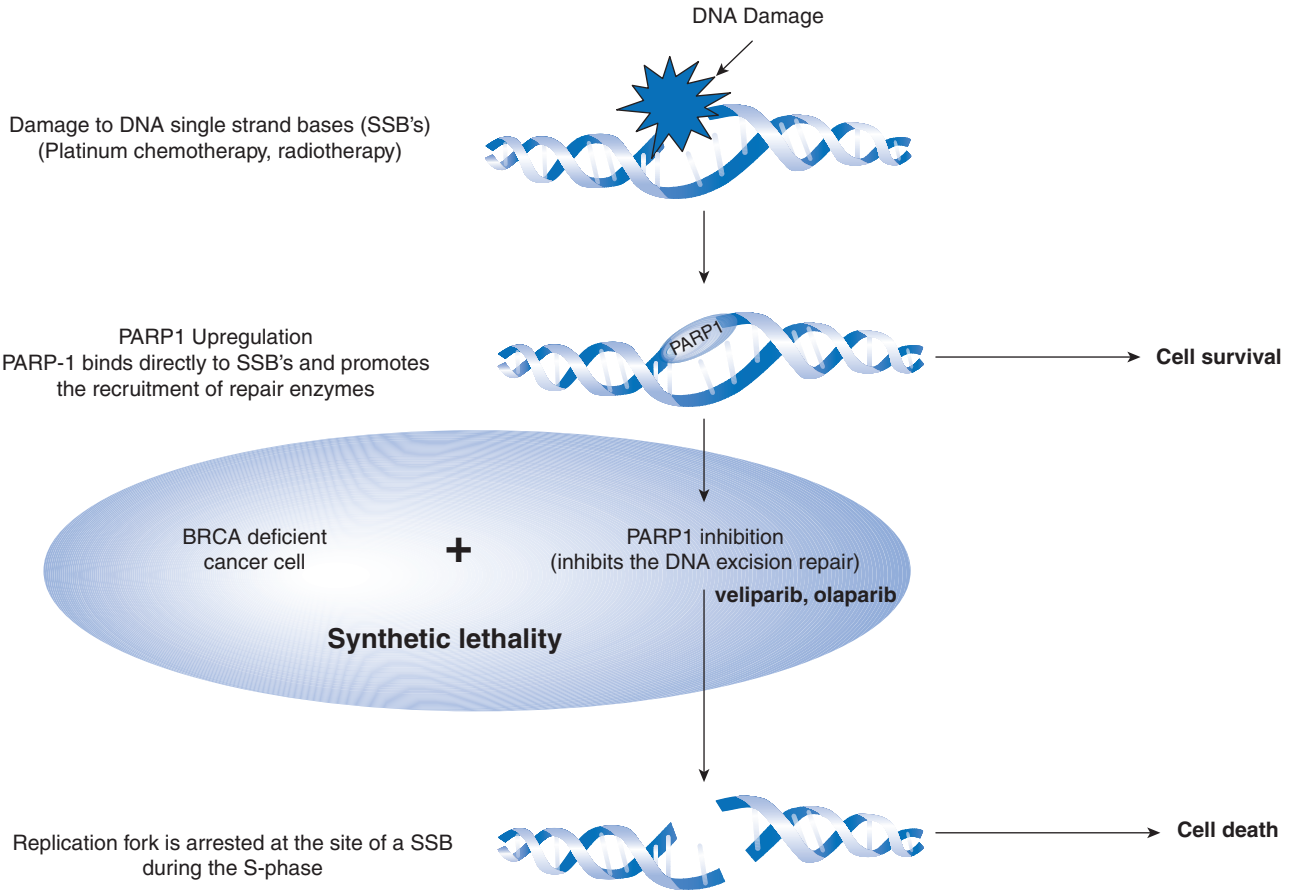



**FIGURE 7-2.** Schematic illustration of synthetic lethality. Synthetic lethality consists of killing cells with a specific DNA repair defect by inhibiting a second DNA repair pathway. In normal replicating cells, double-strand breaks are repaired by the homologous recombination (HR) pathway. BRCA1 or 2 are necessary for the HR pathway to function. The inhibition of a second DNA repair mechanism through PARP inhibitors would promote cell death.

cells with a specific DNA repair defect by inhibiting a second DNA repair pathway, as shown in Figure 7-2. In other words, targeting one of the mechanisms cancer cells use to escape the toxic effect of chemoradiotherapy by altering the ability of cancer cells to activate PARP-related repair can improve cytotoxic effects. This concept has become an important model for the use of PARPi in breast and ovarian cancer patients. Patients defective in BRAC1 and BRAC2 mediated homologous repair are proposed to be sensitive to PARPi which block the nonhomologous repair pathway. Further, in addition to BRCA-1 and -2 proteins, RAD51, RAD54, DSS1, RPA1, NBS1, ATR, ATM, CHK1, CHK2, FANCD2, FANCA, and FANCC have been related to increased sensitivity to PARP inhibition through defective DNA damage repair.[100]

Pre-clinical data have been recently obtained for this class of agents in SCCHN. In one study, the inhibition of DNA repair by the PARP inhibitor GPI-15427 induced significant sensitization to radiotherapy in a xenograft mouse model of SCCHN.[101] Another recent study showed that cetuximab enhances cytotoxicity with ABT-888 in SCCHN cells.[102] This increased cytotoxicity was achieved by cetuximab-mediated reduction of nonhomologous end-joining (NHEJ)- and homologous recombination (HR)-mediated DNA DSB repair, the consequent persistence of DNA damage, and further activation of the intrinsic apoptotic pathway. Several clinical trials are assessing the use of PARPi in combination with radiotherapy. Finally, the effects of olaparib and radiation were assessed in the BRCA1/BRCA2 wild-type SCCHN cell lines, and both radiation and olaparib alone induced DNA damage, and the combination of olaparib and radiation significantly enhanced this response.[103] Several trials with this class of agents in SCCHN are expected in the near future.

## CONCLUSION

In the era of personalized medicine, patients with recurrent/metastatic SCCHN not amenable to curative treatment still have a dismal prognosis with a median survival of around 8 to 10 months. Those patients with locally advanced disease often receive treatments with life-long, lasting toxicities. At the same time, the increased understanding of the biology of cancer and the availability of new technologies, such as microarrays, proteomics, and novel imaging, has allowed the identification of several molecular targets for cancer drug development, with the promise of increasing survival endpoints with more acceptable toxicities. However, the overwhelming number of new drugs and the nonlinear interactions and multiple redundant feedback loops occurring among the key targets in signaling pathways emphasize the challenges to this field. This is exemplified by the fact

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that despite all the agents discussed in this chapter, cetuximab is the only FDA-approved targeted therapy for use in SCCHN.

The way forward inevitably lies on two fronts: the successful development of predictive biomarkers and the reassessment of endpoints in clinical trials. The discovery and development of predictive biomarkers, linking drug discovery to predictors of efficacy early during the agent's research and development phase, would allow these therapies to be used in the subpopulations of patients most likely to benefit from them. For example, a promising technique is mass spectrometry-based proteomics. Chung and colleagues[104] looked at 108 pretreatment serum or plasma of recurrent/metastatic SCCHN tumor samples of patients treated with gefitinib, erlotinib/bevacizumab, or cetuximab. These patients were categorized into good or bad prognosis groups using a MALDI-MS algorithm validated in non–small cell lung cancer. The classification algorithm generated predicted OS benefit in two cohorts: (a) Patients in the good prognosis group having significantly longer OS time compared to the patients in the poor prognosis group: gefitinib-treated patients ($p = 0.007$; HR, 0.41; 95% CI, 0.22–0.79); and erlotinib/bevacizumab treated patients ($p = 0.02$; HR, 0.20; 95% CI, 0.05–0.78). The OS of the cetuximab-treated cohort showed a trend toward statistical significance ($p = 0.06$; HR, 0.26; 95% CI, 0.06–1.06). Beyond identifying patients who may benefit from these therapies, one may argue that identifying the patients who will not benefit from these therapies is equally, if not more, important. Finally, particularly important in individuals with a disease whose cure comes at a high personal and financial cost, as long-term survival becomes more frequent in SCCHN, these agents must also be evaluated from the patient's quality-of-life and financial perspective, and these outcomes should be increasingly incorporated in clinical trials.

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CHAPTER 8

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# Multidisciplinary Reconstruction of the Head and Neck: General Principles

As the management of head and neck cancer has evolved over the last decade, so too has the reconstruction of defects created by ablative surgery. Because of the level of confidence in transferring tissue of various types, thickness, and dimensions to achieve the desired goal, the overall level of sophistication has increased in the various subsites that are restored. As head and neck reconstructive techniques have evolved from the era of pedicled flaps to that of free tissue transfers, the focus has become less of simply covering a defect or "closing a hole" but rather addressing the multifactorial problems of restoring a region to a level of form and function that best replicates the predisease state.

The last two decades have been dominated by the application of microvascular surgery to the head and neck; the early emphasis was on discovering new donor sites for hard and soft tissue and later on a more detailed understanding of the recipient site required to select the best reconstructive technique. Just as head and neck cancer demands a multidisciplinary approach that tailors the treatment of the disease, so too does the reconstructive component in which there is a need for several disciplines working in a collaborative manner. The reconstructive/rehabilitative team should include a reconstructive surgeon, an oral and maxillofacial surgeon, an oral and maxillofacial prosthodontist, an oculoplastic surgeon, and a speech pathologist. Preoperative assessment of each patient by the appropriate disciplines helps ensure that all considerations are taken into account before embarking on the implementation of the reconstructive plan. A careful assessment of the tumor and a prediction of the anticipated three-dimensional defect will help the team anticipate the need for hard and soft tissue as well as prosthodontic rehabilitation. The reconstructive team must determine the goal for each individual patient, which is a balance determined by the components of the defect, the biology of the disease, the comorbidities and motivation of the patient, the wound-healing properties of the recipient site determined by exposure to prior therapy, the patient's nutritional status, and their continued usage of alcohol and tobacco. The goals, therefore, may vary for different patients faced with the same subsite defect because of these variables. If bone is to be a part of the reconstruction, then determination of the method of fixation must be established to ensure flap stability until bony union has occurred. In pediatric patients, there are special considerations related to the impact of bone harvest on the donor site. In addition, there is often a preoperative plan to remove fixation hardware in the early postoperative period, so that growth of the maxillofacial skeleton can continue unencumbered by rigid framework. Meticulous execution of the reconstructive plan must be followed by the appropriate rehabilitative therapy to maximize the recovery of function. The reconstructive team must be dynamic in its approach so that unforeseen circumstances that arise can be addressed during surgery. A positive surgical margin, for example, can substantially alter the reconstructive plan; a larger flap or even one from a different donor site may be required to accomplish the desired goal. Outcome measures specific to each subsite should be critically evaluated to determine the level of functional recovery. The monitoring and evaluation of function that results from reconstructive efforts are essential to the continued progress of these sophisticated and essential techniques. The continued refinement of approaches and the determination of the optimal reconstructive strategies depend on it. Centers vary their approach based on the collective experience and professional expertise within their respective institution, ideally based on this process of critical assessment of the outcome of their reconstructive approach.

The classification of defects is a critical undertaking that allows the reconstructive team to organize its approach to a particular subsite and to communicate, predict, and evaluate functional outcomes. Just as cancer staging provides a common lexicon for treating physicians that leads to therapy selection, prognostication, therapeutic outcomes, and to grouping of similar patients for outcomes analysis, defect classification does the same in head and neck reconstruction. The staging systems that are used to define cancers in particular subsites of the head and neck do not allow sufficient definition of the defect to permit accurate treatment planning. The size of an oral cancer and whether it has invaded mandible or maxilla determines the T stage for that cancer, but it does not provide the necessary ingredients for an accurate selection of the optimal reconstructive technique. This is determined by predicting what soft tissues and how much bone is to be removed. By estimating this, a more meaningful determination of what tissues must be harvested to restore form and function. Cancers of similar dimensions arising in the tongue and the buccal mucosa may lead to similar oncologic staging, but create very different demands for the reconstructive endeavor. Similarly, invasion of bone of the hard palate and the mandible may lead to a comparable T4 oncologic stage, but very different needs and strategies for functional reconstruction/rehabilitation. Moreover, different portions of the mandible and the presence of dentition will lead to very different reconstructive considerations that must be accounted for in the classification of that defect, none of which is addressed in the tumor staging.



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The desirability of using prosthetic restoration, whether it be for dental, auricular, nasal, ocular, or facial restoration, must be determined in the early stages of treatment planning and must be communicated to the patient in a very thoughtful discussion in which they are allowed to articulate their concerns regarding the use of prosthetics versus native tissue to achieve the final goal. Although the restoration of dentition with a conventional denture or more favorably with an implant-supported prosthesis is very well accepted, patients, more often than not, have very strong feelings regarding the application of a prosthetic solution, instead of their own tissues, for restoration of a part or all of the ear, nose, or face. In the past, the concern about loss of retention of the prosthesis to the facial tissues often led to less favorable patient satisfaction. This has largely been overcome by the application of osseointegration and fixation to achieve prosthetic stability and retention. However, there remains a significant bias by patients regarding the use of a prosthetic nose or ear that may lead them to select reconstruction, albeit with the acceptance of a less favorable aesthetic result. It is imperative that the reconstructive team embarks on very frank discussions with the patient and his or her family regarding the availability of a skilled prosthodontist and a skilled reconstructive surgeon with experience in restoring the particular defect at issue. Patients with devastating defects must be provided realistic counsel and perhaps offered alternative centers to undergo treatment. If implants are to be placed to achieve the desired outcome, then consideration must be given to the volume and quality of the underlying bone, the quality of the overlying soft tissue, and the timing of implant placement with respect to the institution of adjuvant radiation. Radiation alters the process of osseointegration and, therefore, compromises the overall success of the implants. Discussion of implant placement and radiation will be provided later in the chapter.

Although much of the emphasis in contemporary head and reconstruction surgery is placed on achieving an optimal restoration, the ability to shorten the recovery from ablative/reconstructive surgery has significant implications for the outcome of the cancer treatment. It is therefore essential for the reconstructive team to outline a restorative strategy that achieves a suitable "packaging" of the entire surgical treatment and recovery in an appropriate time period. The achievement of these goals depends, of course, on the performance of these reconstructive efforts by experienced teams of experts who are able to accomplish this in a predictable and reproducible manner.

The debate of whether it is more appropriate to perform a delayed or primary reconstruction has been waged over the past several decades as primary reconstruction has emerged as a highly predictable and reliable technique. The notion that a delay in reconstruction helps to make patients appreciate more fully the delayed reconstructive efforts may be valid in select subsites such as the nose and the auricle. More often than not, however, such an approach leads to inferior reconstructive results for mandible and maxilla, where primary reconstruction offers superior outcomes. The use of surveillance imaging performed in a sequential manner during the posttreatment period provides a useful method of monitoring the reconstructive site once the bone has been placed to restore the defect. Granted, the hardware that is used to achieve rigid fixation somewhat distorts, and therefore compromises the images, but despite these associated problems the value of improved function and dental rehabilitation that can be achieved by primary reconstruction far outweighs the drawbacks. Specific functional outcome studies for each of these two subsites will be discussed in detail later in the chapter.

In addition to the variables specific to the patient, the selection of donor sites for both hard and soft tissues will be influenced greatly by the experience level of the reconstructive team. The adage that "simple is better" continues to have relevance in reconstructive decision making, that is to say, the concept of starting with simple and moving to complex methods should be considered for each reconstructive challenge. Although selection of a *simpler* technique may utilize a less demanding procedure, it is imperative that all aspects of that procedure be anticipated and understood. A good example of that planning discipline is the decision-making process for reconstructing the floor of mouth. Although it may be tempting to use a split-thickness skin graft for the sake of expediency, the surgeon and the patient must understand the implications of failure of "graft take" on the mobility of the tongue and the architecture of the oral cavity. It must be understood that if an untoward outcome such as loss of a graft should occur, then wound contracture will result in a compromised functional result that can only be partially corrected by further reconstructive efforts.

There are a number of regional flaps that continue to play an important role in the management of patients with head and neck cancer. Certain donor sites, such as the forehead were commonly used as a source of flaps for head and neck reconstruction in the 1960s, but are rarely utilized in contemporary reconstruction. There does, however, remain an important role for the pectoralis major flap, the deltopectoral flap, the trapezius flap(s), and the latissimus dorsi flap. Additionally, there are newer regional sources of soft tissue such as the submental flap, the temporalis and temporoparietal flaps, and the posterior scalping flap. The role of regional flaps serving as carriers for vascularized bone has largely been eliminated due to the emergence of flaps harvested from the fibula, the scapula, the iliac bone, and the radius, which are all much more reliable donor sites for the restoration of the maxillomandibular skeleton.

In the contemporary era of head and neck cancer management, there are certain subsites such as the oropharynx and the laryngopharynx in which ablative surgery is usually reserved for the salvage setting or for less common types of neoplasms such as those arising from the minor salivary glands. There are centers where primary surgery, whether endoscopic, robotic, or open, is applied. It is safe to say, however, that for both the oropharynx and the laryngopharynx, the role of surgery is usually relegated to failures of primary radiation with or without chemotherapy. There are special considerations when performing reconstruction in a patient who has severely compromised tissues as a result of extensive prior treatment. An increased likelihood of wound breakdown and salivary fistula must be accounted for in the reconstructive strategy, and every effort to prevent these sequelae should be instituted. This usually includes the importation of healthy muscle to provide coverage of the carotid artery as well as the microvascular pedicle if a free flap has been transferred; this muscle may come with the free-flap donor site or may require a second donor site, often the pectoralis major muscle flap (Fig. 8-1). There are additional issues related to the availability of recipient vessels in patients who have undergone extensive prior surgery that often makes the conventional recipient vessels unsuitable for use in a microvascular transfer. Knowledge and experience in harvesting recipient vessels, such as the thoracoacromial vessels or the internal mammary artery and vein, are sometimes required to achieve a successful reconstructive result.[1,2]

In keeping with the organization of much of this book, this chapter has been organized according to the various subsites of the head and neck. In each subsite discussion, the major considerations for reconstruction and the defect classification scheme that the authors feel best defines the extent of the reconstructive problem will be presented. In addition, functional outcomes studies, when available, will be reviewed to help understand the impact of the reconstructive techniques on the functional recovery of the patient. A section covering various topics in maxillofacial prosthodontics will be presented to complete a comprehensive

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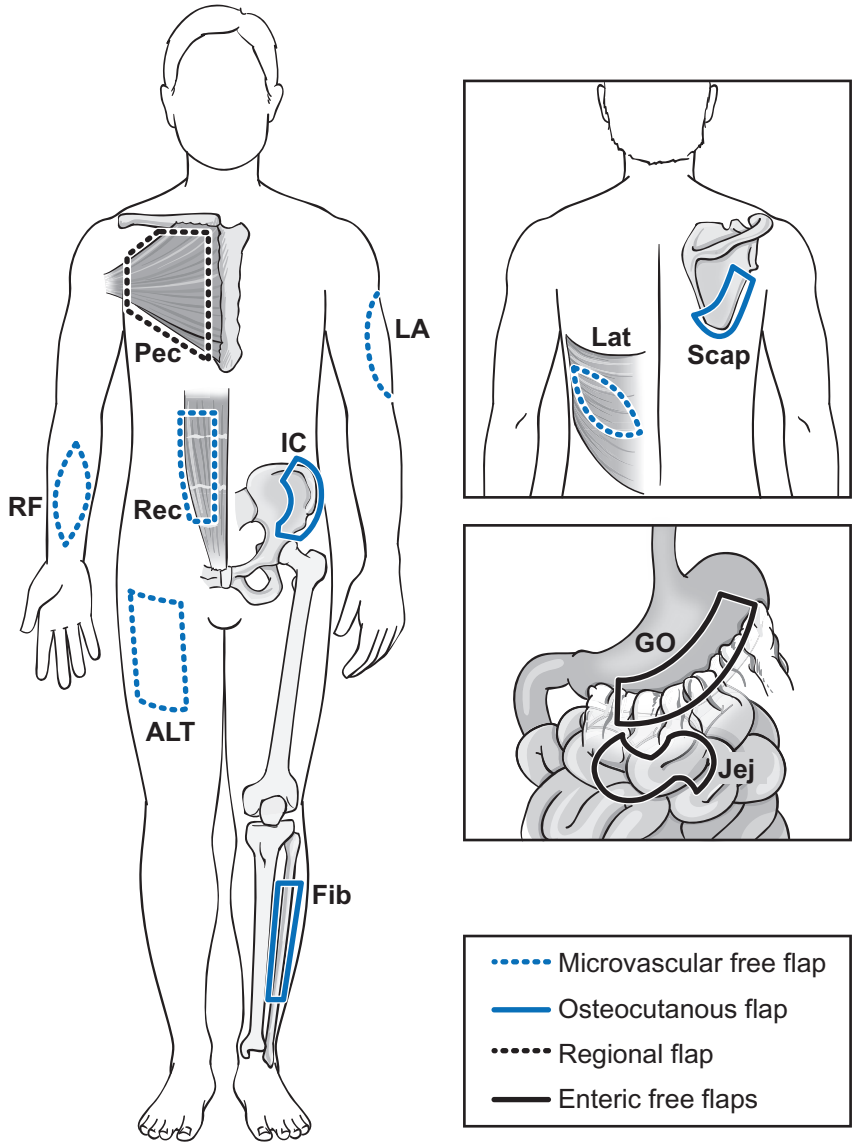



**FIGURE 8-1**. Types of regional and free microvascular, osteocutaneous, and enteric flaps. (See color insert.)

discussion of contemporary head and neck reconstruction/rehabilitation. Unfortunately, the constraints on the length of this chapter do not permit every subsite to be presented. The authors have selected the most common subsites and the topics in which new data are available since the publication of the prior edition of this text.

## ORAL CAVITY RECONSTRUCTION

### Tongue

From the perspective of oral function, the tongue is undoubtedly the most important structure within the oral cavity and its substance and mobility should be preserved whenever possible. Under all but the most extraordinary circumstances, the tongue should not be utilized as a source of mucosa for reconstruction of defects of the oral cavity. In contemporary head and neck cancer management, the oral cavity and therefore cancers of the mobile tongue, the floor of mouth, the gingiva, the palate, and the buccal mucosa are most frequently managed by primary surgery. Although in most centers the treatment of base of tongue squamous cell cancers is by radiation, with or without chemotherapy, there are circumstances in which salvage surgery and treatment of nonsquamous cancers requires the resection and reconstruction of the tongue base. Usually the latter resections include portions of the oropharynx and occasionally the supraglottic larynx. Extirpation of mobile tongue and floor of mouth cancers can be done very effectively and in a manner that preserves oral function. The decision as to whether the mandible should be included in the resection, in the form of a marginal or segmental resection, is discussed in detail in Chapter 16.

### Classification of Glossectomy Defects

Several years ago, the authors' team established a defect classification scheme for glossectomy defects that was designed to assist with the communication between clinicians, to assist with treatment planning, and to allow clinicians to determine the prognosis for functional recovery based on the extent of the tongue removed and the integrity of the innervation to the remaining tongue.[3] At that time, the tongue was divided into mobile and base of tongue defects and further subdivided into quarters to help quantify the extent of the resection. The status of

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the motor (hypoglossal) and the sensory (lingual) nerve supply to the tongue was also included in that scheme.

One of the premises of any reconstructive scheme is that the subdivisions are reflective of the contemporary techniques that are available for reconstruction. Toward that end, the authors have since modified the classification scheme to better reflect the reconstructive approach currently in use.

The separation of the tongue base and the mobile tongue has been retained, and the authors have further subdivided the mobile tongue into the following defects: minimal glossectomy defects that do not involve the floor of mouth, minimal glossectomy defects that do involve the floor of mouth, subtotal glossectomy defects that preserve a portion of the mobile tongue that has intact muscle and an intact nerve supply, and total mobile tongue defects. The total mobile tongue defect is further subdivided into those with an intact mandible and defects that are associated with a segmental mandibulectomy. The base of tongue is divided into three categories of minimal glossectomy, subtotal glossectomy, and total base of tongue resection. Finally the total glossectomy defect is subdivided between those that have an intact mandible and those that are combined with a segmental mandibulectomy.[4]

## Goals of Reconstruction of the Tongue

The fundamental goals of reconstruction of the tongue are to restore the patient's ability to swallow without aspiration and to form words with the greatest possible clarity. Conversational speech both in person and by telephone can be accomplished with a level of effectiveness that permits the patient to resume his or her premorbid quality of life (QOL). There are important components that assist toward that end. Retention of tongue mobility is critical to success and when there is a portion of the tongue that retains a motor supply, then the goal is to restore the missing part with redundant tissue so as to prevent tethering of the tongue to the inner table of the mandible or to the floor of mouth. Restoration of sensation is also an important goal in surgery and assists in giving the patient valuable feedback as to the location of food particles in the oral cavity. With this capability, the patient is better able to move those particles between the occlusal plane for mastication and propel them posteriorly to initiate the pharyngeal phase of deglutition. One of the key goals of restoring larger glossectomy defects is to match the neotongue to the volume of the oral cavity and the pharyngeal chamber. Therefore, any loss of movement can be compensated for by the restoration of volume that preserves the ability of the tongue to contact the palate and the walls of the pharynx, respectively.

## Reconstructive Options

Restoration of mobile tongue defects depends greatly on the amount of the tongue that is resected and whether the floor of mouth mucosa has been preserved. The major consideration noted earlier is related to the preservation of movement and the restoration of volume, which becomes a more significant concern when the size of the defect increases and when the anticipated loss of mobility of the tongue is greater. For minimal glossectomy defects that do not involve the floor of mouth, primary closure provides a simple and effective means of restoring function. However, for minimal glossectomy defects that include the floor of mouth, there is a need to introduce thin pliable tissue to prevent tethering that would otherwise occur with primary closure to the gingival tissue. The workhorse reconstruction for that purpose is the radial forearm free flap that usually provides the thinnest available tissue and which provides excellent lining for the oral cavity (Fig. 8-1). This donor site has a well-defined sensory distribution and large sensory nerves (the medial and the lateral antebrachial cutaneous nerves) that are easily incorporated in the harvest of tissue from the volar surface of the forearm.[5]

As mobile tongue defects increase in size, the need for more tissue is balanced by the integrity of the motor nerve supply and the amount of muscle in the tongue remnant. Through the incorporation of de-epithelialized segments of the forearm soft tissue, bulk can be added to the reconstruction by placing that vascularized subcutaneous tissue under the skin which is used to reline the tongue and the floor of mouth.[3] Alternative donor sites such as the lateral arm flap and the anterolateral thigh (ALT) flap (Fig. 8-1) provide an opportunity to transfer skin with more subcutaneous tissue than is usually present in the radial forearm donor site.

After resection of the total mobile tongue and a segment of the mandible, the reconstruction of the oral cavity requires two separate but integrated strategies for replacing the bone and the soft tissue. In this type of reconstruction, the goal is to match the volume of the neotongue with the volume of the oral cavity. Alternatively, a palatal prosthesis can be used but that involves coverage of the intact palate and the loss of a valuable source of sensate mucosa. One approach that the authors have adopted is the transfer of an iliac crest free flap (Fig. 8-1) with the associated skin paddle and placing that bone in a horizontal orientation so that it serves as a platform for support of the soft tissue. Although this is opposite the usual orientation of the iliac bone (placing it vertically for restoration of the mandibular alveolus), the technique provides valuable support of the neotongue reconstruction with a rigid platform that helps to prevent caudal migration of the soft tissue. Therefore, long-term contact between the neotongue and the palate is achieved.[6]

For total mobile tongue resections with an intact mandible, the technique that the authors employ is to transfer a large soft tissue flap that is inset in a manner that places the soft tissue above the occlusal plane. Achieving long-term stability of that reconstruction, so that gravity does not lead to a decrease in the height of the neotongue, requires a number of intraoperative maneuvers that simulate the strategy noted earlier whereby the goal is to maintain contact of this static reconstruction with the palate. One such maneuver was noted earlier where the introduction of supplemental soft tissue under the skin provides added bulk that is preserved due to the fact that it is vascularized tissue. In addition, suturing the supplemental tissue to drill holes in the lower border of the mandible helps to form a platform to support the overlying neotongue. The authors described the use of a rectus abdominus flap (Fig. 8-1) where the anterior rectus sheath is sutured to the lower border of the mandible and thereby all of the soft tissue above that fascial layer is supported. The muscle component that the authors anticipate will atrophy is below the fascia and does not contribute to the anticipated bulk.[6]

The reconstruction of the base of tongue is very similar to that of the mobile tongue with respect to the goal of achieving primary closure when possible and the introduction of increased bulk to match the volume of the pharyngeal chamber. In the salvage setting, the performance of surgery in this region involves more liberal indications for introducing vascularized tissue to aid the wound-healing process that usually has been substantially compromised by radiation therapy. These defects often involve adjacent anatomic structures, such as the pharyngeal walls and the soft palate (SP), all of which must be addressed at the same time. Primary closure of smaller pharyngeal defects with native tissue helps narrow the caliber of the chamber that places less of a demand on the base of tongue. The restoration of this region has greater functional implications for the patient with respect to safe and effective swallowing. The more efficient the swallowing, the less likely the patient is to aspirate, which when significant can lead to dependence on alternative routes of enteral alimentation such as a gastrostomy tube.

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Although the restoration of a dynamic component of the tongue is a laudable goal, to achieve this in a way that actually provides functional neotongue movement that contributes to swallowing and articulation is very challenging. Movement alone, or demonstration of electromyographic (EMG) activity in transferred muscle that is reinnervated through the hypoglossal nerve (HG), does not constitute appropriate tongue reanimation. It is critical that comparative studies with patients having comparable tongue defects be functionally evaluated following static reconstructions, described earlier, and dynamic reconstructions involving the transfer of reinnervated muscle. To date, such studies have not been conducted.

As a means of helping to overcome the loss of activity of the hyomandibular muscle complex, the authors have found laryngeal suspension to be a very useful maneuver following base of tongue or total tongue resection. By statically positioning the larynx in a more cephalad and more anterior position, the larynx is placed in a more favorable functional position for avoiding and/or minimizing aspiration.

## Functional Outcomes of Tongue Reconstruction

Very little meaningful outcomes research has been done comparing the results of various reconstructive techniques for the specific defects that are mentioned in this discussion. Owing to the lack of sufficient patient volume in any one institution, there are no comparative institutional studies that will help the surgeon decide between various reconstructive options.

These authors have been examining outcomes following tongue resection with and without reconstruction (lateral and anterior resections). To date, oral outcome variables of tongue strength, tongue and jaw range of motion (ROM), and saliva production have not been extensively assessed in this population, nor have they been correlated with performance status on speech and swallowing and patient-rated QOL. Results in a cohort of 28 patients have shown only moderate reductions in lingual strength (mean = 35 kPa) as compared to healthy individuals. Jaw ROM was within normal limits (mean = 40 mm) and tongue ROM was a mean of 82% of normal (utilizing a converted scale). Oral outcome variables of tongue strength, tongue ROM, and degree of jaw opening were found to significantly correlate with all three functional domains of the Performance Status Scale (PSS),[7,8] including Normalcy of Diet, Eating in Public, and Understandability of Speech.[9] Improved functioning on these oral outcome variables were associated with a more normal diet, greater ability to eat in public and improved understandability of speech.[9]

When examining oral outcome variables with patient-rated QOL, tongue strength, jaw opening, and saliva weight were significantly correlated with QOL outcomes for swallowing on the EAT-10,[10] the MD Anderson Dysphagia Inventory (MDADI),[11] and speech (the Speech Handicap Index).[12] Those patients scoring higher on tongue strength, jaw opening, and saliva weight found their QOL to be improved for both speech and swallowing.

Objective performance status on the PSS significantly correlated with patient-rated QOL on all three QOL scales, with improved QOL correlating with a more normal diet and higher Eating in Public scores (i.e., more likely to eat out in public). Interestingly, no significant differences were found by surgical reconstruction type (i.e., free flap vs. primary closure) for PSS score or QOL score, since the primary closure group demonstrated smaller surgical defects and one might anticipate better performance in this group. However, tongue strength scores were significantly higher for the primary closure group, likely due to a greater amount of native tongue muscle.

When examining the effects of postoperative radiotherapy ± chemotherapy across tumor site and reconstruction type, those patients who underwent surgery >12 months from time of assessment and who underwent radiotherapy ± chemotherapy demonstrated significantly lower tongue strength scores than those seen in the surgery-only group. This is not surprising, since tongue strength has been found to be reduced in patients having undergone chemoradiotherapy for oral and oropharyngeal tumors.[13]

Oral outcome variables described previously have also been found to correlate with performance status on PSS and patient-rated QOL in patients having undergone microvascular free-flap reconstruction only, including the lateral tongue, the anterior tongue, and the total tongue sites.[14] Tongue strength was highest in the lateral tongue resection group, as assessed with the Iowa Oral Performance Instrument (IOPI). This device measures tongue force, with placement of an air-filled bulb on the tongue and instruction to press upward with maximum pressure on the bulb against the palate.[15] Three of five total glossectomy patients could perform a similar flap-resistance task and performed surprisingly well, demonstrating 46% of the mean strength seen in lateral tongue patients. No significant differences in Understandability of Speech were observed between groups. Total glossectomy patients scored 75% understandable speech, which was a better outcome than expected for this group of patients.

When examining overall QOL functioning in these three surgical groups utilizing the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Head and Neck Module (EORTC H&N35)[16] significant correlations with the oral outcome variables were found for the Swallowing and Sticky Saliva domains, with greater jaw opening correlating with better Swallowing scores, and reduced jaw ROM and less saliva weight correlating with poorer Sticky Saliva scores.[14] Patient-rated EORTC domains of Swallowing and Speech both correlated significantly with performance status domains of Normalcy of Diet and Understandability of Speech. Thus, patient-rated QOL correlated well with functional outcomes related to diet and speech.

It is clear that surgical resection and reconstruction affect functional outcomes after surgery. The amount of native tongue, degree of lingual mobility and strength, jaw ROM, and saliva weight after oral cancer surgery play a key role in speech and swallowing performance as well as overall QOL. As can be seen from these data, overall functioning across oral tumor site and reconstruction type can be quite high. In addition, patient perception of function correlates well with measured functional outcomes. Data on oral outcome measures in larger groups of patients should help predict functional outcomes and QOL after definitive resection and reconstruction for tongue cancer.

There are very little data concerning the role of sensation in producing a functional advantage for tongue reconstruction. However, Loewen and colleagues[17] found similar sensation ability in patients who underwent oral cavity sensate flaps as compared to healthy individuals. Specifically, these authors found improvement in light touch and two-point discrimination on the tongue. They also found improvement in swallow functioning, with improved oral transit times and improved bolus clearance through the oral cavity, as well as increased diet options when comparing these patients to similar patients cited in the literature. The recovery of sensation after surgery remains somewhat controversial. Boyd et al.[5] reported that some patients with nonsensate flaps placed into the oral cavity experience recovery of sensory feedback, presumably through the growth of sensory nerves from the perimeter and/or the depth of the wound into which the flap is being placed. This provides the most compelling information available on this topic.

In patients destined to undergo a substantial glossectomy, the surgeon must address fundamental questions relating to laryngeal function; specifically, whether he or she will be able to regain function with this organ in place or whether a functional laryngectomy should be performed at the time of primary

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surgery to prevent aspiration. The prediction as to whether a patient will be able to swallow is often difficult and that uncertainty is heightened due to the nature of deglutition, which is multifactorial. When the disease mandates the removal of the larynx to obtain clear margins, the decision is easier. When the disease requires the removal of the supraglottic larynx, then protection of the airway is certainly compromised and the likelihood of safe deglutition is diminished. During the era when partial laryngeal surgery was performed as the mainstay of therapy, the effectiveness of the extended supraglottic laryngectomy in which a portion of the base of tongue was removed was well documented. However, the patient's comorbid conditions, especially chronic lung disease and the amount of tongue that is to be removed certainly impact the likelihood of success. The irreversibility of a total laryngectomy usually leads us to avoid performing it in the primary setting, and often the procedure is reserved for the secondary setting after a period of adaptation and intensive therapy with an experienced speech pathologist. If the patient demonstrates an inability to protect the airway, then a functional laryngectomy can be performed in a secondary setting.

## OROMANDIBULAR RECONSTRUCTION

Success in oromandibular reconstruction is no longer measured simply by achieving a bone restoration of the segmental mandibular defect, but rather by the ability to restore not only the form but also the function of the oral cavity. A great deal of effort has gone into the detailed three-dimensional analysis of composite defects and into selecting the best reconstructive option that will provide both the optimal soft and hard tissue to restore the given defect. In the past, the major emphasis was on the restoration of the bony defect, but with the highly predictable nature of microvascular transfer of composite flaps, the realization that functional recovery was largely dictated by the movement of the tongue, the emphasis shifted to the soft tissue restoration as well as the restoration of functional dentition. One of the most important considerations is the effect of the soft tissue flaps on the form and function of the tongue and the floor of mouth. After a partial glossectomy, the unpreventable sequelae are related to the loss of the intrinsic tongue musculature and the neurologic supply. Preservation or restoration of sulcular anatomy is important for oral competence, tongue mobility, and denture stability. Additional requirements in soft tissue reconstruction may involve the buccal mucosa, the SP, and the pharynx. Lastly, patients with composite defects involving bone, mucosa, and skin require external coverage as well.

### Defect Classification System

A clear definition of the reconstructive options begins with a careful definition of the extent and nature of the defect using a practical classification that will direct the restorative effort. The shortcomings of the previously used classification schemes did not fully take into account the intricate, composite nature of the defects. Furthermore, the resulting neurologic deficit and its impact on the restoration of reasonable function was also largely ignored. The authors felt the need for a more encompassing, yet simple, classification system and in 1991 introduced a new oromandibular classification system to define the physiologic and aesthetic impact caused by the ablative procedure and the challenges that would be faced by the reconstructive surgeon in achieving the optimal functional restoration of the patient.[3] It should be emphasized that although the structure of the mandible is not that difficult to duplicate, the removal of various portions of the mandible leads to disruption of various muscular attachments and, in addition, the components of the temporomandibular joint, both of which impact the function of the reconstructed lower jaw. This system was also designed to aid in the selection of the composite free tissue transfer that would provide the best combination of soft tissue and bone components to restore a given defect.

On the basis of the functional impact from resection of the mandibular condyle, lateral defects are divided into three zones: the condyle, ramus, and body (Fig. 8-2). The rationale for subdividing body and ramus defects is based on the functional impact that will result from the disturbance of the masticator muscle sling. Body defects are defined as the tooth-bearing segment that extends from an area just posterior to the canine tooth to the junction between the horizontal and vertical rami of the mandible (anterior to the attachment of the masticator muscle sling). Finally, ramus defects encompass the entire vertical ramus to the level of the subcondylar region. Symphyseal defects are more challenging to restore due in part to the shape of the bone but also the loss of support of the tongue that is produced when the suprahyoid and extrinsic tongue musculature are completely detached. Contouring of the bone flap to restore the symphyseal anatomy can be quite challenging, requiring multiple osteotomies which adds to the complexity of the reconstruction. Since the initial description of this classification scheme, the authors added the superscript M to denote a marginal resection of the mandible. The classification system also describes the associated soft tissue defects as mucosal defects of the oral cavity, defects of the tongue, and defects of the overlying skin.

Finally, the authors also felt the need to include both sensory and motor nerve deficits that result from the particular ablative procedure. These include deficits of the inferior alveolar, the lingual, the hypoglossal, and the facial nerves.

### Goals of Oromandibular Reconstruction

With the major emphasis being placed on the quality of functional restoration, the following goals have been identified:

1. Reestablishment of mandibular continuity with a bone-containing flap that will reasonably match the height and shape of the resected segment and will form a firm union at the interface with the native mandible
2. Reestablishment of the normal position of the condyles as well as normal occlusal relationships for prosthetic restoration and near-normal mandibular range of motion

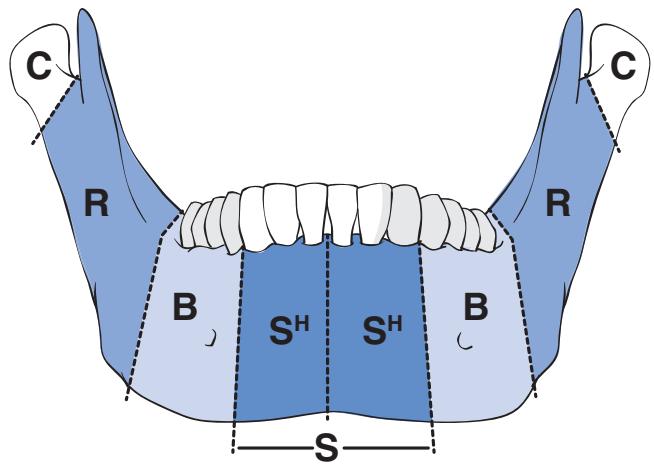



**FIGURE 8-2.** Classification of segmental bony defects of mandible.

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3. Restoration of a functional perioral muscular sphincter to ensure oral competence
4. Restoration of sensation to the lips and oral soft tissues by the use of sensate flaps and nerve grafts when indicated
5. Preservation of tongue motion and restoration of tongue volume as outlined earlier
6. Restoration with a functional dental prosthesis.

## Techniques of Oromandibular Reconstruction

The donor sites available for harvesting vascularized bone-containing free flaps (VBFFs) have provided a menu of choices based on the particular qualities of the different soft tissue regions; therefore, a more critical selection of the ideal type of soft tissue for reconstruction is possible. When dealing with more complex defects, there is often no single flap that provides the ideal tissues to restore all of the missing parts. One of the key provisions is that an adequate amount of bone is supplied for the placement of endosteal fixtures to support a dental prosthesis, thereby restoring the occlusion. It is, however, the soft tissues of the flaps that will frequently determine the ultimate success of the reconstruction and hence soft tissue evaluation plays an important role in the selection of the donor flap.

Four donor sites are routinely used for oromandibular reconstruction: the fibula, the scapula, the iliac crest, and the forearm (Fig. 8-1). Each donor site has advantages and disadvantages related to the amount and quality of the bone and soft tissue needed, the caliber and length of the vascular pedicle, the donor-site morbidity, and, on a practical level, the necessary intraoperative positioning of the patient that will allow for a simultaneous two-team approach.

The fibula osteocutaneous free flap is supplied by the peroneal artery and venae commitantes. It provides bone of sufficient length (up to 25 cm) for reconstruction of subtotal segmental mandibular defects.[18] The height of the fibula is significantly less than that of the normal mandible, making it more ideally suited for the reconstruction of the vertical ramus (including the condyle) as well as the mandibular arch in edentulous patients with a moderate degree of mandibular atrophy. When the defect lies within the tooth-bearing arch in dentate and edentulous nonatrophic patients, the height discrepancy between the reconstructed segment and native mandible must be addressed at the time of prosthetic restoration by the use of an implant supported mesostructure for a fixed denture prosthesis or an implant-assisted removable prosthesis. The skin paddle that can be harvested on the basis of septocutaneous perforators can be used to reline mucosal defects. There is usually a need to perform soft tissue debulking at the time of implant uncovering, owing to the thickness of the subcutaneous tissues and the fact that it is hair bearing. When used externally, the color match can be problematic. Finally, the distance of the donor site from the head and neck facilitates a simultaneous, two-team surgical approach.

The scapular system of flaps offers the widest array of soft tissue components, which accompany the 10 to 12 cm of bone that can be harvested from the lateral scapular border in an adult.[19] The scapular and parascapular cutaneous flaps can be harvested, both of which are based on the circumflex scapular branches of the subscapular vessels. The angular branch of the subscapular vascular system supplies the tip of the scapula, allowing an independent vascularized segment of bone to be harvested. Inclusion of the latissimus dorsi and the serratus anterior muscles can also be accomplished and adds to the versatility of the composite flaps that can be harvested. The main advantages of this donor site are the number and mobility of the soft tissue components relative to the bone, which are supplied by independent vascular pedicles of the subscapular system. The disadvantages of this donor site relate to the variable bone stock that can be harvested from the scapula, which is often inadequate for the placement of dental implants, as well as the need for intraoperative repositioning of the patient into a lateral decubitus position, which makes a simultaneous two-team approach difficult, if not impossible.[20]

The iliac crest osteocutaneous flap is supplied by the deep circumflex iliac artery (DCIA) and vein, branches of the external iliac artery and vein.[21] The vascular pedicle provides both an endosteal and periosteal supply to the iliac bone. The stock of bone that can be harvested is ideal for mandibular reconstruction, and the natural curvature of the ilium often assists in restoring the contour of the ipsilateral hemimandible.[22] The skin overlying the crest is supplied by perforators that traverse the three muscle layers of the abdominal wall. One of the major limitations of this flap, when used in oromandibular reconstruction, is related to the skin paddle, which is often too bulky for use within the oral cavity. In addition, the skin has a relatively fixed relationship to the bone sometimes making it very difficult to restore the complex three-dimensional anatomy required to restore the composite defects. The addition of the internal oblique muscle based on the ascending branch of the DCIA greatly increases the versatility of this donor site.[23] The thin pliable muscle, which undergoes atrophy after denervation, is ideally suited to restore gingival and mucosal defects over the neomandible. In such cases, the skin paddle is used for the restoration of cutaneous defects or simply as an external monitor of the circulation to the flap. A simultaneous two-team approach is possible. The major disadvantages of this donor site are the early gait disturbances and the potential for development of a ventral hernia. This can, to some extent, be avoided through meticulous closure of the donor site and the use of a mesh to augment the repair of the abdominal wall musculature.

The radial forearm free flap, which is based on the radial artery and the cephalic vein, provides thin sensate, pliable skin that can be transferred as an osteocutaneous flap. A segment of radius up to 8 to 10 cm and approximately 40% of its circumference can be transferred with the skin.[24] The bone is of limited dimensions for structural and functional reconstruction of the mandible. The thin, pliable soft tissue component of this flap is ideal for use in relining the floor of mouth, the tongue, and the posterolateral pharyngeal wall defects. This makes the use of this flap ideal in a small subset of patients who have a very limited posterolateral segmental mandibular defects along with a significant soft tissue defect. In these patients, the missing mandibular segment is usually located beyond the dentate segment and, therefore, the inability to place implants is less important. The most significant complication associated with this flap is the overall 25% incidence of pathologic fracture of the remaining radius, an occurrence that can lead to a significant impairment in hand function.[25] Fixation of the graft can also be problematic because it requires some stripping of the periosteum in the area of screw placement. This invariably leads to a decrease in the blood supply to the bone, which is periosteal in nature. These issues, coupled with the limited bone stock, has led to the infrequent use of this donor site for reconstruction of mandibular defects.

## Prosthodontic Management of the Mandibulectomy Defect

The major goals for prosthodontic treatment in this group of patients are to advance and optimize speech and swallowing functions while restoring form to dentoalveolar structures. The incorporation of prosthodontic care into initial treatment planning for surgical reconstruction of the mandibulectomy patient can shorten overall treatment time for functional recovery and improve the QOL. One of the main goals of primary mandibular reconstruction is to functionally rehabilitate the patient by

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restoring occlusal relationships and a denture-bearing surface. Conventional prosthodontic treatment uses the remaining dental arch to stabilize a removable partial denture over a bone-containing free-flap reconstruction to replace lost dentition. The condition of the dentition and periodontium is important for successful prosthodontic restoration. If there is no remaining dentition for clasp stabilization and retention, the edentulous patient will have a nonfunctional dental restoration. Compromised neuromuscular control resulting from a segmental mandibulectomy and related soft tissue deficits of the floor of mouth and/or the tongue can lead to the inability to tolerate a tissue-borne prosthesis and limit functional recovery. Osseointegration of dental implants in this patient population has a large impact on the ability to predictably restore them with stable dentures.

Mandibular prostheses supported by osseointegrated implants have a high rate of success and improved level of patient function and satisfaction by stabilizing occlusal contacts against the maxillary dentition and aiding in the restoration of symmetry and projection of the mouth. These objectives can be achieved with either a fixed or a removable implant-assisted prosthesis. When restoring the dentoalveolar complex with a removable implant overdenture, it is necessary to place a minimum of two fixtures in the symphyseal region. These fixtures can later be connected with a cast metal bar framework. Corresponding attachments are incorporated into the denture base to provide retention and stability of the prosthesis. A removable implant overdenture employs the attached mucosal base for additional tissue support to the prosthesis.

In cases in which the remaining arch is edentulous, and in which a lateral mandibular reconstruction is performed, the surgeon should place the implants in the anterior native mandible. This is an ideal location for fixture placement in patients undergoing a lateral jaw resection for a posterior alveolar, lateral tongue/floor of mouth, or tonsilar primary tumor because this area is usually spared from the radiation.

Fixed implant-assisted prostheses require multiple implants for support of the restoration. A minimum of four or five implants should be placed with the greatest anterior–posterior spread to minimize the cantilever effect of the posterior extension of the prosthesis beyond the most distal fixture. The posterior placement of the distal implant on the contralateral side is limited by the position of the mental foramen. Care must be taken to identify this landmark and avoid injury to the mental nerve.

The authors have adopted the approach of placing dental implants at the time of primary oromandibular reconstruction regardless of whether the patient has already been treated with radiation therapy or is scheduled to do so in the postoperative period. Following primary implant placement, the restorative team must allow a minimum of 12 to 16 weeks of undisturbed healing to achieve the most favorable level of success for osseointegration. When radiation is given after the reconstruction and primary implant placement, the fixtures are uncovered once the soft tissue reaction to radiation has subsided. This usually occurs approximately 6 months after placement. The uncovered implants may require soft tissue modifications such as vestibuloplasty or debulking procedures before definitive rehabilitation. The approach that the authors have developed allows the functional restoration of the patients within a period of approximately 7 to 8 months after their ablative/reconstructive procedure. Therefore, QOL can be expeditiously restored and patients are able to reintegrate into social interactions.

In the primary setting, once the bone flap is fixed to the reconstruction plate and the anastomosis to the recipient vessels is completed, fixture placement is then performed. Access to the new ridge is ideal when the cheek flap is elevated and the oral soft tissue retracted. The number and the layout of fixtures will depend on the size and location of the defect, the bone flap, and the type of prosthetic restoration that is planned for the patient. As noted earlier, the segmental defect reconstructed with a fibula free flap presents certain challenges for successful prosthodontic rehabilitation. To restore the facial outline form, the fibula free flap must be placed at the inferior border of the mandible. This can result in a significant height difference from the occlusal plane of the native dentition to the tissue base of the fibula. If implants are placed into the fibula, this height discrepancy can potentially produce unfavorable lever forces on the implants. One strategy that can alleviate these forces is to use the remaining dental arch to connect and stabilize a removable implant overdenture prosthesis.

The height difference between the native mandible and VBFFs also becomes a consideration for fixed implant prosthetic restorations. A shorter distance from the neoalveolus to the occlusal surface can be achieved more easily when using the iliac crest compared to the fibula. In so doing, there will be less nonvertical forces placed on the implants. In the authors' experience, whether the iliac crest or the fibula is used for the surgical reconstruction, the distance can be overcome by prosthetic design. The bicortical stabilization of the implant placed into the fibular bone adds to the stability of the implant and permits the use of prosthetic and implant framework designs to compensate for height differences between the fibula and the occlusal plane (Fig. 8-3A,B).

For hemimandibulectomy defects in the dentate individual, restoration of the dentition with a fixed implant–borne denture provides the best prosthetic option for the patient. The authors' preference for achieving a functional rehabilitation is to provide the patient with a fixed implant prosthodontic restoration whenever possible. The psychosocial impact of reconstruction and rehabilitation can be minimized with a fixed osseointegrated prosthesis. Oral hygiene and maintenance do not have to be compromised, which eliminates the need for removal and insertion as daily reminders of disease and treatment.

Implant placement in the primary setting also takes advantage of the vascular bed for osseointegration before adjunctive radiotherapy and serves to circumvent the use of hyperbaric oxygen (HBO). The fabrication of an interim tissue-borne removable prosthesis for partially dentate patients who have to undergo mandibulectomy can help to advance function during the osseointegration phase of treatment. An interim prosthesis can also be utilized as a surgical stent at stage II implant surgery for vestibuloplasty and/or debulking procedures. Split-thickness skin grafts can mimic attached mucosal surfaces and minimize peri-implant soft tissue complications. These strategies can lead to favorable outcomes for the patient who has to undergo reconstructed mandibulectomy, but require a high level of preoperative planning and a coordinated effort by the reconstructive team.[26,27]

Another treatment strategy for implant rehabilitation after free-flap reconstruction of maxillo-mandibular defects involves the use of computer-assisted planning and the ability to provide immediate provisional restorations with careful patient selection. Computer-assisted implant rehabilitation of reconstructed maxillo-mandibular defects can achieve superior results to provide fixed dental prostheses (Fig. 8-4A–D). The authors have examined 28 consecutive patients treated with computer-assisted implant rehabilitation.[28] All of the patients were reconstructed with vascularized bone-containing free flaps from the fibula, iliac crest, and scapular donor sites. One-hundred twenty-two implants were planned and 116 were subsequently placed, of which 102 implants (87.9%) achieved osseointegration. Ninety-nine implants were used for prosthetic restorations for an 85.4% success rate. Thirteen of 28 patients received immediate or early fixed restorations at stage I implant surgery. Fifty-six implants were placed into these 13 patients, of which 50 (89.3%) achieved osseointegration and were used for definitive prosthodontic rehabilitation in the immediate load group. Twelve of 13 patients

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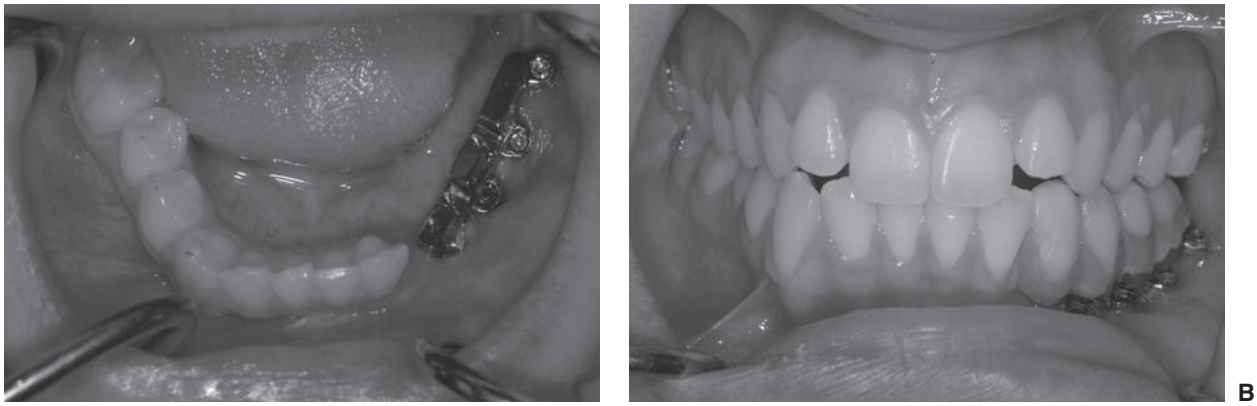



**FIGURE 8-3.** **A:** Mesostructure into left mandibular reconstruction with lingual cantilever design to provide implant support over neo-ridge. **B:** Superstructure in place with screw retention into mesostructure completes implant rehabilitation with a fixed dental prosthesis. This retrievable prosthetic design compensates for the height discrepancy between the native mandible and the fibula free-flap reconstruction. The facial position of the implants can also be negotiated with this design.

in the immediate load group went on to receive a fixed dental restoration. Twenty-five of the 28 patients in the study received fixed dental prostheses after implant rehabilitation.

Definitive restoration of the occlusal surfaces helps to enable the patient to achieve functional mastication, an important, but only a single parameter in the overall swallowing process. The ability of the remaining tongue or the reconstructed tongue to retrieve food particles and present the bolus to the occlusal surfaces, initiating the first phase of swallowing is extremely important in the restoration of function. Other parameters that impact the quality of the functional recovery include lip and cheek competence, the degree of disruption of the neurosensory feedback that effects the determination of the location and size of the food particles within the oral cavity, and the effects of adjuvant therapy on decreasing salivary flow and causing fibrosis of the swallowing muscles.

## PALATOMAXILLARY RECONSTRUCTION

The use of microvascular free-flap reconstructive techniques in the midface region for restoration of palatomaxillary defects is a relatively new application of some of the same strategies that were employed in restoring oromandibular defects. The collective experience in reconstructing the palatomaxillary complex, rather than relying on prosthetic restoration, is much smaller than the experience with oromandibular reconstruction due to the fewer number of maxillary cancers and also because of the relatively recent interest in this form of rehabilitation for these defects.

There are inherent differences between palatal and segmental defects of the mandible that have also contributed to the relatively later use of VBFFs for their rehabilitation. Most importantly, the remaining maxilla will not shift following removal of a portion of the palate, and the use of palatal prosthetics has provided a means for dental restoration at the same time that obturation of the defect is accomplished. Owing to the lack of movement of the remaining maxilla after performing an ablative procedure, the use of soft tissue flaps may play a limited role, which is quite different from the situation in reconstruction of segmental mandibular defects in which soft tissue flaps result in a shift of the remaining mandible. The immobility of the palatomaxillary complex means that the success of its reconstruction will not require a restoration of dynamic activity and therefore the overall restoration is judged on the basis of the quality of the static reconstruction. Finally, the lack of involvement of the tongue in most palatomaxillary resections translates into a much higher expectation for functional recovery than in oromandibular resections where the tongue is often involved leading to challenges in speech and swallowing.

### Classification of Palatomaxillary Defects

The authors' approach to designing a classification scheme for palatomaxillary defects was very different than for any other subsite in the head and neck.[29] Owing to the reasonable degree of success and the ability to restore dentition with an obturator, the authors elected to consider the essential biomechanical properties that lead to success and failure in obturation. As will be discussed later, the features of a palatomaxillary defect that contribute to prosthetic retention and stability include the midline palatal shelf and the scar band that forms at the interface between the skin-grafted maxillectomy cavity and the buccal mucosa. The prosthodontist capitalizes on these anatomic retention spots in the design of a palatal obturator. The obliteration of those structures by the introduction of a flap has implications for the success of restoring dentition to the upper arch. In addition to the midline palatal shelf and the scar band, the remaining maxillary dentition plays a very important role in prosthetic success. In particular, the canine and the molar teeth are particularly important structures due to the superior root form that is capitalized on by the prosthodontist with the use of clasps on those teeth that assist in prosthetic retention.

In 2001, the authors introduced a palatomaxillary defect classification scheme that has been slightly modified in the authors' current utilization.[30] The horizontal component of the defect was classified on the basis of the biomechanical principles noted earlier. The vertical component of the defect was classified on the basis of the extent of disruption of the orbital support and anterior projection of the cheek (Fig. 8-5).[30]

The authors classified central defects of the palate that do not involve the alveolus as **class 1a**. Those defects that involve the posterior alveolus, but do not lead to loss of the ipsilateral canine tooth were labeled as **1b**. Defects that involve up to one half of the palate and, in particular, that lead to removal of both

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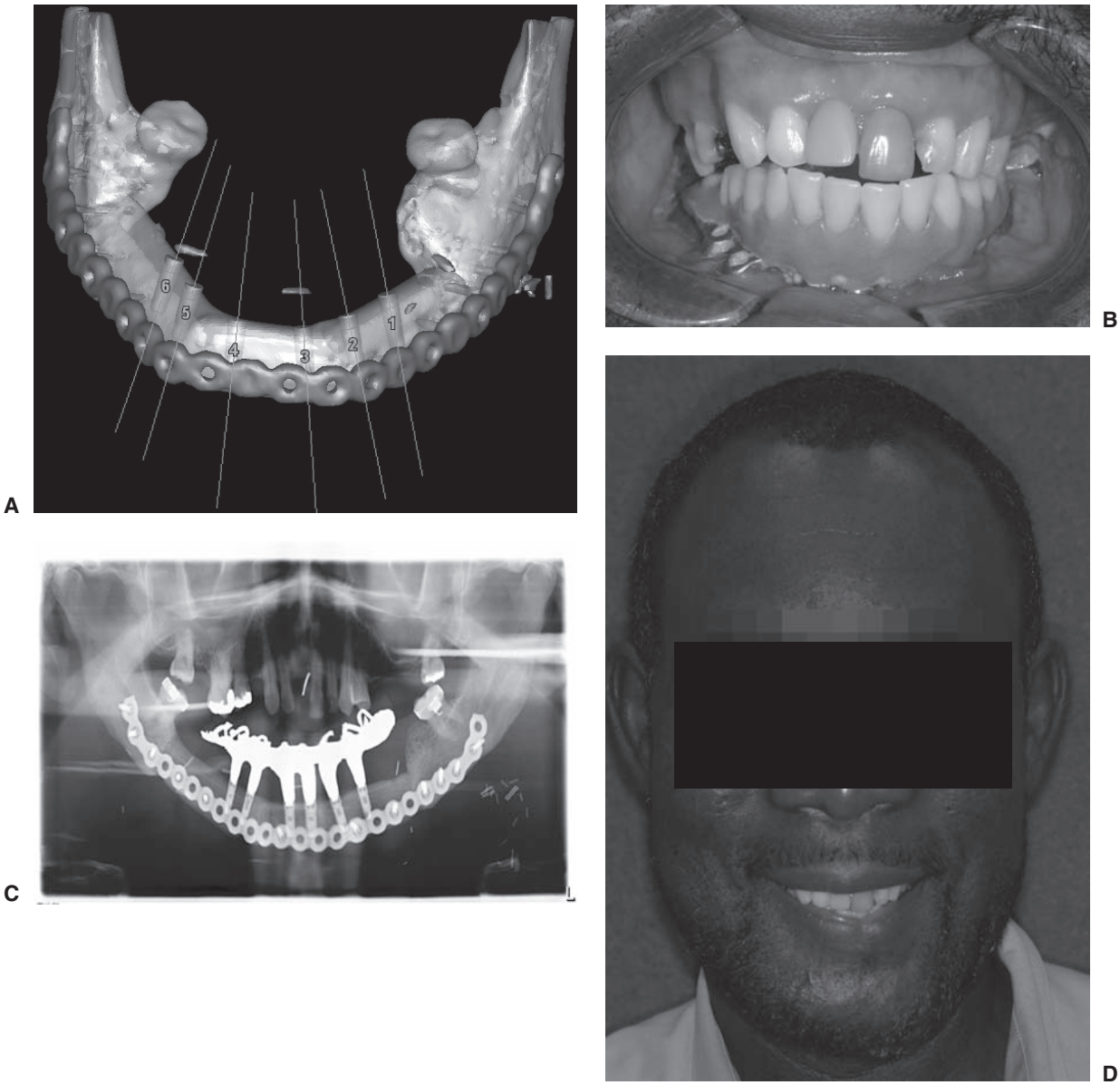



**FIGURE 8-4.** **A:** Three-dimensional reformation of a mandible reconstruction with a composite fibula free flap. Computer planning and virtual placement of six endosteal implants prior to stage I surgery. **B:** Clinical intraoral facial view of implant supported fixed dental prosthesis. Note the restoration of occlusal contacts and the position of some implants along the right facial vestibule to overcome restoration of the dental arch lingual to the reconstructed mandible. Implant restorations are designed as screw retained and retrievable for surveillance. **C:** Panoramic radiograph of fibula free-flap reconstruction of a "bone-symphysis-symphysis-bone" defect and fixation of metal framework to six implants. **D:** Facial view of 48-year-old patient after surgical reconstruction and implant rehabilitation. Note the symmetry of the lower third of the face achieved by the position of the fibula to restore the inferior border of the mandible.

the canine and the molar teeth on one side, are designated as **class 2**. Such defects include the traditional hemimaxillectomy defect. In addition, horizontal defects of the palate that involve one half of the anteroposterior dimension of the palate and include the removal of both canines or both molars are also designated as **Class 2** defects.

**Class 3** defects include subtotal and total defects of the palate. **Class 4** defects were added after the 2001 publication and reflect those defects that involve the suprastructure of the palatomaxillary complex while preserving the native palate. In an effort to indicate the vertical components of a palatomaxillary defect, the superscripts f, z, o, i, and s were added to indicate that the resection included the orbital floor and inferior orbital rim, the zygomatic body, an orbital exenteration, exposure of the intracranial contents, and the overlying skin.[29]

## Goals of Palatomaxillary Reconstruction

It is imperative that the reconstructive surgeon realizes that the time-honored standard for palatomaxillary restoration is the

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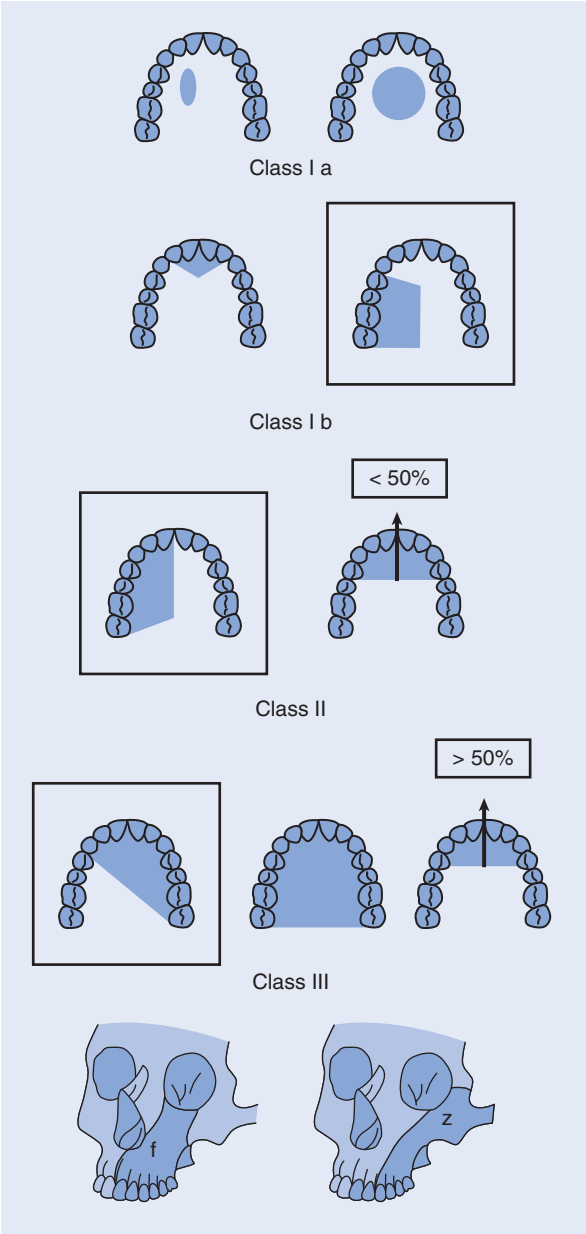



**FIGURE 8-5.** Classificaton of palatomaxillary defects.

Source: Taken with permission from Okay DJ, Buchbinder D, Genden E, et al. Prosthodontic guidelines for surgical reconstruction of the maxilla: a classification system of defects. *J Prosthet Dent.* 2001;86(4):352–363.

use of a palatal obturator, which eliminates the communication between the oral cavity and the sinonasal cavities as well as providing teeth to the maxilla. It is therefore imperative that the utilization of reconstructive options to be described in the sections which follow achieve those goals as well as others to be outlined. Support of the globe to prevent orbital dystopia is imperative in those defects that extend vertically to include the orbital floor and rim. In addition, symmetry of the midface region must be achieved. The avoidance of epiphora and ectropion must also be accomplished. Finally, functional mastication, velopharyngeal competence, and the avoidance of trismus are also important goals of the reconstruction.

## Reconstructive Approach

The basic principle of the classification scheme described earlier is that there are "horizontal and vertical" components to each defect that the surgeon must consider in the decision as to how best to restore an optimal functional and aesthetic result. In addition to the defect-related factors, there are also a number of patient-related and disease-related factors that must be considered, which include the biologic behavior of the disease, whether the disease is being treated for the first time or represents salvage therapy, the exposure to prior radiation therapy, the status of the remaining dentition, the status of the remaining bone stock in the palate, the presence of comorbid conditions, and the motivation of the patient to undergo a more involved surgical procedure. Preoperative discussions should be carried out between the patient, the reconstructive surgeon, and the prosthodontist to provide a clear understanding of the merits of each restorative approach.

After ablative surgery of the palatomaxillary complex, the continued monitoring of the cavity remains a topic of much debate. The authors believe that serial follow-up scans provide an effective surveillance for recurrence of disease. There are certain diseases such as mucosal melanoma and recurrent ameloblastomas, where the ability to visualize the mucosa lining the cavity is as important as the presence of nodularity on a scan. It is imperative for the surgeon to ensure, through very detailed conversations, that the patient fully understands the issues of surveillance and the prognosis for prosthetic success to make the most informed decision on whether to restore a defect with a prosthesis or a reconstructive technique that eliminates the palatal opening. The region of the orbital rim, the orbital floor, and the zygomatic body, however, must be reconstructed because a palatal prosthesis will not address those components of the defect. In defects that warrant open cavity surveillance, however, there may be a need to reconstruct the superior aspect of the defect while addressing the palatal opening with a prosthesis.

In general, the authors' approach to class 1a and 1b defects is to either use a prosthesis or a soft tissue flap. Class 2 defects can be managed either with a prosthesis or the transfer of a vascularized bone containing flap. Class 3 defects have such a poor outlook for long-term prosthetic success that the authors routinely reconstruct with vascularized bone. Class 4 defects require soft tissue and hard tissue replacement.

As noted in the discussion earlier, the horizontal component of the defect is fundamentally based on the size and location of the palatal opening and the presence of favorable dentition to assist in the retention of a palatal obturator prosthesis. For class 1a and b defects, the smaller size of the defect and the presence of one molar and two canine teeth permit the use of soft tissue reconstructions while not compromising the ability to restore dentition to the maxilla. In the event that any of those teeth is not present, then the use of implants can help stabilize the prosthesis, provided that the alveolar bone is adequate for successful osseointegration. In these defects, the authors have employed either a palatal island flap or a radial forearm flap depending on the size of the palatal opening.[30–32] When the transposition of the remaining palate, which is based on one greater palatine vascular pedicle, is sufficient to provide coverage, a palatal island flap is the method of choice. Alternatively, when the defect is too large and the remaining palatal mucosa will not comfortably provide closure, a radial forearm flap is employed and the vascular pedicle delivered to the recipient vessels in the submandibular triangle. One other contraindication to employing the palatal island flap is the exposure to radiation of this region, a circumstance that predisposes to the development of osteoradionecrosis because of the denuding of the palatal bone.

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In class 2 defects, in addition to the increased size of the defect, the loss of the ipsilateral canine and molar dentition makes the use of bony reconstruction important if the surgeon decides to avoid using a prosthetic obturator. The placement of a soft tissue flap into this defect leads to an unfavorable environment for dental restoration due to the loss of essential stabilizing properties in the defect. For class 2 defects that include only the horizontal component, the authors utilize the fibular flap to restore the bone of this region thereby gaining the ability to accommodate implants that are critical to a functional rehabilitation. In defects that extend vertically to include the zygoma and orbital rim and floor, the authors favor utilizing the iliac crest internal oblique flap, as originally described and later modified.[33] This flap transfers a significant volume of bone with sufficient height to restore the vertical components of the defect, including the inferior orbital rim. The iliac bone is placed in a vertical orientation to restore the maxillary alveolus, while the midportion of the palate is replaced with the internal oblique muscle that is transposed through the defect and used to reline the lateral wall of the nose.[34] The internal oblique muscle undergoes denervation atrophy and contours to the palatal vault, and within a very short time, it remucosalizes. One final aspect to the restoration of the vertical component of the defect is the use of onlay bone grafts to restore the anterior projection of the zygomatic body to achieve symmetry in this portion of the midface.

When bone is introduced into the midface region for palatomaxillary restoration, it has been the authors' practice to perform a coronoidectomy to increase the posterior space for placement of the bone and at the same time reducing the risk of trismus due to impingement of the maxillary bone on the anterior ramus.

Class 3 defects are highly unfavorable for prosthetic restoration due to the larger size of the defect and the loss of key retaining properties. The cantilever forces and resulting fulcrum line of the prosthesis place significant stress on the remaining dentition when class assembles are placed onto those teeth. The stress on the dentition is compounded by the detrimental effects of radiation. Restoration of the alveolus is usually best accomplished with a fibular flap, but sealing of the sinonasal cavity is often difficult in these situations and the authors most often employ a bipaddled radial forearm flap that places either skin or fascia on the superior and the oral surfaces of the defect, and the fibular bone in between. Bone-to-bone contact posteriorly and anterior support of the nose are critical for success.

Class 4 defects of the palatomaxillary complex are best restored through a combination of techniques that include the incorporation of either regional soft tissue flaps such as the temporoparietal fascial flap or the temporalis muscle flap in combination with either free bone or an alloplast to achieve support for the globe and projection of the midface region. If skin is removed, then options for facial skin replacement must be considered. This will be more fully discussed in the section on reconstruction of parotidectomy defects.

## Prosthodontic Management of the Palatomaxillary Defect

Maxillary obturators can be fabricated so as to restore speech and swallowing. With larger defects in the palate, however, the prognosis for functional recovery utilizing prosthetic rehabilitation is less. These patients have lower speech intelligibility and tend to avoid social events.[35]

Surgical separation of the oral cavity from the sinonasal cavities is potentially better than artificial closure with a prosthetic obturator. A soft tissue flap can provide absolute closure of the palatomaxillary defect but it may hinder the restoration of a functioning dentition due to the elimination of some of the important properties of the defect that assist the prosthodontist in achieving retention and stability with a palatal obturator. The loss of the midline palatal shelf and the obliteration of the scar band that forms at the interface between the skin graft and the mucosa are critical factors that are exploited by the prosthodontist. Alternatively, the placement of a fasciocutaneous free flap creates a smooth, spongy, and highly compliant surface that provides neither support nor retention and can potentially hinder the stability of the prosthesis in large maxillary defects.

With restoration of the dental arch and maintenance of a stable base as goals, it is apparent that the use of fasciocutaneous free flaps are not ideal for all but the more limited palatal defects. If optimal functional rehabilitation is to be achieved when soft tissue is employed for surgical reconstruction, an adequate remaining palate and dental arch is needed to derive support, stability, and retention for a removable denture.

If surgical reconstruction is anticipated, soft tissue free flaps should be reserved for defects in which the remaining palate and dentition are sufficient for prosthodontic rehabilitation (class 1b). The remaining dentition, arch length, and palatal surface determine whether a removable partial denture provides stability of the prosthesis over the defect through direct retainers and a palatal connector. The superior root form of the canine tooth as a terminal abutment closest to the defect and clasping of molar teeth will promote prosthetic stability as well. Implants in the native maxilla may be necessary to overcome a compromised dentition or edentulism leading to either a fixed or removable implant-assisted restoration (Fig. 8-6A–D).

Total and bilateral maxillectomy defects are more difficult to restore with prosthetic obturators and are more likely to have side effects that can compromise the QOL for the patient. Large maxillectomy defects involving the hemipalate, total maxilla, or bilateral maxillae are more challenging to restore function (class 2 and 3). As a defect increases in size and the remaining palate and dental arch decreases, a VBFF is preferred over a soft tissue free flap. Osseointegration and prosthodontic rehabilitation can restore the dentoalveolar structures and occlusion to optimize speech and swallowing functions. An implant supported fixed dental prosthesis is the authors' preference for restoring patient function in this complex reconstructive approach.

## Functional Outcomes

In the past, a major criticism of oromandibular reconstructions was directed at the time required to perform a primary oromandibular restoration and the limited success in achieving functional dental rehabilitation. The use of root form endosteal titanium fixtures and advances in the field of dental implantology over the last three decades have had a dramatic impact on the functional rehabilitation following oromandibular reconstruction in patients with oral cancer. As stated earlier, the use of dental implants to provide stable anchorage of a denture has been extremely effective. In addition, the predictability has increased dramatically whereas the length of time of performing these reconstructions in the primary setting has diminished with increased experience of busy head and neck surgical teams. Outcome studies that the authors and others have performed on patients following palatomaxillary and mandibular reconstruction were very encouraging in terms of functional outcomes and long-term success.[36] When the authors specifically looked at bite force and masticatory efficiency in a small subset of patients who had undergone a hemimandibulectomy/primary reconstruction with an iliac crest free flap and primary fixture placement, the results were comparable to those of a subset of noncancer

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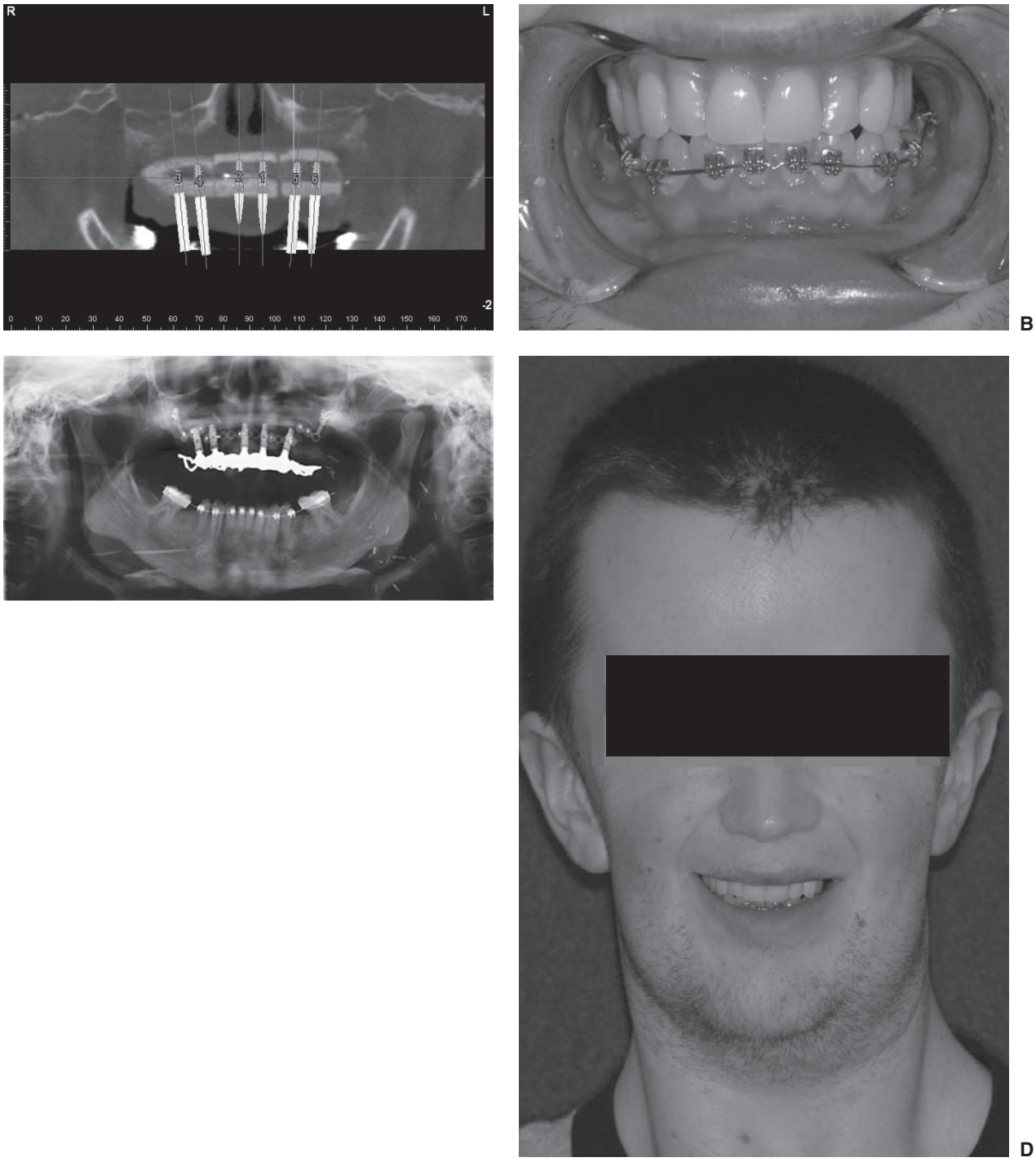



**FIGURE 8-6.** **A:** Panoramic view on computer-assisted planning software of implant placement prior to stage I surgery and after maxillary reconstruction of Class III defect with a fibular free flap. **B:** Intraoral view of esthetic restoration with an implant-supported fixed dental prosthesis and occlusal rehabilitation. **C:** Panoramic radiograph of fibular free-flap reconstruction and implant rehabilitation. Note the ability to avoid reconstruction plating and screws with planning software. Treatment planning of complete arch restorations requires a sufficient number of implants for prosthetic success in the case of implant failure. **D:** Facial view of a 17-year-old patient status postsurgical reconstruction, vestibuloplasty, and implant rehabilitation.

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patients from the prosthetic clinic who had their missing dentition restored by either implant-supported or implant-assisted prostheses. This is a remarkable finding because the noncancer patients were not subjected to the effects of a surgical procedure that disrupted the muscular attachments of the mandible and resulted in significant scarring of the perimandibular tissues. Furthermore, they also did not have the effects of neurosensory loss and radiation therapy associated with the mandibular resection and adjuvant radiotherapy. When the authors compared patients with smaller palatomaxillary defects (Class 1a and 1b) reconstructed with soft tissue–only flaps with a similar number of age- and defect-matched nonreconstructed patients who were using tissue-borne obturators, it was found that although there was no statistically significant difference in the chewing performance, there was a significant difference in the QOL of these patients as measured by patient comfort, social interaction, and convenience.[32] Speech was also vastly improved in the reconstructed patient. As the defects became larger to involve a significant portion of the midface skeleton, the advantage of immediate reconstruction with bone-containing free flaps became more obvious. Reconstructed patients demonstrated a trend toward improved masticatory function, speech, and comfort.[36] The composite bone flaps easily achieved the separation of the sinonasal cavities from the oral cavity. These flaps also provided a bony platform for the placement of titanium fixtures for the retention of the prosthesis as well as support of the globe and projection of the midface (malar projection). Nevertheless, these results must be viewed in the context of the significant complexity of oral function. Adequate restoration of the occlusal surfaces enables the patient to incise and grind a food bolus, which is only one parameter in this complex process. Additional factors include the amount and function of the remaining tongue, the SP, and the pharyngeal structures, the disruption of the neurosensory feedback that allows the determination of the location and size of the food particles within the oral cavity, and, last but not least, the effect of the surgery and radiation therapy on swallowing.

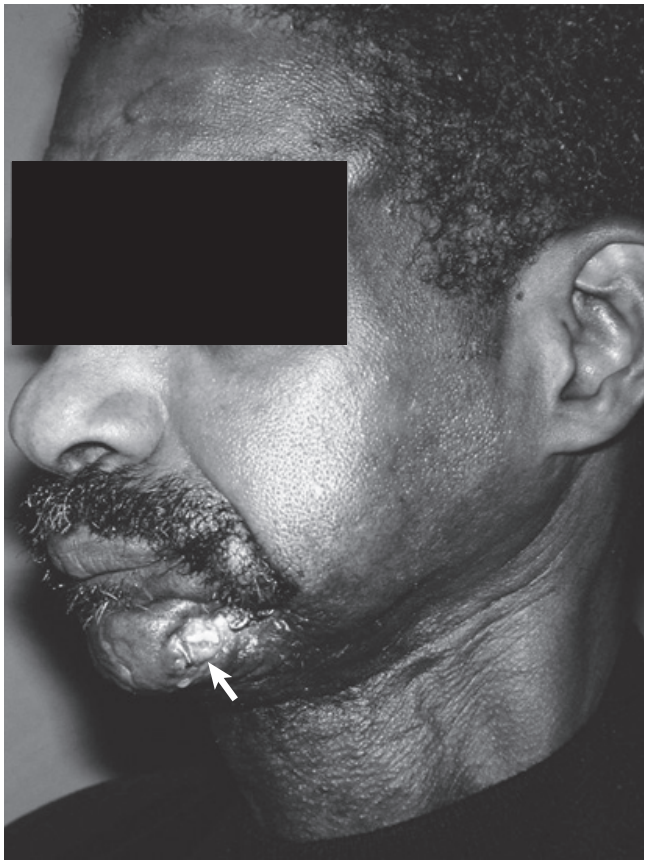


**FIGURE 8-7.** Facial view of patient with cutaneous fistula *(arrow)* due to stage III osteoradionecrosis of the mandible.

## OSTEORADIONECROSIS

Osteoradionecrosis (ORN) can be a devastating complication of radiation therapy. It affects mandibular bone more frequently than any other bone in the head and neck.[37] It can occur as a result of primary or adjuvant radiation therapy and has been reported to occur following either external beam radiation treatment or brachytherapy.[38] The standard of care for patients presenting with advanced osteoradionecrosis, pathologic fracture, fistula, and full-thickness involvement of bone (Figs. 8-7, 8-8A,B, 8-9, 8-10A) is a segmental mandibulectomy with a free osteocutaneous flap reconstruction. Preservation of the inferior alveolar nerve can be accomplished with this procedure (Fig. 8-10B). Reconstruction after surgical replacement of all nonvital bone can be accomplished with a variety of hard tissue free flaps, all of which were previously described (Fig. 8-10C–F). We have examined the impact of ORN surgery on functional outcomes.[39] In a group of 31 patients who underwent ORN surgery, 57% reported improved overall QOL, as reported on a 5-point scale. Performance on objective functional outcome domains of the Performance Status Scale[7] including Normalcy of Diet, Eating in Public, and Understandability of Speech significantly correlated with patient-rated swallowing, speech, and overall head and neck QOL (Table 8.1). For those patients reporting no improvement in QOL after ORN surgery, deficits in speech and swallowing were a result of prior and long-standing postradiotherapy changes and would not have been addressed with ORN surgery. Thus, despite removal of nonvital hard and soft tissue and restoration of mandibular continuity with vascularized bone, functional outcomes as well as QOL may remain impaired due to other chronic problems associated with high-dose radiotherapy to the head and neck.

## OROPHARYNX

The oropharynx is defined as the region of the upper aerodigestive tract (UADT), which is bounded by the nasopharynx superiorly, oral cavity anteriorly, and hypopharynx inferiorly. Conventionally, the oropharynx is subdivided into the posterior pharyngeal (PP) wall, the lateral pharyngeal (LP) walls, the SP, and the base of tongue. Each of these anatomic locations within the oropharynx represents a unique reconstructive challenge. The objective of oropharyngeal reconstruction is the restoration of deglutition, respiration, and speech production. This is accomplished by using contemporary reconstructive techniques to maintain the caliber of the chamber and the function of the velopharyngeal sphincter through the restoration of lining, bulk, and sensation.

To date, there is no universally accepted classification scheme of defects of the oropharynx. The classification system that the authors have developed, and the one that is used in this chapter, is based on the individual regions of the oropharynx and it attempts to categorize the extent of the ablative defect created as well as the functional impairment (Table 8.2). Most

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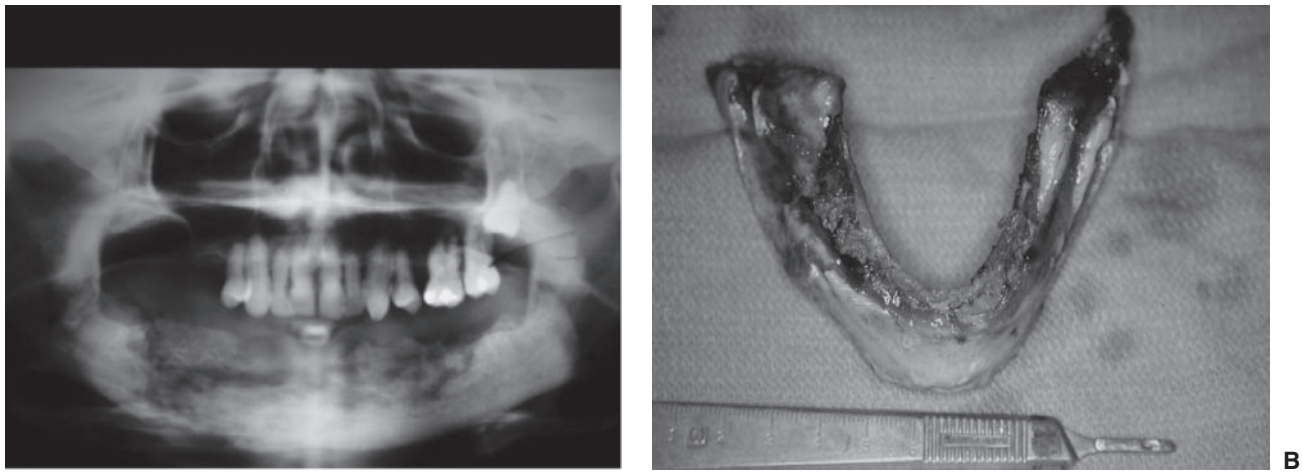


**FIGURE 8-8.** **A:** Panoramic radiograph of necrotic bone in patient with bilateral osteoradionecrosis of the mandible. **B:** Necrotic bone postresection.

oropharyngeal ablation defects involve multiple subsites within the oropharynx.

When faced with an oropharyngeal defect, the reconstructive surgeon is confronted with a major challenge of restoring function to this highly complex region. Choosing the appropriate method requires careful consideration of the subsites involved. Sensory reinnervation of the flaps is preferred whenever possible. Smaller defects (LP1, PP1, PT1, and SP1) can be closed primarily, left to granulate, or covered by a split-thickness skin graft. Larger defects usually require a reconstruction that involves a combination of local flap, regional, and free tissue transfers. Together, the base of tongue and the walls of the pharyngeal chamber together constitute the muscular tube through which air, food, and liquids must pass in a coordinated manner. During swallowing, the pharyngeal walls contract, the SP elevates, and the base of tongue acts as a plunger to move the food bolus into the esophageal inlet. Together these structures act to form a dynamic conduit. If a partial resection of the pharyngeal walls is performed, the remaining pharynx and tongue can compensate for the loss of a dynamic portion of the pharynx. When an ablation defect is small and isolated (LP1, PP1, PT1, and SP1), it is best to use local tissue that maintains the integrity and dynamic activity of this muscular tube. If the defect is large, however, iatrogenic pharyngeal stenosis can occur following primary closure. This results in a suboptimal swallowing outcome. Transferring soft tissue from a regional or distant site helps to prevent pharyngeal stenosis but results in an adynamic area within the oropharynx. When the defect involves multiple subsites within the oropharynx, a smaller pharyngeal chamber may actually enhance the functional outcome of the reconstruction by improving the contact between the base of tongue, the SP, and the pharyngeal walls. With this in mind, the reconstructive surgeon must be conscious of the size and the design of the new pharyngeal chamber; if the diameter is too large or too small, the swallowing outcome will be less than optimal.

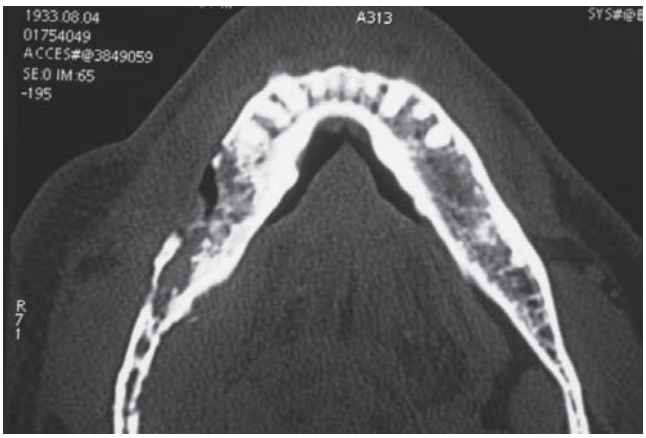



**FIGURE 8-9.** CT scan of mandible showing osteolysis due to osteoradionecrosis.

The base of tongue plays an extremely important role in deglutition because it is responsible for pharyngeal closure during the oral phase of swallowing and is the main driving force of the bolus through the pharyngeal phase. It is imperative that the reconstruction restores adequate bulk and lining apart from ensuring continued mobility of the remaining base of tongue. This will allow the newly reconstructed base of tongue to continue to act as a valve during the oral phase of swallowing and a plunger during the pharyngeal phase. Fasciocutaneous flaps, such as the radial forearm free flap, are excellent for use in base of tongue reconstruction.

The SP is a critical component of the velopharyngeal sphincter and is responsible for proper speech, articulation, and resonance. In the past, velopharyngeal incompetence after a palatal resection was often treated with the use of a palatal prosthesis. Recently, the need to utilize a palatal prosthesis after an SP resection has been reduced because of the advances in SP reconstruction.

Small SP defects can often be compensated for by the remaining pharynx and the base of tongue, providing for excellent functional outcomes by avoiding velopharyngeal incompetence. Small lateral SP defects can be closed primarily or by local advancement flaps. Larger lateral defects often require more complex reconstructions such as a superior constrictor advancement flap combined with a radial forearm flap.[2,40] This technique is effective for resections of up to one half of the SP (SP2). The goal of this reconstruction is to restore the velopharyngeal sphincter to a smaller caliber in an attempt to minimize nasal escape of air and nasal regurgitation of liquids and foods. As the size of the SP defect increases (SP3), a more elaborate reconstruction is necessary. The folded radial forearm free flap has been a workhorse

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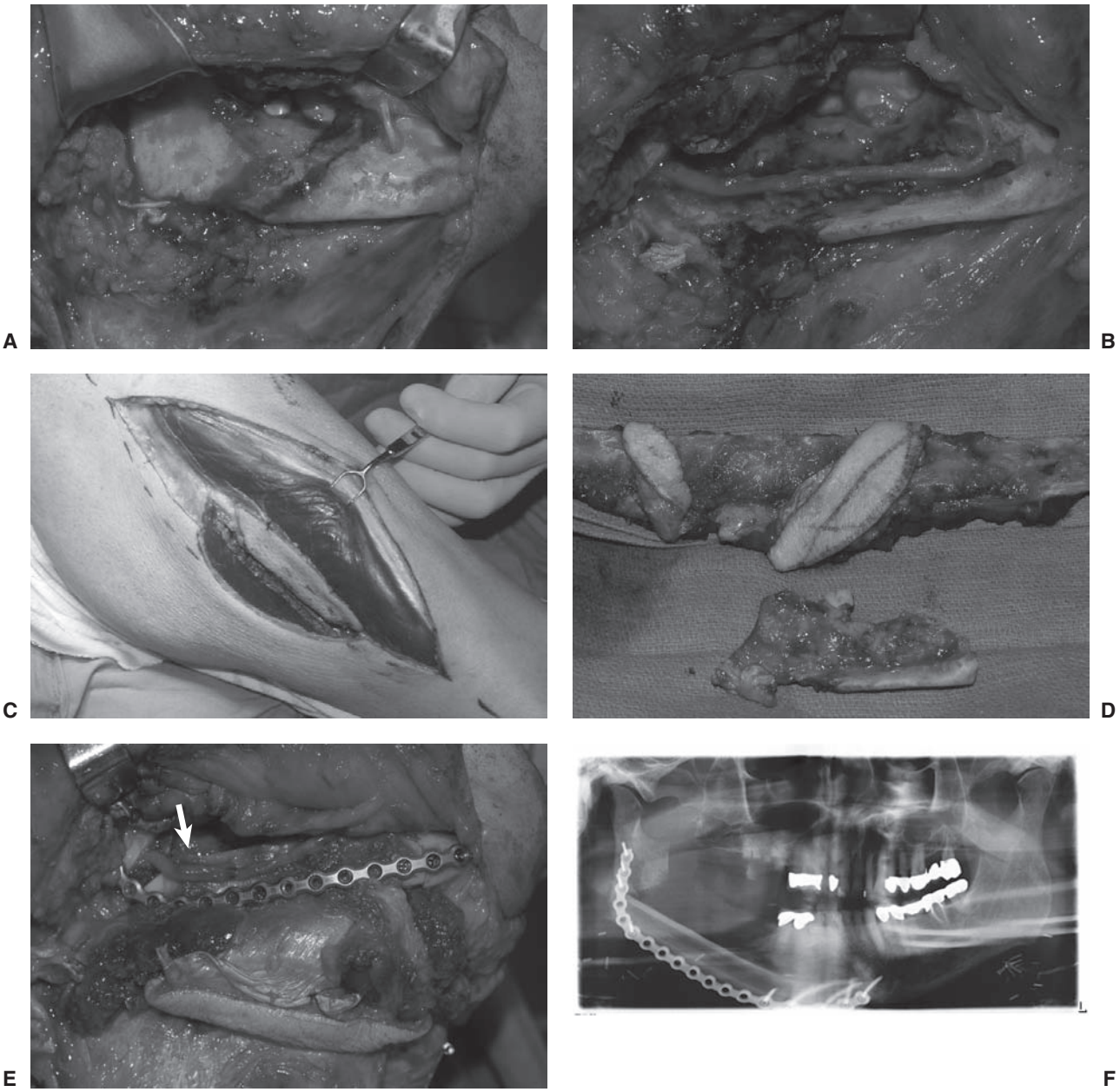



**FIGURE 8-10.** **A:** Intraoperative view demonstrating a pathologic fracture of the mandible prior to surgical resection. **B:** Decortication of the inferior alveolar nerve prior to resection of the mandibular segment. **C:** Harvesting of fibular osteocutaneous free flap. **D:** Fibular osteocutaneous flap harvested from donor site with resection specimen below. **E:** Inset of fibular flap and fixation to reconstruction plate. (Note preservation of inferior alveolar nerve *[arrow]*.) **F:** Panoramic radiograph of surgical reconstruction with fibular free flap and reconstruction plate.

reconstruction for large SP defects (SP3). The flap is folded on itself to provide epithelium on both nasal and oral surfaces so as to limit the contracture expected by allowing mucosalization of the nasal surface.[41]

Commonly, velopharyngeal insufficiency is a major problem with this reconstruction. In an attempt to minimize this problem, an adhesion of the folded free flap to the PP wall is created, leaving only a small unilateral port. The remaining velopharyngeal sphincter should be closed to an opening of no more than 10 $mm^2$.[42] This has become the technique of choice for SP3 defects.

## Functional Outcomes

The goal of treatment of oropharyngeal lesions is to achieve the best possible disease control while minimizing morbidity. The oropharynx is a part of the UADT where a less-than-optimal reconstruction can dramatically affect a patient's ability to speak and swallow. Seikaly et al. examined 27 consecutive patients who underwent oropharyngeal tumor ablation and reconstruction with radial forearm free flaps.[42] The defects produced by the tumor ablation involved multiple subsites within the oropharynx, including the pharyngeal walls, the SP, and the base of tongue.

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**TABLE 8.1 Correlation of Functional Outcomes Utilizing the Performance Status Scale and % Oral Nutrition with Patient-rated Quality-of-life Questionnaires, Including Eating Assessment Tool (EAT-10) and Speech Handicap Index (SHI)**

| | Performance Status Scale | | | |
|---|---|---|---|---|
| **Patient-perceived QOL** | **Normalcy of Diet** | **Eating in Public** | **Understandability of Speech** | **% Oral Nutrition** |
| EAT-10 | –0.79 | –0.72 | –0.65 | –0.76 |
| Speech Handicap Index (SHI) | –0.75 | –0.65 | –0.89 | –0.62 |

The results of this study suggested that the radial forearm free flap is an excellent choice for reconstruction of this particular area.[3] These patients achieved excellent speech and swallowing function. Sinha et al.[43] examined the use of the folded radial forearm free flap in 16 patients for reconstruction of SP and pharyngeal defects. This study examined speech intelligibility, resumption of diet, ability to be decannulated, and postoperative complications. Similar to the results of Seikaly et al.,[42] these authors concluded that the radial forearm free flap provided excellent functional outcomes for SP and pharyngeal reconstruction. Reiger et al.[44] published their functional outcomes for surgical reconstruction of tumors located at the base of tongue in 36 patients. In this series, a resection of 50% or greater of the base of tongue was performed and all defects were reconstructed using a radial forearm free flap followed by postoperative radiation therapy. The results of this report proved that highly functional speech and swallowing is possible after surgical resection and reconstruction of a large portion of the base of tongue.

## HYPOPHARYNX

The restoration of function and avoidance of complications following a hypopharyngectomy is often a significant challenge for the reconstructive surgeon. Classically, a hypopharyngectomy implies resection of a portion or the entirety of the pharynx, with or without resection of the larynx and the cervical esophagus. Reconstruction of the hypopharynx has historically been performed with local flaps as a multistaged procedure, which often led to prolonged hospitalizations and high rates of complications, such as flap loss, fistulae, and strictures. With the advent of microvascular surgery, the reconstruction of the hypopharynx and the pharyngoesophageal segment have evolved into single-stage procedures with vastly improved functional outcomes.

The hypopharynx is a tubed structure that acts as a conduit for the transport of food, liquids, and air, and although it may seem functionally quite simple, it is a dynamic organ endowed with intricate sensory feedback mechanisms that allows food and fluids to be transported posteriorly into the esophageal inlet while air passes anteriorly into the larynx. Tumor ablation can disrupt the function of this structure resulting in temporary or permanent chronic aspiration and dysphagia. The primary goal of the surgeon is to restore the swallowing mechanism in such a way that it provides the ability to maintain nutrition by mouth and to safely manage secretions. The probability of achieving this goal can be vastly different depending on whether the hypopharyngectomy includes a total laryngectomy or not. In the setting of a total laryngectomy, the reconstructive surgeon is charged with restoring the tubed conduit in sufficient caliber to allow for adequate swallowing and tracheoesophageal speech, which is less complex than performing a hypopharyngeal reconstruction in the setting of an intact larynx. In the latter scenario, the challenge is to perform a reconstruction of the pharyngoesophagus with sufficient caliber so that the patient can properly coordinate swallowing to prevent aspiration.

Surgical defects of the hypopharynx can range from small areas that can be closed primarily to very large and complex defects that require free tissue transfers with significant surface area. Each defect requires a different reconstructive approach to adequately restore form and function. In an effort to simplify surgical planning and decision making, the authors have created a defect classification system that is a modification of the one developed by Disa et al.[45] (Table 8.3).

The reconstructive requirement for each type of hypopharyngeal defect is distinct. Noncircumferential defects (type I) are those in which a portion of the native mucosa is retained. In these situations, the reconstruction requires patching the defect while limiting disruption of the native tissues to preserve as much function as possible. Reconstruction of circumferential defects (type II) requires that the entire circumference of the pharynx be restored to allow for unimpeded passage of food and liquid into the esophagus, although this leaves the patient with an adynamic segment. The patient relies mainly on the base of tongue to propel the food bolus into the reconstructed segment. Once in the neopharynx, gravity helps to propel the bolus into the esophagus.

Contemporary reconstruction of circumferential and noncircumferential defects can be accomplished by using either fasciocutaneous or enteric free flaps. The most commonly used fasciocutaneous donor sites are the radial forearm and the ALT. The most common enteric flaps are jejunum and the gastro-omental free flaps. Additionally, one must consider the pectoralis major pedicled flap in the reconstructive algorithm. This regional flap provides a reliable skin paddle for reconstruction of a pharyngeal defect, which requires a patch, but it is usually too thick to consider tubing into a circumferential skin-lined tube for restoration of type II defects.

Although there is a significant debate over which donor site provides the optimal reconstruction for a particular hypopharyngeal defect, each patient represents a unique reconstructive challenge. Type I defects retain a native pharyngeal strip allowing for a noncircumferential closure. These defects require a reconstruction that reconstitutes the tubular structure of the pharynx with a sufficient luminal diameter to prevent pharyngeal stenosis. This defect is most commonly approached with a patch-like reconstruction utilizing either a radial forearm free flap or a pectoralis major pedicled flap. Type II defects involve circumferential defects of the pharynx; therefore, a complete reconstruction of the pharynx must be performed. In this setting, a tubed radial forearm or ALT free flap can be utilized. Additionally, enteric flaps such as the jejeunal free flap or the gastro-omental free flap can be utilized thereby achieving a restoration with a mucosal-lined

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**TABLE 8.2 Oropharynx Ablative Defect Classification System**

| Classification | Definition |
|---|---|
| **Soft palate (SP)** | |
| SP0 | No SP defect |
| SP1 | Minimal defect (<¼) treated by primary closure or healing by secondary intention and unlikely to result in velopharyngeal incompetence (comparable to uvulopalatopharyngoplasty) |
| SP2 | <½ the SP (not including the uvula) |
| SP3 | >½ the SP (including the uvula) |
| **Lateral pharyngeal (LP) wall** | |
| LP0 | No or minimal lateral wall defect |
| LP1 | Involving one LP wall |
| LP2 | Involving both LP walls |
| **Posterior pharyngeal (PP) wall** | |
| PP0 | No or minimal posterior wall defect |
| PP1 | <½ of the PP wall. Implies adequate remaining posterior wall soft tissue to elevate and attach to remaining SP (SP1 or SP2 defect) for closure of the nasopharyngeal side of the defect |
| PP2 | >½ of the PP wall. Inadequate tissue for reapproximation to existing soft tissue |
| **Posterior tongue (PT)** | |
| PT0 | No PT defect |
| PT1 | Minimal defects involving <¼ of the base of tongue, which can either be closed primarily (these defects do not require significant additional bulk for adequate closure) |
| PT2 | Defects involving >¼ of the base of tongue, but less than a total posterior glossectomy (these defects usually require additional tissue to reconstruct lining and bulk) |
| PT3 | Total posterior glossectomy |
| **Hypoglossal (HG)** | |
| HG0 | Both HGs are present and intact |
| HG1 | One HG is not functioning |
| HG2 | Both HGs are not functional |
| **Lingual nerve (LN)** | |
| LN0 | Both LNs are intact |
| LN1 | One LN not functional |

*Source:* Taken from JR Harris, Seikaly H, Urken ML, et al. Oromandibular reconstruction. In: Urken ML, ed. *Multidisciplinary Head and Neck Reconstruction: A Defect-Oriented Approach*. New York, NY: Wolters Kluwer/Lippincott Williams & Wilkins; 2010:647–688, with permission.

segment of tissue. Type III defects are extensive, noncircumferential longitudinal deficiencies involving multiple anatomic levels above the clavicles. These defects are often best approached with a large soft tissue flap such as the ALT, the radial forearm, or a rectus abdominus flap. A rectus free flap can be harvested with a large skin paddle to restore the pharyngeal lining in conjunction with the rectus abdominus muscle, which can provide the soft tissue coverage for an irradiated neck. Type IV defects extend into the thoracic esophagus and are best approached with a total esophagectomy and a gastric pull-up procedure.

## Functional Outcomes

In recent years, the ALT has been frequently utilized for pharyngoesophageal reconstruction. Lewin et al.[46] published the results of their functional outcomes analysis, comparing circumferential pharyngoesophageal reconstruction using the jejunum with the ALT free flap. They reported that the ALT has similar complication rates but shorter intensive care unit (ICU) and hospital stays as well as better speech and swallowing.[46] Yu, Robb, and colleagues also published their results which showed that the ALT flap offers comparable complication rates, but superior speech and swallowing functions, minimal donor site morbidity, a more rapid recovery, and a shorter hospital stay.[47,48]

The radial forearm fasciocutaneous flap has been highly utilized in both partial and circumferential pharyngoesophagectomy defects and has been found to be extremely useful and reliable with respect to speech and swallowing functions. Varvares et al. found that of the 20 consecutive patients reconstructed with the radial forearm, 85% were able to achieve oral alimentation.[49]

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**TABLE 8.3 Hypopharynx Defect Classification System**

| Classification | Definition |
|---|---|
| Type 0 | Small defects amenable to primary closure |
| Type I | Defects that retain a pharyngeal strip so that a noncircumferential closure can be achieved |
| Type II | Defects that require a circumferential closure |
| Type III | Defects that are extensive, noncircumferential longitudinal deficiencies involving multiple anatomic levels above the clavicles |
| Type IV | Defects that extend below the clavicles, into the mediastinum |

## SALVAGE SURGERY

### Salvage Total Laryngectomy

Early-stage (T1, T2) squamous cell carcinoma of the larynx is treated equally effectively with external beam radiation therapy or surgery (transoral or open). Voice quality is generally perceived to be better following radiation therapy.[50,51] For this reason, surgery is often held in reserve for use as a salvage treatment. After primary radiation therapy, the failure rates for T1 disease range between 5% and 10% and slightly higher for T2. It is therefore evident that a certain number of patients with even early-stage laryngeal cancer will ultimately require some form of salvage surgery for persistent or recurrent disease.

Prior external beam radiation therapy has been identified in several studies as a significant risk factor for the development of pharyngocutaneous fistula formation following a laryngectomy.[52–54] Salvage laryngectomy in the setting of prior chemoradiation therapy has been associated with high rates of wound complications ranging from 59% to 77%.[55,56] Additionally, the more damaging effects of chemotherapy and radiation therapy on the wound-healing properties of tissue have been well established.[57,58] For these reasons, many reconstructive surgeons have developed techniques designed to minimize postoperative complications in the salvage setting—techniques that bring healthy, well-vascularized, nonirradiated tissue to the area.

Free and pedicled flaps have been utilized to repair laryngectomy defects when insufficient tissue is available for a primary closure of the pharynx. Withrow et al.[59] recently reported their use of free tissue transfer for reconstruction of a laryngectomy defect in the salvage setting. They compared the rate of pharyngocutaneous fistula, stricture formation, length of hospitalization, and feeding tube dependence between the standard total laryngectomy group and the free-flap reconstruction group. The free-flap group had a lower rate of fistula (18%) compared to the primary closure group (50%). They also had a lower rate of stricture formation (19% vs. 25%) and feeding tube dependence (23% vs. 45%). The authors concluded that planned reconstruction of posttreatment defects with vascularized tissue is the optimal means of reconstruction and is associated with a lower complication rate and may improve long-term outcomes.

Fung et al.[60] published a study in which free flaps were either used to reinforce the pharyngeal suture line in the salvage laryngectomy setting or the free flap was integrated into the neopharynx. The authors described the inset of the free flap with tacking sutures placed in the prevertebral fascia on both sides of the primarily closed pharynx. The patients who underwent free-flap reinforcement were then compared with those in RTOG-91-11, and it was found that the overall rate of pharyngocutaneous fistulas did not differ (29% vs. 30%),[60] but the patients who had undergone the free-flap procedure were treatable with local wound care in the outpatient setting as opposed to requiring major surgical intervention. This led Fung et al. to summarize that the free flap had converted major wound complications to minor wound complications.[60]

The trend seems to be clear that the use of soft tissue flaps as a source of healthy, well-vascularized tissue either in the pedicled or regional form has a beneficial effect in the salvage laryngectomy setting. The issue of which donor site is ideal is highly dependent on the performance and nutritional status, age and body habits of the patients, and the size requirement of the skin paddle. The most commonly used regional flap is the pectoralis major flap. The commonly used free flaps are the radial forearm, the ALT, and the latissimus flaps. Less commonly, enteric flaps such as jejunum or the gastro-omental free flap can be utilized but these surgical options subject the patient to significantly more morbidity associated with a laparotomy.

## MANAGEMENT OF PHARYNGOESOPHAGEAL STENOSIS

Pharyngoesophageal stenosis is a devastating complication following the use of chemoradiation for primary treatment of UADT malignancies. Unfortunately, despite an intact larynx, pharyngoesophageal stenosis can result from this treatment leaving a patient unable to take oral nutrition, as well as unable to tolerate his or her own secretions, and tracheostomy dependent. The tendency for the formation of UADT stenosis may often lead to futile attempts to address this problem through dilation, laser laryngopharyngoscopy, and open surgical procedures due to the damage done to the mucosal lining and the observation that further manipulation may lead to further stenoses that are often worse with each intervention.

The presumed etiology for the development of pharyngoesophageal stenosis following radiotherapy is likely to be multifactorial. Contributing factors may include a combination of long-term nasogastric tube placement and/or chronic gastroesophageal reflux.[61] Perhaps a larger problem is that severe radiation mucositis results in stenosis during healing, which may be exacerbated by using alternative routes for enteral nutrition, placing the cervical esophagus at rest, and thereby allowing denuded surfaces to collapse against each other. In addition, as hypopharyngeal or cervical esophageal tumors respond to treatment, significant portions of the mucosa are eliminated and must then heal by secondary intention.[62] Chemotherapy sensitizes tissues to the effects of radiation, resulting in a greater incidence of both acute toxicity and late complications.[63]

Once identified, pharyngoesophageal stenosis can be managed in a variety of ways as alluded to earlier, but one must consider a number of factors when determining the optimal course of treatment. The authors have developed a new defect classification scheme for defining the key variables leading to posttreatment pharyngoesophageal stenosis.[64]

In this new defect classification system, the degree of pharyngoesophageal narrowing is defined according to the location and completeness of the obstruction, as well as whether the larynx was partially or fully intact, the length of the stenotic segment, and whether prior attempts at dilation led to perforation.

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Surgery usually includes interposition of a skin-lined or mucosal-lined flap to widen the site of stenosis. If the stenotic segment is complete and long, a circumferential resection may be required and a segment of neopharynx must be created. The commonly employed soft tissue flaps are the free jejunal and gastro-omental transfer, radial forearm free flap, and ALT flap. If the region of stenosis extends into the thoracic esophagus, a gastric pull-up is the procedure of choice. Additionally, if the patient has an intact larynx, one must consider whether the stenotic or obstructed segment can be successfully increased in caliber with a flap reconstruction while preserving laryngeal function. If this is not technically feasible, one must give strong consideration to performing a total laryngectomy at the time of the pharyngoesophageal reconstruction. The recommendation to perform a larynx-sparing augmentation of the pharyngeal in patients in whom the intent was to preserve the larynx must be given extensive counseling so that they are well informed as to the possibility that reestablishment of an adequate conduit may not translate into a resumption of safe swallowing. As a result of radiation damage, there are multiple sites of injury that impact normal deglutition, which may be impossible to overcome. Unfortunately, it is not possible to assess the likelihood of recovery of function in patients before opening up the narrowed or obstructed segment. Patients must be advised that there may be a need for a functional laryngectomy if the altered protection of the airway is insufficient despite an open pharyngoesophageal segment. These authors have found improved functioning of voice, secretion management, and diet intake following PE reconstruction surgery in those patients with an intact larynx, those with laryngectomy, and those converted to total laryngectomy due to the severity of stenosis.[64] However, a small subset of patients did not improve in swallow functioning, despite a patent reconstructed segment, due to prior pharyngeal phase dysphagia resulting from radiotherapy.[64]

## CONCLUSION

As the range of reconstructive options has increased, so too has the level of sophistication in addressing defects in the various subsites of the head and neck. The degree of detail that is reflected in the classification schemes outlined in this chapter is a direct reflection of that phenomenon. The extent to which the next generation of surgeons will restore patients afflicted with these diseases and these reconstructive problems will undoubtedly continue to evolve with an even greater attention to detail.

Although there are few studies that prove the direct correlation between advances in reconstruction and survival, there is little doubt that the ability to offer ablative surgery to such patients as shown in Figure 8-7, would not have been considered two to three decades ago. The safety of such a procedure is a product of the level of sophistication in imaging, surgical approach, and the ability to provide safe and reliable reconstruction in a previously irradiated setting. Hanasono et al.[65] found equivalent survival rates and improved local control rates in patients with oral cavity cancers treated prior to the introduction of free tissue transfer surgery versus those treated with microvascular free tissue surgery, despite higher T stage in the microvascular surgery group. In addition, fistula rates and tracheostomy dependence rates were lower in the microvascular surgery group.[65]

QOL and functional outcome studies are greatly needed to allow those involved in the treatment of patients with head and neck cancer to fully understand the impact of their treatment and thereby choose the appropriate therapeutic option. Pooling of patients from multiple institutions will likely be required to accrue sufficient numbers in order to generate meaningful data.

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CHAPTER 9

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# Dental Oncology and Maxillofacial Prosthetics

In caring for head and neck cancer patients, most treatment centers use a team approach. By doing this, each involved discipline (e.g., surgery, radiotherapy, dental oncology, chemotherapy, and speech pathology) determines its role for an enhanced treatment outcome. Rehabilitation of function, aesthetics, and prevention of infection should be a major concern before treatment and following the elimination of disease in the patient with head and neck cancer. Patients with head and neck cancer should be referred to an oncologic dentist or maxillofacial prosthodontist during their initial medical workup for evaluation of their oral and dental health. The results of this evaluation can then be integrated into the primary treatment plan. Early dental intervention can optimize outcome and decrease morbidities such as radiation-induced osteoradionecrosis and chemotherapy-induced systemic infection. Early intervention and planning can also allow surgically removed anatomic structures, such as the maxilla, to be immediately replaced with a prosthesis during the primary ablative procedure.[1,2]

## ORAL AND DENTAL ANATOMY

Surgeons, radiation oncologists, and medical oncologists, who treat patients with head and neck cancer, should be familiar with oral and dental anatomy so that they can accurately communicate with their dental colleagues. Adult teeth are routinely used as landmarks to document the location of tumors of the jaws and to plan intraoral resections and prosthetic procedures before and after surgery. A commonly used scheme for this purpose is the universal numbering system, which is used in the United States to identify the position and type of adult teeth. In this system, adult teeth are numbered sequentially from 1 to 32 (in both the maxilla and the mandible), starting with the right maxillary third molar and proceeding around the arch to the left third molar, down to the left mandibular third molar, and then around the mandibular arch to the right third molar. Missing or impacted teeth are counted in this system.[3] The FDI World Dental Federation Notation (International) is used elsewhere in the world. This system divides the mouth into four quadrants: (a) maxillary right quadrant; (b) maxillary left quadrant; (c) mandibular left quadrant; and (d) mandibular right quadrant. The teeth in each quadrant are then numbered from 1 (central incisor) to 8 (third molar).

The retained, nondiseased anatomic structures of the maxilla and mandible are important for retention and support of prostheses used in rehabilitation of patients with head and neck cancer. In the maxilla, the tissues important for the support and retention of prostheses are the maxillary tuberosity, alveolar ridge, and hard palate. In the mandible, the major supporting structures are the alveolar ridge, retromolar pad, and buccal shelf. Sound and periodontally healthy teeth in both arches are very important in retention and support of prostheses. Conservation of the supporting tissue, without compromising oncologic principles used in the eradication of disease, should be a goal of the surgeon and medical oncologist.[4,5]

## ORAL AND DENTAL EVALUATION

Throughout treatment and follow-up care, the surgeon, radiation oncologist, and medical oncologist should be able to recognize oral pathology secondary to poor dental status, for example, advanced periodontal disease, gross dental caries, tissue irritation secondary to poorly fitting prostheses, and poor oral hygiene. Plaque and calculus formation on teeth is an indication of poor oral hygiene. Preliminary findings of the initial medical examination should be noted. Patients require a pretreatment evaluation by an oncologic dentist, who should do a thorough radiographic and oral/dental examination and make impressions of dental and facial structures as appropriate. Panoramic, periapical, bitewing, and occlusal radiographs can be diagnostic and are inexpensive and easily obtained in the dental office (Fig. 9-1).[6] Stone casts obtained from impressions of the maxilla, mandible, and facial structures can be useful in treatment planning, surgical prosthesis fabrication, and posttreatment rehabilitation. Compromised teeth with a poor prognosis should be extracted before irradiation or chemotherapy (Fig. 9-2). This may require general anesthesia or intravenous sedation with local anesthesia depending on the difficulty of dental surgery and the patient's mental and physical status. Performing dental surgical procedures at the time of the primary ablative procedure will reduce any delay before starting adjunctive treatments such as radiotherapy or chemotherapy. However, appropriate healing time is recommended prior to beginning chemotherapy or radiotherapy. Eliminating sites of infection decreases the chances of osteoradionecrosis in patients who undergo radiotherapy and infectious episodes in patients who receive chemotherapy.[7]

For the first year after cancer therapy, patient follow-up by the oncologic dentist is vital. Patients treated with radiotherapy to the head and neck may experience dry mouth (xerostomia) and a subsequent increase in oral or dental problems such as infection, periodontal disease, and dental caries. All members of the treatment team should understand the importance of fluoride



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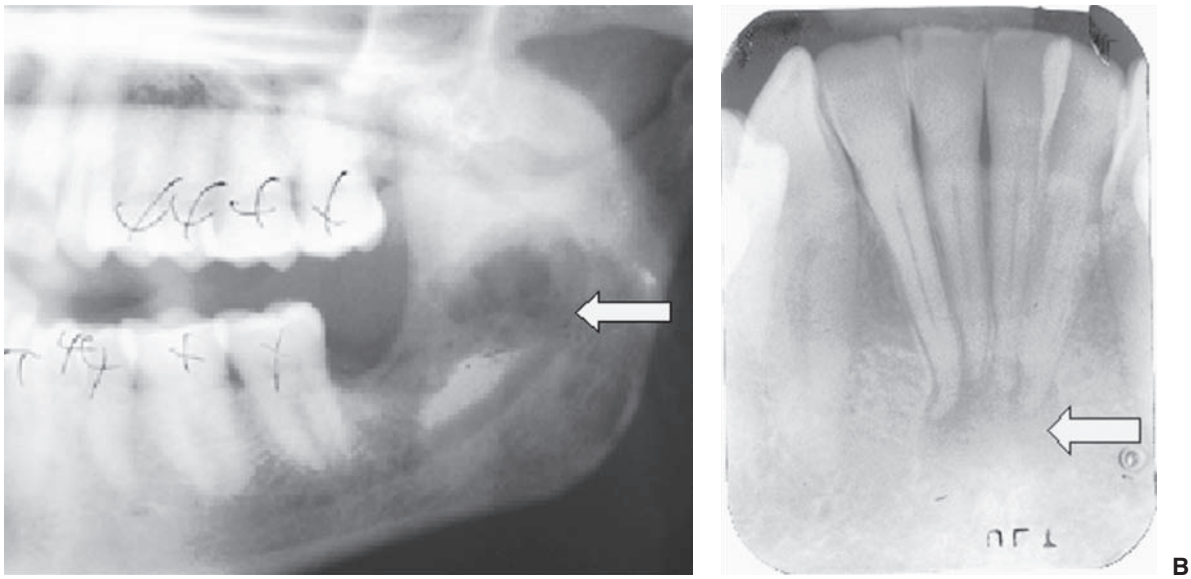


**FIGURE 9-1.** Radiographs obtained in the dental office are relatively inexpensive, easily obtained, and can be diagnostic. The panoramic radiograph **(A)** shows a cancer in the ramus of the mandible. A periapical radiograph **(B)** shows an abscess associated with the anterior mandibular teeth in a patient with lymphoma.

and at each follow-up appointment should encourage the patient to use daily fluoride therapy.[8–10] In many instances, patients can be referred back to their general dentist for routine dental care after the initial posttreatment period.

In summary, a thorough primary, oral, and dental evaluation by an oncologic dentist documents the oral and dental pathology and allows for appropriate intervention before cancer treatment is started. The results of the oral/dental evaluation enable the treatment team to inform the patient about rehabilitation, reduce or eliminate the sites of potential infection, and reveal important information that will be useful during treatment and rehabilitation. To ensure an appropriate level of continued oral care, a dentist should be included as a member of the treatment team.[11]



**FIGURE 9-2.** Patient with poor oral hygiene and periodontal disease will need multiple dental extractions before chemotherapy or radiation therapy. This can be done at the primary ablative procedure or at a separate procedure under local, intravenous, or general anesthesia.

## INTRAORAL PROSTHETIC REHABILITATION

Three phases of prosthetic rehabilitation exist in most cases: surgical, interim, and definitive. Each phase may span several months to 1 year or more, depending on the size and location of the tumor and on the type of treatment required. Initially, surgical and interim prostheses may require frequent follow-up appointments and adjustments. Patients who undergo surgery that involves the maxilla and sinus may experience nasal regurgitation of food and liquids from the mouth into the nose. During and following treatment, meticulous oral and dental hygiene is important as a life-long therapy. Physical therapy may also be necessary to maintain oral opening and prevent trismus.

### Maxilla

Malignant and benign tumors involving the maxillary sinus, hard palate, and upper alveolus often require surgical resection with an infrastructure maxillectomy procedure. The resultant surgical defect is an oral–nasal and/or oral–antral communication, which may cause substantial postoperative speech and swallowing problems. These defects often require prosthetic obturation. Surgical considerations that may improve prosthetic rehabilitation of patients who receive a maxillectomy are described in detail in the following text. In a dentate patient, the head and neck surgeon should make the alveolar osteotomy through the socket of an extracted tooth to preserve bone support around the terminal tooth. In cases in which cuts are made between teeth, both teeth may be lost. The palatal osteotomy should conserve as much of the supporting tissue as possible, for example, premaxilla, tuberosity, and alveolar ridge, consistent with oncologic principles. If possible, a split-thickness skin graft (STSG) should be placed in the maxillary defect. A well-placed STSG reduces postoperative secretions, facilitates oral hygiene, provides a sound tissue base for a prosthesis, and creates a scar band for greater retention of the prosthesis. The palatal mucosa, if it is not affected by disease, can be retained and used to line the midline portion of the palatal cut. This tissue is extremely resistant to the abrasive forces of the prosthesis.

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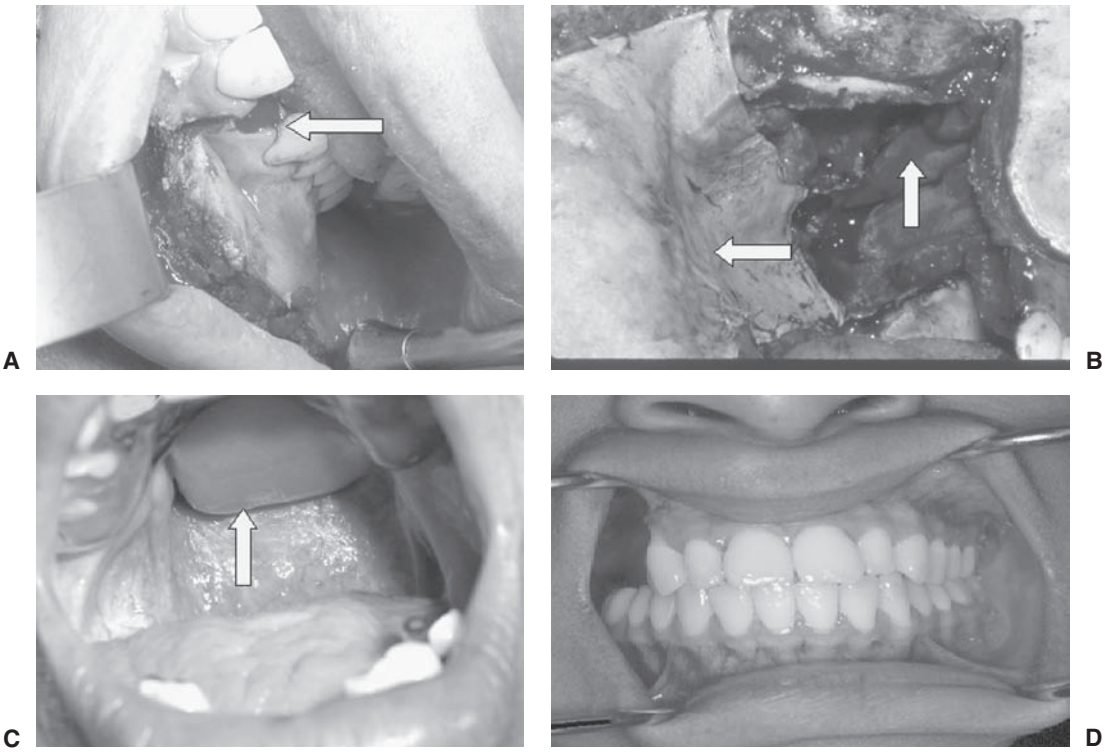



**FIGURE 9-3.** Important surgical considerations in maxillectomy. **A:** Make alveolar cuts through extraction socket in dentate patients. **B:** Remove inferior and middle turbinates and place split-thickness skin graft. **C:** Remove total soft palate to improve prosthesis function. **D:** Perform intraoral resection and spare premaxilla when possible.

The inferior and middle turbinates should be removed to allow extension of the prosthesis into the defect area and will ensure a good prosthetic seal. Mandibular molar teeth on the side of the maxillectomy should be considered for extraction if the opposing maxilla and teeth are resected. These teeth can pose a hygiene problem and are essentially nonfunctional after a posterior maxillectomy. This problem is particularly significant when the resection extends inferiorly in the buccal mucosa. When possible, the maxillectomy should be performed intraorally, thereby eliminating the facial incision and resulting disfigurement (Fig. 9-3).[12]

A surgical obturator prosthesis placed at the time of the ablative procedure reestablishes the palatal contour, restoring speech and swallowing function. This prosthesis also supports the surgical packing and skin graft in position. The surgical obturator can be ligated to the remaining teeth with a 24-G ligature wire or retained with a bone screw in the edentulous patient. The surgical obturator prosthesis may allow the patient to speak and swallow almost immediately after surgery and, in turn, may obviate the need for a nasogastric tube (Fig. 9-4). The prosthesis maintains proper lip and cheek support during initial healing and therefore increases resistance to the contracture and subsequent facial deformity or scar tissue. Patients scheduled for maxillectomy should be referred to an oncologic dentist (presurgical) during their initial oncologic evaluation to ensure adequate time for fabrication of this prosthesis.[13]

An interim obturator prosthesis is placed immediately after the surgical obturator and packing are removed, usually 5 to 8 days postsurgery. The interim obturator prosthesis has an extension that obturates the oral nasal/antral defect. This extension is created with a soft, moldable denture tissue conditioning



**FIGURE 9-4.** Surgical obturator prosthesis retained by interdental wiring negates the use of a nasogastric tube and fixates the split-thickness skin graft reconstruction during initial healing. It also provides postoperative aesthetics and supports the cheek and lips, which resist facial contracture. This prosthesis is removed along with the packing in 5 to 7 days.

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**FIGURE 9-5.** Interim obturator prosthesis is placed after removal of the surgical obturator prosthesis. This prosthesis must be followed closely and modified to accommodate healing. It is usually worn for 3 to 6 months until the surgical defect stabilizes.

material, and is modified as necessary to accommodate healing during the initial healing phase (Fig. 9-5). A minimum of five to ten appointments may be needed to adjust and modify the prosthesis during this distinct phase of rehabilitation.[14]

A definitive obturator prosthesis is made after the surgical defect has stabilized, approximately 6 months after the surgery. This prosthesis allows for enhanced aesthetics and function. The average lifespan of the definitive obturator prosthesis is 3 to 5 years, and close follow-up with adjustments is important to ensure continued accurate fit and comfort (Fig. 9-6).[15]



**FIGURE 9-6.** Definitive obturator prosthesis in place. This prosthesis maximizes function and aesthetics.

Microvascular free-flap surgical reconstruction of the maxilla in patients treated with a maxillectomy is becoming increasingly common. In some cases the use of free flaps may be an excellent alternative to the prosthetic obturator prosthesis, whereas in others this option may not offer acceptable aesthetic or functional results. Older adults, mentally challenged individuals, and those who have lost the dexterity to place and remove a prosthesis should be considered for free-flap reconstruction. Prosthetic rehabilitation after free-flap reconstruction may be difficult due to bulkiness and mobility of the flap. Patients who demand a functional and aesthetic restoration after reconstruction with a free flap should be referred to a maxillofacial prosthodontist before the procedure so that information concerning rehabilitation can be considered before the procedure.[16]

## Soft Palate

When the soft palate is involved in the surgical procedure, the surgeon must consider whether the remaining soft palate will be useful in prosthetic rehabilitation. In most cases, any remaining soft palate that is nonfunctional should be completely removed. Removal of the soft palate allows easy access to the pharynx for fabrication of the pharyngeal obturator prosthesis. Occasionally, a thin strip of soft palate can be vitally important for prosthesis retention in patients with limited supporting tissue (teeth, hard palate), such as when a bilateral total maxillectomy has been completed (Fig. 9-7).[17] In cases where the resection of the soft palate is anticipated, an intraoperative dental consultation may be indicated. Primary radiation treatment of the soft palate may cause muscle fibrosis leading to incompetency of the soft palate. In this situation, prosthetic rehabilitation may be impossible because of poor access to the oropharynx. In some cases, surgical removal of the soft palate may be required before prosthetic rehabilitation. Prosthetic rehabilitation may not restore the pretreatment speech and swallowing function because of radiation-induced fibrosis and limited movement of the muscles of the pharyngeal walls. These muscles are important in compensating for the missing soft palate by contacting the pharyngeal obturator during speech and swallowing.[18]

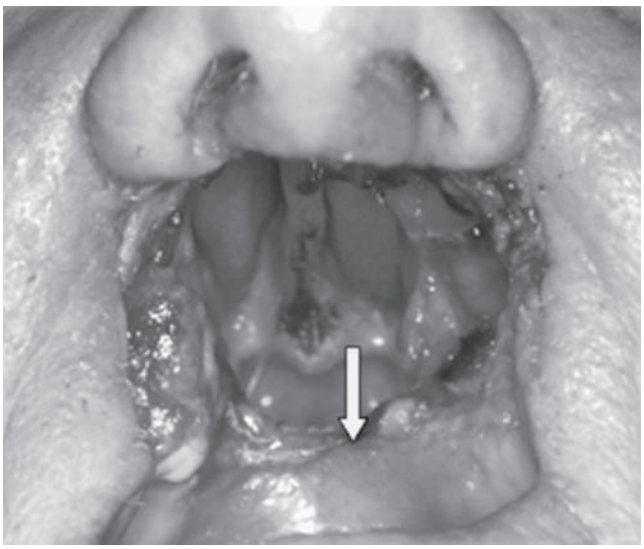


**FIGURE 9-7.** Midface resection with total bilateral maxillectomy. Soft palate (*arrow*) is retained for retention and support of obturator prosthesis.

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## Mandible

Patients requiring a mandibulectomy may need surgical stents to assist the surgeon in realignment of the residual mandible before reconstruction. These stents are custom-made and require preoperative fabrication. Reconstruction plates are medical devices used during the resection and reconstruction of mandibles. The reconstruction plate holds the remnants of the mandible/condyle in its preresected position and attaches to the bony segments of the microvascular flap. This optimizes appropriate mandibular contours and function. These plates must be precisely bent onto the preresected mandible, attached with reconstruction screws, and then removed prior to the resection. Reattachment in the same position later with the microvascular flap ensures accuracy. Intermaxillary fixation with arch bars may also aid in realignment and stabilizing the mandible during reconstruction.[19] The maxillary teeth opposite the mandibular reconstruction may need to be extracted to prevent trauma to bone and soft tissue flaps. In cases in which reconstruction is not being considered for a patient who has received a mandibulectomy, removal of the remnant condyle and ramus on the affected side prevents migration of these structures medially toward the maxilla. Such migration can make prosthetic rehabilitation more difficult and add more frustration to the patient.[20]

In general, soft tissue coverage of the mandible when free flaps are used does not provide adequate supporting tissue for prosthetic rehabilitation (Fig. 9-8). Vestibuloplasty is a surgical procedure designed to restore alveolar ridge support by reducing the attachment of muscles to the buccal, labial, and lingual aspects of the jaw and thinning the existing tissue, such as flaps used in the initial reconstruction. STSGs are important because they provide a sound tissue base for a prosthesis and can also be used to separate the floor of the mouth from the buccal mucosa (Fig. 9-9).[21] When the tongue is sutured to the buccal or labial mucosa, prosthetic rehabilitation is limited if not impossible. As with the maxilla, conservation of the supporting tissue in the mandible, consistent with removal of disease, is important. Dental implants can be placed in the nonirradiated native or reconstructed mandible and may be critical to the stability and retention of the mandible prosthesis. Maxillary and mandibular resection dentures can be fabricated for patients who do not receive reconstructive surgery after mandibulectomy.

## Tongue

Speech and swallowing dysfunction are common problems in patients following glossectomy. Tumors of the oral cavity often involve contiguous structures and resections within the floor of the mouth and are likely to involve the tongue and muscle attachments, or innervation. The ultimate treatment goal is maximum restoration of speech and swallowing, which may require the combination of soft tissue and prosthetic reconstruction.

Palatal augmentation prostheses are removable palatal prostheses that reshape the hard palate to improve contact between the residual tongue and the palate during speech and swallowing (Fig. 9-10). These prostheses improve speech and swallowing function due to impaired tongue mobility as a result of surgery, trauma, or neurologic/motor deficits. Resection sites that are most likely to affect oral components of speech and swallowing are the oral tongue, anterior or posterior mandible, floor of the mouth, and base of the tongue.[22]

The greatest improvement in function with palatal augmentation prostheses results when movement of the residual tongue tissue is retained. Replacing lost tissue bulk with soft tissue may obliterate some of the space that cannot be controlled by the limited range of motion of the tongue. Patients with the greatest movement of the residual tongue benefit the most from the augmentation

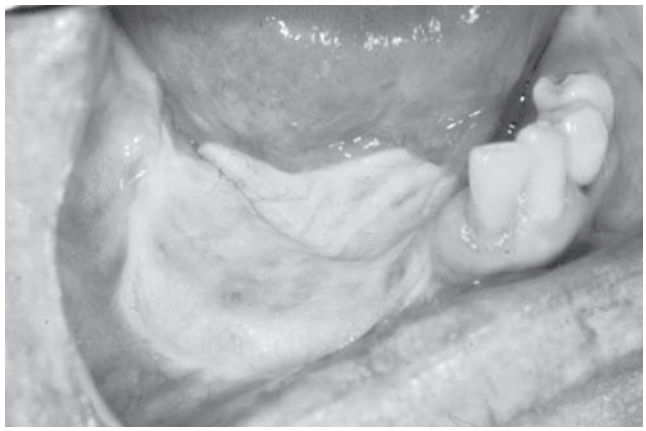


**FIGURE 9-9.** Fibula reconstruction of mandible with split-thickness skin graft vestibuloplasty and dental implant placement. Patient is now ready for prosthetic rehabilitation.

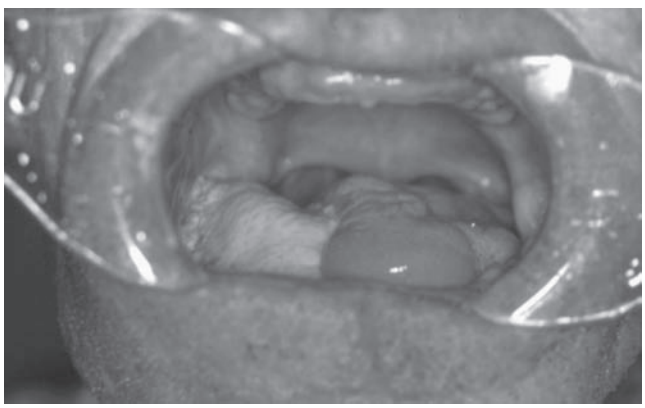


**FIGURE 9-8.** Fibula reconstruction of mandible with skin paddle is reconstructing floor of mouth and covering mandible. This skin paddle is movable, thick, and not satisfactory for prosthesis support.

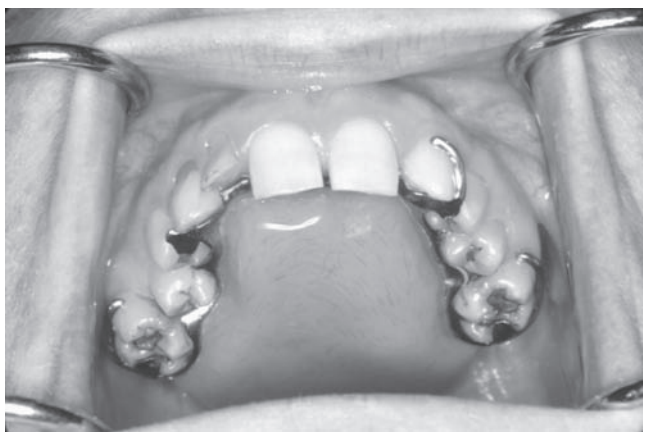


**FIGURE 9-10.** Patient with total glossectomy reconstructed with free flap and palatal augmentation prosthesis. Prosthesis functions against free flap and improves speech and swallowing.

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prosthesis, and patients with a mobile tongue tip have the best function. The use of thinner microvascular flaps for closure of the surgical site allows the residual innervated portion of the tongue to function with minimal impairment of movement. The palatal augmentation prosthesis offers rehabilitation advantages for patients with impaired function of the tongue.

## Oral Hygiene Procedures

Oral hygiene is one of the most important aspects of postoperative care. Initially, the surgical defect should be irrigated with an irrigation system, that is, bulb or syringe irrigation or power-spray units. After initial healing, a power-spray unit such as Water Pik (Teledyne Dental, Buffalo, NY) can be used by the patient. The patient should be instructed in the proper use of the lavage system. Initially after surgery, the patient should rinse three times a day with a saline solution made by adding one teaspoon of salt and one teaspoon of sodium bicarbonate to 16 oz of water. The irrigation system must provide enough pressure to ensure that the rinse reaches all parts of the surgical defect. Routine dental hygiene, that is, tooth brushing and flossing should be started as soon as possible. Patients are usually apprehensive about resuming the brushing and flossing of teeth because of concerns that doing so may harm the surgical site. However, if healing proceeds normally, using a power-spray system (low setting) beginning 4 weeks after surgery should not pose a problem. During the fourth week of healing, a 1:1 dilution of 3% hydrogen peroxide in water can be added to the oral hygiene routine. A sponge-tipped applicator (e.g., Oral-Swab, Crystal Lake, IL) may be used to clean the skin graft portion of the defect. After the surgical site has been cleaned, the entire oral cavity including the teeth, the tongue, the cheek, and the remaining hard palate is cleaned.[13,23]

## Physical Therapy

Conventional oral physiotherapy (i.e., mouth opening exercises) should be performed during and after radiation treatment, especially if the pterygoid regions are included in the radiation treatment fields.[24] If a restricted mouth opening is noted following surgery, tongue blades stacked on each other can be inserted between the posterior teeth until maximum opening is obtained. The blades are held in place for several minutes to allow the forming scar tissue to stretch, and then another tongue blade is added until a pain threshold is reached.

Various passive and active commercial devices to aid in mouth opening are available. Two such devices are the Therabite mouth opener (Atos Medical, Milwaukee, WI) and the Dynasplint (Dynasplint Systems Inc., Severna Park, MD). These devices open the mouth vertically with a manual separation of the jaws or a prolonged stretch (Fig. 9-11). Each of these devices is customized to the patient and has advantages and disadvantages. Users of these devices must follow manufacturers and physical therapy guidelines and ensure that teeth do not incur orthodontic tooth movement or damage. The edentulous patient can use his or her fingers, placing them between the maxillary and the mandibular ridges, to pry open the mouth. The exercises can be combined with extraoral palpation and stretching of the cheek and upper lip to keep the tissue as pliable as possible. During the first 4 weeks, the patient should be instructed to do these stretching exercises three or four times a day (15 minutes each session). In addition, a trained physical therapist can institute more advanced means of physical therapy, such as electrotherapy, ultrasound therapy, and isometric exercises. Daily mouth opening measurements should be recorded to help both the clinician and the patient measure progress resulting from these exercises, that is, rulers or calipers measuring vertical dimension between the maxillary and the mandibular incisors or ridges. In many cases, these physiotherapy techniques should be continued for at least 1 year. If a patient has a sudden loss of mouth opening, the dentist should immediately suspect and rule out recurrence of disease or infection.[25]

# OSSEOINTEGRATED DENTAL IMPLANTS

Osseointegrated implants have been used widely in dental rehabilitation since the 1980s. However, indiscriminate placement of these implants can decrease their effectiveness and increase the cost of rehabilitation dramatically. In patients with a normal mandible and maxilla, the success rate of osseointegration is between 90% and 95%.[26] However, in patients with a reconstructed mandible, the success rate may be lower, depending on



**FIGURE 9-11.** Physical therapy is a very important aspect in the care of the patient who has undergone head and neck surgery. This figure illustrates tongue blades and the Therabite mouth opener (Atos Medical, Milwaukee, WI), which help maintain oral opening during initial healing along with facial massage and stretching.

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the quantity and quality of the recipient bone. Careful planning is required before an implant is placed in any patient.

Implants may be the only means by which some maxillofacial prostheses can be retained, particularly those placed over osteocutaneous flaps. Patients who have undergone a free fibula tissue transfer placed using microvascular techniques make excellent recipients of implants. The fibula's bicortical configuration and vertical height are ideal for endosteal implant placement. Vertical height of the fibula averages 15.2 mm, which is ideal for the standard-sized implant.[27] The number, positioning, and spacing between implants is critical in prosthesis fabrication. These details are best dealt with after reconstructive surgery, in a separate procedure, when a surgical stent made by the dentist responsible for rehabilitation can help guide the surgeon in the exact alignment and positioning of the implants. The information needed to obtain proper fit and positioning of prostheses can be determined only by postoperative evaluations. Some implant systems require two-staged surgical procedures, whereas others require only one stage. The type of implant used should be the choice and responsibility of the dentist responsible for the prosthetic rehabilitation of the patient (Fig. 9-12).[28] Patients requiring postoperative radiation may not be candidates for implants if placed in the volumes of tissue radiated. This subject is discussed later in the chapter in the section "Care of Patients with Head and Neck Cancer Treated with Radiation."

## EXTRAORAL IMPLANTS

In the beginning of 1993, one extraoral implant system had been approved by the U.S. Food and Drug Administration (FDA); however, more have been approved since then and are currently available. Like many of their intraoral counterparts, extraoral implants are placed in two stages; however, the extraoral implants should heal unloaded for 4 to 6 months to allow adequate time for integration. Extraoral implants can be of great benefit for retention and stability of facial prostheses when correctly placed, but do not always guarantee a successful prosthesis.[29] Other retention systems available for facial prostheses are adhesives and tapes. Undercuts in the defect, if properly prepared, can also be used to retain prostheses. When contact between intraoral and extraoral defects results from surgery, the facial portion of the prosthesis can be retained through its attachment to an intraoral component.

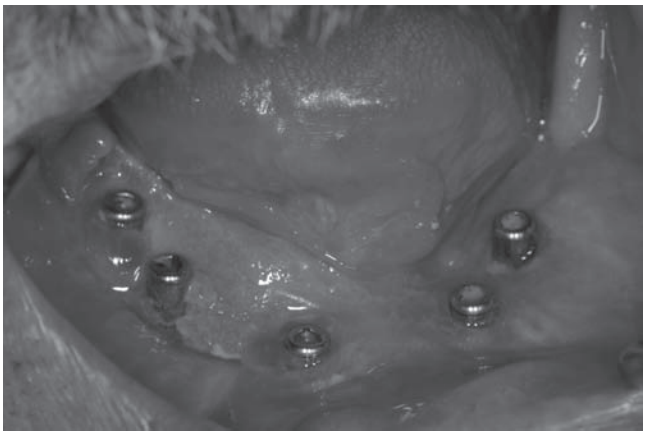


**FIGURE 9-12.** Patient reconstructed with fibula graft and dental implants. Number and position of implants are determined by dentist responsible for rehabilitation.

## RAPID PROTOTYPING

Rapid prototyping is an automated construction of objects with three-dimensional printers, stereolithography machines, or laser sintering devices that are useful in dental implantation. The first rapid prototyping techniques were developed in the 1980s and were used to fabricate prototypes of tools and parts.[30] Currently, it is used in the biologic sciences to create dimensionally accurate models of anatomic structures. Computed tomography and magnetic resonance imaging can be used to transform medical images into resin replicas of skeletal anatomy. A three-dimensional model of an ablated site in the head and neck region can be used in preoperative planning or surgical stent fabrication or to create a template for implant placement. In addition, rapid prototyping provides an accurate spatial reference during surgery (Fig. 9-13).[30,31]

## FACIAL PROSTHETICS

In general, a successful facial prosthesis is aesthetically pleasing, retentive, and tissue compatible. In addition, a prosthesis should be simple in design so that the patient can place and remove it easily. Materials used in constructing facial prostheses should be easy to clean, color stable, resistant to bacterial and fungal growth, durable, and well tolerated by tissues. The two materials that meet these criteria most fully are methylmethacrylate (plastic) and medical-grade silicones. Extraoral prostheses may be combined with intraoral prostheses to enhance retention and aesthetics.

### General Rehabilitative Principles for Ablative and Reconstructive Surgery Involving Facial Structures

***General Principles.*** Numerous general surgical principles can be applied to placement of prostheses at all facial sites. Although basic, these principles are extremely important in ensuring the success of facial prostheses:

- Smooth and round off all bony margins at the conclusion of the ablative procedure.

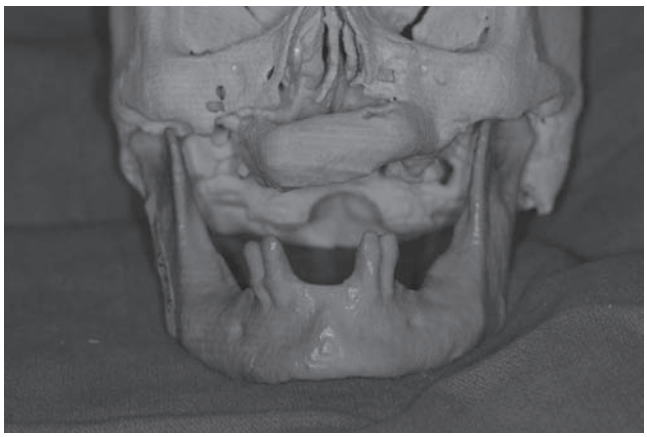


**FIGURE 9-13.** Rapid prototyping model used to plan reconstruction of maxillary defect. This model shows the fibula reconstruction of the maxilla and will be used to plan implant placement necessary for prosthetic rehabilitation.

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- Place an STSG on any exposed bone or periosteum that is not covered with free tissue or a pedicle flap.
- Remove unsupported tissue tags.
- Take replacement tissues from areas that best match the tissues surrounding the recipient bed.
- When using free tissue transfer flaps or pedicle flaps to repair the surgical defect, take care not to overbulk the surgical site in a patient for whom a prosthesis is planned.

***Orbit.*** When the orbital contents are removed in conjunction with a maxillary resection, reconstruction of the infraorbital rim improves the facial contour and enhances the prosthetic rehabilitation. This reconstruction can be accomplished by using a microvascular reconstruction with bone. If the bony structures of the orbit are left intact, an STSG can be placed in the defect, thereby allowing a prosthesis contact with the tissue at the depth of the defect (Fig. 9-14). Care must be exercised in placing the STSG so that the normal position of the eyebrow is maintained. Alternatively, microvascular reconstruction can be used to obliterate the defect entirely.

***Nose.*** Patients who undergo partial or total rhinectomy can be adequately rehabilitated using a removable prosthesis. An STSG should be placed in the defect to stabilize the borders of the defect and to maintain a normal lip position. For patients undergoing total rhinectomy, it is especially important that the inferior border of the nasal defect be fixated and that a dam at the inferior border of the defect be created. If the defect cannot be skin grafted, the surgeon should consider positioning the mucocutaneous junction as far posteriorly into the defect as possible. This measure will fixate the border and help form a dam. If possible, the nasal spine should be spared and the mucosa of the septum covered with a skin graft.

***Ear.*** The superior rim and tragus should be spared if possible (Fig. 9-15). If supported by cartilage, the superior rim can be used to support eyewear. The tragus can be used to hide anterior margins to improve aesthetics. The STSG can tolerate tissue adhesives used to retain facial prostheses and will also improve hygiene.[32]

***Midface.*** To enhance prosthetic rehabilitation at midface sites, several special considerations must be made before and during the reconstructive procedure.[29] During the ablative procedure, the surgical team should conserve as much of the maxilla and associated structures as possible. Respiratory mucosa should be removed from the remaining vomer, nasal floor, and sinuses, and a STSG should be placed.[21] The STSG will allow extension of the removable facial prosthesis into these areas if this extension later becomes necessary and will stop secretions from the replaced respiratory mucosa (crusting), thereby improving overall hygiene.[33]

A free-flap reconstruction with bone can be placed to improve the retention and support of the facial prosthesis. Sufficient space for this purpose is critical because if the graft is placed too far anteriorly, the aesthetics of the facial prosthesis can be diminished. If the reconstruction infringes on this space, placement of the prosthesis may be impossible. In this case, another surgical procedure to reposition the graft would be needed before prosthesis fabrication. The free-graft reconstruction should be done after irradiation if implants are indicated. Once bone is irradiated, its capacity for implant placement and subsequent osseointegration is severely diminished or lost because its osteogenic potential and microvascularity are decreased.[34]

## CARE OF PATIENTS WITH HEAD AND NECK CANCER TREATED WITH RADIATION

The clinical use of radiation is a complex process involving many professionals and a variety of interrelated functions. The aim of radiation therapy is to deliver a precisely measured dose of radiation to a defined target volume, thereby eradicating the tumor while causing minimal damage to surrounding healthy tissue.[35] More than 80% of patients diagnosed with advanced head and neck cancer receive a course of radiation therapy as a component of their treatment.

### Radiation Stents

The use of conformal radiotherapy treatment helps to minimize radiation dose to the adjacent normal oral structures. Despite this, side effects to the adjacent tissues continue to be common. Radiation stents can be fabricated by the dental oncologist under the direction of the radiation oncologist. These intraoral devices can position oral tissues into or away from the radiation treatment fields and help to immobilize the oral cavity structures

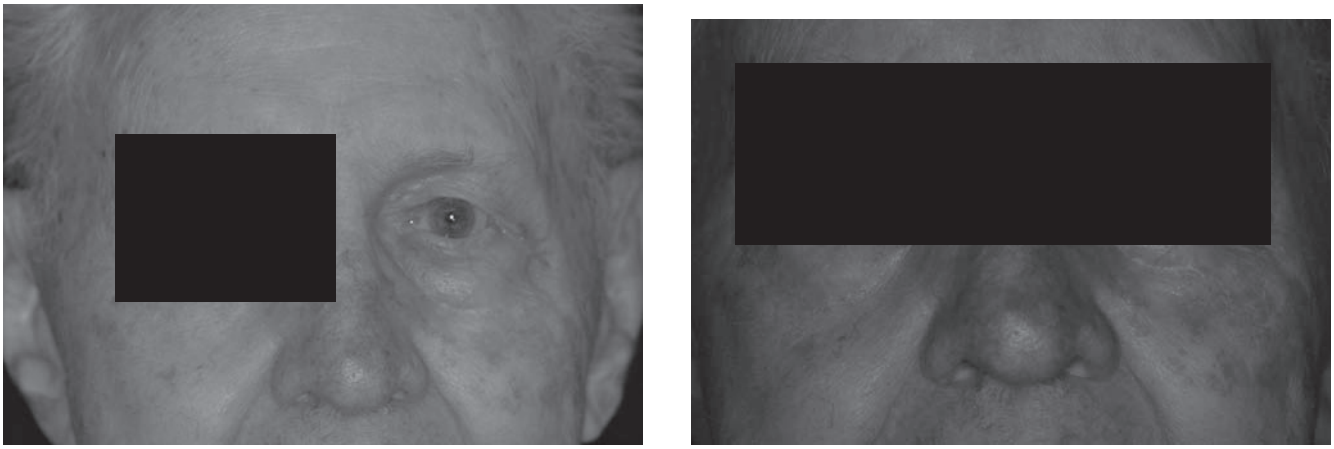


**FIGURE 9-14.** This figure illustrates an excellent split-thickness skin graft (STSG) reconstruction of an orbital defect and rehabilitation with an orbital prosthesis. If the bony structures of the orbit are left intact, an STSG should be placed in the defect. This allows placement of an orbital prosthesis that contacts the tissue at the depth of the defect. Implants placed into the lateral orbital rim help to retain and position the prosthesis.

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**FIGURE 9-15.** Nasal defect that represents basic principles for surgical preparation of facial defects. A split-thickness skin graft reconstruction that stabilizes the borders of the defect and no tissue tags is shown. The superior rim and tragus should be spared if possible when dealing with ear defects.

during each daily treatment.[36] Two common stents are the mouth opening/tongue depressing (MOTD) stent, and the unilateral stent. The MOTD stent separates the maxilla and the mandible by approximately 2 cm. and depresses the tongue into the floor of the mouth. This stent spares the mandible and tongue if the maxillary sinus/nasal cavity structure is being radiated. Conversely, the MOTD stent spares the maxillary sinus/nasal cavity structures if the tongue, mandible, or neck is being radiated. The unilateral stent is utilized during radiotherapy treatment of lateralized malignancies, that is, parotid, buccal mucosa, tonsil, retromolar trigone. This stent positions the tongue to the unaffected side, and positions the maxilla and the mandible in the same position during each treatment (Fig. 9-16).

## Oral Complications

A healthy oral status before radiation therapy reduces the risk for complications from therapeutic administration of ionizing radiation to the head and neck. These complications can be categorized as either acute (e.g., mucositis, infectious stomatitis, alteration of taste or smell acuity, dermatitis, pain, inflammation, and difficulty swallowing) or chronic (e.g., xerostomia, caries, abnormal development, fibrosis, trismus, photosensitivity, osteoradionecrosis, and pain).[37–39] The severity of treatment-induced morbidity depends on multiple factors such as the radiation dose, energy source, volume of tissue treated, pretreatment performance status, and pretreatment periodontal condition.[40] The volume of tissue irradiated is susceptible to dermatitis and mucositis, which are often accompanied by salivary gland hypofunction, dysgeusia, dysphagia, odynophagia, hypovascularity of soft and hard tissues, fibrosis, or trismus.[37,40,41] Widespread oral melanotic hyperpigmentation and hypopigmentation have been reported. Developmental abnormalities of the dentition and jaws may occur in children undergoing head and neck radiation therapy.[42–45] In patients of all ages, altered tissues within the volume of tissue irradiated are highly susceptible to infectious processes, especially with fungal organisms, such as *Candida albicans* or other species; bacterial infections, especially with *Streptococci* and *Staphylococci*; and viral infections, especially with herpes simplex virus (Fig. 9-16).[46,47] Resistant strains can further pose a significant challenge to patients and clinicians.

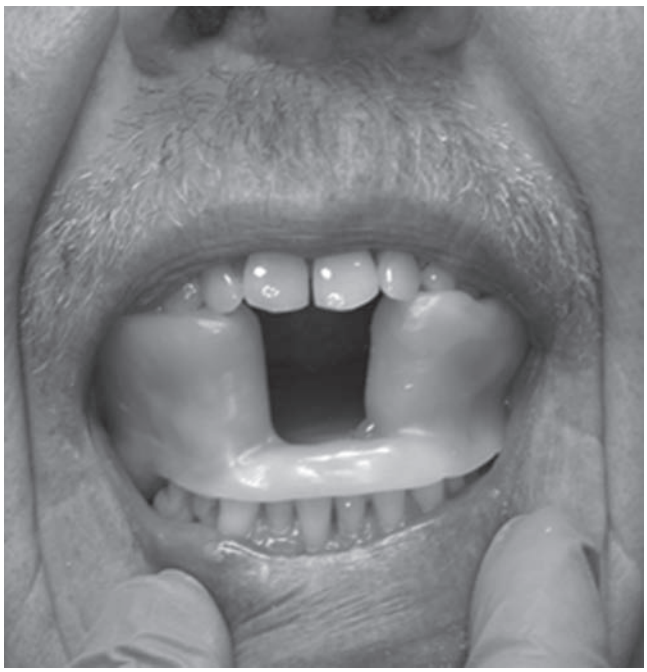


**FIGURE 9-16.** Mouth opening/tongue depressing radiation stent (wax pattern) positioned intraorally. This patient is being treated for a base of tongue malignancy. The stent positions the maxilla away for the radiation field and immobilizes the oral tissues during each radiation treatment.

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**FIGURE 9-17.** Oral candidiasis in a patient undergoing external beam radiation therapy for a base of tongue primary carcinoma.



**FIGURE 9-18.** Radiation-induced mucositis in a patient receiving treatment for a squamous cell carcinoma of the oral tongue with metastatic disease in the cervical region.

## Mucositis

Oral mucositis generally occurs 5 to 7 days after initiation of external beam radiation therapy (Fig. 9-17). Oral mucosal changes depend on the fractionation, energy source, total dose of radiation, and oral and dental status.[40] When an electron beam is used with high-energy photon beams in the treatment of deep lesions, the mucosal reactions on the side of the entering beam may consist of patchy or confluent exudate, whereas the contralateral side may show only erythema. During the course of radiation therapy, the mucosa becomes thin as a result of direct cell death and the sloughing off of rapidly replicating epithelial cells.[48]

Eliminating all secondary sources of irritation such as alcohol, smoking, and coarse products that can further dehydrate oral tissues can decrease the severity of oral mucositis. Hot foods, alcohol- or phenol-containing mouth rinses, and sodium[49] should be avoided. Treatment of mucositis typically consists of palliative pain-reduction therapy. Physicians have advocated several agents for topical use, including benzydamine hydrochloride, allopurinol, sucralfate suspension, kamillosan, povidone-iodine, antacids, sodium bicarbonate, local anesthetic agents (such as lidocaine hydrochloride), chlorhexidine gluconate, oral suspension of prostaglandin E2, and aloe vera with the active ingredient acemannan.[49–53] Unfortunately, very few clinical trials have examined these substances, and the results have shown only moderate clinical efficacy.[54,55] Good oral hygiene is essential for improving oral comfort and reducing the risk for oral contamination. Bacterial, fungal, and viral infections can occur as superinfections with mucositis, but are less likely to induce septicemia in patients undergoing radiation therapy than in patients receiving chemotherapy.[37] Patients receiving a concurrent regimen of radiation therapy and chemotherapy may be at a greater risk for infectious mucositis than patients treated with either therapy alone. With fungal infections, such as oral candidiasis, the pathogenesis can be invasive, refractory to treatment, and potentially septic.[46] Candidiasis can manifest as pseudomembranous, hyperplastic, or atrophic (erythematous) oral lesions.[46] The sites most frequently affected are the tongue, buccal mucosa, hard or soft palate, or the commissurae labiorum oris (i.e., angular cheilitis) (Fig. 9-18). Treatment consists of such topical antifungal agents as nystatin oral suspension or clotrimazole troches, depending on the degree of xerostomia.[46,56,57]

To avoid oral infections and to reduce the mucositis that may arise from radiation therapy, patients must frequently rinse the oral cavity to reduce oral microorganisms and to maintain mucosal hydration. Such oral lavage can be performed by rinsing with a solution of one teaspoon of sodium bicarbonate dissolved in 12 oz water several times each day to alkalinize the oral cavity and to keep the oral and oropharyngeal tissues moist. Mouth rinses, saliva substitutes, and gustatory stimulants are frequently abandoned by patients treated with head and neck radiation therapy because the effect is short-lived or not effective.[37] Such patients should be encouraged to increase water intake, decrease acidic and carbonated beverage intake, and decrease sodium intake.

## Osteoradionecrosis

Radiation can permanently destroy cellular elements of bone and therefore limit the potential for wound maintenance and the ability to heal after infection or trauma (e.g., dental extraction and alveoloplasty).[58,59] The risk for complications following trauma or oral surgical procedures in an irradiated field can be highly significant, depending on a predetermined threshold of irradiation, and result in osteoradionecrosis (Fig. 9-19).[40] For these reasons,



**FIGURE 9-19.** Patient undergoing radiation therapy to the oral cavity with angular cheilitis in the bilateral commissures and a candidal infection on the lower labial tissues.

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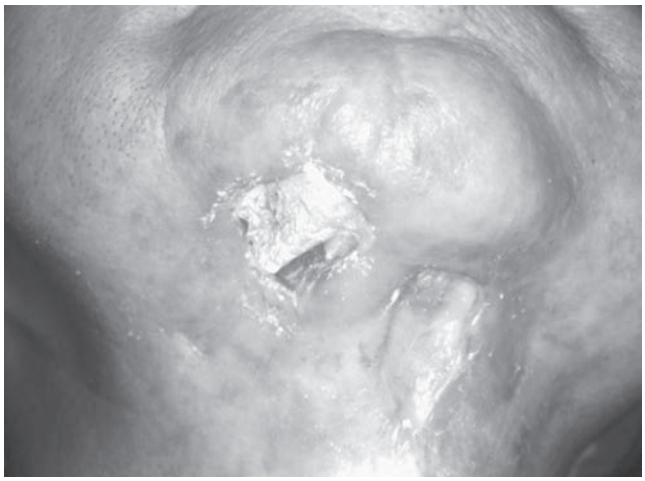


**FIGURE 9-20.** Osteoradionecrosis in the anterior mandible secondary to trauma from a motor vehicle accident. The mandible and upper cervical region were in the radiated field.

elective oral surgical procedures such as extractions or soft tissue surgery are contraindicated within an irradiated field owing to hypovascularity, hypocellularity, and hypoxia (Fig. 9-20).[37] Nonsurgical dental procedures that can safely be performed include routine restorative procedures, oral prophylaxis, radiography, and endodontic and prosthodontic procedures.

If oral surgical intervention is required after radiation therapy, the clinician should discuss the volume of tissue irradiated and specific treatment parameters with the treating radiation therapist and should request a copy of the simulation or port films and treatment summary. Preoperative hyperbaric oxygen therapy may increase the potential of wound healing while minimizing the risk for osteoradionecrosis by promoting angiogenesis and osteogenesis (Fig. 9-21). Hyperbaric oxygen therapy must be used as an adjunct to debridement (sequestrectomy), wound care, parenteral antibiotics (as dictated by bone culture results), and composite bone and muscle grafts by free tissue transfer (subject to the availability of the requisite microvascular skills).[60,61] Antibiotics are chosen on the basis of macrodilution or microdilution sensitivity testing.

Hyperbaric oxygen therapy is time-consuming and expensive and must be performed in an accredited wound care center. However, compared with a postradiation surgical treatment consisting of radical debridement and reconstruction, hyperbaric oxygen treatment can be cost-effective. Hyperbaric oxygen may also preclude the need for jaw amputation, large resection, or microvascular surgery. The Marx protocol, consisting of 20 preoperative hyperbaric oxygen treatments followed by 10 postoperative treatments, is the standard treatment regimen.[60,62] Optimal oral health must be maintained during and after radiation therapy. However, to avoid soft tissue injury during the postradiation healing period, patients must curtail all but the most basic oral hygiene procedures (i.e., brushing, flossing, and fluoride therapy). Following initial recovery from radiation effects, nonsurgical periodontal therapy, usually with prophylactic antibiotic coverage, is appropriate for treatment of the periodontium within the radiation field. It is important to detect and treat dental caries or traumatic dental injury that could lead to disease. If postradiation extractions are necessary, hyperbaric oxygen therapy, along with a specific oral care regimen, is indicated to augment wound healing.[60] In such cases, tissues should be managed gently, and antibiotic coverage is required. Local anesthetics containing epinephrine should be avoided, when possible, to prevent further vascular constriction.[63] The literature has reported successful placement of endosseous implants in irradiated fields, with a pretreatment regimen of hyperbaric oxygen (Fig. 9-22).[64,65] In contrast, osteoradionecrosis has been initiated by such elective surgical intervention.[65,66]



**FIGURE 9-21.** Osteoradionecrosis in the posterior maxilla secondary to a tooth extraction. This patient has radiation-induced hypovascularity in the bilateral maxillae secondary to irradiation of the soft palate and tonsil.

## Caries

Dental caries is a common morbid sequela in patients with head and neck cancer treated with radiation therapy.[67] Irradiation of major salivary glands leads to qualitative and quantitative changes in salivary secretions, reducing the buffering capacity of saliva.[68] The result is a cariogenic environment, particularly in patients who ingest a diet high in carbohydrates or sucrose (Fig. 9-23). Susceptibility to caries is not limited to the dentition within the

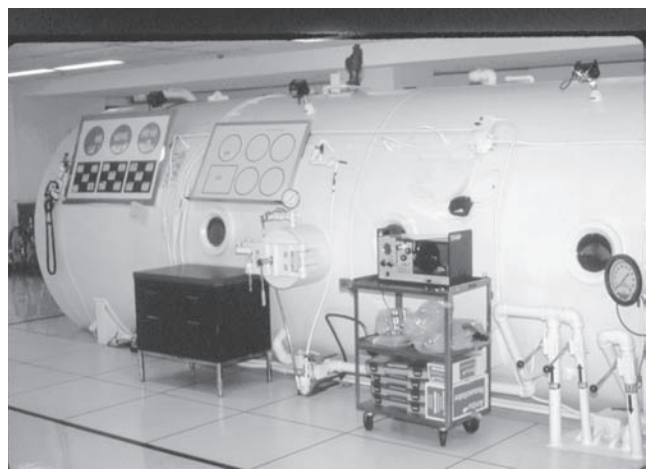


**FIGURE 9-22.** A multiplace hyperbaric chamber. Patients will undergo hyperbaric oxygen treatment using the Marx protocol (90 minutes of treatment, breathing 100% oxygen at 2.2 to 2.5 atmosphere absolute); 20 to 30 preoperative treatments are followed by 10 to 20 postoperative treatments.

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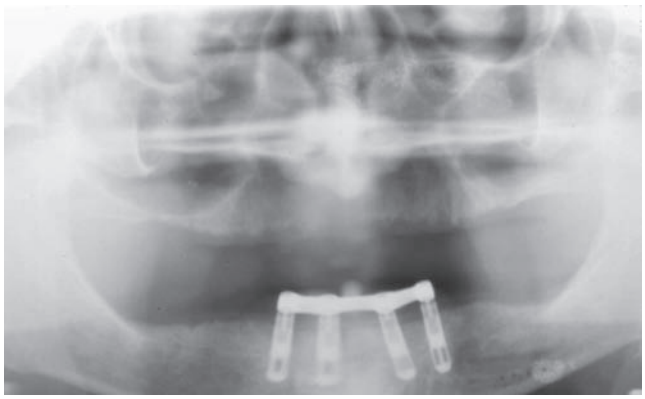


**FIGURE 9-23.** A panoramic radiography revealing endosseous implants (2 years posttreatment) placed in an irradiated mandible following preoperative and postoperative hyperbaric oxygen therapy. By torque evaluation and clinical/radiographic assessment, the implants are considered osseointegrated without evidence of necrosis.

volume of tissue irradiated; it extends to the entire dentition. Patients who have undergone irradiation should be treated with a specific prophylactic regimen consisting of flossing, brushing, and fluoride therapy. Fluoride treatment consists of a daily application of 0.4% stannous fluoride or 1.1% sodium fluoride.[37,40,68] In adults with xerostomia, fluoride leaches out of the enamel within 24 hours; therefore, the fluoride regimen must be performed daily to ensure optimal protection. The most efficient method of fluoride application is to use a custom-made polypropylene fluoride carrier that completely covers, and extends slightly beyond, the tooth surface (Fig. 9-24).[40] Patients load the carriers with fluoride gel and place them onto the dentition daily for 10 minutes. Patients who receive low doses of radiation and are expected to have a slight degree of xerostomia can use a toothbrush to apply the fluoride gel.[69] A daily fluoride program can decrease postradiation dentinal hypersensitivity; remineralize cavitated enamel matrices; and, more importantly, inhibit caries-forming organisms.[37,40] Patients are encouraged to floss their teeth daily, followed by tooth brushing, sodium bicarbonate rinse, and the fluoride treatment.

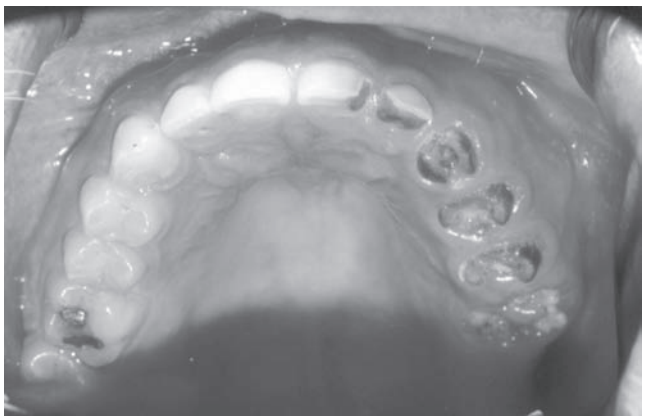


**FIGURE 9-24.** Radiation-induced caries in a patient who has received unilateral external beam radiation treatment for a parotid gland tumor with cervical nodal involvement.

## Xerostomia

Sialagogue therapy, such as with cholinergic agonists (e.g., pilocarpine hydrochloride), has been shown to provide clinically significant relief of symptoms of postradiation xerostomia.[70,71] Other rinses reported to decrease oral discomfort related to xerostomia or mucositis contain cytokines, aloe vera derivatives, or antibiotics. When administered intravenously, during radiation therapy, amifostine, a free radical scavenger, has been shown to diminish toxic effects of irradiation on salivary glands.

If these guidelines are followed, healthy oral tissues can be maintained following radiation therapy. Achievement of this goal depends on the patient's cooperation and compliance, which should be verified by clinicians at follow-up appointments.

# CARE OF PATIENTS WITH HEAD AND NECK CANCER TREATED WITH CHEMOTHERAPY

Most patients with cancer receive chemotherapy as a single- or multiple-drug regimen, either alone or in combination with other therapies.[72,73] The duration of treatment ranges from several months to years, depending on how long the therapy remains effective or how long the patient can tolerate it. Because chemotherapeutic agents damage mitotically active normal tissue cells or multiplying tumor cells, chemotherapy often induces toxicity in the hematopoietic cells, skin, and aerodigestive tract.[38,72] Such toxicity may cause treatment-induced complications in the oral cavity, especially if myelosuppression has occurred. Many of the sequelae of chemotherapy are similar to those induced by radiation therapy, but are sometimes more episodic depending on the dosing schedule or chemotherapeutic agents administered.

## Oral Complications

Acute oral conditions detected during the evaluation of the oral and dental status of patients with cancer must be treated before chemotherapy if the patient's health or hematologic values permit or when the opportunity arises between treatment cycles and when an appropriate performance status has been established. Chronic problems should not go unattended but should be treated strategically as the patient continues with chemotherapy.[38] Through appropriate coordination, acute problems can be treated promptly. If left untreated, chronic conditions may become acute at a time when the patient's physical well-being or hematologic parameters will not allow oral treatment intervention.

## Oral/Dental Treatment

During oncologic chemotherapy, the treatment plan for patients with cancer should be simple, practical, and functional in relation to the patient's oral or dental health and should not be in the realm of cosmetic dentistry, fixed prosthodontics, or advanced periodontal therapy.[38] Dental specialists face an almost overwhelming temptation to give aesthetic possibilities undue consideration while not recognizing the difficulty patients face in coping with their cancer diagnosis and undergoing drug therapies that have serious side effects.[37–39]

The dentoalveolar complex should be thoroughly evaluated for microbial reservoirs or sanctuaries (e.g., plaque, calculus, or periodontal pockets), and these infectious foci should be eliminated before the start of chemotherapy (Fig. 9-25).[74] A diminished periodontal status presents a risk for infection. Clinically, however, the risk for infection depends on multiple interacting factors such as oral hygiene, immunomyelosuppressive status,

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**FIGURE 9-25.** Fluoride carrier filled with 0.4% stannous fluoride and in position over maxillary and mandibular dentition.



**FIGURE 9-26.** Heavy calculus and plaque on dentition providing a sanctuary for microbial and fungal activity.

chemotherapeutic agents used, prophylactic or therapeutic antimicrobial agents used, and the degree of periodontal pathology.

To minimize the risks for periodontal infection, it is important to develop simple and practical guidelines for maintaining periodontal health and for diagnosing, preventing, and treating periodontal infections during therapy.[37,74] Patients with cancer should make regular dental visits for overall dental assessment. Patients receiving chemotherapy can undergo a dental cleaning provided that they meet the following hematologic conditions: first, an absolute neutrophil count of approximately 1,000 per $mm^3$, a level at which the risk for developing an infection is minimal; and second, a platelet count >50,000 per $mm^3$ with a normal coagulation profile.[75] The administration of prophylactic antibiotics is essential in combating induced bacteremia, immunocompromised status, and potential hypofunction of the white blood cells introduced by chemotherapy. The American Heart Association recommends a viable antibiotic regimen for subacute bacterial endocarditis prophylaxis before periodontal procedures. The second dose should be given 6 to 8 hours after the loading dose.[76]

Patients with an uninfected dentition and good periodontal health do not pose a diagnostic treatment challenge, nor do patients with advanced periodontal disease that mandates immediate surgical intervention. However, patients with increased loss of attachment with furcation involvement or periodontal pocket formation with furcation involvement pose a treatment dilemma, particularly for those taking bisphosphonates who are at risk to develop osteonecrosis of the jaws.[38] Patients in whom the soft tissue parallels the bone loss and in whom pocket depth is normal can be treated with regular periodontal care and maintenance. Extraction should be considered only for patients with pathologic mobility of dentition or with a fulminant periapical abscess.[37] Patients with moderate to advanced periodontal disease present a greater challenge and would, under usual circumstances, receive instructions for infection prophylaxis and dental hygiene, as well as surgical correction. However, the feasibility of such comprehensive therapy during chemotherapy can be limited by several factors including performance status, type of malignant disease, cycling of chemotherapy, and hematologic competence. The clinician should strive to provide a thorough scaling and encourage maintenance through exceptional plaque control (i.e., brushing, flossing, and use of chlorhexidine gluconate).[37–39,77] To reduce the risk for sepsis, extractions should be considered for patients with any exacerbated acute periodontal infection, except for those who have had dosing with bisphosphonate therapy. This oral surgical correction should be performed at the appropriate time in the treatment cycle or when the patient's cancer is in complete remission (Fig. 9-26). If chemotherapy is on hold, periodontal surgery could be considered, provided that the hematologic status is appropriate. The oncologic dentist must discuss with the treating medical oncologist the patient's oral status, treatment plan, and contraindications to surgical intervention, as well as the appropriate timing of oral treatment intervention.[37–39,72]

Brushing and flossing of the teeth should continue to be the standard of dental care for patients who routinely brush and floss. However, as in the general population, many patients with cancer either do not floss or floss only infrequently. Therefore, clinicians may either instruct patients to floss or may stress brushing techniques only. In most cases, patient factors and limited time parameters do not permit the patient to become proficient in flossing techniques.[37] Patients who floss regularly are instructed to modify the flossing technique in certain clinical situations. First, patients are instructed to floss gently when the lining of the oral cavity starts to become sensitive to thermal changes or food substances because sensitivity indicates mucosal thinning due to suppressive effects of chemotherapy on the normally proliferative epithelium.[49] Second, patients are instructed to floss only to the gingiva when the platelet count decreases to <50,000 per $mm^3$. This technique removes most of the debris from this area.[38]

In controlling plaque accumulation, it is important to minimize the risk for gingival inflammation, the oral bacterial load, and the potential for infection. Along with routine brushing and flossing, rinsing with chlorhexidine gluconate should be initiated when patients begin chemotherapy. Such rinsing is an adjunct to ideal oral-periodontal care and can also be used when indications arise, such as oral mucosal changes secondary to chemotherapy and subsequent increased soft tissue sensitivity.[37,38,77] Patients undergoing chemotherapy should be encouraged to rinse with a dilute saline and sodium bicarbonate solution (5%) to reduce adherent mucoid debris on oral soft tissues, lubricate oral mucosal and oropharyngeal tissues, and elevate the pH of oral fluids.[39] Patients experiencing nausea and anorexia should be encouraged to rinse with the sodium bicarbonate and saline solution several times throughout the day to reduce oral acidity and minimize the mucosal insult.

Another challenge that patients with cancer face in oral care is the risk for local infection or septicemia associated with dental

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implants. If an implant with its restorative component poses a risk for infection in patients under normal circumstances, this risk will be intensified during chemotherapy. Interventional antibiotics and aggressive hygiene have limited ability to control infection caused by a poorly integrated endosseous implant, whereas a well-integrated implant should not pose problems if its integrity is maintained with effective dental hygiene practices.[78,79]

Appropriate evaluation of the oral cavity and correction of existing oral and dental pathology can minimize, and in some cases eliminate, treatment-limiting toxicities such as mucositis, oral infections, and bleeding that necessitate chemotherapy dose reduction or termination.[72]

## Mucositis

A diagnosis of oral mucositis or oral mucosal barrier injury should be reserved for oral tissue changes that are the direct cytotoxic effects of chemotherapy. The most common acute complication of chemotherapy, mucositis, has a specific and defined mechanism of progression: mucosal erythema progresses to oral sensitivity and then to mucosal denudation (Fig. 9-27).[49,54] All other factors must be ruled out before a condition is diagnosed as mucositis because an incorrect diagnosis of mucositis could cause unnecessary delay, reduction in the dose, or complete discontinuance of effective chemotherapy.[38] Incorrect mucosal assessment can also lead to improper care and treatment and thereby to the persistence of this mucosal pathology. This problem can be further compounded by superinfection, pain, decreased nutritional intake, bleeding, or a focus for sepsis, effects that increase the treatment morbidity, costs, length of hospital stay, need for additional antibiotic therapy, and need for parenteral nutritional support.

Chemotherapeutic agents known to produce mucositis are antimetabolites, antibiotics, and alkylating and vinca alkaloids.[49,80] In cases of appropriately diagnosed mucositis, the emergence of mucosal toxicity would be expected to coincide with the administration of the chemotherapy. However, mucosal herpes simplex virus infections occurring early in the chemotherapy cycle can mimic mucositis. Failure to collect diagnostic cultures with each mucosal reaction can lead to a misdiagnosis of mucositis, in which case the infection would go untreated.[81] Culturing at this early stage of therapy is essential for differentiating mucositis from infectious stomatitis that can be caused by a bacterial, fungal, or viral agent and that is usually associated with low hematologic values (Fig. 9-28).[37–39] Oral mucosal infectious agents must be correctly identified and treated, because the loss of mucosal integrity creates a portal of entry for systemic infection in immunocompromised patients.[82]



**FIGURE 9-27.** Postextraction site with an organized clot in a patient with pancytopenia undergoing myelosuppressive chemotherapy. This patient is at the nadir and should have had no oral surgical intervention until the recovery phase of therapy with hematologic stability. Patient required random donor platelets with antibiotic therapy and a surgical debridement.



**FIGURE 9-28.** Chemotherapy-induced oral mucositis (World Health Organization grade III).

Chemotherapy-induced pancytopenia, combined with mucositis, can lead to oral infection and bleeding events. Patients may also have severe thrombocytopenia (platelets <20,000 per $mm^3$) and neutropenia (neutrophils <500 per $mm^3$) despite having normal-appearing oral mucosa. Serious complications, such as hemorrhagic diathesis or sepsis, can occur if hematologic parameters are not considered in the treatment of the oral cavity. Therefore, clinicians should conduct a benefit-versus-risk analysis of the intended therapy and should thoroughly assess the hematologic values before each treatment intervention. Treatment guidelines based on such assessments have been established.

# BISPHOSPHONATE OSTEONECROSIS

The use of the bisphosphonates both injectable and oral has been associated with mandibular and maxillary osteonecrosis. A substantial number of these cases have been associated with dental procedures such as tooth extraction. The product labels for bisphosphonates were updated in 2004 to include precautions about osteonecrosis of the jaw. Patients with concomitant risk factors such as cancer, chemotherapy, corticosteroids, and poor oral hygiene should undergo a dental examination and preventive dentistry before bisphosphonate treatment. Clinically, bisphosphonate-induced osteonecrosis is indistinguishable from radiation-induced osteonecrosis.

The American Dental Association endorses the 2004 Expert Panel Consensus recommendations (convened by Novartis Pharmaceuticals Corporation) for planning dental interventions in patients with bisphosphonate-induced osteonecrosis. Patients should be educated on maintaining oral hygiene to reduce the risk of infection. Dentists should check and adjust removable dentures to avoid soft tissue injury. Routine dental cleaning should be performed with care not to inflict soft tissue injury. Dental infections should be managed nonsurgically (when possible). Endodontic therapy is preferable to extractions. When necessary, coronal amputation preceded by root canal therapy may be used to avoid the need for extraction.[83,84]

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## Diet

Although generally unrecognized, diet profoundly influences the stability of the oral tissues and can cause mucosal problems when a patient is undergoing cancer therapy.[37] During the myelosuppressive phase of therapy or when the mucosa is thinned owing to chemotherapy, the diet should consist of nontraumatizing, soft foods that cannot puncture, abrade, or otherwise damage the vulnerable mucosal epithelium. Hard or abrasive food items can lead to increased pain, infection, or bleeding episodes.

All patients receiving chemotherapy are at risk for oral complications, and some patients are at a greater risk than others, depending primarily on the type of malignancy and the aggressiveness of the cancer treatment. Patents with hematologic malignancies (e.g., leukemia and lymphoma) have a greater risk than patients with solid tumors (e.g., breast cancer, lung cancer, and sarcomas), because the protective elements that maintain bodily homeostasis are part of the malignant process of hematologic malignancies.[72] Additional aggressive therapy that is given cyclically or that allows hematologic recovery before the start of the next cycle further increases the risk for oral complications in these patient populations.

## Viral and Bacterial Infection

Viral reactivity may lead to severe oral or disseminated infections during periods of myeloimmunosuppression. In particular, herpes simplex virus infections are often associated with severe, painful, and prolonged ulcerations atypical of those found in immunocompetent hosts (Fig. 9-29).[37–39,81] Suspected herpes simplex virus lesions should be treated with antiviral agents, such as acyclovir, administered orally or intravenously and managed as described previously for patients who receive radiation therapy. The diagnosis should be established using viral cultures, direct immunofluorescence or other rapid diagnostic tests, and histologic examination (Fig. 9-30).[81,85] Bacterial infections following chemotherapy can cause localized mucosal lesions, sialoadenitis, periodontal abscesses, pericoronitis, or acute necrotizing ulcerative gingivitis.[38] Because systemic infection is a serious complication in patients with neutropenia, constant vigilance must be maintained to prevent or manage oral infections of any type. Because antileukemic therapy is designed to achieve myelosuppression, this risk may be higher among patients with leukemia than among those with solid tumors.[37] Oral infections should be treated with selected antibiotic combinations (broad-spectrum antibiotics), including an agent effective against anaerobic gram-negative bacilli such as *Pseudomonas*, *Klebsiella*, or enterobacteria, which are often found in the oral cavity of immunocompromised individuals.[37–39] Oral microbial culture testing should be done to ensure antibiotic sensitivity and resistance selection and to assist in identification of the causative organisms.

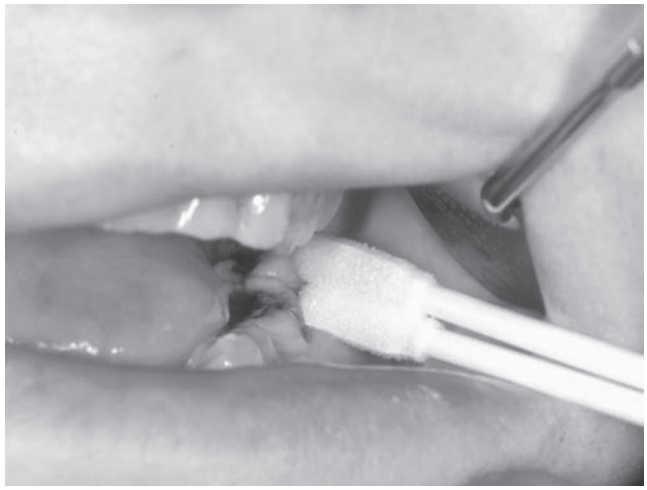


**FIGURE 9-29.** Culturing of an oral bacterial infection.



**FIGURE 9-30.** Culture-positive herpes simplex virus on the mandibular gingiva tissue. Patient placed on an antiviral regimen. Herpes simplex virus is an often overlooked and underdiagnosed oral condition.

# PREMALIGNANT ORAL LESIONS

The oral cavity is continually exposed to a variety of physical, biologic, and chemical carcinogens that can lead to the development of premalignant oral lesions. The reaction of the oral mucosa to these carcinogens is determined by the patient's age, sex, health, and genetic predisposition as well as the duration and intensity of the exposure. Tobacco and alcohol are considered the major etiologic factors in the initiation of premalignant oral lesions. The mean age of onset of premalignant oral lesions is 55.7 years.[86]

Premalignant oral lesions are the most common chronic lesions of the oral cavity. If not diagnosed and treated early, these lesions can progress to malignancy. The anatomic location of premalignant oral lesions is important in assessing their risk for malignant transformation. Lesions of the tongue, gingiva, and floor of the mouth are at a higher risk for transformation than are lesions located in the palate, buccal mucosa, and lips. The transformation of an epithelial premalignant oral lesion to a carcinoma is an extremely complex biologic multistep and nonsynchronous process. Various exogenous and endogenous factors enhance or impede malignant transformation, either directly or indirectly. New research has only recently begun to address these issues. The two epithelial lesions of the oral cavity at the highest risk of malignant transformation are leukoplakia, which presents as a chronic white plaque, and erythroplakia, which presents as a red, somewhat roughened area. In some cases, leukoplakia and erythroplakia occur together, creating a mottled- or speckled-appearing lesion. These lesions can be found anywhere in the oral cavity and cannot be removed by rubbing or scraping. They must be excluded from other clinically similar appearing lesions and do not typically respond to the resolution of known etiologic, traumatic, or inflammatory factors. Leukoplakia and erythroplakia can occur at any site along the aerodigestive tract but are most likely to be initially diagnosed in the oral cavity because of the accessibility of this area.

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Clinicians must be well acquainted with other oral lesions that are clinically similar in appearance to leukoplakia and erythroplakia, such as lichen planus, erosive lichen planus, white sponge nevus, hairy leukoplakia, *C. albicans*, linea alba, leukoedema, and frictional keratosis. Lichen planus, a chronic inflammatory disease, can also present with the clinical characteristics as leukoplakia or erythroplakia. The erosive form of this disease can be painful and interfere with normal oral function. The results of some studies indicate a higher rate of malignant transformation in lichen planus; other studies suggest that the malignant transformation rates are similar to those of other nonpremalignant lesions.

Because most premalignant oral lesions are asymptomatic, they are usually detected during an oral examination by trained professionals. The diagnosis is best determined by soft tissue incisional biopsy, with pathologic interpretation by a pathologist familiar with oral pathologic characteristics. One of the most widely used biopsy techniques is the punch biopsy that is performed using a circular knife with variable diameters. The biopsy can easily be performed in an office setting under minor local anesthesia and in most instances requires no sutures. If necessary, more than one biopsy sample can be obtained from the same lesion. A biopsy is mandatory when a lesion of the oral cavity is not associated with a reversible cause. If a lesion is found to be cancerous, the patient should be referred to an oncologist.

Current treatment modalities for premalignant lesions include surgical excision (knife or electrocautery), laser ablation, and cryotherapy.[86] Localized, relatively small premalignant oral lesions in high-risk areas such as the lateral border of the tongue, floor of the mouth, soft palate, and retromolar triangle can be excised by conventional surgery or electrocautery. Lasers have also been used effectively in the treatment of these lesions. Many different types of lasers and delivery systems are being used and tested. However, recurrence of these lesions is common, even after excision because the entire epithelial surface of the aerodigestive tract has been exposed to the same factors that caused the premalignant oral lesion, a phenomenon termed *field carcinogenesis*. No premalignant oral lesion should be considered cured unless there has been no recurrence after treatment or resolution of the lesion for a minimum of 3 years.[87,88,89]

Chemoprevention is a relatively new investigational approach that addresses field cancerization by reversing the premalignant process, thereby returning the affected tissue to a state of normal maturation and function.[88,89] Multiple randomized trials have been conducted in chemoprevention, and many have had positive results, yielding a tremendous interest in this approach to cancer treatment. Retinoids are the most studied class of compounds in chemoprevention.[85–98]

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CHAPTER 10

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# Interdisciplinary Symptom Management

## INTRODUCTION

In head and neck cancer patients, complex care issues exist that are best addressed by an interdisciplinary approach. Disabilities that can result during and after treatment affect eating, swallowing, speech, and daily social contact, all of which can severely affect a patient's overall quality of life (QOL). Physical, social, and psychological well-being are greatly affected by the potential disfigurement and dysfunction resulting from disease and its treatment.[1]

Several modalities of treatment of head and neck cancer are well established. Radiation therapy, surgery, chemotherapy, and various combinations of these three therapeutic modalities all comprise today's optimal treatment.[2,3] Investigative treatment methods include biological therapy, immunotherapy, and gene therapy. The treatment regimen for a specific patient depends on tumor site, stage, histology, and other factors. Treatment is composed of a single-modality or a combined approach. Each treatment method entails both general symptom management and specific care related to its distinctive side effects.

This chapter presents guidelines for interdisciplinary symptom management for patients receiving treatment for cancers of the head and neck. We begin with a discussion of what constitutes interdisciplinary care, drawing in part on the experience of collaboration at an urban Cancer Center, a center of excellence in head and neck cancer. A discussion of fatigue, a common and troubling symptom, is followed by a section on nutrition. Pain assessment and management, including algorithms to assist in treatment, skin care, and the management of mucositis follow. We have included discussion of psychiatric conditions, psychosocial assessment, the incorporation of integrative medicine in oncology as well as issues of survivorship. Finally, we have included a section on the integration of palliative care within oncology practice, with evidence to suggest this as a best practice model.

## INTERDISCIPLINARY SYMPTOM MANAGEMENT

Comprehensive symptom management that anticipates patient needs helps patients and their families participate in care, complete all treatments without interruption as recommended by their health care team, and adjust to changes in function and appearance brought about by cancer and its treatment.[3] Providing comprehensive symptom management to head and neck cancer patients is uniquely challenging, but is critical to successful treatment outcomes.

The identification of potential problems, as well as individual strengths, should be made at the time of initial contact with patients. These may include physical, psychological, spiritual, practical, social, and cultural issues. A review of information regarding cancer diagnosis, plan of care, treatment-related side effects, and their management may be presented by several providers, before treatment actually begins. Identifying factors which may affect patient learning (e.g., educational level, language barrier, and unfamiliarity with the medical system) can be identified and addressed proactively.

Multimodal treatment for head and neck cancer requires coordination from each member of the interdisciplinary team, especially when care is provided across several ambulatory sites (e.g., radiation oncology and chemotherapy sites) as well as inpatient settings. At the Continuum Cancer Centers of New York, a video conference connecting three physical sites is held weekly.[4] The goal of this conference is to maximize the communication and coordination between providers, by reviewing each head and neck cancer patient's progress through treatment. Disciplines represented include advance practice nurses from radiation oncology, ambulatory and inpatient medical oncology nurses, an integrative oncology nurse, social workers, nutritionists, speech and swallowing specialists, and palliative care specialists. The presence of significant physical symptoms, psychosocial distress, and unusual family circumstances which may impact care are discussed.

In addition to this conference, an interdisciplinary team from three sites, consisting of psychiatrists, social workers, nutritionists, palliative care specialist, and patient advocate collaborates weekly. Individual patients are discussed, as well as sharing of resources and expertise. The time spent on this interdisciplinary communication and collaboration improves patient care, reassures patients that providers are communicating with each other, and assures safe transitions in level of care, especially between inpatient and outpatient settings.

### Fatigue

Fatigue is a common state in patients with head and neck cancer. Although its mechanism of development is undoubtedly multifactorial, it is thought that a variety of circumstances, such as growth of the cancer itself, chemotherapy, radiation therapy,



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compromised nutrition, physical "deconditioning," altered sleep patterns, hormonal changes, anemia, worry, and fear all contribute to a feeling of overwhelming tiredness or exhaustion that interferes with QOL and daily functioning.[5] Although being "tired" is part of the human condition, its intensity is often greatly amplified when the fatigue is induced by cancer or its treatment.

The underlying mechanism causing fatigue is receiving greater attention as survivors of head and neck cancer live longer and experience more intensive multimodal treatments. It has been proposed that fatigue is the result of the production of proteins by actively growing cancer cells. These cytokines or cell proteins may be responsible for fatigue as well as weight loss; both important nonspecific constitutional symptoms that guide clinicians' judgment about a patient's response to treatment or underlying disease progression.[6]

Attempts to successfully address fatigue can help sustain the QOL experienced by patients and their families. A variety of pharmacologic and nonpharmacologic interventions may alleviate patients' fatigue or restore a patient's sense of control over their symptoms and environment. Several factors may contribute to fatigue in the head and neck cancer patient. These include physical decondition, sleep, hormonal changes, and anemia, which are elaborated below, along with nutritional factors as well as mood and anxiety which are addressed in subsequent sections.

### Physical Deconditioning

Energy conservation, a balance between physical (and mental) activity and rest may be both protective and restorative in the midst of, or after multimodal treatment for, head and neck cancer. Patients who overextend themselves describe compensatory periods of rest in the following days. Counterintuitively, an optimal amount of physical activity helps maintain energy rather than deplete it. Self-directed home-based programs or those tailored to patient needs include flexibility training or yoga.[7] Referral to a physical medicine and rehabilitation specialist can help customize a plan for recovery. Special emphasis on the flexibility of the neck and jaw can lead to fewer long-term consequences.

### Sleep Regulation

Too much sleep, too little sleep, or poor-quality sleep can account for a component of the fatigue experienced by head and neck cancer patients.[8] Pain and difficulty clearing oral secretions commonly interrupt sleep in head and neck cancer patients. Patients may even avoid sleep for fear of aspirating. Elevation of the head of the bed, or sleeping in a recliner may alleviate this component. Restorative sleep is an important component of the healing process.

### Hormonal Changes

Hypothyroidism is a well-known sequela of radiation therapy to the head and neck area and needs to be monitored in long-term survivors. Patients whose treatment is limited to surgery to the thyroid or parathyroid similarly need periodic monitoring and adjustment of thyroid replacement. The systemic influence of other hormonal changes, particularly testosterone in men and estrogen in women, may play a significant role in overall energy reserves that are depleted by cancer and its treatment.

### Anemia

The contribution of anemia to fatigue and its potential correction with erythropoietin-$\alpha$ has elevated anemia from a rarely considered state to its current prominence. Guidelines for the correction of anemia to physiologic levels are changing with greater use and outcomes evaluation in head and neck cancer survivors. Iron supplementation is often unnecessary and ineffective to correct fatigue. Correction of anemia may help improve QOL by allowing patients to remain active and functional.[9] Until recently, supplementation of endogenous erythropoietin had been thought to optimize outcomes, especially in QOL, but Henke found that patients with advanced head and neck cancer (T3, T4, or nodal involvement) who received 300 U/kg of erythropoietin-$\alpha$ with 60 to 70 Gy had achieved loco-regional control correlated negatively with the expression of erythropoietin receptors.[10]

### Depression

Low energy is a symptom of depression. A full psychiatric assessment of a patient with fatigue is an important facet of adequately addressing the symptom which may derive from or contribute to an underlying mood disturbance which is commonly experienced in head and neck cancer patients (please refer to Psychiatric Considerations section).

## NUTRITION

The head and neck cancer patient is particularly challenged within the greater cancer population when it comes to sustaining adequate nutrition. This is due in part to the physical location of the cancer itself and its proximity to the mouth and entire upper digestive tract. The long list of potential nutritional problems starts with the head and neck and works its way through the digestive tract for this patient population, who should be closely monitored for symptoms arising throughout treatment. Following a diagnosis, surgical interventions, radiation, and chemotherapy courses can and do have immediate and lasting impact on one's ability to take food and liquids orally.[11] Ongoing consultation with an oncology dietitian/nutritionist is essential in guiding patients throughout treatment and beyond.

### Screening and Assessment of Nutritional Status

Patients may or may not present with preexisting weight loss and/or malnutrition. Some patients enter into treatment reportedly asymptomatic. Others present with diminished ability to eat "normally" due to pain, dysphagia, or oral intake issues due to tumor location or previous surgery. Similarly, some patients will already have a percutaneous endoscopic gastrostomy (PEG) tube in place to facilitate adequate nutrition where a compromised oral route exists.

Patients initiating a treatment regimen of chemotherapy, radiation therapy, or a combination of both require screening and a comprehensive nutritional assessment as early as possible, ideally prior to the start of treatment. Clinicians can assist in screening a patients general nutritional status during an initial consult by noting the following and referring for nutrition intervention and follow-up as indicated:

Screening

- Age and visual exam
- Diagnosis, preexisting disease (i.e., diabetes), s/p head and neck surgery
- Weight/height—Underweight/obese/body mass index (BMI)
- Weight history—Usual body weight/weight change
- Oral symptoms: Ability to eat, dentition, dysphagia, mucositis, odynophagia, etc.
- GI symptoms: Nausea, vomiting, diarrhea, constipation, PEG
- Appetite and intakes (food recall for adequacy of calories/protein/fluids/nutrients)

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- Social support: Ability to shop/purchase/cook and store foods
- Lab values

It is common for patients to express a significant loss of appetite and even aversion to foods, thereby making it challenging to maintain adequate nutrition. Nutrition intervention and counseling can help the patient maintain an optimal weight, facilitate tolerance and healing from treatment, minimize symptoms, maintain or improve QOL, and decrease morbidity.

## Nutritional Needs

During a baseline (or initial) nutrition assessment, the dietitian/nutritionist estimates the patients nutritional needs and provides guidance and specific written information to the patient and their family and/or caregivers. At the minimum, the precachectic patient requires adequate calories and protein to facilitate weight maintenance and healing. Encouraging the patient to continue eating their preferred foods is stressed; however, adjusting food intakes to meet an individual's increased nutritional needs must also be a consideration. Undergoing chemotherapy and radiation treatment increases the bodies need for calories (kcal), protein, and fluids.[12] General guidelines are as follows:

- Patient remain on a regular, nutrient rich, weight-maintaining diet
- Caloric needs: 30 to 40 kcal/kg body weight
- Initiate meal replacement drinks BID in addition to regular meals (see Supplementation section)
- Protein needs: 1.3 to 2.0 g/kg body weight
- Fluid needs: Usually 1 cc per kcal; however, will be dependent on chemotherapy regimen, hydration status, and lab values.
- Modified food texture/composition based on symptom management and specific patient needs (i.e., soft, moist food, nonacidic, liquid diet)
- Enable patient access to foods (i.e., financial assistance, enteral food ordering)

It is worth briefly noting the myriad of symptoms that comprise cancer cachexia in this section about estimating nutritional needs. Cachexia involves metabolic abnormalities and inflammatory processes beyond what is seen in starvation, for example, the loss of lean body mass and production of cytokines. The addition of calories alone will not reverse the loss of weight and muscle mass in the cachectic patient. Clinicians are challenged in recognizing those patients at risk based on their symptoms. Researchers are seeking a consensus that defines cachexia[13] to facilitate best practice for its treatment,[14] and a variety of pharmacological treatments are being explored for efficacy.

## Nutritional Supplements

For patients undergoing chemotherapy and radiation to the head and neck, symptoms can appear gradually and worsen as treatment progresses. Clearly, this will affect the type and texture of food and liquids that can be consumed orally. It is critical to emphasize the additional intake of high-calorie, high-protein food and fluids prior to becoming symptomatic (see recommendations above). Early intervention with nutritional supplementation can reduce the chance of inferior outcome in patients at high risk for weight loss.[15]

Most cancer centers have a multitude of commercial meal replacement drinks at their disposal to provide to patients as samples, such as Ensure, Boost, Orgain, and the like. Most standard supplements have between 250 and 375 calories and between 9 and 15 g of protein per 8-oz can or box. Patients should be encouraged to test different brands and flavors for tolerance and palatability. If a supplement is too dense, it can be thinned with liquid or blended into a milkshake. Patients may augment their diet with supplements between meals or as meal replacement when solid foods are too difficult to consume. Ready-to-drink supplements are convenient to use if a patient has a long travel time to treatment as they do not require refrigeration prior to opening. They are also useful for patients lacking the energy to shop and/or prepare foods at home. Most grocery stores carry generic meal replacement drinks as well as a variety of prepared juice blends or protein-based drinks, which can contain as many calories and protein as commercial supplements.

## PEG Tube

Some head and neck patients may require a PEG tube during the course of their care (Fig. 10-1). This may be due to an extensive surgery or a compromised or unsafe oral route. The purpose of the PEG is to facilitate provision of adequate liquid food (enteral food) and fluid to the patients GI tract when oral ability is compromised, contraindicated, or significantly diminished. It is a clinical decision to determine whether a patient may require a PEG emergently during the treatment course or if it should be placed prophylactically based on the anticipation of significant

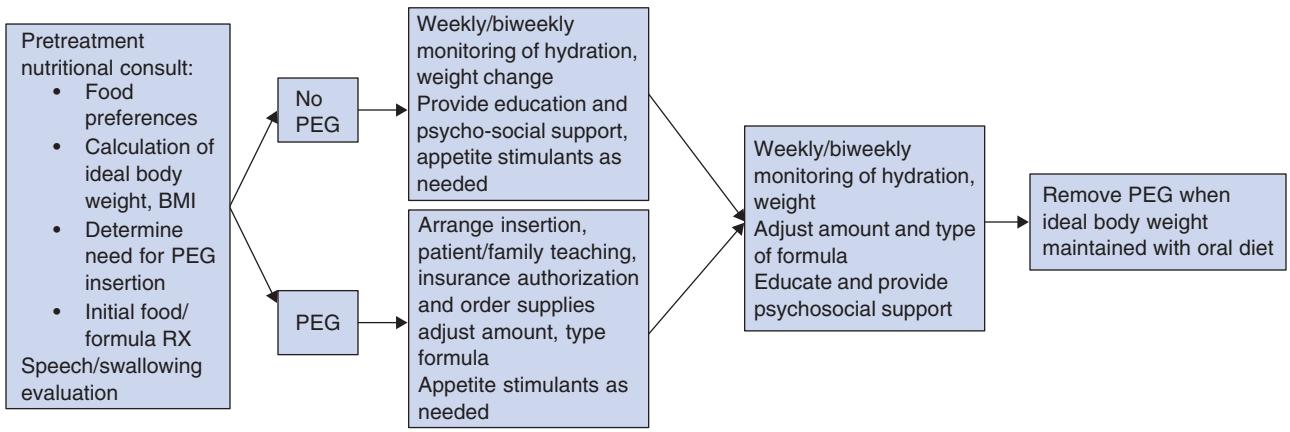



**FIGURE 10-1.** Nutrition assessment and intervention algorithm. BMI, body mass index; PEG, percutaneous endoscopic gastrostomies.

*Source:* Adapted from the National Comprehensive Cancer Network (NCCN). *Cancer and treatment-related anemia: NCCN Clinical practice guidelines in oncology,* Version 2, June 2007, with permission.

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toxicities. More research is necessary to inform physician behavior on whether prophylactic PEG tube placement is warranted in the treatment of head and neck cancer.[16] In any event, the PEG is a valuable tool for maintaining nutrition in patients whose symptoms prevent adequate oral intakes, thus risking significant weight loss. Such a group of patients requires specialized care from their health care team in regard to nutritional support. It is standard to initiate a bolus feeding with a 1.0 to 1.5 kcal/cc enteral formula that contains fiber. Formula selection is tailored to medical history (i.e., diabetes), and patients should be closely monitored for tolerance and appropriate usage. Method of feeding and formula can be modified as needed based on tolerance. PEG feeding frequency should increase as oral intakes diminish; however, oral intake of tolerated foods is encouraged to continue as long as the swallowing ability is safe.

### Counseling and Education

Nutrition education is an extremely helpful means for patients and their family to actively participate in their own care. Ongoing counseling throughout treatment enables clinicians to address issues as they arise. In oncology centers without an oncology dietitian on staff, patients should be screened and receive general nutrition advice from RNs and/or other clinicians. Simple handouts with age and education-level appropriate ideas for high-calorie/high-protein, soft, nonacidic food and liquids can be provided. Patients should be made aware of the normal symptoms they may experience and provided with the tools to minimize them, such as the appropriate diet modifications and/or medications. A combined approach of medications for symptom management and nutritional counseling is utilized.

If patient face-time is limited, develop a resource handout that lists recipes, cookbooks, and websites that are specific to optimizing nutrition through head and neck cancer treatment.

## PAIN ASSESSMENT AND MANAGEMENT

Pain is a significant problem that affects 50% to 80% of patients with cancer and disturbs overall QOL.[17] Yet cancer pain can be effectively managed in up to 90% of patients by following certain guidelines of pain management.[18] Pain in the head and neck patient can be disease-related or treatment-related or a combination of both.[17,19,20] Nearly all patients who receive radiation therapy to the head and neck experience pain at some point during treatment.[19,20] It is important to institute analgesics early in treatment in order to maximize patient comfort.

The assessment of pain should not only include the descriptive dimensions of the pain (location, intensity, quality, temporal features of onset and daily fluctuations, and aggravating and alleviating factors), but assessment of cause and effect on functioning. Once a cause has been identified, disease-modifying treatments may be offered, for example, the use of radiation for bony metastases. A description of burning or shooting pain, for example, can guide treatment toward use of adjuvant medications for neuropathic pain. A thorough initial pain assessment is important to ascertain past use of analgesics and effectiveness as the treatment of opioid-tolerant patients is significantly different than opioid-naive patients.[21]

Awareness of psychosocial aspects of the experience of pain is an important component of assessment: What is the meaning of pain for this patient and family? What cultural, religious, or spiritual dimensions are influencing perception of pain and attitudes toward treatment?[18] For minority patients with pain, significant barriers to effective pain management may exist, including beliefs about stoicism and difficulties communicating with physicians and other health care providers.[22] The ongoing assessment and management of pain includes the psychosocial impact of pain on the patient and family, quality and nature of distress, and the assessment of psychiatric comorbidities, for example, anxiety and depression, as well as history of substance abuse.

Pain management for patients with head and neck cancer should follow established guidelines, based on the original principles elucidated by the World Health Organization (WHO) and the Agency for Health Care Policy and Research (AHCPR).[19,23] These are briefly reviewed in Figure 10-2. Small doses of opioids, for example, morphine or oxycodone, available in either pill or liquid form, may often safely and effectively be used for the treatment of moderate pain.

Evaluation of pain should be part of every assessment as a standard of care.[24] The goal of pain management is to provide sustained comfort with few side effects and in this way to maximize patients' QOL. The treatment of cancer pain commonly includes the use of opioid analgesics, but other categories of treatment may also be included; for example, nonopioid analgesics and other adjuvant medications as well as interventional therapies, neurostimulation, and integrative medicine approaches.[24] The use of nonsteroidal anti-inflammatory drugs (NSAIDs, e.g., naproxen or celecoxib) must be done cautiously due to safety concerns of gastrointestinal and cardiovascular risks.

Frequent reassessment of the analgesic regimen is important to evaluate efficacy and tolerability. Titration of current medications, rotation to other opioids, and/or addition of adjuvant medications may be required, especially if pain has nociceptive and neuropathic components.[18] For more severe and prolonged pain and for patients with history of substance-use disorders, methadone may be used. It is a long-acting opiate that can treat both the incident and neuropathic components of cancer pain. Methadone has a long half-life averaging about 24 hours, can be dosed in 6-to-8-hour intervals, and compared with other opiates is relatively inexpensive. Due to lack of active metabolites, it may be preferable in the setting of renal impairment.[24] In view of its prolonged half-life, as well as individual variation, familiarity with prescribing is essential, as full effects of the medication may be delayed for days and up to a week or more. Patient and family education is essential to reinforce the idea that methadone is not only for maintenance but also for withdrawal from heroin.

### Nonopioid Analgesics

Drugs used to treat the neuropathic component of pain are often part of the analgesic regimen, as nerve involvement is common in cancer pain and treatments. The use of gabapentinoids (gabapentin or pregabalin), glucocorticoids, such as prednisone or dexamethasone, as well as bisphosphonates for bone pain has been well studied.[24]

Patients may have inadequate pain relief due to lack of knowledge, fear of narcotic dependency, fear of acknowledging disease progression, or poor clinical management.[25] Lack of adherence to medication regimens has been studied, with evidence suggesting that around-the-clock (ATC) dosing is more frequently adhered to than as-needed (PRN) and that patients are not always prescribed ATC medications, according to practice guidelines.[26] They may also have comorbid conditions that exacerbate cancer pain. These issues need to be considered in order to achieve maximum patient comfort.

Postoperative pain is initially controlled with parenteral narcotics, administered by continuous intravenous route, patient-controlled analgesia (PCA), or by subcutaneous injection, converted to an oral analgesic via the nasogastric tube or by mouth. For patients who have been treated with opioid analgesics prior to surgery, informing the acute pain management team prior to surgery is important, as these patients may need more than usual amounts of postoperative analgesics. Mild pain should be treated by acetaminophen-based

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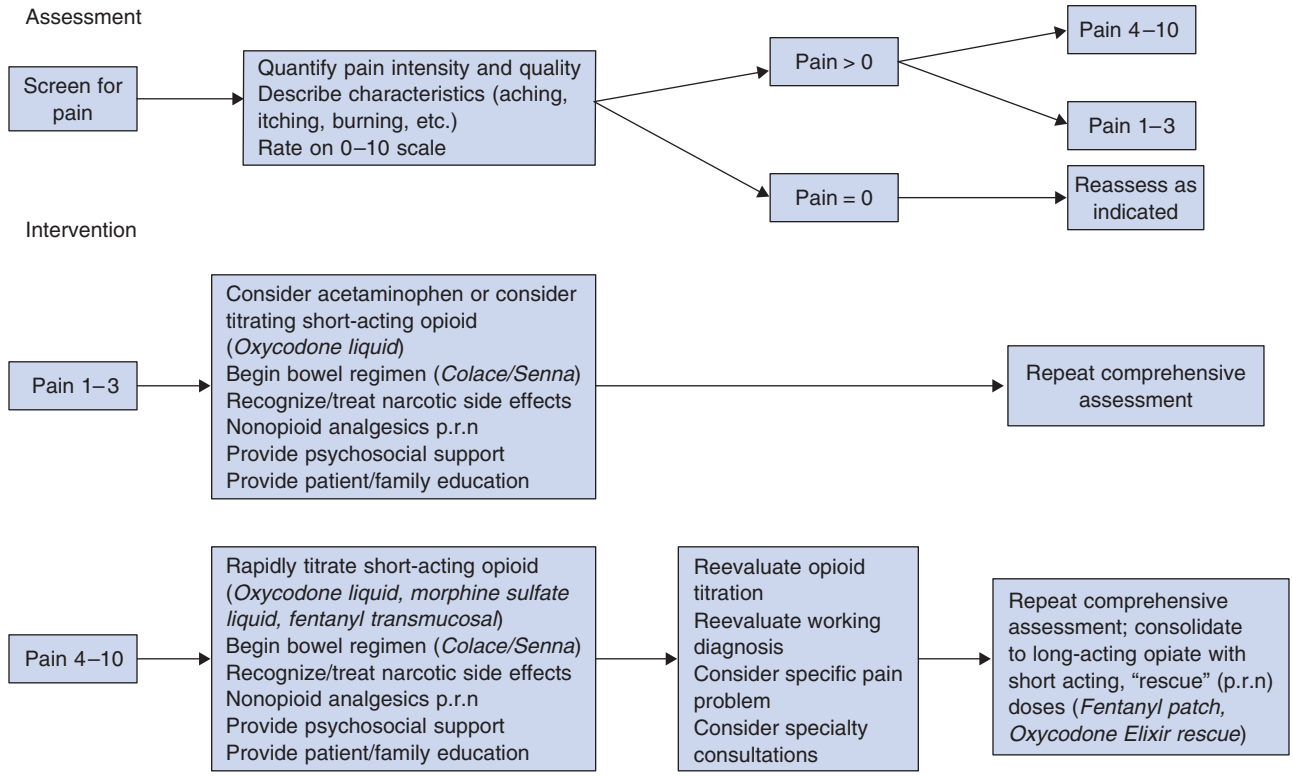



**FIGURE 10-2.** Acute pain assessment and intervention algorithm.

*Source:* Adapted from the National Comprehensive Cancer Network (NCCN). *Cancer and treatment-related anemia: NCCN Clinical practice guidelines in oncology,* Version 2, June 2007, with permission.

products, rather than aspirin or nonsteroidal anti-inflammatory medications, which can reduce platelet aggregation and impede healing or optimal cosmesis.

Moderate levels of pain can be initially managed with codeine-based analgesics,[27] or combinations of acetaminophen and opioids in small doses. Severe pain should be treated with regimens that include opioids (morphine, oxycodone, oxymorphone, or fentanyl-based regimen). With any class of opiates, analgesics with a short half-life should be prescribed based on their period of effectiveness, usually every 3 hours to establish needs, then converted to longer acting preparations orally or parenterally. Longer acting opioids are usually given every 8 to 12 hours, depending on patient response.

Because taking oral medications can be difficult during treatment of head and neck cancers, the transdermal fentanyl patch may be a good choice; however, this is not advised as initial therapy. Patients should begin with short-acting preparations to assess appropriate requirement and tolerance. Typical doses for the transdermal fentanyl patch range from 12 to 100 mcg per hour, but may be titrated up to 200 to 300 mcg per hour. A new patch is applied to clean, dry skin every 3 days; patients are given instructions on how to apply new patches, cautioned about dangers regarding extreme heat (e.g., sun exposure, fever), which can create irregular dose absorption, and educated about slow onset of action.

## Drugs for Breakthrough Pain

Often as regimens are being titrated, or due to the episodic nature of the pain, short-acting drugs are required in between the longer acting opioids. This can be either single-agent formulations, such as morphine, oxycodone, hydromorphone, or combinations with opioids and nonopioid. Fentanyl formulations, which are absorbed quickly, are now available in the form of lozenges, buccal tablets and patches, sublingual tablets, and nasal spray.[24] Regular breakthrough doses signal a need for higher doses of the long-acting preparation, unless the cause is expected to resolve quickly. The dose of the short-acting drug is generally roughly 5% to 15% of the total daily dose, though recommendations are to begin with the lowest dose of fentanyl preparations, as the effects of these medications may not be proportional to the fixed-dose scheduling.[18,24]

Assessment and treatment of severe and refractory pain may require continuous narcotic intravenous infusion delivered through a subcutaneous peripheral site or centrally through an indwelling central venous catheter. A patient-controlled analgesia (PCA) pump is commonly used, most often in hospital settings, because it delivers maintenance ("basal" rate) of analgesia plus a patient-controlled "rescue" dose for breakthrough pain. Morphine, hydromorphone, fentanyl, and methadone are common drugs used for PCA infusion. This method is used frequently for patients with end-stage disease.

Neural blockade approaches and implant therapies encompass a varied group of medications. Neurosurgical pain control for refractory pain and neuropathic pain in specific areas, for example, the brachial plexus, or for cancer-related facial pain may be effective, using chemical or radiofrequency neurolysis.[28]

With any opiate, care must be given to monitor constipation and sedation, as well as mouth dryness or urinary retention, which may require change in dose, preparation, or delivery route. When initiating any narcotic analgesic, patients are instructed to increase fluid intake by at least 1 L per day and to use a docusate-based stool softener liberally and daily to prevent constipation, often with addition of a laxative. Patients who can take medications by mouth should be instructed to take the medication with food or a supplement to minimize potential nausea.

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Education of patients and family regarding pain management is important.[27] As health care has changed and patient care has shifted more to the outpatient area and to patients' homes, knowledge of how to manage pain must be provided to caregivers. Mode of action, expected side effects of pain medications, and implementation of a bowel regimen are important aspects of patient and caregiver teaching. Written and verbal instructions and information should be given.

## Risk Assessment and Addiction Issues

A routine barrier to adequate analgesic treatment is the fear that opiates of any class when used for cancer pain from illness or treatment will become addictive. Patients with a preexisting dependence or substance abuse themselves are the most vulnerable patients, and their management should respect both this predisposition and their need for adequate analgesia.[29] Ironically, patients who have been dependent on opiates, barbiturates, or benzodiazepines in the past likely will need higher than expected doses for pain relief. Such a contradictory pattern mandates good communication and very clear dosage parameters. This involves a minority of patients who are overrepresented among those with head and neck cancers who have a higher incidence of substance abuse. For the majority of patients without substance abuse histories, fears of addiction may interfere with using adequate amounts of analgesics. Reassuring patients that tolerance to a drug is not a sign of drug addiction is very important. Educating medical professionals about the important distinctions between drug tolerance, dependence, and addiction is also important as misconceptions about these terms and their meaning may be barriers to optimum prescribing of the most effective analgesic regimen.

For patients at risk for ongoing substance abuse, referrals to and collaboration with addiction specialists may be a necessary and important part of treatment. The use of additional methadone for pain management in patients who are already enrolled in methadone maintenance treatment programs for heroin addiction may be safer than using other opioids. Other risk assessment strategies may be employed, for example, dispensing smaller quantities with frequent monitoring and screening of urine for prescribed and nonprescribed drugs.

## Residual Pain

Neuropathic pain throughout the face, especially throughout the ear and the mandible, serves as a constant reminder of their cancer to a minority of patients who have undergone multimodal treatment. Often mechanical in origin with resulting nerve compression or irritation, these symptoms are treated with custom-designed oral appliances, exercises, or anticonvulsants. Patients benefit from ongoing assessment with speech and swallow specialists for exercises to maximize function in the face of more chronic, residual pain.

Tricyclic antidepressants and anticonvulsants have been shown to be effective in neuropathic pain syndromes and are a reasonable alternative depending on comorbidities.[30] Duloxetine, a serotonin reuptake inhibitor antidepressant, has been approved for use in diabetic peripheral neuropathy and may be helpful in cancer or chemotherapy-related neuropathic syndromes as well.[30,31] Regular evaluations by a dentist or oral surgeon is often indicated to rule out persistent or recurrent cancer.

# SKIN CARE

Managing skin reactions of patients undergoing therapy is crucial in minimizing patient discomfort and pain. Preventing breaks in treatment which may affect treatment outcomes for patients with head and neck cancer is another reason skin care management is so important. Though there is a paucity of evidence-based literature regarding care of the skin, some principles of skin assessment and management are clearly appropriate.

A radiation skin reaction is an expected, normal, and temporary side effect of radiation therapy. It is also the most frequently experienced side effect of radiation therapy, affecting between 87% and 90% of all patients receiving radiation.[32] The reaction is caused by the effect of radiation on the normal process of epidermal cell turnover. The mitotic ability of stem cells within the basal layer of epidermis is damaged by ionizing radiation. This decreases repopulation of cells which are then more rapidly shed.[33] This causes a thinning of cornified cells at the skin surface, making the skin more vulnerable to further radiation damage. An inflammatory response leads to release of serotonin and histamine and resulting edema. Increased blood flow to the injured tissues leads to erythema. Melanin rises to the surface of the skin, causing the characteristic darkening of the radiated skin.[33,34] Alopecia is common as the hair follicles are affected and is permanent after 5 to 6 weeks of treatment.[34]

Standards of care for managing radiation-induced skin reactions are based primarily on clinical judgment and expert clinician preferences. Randomized clinical trials are few and far between and have not demonstrated strong evidence for any particular skin care regimen.[33,34] Development of standards for skin care, based on what evidence is available, is strongly encouraged.

Assessing patients' skin before radiation begins is an important first step in skin care management. This involves evaluating patients' individual risk of skin breakdown during treatment, due to both patient-related and treatment-related factors (Table 10.1). The entrance and exit portals should be evaluated for obvious

**TABLE 10.1 Risk Factors for Impaired Skin Integrity**

| |
|---|
| **Treatment-related factors** |
| Large treatment field |
| Specific susceptible treatment fields |
| Thin epidermis (face, neck) |
| Bony prominences (clavicle) |
| Body folds (ear lobe, pinna, and nose) |
| Incision line or wound |
| Peristomal skin |
| Treatment with electron-beam therapy |
| Treatment with tangential fields |
| Radiation given postoperatively |
| Radiation given after or concurrently with chemotherapy |
| **Patient-related factors** |
| Poor nutritional status |
| Fair complexion |
| History of severe skin reactions to sun exposure |
| Diabetes |
| Other conditions that affect skin healing ability (lupus, scleroderma, human immunodeficiency virus, burned skin, skin donor sites, etc.) |

*Source:* Adapted from Kelvin JF, Absolon P, Bodansky B, et al. *Radiation Oncology Standards of Patient Care.* New York, NY: Department of Radiation Oncology, Memorial Hospital for Cancer and Allied Diseases; 1996, with permission.

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breaks in skin integrity. Skin folds, lips, and ear lobes are at increased risk of breakdown, as is the thin, sensitive skin of the eyelids.

The acute reaction begins 2 to 3 weeks after starting radiation and continues 3 to 4 weeks after completion of therapy.[32,33] The effect of the radiation on the skin is cumulative and progresses from mild erythema through hyperpigmentation to dry desquamation (dryness, pruritis) and moist desquamation. Moist desquamation, in which loss of the epidermis leads to open, weeping skin, can occur in skin fold areas (ear lobes) and at the point where two treatment fields overlap. Moist desquamation places patients at risk for infection and fluid losses and can cause significant anxiety and discomfort.[33,34] Severe moist desquamation can lead to a treatment break, which may affect the overall effectiveness of radiation treatment.[35]

Providing clear, comprehensive patient education on skin care measure to minimize pain, decrease incidence of skin breakdown, and decrease infection is vital.[32,34] As most skin care measures are done by patients, it is important to obtain their active involvement. Detailed verbal and written instructions for skin care during treatment should be provided to patients. This should begin with a review of what patients may expect, a rough timeline of when each phase of the reaction will most likely appear, and the interventions for each phase. Changes in appearance in each phase as well as information on possible discomfort and pruritis should be described. Reassurance that any discomfort will be addressed promptly is also important.[32]

As previously stated, the evidence for skin care management is sparse and conflicting, without clearly proven "best practices." However, those skin care measures which *are* generally agreed upon are described in Table 10.2. Cleansing the skin within treatment fields involves washing the skin gently with warm water, using only mild soaps (e.g., Dove unscented or Basis soaps), and rinsing well before gently patting the skin dry.[36] A gentle shampoo (e.g., a baby shampoo) is also recommended.[37]

Moisturizing skin within the treatment field using a hydrophilic moisturizer (e.g., Aquaphorâ, Eucerinâ, aloe vera gels) is also generally recommended.[32,33,34,37] Patients should apply moisturizer two to three times per day (depending on risk of breakdown of specific tissue), being careful to wash any residual moisturizer off the skin before treatment. On any day on which treatment is not given (weekends, holidays), moisturizer should be applied after washing in the morning and again at bedtime. Patients should be instructed to prevent irritation of radiated skin by avoiding physical irritants (e.g., tight fitting clothing and shaving), chemical irritants (e.g., perfumes, cosmetics,

**TABLE 10.2 Skin Care Guidelines for Patients**

Skin that receives radiation therapy needs special care. Although a skin reaction is expected and temporary, it can sometimes be uncomfortable. The following tips address how you can help yourself (and your skin) during your course of therapy. These are only guidelines, and if you have any questions or concerns, you should speak with your nurse or physician.

**General skin care instructions**

Wash skin in the treatment field with a mild soap; Dove for sensitive skin or Basis is preferred.

Apply Aquaphor ointment to the skin immediately after each treatment and at bedtime. On weekends, holidays, or any day in which you do not receive radiation therapy, apply the ointment in the morning and at night.

Your skin should be free of any ointment during the treatment. If necessary, wash your skin immediately before each treatment.

Do not apply any other skin cream, makeup, after-shave, or cologne to the area being treated. If you are uncertain about this, please speak with a nurse.

Avoid constrictive clothing, starched collars, tight ties, and other irritants to the skin during your course of radiation therapy.

Always use a sunscreen, SPF-45, when in the sun for >10 min, and wear a face-shading hat when possible.

**Dry desquamation (flaky, itchy skin)**

Increase frequency of moisturizer, and decrease use of soap.

Cornstarch may be used on shoulders and back. Do not use in moist skin folds.

Topical 0.5% hydrocortisone cream applied with Aquaphor twice daily may reduce itching.

Benadryl 25–50 mg may help at bedtime but will increase oral dryness.

**Moist desquamation (moist, blistered skin)**

Goals are to prevent infection, reduce pain, and prevent treatment breaks.

Keep skin clean but minimize use of soap and water when possible.

Air-dry after washing. Fanning may feel cooling.

Continue with use of moisturizer unless directed to stop use. You may add frequent soothing and cooling applications of refrigerated, alcohol-free aloe vera gel throughout the day.

Silvadene ointment may be prescribed. Use as directed by your team.

You may be given nonstick dressings to cover the affected area to prevent clothing from sticking.

If you are uncomfortable, ask your team for medication to reduce discomfort.

Remember, a skin reaction is expected, temporary, and reversible. Skin commonly takes 2–3 wk to fully recover.

If you have a fever, or notice foul-smelling discharge or increased discomfort, speak with your medical team immediately.

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deodorants, and moisturizers other than those recommended), extreme heat or cold, and prolonged, direct sun exposure.[32–34]

Though study patients were women receiving breast irradiation, a recent prospective, double-blinded, placebo-controlled study was done to compare effectiveness of three different skin care products versus placebo in reducing the incidence of radiation-induced skin reactions.[38] Products evaluated included Aquaphor ointment, Biafine RE cream, RadiaCare gel, and a sterile water mist—the placebo. Despite a more-than-adequate sample size and well-executed blinding of researchers, the study revealed no product to be more effective than a sterile water mist in preventing skin reactions.[38] The study did support the evidence that patients prefer using some type of product (ointment, cream, or gel) to water.

Several RCTs of the efficacy of aloe vera gel[39–41] have revealed no statistically significant advantage of aloe vera over routine skin care. Biafine has not been shown to provide a statistically significant advantage over cheaper, more available products,[42] and in a more recent study comparing Biafine with calendula (marigold extract) crème, Biafine was found to be less effective.[43]

Calendula and hyaluronic acid may be somewhat effective in reducing the incidence of radiodermatitis,[44] but more studies are needed to support this. Interestingly, a study done by Wells[45] demonstrated no statistical differences in skin reaction of patients using aqueous creams, sucralfate creams, hydrogels, versus no cream/gel at all. Statistically, increased skin reactions were seen in smokers, patients getting chemotherapy, and patients getting bolus treatments (additional therapy to a specific area).

During radiation therapy, patients' skin is assessed for the degree of skin discomfort, presence of scaling or pruritis, tissue breakdown, or moist desquamation. Patients receiving concomitant chemotherapy, cranial radiation, or nasopharynx radiation may note peeling of the scalp, pruritus, and alopecia. Such patients are instructed to use a mild shampoo and to frequently apply the recommended moisturizer to the scalp.[46] Any signs and symptoms of skin infection (fever, increased pain, purulent, or foul-smelling discharge) should be evaluated promptly, drainage should be cultured if present, and antibiotics should be prescribed.[32,33,46] Skin care continues after radiation therapy has completed. This includes assessment of skin reaction resolution, reinforcement of the need for lifelong prevention of further skin injury by use of sun block (sun protection factor [SPF]–45), and the avoidance of extreme heat or cold to skin in the treated area.

Long-term effects of radiation therapy on skin are noted months or years after completion of radiation therapy and may include thinning of epithelium (with increased risk of skin injury), telangectasia, loss of sweat and sebaceous glandular function, and hyperpigmentation or hypopigmentation. These effects are difficult to predict and are often more related to individual patient characteristics than to radiation dose or technique.[47]

# MUCOSITIS MANAGEMENT

As described throughout this text, treatment of head and neck cancers has evolved to more aggressive therapies with improved outcomes.[48] The incidence of mucositis in patients receiving head and neck cancers is 80%.[48] Mucositis is an expected side effect of radiation therapy to the head and neck. Grade 3 and 4 mucositis causes severe pain, dysphagia, and weight loss due to inability to eat. Mucositis often leads to psychological distress, isolation, fear, depression, and overall decrease in QOL.[49] Profound weight loss and pain may lead to treatment modifications with possible negative implications on treatment efficacy, though research is urgently needed to properly quantify this.[35,48]

A basic understanding of normal oral mucosa is crucial to understanding the changes present with mucositis.[50,51] The oral mucosa overlies connective tissue and bone and consists of squamous cell epithelium. The dorsal tongue is specialized mucosa as it contains the sensory nerves responsible for taste. Masticatory mucosa lines the gums and the hard palate. It is tough and is keratinized, which differs from thinner, nonkeratinized mucosal lining. It covers the inside lips, cheeks, soft palate, and underside of the tongue. As the cells on the surface slough off, they are replaced by new cells generated by the stem cells directly above the submucosa, which contains the blood and nerve supply for the cells. This turnover takes approximately 2 weeks for the lining mucosa and slightly longer for the masticatory mucosa.

## Pathophysiology of Mucositis

The pathophysiology of mucositis is the subject of much recent research and is defined today as a multiphased process.[50,51] The first or "initiation phase" begins immediately following a tissue insult such as mucosal exposure to radiation therapy or chemotherapy. During the initiation phase, the epithelial cells DNA is damaged and ultimately leads to cell death. Two to 3 days later, the "upregulation and message generation phase" begins. During this phase, biological switches such as nuclear factor-$\kappa$B (NF-$\kappa$B) are turned on. These factors upregulate genes which then generate increased amounts of cytokines. During phase II, the radiation and chemotherapy may also directly affect cells by increasing the rate of apoptosis of mucosal cells. As a result of these processes, the mucosa begins to thin, redden, and become painful.[50]

During phase III, or "amplification and signaling phase," direct damage to the oral tissues continue, mainly, below the level of the mucosa. TNF-$\alpha$ activates NF-$\kappa$B and other cytokines which cause more proinflammatory changes with increased activation of TNF-$\alpha$. Thus, a feedback loop is formed. This results in the fourth phase of the mucositis process, "tissue ulceration." This phase is clinically obvious, with ulcers frequently extending downward to the submucosa from the epithelium. Pseudomembranes may cover the lesions or they may be open with exposure of nerve endings and increased pain. Bacteria often colonize the ulcerations, and in neutropenic patients, infections requiring hospitalization may occur.[50,51] From initiation to ulcer formation takes 10 to 15 days. The fifth and final "healing phase" begins 14 to 21 days after mucosal assault. The epithelial cells near the ulcer move to gradually fill in new tissue, and normal flora of the oral cavity is restored. Unfortunately, the layers beneath the surface do not ever fully recover and are vulnerable to further injury as the radiation continues or chemotherapy is readministered.

Assessment of each patients' risk of severe mucositis begins at consultation, when both patient-related and treatment-related factors are evaluated.[52] A list of risk factors is provided in Table 10.3. Reducing risk factors when possible can reduce mucositis severity during treatment.[53] For example, patients who are malnourished and underweight at consultation should have a feeding tube placed and intensive weight-gaining support prior to initiating treatment. Evaluating each individual's risk early allows timely interventions and pinpoints patients needing intensive support.

## Mucositis Assessment

The need for consistent assessment and documentation of mucositis is obvious for both clinical practice and reporting of research outcomes. The assessment tool should be precise, objective, validated, and reproducible as well as sensitive to the subjective components of mucositis.[53] A review of existing oral mucositis measurement tools by Steve Sonis and colleagues[54] demonstrated variability among those used most often. The NCI-CTC, WHO,

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**TABLE 10.3 Risk Factorsfor Mucositi**

**Patient-related factors**

Poor nutritional status, poor dental hygiene, and dental caries all have negative effect.

Immunosuppression (long-term steroid use) increases wound healing time.

Poorly fitting dentures or oral appliances

Cultural habits (use of spicy foods or chewing betel nuts), drinking alcohol, smoking, or chewing tobacco

Previous cancer therapy

Reduced-volume salivary tissue, impaired function of saliva

**Treatment factors**

Concomitant chemotherapy

Chemotherapy agent (5-fluorouracil [FU], methotrexate, and etoposide cause increased mucositis)

Chemotherapy dose (high-dose regimens lead to higher rate and degree of mucositis)

Radiation dose, duration of treatment, and site of treatment

More sensitive—pharyngeal wall, soft palate, tonsillar pillars, buccal mucosa, lateral tongue, and floor of mouth

Less sensitive—hard palate, gingival ridge, and vocal cords

Surgical procedures resulting in altered anatomy (transplanted tissue responds to radiation as it would in original body site)

Metallic dental work or surgical plates will increase "scatter" radiation to proximal mucosa

*Source:* Modified by Carper E. Department of Radiation Oncology, Continuum Cancer Centers of New York, 2007, with permission.

**TABLE 10.4 Patient Self-Care Regimen for Oral Hygiene**

Rinse your mouth and gargle 4–6 times a day before and after meals. Use the following solution:

1 qt water

1 tsp salt

1 tsp baking soda

Use a soft toothbrush or toothette and mild toothpaste (e.g., Biotene, or Arm and Hammer baking soda toothpaste) after every meal and at bedtime. Be sure to clean your dental appliance or dentures at this time.

Continue flossing gently if this is your habit. If you do not normally floss, do not begin flossing during radiation therapy.

Avoid any mouthwashes containing alcohol.

Use a lip moisturizer frequently. Be sure to remove before your treatment!

Wear your fluoride trays (without fluoride during your treatments if ordered by your team).

Use a humidifier or vaporizer in the bedroom. Warm and cool mists are equally effective; the water comes to room temperature by the time it reaches you. Whichever "steamer" you choose, it should be cleaned *daily* and filled with *fresh* water. Position it to direct the spray toward your head. This humidifies secretions that thicken during radiation.

Avoid any oral irritants: spicy foods, scratchy-textured foods (pretzels), *any* type of smoke, and *all* alcohol.

Try to minimize talking by creating a "phone call tree" (updating one to two people a day and asking them to pass on this information to others you designate). Talking can be painful and exhausting.

*Source:* Developed by Carper E. Department of Radiation Oncology, Continuum Cancer Centers of New York, 2002, with permission.

and RTOG scales are commonly used in the clinical arena and in reporting research. These tools combine assessment and measurement of symptoms (pain), signs (erythema), and functional changes (inability to eat solid foods) in order to grade mucositis, with grade 1 being mild mucositis, grade 2 being moderate, grade 3 being severe, grade 4 being life-threatening, and grade 5 being death. Whatever tool is chosen, a systematic assessment and documentation of mucositis should be done with each patient encounter. Interventions are then made based upon grade, individual patient characteristics, and comorbidities.[53–55]

## Mucositis during Radiation Therapy

Mucositis usually begins about 2 weeks after starting radiation therapy and continues with symptoms for 4 to 5 weeks after completion. Mucositis results in several tissue effects such as redness, swelling, tenderness, pain, difficulty swallowing, and hoarseness. These symptoms resolve once the acute mucosal affects have healed.[55]

Evidence-based guidelines for care of patients at risk for mucositis and for treating mucositis are scarce.[12,56] Minimal research has been done to determine the most effective oral care regimen for patients. Studies have demonstrated, however, that a systematic, consistent mouth care regimen is needed throughout radiation.[56,57] Care focuses on promoting patients' oral hygiene to minimize risk of infection, providing measures to treat infection should it occur, and increasing patients' comfort. Patients are taught a self-care regimen that includes the key elements listed in Table 10.4, which is individualized as needed.

Patients are instructed to reduce irritation of mucous membranes during treatment by avoiding chemical irritants such as tobacco, alcohol, commercial mouthwash, spices (e.g., pepper, chili powder, horseradish, curry powder), and citrus fruits and juices (e.g., orange, lemon, lime, grapefruit, pineapple, and tomatoes). Physical irritants to be avoided include the extremes of hot or cold foods, hard or coarse foods (e.g., toast, crackers, raw vegetables, potato chips, pretzels), and ill-fitting dentures. Dietary changes to cool foods and fluids (e.g., ice pops, ice cubes, ice cream, sherbet, and yogurt), a pureed or liquid diet, and increased use of nutritional supplements will be helpful during the course of radiation.[51,56,57]

## A Spray and a Weigh . . . Every Day

As treatment strategies have escalated in intensity, so should symptom management efforts. A daily spray of normal saline, delivered under low pressure, along with weighing patients daily helps maximize support of patients receiving intensive treatment for cancers of the head and neck. The spray cleanses the mouth, liquefies mucus, and provides comfort to patients. During this spray, a gentle flow of saline is directed to all surfaces of the oral

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cavity and oropharynx. This continues until the patient's mouth is clean and moist. Patients with oral cavity, oropharynx, and nasopharynx cancers may benefit most from this regimen, as the extent of irradiated mucous membranes can be quite extensive.

An additional benefit of the daily oral spray is that it provides an opportunity for an assessment of the patient's physical, nutritional, psychosocial status, and a determination of any pain management or dental needs. This also provides a perfect opportunity to reinforce the recommended self-care regimen which enhances patient learning.[57,58] In addition, the oral cavity is inspected for signs of infection. *Candida albicans,* evidenced by white patches, is the most common cause of infection in patients receiving head and neck radiation.[13] If patients develop *Candida* infection, an appropriate antifungal medication (such as fluconazole) should be prescribed.

## Prevention of Mucositis-Related Treatment Break

Patients with moderate to severe mucositis need intensive symptomatic support. They are at high risk for malnutrition, weakness, or pain to a degree that may necessitate a treatment break, with a resultant possible decrease in treatment effectiveness. Early identification and management of mucositis is critical. Intensive nutritional support, early placement of a PEG, and heavy reliance on supplements is often necessary and common, especially for patients receiving concomitant therapies. Usually a combination of both systemic pain medications and local anesthetics are utilized throughout the treatment course, with timely titration of medication and an appropriate bowel regimen employed.[59,60] For an example of a pain medication regimen used for patients receiving radiation therapy, see Table 10.5.

## Local Analgesia

Topical anesthetics for relief of mouth and throat pain may be indicated. This is especially true for patients receiving radiotherapy. Patients need careful instruction on how, where, and when to apply topical medications. A solution composed of equal parts of 2% viscous lidocaine (Xylocaine), diphenhydramine (Benadryl), and aluminum hydroxide–magnesium hydroxide–simethicone (such as Mylanta or Maalox) often is helpful in relieving generalized mouth and throat pain. Patients are instructed to swish 10 to 15 mL of this solution in their mouths for 30 to 60 seconds, to gargle, then to spit out the solution (oral fields) or swallow (hypopharynx, tongue, and larynx fields). This short-acting anesthetic should be taken before meals, at bedtime, and as needed up to eight times in a 24-hour period. Overuse could cause cardiac arrhythmia.

Ulcerations and discrete areas of inflammation, such as scatter-related (from dental fillings) lateral tongue lesions, are often very painful. An ointment containing benzocaine, which may be obtained without prescription, may be helpful in providing a protective film over the area to promote healing and provide near-immediate acute relief of pain. Patients are instructed to apply the ointment directly to the inflamed area by using a cotton-tipped applicator or their fingers. Again, patients must be cautioned not to overuse this cardiac stimulant.

When radiation therapy is complete, reinforcement of self-care measures that promote oral comfort and adequate nutrition is essential. Often, mucositis escalates for 1 to 2 weeks after completion of radiation. Typically, resolution of mucositis is complete within 6 to 8 weeks, and patients begin to resume normal activities of speaking and eating. Patients are informed that prolonged use or stress of the voice may lead to hoarseness even months after treatment, and they are encouraged to avoid smoke and fumes. A slow and gradual increase in texture

**TABLE 10.5 Sample Medication Regimen for Mucositis**

| Weeks 1–2 of treatment | | Weeks 3–7 of treatment and for 4–8 wk following completion of radiation therapy |
|---|---|---|
| Topical anesthetic (Orobase with Benzocaine, viscous Xylocaine 2% jelly) | | Actiq transmucosal "lollipop," 200–600 μg, q 3–4 h prn, *or* |
| Acetominophen 650–1,000 mg, ibuprofen 400–600 mg, q 4–6 h prn | | Oxocodone elixir, 20 mg/mL, 0.25–0.5 mL, q 3–4 h, prn, *plus* |
| Magic mouthwash–*dilute* formula swish/gargle/expectorate prn, no dose limits | | Fentanyl patch, 25–100 mcg, q 72 h |
| 1,000 mL | Normal saline for irrigation | Bowel regimen: |
| | $NaHCO_3$ | Colace, two capsules/liquid equivalent, t.i.d. |
| | Benadryl liquid | |
| | Viscous xylocaine 2% | Senakot, 2–4 tablets/liquid equivalent, qhs, prn |
| Or | | |
| Magic mouthwash–*full strength* formula | | |
| Use before meals, q hs, up to 8x/day maximum | | Fleet oil-retention enema, wait 4–6 h, then regular Fleet enema, q 3 d as needed or |
| 300 mL | 100 mL Mylanta | |
| | 100 mL Benadryl Liquid | |
| | 100 mL Viscous Xylocaine 2% | Glycerin suppository, wait 4 h, then Ducolax suppository |

*Source:* Developed by Carper E. Department of Radiation Oncology, Continuum Cancer Centers of New York, 2012.

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of foods (from liquid to soft to regular) and the cautious addition of seasoned foods is advised. Pain medications and stool softeners are tapered and discontinued as soon as possible.

## Mucositis—Pharmacologic Interventions

Shih and colleagues presented a thorough review of treatments currently used for mucositis caused by radiation and chemoradiation treatment.[47] As previously described, daily rinses of a mixture of water and salt (± sodium bicarbonate) are commonly used due to their cleansing and soothing abilities. Systemic narcotics afford relief from pain. Other medications recently studied for ability to minimize mucositis are categorized in one of four types: antimicrobial, coating, anti-inflammatory, or cytokine-like.[47]

The only intervention with enough evidence for practice recommendation is use of a bland rinse as previously described. Most agents commonly used for treatment of mucositis lack the clinical trial support for treatment recommendation and are described as "effectiveness not established."[47]

This category includes antimicrobial agents and Benzydamine HCl (BZD), a nonsteroidal agent with analgesic, antimicrobial, anti-inflammatory, and anesthetic properties, which work by inhibiting growth of bacteria for the possible result of less bacterial and fungal infections.[47] Not yet approved for use in this country, BZD is commonly used in Europe. Only six studies utilizing randomization and placebo control have been reported thus far in the literature. Results are mixed and are based on a limited numbers of subjects. A recent trial comparing efficacy of BZD and chlorhexidine for preventing and treating mucositis revealed no significant difference.[56,61]

Sucralfate oral suspension has been shown to significantly diminish gastric ulceration and is the coating agent most studied for efficacy in minimizing radiation mucositis. Early studies showed a trend toward decreased mucositis in patients who used sucralfate. However, out of eight randomized clinical trials, only one showed a reduction of mucositis in patients using sucralfate solution.[62] A newer coating product is Gelclair. Gelclair is a concentrated oral gel. It is rinsed and gargled in the mouth for as long as possible to maximize coating of all oral tissues. It forms a protective barrier that reduces pain by soothing tissues. It is used three times daily or as needed.[63] Early studies are promising, but larger, randomized, placebo-controlled studies are needed to establish efficacy.

Exciting, emerging research is being conducted with historically defined nutritional agents. One such agent is glutamine, an amino acid rich in nitrogen believed to be important in cancer cachexia.[64] Savarese and colleagues[65] describe the biology and metabolism of glutamine and then describe possible therapeutic used of glutamine in preventing radiation-induced mucositis. In their small, randomized trial of only 17 patients, those given glutamine swishes reported less objective and subjective signs and symptoms of grade 3 or worse mucositis.[65]

Other agents under investigation include GM-CSF, silver nitrate, topical morphine, and corticosteroids. Studies using less traditional agents are underway such as capsaicin in the form of a pepper candy, chamomile, vitamins, and other antioxidents. Cryotherapy in the form of ice chips and popsicles is being evaluated for radiation-induced mucositis, and honey is also being studied as an oral bacterial modulator.[51]

Palifermin or keratinocyte growth factor (KGF) is another agent under investigation. KGF works by stimulating growth of cells at the surface of the mouth and repairs damage done to the mucous membranes by chemotherapy or radiation therapy. It has proven effect in transplant patients.[25] Studies are ongoing for its efficacy in minimizing radiation-induced mucositis.

# PSYCHIATRIC CONSIDERATIONS

The head and neck cancer population is prone to the general psychosocial challenges that most cancer patients face in adjusting to their illness Fig. 10-3. The disease and its treatment pose psychological distress through interruption to routine daily activity, disturbance in lifestyle, and impairment that prevents engaging in usual interests. Such disruption can lead further delay in functional rehabilitation. Relationships may suffer as patients are faced with a changed role involving increased dependence on those who serve as caregivers, further complicated by its being imposed rather than willfully chosen. Symptoms related to the disease such as fatigue and loss of appetite (anorexia), cause disability, as do other side effects stemming from treatment including radiation therapy. Social issues, not the least of which are financial concerns, are encountered when stricken by the practical losses sustained. Difficulties are encountered over the course of the illness when facing complicated decisions regarding treatment, the overall challenge of resuming self-care activities after its completion, and uncertainty about disease progression. Spiritual needs may be faced when confronting mortality with the threat of death.

Disturbance in psychosocial functioning and psychological distress are reported by many head and neck cancer patients, with the main symptoms being worry, anxiety, fatigue, depression, and mood disturbance.[66]

## General Cancer-related Psychosocial Issues Applied to Head and Neck

Head and neck cancer patients have the highest rate of suicide, depression, and anxiety among cancer patients.[67,68]

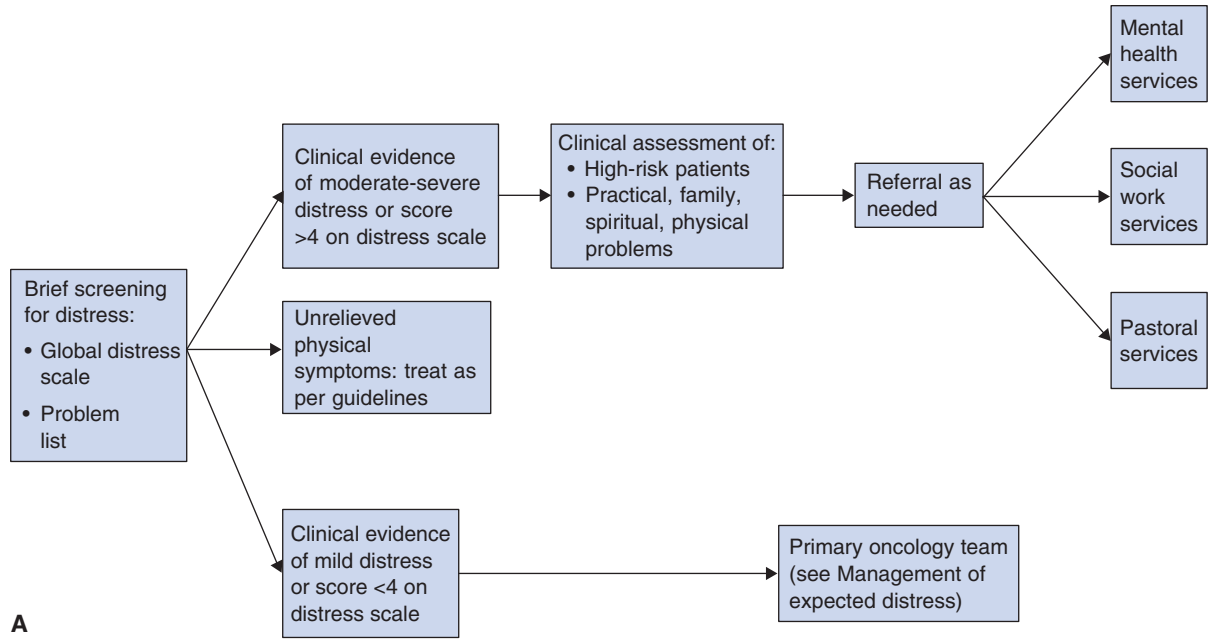
Depression and anxiety may arise from impairment experienced by side effects of treatment for head and neck cancer.[69] A major challenge in treating cancer is preserving form and function while pursuing oncologic control. "Organ preservation" is a particularly important consideration for treatment of all head and neck cancers even as it varies based on subsite because crucial functions, including but not limited to speech and swallowing, are often at risk.[70] Effects of the cancer and its treatment on these functions may be as significant as the cancer itself in impacting QOL.

Pain is a very common and emotionally distressing occurrence in patients with head and neck cancer and, if it is not a presenting symptom, frequently results from treatment which often includes a lengthy course of radiation therapy. By the midpoint of radiation treatment, for head and neck cancer, it has been found in one study that all patients experience pain which, furthermore, can persist in some for up to 6 to 12 months. The experience of pain, particularly of such long-lasting nature, is complex, involving psychological responses through direct interaction across emotional, cognitive, and behavioral dimensions.

## Head and Neck Cancer–specific Issues

Head and neck cancer introduces unique psychosocial challenges and adaptive demands. Behavioral and lifestyle factors play an important role in the etiology of head and neck cancer. As such, patients who develop head and neck cancer may have a high prevalence of preexisting psychosocial issues. Individuals with tobacco dependence are at high risk for developing squamous cell carcinoma of the head and neck, as tobacco use is linked to approximately 85% of cases. The established link between alcohol use disorders, as well as cigarette smoking, and the development of head and neck cancers[71] presents an additional complicating factor and challenge to patients in this population possibly needing to deal with addiction issues and self-blame

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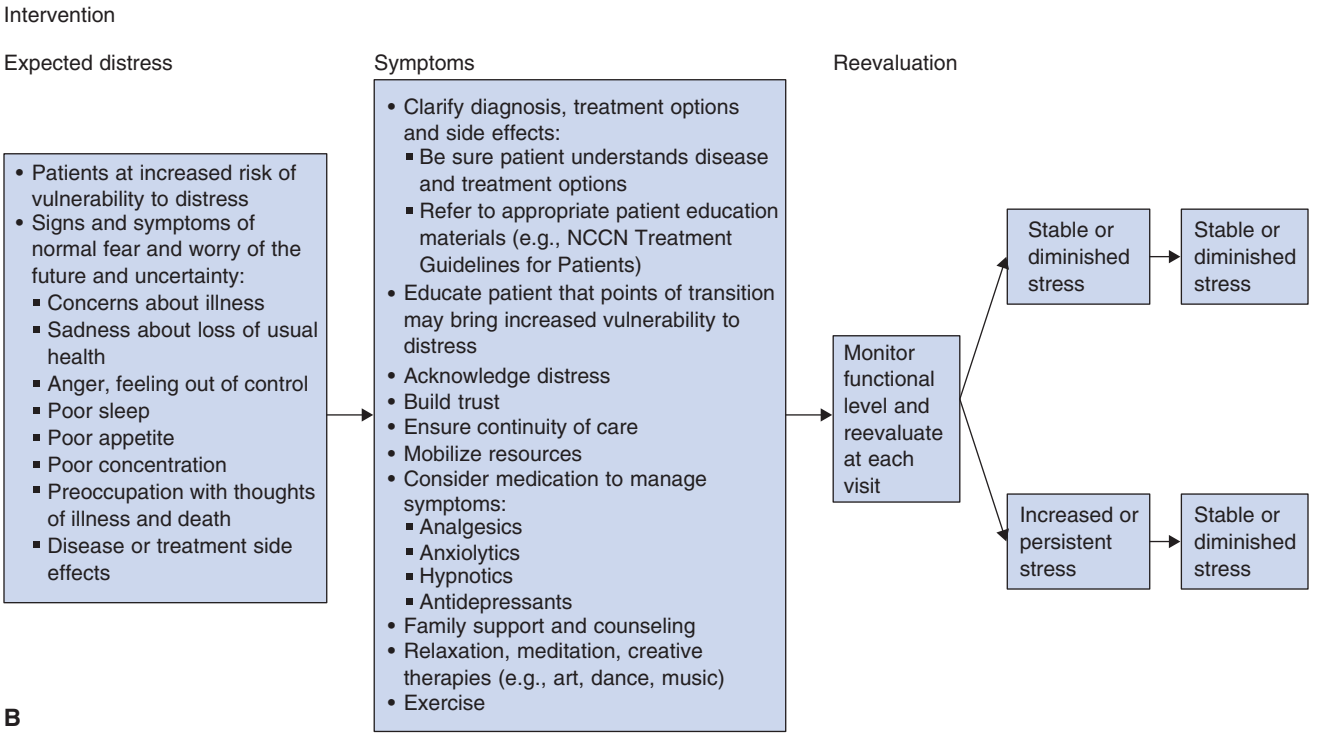



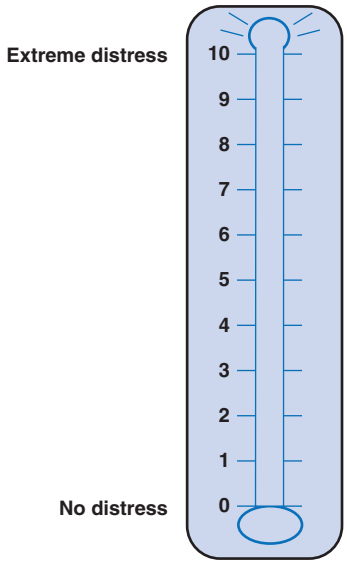

**FIGURE 10-3.** **A** and **B**: Distress assessment and intervention algorithm. (Adapted from the National Comprehensive Cancer Network [NCCN]. *Cancer and treatment-related anemia: NCCN Clinical practice guidelines in oncology,* Version 2, June 2007.) **C**: Screening tools for measuring distress. (Adapted from the National Comprehensive Cancer Network Guidelines, Version 3, 2012.)

along with anxiety, depression, pain, and other physical symptoms directly related to their cancer. Increased number of sexual partners and engaging in promiscuous sexual activity or risky and unsafe sexual practices are tied to a variety of psychosocial issues and psychiatric conditions and associated with head and neck cancer as sexual activity and the number of sexual partners have been associated with human papillomavirus (HPV) and with squamous cell carcinoma of both the oral cavity and the oropharynx. While HPV-associated cancers tend to have an overall better response to treatment and prognosis compared to head and neck cancers in general for a variety of hypothetical reasons, including the psychosocial profiles of such individuals as well as the otherwise relatively robust medical condition of the individuals afflicted given their relatively young age, this latter factor

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**SCREENING TOOLS FOR MEASURING DISTRESS**

**Instructions: First please circle the number (0–10) that best describes how much distress you have been experiencing in the past week including today.**




**Second, please indicate if any of the following has been a problem for you in the past week including today. Be sure to check YES or NO for each.**

| YES | NO | Practical Problems |
|---|---|---|
| ❑ | ❑ | Child care |
| ❑ | ❑ | Housing |
| ❑ | ❑ | Insurance/financial |
| ❑ | ❑ | Transportation |
| ❑ | ❑ | Work/school |
| ❑ | ❑ | Treatment decisions |

| YES | NO | Family Problems |
|---|---|---|
| ❑ | ❑ | Dealing with children |
| ❑ | ❑ | Dealing with partner |
| ❑ | ❑ | Ability to have children |
| ❑ | ❑ | Family health issues |

| YES | NO | Emotional Problems |
|---|---|---|
| ❑ | ❑ | Depression |
| ❑ | ❑ | Fears |
| ❑ | ❑ | Nervousness |
| ❑ | ❑ | Sadness |
| ❑ | ❑ | Worry |
| ❑ | ❑ | Loss of interest in usual activities |

| YES | NO | Spiritual/religious concerns |
|---|---|---|
| ❑ | ❑ | |

| YES | NO | Physical Problems |
|---|---|---|
| ❑ | ❑ | Apperance |
| ❑ | ❑ | Bathing/dressing |
| ❑ | ❑ | Breathing |
| ❑ | ❑ | Changes in urination |
| ❑ | ❑ | Constipation |
| ❑ | ❑ | Diarrhea |
| ❑ | ❑ | Eating |
| ❑ | ❑ | Fatigue |
| ❑ | ❑ | Feeling Swollen |
| ❑ | ❑ | Fevers |
| ❑ | ❑ | Getting around |
| ❑ | ❑ | Indigestion |
| ❑ | ❑ | Memory/concentration |
| ❑ | ❑ | Mouth sores |
| ❑ | ❑ | Nausea |
| ❑ | ❑ | Nose dry/congested |
| ❑ | ❑ | Pain |
| ❑ | ❑ | Sexual |
| ❑ | ❑ | Skin dry/itchy |
| ❑ | ❑ | Sleep |
| ❑ | ❑ | Tingling in hands/feet |

**Other Problems:** _____

_____

**C**

**FIGURE 10-3.** *Continued*

yields a host of psychosocial concerns related to suffering serious illness in youth.

Head and neck cancer is considered to be highly traumatic and, stemming from this, yields profound psychological morbidity.[66] This patient population faces a unique set of obstacles including disfigurement and functional impairment. As a result, head and neck cancer has an enormous impact on the QOL of patients.[69] The tumor and the consequences of its treatment can significantly impact one or more of the several important functions that the oral cavity, oropharynx, nasopharynx, larynx, and hypopharynx normally serve. Alteration of functions, including mastication, speech, taste, swallowing, salivation, and oral sensation, as well as negative view of body image can be devastating to patients.[66,72] Head and neck cancer patients are prone to treatment-related side effects, which make their care complex.[67] Despite regimens of concurrent radiation and chemotherapy and targeted-radiation delivery using intensity-modulated radiation therapy and other advances to reduce collateral damage to normal surrounding tissue while maximizing dosage delivered to the tumor volume, side effects from the treatments, particularly radiation, can be life altering. These often include, but are not limited to, pain that may become chronic in nature, including oral pain and pain when swallowing (odynophagia); difficulty swallowing (dysphagia) from fibrosis of subcutaneous tissues; and, occasionally, stricture formation. Other feeding problems associated with difficulty eating, drinking, and chewing that may be related include impaired jaw opening (trismus), possible substantial and permanent dry mouth (xerostomia) resulting from reduced saliva production, and taste distortion (dysgeusia), which may be diminished (hypogeusia) or, rarely, lost (ageusia). These can lead to long-term feeding-/gastrostomy-tube dependence. Alterations in patterns of breathing and speech (dysphonia) such as hoarseness, diminished production (hypophonia), or, rarely, loss of voice (aphonia), may result from airway problems or from radiation-related fibrosis or edema. Other problems include earache (otalgia), mouth sores, and the general problems of hair loss, nausea, and fatigue, as well as skin rash or changes, and problems related to sexual adjustment. All of these problems can become more intense with continual treatments.[73,74] Dysfunction or loss of the sense of smell is not commonly reported, and tinnitus or disturbance in hearing is not reviewed prominently in the literature. Depression and anxiety often experienced by head and neck cancer patients can result from these treatment-related side effects.

Head and neck cancer also differs from some other cancers in that both the tumor and side effects of treatment, such as skin reactions or surgical grafts, are often visible, and, as such, can greatly affect body image.[74] Additionally, undesirable cosmetic outcomes can occur from chronic tracheostomy dependence, face and neck incisions, and whole-organ extirpation (i.e., eyes, nose, larynx, tongue, and mandible). Changes to body image as a result of the cancer and disfiguring treatment can give rise to diminished self-esteem and sexual functioning.[66,75] Facial disfigurement can lead to shame and social avoidance that compromises QOL. The ability to socialize can also become significantly challenged with marked impairment in eating and speaking. Patients often need to stop working during treatment, presenting

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an additional financial burden to themselves and their families. When head and neck cancer patients require tracheostomy and/or feeding tubes, their daily functioning is impacted by having to adjust to this markedly altered and challenging way of living. Despite the numerous side effects associated with these cancers, there is limited research on the psychological and psychosocial implications of head and neck cancer.[69]

## Eating and Drinking

Head and neck cancer and side effects from its treatment including dysgeusia, xerostomia, dysphagia, odynophagia, oral pain, and trismus cause a decreased ability to eat by mouth or in a manner comfortable in typical social settings. Forced change in diets to meet nutritional needs in the context of change in tolerability of foods, often entail blended or bland foods or supplements, and problems with oral intake may present hazardous nutritional deficits requiring bypassed feeding through gastrostomy tubes, presenting a substantial challenge to patients within a basic element of lifestyle and social interaction. Patients may feel uncomfortable, awkward, or embarrassed in these settings, as a result of self-consciousness about their eating, which has become mechanically compromised as a result of difficulty with jaw opening, abnormal anatomy of the oral cavity, or altered and decreased sensation of mouth structures, and, once taken for granted as effortless, is now a cumbersome and onerous task. Patients often experience altered taste sensation which, compounded by dry mouth and hyposalivation, reduces the enjoyment formerly associated with eating and drinking. Patients may remove themselves from the family meal, yielding increased isolation that risks exacerbating mood symptoms and a sense of despair at a time when they are most in need of social contact and support. These impairments in behavior so essential to livelihood and survival often represent a substantial loss to the patient on physical, psychological, and social levels. Persistent encouragement and support from friends and family is helpful in dealing with these difficulties. Patients may emerge with a new appreciation for such basic elements of life.

## Speech

In a similar vein, verbal communication obviously plays an important part in one's day-to-day functioning. As such, a profound physical loss is understandably difficult to face emotionally when surgical treatment of head and neck cancer leads to vocal alteration. If speech is maintained but distorted, the ability to engage in routine conversation may still be dramatically impacted. The diminished capacity to accurately convey emotions through voice tone may be experienced as exceedingly frustrating to the patient. The vocal deficit may only affect special circumstances such as speaking before an audience or singing, but may nonetheless be markedly impairing. In the case of total laryngectomy, speech can be produced though artificial means, and communication may still be achieved in other ways and through alternative or assistive devices, as simple as a laptop computer, though the adjustment curve is quite steep. Positive predictive factors in speech rehabilitation include age, marital status or the presence of an external support system, and engagement in problem-solving behavior.[69] Understanding and patience are needed to assist the patient in addressing this difficulty.[69] If presented with the scenario, choosing between the latter two vital functions is obviously a very grave process.

## Sexual Adjustment

Due to concerns about body image and facial disfigurement as well as odor, sexual functioning can become a major issue for head and neck cancer patients and their partners or spouses. These problems may interact with additional factors affecting sexuality in head and neck cancer, including alcohol abuse, aging, depression, and anxiety. Interest in sexual activity may decline or the pleasure derived from it may be markedly diminished. Abatement or complete termination of sexual relationship is a common occurrence in couples in which a member has head and neck cancer. This issue can itself become parasitic to a relationship in need of healing from strains to which it was exposed in going through cancer treatment. This issue is of particular vulnerability because the tendency to suffer in silence without seeking help is reinforced by feelings of shame that may already be present. It is especially important for health care providers to prompt patients about this issue, and at an early stage, because, in doing so, it is presented as an appropriate and acceptable topic to discuss and an issue that the team is willing to address, thereby providing helpful reassurance.[69]

## Disfigurement

Facial disfigurement, mainly from surgery, is not only considered to be among the most disturbing stressors associated with head and neck cancers, but also possibly the most poorly addressed. Head and neck cancers are difficult to conceal as the location of the tumors are in visually prominent areas of the body. Impairment in important functions of the face such as emotional expression, reflecting animation, as well as verbal communication presents challenges with its distortion. The face is also essential to the sense of self and to interpersonal interaction and relationships, so it is not surprising that research has confirmed that disfigurement is associated with negative effects on mood,[76] self-image, and romantic, family, and other relationships.[77] These can be greater in marital partners than patients.[78] Even small alterations in one's appearance can have a major adverse impact on one's body image and self-esteem.[75] Just maintaining privacy about one's diagnosis is often impossible. However, both individual characteristics and the social environment may moderate the effect of disfigurement following head and neck surgery. Social support, particularly among women surgically treated for head and neck cancer,[79] and social self-efficacy[80]—the belief that one can exercise control over the reactions and openness of other people—may moderate and buffer the psychosocial impact of disfigurement.

The process of adjustment to facial disfigurement is extremely difficult from a psychological perspective.[81] Prior to even dealing with the fear of facial disfigurement, the head and neck cancer patient initially confronts and must cope with the possibility of imminent and premature death encountered by many cancer patients. Dealing with these existential issues may be particularly intense for those with head and neck cancer because facial disfigurement is so visually evident, acting as a frequent reminder of the pathology that the patient is repeatedly forced to face directly. At first overshadowed by these other challenges, adjusting to facial disfigurement eventually comes to the fore. Facial appearance is a central feature of physical attractiveness, which is highly emphasized in various domains of social status, in addition to its role in reflecting animation, intellect, and emotion, and serving as a means of communication with others. The difficult task of coming to terms with one's facial disfigurement involves recognizing and accepting that people will respond differently to the individual. Through the process of body image reintegration, occurring gradually over time, the patient learns to accept and compensate for anatomic alterations.[82] It seems important for a patient to begin to establish a revised self-image, as such, before attempting to fully resume social activities such as employment. Encountering relatives and friends poses special concerns for some patients. The immediate family frequently provides an

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important support system, usually reacting with compassion. Reactions from others in the patient's life may be variable, and conflicting responses may impact the patient's coping process. Patients who experience facial disfigurement may find the medical setting frustrating, especially when encountering visit delays, scheduling difficulties, or perceived lack of empathy from staff. Continuity of care and continuous exchange of information among team members may assist in the recovery process. Factors affecting reintegration of body image in head and neck cancer patients include age, sex, marital status, previous body image acceptance, the extent of structural and functional loss, extent of disfigurement, state and trait anxiety (experienced at a particular interval and as a stable factor over time, respectively), previous emotional stability, capacity for self-care, and self-acceptance in social situations.[69]

## Addiction

Head and neck cancer patients may often express feelings of guilt or self-blame due to perceived culpability and responsibility for their illness from having engaged in unhealthy behaviors that may have caused their malignancy, such as smoking or drinking alcohol which may figure to varying degrees in their history.

Less than 20% of patients who smoked prior to their diagnosis quit afterward, and relapse rates are high.[83] One study found that more than one quarter of the larynx cancer patients continued to smoke after treatment.[66] Another study found that approximately 35% of head and neck cancer patients continued to smoke or consume alcohol following surgical removal or radiation of the primary tumor. Managing addiction in patients with cancer can be time consuming, labor intensive, and challenging.[84] Furthermore, patients who continue to use tobacco or alcohol following treatment for head and neck cancers are at a greater risk for cancer recurrence and mortality.[66,71,85] Studies have found that continued smoking among patients with head and neck cancer has greatly increased the risk of recurrence compared to nonsmokers and doubled the risk compared with patients who stopped smoking.[66] Abusing alcohol or smoking is also one method patients may use to cope with their illness. It has been suggested that patients may use smoking as a means of reducing pain and self-medicating. Nicotine is known to have analgesic properties, which may impact cancer patients' willingness to quit smoking without reassurance that their pain will be managed.[83]

Alcoholism often develops or recurs as a consequence of severe psychological stress, chronic medical conditions, or terminal illness.[86] Cancer patients have numerous barriers to smoking cessation including heavy nicotine dependence, urgency of cessation, fatalistic attitudes about cessation benefits, cancer-related psychological distress and treatment factors, and presence of smokers in their social networks.[87] The high prevalence and clinical implications of continued substance use highlights the importance of psychosocial interventions for head and neck cancer patients. Furthermore, the IOM report recommended behavioral interventions such as smoking cessation programs to address patients' psychosocial needs.[88]

## Treatment

Normalizing the experience, providing education, and the proper services at treatment centers can help reduce distress, depression, and anxiety prevalent in head and neck cancer patients. Referral to substance abuse programs is essential for those patients whose recidivism may predispose to a recurrence, apart from the effects on general health.

Patients' natural fears about mortality, difficulties swallowing, breathing, or eating may progress to disabling depression or anxiety requiring formal treatment. A psychosocial intervention (education, individual, or group counseling) and judicious use of anxiolytics or antidepressants can be pivotal in patients' adjustment to cancer, adherence to full treatment schedules without missed appointments for radiation, chemotherapy or surgery, and improvements in QOL.[89] Anxiolytics such as lorazepam, so commonly used as antiemetics, can be more regularly dosed, or benzodiazepines, with a longer half-life (such as clonazepam), can be substituted for ease in dosing. Selective serotonin receptor antagonist antidepressants have minimal drying effects, better suited for patients with thickened secretions or xerostomia. Agents such as fluoxetine, sertraline, citalopram, or escitalopram lack significant sedation that can compound cancer-induced fatigue. Patients with insomnia or agitation may welcome the addition of a more sedating serotonin reuptake inhibitor such as paroxetine or venlafaxine at bedtime.

Long-term group and short-term psychoeducational programs have been shown to be effective in improving QOL for head and neck cancer patients.[90] Additionally, individual psychotherapy incorporating a variety of standard approaches may be beneficial, including psychoeducation to provide information about the disease and its treatment in a therapeutic context addressing ways to manage these challenges, cognitive-behavioral strategies to attend to maladaptive coping response that compromise psychological well-being, and supportive-expressive techniques useful particularly for symptoms of depression and anxiety.[65]

***Psychosocial Distress Assessment.*** Presently, the understanding of the emotional effects of cancer and its treatment on the patient and family and the role of psychosocial support is better integrated with surgery, chemotherapy, and radiation treatment for cancer. Also, symptom management is adapted from the palliative care and hospice world and modified for use in curative as well as palliative care of head and neck patients. In recognition of the need for such integration, the National Comprehensive Cancer Network (NCCN) has established Distress Management Guidelines in tandem with its site-specific guidelines[91] (see Fig. 10-3).

Distress has been defined as a multifactorial unpleasant emotional experience of a psychological (cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis.

Distress should be recognized, monitored, documented, and treated promptly at all stages of cancer. All patients should be screened for distress at their initial visit, at appropriate intervals, and as clinically indicated, especially with changes in disease status. Screening should identify the level and nature of the distress, using an instrument with qualitative and quantitative measures. An example of the distress thermometer used at Continuum Cancer Centers is in Figure 10-3.[92] A similar distress thermometer has been validated in the ambulatory setting.[93]

The most commonly endorsed items: pain, fatigue, worry, sadness,[94] and eating should be managed using best practices adapted from the NCCN Clinical Practice Guidelines. Patients, families, and treatment teams should be informed that management of distress is an integral part of total medical care and provided with appropriate information about symptom management and psychosocial services available in the treatment center and the community. Quality of distress management should be included in institutional continuous quality improvement (CQI) projects.

Specific to head and neck cancer, fatigue and pain are likely to spike at predictable times as treatment progresses and varying with the timing of the surgical intervention or chemotherapy

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schedule for patients receiving combined treatment. As treatment ends, patients may be relieved, reflected in lower distress levels, or frightened of an immediate recurrence, causing an increase in distress scores. Effective symptom management and patient education may actually maintain distress ratings lower than would be anticipated as the symptoms are optimally managed, and patients and families know what to expect.

## INTEGRATIVE ONCOLOGY

There is an emerging recognition for the importance of integrative medicine in cancer care. Integrative oncology is a practice that combines the strengths of traditional allopathic Western medicine with the best approaches of complementary and alternative medicine (CAM).[89] It brings additional dimensions to patient care, increasing overall QOL through the use of supportive therapies coordinated with conventional therapies already integral to clinical care. CAM practices are focused on addressing the needs of body, mind, and spirit or, more specifically, the entire psychosocial experience of a cancer occurrence and its treatment rather than simply addressing the physical aspect of cancer.[89] By addressing these additional facets of patient care, integrative oncology can effectively make use of unconventional treatment modalities and approaches that are nonsurgical and nonpharmaceutical but have known efficacy.

Defining exactly what components comprise a complementary intervention varies widely between clinicians, treatment centers, and the public.[89] Using a wide definition, patients use integrative modalities without even realizing it. These include dietary changes (vitamins at usual or mega-doses, herbs, and supplements), mind–body techniques (massage, chiropractic adjustment, energy healing, biofeedback, acupuncture), relaxation techniques (guided imagery, hypnosis), psychosocial support (individual counseling, professionally led support groups, self-help groups), and spirituality (prayer, spiritual healing).[89,95] Recommendations for complementary and alternative therapies are provided in Table 10.6.

Complementary integrative oncology programs are already a core part of many major cancer centers for patients undergoing allopathic cancer treatment and include dietary education, counseling, and prayer.[96] Such programs also provide selective encouragement and discouragement of potential treatment modalities.[97] As early as 1998, a survey of 117 of the 125 US medical schools indicated more than half offered courses in CAM topics, either as required or elective classes. At that time, however, there was lack of standardization and quality in the content, format, and core requirements of CAM courses.[97,98] Currently, more programs that focus on lessening chemo and radiation treatment side effects and decreasing pain and the need for postoperation medication have been incorporated into pre-op teaching curriculums intended to prepare patients for surgery. One such program, The Bravewell Collaborative, offers a distance-learning fellowship at the University of Arizona Center for Integrative Medicine in a 1,000-hour training program to readdress patient care for preventative and individualized practice. At New York's Beth Israel Medical Center Residency Program in Urban Family Practice, family medicine residence are required a 1-month block rotation in CAM training and practice, receiving 20 hours

**TABLE 10.6 Grading Recommendation for Complementary or Alternative Therapies**

| Grade | Recommendations | Benefit vs. Risk | Strength of Evidence | Implication |
|---|---|---|---|---|
| 1A | Strong recommendation, high-quality evidence | Benefits clearly outweigh risk and burdens, or vice versa | RCTs without important limitations or overwhelming evidence from observational studies | Strong recommendation, can apply to most patients in most circumstances without reservation |
| 1B | Strong recommendation, moderate-quality evidence | Benefits clearly outweigh risk and burdens, or vice versa | RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies | |
| 1C | Strong recommendation, low- or very low-quality evidence | Benefits clearly outweigh risk and burdens, or vice versa | Observational studies or case series | Strong recommendation may change when higher-quality evidence is available |
| 2A | Weak recommendation, high-quality evidence | Benefits closely balanced with risk and burden | RCTs without important limitations or overwhelming evidence from observational studies | Weak recommendation; best action may differ depending on circumstances or patients' or societal values |
| 2B | Weak recommendation, moderate-quality evidence | Benefits closely balanced with risk and burden | RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies | |
| 2C | Weak recommendation, low- or very low-quality evidence | Uncertainty in estimates of benefits, risk, and burden; may be closely balanced | Observational studies or case series | Very weak recommendations; other alternatives may be equally reasonable |

*Source:* Oncology Nursing Society, 36th Annual Congress, April 28, 2011.

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per week of didactic/experiential education in herbal medicine, hypnotherapy/mind–body medicine, nutritional medicine, and osteopathic manipulation (see listed resources).

Demonstrating a wider understanding and acceptance of treatment options may alleviate the routine occurrence of adverse interactions or reduced efficacy between traditional and complementary therapies, as a large majority of patients often do not disclose their involvement in complementary therapies to physicians for fear of receiving a disapproving response.[96] Estimations of patients' use of complementary therapies range from 10% to >60% depending on applied definitions; a Data Monitor 2002 Survey indicated 80% of cancer patients utilized CAM, many as complementary to traditional treatment.[96] It is therefore imperative to discuss and monitor CAM usage; to encourage treatments that have proven effective as well as to discourage treatments that may be unsafe or that show little evidence of success. The recommendations by the Society of Integrative Oncology, a multidisciplinary panel of professionals who provide a forum for discussion and peer review of evidence-based research and treatment modalities, are to evaluate alternative medicine options based on evidence provided by credible information sources (see attached resources list), thereby avoiding discouraging patients from potentially helpful intervention modalities.[96]

## Mind–Body Techniques: Hypnosis/Guided Imagery/Yoga

With regard to fatigue, pain, and emotional distress, studies suggest that complementary techniques such as guided imagery and yoga have beneficial effects and can improve function and overall survival in cancer patients. A meta-analysis of 116 studies demonstrated "that mind–body therapies reduced anxiety, depression, and mood disturbance in cancer patients and assisted them in their coping skills."[96]

Psycho-neuroimmunological theories suggest that psychological response to guided imagery may down-regulate the hypothalamic-pituitary axis, resulting in reduced stress response and increased state of well-being.[99] Cognitive theory suggests that changing negative thought patterns leads to a reduction in the autonomic nervous system's arousal. Pickett et al. (1982) hypothesized that the effect of guided imagery may be due to its action as a coping mechanism, giving an individual a greater sense of control and empowerment when dealing with a difficult situation.[99] The use of progressive muscle relaxation reduces psychological distress and improves cancer patients' ability to cope with their disease.[100]

In a postoperative study on same-day surgical procedures, patients who listened to guided imagery compact disks reported less pain and decreased anxiety levels than patients who did not receive this therapy method. In ambulatory surgery, guided imagery led to significantly reduced preoperative anxiety, which can result in less postoperative and pain and earlier discharge times.[101]

The use of an "optimal healing environment"[102] was studied by implementation of the Urban Zen Initiative at Beth Israel Medical Center in New York City, in which physical space was remodeled, nursing staff received specialized training in complementary therapies, and yoga therapists were available for one-on-one sessions with patients. Results indicated significantly lower levels of tension, depression, fatigue, and mood disturbance after implementation, as well as a greater rate of improvement and lowered medication costs per patient.[102] The practices of mind–body techniques are recommended as supportive modalities in reducing anxiety and pain.

Hypnosis is defined as a state of restful alertness in which a person has a level of focused concentration. An independent panel convened by the National Institute of Health found that it may be helpful for treating chronic pain issues when used with standard medical care. Hypnosis proved helpful in the reduction of pain and distress during medical procedures in children with cancer, in addition to effectively reducing fear and anxiety.[103] A growing body of research has evaluated the effectiveness of behavioral interventions on QOL for cancer patients. Hypnosis has been applied to chronic pain conditions including those from cancer.[104] However, most of the studies are related to intervention with breast cancer and not head and neck patients.

## Psychosocial Techniques: Music/Pet

Clinical studies have shown that the use of music applied within a therapeutic context provide a myriad of benefits for cancer patients managing pain. Music therapy can be provided in both individual settings, such as during simulation and radiation therapy, as well as in group sessions, including waiting areas and chemotherapy suites. Music therapy leads to reduced nausea, emesis, and illness-related anxiety. Additionally, patients have reported increased comfort and less fatigue, tension, and decreased procedural and treatment-based stress, such as in radiation and chemotherapy.[105–107]

A growing body of evidence points toward positive interactions with companion animals and visitations by therapy dogs. Animal contact has been shown to lower blood pressure, reduce anxiety, decrease depression, and reduce pain perception in children.[108–112] Therefore, therapy is generally assessed for QOL issues for patients undergoing treatment and suffering from general distress and pain management. Beth Israel Medical Center in New York, Taussig Cancer Center of the Cleveland Clinic, and Denver Children's Hospital, all have ongoing visiting dog program or animal-assisted therapy, though data have yet to be collected for review.

## Symptom Management: Anxiety/Pain/Fatigue

Complementary therapies such as acupuncture, mind–body techniques, and massage therapy can help when conventional treatment does not bring satisfactory relief or causes undesirable side effects. Acupuncture is a treatment modality originating from China, involving insertion of sterile needles along established meridians in the body to allow flow or energy, known as qi.[96] The manual stimulation of each point by rotation, thrust, and lifting motions achieve feelings of heaviness or tingling at the point of insertion, indicating that the site has been correctly stimulated.[95] Acupuncture's contribution to cancer pain management has been studied as complementary rather than alternative modality, but has demonstrated proven effectiveness in randomized controlled trials testing for pain reduction.[96,113]

For head and neck cancer patients, xerostomia is a common side effect that has successfully been alleviated by acupuncture, a low-cost therapy with minimal side effects. Studies conducted in 2009 demonstrated a lasting response of higher salivary flow rates, and that, when given alongside radiation therapy for head and neck cancer, acupuncture reduced the debilitating effect of xerostomia and provided an acute benefit for chronic pain.[96,113] Saliva flow rates were significantly greater in a group of patients who received acupuncture concurrently while treated compared to a control group beginning just 3 weeks into radiotherapy and persisting through a 1- and 6-month follow-up. Several uncontrolled studies have indicated that acupuncture also helped with other cancer-related symptoms such as chronic pain, hot flashes, and fatigue.[96,114]

## Energy-Based Therapies

Therapeutic touch, reiki, qigong, and tai chi are energy-based therapies. For therapeutic touch and reiki, biofield energies are used in the form of healing intent or life energy, which are conducted into patients for the purpose of unblocking energy centers and increasing self-healing abilities.[96,97,115] In an *in situ*

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cell-based RCT to verify the efficacy of therapeutic touch, fibroblasts, tenocytes, and osteoblasts in culture were twice-weekly treated by therapeutic touch, resulting in significantly stimulated cell proliferation compared to control and sham/placebo treatment arms.[115] In RCT studies conducted on 189 cancer patients receiving chemotherapy, however, both Reiki and placebo therapies were statistically significant in raising comfort and well-being of patients postinfusion, with no adverse results.[116] Conclusions from the trial indicated that the presence of an "RN providing one-on-one support during chemotherapy was influential in raising comfort and well-being levels, with or with an attempted healing energy field".[116] Some nurses practice therapeutic touch and Reiki therapy, with many professional nursing organizations available that offer training and certification programs. Qigong and Tai chi are energy-based practices of individual daily exercises and awareness of breath, providing the patient comfort through self-induced treatment.[96]

### Supplementation: Herbs and Botanicals

The concurrent use of dietary supplements, herbs, and other botanicals while undergoing chemotherapy, radiotherapy, or surgical treatments pose the greatest hazard as the most number of adverse interactions occur between this method of CAM and conventional medicine. As an example, patients who use the commonly available herbal supplement St. John's wort while receiving a taxane risk unexpected toxicities.[117] However, such supplementation may prove beneficial: In a 2000 study, oral glutamine demonstrated potentially significant reductions in the duration and severity of objective oral mucositis during radiotherapy, with a study dose of 2 g/30 mL liquid swished and swallowed four times a day.[118]

## INTEGRATION OF PALLIATIVE CARE WITHIN ONCOLOGY PRACTICE

Palliative care is an interdisciplinary approach that focuses on the care of patients with serious or life-threatening illness. The focus is on comprehensive symptom management, as well as attention to the psychosocial aspects of illness (psychological, social, emotional, spiritual dimensions) which contribute to the experience of suffering. For cancer patients, palliative care should be an integral part of the treatment from the time of diagnosis and not reserved for the time when all disease-modifying treatments have been exhausted. Recent studies have shown that involvement of palliative care specialists earlier in the course of serious and life-threatening disease can be beneficial not only in supporting patients through treatments, but even in prolonging survival, despite less frequent use of aggressive end-of-life care.[119]

The goal of palliative care to be delivered concurrently with all modalities of treatment is part of practice guidelines established in 2001.[120] The goals set forth in these guidelines are to enhance the QOL for patients and their families through optimizing function and assisting with decision making. Palliative care interventions are intended to address the multidimensional aspects of suffering, to assist in developing coping strategies, to facilitate communication with oncologists and other medical professionals, to support decision making, and to facilitate the often difficult conversations regarding advance directives and goals of care. Recommendations are that palliative care should be integrated in a seamless manner with other aspects of care.

In particular, referrals to palliative care specialists should be considered for patients with advanced disease, where progression of symptoms is likely and treatments are aimed at palliation; for patients with multiple symptoms or symptoms of unclear etiology; for patients with complex pain not controlled on current regimen; for patients with advanced or recurrent disease, regardless of current symptoms; for patients with high levels of distress; or when decision making is complex.

A model of concurrent care, in which palliative care specialists are colocated within a cancer center, is ideal for several reasons.[121] Patients undergoing cancer treatments are already burdened by multiple appointments and time spent in radiation and chemotherapy treatment sessions. It may be very difficult to schedule additional appointments for assessment by palliative care specialists. The presence of a palliative care team within a cancer center allows optimum support for patients, assisting them during cancer treatments. This allows oncologists to focus primarily on the management of cancer. The interdisciplinary team provides ongoing dialogue and assessments to maximize comfort, clarify patient and family priorities, minimize need for emergency room visits, and decrease patient and family distress during treatments.

The integration of palliative care specialists in oncology practice eases the clinical burden on oncologists.[122] Conversations about physical and emotional symptoms are time-consuming and collaboration with interdisciplinary team requires coordination and continuity. Patients may need help in interpreting clinical information and, frequently, the goals of care change during course of treatment. Palliative care specialists who work within an oncology practice form relationships with oncologists, nurses, social workers, dietitians, and chaplains. This facilitates the smooth flow of clinical information, especially when patients' care moves between inpatient and outpatient settings.

Improving linkages between palliative care and oncology practice can limit the burden of suffering in patients with progressive cancer. The two goals of actively treating the disease and managing symptoms may be best achieved using an "integrated model." Currently, referrals to palliative care occur late in the course of disease, within 30 to 60 days before death.[122] Early referral to palliative care can improve symptom management, provide psychosocial support throughout the continuum of the disease, and assist with transitions of care, when disease-modifying therapies are no longer effective, no longer tolerable, or no longer desired. Evidence suggests that early referral to palliative care can improve the QOL of patients with advanced disease as well as relieve family stress.[122] When patients are referred to palliative care teams early in the course of treatment, it allows time to form relationships with palliative care team members, who remain involved in their care as their disease progresses. Time spent in this relationship can ease the transition to hospice care if and when this is desired and appropriate.

In addition to improving patients' QOL, early involvement of palliative care teams facilitates patients' participation in their plan of care, without having to choose between usual care and hospice.[123] The cost savings of such an approach has been studied in clinical trials, with evidence suggesting cost savings of more than US$4,800 per patient.[123] Additional randomized trials of various palliative care initiatives and interventions have confirmed the improvement in symptom control, QOL, and satisfaction with care for patients and their family caregivers.[124]

Encouraging conversations between palliative care specialists, oncologists, patients, and their families about the continued benefits of ongoing treatments, in the face of progressive disease, highlighting both personal choice and functional status is a priority in providing supportive care to patients and their families during and after treatment.

### Survivorship

A report from the Institute of Medicine in 2005, "From Cancer Patient to Cancer Survivor: Lost in Transition," describes cancer survivorship as a distinct phase of the cancer trajectory and

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suggests that a strategy is needed for the ongoing clinical care of cancer survivors. The IOM report recommended that, after completing primary treatment for cancer, patients be given a summary of their treatment and a comprehensive plan for follow-up, including the long-term effects of cancer and its treatment, as well as the identification of psychosocial support resources in their communities. It should include guidance on follow-up care, prevention, and health maintenance.[125]

According to the organization Support for People with Oral and Head and Neck Cancer, Inc. (SPOHNC), there are presently more than 500,000 survivors of oral and head and neck cancer living in the United States. In addition, 58,000 people in the United States will be diagnosed with this disease this year.[126] SPOHNC is recognized by the American Cancer Society, the National Cancer Institute, and many medical centers and health care professionals as an organization dedicated to meeting the needs of oral and head and neck cancer patients. New guidelines and standards of care have been updated for 2012 which widen the scope of practice. Recent publications focuses on patient-centered needs.[126]

The mnemonic LEARN is a recovery plan for patients and families to better organize information and tasks as a new cancer survivor, starting at time of diagnosis through a period of "disease-free survivorship or recurrence/relapse."[126] It focuses on information that can be learned from "providers about a particular clinical course, with an emphasis on five basic tasks"[126]:

L—**Living**—Focus regularly on an aspect of living outside of the treatment with a broader life perspective.
E—**Education**—Learning as much as fits your style about one's cancer and its treatment to expedite recovery.
A—**Activity**—Physical activity to the extent able during and after treatment minimizes deconditioning afterward.
R—**Rest**—Using periods of rest and energy conservation to optimize energy during and after treatment.
N—**Nutrition**—Good nutrition paired with the limitations of treatment to maintain lean body mass, energy, and healing.

# RESOURCES

## Organizations/Associations/Institutions

- Society for Integrative Oncology
  - www.integrativeonc.org
- American Holistic Medical Association
  - www.holisticmedicine.org
- National Certification Commission for Acupuncture and Oriental Medicine
  - www.nccaom.org
- National Cancer Institute: Office of Cancer Complementary and Alternative Medicine
  - www.cancer.gov/cam/health_patients.html

## Professional Education and Certification Schools

- Institute for Complementary and Alternative Medicine, University of Medicine and Dentistry
  - www.umdnj.edu/icam/education
- University of Arizona College of Medicine
  - integrativemedicine.arizona.edu/education/fellowship/index.html
- University of Minnesota, The Center for Spirituality & Healing
  - www.csh.umn.edu/modules/index
- American Holistic Nursing Association
  - www.ahna.org
- Therapeutic Touch International Association
  - www.therapeutic-touch.org

## Databases of Botanical and Herbs

- Natural Comprehensive Database
  - www.naturaldatabase.com
- Memorial Sloan-Kettering Cancer Center Herbals and Botanicals Database
  - www.mskcc.org/cancer-care/integrative-medicine/about-herbs-botanicals-other-products
- American Botanical Council
  - www.herbalgram.org

## Mind/Body/Health Institutions

- The Center of Health and Healing
  - www.healthandhealingny.org
- Center for Mindfulness in Medicine, Healthcare and Society
  - www.umassmed.edu/cfm
- The American Institute of Stress
  - www.stress.org/about.htm
- Mind/Body Medical Institute
  - www.mbmi.org
- The Center for Mind–Body Medicine
  - www.cmbm.org
- National Institute for Clinical Applications of Behavioral Medicine
  - www.nicabm.com

## Integrative Oncology Comprehensive Research Databases

- National Center for Complementary and Alternative Medicine
  - http://nccam.nih.gov/research/
- The Cochrane Library
  - www.thecochranelibrary.com
- PubMed
  - http://www.ncbi.nlm.nih.gov/pubmed/

## Nutrition Resources

- American Institute for Cancer Research
  - www.AICR.org
- Support for People with Oral and Head and Neck Cancer SPOHNC cookbook: Eat Well—Stay Nourished
  - www.SPOHNC.org
- National Cancer Institutes: Eating Hints for Cancer Patients Before, During & After Treatment
  - 25 free per facility per month 800-4-CANCER

## Survivorship

- Support for People with Oral and Head and Neck Cancer (SPOHNC)
- Cancer Survivors Network
  - www.acscsn.org
- National Comprehensive Cancer Network (NCCN)
  - www.nccn.org

## Pain Management Database

- NCCN Guidelines™ version 2.2011 updates: Adult Cancer Pain:
  - http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

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## Palliative Care

- National Consensus Project for Quality Palliative Care: Clinical Practice Guidelines:
  - http://nationalconsensusproject.org

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CHAPTER 11

Jan S. Lewin and
Katherine A. Hutcheson

# Evaluation and Rehabilitation of Speech, Voice, and Swallowing Functions After Treatment of Head and Neck Cancer

"Few other cancers demonstrate the need for anticipatory treatment and rehabilitation to the magnitude required in the management of head and neck cancer."

—Myers, Barofsky, and Yates, 1986.[1]

Head and neck cancer often results in significant functional changes including alterations in or loss of human voice, disruptions in speech production, and deterioration of swallowing ability. These problems can occur as the result of the disease as well as the primary treatment, whether surgery, radiation therapy (RT), or both. Adjuvant treatments that include RT generally increase functional deficits. A thorough understanding of the functional effects associated with the given treatment modality or combination of modalities is essential and must be conveyed adequately to the patient as the patient's choice of treatment modality and their compliance with therapy often depend on functional restoration. A multidisciplinary team approach and ongoing communication among clinicians is critical to successful rehabilitation and optimal speech, voice, and swallowing outcomes.

Experience has shown that patients with head and neck cancer express similar concerns and functional goals. What seems to be most important to patients is to avoid a stoma, to speak with laryngeal voice, to eat and drink by mouth, and to avoid the use of adaptive equipment for either speech or swallowing. In a multicenter study, speaking abilities ranked as the primary contributor to psychosocial outcomes and quality of life after treatment for head and neck cancer followed by swallowing function.[2]

## OVERVIEW OF SPEECH AND SWALLOWING IMPAIRMENTS

Speech, voice, and swallowing are highly complex processes that depend on a series of precisely coordinated biomechanical events and physiologic interactions of the oral, pharyngeal, and laryngeal anatomy. Oropharyngeal anatomy and movement are the key determinants of speech intelligibility, vocal resonance, and swallowing competency. Therefore, any alteration in structure or physiology, such as those that result from head and neck cancer, will ultimately affect aerodigestive tract functioning.

## EVALUATION OF SPEECH, VOICE, AND SWALLOWING

### Pretreatment Evaluation

Rehabilitation, more specifically its planning, should begin at the time of diagnosis with patient counseling and a thorough baseline evaluation provided by a speech pathologist who is an expert in the management of functional disorders associated with head and neck malignancies. For many patients, the need for speech and swallowing treatment is unexpected and, therefore, difficult for the patient to accept. Fears and misconceptions associated with cancer treatment and its outcomes are often alleviated by providing realistic expectations for recovery and discussing the rehabilitative options that are available to the patient for functional restoration. Subsequent understanding and acceptance often leads to better follow through with the cancer treatment and rehabilitation.

Pretreatment evaluation establishes a baseline of speech and swallowing ability for appropriate treatment planning and posttreatment comparison. The plan for posttreatment rehabilitation, which should be based on both clinical and objective measures of examination, will depend on the site of the disease and the type of cancer treatment selected.

### Swallowing Evaluation

The act of swallowing includes the oral preparatory, oral, pharyngeal, and esophageal stages. The oropharyngeal swallow consists of the first three stages only, which include all events occurring from the lips to the upper esophageal sphincter (UES). It is the oropharyngeal swallow that is most often affected by head and neck cancer.

Speech pathologists evaluate and treat oropharyngeal swallowing disorders. Unlike esophageal swallowing problems, disorders of the oral preparatory, oral, and pharyngeal stages of the swallow can be treated with functional interventions such as changes in posture and exercises that strengthen and increase the range of motion of muscles involved in the act of swallowing.



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Gastroenterologists generally manage esophageal causes of dysphagia, such as esophageal stricture, for which the main treatment is dilation.

Oral tongue control and strength are important to ensure efficient movement during mastication and posterior propulsion of foods and liquids to the pharynx. Regardless of the type of cancer treatment, surgical or nonsurgical, the primary correlates of pharyngeal swallowing proficiency are tongue base retraction, pharyngeal contraction, and laryngeal elevation and anterior excursion.[3] Tongue base retraction and pharyngeal contraction act as the driving force to move the food through the pharynx, whereas hyolaryngeal excursion is essential to open the cricopharyngeus and deflect the epiglottis downward for airway protection. The ability of the true vocal folds (TVFs) to completely close is important but not essential to airway protection and functional swallowing. For example, patients with unilateral TVF paralysis often compensate for glottic incompetency by using other mechanisms of airway closure to safely swallow without aspirating; therefore, safe swallowing is not solely dependent on TVF closure. Thus, procedures that augment the TVFs to improve airway closure and reestablish subglottic pressure may help swallowing but may not always prevent aspiration if the dysphagia etiology includes more than impaired glottic closure. Therefore, the results from objective instrumental examinations should clearly define the etiology of the aspiration to help guide rehabilitation and avoid the use of techniques, surgical or otherwise, that are not indicated or useful in remediating the dysphagia.

The assessment of swallowing competency relies on comprehensive examination including patient interview, clinical observation, and physiologic findings from instrumental examinations. The *clinical or bedside swallowing examination* allows observation of important events in the oral stage of swallowing, including labial and lingual control, adequate clearance of food from the oral cavity after the swallow, and oral sensitivity. However, the clinical swallowing evaluation is not reliable to diagnose pharyngeal swallowing disorders because clinicians must infer problems that occur during the pharyngeal stage. Despite this limitation, the examiner can detect signs and symptoms suggestive of pharyngeal swallowing problems. A well-trained clinician synthesizes overt as well as subtle observations from the clinical or bedside examination and uses this knowledge to make recommendations including the need for further objective swallowing assessments.

The need for objective, instrumental swallowing evaluation in patients with head and neck cancer cannot be overemphasized. Instrumental evaluation is essential because swallowing physiology cannot be reliably inferred from subjective patient reports.[4] For example, patients may report no problems swallowing when in fact, they are actually silently, without coughing or exhibiting any other indication, aspirating what they swallow. In studies of patients with advanced laryngeal cancer, aspiration has been reported as high as 36% in unselected samples with rates up to 82% in patients who complain of dysphagia. More concerning are the data that show between 36% and 80% of patients who aspirate do so silently.[5–7] In fact, as many as 60% of patients with head and neck cancer have speech and/or swallowing impairments but may not fully perceive them.[8]

The most widely used instrumental swallowing evaluations are the modified barium swallow (MBS) study and the fiberoptic endoscopic evaluation of swallowing (FEES). The choice of either test usually depends on the type of swallowing problem and the ability of the patient to undergo a radiologic procedure. In any case, an instrumental examination, MBS, and/or FEES should be used for any patient with head and neck cancer and/or who is at risk for swallowing problems or aspiration.

The MBS study is generally most preferred for assessing the oropharyngeal swallow. It allows the examiner to radiographically assess all three stages of the oropharyngeal swallow, from the point at which the food is placed in the mouth to the time it enters the cervical esophagus. The MBS study is performed jointly by a speech pathologist and a radiologist. The swallowing assessment should include the use of radiopaque liquids, pastes, and solids because swallowing physiology will vary according to the consistency and amount of food. This is in contrast to the traditional barium swallow study or esophagram, the primary purpose of which is to evaluate the structural integrity of the esophagus and identify aspiration while a large liquid bolus is continuously swallowed. The barium esophagram is not the evaluation of choice for examining oropharyngeal swallowing physiology as the results do not provide the information necessary to differentially diagnose oropharyngeal swallowing disorders and the causes of aspiration. In contrast, the primary purpose of the MBS study is to obtain information that is essential to understanding oropharyngeal swallowing physiology. An additional benefit of the MBS examination is the ability to immediately assess the usefulness of selected compensatory swallowing strategies to relieve the dysphagia. Therapeutic recommendations are made on the basis of the physiologic findings shown on the MBS study. Figure 11-1 shows the normal oropharyngeal anatomy viewed laterally on an MBS study. Figure 11-2 shows a normal swallow viewed laterally on an MBS, and Figure 11-3 shows an abnormal swallow with aspiration.

Alternatively, FEES uses a flexible endoscope placed transnasally to examine the pharyngeal swallow while providing direct visualization of laryngeal anatomy. The main advantages of FEES are that it does not expose the patient to radiation and that it can be easily performed as a clinical procedure for patients who cannot tolerate or are not candidates for the MBS study. FEES has been shown to be equivalent to the MBS study in its ability to detect aspiration.[9] It is a particularly excellent examination for patients who have larynx cancer because it provides the best view of glottic competency, including airway protection and vocal fold mobility. Unlike the MBS study, FEES can be paired with sensory testing to help determine laryngeal sensitivity.[10]

The primary disadvantages of FEES are its inability to visualize the oral preparatory and oral phases of the swallow and the period of "white-out" that occurs at the onset of the pharyngeal stage of swallowing that obscures visualization during peak of

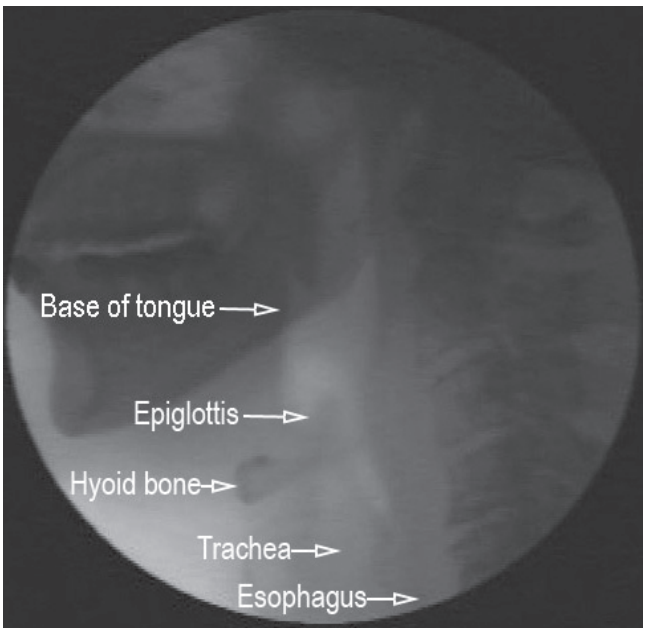



**FIGURE 11-1.** Normal anatomy.

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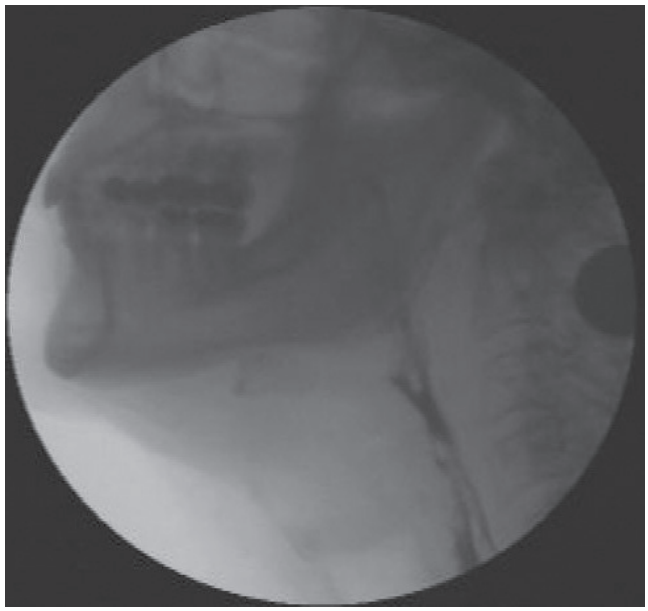


**FIGURE 11-2.** Normal airway closure during the swallow with food passage through the esophagus.

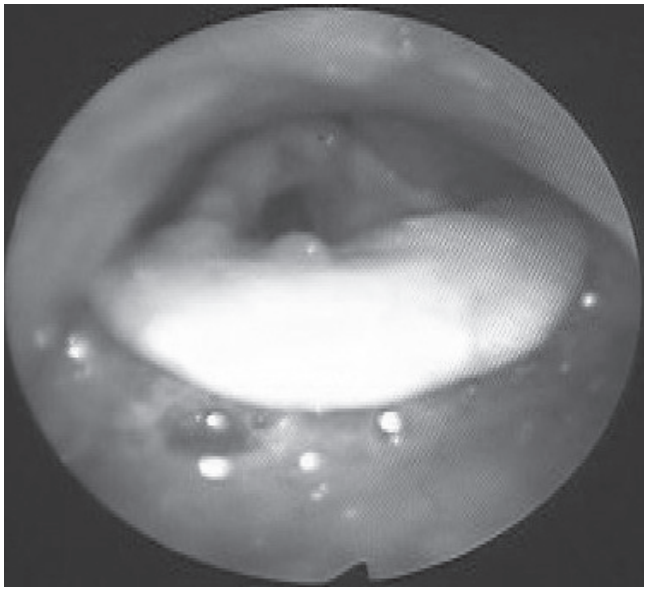


**FIGURE 11-4.** Fiberoptic endoscopic evaluation of swallowing (FEES) with food residue in the pharynx and on the laryngeal surface of the epiglottis after the swallow.

deglutition. Therefore, because all oral phase disorders as well as some pharyngeal disorders of swallowing must be inferred, the usefulness of FEES is more limited in patients with tumors of the oral cavity and oropharynx. However, like the MBS study, FEES provides critical feedback regarding the effectiveness of swallowing compensations and strategies. FEES is also useful in its ability to provide the patient with immediate biofeedback and visualization during therapy sessions. Figure 11-4 demonstrates FEES with food residue in the pharynx after the swallow has occurred.

## Voice Evaluation

Voice evaluation should assess the perceptual, vibratory, acoustic, and aerodynamic parameters of voice production.

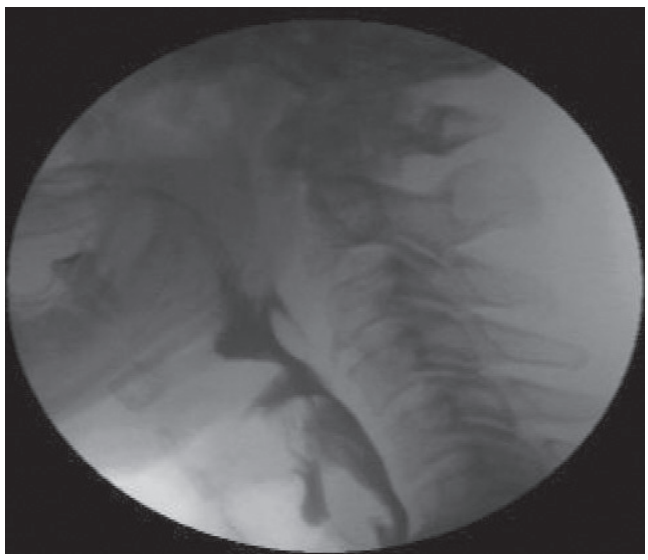


**FIGURE 11-3.** Aspiration into the trachea during the swallow.

A comprehensive evaluation should at a minimum include assessment of the fundamental frequency of sound production, the ability to vary pitch and intensity, phonatory duration, and properties of airflow, air pressure, and glottal resistance.

Laryngeal videostroboscopy provides a critical assessment of patients with head and neck cancer and vocal abnormalities. Videostroboscopic assessment employs the use of an endoscope that uses a straight and pulsed light source to assess vocal fold movement and vibration. Like FEES, videostroboscopy can be performed as an office procedure. This examination provides valuable information regarding vocal fold vibration as well as an immediate and magnified image of the presence or absence of laryngeal pathology that is often undetectable using standard methods of indirect laryngoscopy. The clinician can observe patterns of TVF approximation, symmetry and regularity of motion, and the presence of mucosal wave that will be affected by laryngeal disease and its treatment. Videostroboscopy is an essential component of the physical examination of patients with head and neck cancer and provides a permanent record for documentation and comparison of laryngeal functioning over the course of treatment. Videostroboscopic results are illustrated in Figures 11-5, 11-6, and 11-7.

## Speech Evaluation

Speech evaluation generally encompasses the administration of a combination of perceptual measures of articulation and speech intelligibility that include examination of the rate of speech, articulatory precision, and intelligibility in single words, phrases, and conversation. Formal test batteries that have been standardized on targeted populations provide an objective appraisal of speech production that can be used for comparison over time. A combination of formal and perceptual measures of speech production and a physical examination of the structures of the oral cavity and their patterns of movement are the most useful tools for differentially diagnosing speech disorders and planning effective treatment.

The findings from a thorough speech assessment are also critical to other members of the multidisciplinary rehabilitation

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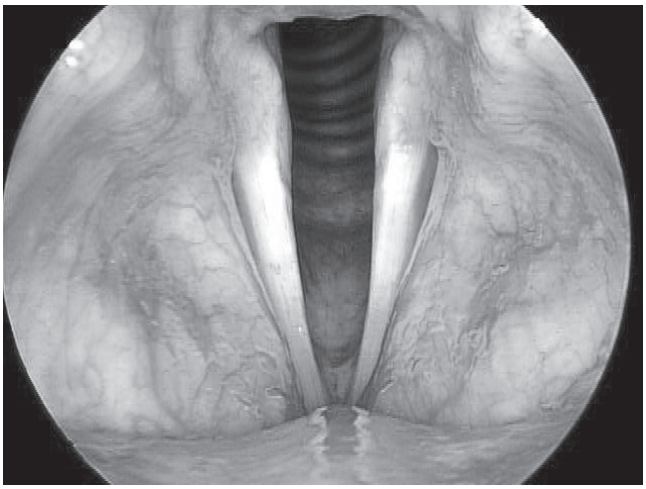


**FIGURE 11-5.** Vocal fold abduction.



**FIGURE 11-6.** Open for vibration.

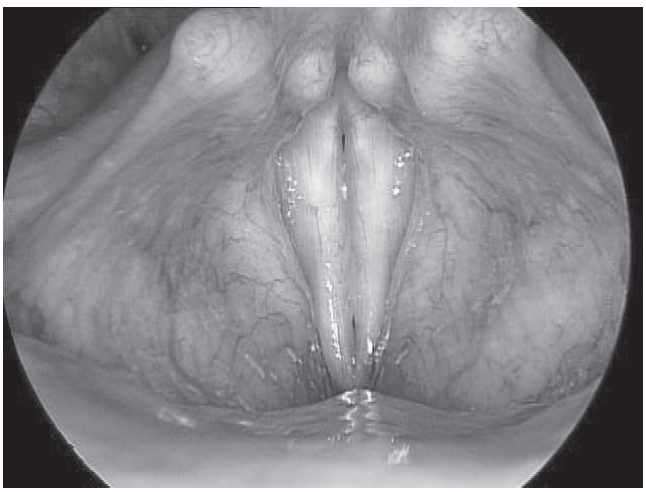


**FIGURE 11-7.** Fully adducted.

team. Information regarding articulation and vocal resonance assists maxillofacial prosthodontists in determining candidacy for and manufacturing of palatal augmentation prostheses, obturators, and lifts for patients with defects of the oral cavity and soft palate. Additionally, information regarding speech articulation and intelligibility helps plastic surgeons select reconstructive procedures and techniques that will optimize cosmetic and functional outcomes.

## REHABILITATION AFTER SURGICAL RESECTION

Any surgery that resects critical structures of the upper aerodigestive tract and disrupts oropharyngeal physiology will result in problems with both speech and swallowing. The functional disability that occurs after head and neck surgery is usually proportional to the volume and site of resection. The correlates of dysfunction depend on the site of lesion and include oral tongue mobility, base of tongue retraction, pharyngeal motility, glottic closure, and laryngeal excursion.[3] The rehabilitative focus varies depending on the type of surgery and reconstruction. For example, patients who undergo glossectomy will require both speech and swallowing rehabilitation to improve speech intelligibility and facilitate the return to oral alimentation. Alternatively, the focus of rehabilitation after total laryngectomy is usually to restore voice or sound production.

### After Oral Cavity Resection

The size and location of the tumor, extent of surgery, and type of reconstruction greatly impact functional outcomes after oral cavity resection. Because the tongue is a fundamental structure to both speech and swallowing, the degree of dysfunction often correlates with the extent and location of tongue resection. Studies have shown that resections of the tongue base and anterior tongue are associated with significant functional deficits.[8] Despite the importance of the oral tongue, data clearly show that the tongue base remains the most essential lingual region for normal swallowing.[3] Even after a total resection of the oral tongue, a patient can learn to swallow safely as long as the base of the tongue is preserved and continues to function.

Reconstructive procedures for oral cavity defects are often challenging because they require sufficient tissue to preserve function while avoiding overcorrection with tissue bulk that obstructs adequate speech and swallowing. Reconstructions of the oral cavity should aim to preserve mobility, shape, and volume of remaining structures and prevent pooling of secretions and food. Resections of the oral cavity that preserve sensorimotor innervation in combination with reconstructions that allow residual tongue mobility generally result in better speech and swallowing function. The degree of functional impairment often depends on the quality rather than the extent of the reconstruction; experience has shown that some patients who have undergone total glossectomy swallow better than patients who have undergone partial resections that use bulky flap reconstructions or those that tether the tongue.

In addition to the importance of the tongue during the oral phase of swallowing, the tongue plays a critical role during the pharyngeal phase of swallowing. Oral cavity resections may impact oral transit and control and consequently affect the ability to elicit a safe pharyngeal swallow. There is an increased risk for aspiration as resections of the oral cavity become larger and more extensive and interfere with oropharyngeal physiology. In particular, patients whose surgeries affect the suprahyoid musculature may aspirate because of the disruption to the elevation and anterior tilting action of the larynx, which is needed to protect

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the airway during swallowing. Thus, the ability to spare adjacent musculature, such as the suprahyoid elevators, is an attractive feature of transoral endoscopic surgical approaches.

In addition to swallowing, resections that affect critical structures and physiology of the oral cavity will also affect speech production and intelligibility. The severity of speech and swallowing dysfunction usually parallel each other. The mechanisms for articulatory compensations may include exaggeration of remaining labial, jaw, dental, pharyngeal, and laryngeal movements. Surgical alterations of the tongue and oral cavity can also change the characteristics of vocal tract resonance such as pitch, nasality, and vocal quality by changing the shape and vibrating properties of the vocal tract.

Most patients are able to achieve understandable speech and some degree of oral nutrition after adequate postoperative healing and rehabilitation. A recent systematic review suggests that speech remains largely intelligible (sentence level: 92% to 98% intelligibility) for a majority of surgically treated patients with advanced-stage oral cancer, including those with involvement of the tongue. However, deviant speech characteristics such as abnormal articulation were reported in most cases despite intelligible speech ratings.[11]

After oral cavity resections, a variety of rehabilitative techniques are used to maximize speech and swallowing function that may include targeted exercise regimens, articulatory compensations, postural adjustments, swallowing maneuvers, or the use of adaptive equipment. The selection of the appropriate intervention should be based on a thorough examination of functional deficits. Again, multidisciplinary interaction and communication cannot be overemphasized. This is particularly true for patients who require palatal prostheses after oral cavity resections that include the hard palate and/or tongue. For these defects, the speech pathologist and maxillofacial prosthodontist work together to fabricate a prosthesis that is tailored to the patient's individual needs.

Hard palate resections that result in oronasal fistulas are usually addressed at the time of surgery with a prosthetic obturator. However, patients who also require partial resection of the soft palate cannot be easily obturated due to the dynamic nature of the residual soft palate and are therefore more difficult to rehabilitate than patients who have undergone total soft palate resection. As is the case for patients with hard palate resections, our experience shows that patients who have undergone total soft palate resection and who are adequately obturated usually speak and swallow without difficulty.

When there is minimal lingual range of motion, or when 50% or more of the tongue is resected, a palatal augmentation prosthesis is generally designed to lower the palatal vault so that the remaining native or reconstructed tongue can contact the prosthesis. Generally, palatal prostheses are more useful for speech than they are for swallowing except in cases in which the prosthesis fills a defect in which food may collect.

## After Total Laryngectomy

Total laryngectomy results in a variety of functional changes; however, the most debilitating is the loss of verbal speech production. Verbal communication is restored using three major approaches: (a) the artificial larynx or electrolarynx, (b) esophageal speech production, and (c) surgical prosthetic voice restoration, the most common of which is tracheoesophageal (TE) voice restoration. However, not all approaches are appropriate for every laryngectomized individual because not every patient is capable of or interested in all methods of restoration. The alaryngeal method of choice is a patient-specific decision and should never be made solely by the physician, family, or speech pathologist. However, clinician experience with the specific alaryngeal voice alternative will play a large part in the patient's overall success in acquiring alaryngeal speech production. Given the current state of rehabilitation, no patient should be without some method of functional speech restoration after total laryngectomy. Figure 11-8 illustrates anatomy before and after total laryngectomy.

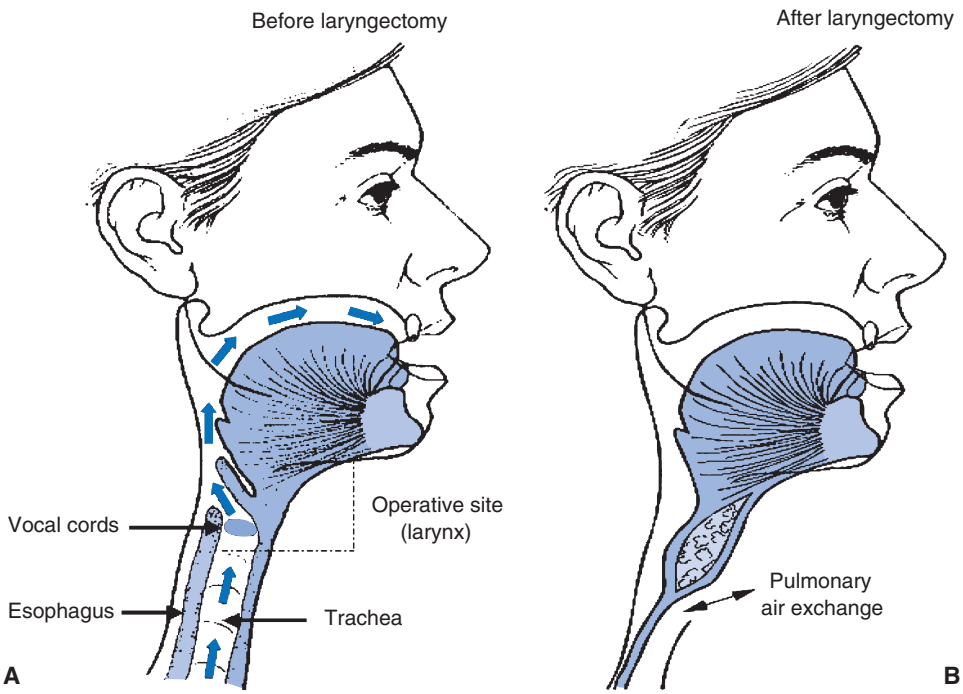



**FIGURE 11-8. A:** Before laryngectomy. **B:** After laryngectomy.

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## Electrolarynx

The electrolarynx, or artificial larynx, as shown in Figure 11-9 A and B provides an external, mechanical sound source that is placed against the neck or intraorally for speech production after laryngectomy. All laryngectomized individuals should be encouraged to learn to use an artificial larynx because it provides a simple means of immediate verbal communication and requires little maintenance. Use of the electrolarynx does not interfere with subsequent development of esophageal or TE speech. The electrolarynx is often the first alternative an individual uses to communicate during the immediate recovery period after laryngectomy. In the long term, the electrolarynx can serve as a backup method of communication for individuals who acquire other forms of alaryngeal speech production. It also becomes the alternative of choice for patients who are not interested in or who are unable to learn or use esophageal or TE speech. Despite the advances in alaryngeal voice restoration, particularly surgical prosthetic alternatives, the electrolarynx remains the most commonly used method of alaryngeal communication worldwide.[12]

## Esophageal Speech

Historically, esophageal speech production was the alternative of choice for alaryngeal speech rehabilitation. Esophageal speech depends on the transfer of air from the oral cavity into the esophagus for vibration of the pharyngoesophageal walls to provide a sound source for speech production. Although esophageal speech production provides the advantage of oral communication without the use of mechanical or prosthetic devices, it is rarely the method of choice for alaryngeal communication after total laryngectomy in current practice. Conservative estimates suggest that it takes 4 to 12 months of consistent therapy and daily practice to learn this method, and <30% of patients actually acquire functional esophageal speech production.[13] In addition, studies have found that the quality of esophageal speech is reduced in comparison to TE speech.[14] For these reasons along with the lack of good esophageal speakers and clinicians who can reliably teach esophageal speech production, alaryngeal communication using esophageal speech has become much less common and is generally preferred for select patients only. Patients who are not surgical candidates for TE voice restoration but have viable sound production of the pharyngoesophagus, and do not wish to use an artificial larynx for primary communication, should be considered candidates for esophageal speech. Figure 11-10 illustrates the method of esophageal speech production.

## Tracheoesophageal Voice Restoration

TE voice restoration remains the gold standard for alaryngeal speech production after total laryngectomy because it provides the highest quality of alaryngeal voice and patient satisfaction.[12] The method depends on the surgical creation of a small hole or fistula in the TE wall, commonly referred to as the *tracheoesophageal puncture* (TEP). A unidirectional valved prosthesis is placed to maintain the TEP. The valve of the prosthesis remains closed to protect the airway during swallowing and opens to divert pulmonary air across the pharyngoesophageal mucosa for phonation when the tracheostoma is occluded. The resulting sound is shaped into words by articulatory movements of the structures of the oral cavity. The tracheostoma can be manually

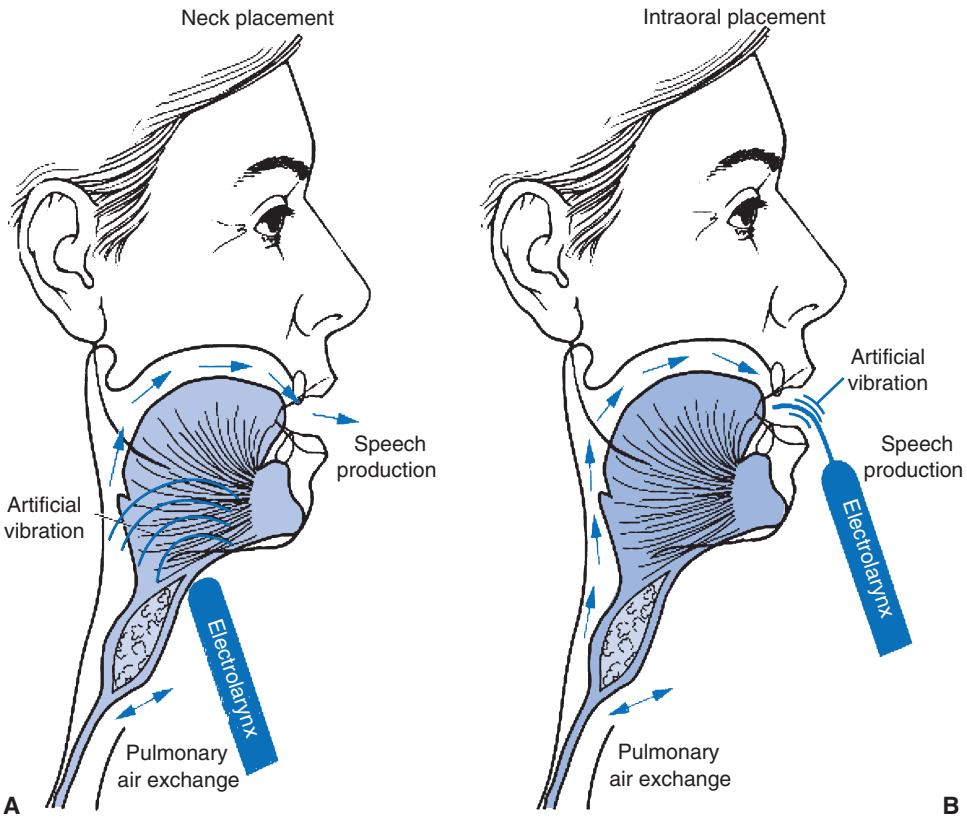



**FIGURE 11-9.** Artificial larynx (electrolarynx).

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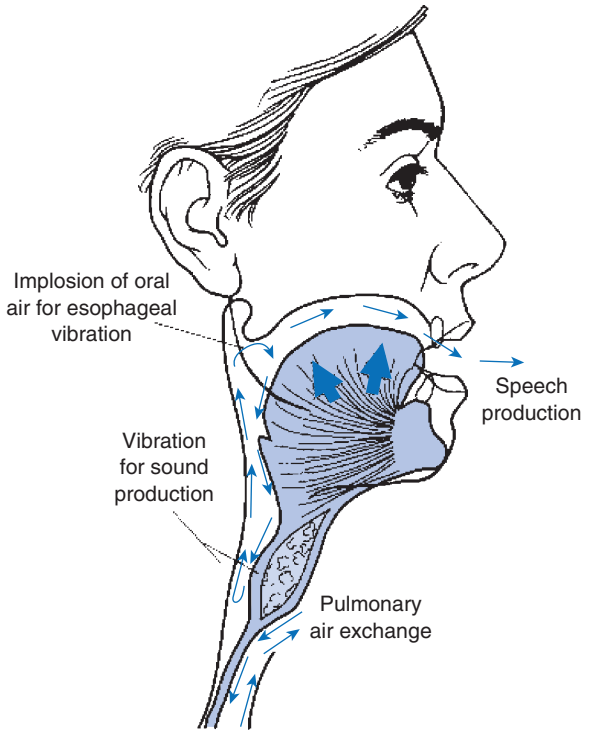



**FIGURE 11-10.** Esophageal speech.

occluded by the patient or automatically occluded by means of a hands-free valve to shunt air into the pharyngoesophagus for sound production. TE voice restoration and methods of stomal occlusion are shown in Figure 11-11.

TE voice restoration has been associated with the highest patient satisfaction because it offers the advantage of a rapid return to more natural-sounding verbal speech production. TE voice production is frequently documented as the alaryngeal speech alternative most comparable to normal laryngeal speech in quality, fluency, and ease of production. Superior vocal quality, phonatory duration, and vocal intensity have been found in comparisons of TE voice production to other alaryngeal speech alternatives.[14]

The TEP can be performed as a primary procedure at the time of the total laryngectomy, or secondarily after the patient has fully healed from surgery. Data have shown that TE voice restoration outcomes are comparable whether the procedure is performed primarily or secondarily[13–15]; however, the choice of timing is generally dependent on patient characteristics along with physician preference and experience. TEP was first introduced as a secondary procedure.[16] Primary puncture then became the treatment of choice for most patients because surgical experience and clinical data demonstrated no significant occurrence of complications associated with the procedure nor difference in the ultimate quality of TE speech production. One of the most compelling arguments for primary puncture remains the psychological advantage of an early return to oral speech production. However, as cancer treatments have evolved and become more aggressive, often combining radiation and chemotherapy with more complex surgical reconstructions, patient selection has become even more

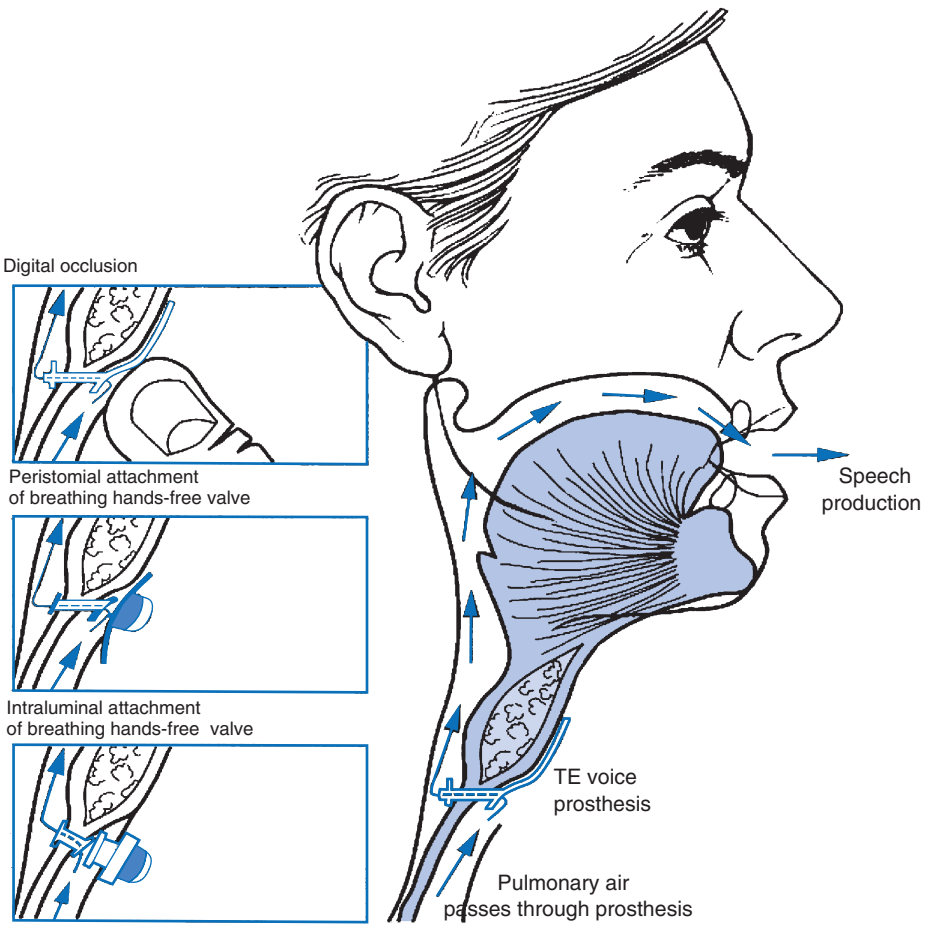



**FIGURE 11-11.** Tracheoesophageal (TE) speech.

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**TABLE 11.1 Considerations for the Timing of the Tracheoesophageal Puncture (TEP)**

| Primary TEP | Secondary TEP | No TEP |
|---|---|---|
| Standard laryngectomy | Complicated medical history | Marked cognitive impairment |
| Motivated patient | Extended surgeries | Severe substance abuse |
| Compliance | "At-risk" patients | Poor compliance[a] |
| Independence and support | Limited readiness and independence | Limited rehabilitative access[a] |
| Rehabilitative access | | No support[a] |

[a]In combination, these three factors are felt to be a poor indicator for tracheoesophageal speech success.

important. The universal application of primary or secondary puncture is no longer appropriate, nor is it the best procedure for all patients. Our experience suggests that the use and timing of TEP depend on existing patient characteristics and medical factors. These indicators are outlined in Table 11.1.

## General Considerations for Alaryngeal Voice Rehabilitation

The choice of alaryngeal speech method centers on the evaluation of the patient's psychological factors, treatment history, and comorbidities along with his/her motivation for TE voice restoration. In general, age alone is not predictive of rehabilitative success. The artificial larynx may be preferred in older and more sedentary patients, but some of the best TE speakers are those in their 70s and 80s. Alternatively, the traditional method of esophageal speech production is often the best choice for children, adolescents, and young adults, who will readily learn to incorporate this method of communication as their own over their lifespan. Despite the popularity of TE voice restoration, the method relies on the use and maintenance of prosthetic devices. Thus, TE speech production brings added attention to anatomic and physiologic changes in young patients that only serves to further differentiate them from their peers.

Probably the single most important characteristic of the patient that influences the choice of alaryngeal speech method is cognitive or mental status. An impaired mental status may prevent acquisition of alaryngeal speech despite adequate physical capability. For example, although a viable vibratory segment is the key determinant of successful esophageal and TE voice production, a patient with severe cognitive dysfunction will not be able to learn the technique of esophageal speech or manage a TE voice prosthesis. Hence, high levels of motivation and the presence of necessary anatomy are not sufficient without adequate cognitive functioning. Even the use of the artificial larynx is dependent on learned behavior. Patients with extreme cognitive impairment may find the use of standard communication board systems most effective for daily routine needs.

Patients with head and neck cancer often present with a variety of comorbidities that may impact the choice of alaryngeal speech alternative and rehabilitative success. Patients who have pulmonary diseases, such as emphysema or chronic obstructive pulmonary disease (COPD), often find it more difficult to achieve TE voice production. Their reduced lung capacity inhibits the ability to clear secretions from the airway and provide adequate pulmonary support for speech production. Likewise, pulmonary disease may impede the coordination and control of air transfer for esophageal speech production. In addition, degenerative conditions such as arthritis, neuromuscular disorders, or visual and hearing impairments may require modifications to the standard manner of execution of the particular method of alaryngeal speech production, but they do not prevent the acquisition of alaryngeal speech. For instance, an individual with poor manual dexterity, who is unable to occlude the stoma for TE speech production, may be a successful TE speaker by using a hands-free valve. Potential barriers to TE speech success should be thoroughly communicated to the patient to ensure realistic expectations for recovery because the presence of comorbid conditions may complicate the rehabilitative process and affect the final speech outcome.

Persistent or recurrent cancer in the head and neck region may also affect the choice of alaryngeal speech communication. The presence of a tumor may increase the likelihood of complications, particularly in patients who are TE speakers. In general, however, persistent or recurrent disease has little effect on the use of an artificial larynx unless the structures and movements of the oral cavity or neck are involved.

Although radiation is not a contraindication to any method of alaryngeal speech production, the initiation of alaryngeal speech therapy may need to be delayed when the effects of radiation are significant. During RT, patients often experience transient difficulties in producing alaryngeal voice or speech, and inflammatory reactions around the stoma and stomal stenosis are not uncommon. The magnitude of the effect varies from patient to patient, but in general, radiation affects tissue elasticity, viscosity, vascularization, and healing ability. In severe cases, extensive fibrosis, necrosis, and poor wound healing may limit the choices for alaryngeal voice restoration. Additionally, radiation-induced edema may interfere with accurate preoperative assessment and prediction of postoperative TE speech fluency. We generally recommend that evaluation for TEP be delayed 4 to 6 weeks after the completion of RT to allow the effects of edema to subside. Patients who have been heavily irradiated and demonstrate severe tissue changes are at risk for significant complications and may be better suited for secondary TEP.

One of the most challenging complications to manage after TE voice restoration is enlargement of the TEP and therefore this complication has become a focus of recent studies. An enlarged TEP significantly increases the risk of aspiration pneumonia resulting from leakage of liquids, saliva, or food around the TE voice prosthesis into the airway.[17] Although recent studies report the incidence of enlarged puncture between 8% and 18%, the individual risk of enlarged TEP is influenced by specific clinical factors.[18,19] A diagnosis of loco-regional recurrence or distant metastasis after laryngectomy, postoperative stricture, and advanced nodal staging have been identified as independent risk factors for TEP enlargement. In addition, extended resection requiring pharyngeal reconstruction, postoperative radiotherapy,

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and preoperative nutritional deficiencies portend a higher risk of TEP enlargement.[18] Although a number of methods have been proposed to control aspiration from an enlarged TEP,[19] there is general consensus that conservative nonsurgical methods are preferred over surgical reconstructions that permanently close the TEP. Prospective data suggest that customization of the TE voice prosthesis achieves immediate relief of aspiration in >75% of cases. The immediate success of prosthetic customization is attractive in a clinical setting, but promising long-term success rates of 80% are also reported.[20]

Finally, patients who require pharyngeal reconstruction show a higher rate of morbidity, elevated risk of complications, and less optimal recovery of voice and swallowing functions. Pharyngeal reconstruction is used after extended resections that create a pharyngoesophageal defect or in salvage total laryngectomy cases after chemoradiation failure to decrease the risk of pharyngocutaneous fistula. A variety of reconstructive choices are available. The two primary options for circumferential defects include tubed fasciocutaneous flaps and alimentary tract organ transposition. Alternatively, partial pharyngeal defects may be reconstructed using fasciocutaneous "patch" flaps. Numerous studies have demonstrated the feasibility of TE voice restoration after pharyngeal reconstruction, but the choice of reconstruction has been shown to affect TE voice and swallowing outcomes. Circumferential pharyngoesophageal defects that are reconstructed with a tubed anterolateral thigh flap are associated with higher rates of TE speech fluency, routine use of TE voice, and oral alimentation compared with those using jejunal interposition.[21]

## REHABILITATION AFTER ORGAN PRESERVATION

Organ preservation, either surgical or nonsurgical, is now a primary consideration when treating head and neck cancer. As organ-sparing treatments have evolved and improved, a greater focus on preservation of speech and swallowing function and quality of life has emerged. Data have shown that even those treatments that are designed specifically for organ preservation, such as RT, chemotherapy, and partial surgical resections, alone or in combination, frequently result in marked functional sequelae.[22] Clearly, anatomic preservation does not always ensure preservation of speech or swallowing function. For patients with larynx cancer, the ability to eat, swallow, and speak intelligibly after total laryngectomy may be preferred to feeding tubes, gestures, and writing when anatomic preservation of the larynx fails to preserve function.

Again, it is important to discuss realistic expectations for speech and swallowing recovery after organ-sparing procedures. Despite the often-subtle changes in vocal quality, speech is generally adequately intelligible unless significant alterations in the structures and physiology of the oral cavity have occurred. Unlike speech, however, swallowing function is at a greater risk for impairment, and outcomes vary greatly depending on the site of disease and the type of organ preservation regimen chosen. For example, a unilateral pharyngeal wall tumor treated with radiotherapy will have very different swallowing outcomes compared with those following treatment of a posterior pharyngeal wall tumor that crosses midline and is treated with a combined regimen of radiation and chemotherapy. In some cases, patients return to oral nutrition and regular diets after treatment, whereas others remain gastrostomy tube dependent for the remainder of their lives. We are only beginning to understand the impact of organ preservation techniques on long-term speech and swallowing function in patients treated for head and neck cancer.

### After Nonsurgical Organ Preservation

Nonsurgical organ preservation alternatives primarily include regimens of RT, combined chemoradiotherapy (CRT), and experimental chemotherapy protocols. Targeted molecular therapy is offered with increasing frequency in organ-sparing protocols, and promising functional data are emerging following use of these regimens.[23] The effects of RT or CRT produce immediate as well as long-term alterations in speech, voice, and swallowing that may increase in severity even years after the completion of radiation treatment. The magnitude of the effects from RT or CRT varies among patients but the majority experience some degree of speech and swallowing impairment.[22,23] RT may adversely affect speech production, intelligibility, and vocal quality resulting in slurred speech, problems with articulation, and changes in sound quality.

In general, however, RT has a greater and more persistent effect on swallowing than it does on speech, yet dysphagia and aspiration remain underreported and underappreciated consequences of RT and CRT despite this finding.[22] The true extent of this toxicity is unknown; however, it has been estimated that up to 50% of survivors of advanced head and neck cancer have dysphagia.[4] Studies report aspiration rates between 30% and 62% after RT or CRT, and silent aspiration is observed in at least one-third of aspirators after CRT.[5] Radiation-induced dysphagia most commonly results from oropharyngeal fibrosis, cranial neuropathy, and sensory alterations associated with acute and chronic tissue changes. The extent of dysfunction varies with the total dose, schedule, and duration of RT, as well as the extent of the radiation field. Recent investigations have identified associations between swallowing outcomes and dose-volume distributions to key structures including the pharyngeal musculature, supraglottic larynx, esophageal inlet, and oral cavity. Several investigators have identified key organs at risk (OARs) and are developing dose-limiting treatments that use intensity-modulated radiation therapy (IMRT) to reduce normal tissue damage and preserve function. However, the ability of these treatment regimens to improve long-term function, generally >5 years, through dysphagia-specific dose constraints continues to be investigated.[24] Additionally, data from clinical and population-based studies suggest that chemotherapy exacerbates the effects of RT on dysphagia,[25] particularly when delivered concurrently with radiotherapy. Again, the long-term effects remain unknown.

Acute tissue edema and erythema during RT or CRT may result in swallowing dysfunction by reducing mastication and slowing the movement of food through the oral cavity. When the impairment is severe, aspiration may occur. Acute swallowing impairments generally resolve as edema and mucositis improve, but it is not uncommon for dysphagia to persist or occur months or years after the completion of RT or CRT. We are just beginning to appreciate the devastating effects to swallowing as long-term head and neck cancer survivors treated with regimens of radiation 5 to 10 years ago return complaining of increasing difficulty maintaining oral nutrition and an inability to swallow their own saliva. Instrumental examinations in cases of late dysphagia after RT or CRT are characterized by significantly impaired range of motion of the laryngopharynx leading to profound pharyngeal residue and a tendency for silent aspiration.[26] Unfortunately, the exact combination of risk factors that result in long-term dysphagia are unknown; therefore, any patient with or at risk for dysphagia should be evaluated by an experienced speech pathologist.

Although current knowledge limits our ability to identify those patients who are likely to develop long-term dysphagia after radiation treatment, several risk factors have been reported. Investigators have shown that the site of the primary tumor and T stage impacts the type and severity of dysphagia after definitive RT

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or CRT. Of all patients with head and neck tumors, swallowing dysfunction is most pronounced in patients with oropharyngeal, supraglottic, laryngeal, and hypopharyngeal tumors, but overall, patients with hypopharyngeal tumors have the greatest degree of swallowing impairment.[27] Patients who have difficulty swallowing before treatment are also at higher risk for chronic dysphagia and permanent feeding tube dependency.[5] Likewise, prolonged intervals of nothing per oral (NPO) >2 weeks during RT or CRT are associated with poorer swallowing outcomes.[4] Therefore, patients should be encouraged to swallow throughout the course of RT or CRT as much as possible, and even brief NPO intervals should be avoided.[22]

Head and neck cancer patients commonly require nutritional support during RT or CRT due to mucositis and other acute toxicities of therapy. However, there is a lack of consensus about clinical practices concerning enteral nutrition during RT or CRT.[28,29] Although studies demonstrate that prophylactic or early placement of feeding tubes decrease acute weight loss and treatment interruptions, data also suggest that many prophylactic PEG tubes may be placed unnecessarily, resulting in undue patient burden and expense. In addition, the unnecessary placement of feeding tubes puts patients at significant risk for long-term g-tube dependence and swallowing dysfunction. A recent survey found that almost half of patients who had a prophylactic PEG tube prior to RT or CRT had limited use of the tube. Other reports suggest that between 30% and 60% of patients may be able to maintain oral nutrition during RT or CRT and avoid unnecessary feeding tube placement.[29–31] Data demonstrate an important association between function and long-term swallowing deterioration and g-tube placement. Based on a study of 474 patients with oropharyngeal cancer, 62% required the use of a g-tube during the 5-year study period. In addition, patients who presented with baseline swallowing dysfunction were more likely to need a g-tube for nutrition. Additionally, comparisons from observational studies have also reported a higher incidence of severe dysphagia and esophageal stricture, lower swallowing-related quality of life, and longer duration of feeding tube dependence in patients who received gastrostomy tubes prophylactically.[31]

Investigators are now focusing on the benefit of targeted swallowing therapy to prevent long-term swallowing dysfunction after radiation therapy alone or in combination with regimens of chemotherapy. Early data regarding patient adherence to appropriately selected swallowing exercises show that patients who reported exercise adherence were less likely to undergo gastrostomy tube placement compared with those who did not report adherence (RR = 24.0, $p < 0.001$).[31] It is therefore not surprising that the current emphasis of treatment for patients with radiation-induced dysphagia has shifted from rehabilitation to prevention. Nonsurgical organ preservation treatment regimens should include targeted swallowing intervention based on the findings of instrumental examinations that aim for maximal swallowing recovery quickly. Studies have shown that any delay in swallowing intervention may prevent maximal functional recovery due to the cumulative effects of RT. Fibrosis, once present, becomes nearly impossible to reverse, and therefore early concentrated intervention is critical. Data reinforce the importance of daily exercise that targets the strap musculature, pharyngeal constrictor complex, and the base of the tongue during radiation therapy. These same data show improved swallowing outcomes after the completion of radiation therapy. Preventive swallowing exercises have been associated with superior swallowing-related quality-of-life scores, better base of tongue retraction and epiglottic inversion, preservation of postradiotherapy muscle mass of critical swallowing musculature, and shorter duration of gastrostomy tube dependence after RT or CRT.[31–33] Therefore, timely therapeutic regimens of swallowing exercises designed to strengthen musculature and maintain range of motion cannot be overemphasized as they may provide the best prevention of long-term swallowing dysfunction in patients who have received RT or CRT for head and neck cancer.

## After Surgical Organ Preservation

Along with improvements in nonsurgical organ preservation techniques, new surgical techniques that include endoscopic laser and robotic procedures have shown dramatic evolution in their ability to surgically preserve the organ and its function. This is particularly true for cancers of the larynx, in which surgical organ preservation conserves the airway and allows for laryngeal speech production without a permanent tracheostoma. The options for surgical preservation of the larynx include transoral laser microsurgery (TLMS) and conservation surgeries. Historically, cordectomy, supraglottic laryngectomy, and vertical partial laryngectomy have been the most common examples of open conservation surgeries. However, the disadvantage of open surgical conservation procedures has been the significant disruption to the adjacent suprahyoid musculature that is critical to swallowing function. The supracricoid partial laryngectomy (SCPL) provides an alternative for patients who might otherwise require a total laryngectomy. Most recently, transoral robotic surgery (TORS) is used as a conservation surgery for frontline management, most commonly for pharyngeal cancers as an alternative to definitive radiotherapy-based regimens. These data along with prospective comparisons are forthcoming, but preliminary small studies suggest satisfactory functional outcomes after TORS and TLMS as frontline treatment for a variety of disease sites.[34]

The choice of any surgical organ-sparing procedure requires appropriate patient selection to achieve successful recovery and optimal functional outcomes. This remains true for patients with advanced as well as early disease. When the probability of patient survival remains equal regardless of the treatment alternative, surgical or nonsurgical, as is the case for patients with early glottic cancers, the choice of treatment then centers around long-term functional outcomes. Hence, thorough evaluation and patient selection is critical for both survival and optimal quality of life.

Depending on the choice of surgery, patients must often be able to tolerate the effects of aspiration that result from a severely compromised glottic or supraglottic sphincter. Rehabilitative intervention should begin with preoperative examination to establish baseline function. The choice of instrumental evaluation (FEES or MBS study) depends on the type of conservation laryngeal surgery. Studies have shown that levels of pretreatment functioning are frequently predictive of postoperative rehabilitative potential. The findings from postoperative instrumental swallowing examination should be used to guide the rehabilitative course of swallowing recovery because of the high risk for a sensate aspiration. Experience has shown that patients' readiness to begin oral intake following organ preservation surgeries varies. Recommendations regarding the initiation of oral intake and the types and quantities of food the patient will best tolerate are based on objective swallowing data with the final goal of swallowing rehabilitation to advance the patient to the least restrictive diet they are able to tolerate.[35]

# CONCLUSION

Rehabilitation of patients with head and neck cancer is a multidisciplinary team effort that must include a speech pathologist who is an expert in evaluating and managing patients with head and neck malignancies. Rehabilitation should start early to maximize the functional restoration of speech and swallowing. Future research will identify the critical determinants to help clinicians

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predict long-term functional outcomes in patients treated for head and neck cancer. In the meantime, patients who are at risk for speech and/or swallowing problems must be properly evaluated before treatment begins so that appropriate rehabilitative interventions can be initiated to prevent long-term functional deterioration.

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CHAPTER 12

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# Human Papillomavirus–associated Head and Neck Carcinoma

## INTRODUCTION

Worldwide, head and neck squamous cell carcinoma (HNSCC) accounts for a relatively small percentage of all cancers, with notable exceptions of high nasopharyngeal cancer incidence in Southeastern China and Southeastern Asia and high oral cavity cancer incidence in Melanesia and South-Central Asia.[1] More than 600,000 people were diagnosed with HNSCC worldwide in 2008.[2] In the United States, HNSCC accounted for only 3% (about 53,000) of all new cancer cases and only 2% (approximately 12,000) of all cancer deaths in 2010.[3] HNSCC affects men 2 to 4 times more commonly than women.

Intensive laboratory and clinical investigations conducted during the past few decades along with technological advances have significantly improved our knowledge of the biology of HNSCC and led to the establishment of new multimodality treatment regimens, improved surgical and radiation therapy methods, and refined management strategies for HNSCC originating at different subsites to optimize tumor control while preserving organs and physiologic functions. As these research efforts have been evolving, the epidemiology and demographics of HNSCC have been changing, particularly during the past decade, mainly because of the appearance and increasing incidence of human papillomavirus (HPV)–related carcinoma.

In this chapter, we address the changing demographics of HNSCC, its diagnosis, and the clinical behavior of HPV-associated oropharyngeal carcinoma, focusing on studies devoted to assessing the discovery of prognostic and predictive biomarkers. Rather than providing an exhaustive review, we chose to present pertinent data to illustrate important discoveries relevant to clinical practice. We also discuss briefly the current research strategies aimed at changing treatment paradigms so as to reduce morbidity while preserving high tumor control rates through well-coordinated clinical trials.

## CHANGING EPIDEMIOLOGY OF HEAD AND NECK CANCER

### Decline in Tobacco Use and Smoking-related HNSCC

As presented by Giovino in an overview paper and illustrated in Figure 12-1A,[4] smoking of manufactured cigarettes accounted for 1% of all tobacco consumed in the United States in the 1880s but this form of use increased progressively to about 80% by 1950, when overall annual tobacco consumption peaked at about 13 lb per person. As evidence mounted regarding the association between tobacco use and lung cancer, cardiovascular disease, and other illnesses, and with the Surgeon General's warning about the hazards of cigarette smoking, its use diminished consistently since the mid-1960s and dropped to 3.7 lb annually per capita by 2006.[4,5] More than half of men and one-third of women in the United States smoked in 1965 but less than a quarter of men and less than one-fifth of women smoked in 2006.[4]

HNSCC is one of several cancers that are strongly associated with tobacco use.[6] As might be expected for diseases with a long initiation phase associated with chronic tobacco exposure, the primary public health goal of reducing cancer incidence by smoking cessation did not begin to occur until the late 1980s.[5] Cancer statistics data available at the Surveillance, Epidemiology, and End Results (SEER) website (http://www.seer.cancer.gov/faststats) indeed reveal a steady decrease in the age-adjusted incidence rates of carcinoma of the larynx, the floor of mouth, the gingiva, and most other oral cavity sites since early 1980s Figure 12-1B.[7] In contrast, however, the age-adjusted incidence rates of carcinoma of the tongue, the tonsil, and other pharyngeal regions have not decreased over the years and, in contradiction to expectations, even began to increase since approximately the turn of the millennium. These complex trends in oropharyngeal cancer incidence are consistent with the decline of one carcinogenic exposure (smoking) but the emergence of another unrelated etiologic exposure during the same period.

Significant site admixture occurs in the annual U.S. "Cancer Statistics" overview, where all subsites of pharyngeal cancer are listed as a single site, "pharynx" (including not only oropharyngeal cancers but also hypopharyngeal and nasopharyngeal cancers) and where base of tongue (lingual tonsil or oropharyngeal tongue) cancers are often listed collectively with oral (mobile or oral cavity) tongue cancers as the generic site "tongue."[3] More thorough analysis, however, revealed that the age-adjusted incidence of oropharyngeal carcinoma is rising dramatically (about 5% annually) in the United States while that of oral cavity cancer is diminishing (approximately 2% annually).[8] Furthermore, the increase in oropharyngeal cancer incidence seems to be primarily represented by middle-aged (40–59-year-old) white men.[8] These contrasting changes in trends suggest that exposures to other carcinogens are emerging in the pathogenesis of HNSCC. As summarized below, an increasing body of data now demonstrates



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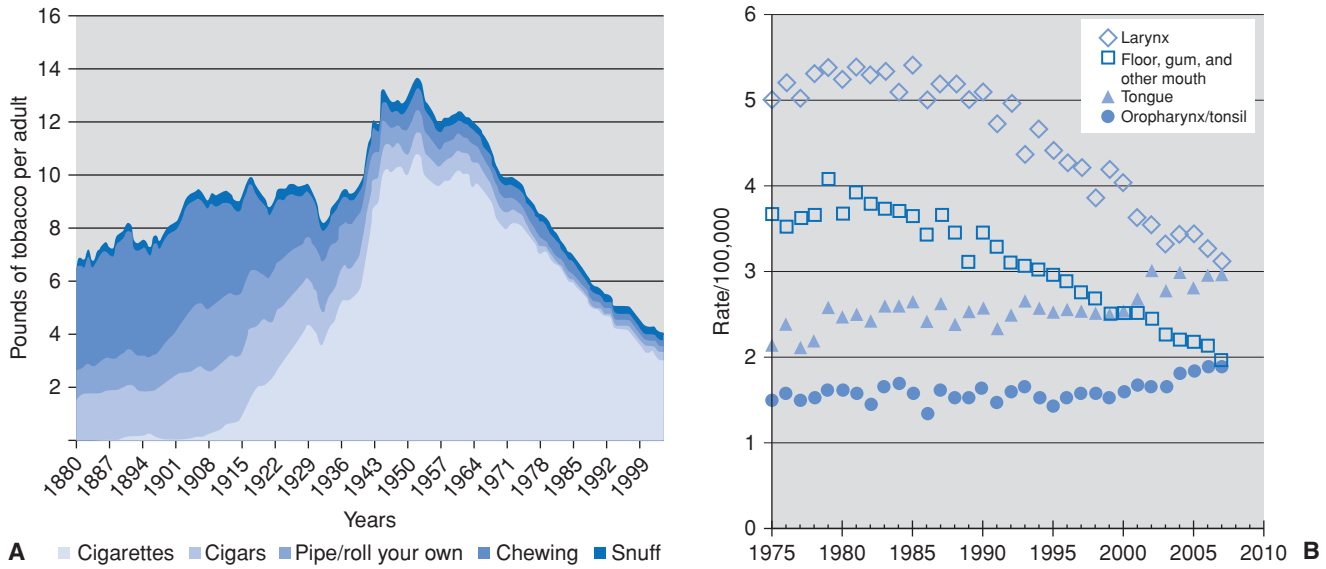



**FIGURE 12-1.** **A:** Trends in per capita consumption of various tobacco products in the United States, 1880 to 2004[4]; reproduced with permission. **B:** Age-adjusted SEER incidence rates for laryngeal cancers, floor of mouth/gingival/other mouth cancer, tongue cancers, and oropharyngeal cancers in the United States. (See color insert)

that HPV is the main contributor to the changing demographics and epidemiologic trends of HNSCC. In fact, U.S. and Swedish subsets from population-based registries have demonstrated that over time an increasing proportion of oropharyngeal cancers are HPV positive.[9–12]

## Emergence of HPV-Associated Oropharyngeal Carcinoma

The role of some types of HPV, most notably HPV-16 and HPV-18, in the pathogenesis of cancer of the uterine cervix has been recognized for more than two decades (reviewed by zur Hausen[13,14]). It is now accepted that carcinogenic effects are mediated mainly through two high-risk HPV oncoproteins, E6 and E7, which inactivate the *TP53* (also referred to as *p53*) and retinoblastoma (also referred to as *Rb*) tumor suppressor gene products, respectively,[15,16] and thereby disrupt cell-cycle regulatory pathways.

More recently, several lines of evidence have established the potential of HPVs to induce HNSCC, specifically oropharyngeal cancer. In reviewing epidemiological and experimental evidence, Franceschi et al.[17] showed that at least a proportion of cancers of the upper aerodigestive tract harbor relatively high copy numbers of HPV-DNA and transcripts of viral E6/E7 genes, and a clonal association with HPV has been demonstrated in these tumors. A case-control study showed that the presence of HPV DNA in the oral cavity was associated with a higher risk of oral cancer, independent of alcohol and tobacco consumption, with an odds ratio of 3.7 (95% confidence interval [CI], 1.5–9.3). Notably, however, this study suffered from site admixture of oral cavity and oropharyngeal cancers.[18] Another study revealed that after adjustment for cotinine levels, the odds ratio for HNSCC in subjects who were seropositive for HPV-16 was 2.2 (95% CI, 1.4–3.4) with no increase in risk observed for other HPV types.[19] Remarkably, the odds ratio for oropharyngeal cancer specifically was >14.

A systematic review and meta-analysis revealed that HPV-associated HNSCC is located mainly in the oropharynx and that HPV-16 accounts for the vast majority of these carcinomas.[20,21] The prevalence of HPV in oropharyngeal carcinomas has increased steadily in Western countries. Cohorts of patients mainly from the 1990s had prevalence rates of ≤50% whereas more recent series reported rates in the 70% to 80% range.[8,10,11,20–24] Chaturvedi et al.[8] found in analyzing SEER data that the incidence of all oropharyngeal carcinomas increased significantly between 1973 and 2004, with an annual percentage increase of 0.8 during that time. In a review of tumors from three registries within the SEER, Chaturvedi et al. found HPV prevalence rates increasing over time and were able to estimate that the incidence of HPV-associated oropharyngeal cancer has been increasing over the past two decades, while the incidence of HPV-negative oropharyngeal cancers has declined by approximately half, similar to incidence trends for oral cavity and laryngeal cancer.[12] The authors go on to estimate that the number of HPV-positive oropharyngeal cancers will surpass the number of cervical cancers in 2020.[12]

Interestingly, across the oropharyngeal subsites, the incidence of base of tongue and tonsil carcinomas increased most significantly during this period (with annual incremental rates of 1.3% and 0.6%, respectively) whereas that of pharyngeal wall cancers was stable. In contrast, the incidence of HNSCC originating at anatomical sites unrelated to HPV infection (oral cavity) declined significantly between 1973 and 2004 at a yearly rate of –1.9%. Consequently, the proportion of HNSCC that originated from oropharynx has increased from 18% in 1973 to 31% in 2004. The same phenomenon has been observed in other Western countries such as Sweden.[25]

# HUMAN PAPILLOMAVIRUS

## Characteristics of HPV

HPV is a double-stranded DNA virus that infects human epithelia. The >100 existing genotypes are broadly classified as high-risk or low-risk based upon their oncogenic capabilities.[14,26]

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Low-risk types (such as HPV-6 and HPV-11) are associated with both cutaneous and mucosal papillomas, whereas high-risk types (such as HPV-16, HPV-18, HPV-31, and HPV-33) can induce squamous cell carcinomas and are thus termed "oncogenic."[14,26,27] The structure is that of circular viral DNA (approximately 8,000 base pairs) surrounded by viral capsid proteins arranged in a capsule. The approximately 80 genes in the HPV genome are referred to as early (E) or late (L) based upon when during the cell differentiation process they are transcribed and the remaining long control region made up of transcriptional regulators. The early proteins are expressed typically in the basal layer of the epithelia (early in the viral life cycle) and are responsible for gene regulation and replication, whereas the late proteins expressed in more differentiated layers make up the viral capsule,[14,26,27] as described below.

HPV infects the basal layer of the epithelium through breaks in the stratified (differentiated) layers of the epithelium. How and why these breaks in the epithelium occur differs according to the site of infection. HPV affinity for the basal epithelium of different anatomic sites is, in theory, due to variations in the mechanisms and frequency of access to the basal layer as well as tissue-specific differences in the extracellular matrix and cell surface receptors (principally integrins) at each anatomic site.[26] Endocytosis brings the virus into the cell, and subsequently the viral DNA persists as an episome (circular form) in the nucleus.[26–28] At this point, the episome relies upon the host cellular machinery to replicate along with the host DNA. As the host cell differentiates and moves progressively to the superficial layers, the replicated viral DNA is packaged within viral capsids produced during expression of the late genes. The virus is subsequently released as the superficial epithelial layers are desquamated.

## Viral-Mediated Carcinogenesis

The E6 and E7 proteins seem to be critical to the oncogenic potential of HPV because these proteins have the ability to inhibit important tumor suppressor pathways (reviewed by Allen et al.).[26] The principal effect of the E6 protein is the binding and enhanced degradation of the *p53* protein, thus allowing unregulated cell proliferation. Other *p53*-independent effects seem to include effects on telomerase. The E7 protein inactivates another tumor suppressor pathway (the Rb pathway) by binding to Rb proteins, thereby allowing release of the transcription factor E2F and subsequent cell proliferation. E7 also seems to have Rb-independent effects by enhancing the transcriptional activity of E2F through direct binding to E2F-DNA complexes as well as by facilitating HPV avoidance of host immune defenses. Although both E6 and E7 are produced by high-risk (oncogenic) and low-risk HPV, differences in the binding affinities with tumor suppressor proteins among HPV genotypes may account for the observed difference in oncogenic potential.[29]

Most adults have been exposed to HPV, with >80% of women and 60% of men having had a genital infection in their lifetimes.[29,30] Lifetime prevalence rates for oral HPV infection are not known, but point prevalence estimates are generally in the 5% to 10% range[31] and seem to increase with age and to be higher in men than in women.[32] In the largest study to date (>5,500 individuals), oral HPV prevalence, determined by oral rinse and gargle sampling, demonstrated that HPV-62 (followed by types 55, 84, 72, 89, 61, and 6) were the most common low-risk HPV types and HPV-16 (followed by type 66 and less commonly types 51, 39, 56, 52, 59, and 18) were the most common high-risk types.[32] In multivariate analyses, these oral infections were associated with older age, male sex, cigarette smoking, and lifetime number of sexual partners (oral sex partners, vaginal sex partners, and any sex partners).[32] Most of these infections are cleared,[29] and in terms of relative numbers few new cases of cervical, other anogenital, or oropharyngeal cancer are diagnosed annually (<40,000).[3]

Incorporation of the viral genome into the host genome (rather than remaining in the episomal form) may be a critical step in carcinogenesis.[29] Viral DNA insertion tends to occur at certain risk sites (fragile sites) of the host genome, and changes in the viral genome with insertion (particularly interruption of the E2 gene) affect E6 and E7 oncoprotein expression levels.[33] Each step raises important prevention opportunities: the possibility of determining who (by genetic variations) is at risk of HPV-associated cancers among those exposed as well as which viral genotypes are the most oncogenic.

Gillison et al. generated evidence in support of the causal relationship between HPV infection and a subset of HNSCC.[34] This group of investigators assayed tumor specimens from 253 patients with newly diagnosed or recurrent HNSCC for the presence of the HPV genome by polymerase chain reaction (PCR), Southern blot hybridization, and *in situ* hybridization; they also sequenced the viral E6 coding region to confirm the presence of tumor-specific viral isolates as well as sequencing exons 5 to 9 of the *TP53* gene from 166 tumors. HPV was detected in 62 (25%) of 253 cases. HPV-16 was identified in 90% of the HPV-positive tumors and was localized within the nuclei of cancer cells in preinvasive, invasive, and lymph node disease. Southern blot hybridization patterns were consistent with viral integration. As compared with HPV-negative oropharyngeal cancers, HPV-positive oropharyngeal cancers were less likely to have *TP53* mutations. On the basis of available evidence, the International Agency for Research on Cancer concluded in 2007 that HPV type 16 is a cause of oropharyngeal carcinoma (Monograph Volume 90, 2007, which can be accessed from the following website: http://monographs.iarc.fr).

A more recent study compared 28 HPV-16-associated (determined by HPV-specific PCR and fluorescence *in situ* hybridization [FISH] analysis and positive *p16* immunostaining) and 32 HPV-unrelated oropharyngeal carcinomas by comparative genomic hybridization to identify differences in chromosomal and genetic profiles.[35] This work showed that HPV-negative tumors had (a) higher numbers of chromosomal alterations ($p = 0.03$) and amplifications ($p = 0.039$); (b) more losses at 3p ($p = 0.002$), 5q ($p = 0.03$), 9p ($p < 0.001$), 15q ($p = 0.02$), and 18q ($p = 0.004$) and gains/amplifications at 11q13 ($p = 0.001$); and (c) less often 16q losses ($p = 0.02$) and Xp gains ($p = 0.03$). Interestingly, 16q loss, predominantly identified in HPV-related oropharyngeal carcinoma, was a strong determinant of better overall survival ($p = 0.008$) and disease-free survival ($p = 0.01$) and none of those patients had a tumor recurrence.

# DIAGNOSIS AND CLINICAL FEATURES OF HPV-ASSOCIATED OROPHARYNGEAL CARCINOMA

## Histology

No uniform terminology has existed until recently for reporting HPV-associated oropharyngeal carcinoma. Histologically, HPV-associated oropharyngeal carcinomas have been misinterpreted as poorly differentiated carcinomas based on the immature appearance of tumor cells or often described as "basaloid" carcinoma based on the lobular growth of cells with hyperchromatic nuclei and a high nuclear-to-cytoplasmic ratio. A recent study showed that the "basaloid" subtype consists of a mixed group of HPV-positive and HPV-negative carcinomas with very different behaviors.[36] The presence of HPV denotes a subset of basaloid squamous carcinoma with a more indolent behavior.[36] Therefore,

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the recommendation was made to classify this subset of tumors as *nonkeratinizing squamous cell carcinoma* to avoid confusion and to routinely test all carcinomas arising in the oropharynx for the presence of HPV, as described below.

## Methods of HPV Detection

Methods of HPV detection have evolved substantially since a connection between HPV and cancer of the uterine cervix was postulated in the 1980s. Currently available methods include detection of serum antibody against several HPV epitopes, type-specific and consensus (broad spectrum) PCR assays, real-time PCR (RT-PCR) to quantify viral load, type-specific DNA *in situ* hybridization, and immunohistochemical detection of surrogate markers, particularly a known biomarker of HPV E7 oncoprotein function, the cyclin-dependent kinase inhibitor p16 protein. As recommended at the 2008 meeting of the task force of the National Cancer Institute's head and neck steering committee, the choice of HPV assay depends on how the information obtained is to be used.[37] In short, HPV serology and PCR-based methods have been used mostly for studying the natural history of HPV infection. A weakness of the nonquantitative PCR-based assay is that it cannot distinguish oncogenic virus from biologically irrelevant (trancriptionally inactive) virus. These methods are being refined, and more sophisticated forms may become available for clinical use.

*In situ* hybridization (ISH) and immunohistochemical (IHC) assays are now widely used for characterizing oropharyngeal carcinoma, and each has strengths and limitations. The presence of punctate hybridization signals within the nuclei of tumor cells is seen only after the HPV DNA has been integrated into the host genome and is thus more biologically relevant.[38] The introduction of various signal amplification steps has significantly improved the sensitivity of this technique, even to the point of viral detection down to one viral copy per cell.[38] Recent advances also make ISH more practical and cost-effective for everyday use in most diagnostic laboratories that routinely process formalin-fixed and paraffin-embedded (FFPE) tissue blocks. For example, the development of nonfluorescent chromogens now allows display of DNA hybridization using conventional light microscopy, and adaptation of ISH to FFPE tissues has made this technique compatible with standard tissue-processing procedures and amenable to retrospective analysis of archival tissue blocks.[37] A type-specific probe is very sensitive for detecting the presence of HPV-16, and a consensus ISH probe can detect 15 HPV types.

Because of its simplicity and ease of interpretation (almost a binomial distribution of staining), the *p16* IHC assay has been advocated as a reliable surrogate marker of HPV-associated oropharyngeal carcinoma.[39,40] Direct comparison of *p16* IHC assay and HPV-16 ISH for relatively large series of HNSCCs reveals a discordance rate of up to 25%. The discrepancies mostly consist of carcinomas that are negative by HPV-16 ISH but are positive by *p16*. In about half of discrepant cases, *p16* expression is attributed to the presence of some other HPV types, as confirmed by wide-spectrum ISH. When E6/E7 mRNA levels were used as a standard of biologically relevant HPV infection, positive *p16* was found to be 100% sensitive but only about 80% specific.[41] The remaining discordance between HPV ISH and *p16* IHC likely reflects the imperfection of *p16* as a surrogate marker, as it is also expressed in basaloid carcinomas that are not related to HPV infection (e.g., carcinomas of the breast, lung, and skin).[37] Overexpression of *p16* could result from perturbations, such as mutational inactivation of the pRB pathway through other mechanisms and perhaps altered methylation or mutation of the *p16* gene.[42] Overexpression of *p16* by IHC has also been documented in HPV-negative nasopharyngeal carcinomas.[43]

Standardization of assay methods is urgently needed so that reproducible results can be obtained from and compared among diagnostic laboratories. A logical and practical HPV detection strategy is also required to improve consistency in daily clinical practice. An algorithm proposed by Westra at a National Cancer Institute State of the Science Meeting that took place in November 2008[37] combines the sensitivity and simplicity of *p16* IHC with the specificity of HPV ISH. IHC for *p16* is recommended as a good first-line assay for eliminating HPV-negative cases from any additional analysis. HPV-16 ISH can be run concurrently with *p16* IHC or as a second-line assay after a positive *p16* result. Given a specificity approaching 100%, a positive HPV-16 ISH reduces the numbers of false-positive cases by *p16* staining alone. A *p16*-positive/HPV-16-negative result identifies a subset of tumors that qualify for rigorous third-line analysis for other oncogenic HPV types by using a consensus ISH probe that detects 15 other HPV types. This strategy can accurately establish the HPV status of the vast majority of oropharyngeal carcinomas while minimizing the expenditure of resources by limiting the cases requiring multiple assays.

## Clinical Features of HPV-Associated Oropharyngeal Carcinoma

HPV-positive oropharyngeal cancers tend to occur in either the tonsils or the tongue base rather than in other oropharyngeal subsites. Numerous case series have established that HPV-positive oropharyngeal cancers have unique demographic, behavioral, and clinical characteristics. A case-control analysis showed a strong association between lifetime sexual behavior and marijuana use for HPV-associated carcinomas, whereas strong trends were observed between consumption of alcohol and tobacco, poor oral hygiene, and HPV-negative cancers.[44]

Most patients with HPV-positive oropharyngeal carcinoma are middle-aged white men, often with higher socioeconomic status, who consume no or relatively low amounts of tobacco or alcohol.[23,44–46] As a group, patients with HPV-positive oropharyngeal carcinoma tend to have higher numbers of sexual partners, and in particular, more oral sex partners.[44,46–48] Though oral mucosal HPV infection is generally thought to be sexually transmitted,[32,49] the reason why HPV-related oropharyngeal carcinoma predominantly affects men is not well understood. Possibly, higher HPV viral loads in infected cervical tissues than in penile tissues might result in a higher viral exposure dose and thus increase the probability of contracting HPV infection when performing oral sex on a woman.[50]

Differences have also been noted in the TNM distribution at the time of diagnosis between HPV-positive and HPV-negative carcinomas. However, published data are not entirely consistent, and the magnitude of these differences varies among series. This discrepancy likely results, to some extent, from the heterogeneous composition of the study population in terms of the primary tumor sites, particularly whether laryngeal cancer was included, and other eligibility criteria for various prospective trials, which limit the generalizability of their results to the oropharyngeal cancer population at large.

Two clinical trials have reported findings from patients with carcinoma at various head and neck sites. The prospective Eastern Cooperative Oncology Group phase II induction chemotherapy trial (protocol ECOG 2399), for example, enrolled patients with stage III or IV squamous carcinoma of the oropharynx or the larynx; tumor specimens were available for assays from 96 patients. More HPV-positive carcinomas were found to have been in earlier T categories (T2, 58% vs. 33%; T3–4, 42% vs. 67%) but in more advanced N categories (N2–3, 66% vs. 50%) compared with HPV-negative tumors.[51] The Danish Head and Neck Cancer

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Group trials (DAHANCA 6&7) enrolled patients with stage I to IV carcinoma of the larynx, pharynx, or oral cavity and found no significant difference between *p16*-positive and *p16*-negative tumors in terms of T category, although *p16*-positive tumors were more likely to have had nodal involvement than *p16*-negative tumors (81 of 179 [45%] vs. 192 of 615 [31%]; $p = 0.001$).[52]

Three clinical trials with large number of patients with oropharyngeal carcinoma had similar patterns of distribution by T and N categories. In the series of 323 patients enrolled in a Radiation Therapy Oncology Group (RTOG 0129) phase III trial,[53] HPV-positive carcinomas were on average smaller at diagnosis (T2 34.5% vs. 23.9%; T3 40.8% vs. 36.8%; T4 24.8% vs. 39.3%; $p = 0.006$) compared with HPV-negative tumors, but no significant difference was found in the distribution by N category between the two groups (N0 7.3% vs. 7.7%; N1 10.7% vs. 20.5%; N2 71.4% vs. 64.2%; N3 10.7% vs. 7.7%; $p = 0.46$). Notably, however, patients with T1–2 N0–1 disease were not eligible for this trial. Findings from the TAX-324 series of 111 patients were similar to those from the RTOG series, that is, the incidence of T1–2 tumors was higher for HPV-positive carcinomas than for HPV-negative tumors (49% vs. 20%; $p = 0.001$) but no significant differences were found in nodal status or N category between the two groups.[54] In the Trans Tasman Radiation Oncology Group (TROG) trial of 185 cases, however, patients with *p16*-positive carcinomas had less advanced T category (T1–2 37% vs. 15%; $p = 0.001$) but more advanced N category (N2–3 86% vs. 65%; $p = 0.001$).[55]

Taken together, these findings show that HPV-positive oropharyngeal carcinomas are generally diagnosed at an earlier T category than are HPV-negative tumors. Findings on the extent of nodal involvement at diagnosis are less consistent among series but a trend seems evident toward HPV-positive oropharyngeal carcinomas presenting at more advanced N categories. Of clinical interest is that involved lymph nodes from HPV-positive carcinoma often appear cystic on imaging.[56] This feature is now recognized as a trait of HPV-associated carcinomas, particularly those originating from the tonsil or base of tongue and, therefore, is considered an indication for diagnostic tonsillectomy and multiple base of tongue biopsies when a clinical workup, including examination under anesthesia, fails to detect the primary tumor.

As outlined above, HPV-associated oropharyngeal cancers, as described chiefly in single-institution case series or clinical trials with specific entry criteria, have distinctive demographic, behavioral, and clinical characteristics. Population-level trends in oropharyngeal cancer mirror these characteristics and support HPV as the cause of the national increase in the incidence of oropharyngeal cancer, which is greatest among middle-aged white men.[8] Although many behavioral researchers have suggested that the prevalence of oral sex has risen over the past three decades, reliable data on such national trends are lacking. However, it is clear that smoking prevalence has dropped over this period and, as expected, the incidence of tobacco-associated neoplasms have subsequently declined.[5,8,57–59] National trends also reveal a rising proportion of cancers of the tongue and tonsil presenting as higher-grade tumors, but this is not the case for tumors at other sites.[60] In addition, several groups using population-based registries have described dramatic increases in HPV-positive oropharyngeal cancer among archived tumor specimens over time.[9,10,12,24,61]

## TREATMENT OUTCOMES OF HPV-ASSOCIATED HEAD AND NECK CARCINOMA

### Case-Control Series

Several single-institution retrospective series published about a decade ago suggested that the prognosis for patients with HPV-positive oropharyngeal carcinomas was much better than for those with HPV-negative tumors (Table 12.1). Most of these early series used PCR-based methods to detect the presence of HPV.

Mellin et al., for example, assayed pretreatment biopsy specimen from 60 patients with primary tonsillar carcinomas, treated with radiotherapy alone (45%) or radiation and surgery (55%), for the presence of HPV DNA and also for HPV type with PCR.[62] HPV-16 was detected in 26 (43%) of the cancers, including one double infection with both HPV-16 and HPV-33. Patients with HPV-positive tonsillar cancer had a lower risk of relapse within 3 years after diagnosis than did HPV-negative patients (odds ratio [OR], 4.2; $p = 0.025$). Furthermore, cause-specific survival was significantly ($p = 0.047$) better in patients with HPV-positive tonsillar carcinomas: 5-year survival rates were 53.5% for patients with HPV-positive tumors and 31.5% for those with HPV-negative tumors. The better outcome for patients with HPV-positive tonsillar cancer was independent of TNM classification, nodal status, gender, and age.

Gillison and colleagues tested tumor tissues from 253 patients with newly diagnosed or recurrent HNSCC of the oral cavity, the oropharynx, the hypopharynx, the larynx, or the nasopharynx for the presence of the HPV genome by PCR-based assays, Southern blot hybridization, and ISH.[34] Most patients were treated with surgery with postoperative radiotherapy (49%) and the remainder with surgery alone (17%), radiotherapy alone (25%), or other modalities. HPV was detected in 62 (25%) of the

**Table 12.1 Treatment Outcome by Tumor HPV Status from Single-institution Retrospective Series**

| | | | Outcome HPV-positive vs. HPV-negative | | |
|---|---|---|---|---|---|
| **Author (year)** | **N** | **Assays** | **Endpoint** | **HR or OR (95% CI)** | ***p*-Value** |
| Mellin (2000)[62] | 60 | PCR (*L1*) | Risk of relapse | 0.24* (not reported) | 0.025 |
| Gillison (2000)[34] | 253 | PCR, ISH, etc. | Disease-specific survival | 0.41 (0.20–0.88) | 0.020 |
| Schwartz (2001)[63] | 254 | PCR (*L1* & *E6*) | Overall survival | 0.34 (0.14–0.83) | — |
| Lindel (2001)[64] | 99 | PCR (*L1* & *E2*) | Local failure | 0.31 (0.09–0.99) | 0.048 |
| Weinberger (2004)[96] | 120 | p16 | Overall survival | 0.42 (0.2–0.9) | 0.021 |

HPV, human papillomavirus; HR, hazard ratio; OR, odds ratio; CI, confidence interval; PCR, polymerase chain reaction; ISH, *in situ* hybridization.

*Converted from the original paper to reflect that patients with HPV-positive tumors had lower risk of relapse.

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253 cases, and HPV-16 was identified in 90% of the HPV-positive tumors. After adjustment for some known prognostic variables such as the presence of lymph node disease, heavy alcohol consumption, and age older than 60 years, the reduction in risk of death from cancer for all patients with HPV-positive tumors was 59% compared with HPV-negative HNSCC patients (hazard ratio [HR], 0.41; 95% CI, 0.20–0.88; $p = 0.02$), and those with HPV-positive tumors may have had better overall survival as well (HR, 0.60; 95% CI, 0.35–1.0; $p = 0.07$).

Schwartz and colleagues identified through the Cancer Surveillance System (a participant in the SEER program) 254 patients who had received surgery, radiotherapy, or both for primary cancer of the oral cavity, tonsil, or other oropharyngeal sites and who had provided tumor specimens for assays.[63] They tested tumor HPV-16 status by PCR for the presence of the *L1* and *E6* regions and compared the results with treatment outcome. Forty tumors (15.7%) tested positive for HPV-16, and 22 (8.7%) for other HPV types. Patients with HPV-16-positive tumors had significantly lower all-cause mortality (HR estimates, 0.34; 95% CI, 0.14–0.83) and disease-specific mortality (HR, 0.17; 95% CI, 0.04–0.76) than did those with HPV-16-negative patients after adjustment for age, disease stage, treatment, smoking, alcohol use, education, and comorbid diseases. Although not statistically significant ($p = 0.355$), the interaction term for radiation and HPV-16 in the models suggested that HPV-16 positivity was associated with better survival among patients receiving radiotherapy (HR, 0.29; 95% CI, 0.11–0.77) whereas little association was noted among those who did not receive radiation therapy (HR, 0.84; 95% CI, 0.11–6.65).

Similarly, Lindel et al. analyzed biopsy samples from 99 patients with oropharyngeal carcinomas treated with radiation alone (72 patients) or radiation combined with chemotherapy (27 patients) by multiplex PCR for the presence of the L1 open reading frame and *E2* gene.[64] They found 14 tumors to be HPV-positive (11 HPV-16, 1 HPV-33, 1 HPV-35, and 1 HPV-45). Patients with HPV-positive tumors had significantly better local control and overall survival rates. In multivariate analysis, HPV positivity remained associated with a lower risk of local failure (risk ratio [RR], 0.31; $p = 0.048$). Of interest is that four of 11 HPV-16-positive tumors had a disrupted *E2* gene and only tumors with a disrupted *E2* gene manifested local treatment failure.

Weinberger et al. compared *p16* expression by IHC with treatment outcome for 123 patients with primary or recurrent oropharyngeal carcinoma treated with radiotherapy alone (73 patients), surgery with postoperative radiotherapy (44 patients), or other regimens.[40] Good-quality assays were obtained for 120 tumors, of which 24 (20%) were scored as positive for *p16* expression. This study showed that *p16* overexpression was associated with lower 5-year local recurrence rates (11% vs. 53%) and higher rates of 5-year disease-free survival (62% vs. 19%) and overall survival (60% vs. 21%). In multivariate analysis, *p16* expression status remained an independent prognostic factor for local recurrence, disease-free survival, and overall survival.

A meta-analysis of the relationship between HPV status and overall survival and disease-free survival revealed that patients with HPV-positive HNSCC had a lower risk of dying (meta-HR, 0.85; 95% CI, 0.7–1.0) and a lower risk of recurrence (meta HR, 0.62; 95% CI, 0.5–0.8) than HPV-negative HNSCC patients.[65] In addition, tumor site–specific analyses showed that patients with HPV-positive oropharyngeal carcinoma had a 28% reduction in risk of death (meta HR, 0.72; 95% CI, 0.5–1.0) compared with patients with HPV-negative oropharyngeal tumors. Similar observations were made for disease-free survival (meta HR, 0.51; 95% CI, 0.4–0.7). No difference was found in overall survival between patients with HPV-positive or -negative nonoropharyngeal cancer, which supports the notion that the effect of HPV is limited to oropharyngeal cancer and its presence may not be relevant to the etiology or clinical behavior of nonoropharyngeal cancers.

Although these early series have the usual weaknesses of relatively small sample sizes with significant heterogeneity of tumor subsites, disease stage, and treatment administered, confounding by known prognostic variables, assay methods, and so on, the consistency of the findings was rather remarkable and thus provided the impetus for studies using annotated samples of patients enrolled in prospective studies, particularly large phase III trials, as described below.

## Cooperative Group Trial Series

Based on the encouraging findings from early small retrospective series, several subsequent studies were undertaken using annotated archived tumor specimens from well-characterized patients enrolled in phase II and III trials and receiving specific protocol treatment regimens (Table 12.2).

***ECOG 2399 trial.*** Fakhry and associates analyzed samples from patients enrolled in this ECOG phase II trial testing the nonsurgical management of clinical stage III or IV squamous cell carcinoma of the oropharynx or the larynx.[51] Of the 111 patients

**Table 12.2 Treatment Outcome by Tumor HPV Status from Patients Enrolled in Multi-institutional Trials**

| | | | Outcome HPV-positive vs. HPV-negative | | |
|---|---|---|---|---|---|
| **Author (year)** | **N** | **Assays** | **Endpoint** | **HR (95% CI)** | ***p*-Value** |
| Fakhry (2008)[51] | 96 | ISH, p16, etc. | Tumor progression | 0.27 (0.10–0.75) | 0.01 |
| *Ang (2010)[53] | 323 | p16 and ISH | Overall survival | 0.33 (0.21–0.53) | <0.001 |
| | | | Progression-free survival | 0.42 (0.28–0.64) | <0.001 |
| *Richin (2010)[55] | 185 | p16 | Overall survival | 0.36 (0.17–0.74) | 0.004 |
| | | | Failure-free survival | 0.39 (0.20–0.74) | 0.003 |
| *Posner (2011)[54] | 111 | PCR (E6–E7) | Overall survival | 0.20 (0.10–0.38) | <0.0001 |
| Lassen (2011)[52] | 794 | p16 | Disease-specific survival | 0.58 (0.41–0.81) | 0.001 |
| | | | Overall survival | 0.62 (0.49–0.78) | <0.001 |

HPV, Human papillomavirus; HR, hazardratio; CI, confidence interval; ISH, *in situ* hybridization; PCR, polymerase chain reaction.

*Series consisting exclusively of patients with oropharyngeal carcinoma.

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enrolled, tumor specimens were available for correlative analysis from 96 patients, most of whom were white men, often with fewer than 20 pack-years of cigarette consumption. Treatment consisted of induction chemotherapy with two cycles of carboplatin and paclitaxel followed by weekly paclitaxel concurrent with standard-fractionation radiotherapy (70 Gy in 35 fractions over 7 weeks). Tumor specimens were evaluated by HPV ISH and *p16* IHC. HPV ISH was positive in 38 (40%) of 96 tumor specimens (36 were positive for HPV-16 and one each for types 33 and 35). Sufficient specimens were available for IHC assay in 36 of the 38 HPV-positive tumors, and all of those 36 samples showed high *p16* expression. Comparisons with clinical outcome data showed that the response rate to induction chemotherapy was higher for HPV-positive carcinomas than for HPV-negative tumors (82% vs. 55%; $p = 0.01$). More importantly, compared with patients with HPV-negative tumors, those with HPV-positive carcinomas had a better 2-year overall survival rate (95% vs. 62%; $p = 0.005$) and, after adjustment for age, disease stage, and ECOG performance status, a lower risk of tumor progression (HR, 0.27; 95% CI, 0.10–0.75; $p = 0.01$). When the analysis was restricted to the subgroup with oropharyngeal tumors, patients with HPV-positive carcinoma had lower risks of both death (HR, 0.39; 95% CI, 0.15–1.05; $p = 0.06$) and tumor progression (HR, 0.38; 95% CI, 0.12–1.15; $p = 0.09$) than patients with HPV-negative tumors after adjustment for ECOG performance status. As the investigators pointed out, sample size constraints limited the number of variables that could be included in the multivariate adjustment. Consequently, larger confirmatory studies were recommended to provide definitive evidence that tumor HPV status is an independent prognostic determinant of survival among patients with oropharyngeal cancer.

***RTOG 0129 Trial.*** Ang et al. undertook a study using tumor specimens from patients in a large phase III trial of HNSCC to assess the demographics and the independent prognostic significance of HPV-related oropharyngeal carcinomas.[53] In that trial, eligible patients with pathologically confirmed, stage III or IV squamous cell carcinoma of the oropharynx, the larynx, the hypopharynx, or the oral cavity without distant metastases were randomly assigned to receive high-dose cisplatin (100 mg/m$^2$) concurrently with either accelerated fractionation (by means of concomitant boost regimen [the experimental arm]) or standard fractionation radiotherapy (the control arm). A total of 721 patients meeting the protocol criteria were enrolled, of whom 433 (60%) had oropharyngeal carcinoma. Tumor samples of sufficient quality were available for marker assays from 323 (75%) of the 433 patients. Tumor specimens were evaluated for HPV-16 DNA by ISH and for *p16* expression by IHC assays. HPV-16-negative tumors were further evaluated for 12 additional oncogenic HPV types (18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). No significant differences in baseline characteristics, overall survival, or progression-free survival were detected between patients with or without available tumor specimens, and the two treatment groups were balanced with regard to tumor HPV status, which suggests that no systematic biases were present. After a median follow-up time of 4.8 years (range 0.3–6.5 years), the 3-year overall survival rate was not significantly different in the accelerated fractionation or the standard fractionation groups (70.3% vs. 64.3%; $p = 0.18$). Therefore, data for all patients with oropharyngeal carcinoma were combined to analyze the association between tumor *p16* status and treatment outcomes. In a Kaplan-Meier analysis, patients with *p16*-positive oropharyngeal carcinoma had better survival outcomes than patients with *p16*-negative oropharyngeal tumors (Table 12.2). The corresponding 3-year rates of overall survival were 83.6% and 51.3% ($p < 0.001$), and the 3-year rates of progression-free survival were 74.4% and 38.4% ($p < 0.001$). An analysis of patterns of relapse revealed a significantly lower 3-year rate of local-regional relapse among patients with HPV-positive oropharyngeal carcinoma (13.6% vs. 35.1%; $p < 0.001$), but an apparent difference in 3-year rates of distant metastasis was not significantly different (8.7% vs. 14.6%; $p < 0.23$). The cumulative incidence of second primary tumors was significantly lower among patients with HPV-positive tumors (5.9% vs. 14.6%; $p = 0.02$), largely because of lower prevalence of smoking-related second cancers in that group.

In the multivariate analysis, age, race, performance status, tumor stage, nodal status, and number of pack-years of tobacco smoking were also significant determinants of overall survival and progression-free survival. Comparing the unadjusted hazard ratios for *p16*-positive versus *p16*-negative tumor status with the corresponding adjusted hazard ratios led to estimates that these factors accounted for a relative difference of approximately 9% in the rates of overall survival and progression-free survival between patients with *p16*-positive versus those with *p16*-negative oropharyngeal squamous cell carcinoma. After this adjustment, patients with *p16*-positive tumors still had a 67% reduction in the risk of death compared with patients with HPV-negative tumors (HR, 0.33; 95% CI, 0.21–0.53; $p < 0.001$) and a 58% reduction in the risk of relapse or death (HR, 0.42; 95% CI, 0.28–0.64; $p < 0.001$) (Table 12.2).

***TROG 02.02 Trial.*** Richin and colleagues studied the prognostic significance of *p16* expression in patients with oropharyngeal carcinoma enrolled in a large phase III trial of the Trans Tasman Radiation Oncology Group (TROG).[55] This protocol randomly assigned patients with previously untreated stage III or IV squamous cell carcinoma of the oral cavity, the oropharynx, the hypopharynx, or the larynx to receive radiotherapy (70 Gy in 7 weeks) with cisplatin (100 mg/m$^2$, on day 1 of weeks 1, 4, and 7) or radiotherapy (70 Gy in 7 weeks) plus tirapazamine (290 mg/m$^2$, on day 1 of weeks 1, 4, and 7 and 160 mg/m$^2$ three times per week in weeks 2 and 3) and cisplatin (75 mg/m$^2$, given 1 hour after tirapazamine on day 1 of weeks 1, 4, and 7). A total of 861 patients were enrolled, of whom 465 (54%) had oropharyngeal cancer. Tumor specimens from 185 patients with oropharyngeal carcinoma who received at least 60 Gy of radiation were available for assay, and overall 106 (57%) of these samples tested positive for *p16* expression. A caveat of this study is that the clinical features of patients with slides available for assay differed from those of patients without available slides in that those with available slides had better performance status, lower T category, and higher hemoglobin levels and were less likely to be current smokers.

Overall survival was better in the *p16*-positive group than in the *p16*-negative group, with 2-year survival rates of 91% and 74% (HR, 0.36; 95% CI, 0.17–0.74; $p = 0.004$) (Table 12.2). Failure-free survival was also better in the *p16*-positive group, with corresponding 2-year rates of 87% and 72% (HR, 0.39; 95% CI, 0.20–0.74; $p = 0.003$). On multivariate analysis, *p16* was a significant prognostic factor (HR, 0.45; 95% CI, 0.21–0.96; $p = 0.04$). Analysis according to treatment regimen showed that the 2-year overall survival rates in the cisplatin group were 89% for *p16*-positive patients and 68% for *p16*-negative patients (HR, 0.34; 95% CI, 0.14–0.86; $p = 0.021$). The corresponding 2-year overall survival rates in the tirapazamine group were 94% and 80% (HR, 0.36; 95% CI, 0.11–1.18; $p = 0.094$). The test for interaction between *p16* and treatment group was not statistically significant ($p = 0.95$). However, a trend was evident for improved local-regional control with the tirapazamine regimen for the *p16*-negative patients.

HPV ISH analysis of 102 of the *p16*-positive tumors showed that 58 (57%) of these tumors were ISH-negative. However, additional assay with PCR demonstrated the presence of HPV in

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44 (76%) of those 58 tumors, suggesting that some commercially available HPV ISH assay kits may have lower sensitivity than others.

***TAX-324 Trial.*** Posner and colleagues assessed the prognostic significance of *p16* expression in patients with oropharyngeal carcinoma enrolled in a phase III trial.[54] This protocol randomly assigned patients with previously untreated stage III or IV squamous cell carcinoma of the oral cavity, the oropharynx, the hypopharynx, or the larynx to receive induction chemotherapy with three cycles, given every 3 weeks, of docetaxel (75 mg/$^2$) plus cisplatin (100 mg/m$^2$) and fluorouracil (1,000 mg/m$^2$ for 4 days) (TPF) or three cycles of cisplatin and fluorouracil at the same doses (PF) followed by radiotherapy (70–74 Gy in 7–7.5 weeks) with concurrent weekly carboplatin (area under the curve of 1.5). Of the 501 patients enrolled, 264 (53%) had oropharyngeal cancer. Tumor specimens from 111 patients with oropharyngeal carcinoma were subjected to HPV-16–specific E6 and E7 viral oncoprotein PCR, and 56 (50%) tested positive. No obvious differences were apparent in the clinical features of patients with or without available specimens for assay. At the time of analysis, at a median follow-up time of >80 months, 79% of patients with HPV-positive oropharyngeal carcinoma were alive and their progression-free survival rate was 73% compared with 31% alive and 29% alive without progression with HPV-negative oropharyngeal carcinoma ($p = 0.0001$). HPV-positive oropharyngeal carcinoma was associated with an 80% reduction in mortality (HR, 0.2; 95% CI, 0.10–0.38; $p < 0.0001$). Analysis of the pattern of failure showed a significantly lower local-regional failure rate (13% vs. 42%, $p = 0.0006$) for patients with HPV-positive tumors, but the rates of distant failure, which were low in both subgroups (5% and 11%), were not significantly different. Comparison of the effects of treatment with TPF or PF in patients with HPV-positive or HPV-negative oropharyngeal carcinoma revealed no statistical differences between the regimens, but the sample size for this subgroup analysis was small.

***DAHANCA Trials.*** In this study, Lassen and colleagues correlated *p16* expression with the outcome of patients enrolled in two phase III trials of the Danish Head and Neck Cancer Group (DAHANCA 6&7).[52] These protocols randomized 1,476 patients with primary invasive (stage I–IV) carcinoma of the larynx, the pharynx, or the oral cavity to receive radiation in 2-Gy fractions, given either in 5 fractions (control) or 6 fractions (experimental) per week to total doses of 66 to 68 Gy. Patients with pharyngeal or oral cavity tumors also received the hypoxic cell radiosensitizer nimorazole (1,200 mg/m$^2$). Tumor specimens were available from 794 (54%) patients for *p16* assay, of which 179 (23%) were positive. The proportion of *p16*-positive carcinomas differed significantly ($p = 0.001$) according to primary tumor site: 83 (42%) of 200 oropharyngeal carcinomas, 71 (16%) of 428 laryngeal tumors, 12 (16%) of 74 other pharyngeal cancers, and 13 (14%) of 92 oral cavity neoplasms.

Patients with *p16*-expressing tumors had significantly better local-regional tumor control (HR, 0.66; 95% CI, 0.49–0.88; $p = 0.004$), disease-specific survival (HR, 0.58; 95% CI, 0.41–0.81; 5-year estimates 78% vs. 64%; $p = 0.001$), and overall survival (HR, 0.62; 95% CI, 0.49–0.78; 5-year estimates 62% vs. 47%, $p < 0.0001$). The significantly higher probability of local-regional control obtained with accelerated fractionation was found to apply to both *p16*-positive tumors (HR, 0.58; 95% CI, 0.35–0.99; $p = 0.05$) and *p16*-negative tumors (HR, 0.77; 95% CI, 0.60–0.98; $p = 0.04$). In the group with *p16*-positive tumors, disease-specific survival was significantly improved with the accelerated regimen (HR, 0.47; 95% CI, 0.25–0.89) but no significant overall survival benefit could be demonstrated (HR, 0.78; 95% CI, 0.51–1.19). In the *p16*-negative group, neither disease-specific survival (HR, 0.86; 95% CI, 0.66–1.31; $p = 0.28$) nor overall survival (HR, 1.02; 95% CI, 0.84–1.25; $p = 0.8$) was significantly improved by accelerated radiotherapy.

In the multivariable analysis using risk of local-regional failure as the endpoint, low T category, no lymph node involvement, good performance status, positive *p16* status, and treatment with accelerated fractionation were independent factors of good prognosis. Subgroup analysis showed that for local-regional tumor control, accelerated fractionation remained of independent prognostic significance in both *p16*-positive (HR, 0.56; 95% CI, 0.33–0.96) and *p16*-negative tumors (HR, 0.88; 95% CI, 0.67–1.15). For cancer-specific death, the accelerated regimen was independently associated with better outcome for the *p16*-positive group (HR, 0.43; 95% CI, 0.22–0.82), but not for the *p16*-negative group (HR, 0.86; 95% CI, 0.66–1.31). In terms of overall survival, the accelerated regimen had no significant benefit, with HRs of 0.68 (95% CI, 0.44–1.04) for the *p16*-positive group and 1.05 (95% CI, 0.87–1.29) for the *p16*-negative group. Moreover, no interaction between *p16* status and fractionation regimen could be demonstrated ($p = 0.40$).

## HPV *In Situ* Hybridization versus *p16* Immunohistochemistry

Weinberger and colleagues undertook a combined analysis of *p16* expression by IHC analysis and HPV-16 DNA viral load by RT-PCR in a retrospective series of 107 patients with primary or recurrent oropharyngeal carcinoma treated with radiotherapy with or without surgery.[40] The final analysis included 77 patients with tumors for which data on both HPV-16 and *p16* expression were available. These investigators found that the discriminatory power for local recurrence, disease-free survival, and overall survival increased dramatically when patients were segregated into three classes, that is, low *p16* and HPV-16-negative (Class I, $n = 30$), low *p16* but HPV-16-positive (Class II, $n = 29$), and high *p16* and HPV16-positive (Class III, $n = 18$). In multivariate analysis, no significant difference was found between patients in Class II and Class I. However, patients in Class III had significantly lower risk of death (HR, 0.19; $p = 0.013$) and risk of relapse or death (HR, 0.20; $p = 0.005$) than did patients in Class I. The inclusion of patients with recurrent disease and the heterogeneity in therapies administered may have confounded the results. The absence of tumors that were *p16*-positive but HPV-16-negative was surprising and inconsistent with findings of other series, as described below. These investigators further characterized the expression levels of 13 downstream proteins by using tissue microarray slides containing specimens from 77 patients by AQUA quantitative fluorescent immunohistochemistry and found that relative to Class II (HPV+/*p16*–, referred to as HPV-inactive) tumors, Class III (HPV+/*p16*+, labeled HPV-active) carcinomas had a significantly higher expression of β-catenin and a trend for higher expression of epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR).[66] Findings on potential correlations between HPV/*p16* and EGFR, however, were not consistent with the findings of other series (see below).

The large sample size and the uniformity of treatment in the RTOG 0129 series made it possible to assess the relative strength of HPV ISH vis-à-vis *p16* IHC as a prognostic marker.[53] The presence of HPV DNA was strongly associated with *p16* expression. Of the 315 tumors tested with both assays, 192 (61%) were positive and 92 (30%) were negative for both HPV ISH and *p16* IHC; 22 tumors (7%) were HPV ISH–negative but *p16*-positive, and only 7 tumors (2%) were HPV ISH–positive

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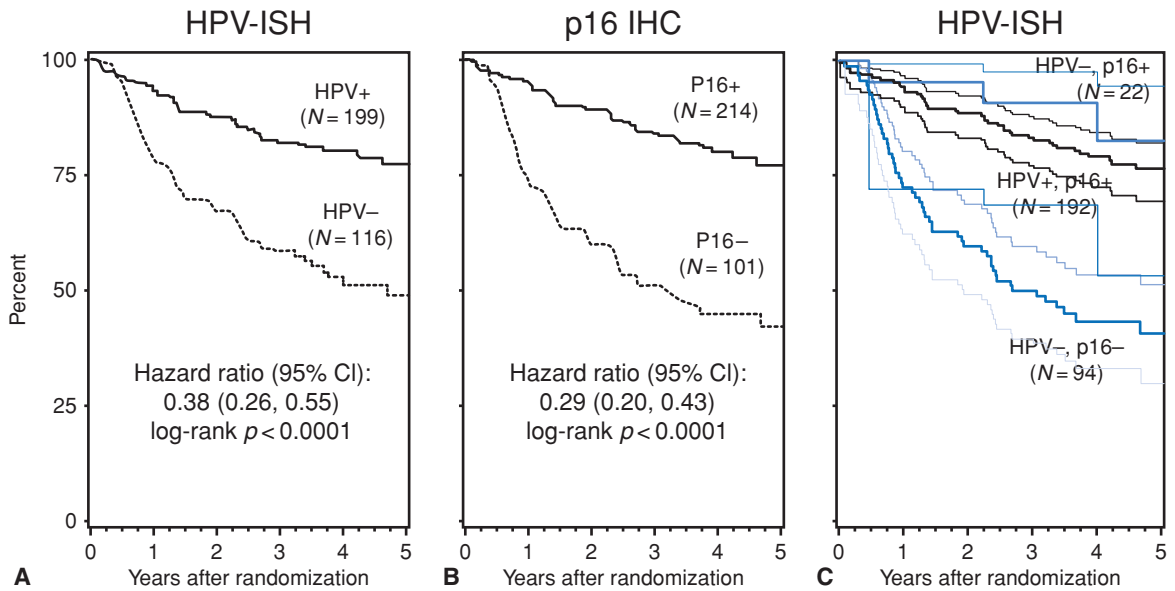



**FIGURE 12-2.** Kaplan–Meier estimates of survival of study patients with oropharyngeal carcinoma according to the results of HPV status by in situ hybridization assay **(A)**, p16 immunohistochemical staining **(B)**, or the combination of both assays **(C)**.

*Source:* Modified from Ang KK, Harris J, Wheeler R, et al. Human papillomavirus (HPV) and survival of patients with oropharynx cancer *N Engl J Med.* 2010;363:24–35, with permission.

but *p16*-negative. Results of analyses using *p16* expression as a stratification factor were consistent with those based on HPV status. However, the difference between *p16*-positive versus *p16*-negative groups seemed to be slightly more pronounced in these analyses (Fig. 12-2A, B), with HR for death of 0.29 (95% CI, 0.20–0.43) and HR for progression-free survival of 0.33 (95% CI, 0.24–0.46). The corresponding HRs after adjustment for other prognostic factors were 0.33 (95% CI, 0.21–0.53) and 0.42 (95% CI, 0.28–0.64), respectively. Notably, the Kaplan-Meier survival curve for the 22 patients with tumors that were HPV ISH–negative but *p16*-positive was similar to the survival curve for patients with tumors positive by both HPV ISH and *p16* (Fig. 12-2C).

Assay methods have varied among series, and available data are still conflicting in terms of the proportion of tumors that are HPV-positive but *p16*-negative or vice versa. To formulate a rationale for routine clinical application, further studies are needed to resolve whether *p16* IHC is a better marker than the more cumbersome HPV ISH or whether having both assays would be useful for a more refined stratification of oropharyngeal cancer behavior. Only thorough studies using annotated specimens of patients enrolled in prospective trials with stringent quality assurance can provide clearer answers to these questions.

## HPV or *p16* Expression as a Strong Independent Prognostic Marker

The field of biomarker research is still evolving. The distinction between prognostic and predictive biomarkers has not been widely appreciated until recently. Therefore, these terms have been used rather loosely and interchangeably. Figure 12-3 illustrates the concept and definition of the different classes of markers. The rates and extent of separation among the curves will vary with the disease type and stage and the efficacy of therapy, but the general principles and the relative ranking are applicable. In panel A, marker X represents a *prognostic* marker for an aggressive tumor, the presence of which is associated with poorer survival rate after both treatment (Rx) 1 and 2, although Rx 2 is more effective than Rx 1. Marker Y (panel B), on the other hand, exemplifies a *predictive* marker for response to Rx 2. Its presence is associated with better survival after Rx 2 (solid red curve). Panel C illustrates that some markers could have both prognostic and predictive value. For example, the absence of Marker Z is associated with better prognosis (solid and dotted black curves vs. dotted purple curve). However, because this marker also predicts response to Rx 2, its presence is associated with better outcome after Rx 2 (solid purple curve) relative to Z+ after Rx 1 (dotted purple curve) and Z– after Rx 2 (solid black curve).

Figure 12-3 also shows that carefully designed clinical trials incorporating patient stratification according to biomarkers and randomly assigning patients to receive distinct therapy modalities are needed to yield a conclusive answer as to whether a marker (such as HPV ISH or *p16* IHC) is prognostic, predictive, both, or neither. Because reported clinical trials were designed before the knowledge of the emergence and the distinct nature of HPV-associated oropharyngeal carcinoma, none of the phase III trials completed to date has incorporated prospective marker assessment. Therefore, the predictive nature of HPV ISH or *p16* IHC cannot be properly assessed at this time.

The available data, however, show firmly that HPV positivity or *p16* expression is a strong prognostic biomarker for oropharyngeal carcinoma. Their presence is associated with better tumor control and survival outcomes after radiotherapy alone,[52] concurrent radiation and cisplatin,[53,55] and platinum- and taxane-based induction chemotherapy.[51,54] For example, the multivariable analysis of the RTOG data showed that HPV status was the strongest prognostic determinant.[53] The HR of HPV status (negative vs. positive) for death from all causes was 2.44 (95% CI, 1.75–3.41; $p < 0.001$). In contrast, the HRs by T and N categories were 1.85 (95% CI, 1.46–2.34; $p < 0.001$) and 1.68 (95% CI, 1.33–2.14; $p < 0.001$), respectively.

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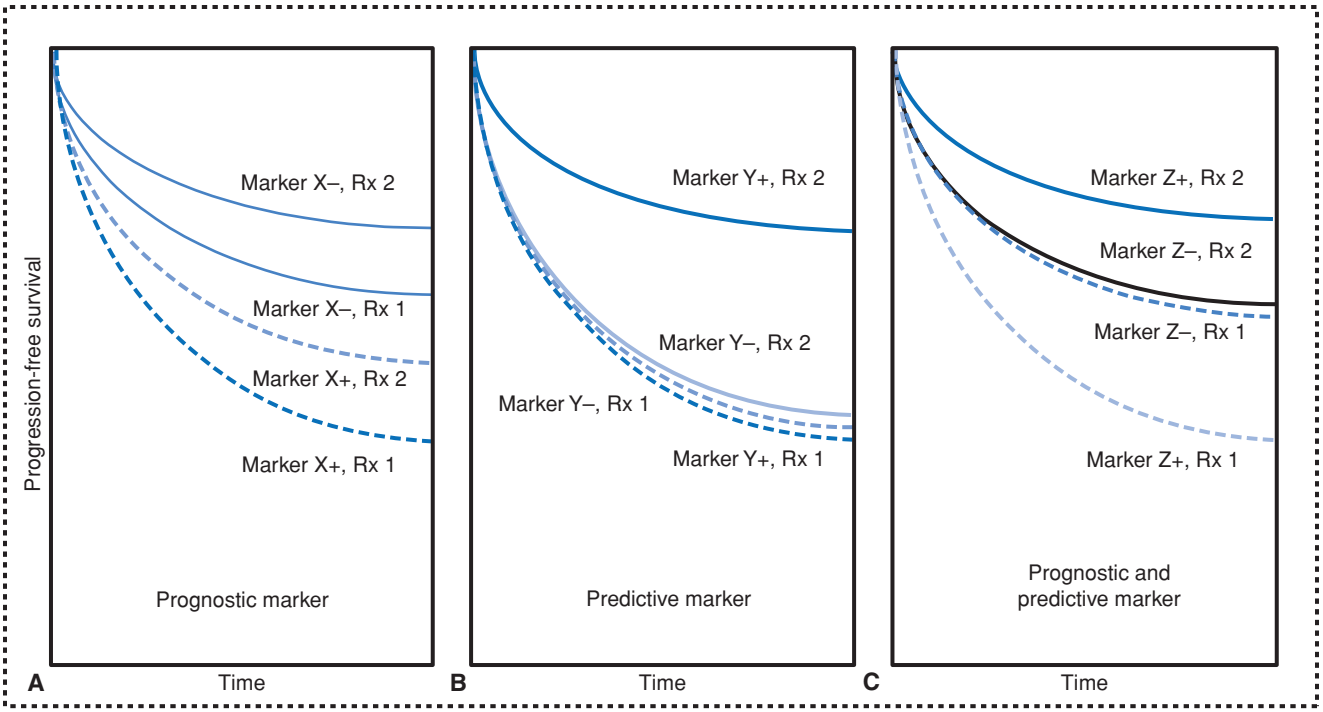



**FIGURE 12-3.** Schematic illustration of prognostic and predictive biomarkers. X and Y (panels **A** and **B**) represent pure prognostic and predictive markers, respectively, whereas Z (panel **C**) stands for a marker that predicts favorable response to treatment (Rx) 2 in addition to prognosis (see text for details).

*Source:* Reproduced with permission from Ang KK, Garden AS. *Radiotherapy for Head and Neck Cancers.* 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.

## INTERACTION BETWEEN HPV STATUS AND OTHER MOLECULAR CHANGES

### Tobacco Smoking

Although cigarette smoking has been well documented as being an important and independent prognostic factor for outcome in patients with HNSCC,[67] the interaction between smoking and HPV status on clinical outcomes was less well known. The large sample size of the RTOG 0129 series and the systematic data collection in this trial allows assessment of the interaction between tumor HPV status and smoking.[53] Of the 206 patients with HPV-positive oropharyngeal carcinoma, 59 (29%) were never-smokers and 110 (53%) were former smokers. The corresponding numbers for the 117 patients with HPV-negative oropharyngeal tumor were 14 (12%) never-smokers and 54 (46%) former smokers. The median numbers of pack-years of tobacco smoking were 12.2 (range 0–152) for the HPV-positive subgroup and 36.5 (range 0–96) for the HPV-negative subgroup.

Further analysis identified tobacco smoking to be independently associated with overall survival and progression-free survival both in the subgroup of patients with oropharyngeal carcinoma and in the entire study population. The risks of death and cancer relapse or death increased significantly by 1% for each additional pack-year of tobacco smoking, and the magnitude of the tobacco effect was similar for patients with HPV-associated oropharyngeal carcinoma (HR, 1.01; 95% CI, 1.00–1.02) and for those with HPV-negative cancer (HR, 1.01; 95% CI, 1.00–1.03).

Recursive partitioning analysis was undertaken in an attempt to stratify patients into distinct risk classes. In this analysis, the *p16* status of the tumor came out as the strongest determinant of overall survival, followed by the number of pack-years of tobacco smoking (≤ 10 vs. >10) and then N category (N0–N2a vs. N2b–N3), for *p16*-positive tumors or T category (T2–3 vs. T4), for *p16*-negative tumors (Fig. 12-4A). With this method, patients with oropharyngeal squamous-cell carcinoma could be separated into low-, intermediate-, and high-risk classes with 3-year overall survival rates of 93.5%, 67.0%, and 41.6%; corresponding 3-year local-regional control rates were 90.4%, 80.9%, and 57.3%.

Compared with the low-risk group, patients in the intermediate-risk class had a 4.06-fold (95% CI, 2.22–7.43) higher risk of dying, and those in the high-risk class had an 8.75-fold (95% CI, 4.89–15.66) higher risk of dying (Fig. 12-4B). Interestingly, patients with *p16*-positive tumors were at low risk, except for smokers with N2b to N3 disease, which moved them to the intermediate-risk class; patients with *p16*-negative tumors were at high risk except for nonsmokers with T2 or T3 tumors, which shifted them to the intermediate-risk class.

These findings strongly suggest that tobacco smoking induces additional molecular alternations in HPV-associated oropharyngeal carcinomas that alter their biological behavior and response to therapy. It is hoped that further studies will identify these "driver" molecular alterations and how to target them to improve treatment outcome.

### *TP53* Mutation

Licitra and colleagues conducted a combined analysis of the presence of integrated HPV-16 and HPV-18 DNA (by RT-PCR) and *TP53* mutation in 90 patients with HNSCC who underwent surgical resection with or without postoperative radiotherapy. These investigators found that patients with tumors that were

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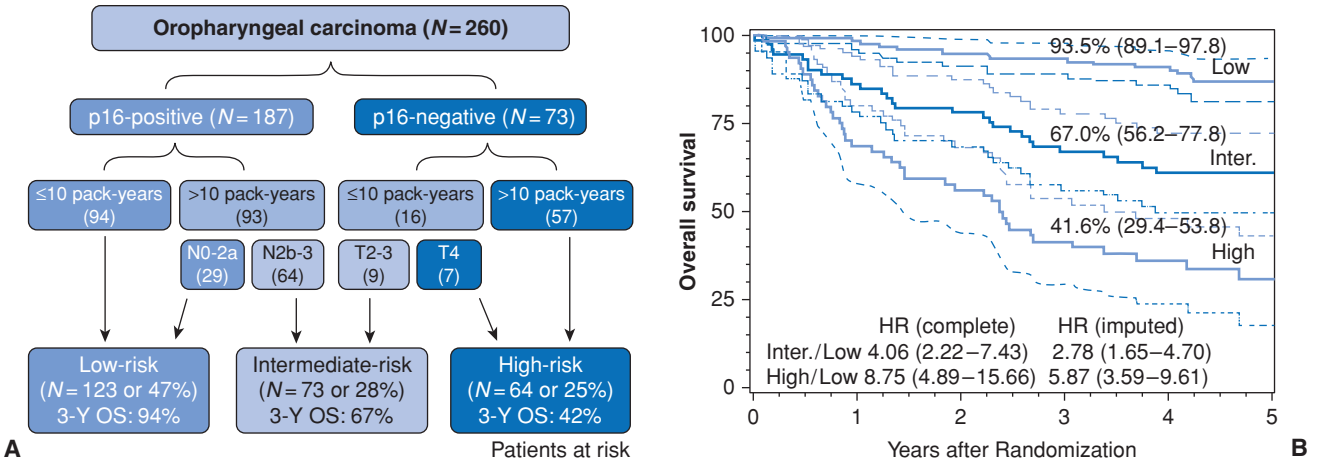



**FIGURE 12-4.** Classification of patients with oropharyngeal cancer from RTOG 0129 into three risk-of-death categories by recursive partitioning analysis **(A)** and Kaplan-Meier estimates of overall survival according to those categories **(B)**.

*Source:* Modified from Ang KK, Harris J, Wheeler R, et al. Human papillomavirus (HPV) and survival of patients with oropharynx cancer. *N Engl J Med.* 2010;363:24–35, with permission.

HPV-positive and *p53* wild-type had a 5-year overall survival rate of 79%. In contrast, patients with tumors that were HPV-negative and had wild-type *p53* or tumors that harbored *p53* mutations (mostly nonsense or missense mutations) regardless of HPV status had a 5-year overall survival rate of only 46%.

## EGFR Protein Expression or Gene Copy Number

Hong and colleagues analyzed 266 patients with biopsy-proven oropharyngeal carcinoma who underwent curative treatment (information on the regimens used was not presented) at hospitals in Sydney for the presence of HPV DNA along with expression of *p16* and EGFR.[68] The presence of HPV DNA in tumors was assayed by an E6-based multiplex tandem-PCR method that simultaneously detects and identifies 21 HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 70, 73, 82, 53, 6, 11, and 26), and tumor expression of *p16* and EGFR was assessed by semiquantitative IHC assay. Overall, 99 (37%) of 266 tumors were HPV-positive (91 of which were positive for HPV-16) and 217 (87%) of 249 tumors were EGFR-positive. EGFR expression differed significantly ($p = 0.005$) by HPV status: 78% of HPV-positive tumors were positive for EGFR as opposed to 93% of HPV-negative cancer. In multivariable analyses, after adjustment for age, year of diagnosis, gender, tumor grade, T and N category, primary site within the oropharynx, and treatment modality, patients with HPV-positive cancers were found to be at significantly lower risks of local-regional failure (HR, 0.33; 95% CI, 0.17–0.61; $p = 0.003$), of an event (HR, 0.33; 95% CI, 0.20–0.52), or of death from any cause (HR, 0.37; 95% CI, 0.21–0.62) relative to those with HPV-negative cancers. After the same adjustments, patients with EGFR-positive carcinomas were found to have significantly higher risks of local-regional failure than those with EGFR-negative cancers (HR, 5.16; 95% CI, 1.52–32.29; $p = 0.006$), but the associations were weaker between EGFR and event-free survival (HR, 1.71; 95% CI, 0.86–3.78; $p = 0.13$) and EGFR and overall survival (HR, 2.48; 95% CI, 1.04–7.33; $p = 0.039$).

In another multivariate analysis of the effects of the combination of EGFR and HPV on outcomes, the best outcomes, after adjustment for age, year of diagnosis, gender, tumor grade, T category, N category, primary site within the oropharynx, and treatment modality, were seen in patients with HPV-positive/EGFR-negative cancers and the worst in those with HPV-negative/ EGFR-positive cancers. Relative to patients with HPV-positive/EGFR-negative cancers, those with HPV-negative/EGFR-positive cancers had an adjusted 13-fold increased risk of local-regional failure (HR, 12.79; 95% CI, 1.70–96.26), an almost fourfold increased risk of an event (HR, 3.89; 95% CI, 1.61–9.37), and a more than fourfold increased risk of death from all causes (HR, 4.49; 95% CI, 1.34–15.03). That the HRs for EGFR were substantially greater in HPV-negative than HPV-positive cancers suggests that the impact of EGFR expression on outcome was limited to patients with HPV-negative cancers. However, the authors pointed out that the evidence for this proposition is rather weak because only 7% of HPV-negative patients were also EGFR-negative. Consequently, this result is based on a small sample (11 patients) with a limited number of events.

Young et al. investigated the relationships between *p16* expression, *EGFR* gene copy number, and EGFR protein expression in patients with oropharyngeal carcinoma enrolled in three successive clinical trials at the Peter MacCallum Cancer Centre in Melbourne.[69] *EGFR* gene copy number was assayed by FISH and EGFR protein expression by IHC staining. The study patients received radiotherapy plus concurrent cisplatin plus tirapazamine (phase I), cisplatin with tirapazamine or fluorouracil (phase II), or cisplatin with or without tirapazamine (phase III). This study showed that *p16* expression and *EGFR* FISH positivity (defined as either high polysomy or gene amplification) were almost mutually exclusive, as only 2 (1.6%) of 126 tumors were found to be positive for both markers. No evidence was found for an independent effect of *EGFR* FISH positivity on outcome for patients with oropharyngeal carcinoma. However, *p16* was predictive of both failure-free survival (HR, 0.30; 95% CI, 0.15–0.58; $p < 0.001$) and overall survival (HR, 0.29; 95% CI, 0.13–0.62; $p = 0.001$) independent of *EGFR* FISH. Unfortunately, assays for both *p16* and EGFR protein expression were available from only 64 oropharyngeal carcinomas. Again, *p16* was found to be significantly related to failure-free survival (HR, 0.33; 95% CI, 0.14–0.78; $p = 0.023$) and overall survival (HR, 0.36; 95% CI, 0.15–0.88; $p = 0.037$). Interestingly, however, of 10 patients who were scored as EGFR-negative, 8 were *p16*-positive, and no deaths or events were recorded for these patients for the duration of the follow-up period.

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## Combinations of Various Markers

Kumar and colleagues examined pretreatment biopsy samples from 50 patients with oropharyngeal carcinoma for the expression of *p16*, EGFR, *p53*, Bcl-xL, and *TP53* mutation.[70] Patients in this study received one cycle of induction chemotherapy with cisplatin (100 mg/m$^2$ for 1 day) or carboplatin (AUC 6) and fluorouracil (1,000 mg/m$^2$/d for 5 days), and responders received a combination of chemotherapy with radiation but nonresponders received surgery and radiation. This study showed that *p16* expression was significantly associated with HPV copy number ($p < 0.0001$), younger age ($p = 0.002$), response to induction chemotherapy ($p = 0.008$), receipt of chemoradiation therapy ($p = 0.009$), overall survival ($p = 0.001$), and disease-specific survival ($p = 0.003$). EGFR expression intensity was also associated with poorer response to induction chemotherapy ($p = 0.01$), marginally poorer response to chemoradiation therapy ($p = 0.055$), and poorer overall survival ($p = 0.001$) and disease-specific survival ($p = 0.002$). As single markers, neither *p53* expression nor Bcl-xL expression was significantly associated with treatment response or survival outcomes. *TP53* mutations (all missense, all overexpressed) were found in 6 (14.3%) of 42 tumors but were not associated with treatment response or survival.

Multimarker analysis showed inverse correlation between HPV titer or *p16* expression and EGFR expression. The combination of higher HPV titer and lower EGFR intensity was associated with better overall survival and disease-specific survival, as was high *p16* combined with low EGFR. The effect of EGFR remained after adjusting for *p16* on overall survival ($p = 0.03$) and disease-specific survival ($p = 0.04$). The prognostic value for *p53* depended on Bcl-xL expression status; patients with low *p53* and low Bcl-xL expression had better overall and disease-specific survival than did those with other permutations.

Further analysis showed that the poorer prognostic profile of lower HPV titer and higher EGFR intensity ($p = 0.001$ for overall survival; $p = 0.0002$ for disease-specific survival), lower *p16* and higher EGFR intensity ($p = 0.001$ for overall survival; $p = 0.002$ for disease-specific survival), and low *p53* and high Bcl-xL ($p = 0.003$ for overall survival; $p = 0.0001$ for disease-specific survival) was maintained after adjustment for age, gender, T category, N category, smoking status, and primary tumor site. Although Karnofsky performance status influenced overall survival, it was not significant in the multivariate analysis after other variables were considered.

Al-Swiahb et al. studied the effects of HPV genome and expression of *p16*, *p53*, and EGFR on survival in 220 patients with oropharyngeal carcinoma treated with surgical resection followed by adjuvant therapy, primary radiotherapy, or concurrent chemoradiotherapy at Chang Gung Memorial Hospital in Taiwan.[71] The proportion of patients receiving each type of therapy was not clearly spelled out. The HPV genome was assayed by a PCR-based method and ISH of tumor tissues from paraffin blocks, and *p16*, *p53*, and EGFR was assayed by IHC staining. Notably, 160 (73%) of these 220 patients had a history of chewing betel nut. In univariate analysis, 5-year survival rates were found to be better for patients with tumors that were positive for HPV (59.4% vs. 31.2%; $p = 0.008$), positive for *p16* (54.7% vs. 32.2%; $p = 0.04$), negative for EGFR (60.8% vs. 32.7%; $p = 0.01$), or low for *p53* expression (62.3% vs. 31.4%; $p = 0.01$). A high correlation was noted, however, between these variables: HPV-positive tumors were significantly more likely to express *p16* and were inversely associated with EGFR and *p53* expression ($p < 0.001$ for overall comparison). A Cox proportional hazards regression analysis revealed that HPV status ($p = 0.02$) and T category ($p < 0.001$) were the only independent factors associated with cumulative 5-year overall survival in this cohort.

## Current Status of Biomarker Discovery

Taken together, the findings from the studies summarized above show that HPV-associated oropharyngeal carcinoma has a distinct behavior but that the presence of other molecular changes such as mutations in *TP53*, upregulation of EGFR expression, or other alterations can change the biology of HPV-related carcinomas in ways that make them less responsive to currently available therapy modalities. Because the assay methods used were not standardized and because these series were generally small and highly heterogeneous in terms of patient composition and therapy administered, the results have not always been consistent. Consequently, the magnitude and relative contribution of these molecular changes on outcome are uncertain. Further systematic studies using well-characterized cohorts of patients are necessary to yield clinically useful data.

# ONGOING CLINICAL TRIALS

The recognition that patients with HPV-associated oropharyngeal carcinoma have excellent long-term survival and that the standard multimodality therapy options combining radiation with chemotherapy, with or without surgery, can induce rather severe persistent difficulties with swallowing, aspiration, and other morbidities have motivated many investigators to study less-intensive treatment combinations aimed at reducing long-lasting morbidity without compromising tumor control or survival. Many trials designed specifically for patients with HPV-positive oropharyngeal carcinoma also incorporate modern precision radiation planning and delivery techniques (e.g., intensity-modulated radiation therapy) to minimize the radiation dose delivered to critical normal tissues such as parotid glands, pharyngeal constrictors, and esophageal inlet. A comprehensive review of regimens being tested in ongoing clinical trials and those to be launched in the near future is beyond the scope of this chapter. Briefly, two cooperative group trials are ongoing in the United States. The ECOG phase II protocol E1308 is designed to assess induction paclitaxel, cisplatin, and cetuximab followed by 54 Gy of radiation with concurrent cetuximab for patients who had a clinical and radiographic complete response of the primary tumor, or 69.3 Gy with concurrent cetuximab for those who had a less than complete response of the primary tumor. The RTOG phase III trial (protocol 1016) was launched to formally compare 70 Gy of radiation in 35 fractions over 6 weeks with concurrent cisplatin versus the same radiation regimen with concurrent cetuximab. The study was designed to accrue 700 patients with *p16*-positive oropharyngeal cancer to test the hypothesis that the tumor control endpoint of the cetuximab arm is not inferior to that in the cisplatin arm but that the toxicity profile is more favorable. This trial will also prospectively collect smoking data to confirm and quantify the extent of detriment of cigarette smoking in patients with HPV-associated oropharyngeal cancer and also includes quality-of-life and patient-reported outcome assessments.

Additional cooperative group trials are being designed for the inclusion of transoral robotic or endoscopic surgical resection, both as a means to de-intensify therapy in HPV-associated oropharyngeal cancer (ECOG trial in development) and to intensify therapy for HPV-negative oropharyngeal cancer (RTOG trial in development).

# PROPHYLACTIC HPV VACCINATION

The findings within case series and clinical trials as well as national epidemiologic trends support the assertion that the United States is experiencing an epidemic of HPV-associated

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oropharyngeal cancer, in direct opposition to declining incidence of tobacco-associated cancers. Two FDA-approved vaccines are presently available. HPV4 (Gardasil™), produced by Merck, provides protection against oncogenic HPV types 16 and 18 as well as types 6 and 11 that cause genital warts. HPV2 (Cervarix™), produced by Glaxo Smith Klein, provides protection against oncogenic HPV types 16 and 18. These vaccines are of similar design, both being basically simulated type-specific virus capsids almost identical to the native virus but empty of DNA. Large clinical trials have demonstrated that these vaccines are effective in preventing type-specific HPV-related premalignant lesions and cancers in women. Unfortunately, even though these vaccines would likely prevent cancer induced by HPV-16 and HPV-18, including oropharyngeal carcinoma, they have not received widespread acceptance. The vaccination rates in the United States remain low (only 32% of 13- to 17-year-old girls received the recommended 3-dose coverage)[72] in spite of the recommendation of the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) to routinely vaccinate girls aged 11 to 12 and for girls/women aged 13 to 26 who have not been previously vaccinated.[73] Large clinical trials have also demonstrated the effectiveness of vaccinating men for the prevention of genital warts and anal dysplasia. Although cost analyses thus far have failed to support vaccination of boys for specific prevention of cancer in men,[74] analyses conducted to date have not adequately accounted for the costs (both monetary and quality-of-life lost) of HPV-associated cancers (especially oropharyngeal cancers) in men.[75] This is particularly concerning given recent estimates that oropharyngeal cancers are becoming more numerous than cervical cancers and that HPV-associated oropharyngeal cancers are estimated to become more numerous than all cervical cancers before the end of the decade.[12]

The CDC recently recommended routine HPV vaccination of boys age 11 to 12 and for boys/men aged 13 to 21 who have not been previously vaccinated. Because the current vaccination rates in girls are so low, this CDC recommendation was made principally to advance population ("herd") immunity to prevent cervical infection and subsequent premalignant lesions and cancers rather than preventing HPV-related cancers in men.[76] Evidence is already emerging to support the concept of herd immunity. Lower rates of HPV-associated genital warts have been observed in both young females (59% decline) and heterosexual males (28% decrease) in Australia, where high vaccination rates for girls (65%) against multiple HPV types have been achieved.[77] Ongoing clinical trials are investigating the next generation of HPV vaccines, which will protect against even more HPV types.

## THERAPEUTIC STARTEGIES TARGETING HPV OR HPV-ENCODED ONCOPROTEINS

The proteins encoded by the HPV genome provide unique targets for therapy of HPV-associated cancers, which in theory would avoid toxicity for normal human tissues that lack these proteins. Immune-based approaches targeting these oncoproteins have shown initial success in the treatment of genital premalignant lesions[78,79] and are already being tested in clinical trials in patients diagnosed with HPV-associated oropharyngeal cancer. The safety of and response to the MAGE-A3/HPV-16 vaccine for recurrent, progressive, or metastatic oropharyngeal cancer is being explored at the University of Maryland. A phase I trial of recombinant *Listeria monocytogenes* HPV-16 vaccine (REALISTIC trial) as an adjunct to standard definitive therapy is being conducted at three centers (Liverpool, Royal Marsden, and Cardiff) in the United Kingdom. This Listeria vaccine was shown to be safe in a phase I study of 15 patients with previously treated recurrent, metastatic, or refractory cervical carcinoma, among whom 8 patients had stable disease.[80]

Therapeutic DNA-based vaccine approaches are also being explored in clinical trials (reviewed by Monie et al.[81]). The central safety concern regarding the oncogenic potential of administering E6 and E7 DNA is addressed by using altered E6 and E7 sequences that disrupt the normal transforming potential of the transcribed protein. At present, five phase I clinical trials are underway with this therapeutic HPV DNA vaccine approach, mostly for patients with high-grade cervical intraepithelial neoplasia. Patients with oropharyngeal cancer are included in one such study and in another study that also includes a boost using a recombinant vaccinia virus encoding HPV-16 and HPV-18 E6 and E7 antigens.[81]

Because the E6 and E7 oncoproteins are constitutively expressed by HPV-associated cancers and as a consequence inhibit apoptotic mechanisms through the *p53* and Rb pathways, therapies that directly target these proteins and eliminate their functions could have both direct therapeutic effects and improving the sensitivity of tumors to radiation and chemotherapy.[82,83] At present, such E6- and E7-specific targeting remain in the preclinical stage. Several targeted agents that might improve the sensitivity of HPV-associated cancers to radiation of chemotherapy are being tested. For instance, although HPV data were not available, a secondary analysis of a phase III trial of radiation alone versus radiation with concurrent cetuximab for head and neck cancers[84] showed that improved survival resulting from adding cetuximab to radiotherapy was observed principally in subgroups having demographic profiles consistent with HPV-positive tumors. Although such interpretations are speculative, RTOG 1016 is currently addressing whether concurrent cetuximab shows the same efficacy as concurrent cisplatin in enhancing the radiosensitivity of HPV-associated oropharyngeal cancers. Other cooperative group trials for both cervical cancer and oropharyngeal cancer will ultimately identify and determine the effectiveness of agents that directly or indirectly target HPV oncoproteins.

## SUMMARY AND CONCLUDING REMARKS

The decline in tobacco consumption coupled with changing sexual behavior has altered the demographics of HNSCC, particularly in industrialized countries. The most striking change is the emergence of HPV-associated oropharyngeal carcinoma that affects predominantly middle-aged white men having higher socioeconomic status and having no or relatively low smoking history. Given the widespread nature of HPV infection, why HPV-associated carcinoma affects predominantly men is not well understood. The prevalence of HPV-associated oropharyngeal carcinoma is expected to increase further during the next two decades. How and to what extent HPV vaccination, which is being increasingly adopted for girls and now for boys, will affect the prevalence of HPV-associated oropharyngeal carcinoma remains to be determined.

HPV-positive oropharyngeal carcinoma is now widely recognized as a distinct head and neck cancer entity. At diagnosis, HPV-positive primary carcinomas are on average smaller than their HPV-negative counterparts. Although the data on N classification are less consistent, nodal disease seems to be slightly more extensive in HPV-positive oropharyngeal carcinoma at diagnosis. The discrepancy in the literature data can be ascribed in part to the selection of specific stages included in clinical trials as well as the use of various methods, each with strengths and weaknesses, for diagnosing HPV-positive tumors, as summarized in Tables 12.1 and 12.2. Whether *p16* IHC staining is a better surrogate assay than ISH has not been clearly resolved. The advantages of the *p16* assay are its simplicity, nonspecificity

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for HPV type, and reflection of functional downstream effects of HPV DNA integration; but *p16* is not a flawless surrogate. Assay standardization to improve interlaboratory reproducibility is needed in the near future, both for day-to-day patient care and for proper patient stratification or selection for prospective trials but, unfortunately, funding for such efforts has been difficult to obtain.

Clear evidence now exists that, relative to HPV-negative oropharyngeal cancer, HPV-associated oropharyngeal carcinoma responds better to current standard treatment modalities including radiation therapy alone, surgery with or without adjuvant radiotherapy, or combinations of radiation with chemotherapy, given concurrently or as an induction regimen. Consequently, patients with HPV-positive oropharyngeal carcinoma as a group have much better prognosis than those with HPV-unrelated carcinoma of the oropharynx or other head and neck subsites. The better long-term overall survival and progression-free survival rates of patients with HPV-positive carcinomas result predominantly from improved local tumor control and, to a lesser extent, from lower incidence of second primary tumors. The difference in the rate of distant metastasis is small. Unfortunately, no validated predictive biomarkers have been discovered for the rational selection of specific therapy for patients with HPV-positive carcinoma.

An increasing body of data suggest that smoking and additional molecular deregulations, such as *TP53* mutation and high EGFR expression, can increase the resistance of HPV-positive carcinoma to therapy. However, the underlying mechanisms, the magnitude of the effects, and how to overcome them to improve outcome have yet to be elucidated. Until many scientific issues are resolved, there is no scientific basis for altering the treatment for patients with HPV-positive carcinoma outside of well-monitored clinical trials. The current frontline standard treatment for patients with stages I to II (T1–2N0) HPV-positive oropharyngeal carcinoma is single-modality treatment with either radiotherapy or surgery. Several options are available for those with locally advanced disease (T3–4 or N2–3). One such option is surgery followed by adjuvant radiotherapy with or without concurrent cisplatin depending on surgical pathologic findings.[85–87] Nonsurgical choices, established through phase III trials and adopted in many centers, are radiation with concurrent platinum-based chemotherapy,[88–91] radiation plus cetuximab,[84,92] and induction chemotherapy with TPF followed by radiation with or without concurrent carboplatin.[93,94] Because these regimens have not been compared head-to-head, there is no validated strategy for choosing among them for individual patients. The choice depends thus mostly on the preferences and expertise of the multidisciplinary oncology team. Although many phase II studies have yielded interesting results with various regimens, these results need to be validated in randomized trials. Whether aggressive multimodality therapy can be spared for patients with low-volume stages III to IV disease, for example, T1–2 and N1–2a or N2b with small level II nodes, is unclear at the present time, as radiation alone might suffice for at least some of patients in this category.[95]

Given that patients with HPV-associated carcinoma have an excellent prognosis and that standard multimodality therapy options combining radiation with chemotherapy can induce rather severe long-term morbidities, much interest is devoted to launching clinical trials designed specifically for patients with HPV-positive oropharyngeal carcinoma. Two cooperative group trials are ongoing in the United States: the ECOG phase II protocol (E1308) assesses induction chemotherapy followed by reduced-dose radiation with concurrent cetuximab for patients who had a clinical and radiographic complete response of the primary tumor; and the RTOG phase III trial (protocol 1016) addresses 70 Gy of radiation with concurrent cisplatin or with concurrent cetuximab. Given the excellent survival outcome of patients with HPV-associated oropharyngeal cancer, it will take many years for these prospective trials to mature. Hopefully, the joint efforts of many investigators will answer some important scientific questions related to HPV-associated oropharyngeal carcinoma and contribute to defining the best management strategies for patients with various stages of HPV-associated carcinoma.

The presence of viral DNA and oncoproteins provides unique targets for therapy. The safety of and response to therapeutic empty capsid or altered HPV DNA vaccines are being investigated in clinical trials. Other therapeutic approaches targeting viral oncoproteins are being addressed in preclinical models. It will likely take many years to sort out the potential value of these novel therapeutic strategies.

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CHAPTER 13

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# Chemoprevention

## INCIDENCE AND PREVALENCE OF HEAD AND NECK CANCERS

A majority of head and neck cancers arise in the mucosa of the upper aerodigestive tract and are squamous cell in origin. Most of the literature in head and neck premalignancy and chemoprevention has focused on head and neck squamous cell carcinoma (HNSCC) from the oral cavity. The worldwide incidence of head and neck cancer exceeds half a million cases annually, ranking it as the fifth most common cancer worldwide.[1] Males are more affected than females. The incidence is high in some regions of Europe, Hong Kong, India, and Brazil and among African Americans in the Unites States. Oral cavity squamous cell carcinomas (OSCC) are more common in India, and pharyngeal and/or laryngeal cancers are more common in other populations.[2] In the United States, 52,000 Americans develop head and neck cancer annually and 11,500 die from the disease.[3] We see three main reasons that should encourage the scientific community and stakeholders to invest in the prevention of HNSCC: (a) HNSCC are second only to lung cancer as the most common smoking-related cancer; (b) the treatment often results in substantial morbidity; and (c) compared to other tumor types, the mutational etiology is diverse, and HNSCC have few targetable mutations according to most recent reports.[4,5] These facts further emphasize the need to improve our prevention strategies.

## RISK FACTORS ASSOCIATED WITH HEAD AND NECK CANCERS

The primary risk factors associated with HNSCC cancer include tobacco use and alcohol consumption.[2] The increased risk of HNSCC is ranging from a 5- to 25-fold in cigarette smokers compared to nonsmokers, with a dose–response relationship.[6,7] Alcohol consumption independently increases the risk of cancer in the upper aerodigestive tract.[6,8–10] The increased risk of HNSCC due to alcohol is dose dependent with a relative risk (RR) of 5 to 6 with alcohol intake >50 g/day versus <10 g/day.[9–11] Alcohol and tobacco have a synergistic effect on the risk of developing HNSCC.[6,7,9,11–13] Betel nut chewing, which is widespread in certain regions of Asia, is an independent risk factor for the development of HNSCC[14–17] and has synergistic effects with tobacco and alcohol.

Epidemiologic and molecular evidence has established a causal role for human papillomavirus (HPV), primarily type 16, 18, and 33, in the recent increase in oropharyngeal squamous cell carcinoma (SCC). Those tumors are typically seen in younger patients, never smoker and drinker.[18] Patients infected with the human immunodeficiency virus (HIV) have an increased RR of 2 to 3 to develop HNSCC.[19] Nasopharyngeal carcinoma is a relatively rare malignancy in most populations except in southern China and is associated with Epstein-Barr virus (EBV). Epstein-Barr virus is also the primary etiologic agent for oral hairy leukoplakia, although the relationship of oral hairy leukoplakia with SCC is unclear.[20–23]

Constitutional genetic alteration may contribute to an increase in risk of head and neck cancer, and these factors may interact with other known risk factors. They will be developed in the Prevention and Risk Assessment section of this chapter.

## FIELD CANCERIZATION

The concept of field cancerization refers to the effects of chronic exposure to smoking and alcohol in patients with or without cancer, with progressive onset of molecular alterations in initially histologically and clinically normal epithelia. It was first used by Slaughter et al. in a study of more than 700 HNSCC from the oral cavity and pharynx.[24] The observation of the authors was that the grossly normal epithelium adjacent to the invasive carcinoma frequently demonstrated dysplasia or carcinoma *in situ*. The mucosa of the upper aerodigestive tract was described as "condemned" by the authors, reflecting repetitive damage of the entire mucosal field by carcinogens. Later, the concept of field cancerization was supported by the identification of similar genetic alterations in matched dysplastic and malignant lesions from the oral cavity.[25] This observation provided some evidence that dysplasias were precursor lesions and that the lateral migration of genetically altered cells through the oral mucosa can form multiple lesions, a phenomenon called *clonal cancerization*.[26] In other cases, genetic alterations found in dysplastic lesions were not found in matched cancer. This observation provided some evidence that multifocal disease can arise from the development of several genetically altered clones from different initiating events. Finally, the frequent development of synchronous or metachronous second or multiple primaries in the head and neck and/or the lung also supports the concept of field cancerization.[27] The second tumors may be clonally similar to or distinct from the primary tumor.[28]

The use of molecular markers has validated the concept of field cancerization. A recent study has investigated whether oral



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epithelium may be used as a surrogate tissue for assessing tobacco-induced molecular alterations in the lungs by studying the methylation status of CDKN2A and FHIT in oral and bronchial brushes specimens from smokers enrolled in a chemoprevention trial.[29] A dose–response relationship between the number of sites methylated in the lung and the presence of oral methylation was observed for CDKN2A. Others have demonstrated that the concomitant methylation of three or more genes in the sputum is associated with a 6.5-fold increased risk for lung cancer.[30] Recent studies have reported consistent global gene expression changes in response to cigarette smoke throughout the respiratory tract, including the bronchus, the nose, and the mouth.[31] Consistent results were obtained with proteomic and gene expression profiling.[32,33]

## MULTISTEP CARCINOGENESIS

Vogelstein et al. was the first to propose a multistep pathogenesis for colorectal cancer, in which at least four mutations in oncogenes and tumor suppressor genes being necessary for malignant transformation.[34] These genetic events result in stepwise advances including initiation, promotion, and progression leading to the development of invasive carcinoma. Later, Califano et al. proposed a "Vogelgram" for HNSCC, which linked histologic changes to specific molecular alterations.[35] They proposed that the accumulation of genetic events, rather than a specific sequence, drives the transformation of squamous mucosa of the head and neck. They evaluated global gene expression changes between malignant lesions (M), premalignant lesions (PM), distant, and histopathologically normal mucosa from patients with premalignant or malignant lesions (MN), and normal mucosa from the upper aerodigestive tract of patients with noncancer diagnoses (N). They observed a consistent separation between the N, PM, and M groups, with a closer association between the PM and M groups. They conclude that the majority of alterations occurs before the development of malignancy.[36]

Histologically, changes occur from normal to hyperkeratosis, hyperplasia, mild, moderate, and severe dysplasia and then carcinoma *in situ* before becoming invasive carcinoma. Molecular alterations in epithelial cells precede histological changes. These histological alterations or clinical lesions can be unifocal, or multifocal and represent clonally independent premalignant lesions that may or may not transform into invasive carcinoma. Clinically, mucosa may appear normal, or demonstrate various aspects such as leukoplakia, erythroplakia, leukoerythroplakia, lichen planus, or subcutaneous fibrosis.[37]

The concept of multistep carcinogenesis has several limitations. The first one is practical: the histological classification is subject to a high interobserver variation.[38] Second, it has been challenged by the fact that preneoplastic lesions can regress as well as progress to higher grade lesions, either spontaneously or by avoiding further carcinogenic exposure, or by using a chemopreventive agent to reverse or inhibit carcinogenic progression.[37] It is unknown whether specific alterations are necessary and sufficient to make the progression irreversible. Finally, it does not fit the group of never-smoker-never-drinker that represents 10% to 15% of patients with HNSCC more commonly seen in young women with oral tongue cancer, elderly women with gingival/buccal cancer, or young to middle-aged men with oropharyngeal cancer positive for HPV.[39] In this population, the identification of new driving mutations may support the concept of nonlinear progression proposed recently in lifetime never smokers with lung adenocarcinoma harboring epidermal growth factor receptor (EGFR) mutations.[40]

## MOLECULAR ALTERATIONS IN PREMALIGNANCY AND INVASIVE SCC

Hallmarks of cancer as described by Hanahan et al. include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, reprogramming of energy metabolism, and evading the immune system. Genome instability, epigenetic changes, and tumor microenvironment are underlying and fostering these hallmarks.[41] Head and neck squamous premalignant lesions and HNSCC have been shown to harbor many of these hallmarks. With respect to chemoprevention, those molecular alterations are important as they may represent biomarkers to help identify patients at high risk to develop invasive SCC; they may also represent potential therapeutic targets for rationally based chemopreventive intervention. An approach has recently been proposed to drug development in the chemoprevention setting, called *reverse migration*, which is taking advantage of our experience in the treatment of advanced cancer to bring agents, biomarkers, and study designs into the prevention setting.[42]

### Genomic Changes

HNSCC have complex karyotypes, with the most common change being tetraploidization, and an average of 15 aberrations including deletions, translocations, isochromosomes, and less frequently amplifications.[43] Losses of genomic material are more frequent than gains and affect 3p, 9p, 21q, 5q, 13q, 18q, and 8p.[44] Chromosomal gains affect 3q, 8q, 9q, 20q, 7p, 11q13, and 5p. Tumor suppressor genes or oncogenes have been associated with some of those alterations.[34] Loss of 3p is the most frequent genomic loss and involves FHIT and RASSF1A. Other examples are losses of 9p21 (*CDKN2A*) and 17p13 (*TP53*). Specific sites of loss of heterozygocity (LOH) have been associated with a risk to develop HNSCC in patients with oral leukoplakias (OLs).[45] They are discussed in the Prevention and Risk Assessment section of this chapter. Gain in 3q is among the most frequent gain and includes *TP63*, an epithelial developmental gene, and *PIK3CA*. Other examples are gains in 7p (*EGFR*), 8q (*MYC* oncogene), and 11q13 (*CCND1*). Dysplasias and carcinoma *in situ* have fewer imbalances compared with OSCC (3.2 vs. 11.9).[46] An increasing trend of microsatellite instability, which reflects a reduced DNA repair capacity by mismatch repair proteins, has also been reported in hyperplasia (6%), dysplasia (15%), and HNSCC (30%).[47] The "Vogelgram" proposed by Califano et al. for HNSCC is the following[35] : The loss of 9p, leading to inactivation of *CDKN2A*, is a very early event and found in 70% of HNSCC[48]; it is frequently followed by the loss of 3p (*FHIT*, *RASSF1*) and 17p (*TP53*) in transition to dysplasia.[49]

Two important studies published recently provided new information on the mutational landscape of HNSCC using whole exome-sequencing technology.[4,5] Far fewer genes were found to be mutated per tumor in HPV-associated tumors (5/tumor) compared to HPV-negative ones (20/tumor), independent of smoking status. More mutations were identified in tumors from patients with a smoking history (22/tumor) as compared with those from never smokers (10/tumor). Among smokers, tumors with the highest fraction of G > T transversions showed a trend toward increase in overall mutation rates. Interestingly, several outliers were observed in tumors from never smokers with low fraction of G > T transversions but very high mutation rates, including mutations in some DNA repair genes, which may explain this paradox. Most frequent somatic mutations were found in *TP53*, *NOTCH1*, *CDKN2A*, *PIK3CA*, and *HRAS* were seen in 47% to 62%, 14% to 15%, 9% to 12%, 6% to 8%, and 4% to

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5% of patients, respectively. The most frequently mutated genes were often affected by copy number alterations. LOH of *NOTCH1* were observed in tumors with mutations in the same genes, and most *NOTCH1* mutations were predicting truncated mutations or deleting critical functional residues. These observations support its role as a tumor suppressor gene in HNSCC. Less frequent mutations included *PTEN*, *MLL2*, *TP63*, *EZH2*, *NOTCH3*, *NOTCH2*, *DICER1*, and *RB1*. A significant proportion of mutated genes are involved in epidermal development and squamous differentiation. Similar studies using next-generation sequencing technology remain to be done to characterize premalignant lesions.

The specific case of *TP53* tumor suppressor gene is interesting. The gene encodes a nuclear protein with transcription factor activity that is a necessary component of the G1-S transition checkpoint, thereby contributing to cell cycle control, DNA repair and synthesis, and genomic integrity.[50,51] The wild-type p53 protein can induce either programmed cell death or growth arrest at the G1 phase of the cell cycle. *TP53* inactivation is nearly universal in HNSCC, although the mechanism of loss of function depends on the etiology: inactivating *TP53* mutations are identified in 78% of the HPV-negative tumors that are usually associated with an alcohol and smoking history; in the setting of HPV infection, *TP53* gene is typically none mutated but p53 is inactivated by binding to the E6 viral protein.[5,52,53] *TP53* mutation and binding to other proteins can lead to overexpression of p53 protein that is reported in 19% of adjacent normal mucosa, 29% of hyperplastic lesions, 46% of dysplastic lesions, and 58% of HNSCC. Increase in p53 expression has been associated with increased genomic instability.[54] The timing of p53 inactivation remains controversial, with some reports demonstrating aberrant expression in premalignant lesions, but the majority suggesting mutation only late in tumor evolution.[35,55–57]

## Epigenomic Changes

The inactivation of individual tumor suppressor genes such as *CDKN2A*, *CDH1*, *DAPK1*, *RASSF1*, *RAR*-β, *DCC*, *MGMT*, *NDRG2*, and *DLEC1* by promoter DNA methylation has been reported in HNSCC.[58–61] Using high-throughput DNA promoter methylation profiles, it has been shown that the overall pattern of epigenetic alteration can significantly distinguish tumor from normal head and neck epithelial tissues more effectively than specific gene methylation events. Tobacco smoking and alcohol exposures are associated with specific DNA methylation profiles.[58] Another important feature of malignant tumors is global hypomethylation, which is measured by the degree of methylation of repetitive sequences across the genome such as *LINE1*, and has been associated with genome instability. Poage et al. found that global methylation was different according to tumor site and *LINE1* methylation was associated with HPV16 E6 serology. The authors identified a distinct subset of CpG loci with significant hypermethylation associated with *LINE1* hypomethylation.[62] Few studies have looked at methylation levels of individual genes in preneoplastic lesion. *RAR*-β– silencing by methylation has been shown to be an early event in HNSCC carcinogenesis; 66% of the HNSCC showed hypermethylation of *RAR*-β versus 53% of OLs and 27% in adjacent normal tissue.[63] *CDKN2A* methylation was never detected in normal individuals, but in 5% of leukoplakia with hyperplasia, 18% of leukoplakia with mild dysplasia, 10% of leukoplakia with moderate dysplasia, 22% of leukoplakia with moderate dysplasia, and in 50% or more of OSCC.[64] In patients with betel-quid chewing in Sri Lanka, a high frequency of hypermethylation of p14, p15, and p16 was detected in precancerous lesions, although no hypermethylation was found in normal epithelium.[65]

## EGFR, PI3K/AKT/mTOR, and MET Pathways

All three pathways represent potential targets for chemoprevention, although only EGFR pathway has been studied in premalignant lesions. EGFR activation by its ligand transforming growth factor–alpha (TGF$\alpha$), activates STAT3 which increases proliferation, suppresses apoptosis, and decrease differentiation. EGFR and TGF$\alpha$ are upregulated in HNSCC, constituting an autocrine activation loop.[66–73] EGFRvIII, a variant detected in 42% of HNSCC, is associated with increased proliferation *in vitro* and *in vivo* and with decreased apoptosis in response to cisplatin and cetuximab.[74] High EGFR expression and high EGFR gene copy number have been associated with poor survival in patients with HNSCC.[56,68,75] Cetuximab, an anti-EGFR antibody, is now approved in the treatment of locally or regionally advanced HNSCC or as a single agent for the treatment of patients with recurrent or metastatic disease for whom prior platinum-based therapy has failed.[76,77] EGFR is overexpressed in malignant, premalignant, and normal-appearing tissues from HNSCC patients. EGFR expression increases progressively with increasing degree of dysplasia and is markedly elevated in more than 90% HNSCC.[67,68] We have reported that increased EGFR gene copy number in OLs was frequent and associated with an increased risk of developing OSCC.[78] Erlotinib has been shown to decrease the incidence of OSCC in a chemically induced mouse model.[79] The use of EGFR tyrosine kinase inhibitor (TKI) in the chemoprevention setting is discussed below.

PI3K/AKT/mTOR pathway has been shown to be activated in approximately 50% of HNSCC.[80–82] Mechanisms of this activation include activation of upstream tyrosine kinase receptors (EGFR, IGF-1R…), frequent amplification of *PIK3CA* (3q26) that is associated with poor prognosis, *PI3KCA* activating mutations that have been reported in up to 10% of the cases, and *PTEN* downregulation in rare cases.

MET pathway activation has been recently reported in HNSCC. Knowles et al. have shown that 80% of HNSCC express MET, its ligand HGF, or both.[83] Seiwert et al. have shown that 84% of HNSCC samples showed MET overexpression and 45% HGF overexpression.[84] MET gene copy number was increased in a significant proportion of HNSCC cell lines and tumors. The rate of MET tyrosine kinase domain mutations was 3% and the rate of non-TK domain mutations was 9%. MET inhibition was associated with decreased proliferation, migration and motility, and angiogenesis and with a greater-than-additive inhibition of cell growth in combination with cisplatin or erlotinib. The functional role of TK domain mutations in HNSCC remains to be determined.

## Cyclooxygenase-2

At least two isoenzymes, COX1 and COX2, have been described. COX1 is constitutively expressed in most tissues, while COX2 is inducible. COX2 has been shown to be frequently overexpressed in oral dysplasias and HNSCC.[85–90] COX catalyzes the synthesis of prostaglandins from arachidonic acid. Levels of prostaglandin E2 (PGE2) are elevated in HNSCC as well and correlate with poor survival.[91] COX2 inhibitors have shown to decrease proliferation and induce apoptosis in both *in vitro* and *in vivo*.[92] *In vitro*, PGE2 causes dose-dependent stimulation of cellular growth of the nontumorigenic MSK-Leuk1 oral epithelial cell line, thus providing further evidence for a possible role COX and prostaglandins in oral carcinogenesis.[93] Using immortalized oral epithelial cells and HNSCC cell lines, Abrahao et al. have shown that COX2 overexpression in cancer and inflammatory cells induce PGE2 production in the tumor microenvironment that promotes HNSCC cell growth in an autocrine and paracrine fashion.[94] COX2 has been shown to be upregulated by Snails that

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impedes terminal differentiation, invasion, and inflammation in oral keratinocytes.[95] COX inhibition has been shown to prevent premalignant lesions in preclinical and clinical studies, especially as it pertains to colonic polyps.[96] In murine models of oral carcinogenesis, COX2 inhibitors were found to have chemopreventive effects.[97–99]

## Transforming Growth Factor–Beta Signaling Pathway

Transforming growth factor–beta (TGF$\beta$) is a key regulator of epithelial homeostasis, immune function, and angiogenesis. TGF$\beta$ signaling dysregulation is common in HNSCC.[34] Defective TGF$\beta$ signaling in epithelial cells increases proliferation reduces apoptosis and increases genomic instability. The compensatory increase in TGF$\beta$ production by tumor epithelial cells further promotes tumor growth and metastases by increasing angiogenesis and inflammation in tumor stromal cells.[100] RAS mutations are rare in HNSCC in the Western countries, although its overexpression is common. Lu et al. have shown that combining TGF$\beta$RII loss with KRAS or HRAS overexpression in a murine model resulted in HNSCC tumor formation. Neither alteration alone resulted in a malignant phenotype.[101]

## Retinoid Receptors

Retinoids are naturally occurring and synthetic vitamin A (retinol) metabolites and analogues. Retinoids are involved in many physiologic processes including cell differentiation that they promote, proliferation, and apoptosis that they decrease. Two families of retinoid receptors have been characterized: RAR and RXR. RAR is endogenously activated by all-trans-retinoic acid and 9-cis-retinoic acid; RXR is endogenously activated by 9-cis retinoic acid only. 13-cis-retinoic acid (13cRA) is readily converted to all-trans-retinoic acid, which in turn primarily regulates gene transcription through RAR. The "retinoid axis" also includes repressors and coactivators that form interacting complexes that ultimately define regulation of genes and cellular function.[102] Cattle that are vitamin A deficient develop tumors of the aerodigestive tract and lung at a relatively high frequency.[103] Loss of nuclear RAR$\beta$ is an early event observed in premalignant dysplastic lesions.[104] This has triggered evaluation of retinoids in chemoprevention trial that is discussed below.

## Cell Cycle

Cell cycle regulation in HNSCC is altered through various mechanisms that are not exclusive to each other. One includes activation of *CCND1* and *MYC* oncogene that are often amplified and/or overexpressed.[105] *MYC* overexpression has been associated with poor survival of patients with HNSCC.[106] Other mechanisms involve inactivation of *TP53* and inactivation of the p16/p14 ARF locus, both being frequent in HNSCC.[107] Both the inactivation of *CDKN2A* and overexpression of *CCND1* increases CDK4/6 activity and RB phosphorylation that in turn promotes cell proliferation.[108,109] Soni et al. studied the expression of *CDKN2A*, *CCND1*, and *pRB* using immunohistochemistry in normal-appearing oral mucosa, hyperplastic, and dysplastic lesions and in HNSCC.[110] Alterations in all three genes were demonstrated in 11% hyperplastic and dysplastic lesions and in 18% of HNSCC. Loss of *CDKN2A* was the earliest event, loss of *pRB* was associated with the transition hyperplasia to dysplasia, and *CCND1* or *p53* overexpression was associated with the transition to HNSCC. Finally, a *CCND1* polymorphism, thought to alter cyclin D1 expression, has been associated with HNSCC risk, tumor grade, tumor recurrence, and survival.[111–115]

## Telomerase

Reactivation of telomerase is a common feature of malignant tumors. Using a telomerase rapid amplification protocol (TRAP) assay, Patel et al. identified telomerase activation in 78% to 82% of HNSCC, 55% to 85% of premalignant lesions, and 39% to 53% of adjacent normal-appearing tissue.[116,117] A higher telomere length was associated with a poor survival.[117] Thus, reactivation of telomerase appears to be an early molecular alteration. Interestingly, telomerase activity in peripheral blood mononuclear cells was correlated with higher T and N stages and was an independent predictor of survival.[118]

## Angiogenesis

Angiogenesis contribution to HNSCC progression has been studied. Angiogenesis is required for the tumor growth and the metastatic spread. The majority of HNSCC overexpress the vascular endothelial growth factor (VEGF) or the VEGF-2 and VEGF-3 receptors.[119,120] A meta-analysis involving 1,002 patients showed that VEGF tumor overexpression evaluated by immunohistochemistry was associated with a decreased survival.[121] The role of angiogenesis in progression of premalignant lesions has been recently outlined using a chemically induced mouse model and will be discussed below.[122]

## HPV-Related HNSCC

HPV-related HNSCC usually arise in the oropharynx (tonsillar crypts), they are infiltrated by lymphocytes, do not undergo significant keratinization, have basaloid morphology, affect younger individuals, and are usually stage Tx or T1–2 with early and large lymph node involvement with better outcome compared to HPV-negative HNSCC.[18] After HPV integrates its DNA within the host nucleus, it overexpresses oncoproteins E6 and E7. E6 induces *p53* degradation, and E7 binds and inactivates *RB*.[123] HPV-related HNSCC have also been shown to have a unique transcriptional profile for both mRNA and miRNAs, as well as a unique DNA methylation profile.[62,124,125] The genomic profile is also different as almost all HPV-associated tumors express wild-type *TP53* and *CDKN2A* and have a lower rate of mutations as opposed to HPV-negative HNSCC.[4,5] This would suggest that HPV infection is an early event in head and neck squamous cell carcinogenesis. With regard to the prevention setting, they are not associated with dysplasia of surface epithelium which makes early detection challenging.[126] HPV positivity in normal adjacent tissues is considered a rare occurrence. In a recent study of 200 normal tonsils, the prevalence of HPV16 and 18 was found to be zero. Although there appears to be some link between HPV and OL, evidence supporting a causal role of HPV in oral squamous cell tumorigenesis is not convincing. The exact anatomical site is not always reported with the risk to include both oral cavity and oropharynx SCCs. The detection of HPV virus does not necessarily mean HPV integration in the host genome and E6/E7 oncoproteins activation. HPV serotypes are not available in all the studies and not all HPVs are oncogenic. Finally, the magnitude of association consistent with an infectious etiology is only achieved for SCC of the oropharynx.[127–131]

# PRECLINICAL MODELS OF HEAD AND NECK SQUAMOUS TUMORIGENESIS

Few *in vitro* models are available to study head and neck tumorigenesis.[132] MSKLeuk1 and MSKLeuk1s are immortal and nontumorigenic and established from a nonsmoking patient with

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moderately dysplastic leukoplakia of the oral cavity adjacent to a SCC of the tongue.[133] Normal oral mucosa-9 (NOM9) cell lines were established from histologically normal buccal mucosa of a patient with tongue cancer. NOM9/TK was immortalized by overexpressing the telomerase (T) and CDK4 (K). NOM9/TKp53 was made from NOM9/TK using shRNA against *p53*. They are nontumorigenic human oral keratinocytes (HOKs).[134] HOK-16A and HOK-16B are primary HOKs transformed by transfection with recombinant HPV-16 DNA; they are immortal but not tumorigenic.[135] HaCaT is a human keratinocyte cell line. It was created from histologically normal adult body skin obtained from the distant periphery of a melanoma and is spontaneously transformed, immortalized, but is not tumorigenic and noninvasive *in vivo*.[136,137]

Premalignant cell lines being nontumorigenic, subcutaneous xenograft and orthotopic models do not allow modeling of the premalignant process. Carcinogen-induced and transgenic murine models have been developed for that purpose. Several transgenic mouse models of OSCC have been described. Caulin et al. created a transgenic mouse with inducible $KRAS^{G12D}$ activated oncogene driven by either keratin (K) 5 (expressed in the basal epithelium of the tongue and forestomach) or K14 (expressed mainly in the basal layer of the oral mucosa and tongue) promoter.[138] They observed formation of squamous papilloma of the oral cavity and subsequently found that activation of the endogenous *p53* gain-of-function mutation $TP53^{R172H}$, but not the deletion of *TP53*, cooperates with oncogenic *KRAS* and promotes progression to invasive carcinoma in few cases.[139] Using a similar approach, Vitale-Cross et al. reported various degrees of dysplasia, as well as invasive SCC in the skin, the oral mucosa and the tongue, the esophagus, the forestomach, and the uterine cervix.[140] Raimondi et al. crossed an inducible $KRAS^{G12D}$ oncogene-driven model with *TP53* conditional knockout mice, resulting in OSCC within 2 weeks.[141] Moral et al. created a mice displaying constitutive Akt activity under the control of K14 promoter (myrAkt).[142] The myrAkt mice developed oral premalignant lesions, few of them progressing into invasive SCC. When myrAkt were crossed with mice bearing *TP53* loss, the mouse developed OSCC with metastatic spreading to regional lymph nodes, activation of *NFKB* and *STAT3*, and decreased TGF$\beta$IIR expression and increased number of putative tumor stem cells.

Several methods have been used to induce OSCC in animals using carcinogenic agents. A technique developed by Salley et al. used a polycyclic hydrocarbon 9,10 dimethy-1,2 benzanthracene (DMBA) to paint the buccal surface of the cheek pouch of hamsters.[143] Lin et al. refined the technique by promotional painting with arecaidine, allowing increasing tumor incidence up to 100%.[144] Others have utilized painting with 4-nitroquinoline 1-oxide (4NQO) or 12-O-tetradecanoylphorbol-13-acetate after initial exposure to DMBA.[145] Tumors produced this way have been shown to overexpress EGFR, TGF$\alpha$, RAS, and p53 protein,[146–149] and mutations of *TP53* and *HRAS* have been reported.[122]

The 4NQO model utilizes the chronic administration of 4NQO to rodents. 4NQO is added to the drinking water of rodents and induces SCC of the palate, the tongue, the esophagus, and the stomach. The development of fully malignant SCC is preceded by increasing grades of hyperplasia and dysplasias that mimics the development of oral cancer in human.[150] Disadvantages are that the reliable development of tumors requires the administration of 4NQO over 2 to 3 months, and the detection of premalignant lesions or early SCC within the oral cavity can be difficult. Hasina et al. recently characterized the optimal dosage and timing of 4NQO treatment and established a timeline for the reproducible development of lesions showing hyperkeratosis, dysplasia, and HNSCC.[122] Interestingly, they observed increased microvessel density and VEGF expression in hyperkeratotic lesions, providing evidence that the initiation of the angiogenic phenotype occurred before the dysplasia. Inhibition of angiogenesis significantly decreased the overall incidence of OSCC.[122] Using the same model, they reported that ZD6474, a dual inhibitor of EGFR and VEGFR2, reduced the incidence of OSCC.[151] Interestingly, OSCC from ZD6474-treated mice exhibited features of epithelial-to-mesenchymal transition suggesting that this could be a mechanism of resistance to the drug. Erlotinib, an EGFR TKI, has also been shown to decrease the incidence of dysplasia and OSCC compared to the control.[79] Bexarotene failed to show any preventive effect on the incidence of OSCC induced by 4NQO.[152]

## PREVENTION AND RISK ASSESSMENT

Primary prevention of HNSCC refers to the prevention of cancer by avoiding known carcinogens.[153,154] Secondary cancer prevention refers to the treatment of preneoplastic lesions to halt progression to invasive cancer. Tertiary cancer prevention is preventing second primary cancers in patients have been cured with surgery and/or radiation therapy. This is particularly important for patients treated with HNSCC due to the "field cancerization."[27] Primary, secondary, and tertiary prevention approaches should all be considered to decrease the incidence of HNSCC. Four groups of individuals or patients with increasing risks of developing HNSCC can be defined: individuals with tobacco and/or smoking history and normal appearing mucosa, patients with a potentially malignant lesion, and patients that have been treated for HNSCC and at risk for recurrent disease and second primary tumor. In each case, individualized cancer risk assessment is a key element.

### Tobacco Smoking and Alcohol Drinking Cessation

Quitting tobacco smoking and alcohol reduces the risk of developing HNSCC. The International Head and Neck Cancer Epidemiology (INHANCE) consortium reported that a benefit for smoking cessation was realized in a short period of time with a significant 30% lower risk for HNSCC observed after stopping smoking for >1 to 4 years. The risk of HNSCC dropped to that of never smokers after having quit for 20 or more years. The cessation of alcohol drinking was associated with a reversal of HNSCC risk after quitting for 20 or more years.[155]

### Early Diagnosis

Diagnostic delay is a recognized challenge in the population of patients diagnosed with HNSCC, especially in the case of OSCC, and is often categorized as patient delay, accessibility to health care system, and health care provider delay.[156] A recent meta-analysis has shown that diagnostic delay is a risk factor for tumor growth.[157] Diagnostic delays have also been related to survival in some recent studies.[158] Therefore, public awareness of early symptoms as well as health care providers' education should allow early detection, increase cure rates, and decrease treatment-related morbidity.[156]

Recommendations regarding screening for OSCC have been recently published.[159] Screening by means of examination can detect potentially malignant and malignant lesions.[160] However, clinical features alone cannot reliably distinguish between malignant and benign lesions and the clinician cannot accurately predict the risk of malignant transformation on the basis of routine biopsy.[161–163] Only one randomized clinical trial has evaluated the effect of screening by means of visual and tactile examination on oral cancer mortality in India.[164] Between 1996 and 2004, of the 96,517 eligible participants in

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the intervention group, 87,655 (91%) were screened at least once, 53,312 (55%) twice, and 29,102 (30%) three times. Of the 5,145 individuals who screened positive, 3,218 (63%) only complied with referral. In the control group, 95,356 eligible participants received standard care. Mortality rate ratio was significantly decreased only in tobacco or alcohol users.[159] The applicability of these findings in Western countries remains to be demonstrated. The only recommendation is the need for the clinicians to remain alert for signs of potential malignancy when performing a routine visual and tactile examination in dental patients, especially when they have a history of smoking and heavy alcohol use.[159] Another recommendation is to develop screening tests in high-risk population in countries with low prevalence of potentially malignant and malignant oral lesions as the United States.

## Posttreatment Follow-up

Regular posttreatment follow-up is essential in patients after potentially curative treatment of HNSCC. The evidence documenting a survival benefit in this population is poor. The recommendations from the National Comprehensive Cancer Network (http://www.nccn.org) emphasize early detection of a second primary cancer in the head and neck or lung and detection and management of treatment-related complications. A major goal should also include smoking and alcohol cessation. In patients with a smoking history of ≥20 pack years, low-dose helical CT scanning of the lung can be discussed for screening of a second primary tumor in the lung.

## Biomarkers of Risk for Head and Neck Cancer

Molecular epidemiologic studies have identified genetic polymorphisms associated with the risk of HNSCC. Most of studied genes are related to single nucleotide polymorphisms (SNPs) in metabolic genes, cell cycle control, and alcohol metabolism.[165] Among these, significant associations were reported for glutathione S-transferase Mu 1 (*GSTM1*), glutathione S-transferase theta-1 (*GSTT1*), human microsomal epoxide hydrolase 1 (*EPHX1*) genes, *TP53*, aldehyde dehydrogenase 2 (*ALDH2*), and alcohol dehydrogenase variant genes (*ADH1B, ADH7*, and *ADH1C*). Recent genome-wide association studies (GWAS) have identified variants in the nicotinic acetylcholine receptor associated with nicotine dependence and lung cancer risk.[166–168] Interestingly, one variant was shown to be associated with the risk of HNSCC and esophagus cancer in women but not in men.[169] This finding was replicated in the INHANCE consortium cohorts.[170] A particular situation is Fanconi anemia that represents a well-identified population at higher risk of developing HNSCC as well as myelodysplastic syndrome and acute myelocytic leukemia.[171–173] In those patients, HNSCC arise at an earlier age and in the absence of other risk factors (tobacco, alcohol).

Wu X et al. recently genotyped 150 early-stage HNSCC patients with and 300 matched patients without second primary tumor/recurrence from a prospectively conducted randomized trial and assessed the association of these SNPs with risk of SPT/recurrence.[174] Using a custom chip containing a comprehensive panel of 9,645 SNPs representing 998 cancer-related genes, they identified six chromosomal SNPs and seven mitochondrial SNPs significantly associated with risk of second primary tumor/recurrence after adjustment for multiple comparisons. A strong gene-dosage effect was observed when these SNPs were combined. This study underscores the importance of incorporating germline genetic variation data with clinical and risk factor data in constructing prediction models for clinical outcomes but will require further validation in independent cohort of patients.

## Biomarkers of Risk for Oral Cancer

The term *potentially malignant disorder* (PMD) was recommended to refer to precancer as it conveys that not all disorders may transform into cancer.[37,38,161,175] PMDs include OL, erythroplakia, palatal lesions in reverse smokers, oral submucous fibrosis, actinic keratosis, lichen planus, and other rare diseases.

Most of the studies developing biomarkers of risk to develop HNSCC have included patients with OL, the most frequent PMD.[37] Clinical factors associated with malignant transformation of OL are female gender, long duration of leukoplakia and older patients, never smokers, size >200 $mm^2$, nonhomogeneous type, lateral and ventral tongue, floor of mouth, and retromolar/soft palate sites.[161] However, the presence of dysplasia is often the criterion that influences clinical management of OLs. The challenges are that OL without dysplasia may still progress to cancer, that a high inter- and intra-observer discordance rate has been reported in the evaluation of dysplasia, that the degree of dysplasia has not always been associated with increased cancer risk, and that OL may be reversible even when dysplasia is identified, irrespective of environmental factors.[38] Three classifications have been proposed to describe the degree of dysplasia.[176–178] To increase the likelihood of agreement between pathologists, a two-class classification has been recently proposed (no/questionable/mild: low-risk and moderate/severe: high-risk) that will need to be evaluated prospectively.[38] Liu et al. studied the usefulness of the binary system of grading dysplasia by reviewing retrospectively 218 Chinese cases of OL with a median follow-up period of 5.3 years.[179] High-risk OL had a hazard ratio of 4.6 (95% CI, 2.36–8.84) to develop OSCC and was an independent risk factor of transformation. The risk was particularly high during the first 2 to 3 years of follow-up.

The natural history of OL remains poorly understood.[161] OL can remain many years without changing, can regress spontaneously or after cessation of tobacco or alcohol, and can transform to invasive SCC. The reported rate of malignant transformation has been low in community-based studies in developing countries (0.06% per year) and higher in observational studies in Western countries involving patients followed in hospital-based academic centers (1%–5% per year). Majority of the studies in the United States found a rate of malignant transformation between 17% and 24% during periods of up to 30 years.[180–182]

No consensus is available for the treatment of OL.[175] Removal of the lesion remains the predominant method of treatment, although no randomized controlled trials have been done to test whether the excision versus observation decreases the risk of recurrence or the risk of malignant transformation.[183] Several studies have shown tobacco cessation was associated with decreased incidence and resolution of OLs.[184–186] Although it is tempting to believe that alcohol and/or tobacco cessation is associated with a decreased risk of malignant transformation, no evidence is available. Patient follow-up strategies are discussed elsewhere but have not been prospectively evaluated.[175] A clinician survey has indicated follow-up regimens of 6 monthly for lesions without dysplasia, 3 monthly for mild/moderate dysplasia, and monthly for severe dysplasia/carcinoma *in situ*.[183,187] The degree of dysplasia and the anatomical site were the two factors influencing the follow-up schema.

Inconsistencies in the value of clinical and pathological factors to predict the risk of malignant transformation of OL led to the development of biomarkers. Challenges are that OL has a low prevalence at least in Western countries, there are often not biopsied, and the rate of malignant transformation per year is generally low, which requires long follow-up periods in both retrospective and prospective cohorts to be able to drive any conclusion.[187] Chemoprevention studies with retinoids allowed unique prospective collections of biospecimens that led to biomarker development.[188]

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The most robust and validated one are LOH discovered by Mao et al. in 1996.[45] OL harboring LOH at 3p14 and/or 9p21 were associated with a risk of invasive cancer of 37%, compared with only 6% in lesions without LOH at 3p14 and/or 9p21. These findings were subsequently validated by larger retrospective studies from two independent groups.[189–191] OLs at former cancer sites with LOH at 3p and/or 9p were associated with a higher risk of development of invasive cancer (72% at 5 years) compared with leukoplakias without LOH (6% at 5 years).[192] The presence of LOH at the histologically negative margins of resection in patients with surgically treated HNSCC was a marker of risk of recurrence.[193] Lee et al. have shown that the most predictive factors of risk of cancer are the degree of dysplasia, previous cancer history, and three of the five biomarkers assessed: chromosomal polysomy, p53 protein expression, and LOH at 3p or 9p. In a multicovariate analysis, histology and the combined biomarker score of polysomy, p53, and LOH were the strongest predictors for cancer development.[182] A recent study has prospectively validated LOH profiles as risk predictors of progression in a prospective cohort of 296 patients with primary mild/moderate oral dysplasia. Authors used progression as the event outcome, including progression to severe dysplasia ($N = 17$), carcinoma *in situ* ($N = 2$), and invasive cancer ($N = 22$). High-risk lesions (3p and/or 9p LOH) had a 22.6-fold increase in risk compared with low-risk lesions (3p and/or 9p retention). Addition of another two markers (loci on 4q/17p) further improved risk prediction, with 5-year progression rates of 3.1%, 16.3%, and 63.1% for the low-, intermediate-, and high-risk lesions, respectively.[194]

In a prospective trial using 13-cis retinoic acid, IFN-alpha, and alpha-tocopherol for 12 months for patients with OL, Mao et al. reported that among patients who exhibited LOH at chromosome 9p21 in pretreatment biopsy specimens and who had completed at least 5 months of therapy, the genetic loss persisted in almost all of them, including patients who exhibited complete histologic responses.[195] In the same cohort, authors documented the reappearance of the wild-type *TP53* gene in posttreatment biopsies in patients whose pretreatment tissue samples expressed mutant *TP53*, as well as *TP53* mutations emergence during therapy in patients who did not achieve any clinical response.[196] Finally, *CCND1* overexpression was found in 50% and decreased under treatment in almost half of the cases. *CCND1* overexpression was associated with histological progression and cancer development.[197] A specific *CCND1* genotype was associated with a diminished treatment-induced decreased expression of cyclin D1, a decreased likelihood of response to the intervention, and an increased rate of progression to cancer.[197,198]

*TP63* has been involved in the stem cell biology of stratified epithelium, is a marker of SCC commonly used in clinical practice; deltaNp63 isoform has oncogenic properties.[199] Podoplanin was shown to promote invasion in different cancer types and was shown to be associated with poor prognosis in OSCC.[200] We reported that overexpression of podoplanin and deltaNp63 were prevalent in OL and associated with a higher risk to develop OSCC[199,201] using the largest prospective chemoprevention trial ($N = 162$ patients, median follow-up 7.5 years, transformation rate 24%) comparing 13-cis retinoic acid, beta-carotene plus retinyl palmitate, and retinyl palmitate in patients with OL.[201,202] We have also reported an *EGFR* increased gene copy number in 41% of OLs and have shown a strong association with the risk of developing OSCC in patients with OLs overexpressing EGFR.[78]

In the same cohort of patients, we have generated gene expression profiles of 86 OLs, including 35 from patients who developed OSCC.[33] We reported a strong association between gene expression and OSCC risk; with an 11% false discovery rate, more than 2,000 genes were associated with a high or low risk to develop OSCC ($p < 0.01$). Using multiple independent and publicly available data sets of HNSCC and normal mucosa with available gene expression profiles, we have shown that the vast majority of the genes associated with a high or low risk to develop OSCC were upregulated or downregulated in HNSCC, respectively. We have shown that a 25-gene signature improved our prediction of OSCC development over clinical and pathological biomarkers, including the degree of dysplasia and the expression of deltaNp63 and podoplanin.

Other biomarkers have been associated with the development of OSCC in patients with OL[187]: survivin, *MMP9*, activated Chk2, *CDKN2A* promoter methylation, mcm2, geminin/mcm2 and geminin/Ki67 ratios, SIBLING family of proteins, allelic index >2, DNA content, LOH at 11q, and DNA ploidy. Others have failed to show any value: p53 protein expression, cathepsin L mRNA, MMP1/2 mRNA, p73, LOH at 8p, cornulin, keratin 4 and 13, osteopontin, and promoter methylation of cyclin A1, cytoglobin, and *MGMT*.

Except for LOH, none of those biomarkers have been validated in multiple cohorts of patients. Ideally, this will have to be done prospectively. A complete characterization of genomic and epigenomic changes in the premalignant and subsequent OSCC from the same patient and their functional consequences on gene expression profiles and pathway activation would provide a unique opportunity to identify early key molecular events.

## Biomarkers of Risk for Larynx Cancer

Between 2 and 10 laryngeal dysplasia are reported per 100,000 of the population.[203] The main treatment modality is surgical excision. No evidence is available that it significantly affects the transformation rate.[204,205] A recent review of the literature has reported an overall malignant transformation rate of 14%.[204] The rate is 11% for mild/moderate dysplasia and 30% for severe dysplasia and carcinoma *in situ* with a mean time to transformation of 5.8 years. Some biomarkers have been evaluated for their ability to predict malignant transformation.[205,206] *p53* expression failed to show any predictive ability. Other markers studied are Ki67, cyclin D1 expression, cortactin, cyclin E, cyclin A, *CDC25A*, *CDC25B*, mdm2, bcl-2, p27, p21, and ST3. RRs ranged from 0.60 (95% CI, 0.10–3.75) for mdm2 to 85 (95% CI, 5.30–1,350) for cortactin with wide confidence intervals to the small number of patients in those studies. There is currently not enough evidence for using those markers to predict the transformation of dysplastic lesions.

## The Specific Case of HPV-Related HNSCC

A possible reason for the increasing incidence of HPV-related HNSCC has been temporal changes over the last decades in sexual behaviors, including younger age of sexual debut, increased number of lifetime partners, and oral sex.[207] No premalignant lesion has been reported in HPV-related oropharynx SCC.[18] Prevention of HPV-related cancers (cervical, vaginal, vulvar and anal cancers, as well as genital warts in both genders) with HPV vaccines is recommended.[208,209] Clinical trials for HPV vaccines have now followed women out to 5 to 8 years. Data show that the clinical protection remains high with time.[210] Such trials will not be able to assess directly whether HPV vaccines impacts HNSCC which are typically affecting individuals in their 50s or 60s. Longitudinal studies comparing rates of HNSCC before and after the introduction of HPV vaccines may answer this question. However, considering that the increased incidence of HPV-related HNSCC is related to changes in sexual behaviors and hoping that HPV vaccines confer long duration of clinical efficacy, it is reasonable to expect a decrease in the incidence of those tumors in the future.[207]

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## CHEMOPREVENTION CLINICAL TRIALS

In this section, we will present the rationale and findings from the main chemoprevention clinical trials for HNSCC conducted to date. It should be noted that none of these studies resulted in a strategy that can be considered standard of care. However, advances in cancer risk assessment were achieved from correlative studies of clinical specimens obtained through these efforts. The results have paved the way for the development of a new generation of clinical trials, briefly discussed herein as well.

### Retinoids

Clinical trials with retinoids to prevent HNSCC focused on individuals with oral premalignant lesions (i.e., secondary prevention) or with a history or curatively treated head and neck malignancies (i.e., tertiary prevention).

***Retinoids for Oral Premalignant Lesions.*** Most of the studies using retinoids for secondary prevention focused on OL clinical and/or histological response as the primary endpoint. This approach bears several criticisms, including the fact that clinical response only marginally correlates with long-term oral cancer-free survival,[202] and the fact that molecular abnormalities in the oral mucosa may still persist despite disappearance of the lesion following the chemoprevention intervention.[195] Hence, the results of the studies must be interpreted in light of these limitations.

The first chemoprevention trials of systemic and topical vitamin A for oral premalignant lesions were conducted in the late 1950s and showed some evidence of efficacy.[211,212] In 1986, Hong et al. reported the first double-blind, placebo-controlled trial of high-dose 13cRA (1–2 mg/kg/day for 3 months) in this setting. The clinical response rate was 67% in the retinoid arm and 10% in the placebo arm ($p = 0.00002$). The rate of histologic improvement was also significantly better in the retinoid arm (54% vs. 10%, $p = 0.01$). However, toxic effects were frequent and severe, with two-thirds of the retinoid-treated patients experiencing mucocutaneous adverse events and hypertriglyceridemia; dose reductions were required in approximately 50% of patients treated with 2 mg/kg/day. Moreover, remission was short lived, and more than half of the patients experienced a relapse within 3 months of treatment cessation.[213] Stich et al. also demonstrated, in the 1980s, that 6-month treatment with vitamin A (200,000 IU/week) led to a higher complete response rate than placebo (57% vs. 3%) in tobacco/betel nut chewers.[214] Similar results were also seen in a second study of placebo versus beta-carotene versus beta-carotene plus vitamin A in individuals with a history of exposure to smokeless tobacco. The 6-month leukoplakia-remission rates were 3%, 15%, and 28%, respectively.[215] A later study also demonstrated that treatment with vitamin A or beta-carotene for 12 months produced higher response rates compared to placebo (52%, 33%, and 10%, respectively). However, as had previously been observed by Hong et al., 50% to 66% of the patients experienced a relapse after treatment discontinuation.[216]

To address the issues of toxicity with high-dose 13-cis retinoic acid and the short duration of response following the brief 3-months treatment period, Lippman et al. conducted a phase IIb maintenance trial following induction retinoid therapy.[217] In this study, patients with oral premalignant lesions were treated with 13-cis retinoic acid 1.5 mg/kg/day for 3 months (induction phase), followed by either low-dose 13-cis retinoic acid (0.5 mg/kg/day) or beta-carotene (30 mg/kg/day) for 9 months in individuals not experiencing progression of the lesion (maintenance phase). Consistent with the previous trials, 55% of the patients had a clinical response to the induction therapy (and reversal of dysplasia occurred in 43% of the responders). After the maintenance phase, 53 patients were evaluable for the primary endpoint. Further lesion response was observed in 33% of the patients receiving 13cRA and in 10% of the beta-carotene-treated patients. Severity of adverse events was lower during the maintenance phase, with a more favorable toxicity profile in the beta-carotene arm. The study underscored the importance of a longer retinoid treatment period to maintain clinical responses. However, on long-term follow-up, the incidence of *in situ* or invasive carcinoma was not different between the 13-cis retinoic acid and beta-carotene groups (23% vs. 27%, respectively).[180]

The follow-up trial to the phase IIb study by Lippman et al. was designed to prolong even more the duration of treatment with 13-cis retinoic acid. The doses were once again reduced to ameliorate the toxicity profile. This study's original treatment arms consisted of 13-cis retinoic acid (0.5 mg/kg/day for 1 year followed by 0.25 mg/kg/day orally for 2 years) versus vitamin A (retinyl palmitate 25,000 IU/day) plus beta-carotene (50 mg/day) for 3 years. The initial statistical design aimed at determining noninferiority of vitamin A plus beta-carotene compared to 13-cis retinoic acid in terms of clinical response.[202] However, during the conduct of the study, data became available as regard to the increased lung cancer incidence and mortality associated with beta-carotene in other ongoing chemoprevention studies.[218,219] As a result, the experimental arm was modified to vitamin A single agent. The final analysis of the trial demonstrated that patients receiving 13cRA more frequently experienced grade 2 or higher toxicities. Vitamin A single agent was associated with a lower 3-month clinical response rate (20%) compared to beta-carotene plus vitamin A (32.5%) and 13cRA (48.1%). Noninferiority could not be determined between the control and experimental arm(s). More importantly, the 5-year oral cancer-free survival was similar across the treatment groups (78%–84%), and clinical response at 3 months was only marginally correlated with long-term oral cancer-free survival. This was one of the largest and longest term studies in oral premalignant lesions ever conducted and demonstrated that 13-cis retinoic acid is not well tolerated even at lower doses and that a treatment that can prevent oral invasive cancer long-term is yet to be developed. The study also questions the use of clinical response as a valid endpoint in trials of oral premalignant lesions.

Synthetic retinoids have also been studied for secondary HNSCC prevention. Fenretinide is the agent that has been more extensively evaluated in this setting. Potential advantages of fenretinide over 13cRA include a more favorable toxicity profile and enhanced activity due to both RAR/RXR-receptor dependent (i.e., cell differentiation at lower doses) and independent (i.e., cell apoptosis at higher doses) effects.[220–223] In a 4-month placebo-controlled study, Han et al. observed significant activity of fenretinide in reversing oral premalignant lesions.[224] In a randomized study including 170 patients with resected oral premalignant lesions, Chiesa et al. demonstrated that, compared to observation, treatment with fenretinide 200 mg/day for 12 months was associated with a significant reduction in the risk of relapse 19 months after randomization. The drug was well tolerated. Unfortunately, the trial had to be stopped prematurely due to slow accrual, and a confirmatory study has not been done.[225] Fenretinide was also evaluated in individuals with retinoid-resistant OL. In a single-arm, phase II study, the response rate at 3 months was 34%, partial in all cases, often short lived, and correlated with previous response to retinoids.[226] In a follow-up study using higher doses of fenretinide (900 mg/m$^2$ /day) in the same setting, no significant clinical activity was seen (20% response rate only), prompting a planned discontinuation of the trial due to futility.[227]

***Retinoids to Prevent Second Primary Tumors.*** In 1990, Hong et al. reported the results a randomized trial of 13cRA (50–100 mg/m$^2$ /day) versus placebo for 12 months in patients with stage I to IV

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HNSCC who completed definitive therapy. The major endpoints of this study were disease recurrence and incidence of second primary tumors. Retinoid treatment was not associated with a reduction in local, regional or distant recurrence, or overall survival, but after a median follow-up of 32 months, patients in the retinoid arm had a lower incidence of second primary tumors compared to placebo.[228] The difference remained significant, albeit smaller, after long-term follow-up.[229] Again, retinoid therapy was associated with significant toxicities, and only two-thirds of the patients completed the full 12 months of treatment. In follow-up to this study, a large, multicenter, phase III, placebo-controlled trial of 13cRA 30 mg/day for 3 years was launched, enrolling 1,190 patients with stage I or II HNSCCs who completed definitive treatment. Unfortunately, this study failed to confirm the results originally reported by Hong et al. There were no differences in the rate of second primary tumors, local, regional or distant recurrence, or overall survival between the arms.[230] Recently, the association between SNPs and outcome has been studied in 450 patients included in this trial.[231] Patients carrying the common genotype of rs3118570 in *RXRA* were at a 3.33-fold increased risk and represented more than 70% of the study population. Interestingly, this locus also identified individuals who received benefit from chemoprevention with a significant 38% reduced risk (95% CI, 0.43–0.90). This study suggests that a pharmacogenetic approach could help select patients for 13-cRA chemoprevention.

The Northern California Oncology Group (NCOG) and the Eastern Cooperative Oncology Group (ECOG) conducted a phase III study with 13cRA (0.15 mg/kg/day) versus placebo for 2 years in 189 patients with stage I or II who completed surgery and/or radiation therapy. There were no differences in the rate of second primary tumors between the treatment arms.[232]

Meanwhile, the second-generation retinoid etretinate was evaluated in France in patients with early stage SCCs of the head and neck in the adjuvant setting. In this randomized study, 316 patients received placebo or the retinoid (50 mg/day for 1 month followed by 25 mg/day for 23 months). At 41 months of follow-up, second primary tumors developed at a similar frequency in the two treatment arms (24% for placebo, and 38% for etretinate). There were no differences in overall survival or recurrence.[233]

The largest study to prevent second primary aerodigestive tumors was conducted by the European Organization of Research and Treatment of Cancer (EORTC). The trial titled European Study on Chemoprevention with Vitamin A and N-Acetylcysteine (EUROSCAN) randomized 2,592 patients with treated lung (40%) or head and neck (60%) malignancies to receive no intervention, retinyl palmitate (300,000 IU/day for 1 year followed by 150,000 IU for 2 year), N-acetylcysteine (600 mg/day), or both in a two-by-two factorial design. It was based on the previous experience by Pastorino et al. showing a longer time to development of second primary tumors within the carcinogen-exposed field in patients with stage I non–small cell lung cancer treated for 12 months with retinyl-palmitate versus placebo.[234] Unfortunately, the EUROSCAN failed to show a benefit from either n-acetylcystein or retinyl palmitate in terms of survival, event-free survival or second primary tumor rates.[235]

Beta-carotene was evaluated for prevention of second primary HNSCC in two phase III studies. Mayne et al. randomized 264 patients with early stage head and neck cancers after completion of definitive treatment to receive placebo versus beta-carotene 50 mg/day. The study was terminated early due to slow accrual. After a median follow-up of 51 months, no differences were seen in time to second primary tumors and/or recurrences, or overall survival.[236] Bairati et al. randomized 540 patients with stage I or II HNSCC treated with radiation therapy to receive alpha-tocopherol (400 IU/day) plus beta-carotene (30 mg/day) versus placebo for 3 years.[237] After enrollment of 156 patients, beta-carotene supplementation was discontinued given the increased risk of lung cancers observed in other ongoing chemoprevention studies.[218,219] The remaining of the patients received alpha-tocopherol or placebo. After a median follow-up of 52 months, there was a higher rate of second primary cancers during the alpha-tocopherol supplementation period, but a lower rate after supplementation was discontinued. After 8 years of follow-up, the proportion of patients free of second primary tumors was similar between the groups.[237]

Taken together, the aforementioned studies do not support the use retinoids for tertiary prevention of head and neck cancers.

## Cyclooxygenase (COX) Inhibitors

Mulshine et al. randomized 57 patients with oral premalignant lesions to receive placebo or a 0.1% oral rinse solution of the pan COX inhibitor ketorolac for 30 days. The primary and secondary endpoints of the study were clinical and histological response, respectively. The placebo group had a high rate of clinical response (32%), and there were no significant differences in either of the endpoints between the groups. The authors concluded that the topical form of delivery of the drug may not be optimal for tissue penetration, thus explaining the lack of clinical activity.[238]

Papadimitrakopoulou et al. conducted a pilot, randomized study of the COX2 selective inhibitor celecoxib in individuals with oral premalignant lesions. Patients were treated with placebo, celecoxib 100 mg twice daily or 200 mg twice daily for 12 weeks during the blinded phase of the study. Six additional patients received celecoxib 400 mg twice daily on an open-label extension phase. Celecoxib was well tolerated, but there were no differences in the response rates between the groups. Interestingly, patients with higher baseline COX2 mRNA expression had an increased risk of disease progression within 3 months.[239]

Taken together, the two aforementioned COX inhibitor chemoprevention trials do not support the use of these agents for management of oral premalignant lesions. The cardiovascular toxicities associated with COX2 inhibitors observed on chemoprevention studies of colonic polyps [240] have decreased the enthusiasm for further evaluation of these drugs for HNSCC prevention.

## Green Tea Polyphenols

The polyphenol (–)-epigallocatevhin-3-gallate (EGCG) is the most abundant antioxidant present in green tea extract. Multiple signaling pathways are modulated by EGCG, including inhibition of activation of receptor tyrosine kinases (such as EGFR, insulin-like growth factor receptor, VEGF), their downstream pathways (including Akt, ERK, and STAT 3), inhibition of NF-kappa-B (a transcription factor involved in inflammation, immunity, and carcinogenesis), activation of the *p53* pathway and its downstream targets *p21*, *p27*, and *Bax*, as well as stimulation of *p73*. The combined effects of EGCG may, potentially, ultimately lead to apoptosis, cell cycle arrest, growth inhibition, antiangiogenesis, and inhibition of metastasis (reviewed in detail by Kim et al.).[241]

Clinical trials with green tea extracts for cancer prevention and treatment have been completed. These studies have used different preparations of green tea extracts, which contain varying amounts of EGCG and other potentially active ingredients. Therefore, results from these studies should be interpreted carefully and may not be extrapolated to ingestion of usual amounts of green tea in nonpharmacological formulations.

Li et al. reported the first placebo-controlled, randomized study of green tea in 59 patients with oral premalignant lesions. Patients assigned to the experimental arm received 760 mg of mixed tea capsules orally four times per day and 10% of mixed tea ointment topically (EGCG content not known). There was a favorable clinical response rate in the experimental arm (37.9%) compared to placebo (10%).[242]

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Recently, Tsao et al. conducted a placebo-controlled, phase II study of three different doses of green tea extract for 12 weeks in 41 patients with oral premalignant lesions. Each 350 mg green tea extract capsule contained 13.2% of EGCG. The dose levels were 500 mg/m$^2$ versus 750 versus 1,000 mg/m$^2$ three times per day. The higher doses of the drug were associated with insomnia/nervousness. The response rates in the two higher-dose arms combined (58.8%) were significantly better than in the 500 mg/m$^2$ arm (36.4%), and placebo (18.2%), suggesting a dose–response effect. There was also a trend toward improvement in histology. There were no differences in oral cancer-free survival. Biomarkers associated with response included baseline stromal VEGF expression, and downregulation of cyclin D1 expression and stromal VEGF receptor after treatment. Interestingly, nonresponding lesions had up-regulation of the latter biomarkers, indicating that the efficacy of the drug could be mediated by a reduction in angiogenic stimuli. This study supports the evaluation of green tea extracts in longer-term trials.[243] Different formulations of green tea extracts[244] and combination with other agents (e.g., EGFR inhibitors)[245] are being developed.

## *p53*-targeted Agents

Attempts at restoring *p53* function in premalignant lesions or targeting *p53* mutant premalignant cells have been described. ONYX-015 is an attenuated adenovirus cytotoxic to cells with dysfunctional *p53*-dependant signaling pathways. Rudin et al. enrolled 22 patients with dysplatic lesions of the oral mucosa in a study of three different schedules of a mouthwash of ONYX-015. Histologic resolution of dysplasia occurred in 37% of the patients, but the majority of the responses were short lived. Lesions that had histologic regression had a decrease in *p53* expression levels by immunohistochemistry over time, but baseline *p53* expression did not predict for response to ONYX-015. Two out of three lesions had confirmed viral replication.[246]

Li et al. evaluated the effects of multipoint intraepithelial injections of a recombinant human adenovirus-*p53* in 22 patients with dysplastic OL. This adenovirus is replication-incompetent, with an E1 gene region replaced by an expression cassette containing human wild-type *p53* cDNA. After treatment, 100% of the lesions demonstrated a positive staining for p53 protein expression, mainly located in the basal and spinous layer of the epithelium. Likewise, p21 protein expression was increased post treatment in 19 of the 22 case; bcl-2 protein expression significantly decreased post treatment. After 24 months of follow-up, 22.7% of the patients had a complete response, 50% of the patients had a 20% to 70% reduction in the size of the leukoplakia lesions, 18.2% had stable lesions, and 9.1% developed invasive cancer.[247]

While the results of the aforementioned clinical trials provide proof of principle of the potential role for targeting *p53* in oral premalignant lesions, the greatest limitation of the studies is the mode of delivery of the agents. As previously discussed, field cancerization is an important aspect of head and neck carcinogenesis, and strategies using topical or local therapies may not address the remaining of the mucosa at risk, thus possibly diminishing the potential for long-term prevention of aerodigestive tract cancers more broadly.

## Thiazolidinediones

Peroxisome activator receptor–gamma (PPAR$\gamma$) is activated by natural or synthetic ligands. Following binding of the ligand to the receptor, PPAR$\gamma$ heterodimerize with RXR and the complex binds to response elements of target genes and regulate their transcription. PPAR$\gamma$ activity may also be regulated by sumoylation and phosphorylation. PPAR$\gamma$ agonists have been shown to promote terminal differentiation, inhibition of proliferation, and stimulation of apoptosis in cancer cell lines *in vitro*. In preclinical animal models, the thiazolidinediones pioglitazone[248] or troglitazone[249] decreased the tongue carcinoma multiplicity and incidence, respectively, compared to placebo. Diabetic patients treated with thiazolidinediones had a reduced incidence of lung[250] and head and neck[251] cancers in retrospective epidemiologic studies, when compared to diabetic patients receiving alternative oral hypoglycemic agents. In a randomized, placebo-controlled, phase II study including 43 patients with OL, treatment with pioglitazone daily for 3 months led to a higher clinical and/or histological response rate compared to placebo (68% vs. 0%, respectively).[252] This trial formed the basis for a larger, ongoing, multicenter, phase IIb study of pioglitazone versus placebo in patients with oral premalignant lesions.

## EGFR Inhibitors

Because of the lack of significant progress with retinoid-based chemoprevention strategies in the last three decades, associated with the parallel development of effective and well-tolerated targeted drugs for treatment of invasive disease, several clinical trials have been launched to assess the efficacy of these agents on early stages of cancer/premalignancy. Within the context of the recently proposed paradigm termed *reverse migration*,[42] EGFR inhibitors are nearly ideal drugs to be evaluated in the setting of oral premalignant lesions, given the efficacy of cetuximab-based therapies in locally advanced and metastatic disease.[253] Chemoprevention clinical studies with the EGFR monoclonal antibody cetuximab or the EGFR TKI erlotinib were launched, even before preclinical data were obtained to support their use.

In 2006, the erlotinib prevention of oral cancer (EPOC) study was activated. In this trial, patients with oral premalignant lesions (with or without a prior history of OSCC) are first evaluated for the presence of LOH at 3p, 9p, and other key chromosomal sites. As previously discussed, this molecular abnormality is associated with a substantial risk of subsequent invasive cancer.[45,189,192] All patients are followed for development of OSCC, but only the molecularly defined high-risk patients are randomized to receive placebo or erlotinib 150 mg orally daily for 1 year. Definitions of high risk includes LOH at 3p and/or 9p in patients with a prior history of oral cancer, and LOH at 3p14 and/or 9p21 plus an additional chromosomal site in patients without a prior history of oral cancer. After treatment discontinuation, patients are followed for at least 2 more years. Unlike most previous studies in oral premalignant lesions, the primary endpoint of this trial is incidence of OSCC. EPOC is an example of more efficient clinical trial designs for cancer prevention. Because it focuses on a high-risk population, it allows for a smaller trial ($N = 150$ total patients), yet with sufficient power to detect a possible effect of erlotinib in inhibiting the development of invasive cancer, a clinically more meaningful endpoint than clinical or histological response of the oral premalignant lesions.[254]

The planned accrual for EPOC includes 100 LOH positive patients with a history of prior oral cancer, and 50 LOH positive patients without a history of oral cancer. According to previous retrospective studies discussed above,[189,192] 65% of the patients with oral premalignant lesion/LOH associated with curatively treated oral cancer are expected to develop oral cancer in 3 years, and 35% of the LOH positive patients without a prior history of oral cancer are expected to develop oral cancer in 3 years. It is estimated that erlotinib will reduce the incidence of oral cancer in the two cohorts by 40%, corresponding to a hazard ratio of 0.47. With this design, the study has 85% power with a two-sided 5% type I error rate. Several correlative studies are built into the study as well, including evaluation of biomarkers at baseline and in 3- and 12-month tissue biopsies that

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will shed light on the biology of these high-risk lesions and may assist in developing predictive markers of response, as well as additional markers of cancer risk. After screening approximately 400 patients in five different institutions in the United States, EPOC has completed accrual, and final data are eagerly awaited. Results of other smaller studies using cetuximab, and erlotinib plus celecoxib for head and neck cancer prevention are also yet to be presented.

## CONCLUSIONS

Significant advances in HNSCC chemoprevention field have been achieved over the past decades. There is now a better understanding of molecular and phenotypic determinants of the tumorigenic process, and risk models are currently being refined to predict development of oral cancer. This will certainly allow for an improvement in chemoprevention strategies in the future. Studies with retinoids, COX inhibitors, green tea extracts, *p53*-targeted agents, and thiazolidinediones have not resulted in the development of an intervention that can be standardly used for head and neck cancer prevention, but they set the stage for a model of translational science that will hopefully accelerate drug development in this setting. According to recent sequencing efforts of HNSCC, the mutational etiology is diverse, and most importantly with regard to chemoprevention, HNSCC have few targetable mutations, further emphasizing the need to improve prevention strategies.[4,5] A complete genetic and epigenomic characterization of preneoplastic lesions and subsequent SCC will allow a comprehensive characterization of the dynamic changes occurring during early cancer development. Using a systems biology approach to integrate multidimensional high-throughput molecular profiles as well as preclinical models should allow the identification of pathways driving carcinogenesis and potentially targetable. We are entering a new era of chemoprevention clinical research, employing novel trial designs and agents, focusing on molecularly defined high-risk cohorts, and supported by improved preclinical models. This will hopefully lead to effective strategies to reduce the incidence, morbidity, and mortality from head and neck cancers in the near future.

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SECTION 2

# Site-Specific Principles of Management of Head and Neck Cancer

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CHAPTER 14

# Management of the Neck

## PART A:
## General Principles and Management

Kenneth S. Hu, Adam S. Jacobson, Mark S. Persky, and Louis B. Harrison

### INTRODUCTION

Successful management of the neck is a prerequisite for the cure of most head and neck squamous cell carcinomas (HNSCC). Tumor spread to the regional nodes signals the transformation of the primary tumor to a more malignant phenotype with the ability to not only invade lymphatics but also spread hematogenously. Indeed, the clinical involvement of the regional node decreases the chance for cure by at least one-half.[1] Even in a clinically negative neck, surgical data have demonstrated high rates of occult nodal involvement for the majority of head and neck primary sites. Usually, such regional spread occurs in a predictable, progressive pattern depending on the mucosal site of origin, local richness of lymphatics, proximity to midline, and tumor stage. Thus, in a clinically negative neck, the first echelon nodes and levels of potentially involved nodal stations are evaluated and risk of involvement assessed before a decision is rendered regarding selective management. For clinically node-positive patients, more comprehensive, intensive treatment is required that addresses the greater tumor burden and larger areas of potential spread. How the neck is managed usually follows the manner in which the primary site is addressed. Single modality therapy, either surgery or radiation, is used to manage early stage primary tumors and regional lymphatics at risk for harboring occult disease, whereas multidisciplinary approaches are required for advanced primary tumors. Although surgery was traditionally considered the mainstay of treatment of the primary site and neck, decades of randomized trials have established radiation therapy as an effective alternative. In that regard, advances in organ preservation therapies have resulted from the integration of concurrent chemotherapy with radiation[2–6] altered fractionated radiation therapy,[7–10] introduction of new chemotherapeutic/biologic agents,[11] use of induction chemotherapy,[12,13] better understanding of the role of functional imaging improved treatment techniques such as intensity-modulated radiation therapy (IMRT)[14,15] as well as advances in molecular profiling, especially with regard to the human papilloma virus and epidermal growth factor receptor. Recent improvements in transoral robotic techniques have renewed primary surgical approaches for multiple sites (oropharynx and hypopharynx). In this regard, a neck dissection is usually performed in a staged manner, which has emphasized risk-adapted adjuvant treatment based on pathologic factors.

The purpose of this chapter will be to discuss the role of surgery and radiation therapy in the elective, adjuvant, and definitive management of the neck. Additionally, this chapter will discuss the use of imaging to assess oncologic response and to discuss evolving concepts which may better tailor treatment of regional disease. The management of regional metastatic disease from nasopharyngeal cancer will be discussed in a separate chapter.

### CERVICAL LYMPH NODE LEVELS

The Committee for Head and Neck Surgery and Oncology of the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) first published the guidelines for anatomic boundaries of the various cervical levels in 1991,[16] which were modified and updated in 2002.[17] These guidelines were all based on the original level designations that were created at Memorial Sloan Kettering Cancer Center to refer to the particular topographical location on the neck under which a consistent pattern of lymph nodes existed (Fig. 14-1).

### NECK STAGING

It is clear that metastases to cervical lymph nodes has a profound impact on the prognosis of a patient. The current staging system is based on a consensus between the European UICC and American Joint Cancer Committees. This system utilizes the



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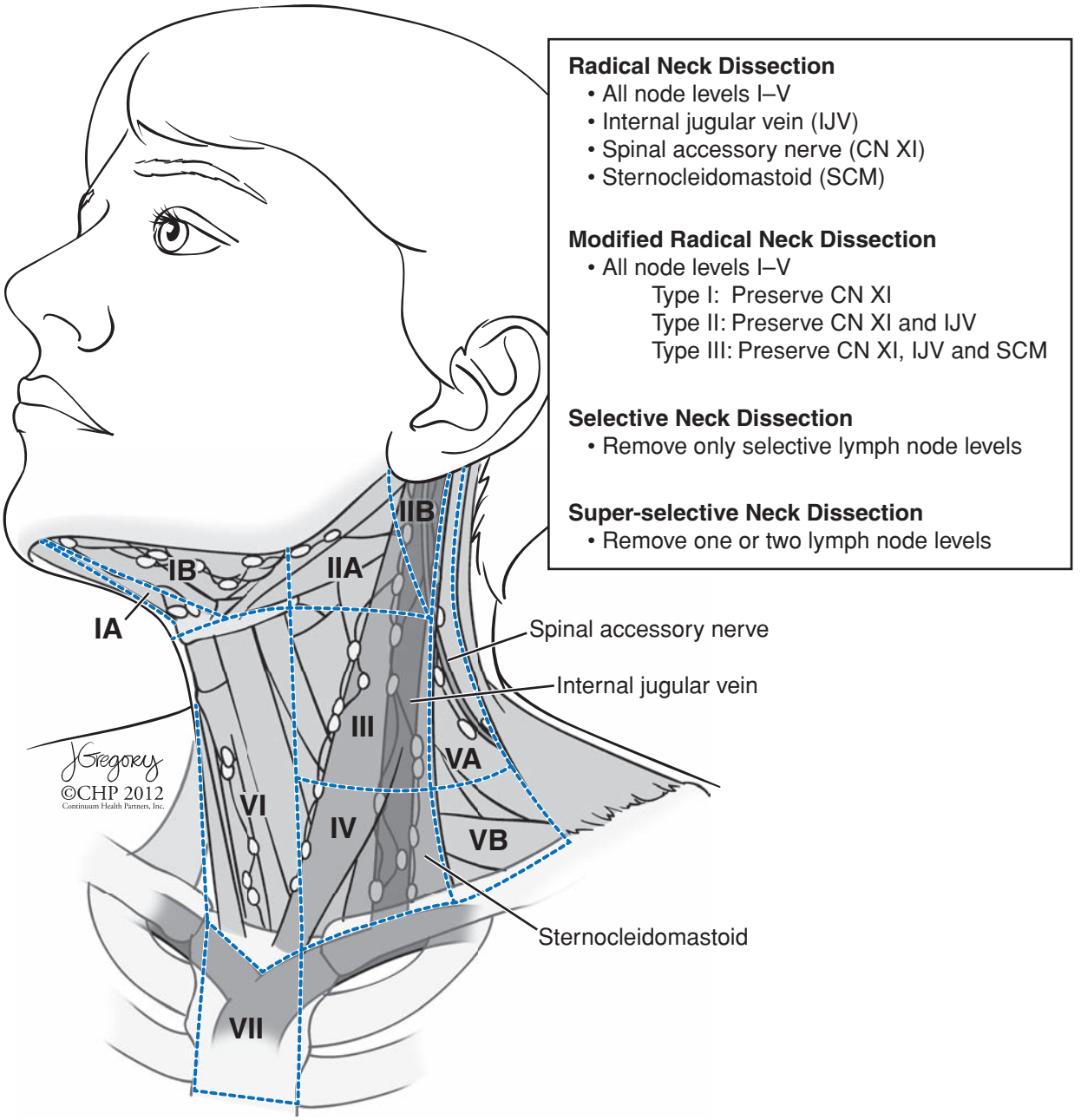



**FIGURE 14-1.** Nodal delineation for the electively treated node-negative and node-positive neck. On the left, are nodal stations delineated in a node-negative neck. On the right, are target delineation of level II nodal level up to the skull base in a node-positive neck. On the left, is shown the target delineation of level II in an electively treated neck. Note the differences in the superior margin allows substantial sparing of the parotid gland. RP, retropharygeal node; ICA, internal carotid artery; JV, jugular vein; PG, parotid gland; PB of JGD, posterior belly of the jugulodigastric muscle; BP, brachial plexus. See Table 14.10 for boundaries of nodal stations. (See color insert.)

clinical features of nodal size, number, and laterality. It does not integrate imaging features suggestive of extranodal extension, which is well known to adversely affect prognosis. Table 14.1 describes the N staging.

Patients staged as Nx have regional lymph nodes that cannot be assessed. N0 patients have no identifiable regional nodal metastasis. N1 patients have a single nodal metastasis, ipsilateral to the primary tumor site, and ≤3 cm in greatest dimension. Patients staged as N2a have a metastasis to a single ipsilateral node, which is >3 cm but <6 cm in greatest dimension. Patients staged as N2b have metastasis to multiple ipsilateral lymph nodes and none are >6 cm in greatest dimension. Patients staged as N2c have metastatic disease in bilateral or contralateral lymph nodes; none are >6 cm in greatest dimension. Patients staged as N3 disease have a lymph node or conglomerate of lymph nodes >6 cm in dimension.

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**TABLE 14.1 Cervical Lymph Node Staging System**

| | AJCC 1976 | AJCC 1983 | UICC-AJCC 1987–2002 |
|---|---|---|---|
| N0 | No involved node | No involved node | No involved node |
| N1 | Single ipsilateral node <3 cm | Single ipsilateral <3 cm | Single ipsilateral <3 cm |
| N2 | 1. Single ipsilateral node >3 cm, <6 cm<br>2. Multiple ipsilateral <6 cm | 1. Single ipsilateral >3 cm, <6 cm<br>2. Multiple ipsilateral >3 cm, <6 cm | 1. Single ipsilateral >3 cm, <6 cm<br>2. Multiple ipsilateral <6 cm<br>3. Bilateral or contralateral <6 cm |
| N3 | | 1. Ipsilateral node(s) >6 cm<br>2. Bilateral<br>3. Contralateral only | Node >6 cm |

## NECK DISSECTION TERMINOLOGY

*Radical neck dissection:* Radical neck dissection involves removal of lymph node levels I to V, including the submandibular gland, tail of the parotid gland, sternocleidomastoid muscle, internal jugular vein, and spinal accessory nerve (Fig. 14-2).

*Modified radical neck dissection (MRND):* MRND involves removal of lymph nodes from levels I to V (as in the radical neck dissection) but with preservation of at least one of the nonlymphatic structures (i.e., sternocleidomastoid muscle, spinal accessory nerve, and/or internal jugular vein).Modifications to the radical neck dissection include the following: (a) Type I: The spinal accessory nerve is preserved; (b) Type II: The spinal accessory nerve and the internal jugular vein are preserved; (c) Type III: The spinal accessory nerve, the internal jugular vein, and the sernocleidomastoid muscle are preserved.

*Extended radical neck dissection:* Extended radical neck dissection refers to removal of additional lymph node levels or groups and/or nonlymphatic structures (i.e., muscle, blood vessels, nerves) not normally removed with a radical neck dissection. Examples of additional lymph node groups include superior mediastinal, parapharyngeal, retropharyngeal, periparotid, postauricular, suboccipital, and buccinator. Examples of other nonlympahtic structures are the external carotid artery, hypoglossal and vagus nerves, and other neural, osseous, cutaneous, muscular, or vascular structures that are potentially involved with tumor.

*Selective neck dissection (SND):* SND refers to preservation of one or more lymph node levels and sparing all vital structures (sernocleidomastoid muscle, internal jugular vein, spinal accessory nerve). There are several variations of the SND, which have been given specific names (i.e., lateral, supraomohyoid, extended supraomohyoid, posterior, and central) (Fig. 14-3A–C).

*Super selective neck dissection:* Super selective neck dissection involves complete removal of all fibrofatty tissue contents, including lymph nodes, along the defined boundaries of one or two contiguous neck levels.[18]

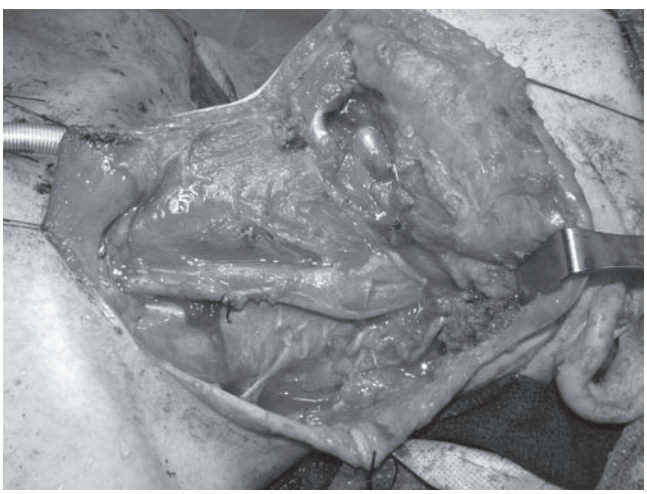


**FIGURE 14-2.** Removal of lymph node levels I to V.

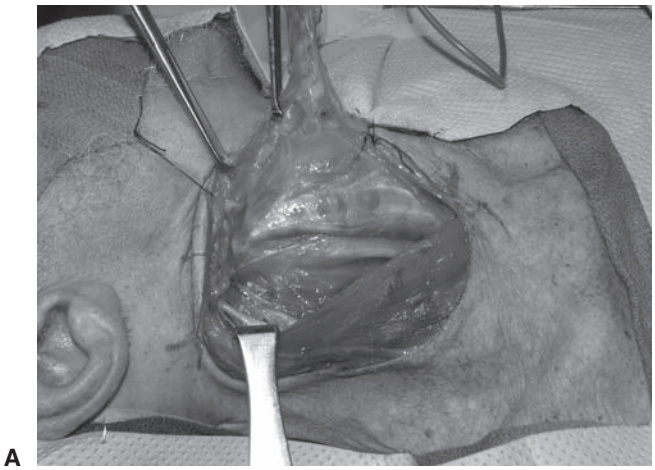
The super selective neck dissection has been pioneered by Robbins et al. who have utilized the super selective neck dissection in patients with advanced head and neck cancer that have been treated with primary chemoradiation and have residual pathologic lymphadenopathy limited to a single lymph node level.[18,19] It is believed that by minimizing the surgical field, soft tissue fibrosis is reduced and its impact on swallowing, mastication, and range of motion of the neck are minimized.

## THE EVOLUTION OF THE NECK DISSECTION

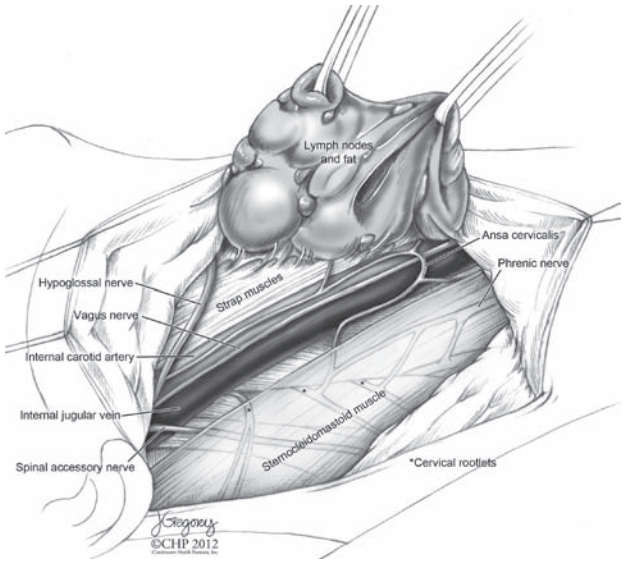
Surgeons of the early 19th century were aware that cancers of the head and neck metastasized to cervical lymph nodes; they often regarded this as a sign of incurability.[20] It was believed that the cervical metastases needed to be removed with the primary tumor, in order for the patient to have any chance of survival. In 1888, Jawdynski published the first description of an en bloc neck dissection, which was later popularized by George W. Crile, who published a systematic approach to the neck dissection in 1906.[21] In this procedure, all lymphatic tissue between the superficial and deep cervical fascial layers of the lateral neck were removed en bloc, including the sternocleidomastoid muscle, internal jugular vein, tail of the parotid gland, submandibular gland, and spinal accessory nerve.

In 1951, Hayes Martin and colleagues published their experience with 1,450 cases of neck dissections.[22] This paper helped to define the technique, as well as gain acceptance within the surgical community. In 1952, Suarez published his modifications of the classical radical neck dissection, which he called the "functional neck dissection." The goal of the functional neck dissection was to reduce morbidity while preserving the oncologic efficacy of the classic radical neck dissection. The modifications made by Suarez were preservation of the sternocleidomastoid muscle, internal jugular vein, omohyoid muscle, and, whenever possible, the spinal accessory nerve. Bocca and colleagues went on to popularize the selective removal of cervical lymphatics with preservation of vital structures (i.e., sternocleidomastoid

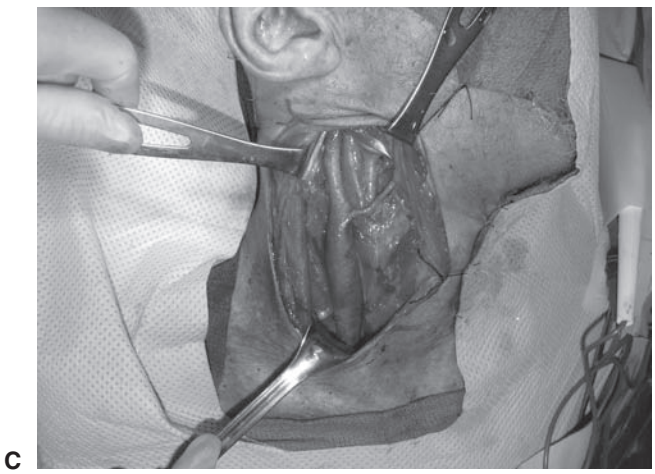
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A




B



C

**FIGURE 14-3.** Selective neck dissection. **A:** Selective removal of lymph node levels II, II, and IV. **B:** Illustration of selective removal of lymph node levels II, II, and IV. **C:** Neck after selective removal of lymph node levels II, II, and IV. (See color insert for Part **B**)

muscle, spinal accessory nerve, internal jugular vein).[23] Preserving these structures allows for maximization of control of the regional disease with minimization of the morbidity associated with a radical neck dissection (chronic neck and shoulder pain, cosmetic deformity, facial edema, etc.).

At this point, surgeons had become adept at systematically removing cervical lymphatics, but it was not until 1972 when Robert Lindberg first recognized patterns of cervical metastases in correlation with the primary tumor location.[24] This publication revealed that there were clear and predictable patterns of spread in the cervical lymphatics from each subsite within the upper aerodigestive tract. This observation that the patterns of cervical nodal disease are dictated by the location of the primary tumor has enabled surgeons to selectively remove nodal basins at risk for metastases based on the primary site of disease. This newfound knowledge opened the doors for preservation of low-risk nodal basins, thus decreasing patient morbidity. In the 1980s, Ballantyne from M. D. Anderson Cancer Center became one of the initial proponents of the SND. In 1988, Byers et al. described the patterns of nodal metastasis among 428 patients with HNSCC.[25] In 1990, Shah reported the progression of metastatic disease in the neck in a consecutive series of 1,081 patients with primary tumors of the oral cavity, the oropharynx, the hypopharynx, and the larynx.[26] The SND is now routinely used as a staging procedure to determine the presence or lack of occult metastases (which can help in the decision to apply adjuvant radiation therapy). More recently, the SND has been utilized in N+ necks as well as in postchemoradiation planned neck dissections. The use of the SND in clinically positive necks has been gaining widespread acceptance in recent years.

## CURRENT PHILOSOPHY FOR LATERAL COMPARTMENT NECK DISSECTIONS

The contemporary approach to removing cervical lymphatics has evolved from the highly morbid radical neck dissection to the much less morbid yet effective SND. Although the pendulum has shifted to a much less aggressive extirpation of lymphatic and nonlymphatic tissues, the radical neck dissection still remains the gold standard by which all modifications to the neck dissection must be compared. The current philosophy of ablative surgeons can be distilled down to a few simple goals. The first is the removal of all clinically positive lymph nodes and all involved nonlymphatic structures. The second goal is to preserve all nonlymphatic structures, which are not diseased, to optimize functional outcomes. The third goal is removal of all lymph node levels, which are at high risk for harboring metastatic disease. With these simple but clear goals, ablative surgeons are now more thoughtful in their extirpation.

## CENTRAL COMPARTMENT NECK DISSECTION

The central compartment (level VI) is important to address when managing patients with thyroid cancer and those tumors with subglottic extension. The boundaries for the central compartment of the neck (level VI) are the carotid arteries laterally, the hyoid bone superiorly, and suprasternal notch inferiorly. The inferior border of a central compartment neck dissection is located below the sternal notch at the level of the innominate artery and brachiocephalic vein (level VII). A comprehensive central compartment neck dissection incorporates level VI and level VII lymph nodes. These lymph node echelons are most commonly associated with metastases from thyroid cancer. In papillary thyroid

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cancer, the incidence of central compartment metastases has been reported between 21% and 60%.[27,28] Lymph node metastases in patients with papillary thyroid cancer are associated with a higher recurrence rate.[29] There is evidence that patients 45 years of age or older with regional nodal metastases have a higher mortality rate.[30] There is also evidence that patients with clinically evident nodal disease who undergo lymphadenectomy may have a reduced rate of recurrence and mortality.[29,31,32] Therefore, there is general agreement that clinically involved lymph nodes should be removed and comprehensive central compartment neck dissection should be performed in this situation.

A prophylactic central compartment neck dissection is defined as a level VI lymph node dissection in patients with no evidence of lymph node metastases on preoperative physical examination or imaging. A prophylactic central compartment dissection remains controversial because occult metastatic disease within the central compartment of patients with papillary thyroid cancer have been reported to range between 31% and 62% and rarely become clinically relevant.[28,33,34] In most series, the rate of recurrence in the central neck for patients with a papillary thyroid cancer >1 cm that were clinically node negative and were treated with total thyroidectomy without a central compartment neck dissection is 2% to 3%.[33–36] Currently, there has been no proven benefit for a prophylactic central compartment neck dissection.

## ROLE OF CAROTID ARTERY RESECTION IN NECK DISSECTION

Direct invasion or encasement of the carotid artery may occur in cases of advanced HNSCC. Resection of the carotid artery remains controversial because of the significant morbidity and mortality which may be associated with it. The prognosis for these patients is poor with the 1-year disease-free survival (DFS) ranging from 0% to 44%.[37,38] The surgical alternatives consist of peeling the tumor off the carotid artery which may be palliative or curative, carotid resection without revascularization, and carotid resection with vascular bypass grafting. Since complete tumor removal is the most important prognostic factor in head and neck surgery, peeling the tumor of the carotid artery is not considered an oncologically sound resection.[39]

The indication for carotid resection is based on preoperative imaging such as magnetic resonance imaging (MRI) and computed tomography (CT). When studies suggest carotid involvement with no evidence of distant metastases (DM) consideration for carotid artery resection is given and a preoperative assessment is made to determine the patient's risk for cerebrovascular accident when perfusion is interrupted during this procedure. A balloon occlusion study is often performed preoperatively in order to determine the patient's ability to temporarily tolerate complete obstruction of blood flow through the carotid artery. If the patient is able to tolerate a balloon occlusion study, then they are considered a candidate for a carotid artery resection. If the patient is not able to tolerate the balloon occlusion study, then the consideration of a carotid artery resection is no longer a viable surgical alternative.

There are only a limited number of publications discussing the outcomes of a carotid artery resection during treatment for head and neck cancer. Brennan et al. reported their 10-year experience of carotid artery resection without revascularization in advanced squamous cell carcinoma of the neck.[40] Seven patients underwent elective carotid artery resection, and all seven specimens showed invasion of the carotid artery fascia on pathological exam. Cerebrovascular accident occurred in two patients and the perioperative mortality was 29%.[40] The 5 remaining patients all died of locoregional recurrence or metastatic disease within 1 year after surgery.[40] The largest series reported in the literature is by Sessa et al. with 30 procedures reported.[41] In this series, a 35% DFS rate at 2 years was reported.[41] In 2001, Katsuno et al. performed a retrospective review via a computer search of all articles published in the English literature dealing with carotid artery reconstruction for head and neck cancer from 1987 to 1998.[42] Studies of patients who underwent a carotid artery resection without a reconstruction were excluded and case reports were excluded. Only 11 articles met criteria for inclusion allowing for a total of 148 patients to be compiled in this series.[42] Major neuromorbidity was 4.7% and mortality was 6.8% and the combined major neuromorbidity and mortality were 10.1%.[42] The oncologic outcomes were surprisingly interesting. Four of 10 patients from one of the series were reported as disease free for >2 years.[43] The Sessa series reported a 35% DFS rate at 2 years.[41] Other articles also reported justifiable oncologic results.[37,44–46]

## ELECTIVE MANAGEMENT OF THE CLINICALLY N0 NECK

The basis and need for elective nodal treatment in head and neck cancer have been based largely on surgical series evaluating pathologic nodal involvement found on elective neck dissection in patients with clinically negative necks. In a consecutive series of 1,081 head and neck cancer patients undergoing radical neck dissection, the incidence of pathologic node involvement was 33% among those undergoing elective neck surgery.[47] The pathologic findings identified the nodal stations at risk by tumor site to establish the rationale for SND as the elective surgical procedure.

Several reports have summarized the risk for metastases and nodal stations at risk.[24,48–51] Some general observations from such data can be made. Regarding larynx cancers, Candela reported the Memorial Sloan Kettering Cancer Center experience in determining the patterns of cervical nodal metastases in 247 larynx cancer patients undergoing 262 radical neck dissections.[52] Seventy-eight underwent elective radical neck dissection whereas 118 underwent immediate radical dissection for clinically node-positive disease. The majority of patients ($n$ = 189) were supraglottic larynx and 58 were glottic. Pathologic nodal involvement was found in 37% undergoing elective neck dissection. It is noted that cervical nodes spread in a similar fashion whether the patients are clinically node negative or positive with predominant involvement of level II and III jugular nodes. In clinically node-negative patients, the incidence of involvement of level I and V is <5% with <10% involvement of level IV. In node-positive patients, the incidence of level IV node increases from 15% to 31% with greater involvement of levels II and III. In clinically node-positive patients, very rarely did patients present with isolated level I nodal metastases without involvement of the jugular nodes.

Similarly, Shah and Candela reported that among oropharynx or hypopharynx cancers treated with elective radical neck dissection occult metastases are found in 26% and that level I and V were involved in only 1.4%, always in association with nodal disease at level II to IV.[47,52] No skip metastases were reported. Among oropharynx patients, levels II to IV were predominantly involved, and in the hypopharynx lesions, the primary levels involved were levels II and III. In patients clinically node positive undergoing therapeutic neck dissection, the incidence of level I and V involvement increased to about 10% to 15%; however, levels II to IV were predominantly involved (Table 14.2). Level V involvement only occurred in association with nodal involvement at levels II to IV whereas the incidence isolated level I involvement without levels II to IV involvement ("skip metastasis") occurred in 0.4%. Thus, based on these studies, elective treatment of the neck in oropharynx or hypopharynx can be directed at levels II to IV.

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**TABLE 14.2 Percentage Incidence and Distribution of Pathologically Involved Nodes in a Clinical Node-Positive after Therapeutic Radical Neck Dissection**

| | I | II | III | IV | V |
|---|---|---|---|---|---|
| Oropharynx $n = 165$ | 14 | 71 | 42 | 28 | 9 |
| Larynx $n = 183$ | 7 | 57 | 59 | 29 | 4 |
| Hypopharynx $n = 104$ | 10 | 76 | 73 | 46 | 11 |
| Oral cavity $n = 324$ | 46 | 43 | 33 | 15 | 3 |

*Source:* From Shah JP. Patterns of cervical lymph node metastasis from squamous carcinomas of the upper aerodigestive tract. *Am J Surg.* 1990;160(4):405–409, with permission.

Among oral cavity patients, the incidence of nodal disease was 34% on elective evaluation. The majority of metastatic nodes involved levels I to III with only 1.5% incidence of skip metastasis to level IV. Level V involvement is found in only 0.5% with occult disease simultaneously involving other levels. Among those undergoing therapeutic neck dissections, the incidence of level IV involvement increased to 20% while that at level V was 4% always restricted to lower gum or floor of mouth primary sites.

The need for elective treatment not only relates to the estimated probability of nodal involvement and usually is implemented when the risk is 20% or greater but also relates to the morbidity of such treatment as well as the adequacy of coverage. Table 14.3 demonstrates the incidence of nodal involvement of the most common head and neck cancer sites. It should be noted that such data are invaluable but do not address areas that are not addressed surgically, such as the retropharyngeal or pretracheal nodal basins.

Elective nodal treatment by radiation or surgery both offer distinct advantages as radiation may add more comprehensive nodal coverage including the contralateral neck and in regions difficult to surgically address such as the retropharyngeal nodes, inner mandibular nodal areas, and high subdigastric near the exit of the facial nerve at the mastoid process. However, surgery offers important pathologic data, which is useful prognostically, and tailors further therapy according to risk stratification. It should be noted that no randomized or comparative studies of observation versus neck dissection versus ENI have been reported, nor will likely be completed.

**TABLE 14.3 Percentage Incidence and Distribution of Pathologically Involved Nodes in a Clinical Node-Negative Neck after Elective Radical Neck Dissection**

| | I | II | III | IV | V |
|---|---|---|---|---|---|
| Oropharynx $n = 48$ | 2 | 25 | 19 | 8 | 2 |
| Hypopharynx $n = 24$ | 0 | 13 | 13 | 0 | 0 |
| Larynx $n = 79$ | 5 | 19 | 20 | 9 | 2.5 |
| Oral cavity $n = 192$ | 20 | 17 | 9 | 3 | 0.5 |

*Source:* From Shah JP, Candela FC, Poddar AK, et al. The patterns of cervical lymph node metastases from squamous carcinoma of the oral cavity. *Cancer.* 1990;66(1):109–113, with permission.

## Elective Surgical Treatment

Byers reported a series of patients undergoing elective treatment with SND demonstrating excellent outcomes and thus establishing this procedure as a standard of care for elective treatment.[53]

Retrospective studies point to an improvement in disease-specific survival with the addition of elective neck dissection. Piedbois et al. reported a retrospective comparative study of 233 patients with early stage oral cavity carcinoma with the primary site treated with an interstitial iridium-192 ($^{192}$Ir) implant who underwent either elective neck dissection or neck observation resulting in two cohorts of patients for analysis.[54] This resulted from a change in departmental policies minimizing the impact of potential selection biases. Neck dissection revealed metastases in 25% who then received postoperative radiotherapy. Among those observed, 17% developed a neck relapse with salvage surgery successful in 62%. Some patients were unable to undergo surgery because of unresectability of disease or poor patient performance status. The 10-year survival was 37% and 31%, respectively, with regression analysis demonstrating that neck observation was associated with an adverse risk for disease-related mortality ($p < 0.04$). Haddadin et al. reported on a retrospective analysis of 137 patients with T1 to T2 N0 oral tongue carcinomas with at least 2 years of follow-up who either received an elective neck dissection, neck observation with salvage therapeutic neck dissection, or no neck surgery at all.[55] The cohort receiving elective neck dissection had a superior 5-year cause-specific survival compared with the two other groups despite a negative bias due to a greater proportion of pathologic upstaging of the primary tumor and clinical T2 lesions.

Two randomized studies of patients with early stage oral cavity lesions failed to show a survival benefit in patients randomized to receive elective neck dissection compared to observation with salvage neck dissection if nodal disease developed. In one study, the primary site was managed with primary brachytherapy whereas in the other study the primary site was managed with radical resection.[56,57] In the Vandenbrouck study, a 49% incidence of nodal involvement was reported in electively treated patients whereas nodal disease subsequently developed in 47% in the observation group. In the observation arm, the nodal disease appeared to become more aggressive with a higher incidence of extracapsular extension (25% vs. 13%) compared to the electively treated patients and 10% of patients could not undergo therapeutic dissection. However, no survival difference could be detected between the two groups. The authors recommended observation in patients with early stage lesions who could be followed regularly. In the second study of early stage oral tongue cancers, patients undergoing hemiglossectomy and elective neck dissection showed no difference in DFS or overall survival (OS) compared to patients undergoing hemiglossectomy alone.[57] The number of patients enrolled on these trials was small and not powered to show equivalence of survival.

## Elective Nodal Irradiation

The efficacy of elective nodal irradiation (ENI) is largely based on single institutional studies demonstrating reduced neck relapse.[48,58] Fletcher established the dosimetric basis for elective nodal treatment and the need for comprehensive treatment. Delivering elective doses of 50 Gy to a clinically negative neck results in neck control in 95%.[58] At a dose of 50 Gy in 5 weeks, the incidence of neck failure was 0% whereas doses of 30 to 40 Gy were associated with regional failure in 9% to 10.5%.[58] Further support for ENI is reported by Mendenhall who reported a retrospective review of 125 patients with squamous cell carcinoma of the oral cavity, the oropharynx, the nasopharynx, the hypopharynx, and the supraglottic larynx with a clinically negative neck

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and control at the primary site.[48] The neck failure rate was 1.9% with ENI and 18% without ENI. Among a group of patients expected to have a <20% risk for occult nodal metastases, the neck relapse rate was 13% in patients who did not receive ENI versus 6% in patients who received ENI. Similarly, among a group of patients with an expected risk for occult nodal metastases >20%, the neck relapse rate was 31% and 5%, respectively. In a separate report, Mendenhall et al. demonstrated 100% disease control after ENI with 50 Gy in 25 fractions and 99% at a dose of 40.5 Gy in 15 fractions both given as daily fractions.[59]

Vergeer reported on a large Dutch experience evaluating the benefit of elective radiation therapy treatment of a N0 neck. Nodal irradiation was delivered to 785 N0 hemi-necks in 619 head and neck patients. Necks were clinical N0 (cN0) in 558 and pathologically N0 (pN0) in 227. About 47% of patients were oral cavity and well balanced between the two subgroups, with more larynx (22 vs. 13.6) and fewer oropharynx (25 vs. 31%) and hypopharynx (5.7% vs. 7.5%) in the pN0 subgroup. Positive margins were noted in 17.0% versus 21.5% along with greater proportion of T3/4 (77% vs. 59%) in the pN0 group. Patients were treated with a radiotherapy dose of 46 to 50 Gy. At 3 years, the regional failure for the entire cohort was 5% with a trend toward greater failure in the cN0 of 6% versus 3% in the pN0 ($p = 0.08$) and 10% in the ipsilateral neck compared to 4% in the contralateral neck ($p = 0.006$). Positive margins at the primary site increased the risk of regional failure in the ipsilateral cN0 neck to 22% but not in the contralateral cN0 neck, where it was 4%, and was significantly higher than those with close or negative margin with regional failure <1%. On multivariate analysis, the laterality (ipsilateral), positive margin status and clinically staged necks had worse regional failure.

Based on older radiation-delivery techniques, traditional ENI involves treatment of bilateral necks with generous coverage of the jugular nodes and major salivary glands with various degrees of coverage of the retropharyngeal, level I and level V nodes depending on the primary site. With the advent of IMRT, such comprehensive coverage can be duplicated or tailored much more extensively. The ability to treat lymphatic areas more discriminately has challenged radiation oncologists to integrate clinical judgment, experience, and understanding of the surgical data to adequately plan regional coverage that it is tailored appropriately for each case. There have been several excellent reviews regarding the delineation of lymph node target volumes indicated for head and neck radiation therapy.[14,15,51,60] These summaries have served as a basis for axial-based image treatment planning guidelines that is used for conformal irradiation and IMRT.[51] In general, surgical levels defined by Robbins et al. (America Academy of Otolaryngology–Head and Neck Society) are used as the basis for regional target delineation.[61] However, there are a wide variety of radiographic landmarks that have been proposed.[51,60,62,63] A transatlantic consensus has been reported for the electively treated neck as well as the clinically involved and postoperative neck. Gregoire et al. provide a summary recommendation of the nodal groups that should receive ENI in the neck without altered lymphatic flow (see Fig. 14-1; Table 14.4A).[51] These recommendations do not address specific presentations that may modulate the risk for occult metastases. It has been accepted in practice that a risk for <20% warrants at least a deliberation for ENI considering the competing issues of potential benefit and toxicities and risk for secondary HNSCC requiring further therapy.

## Elective Surgical versus Radiation Therapy Treatment

The efficacy of ENI versus elective neck dissection showed no obvious differences as reported by Barkley in a major retrospective experience of neck management in 596 patients with oropharynx, larynx, or hypopharynx carcinoma treated at MD Anderson Cancer Center.[64] Two hundred thirteen were oropharynx, 202 larynx, and 181 hypopharynx. Of these, 226 were N0 whereas 370 were node positive. Patients underwent radiation therapy ($n = 292$), surgical management ($n = 199$), or combined modality therapy ($n = 105$) of the neck. All patients had a minimum follow-up of 2 years and a median follow-up of 4 years. Among the electively treated patients, regional control was >90% regardless of the treatment approach as long as comprehensive neck treatment was implemented. However, partial treatment of the neck resulted in 15%, 35%, and 20% regional failure after radiation, surgery, or combined therapy, respectively.

# RECOMMENDATIONS REGARDING ELECTIVE TREATMENT OF COMMON HEAD AND NECK CANCER SITES

Given the significant risk for occult nodal involvement, the standard of care has evolved to electively treat such patients despite the lack of confirmatory randomized trials. Nodal coverage of levels I to III for oral cavity tumors and levels II to IV for oropharyngeal, hypopharyngeal, and laryngeal tumors are mandatory as elective treatment[24,47,52,65,66] (Table 14.4B). Elective nodal irradiation including the retropharyngeal lymph nodes is added for primary tumors involving the nasopharynx, tonsil, pharyngeal wall, and the soft palate. Bilateral ENI should be considered for tumors arising from or extending to midline structures such as the soft palate, the base of tongue, and the pharyngeal wall. Tumor sites such as the hypopharynx and the supraglottic larynx require bilateral ENI regardless of the specific tumor stage given high risk for contralateral nodal involvement. In contrast, tumor involvement of ipsilateral structures such as the parotid, the buccal mucosa, and selected tonsil cancers warrants consideration of ipsilateral ENI.[67,68] Elective nodal irradiation including level IV lymph nodes should be considered in those with tumors involving the tip of the oral tongue due direct drainage to this area that bypass the orderly contiguous progression in the anterior jugular nodes.[47,69] Involvement of the ipsilateral level V lymph nodes in node-negative oral cavity tumors is rare, occurring in <1%, and does not warrant ENI. However, with increasing involvement of levels I to III or the involvement of level IV, the risk for level V involvement increases warranting ENI. In contrast, involvement of only the true vocal cords does not warrant ENI due to the paucity of lymphatic drainage.

# IPSILATERAL NECK RADIATION IN LATERALIZED OROPHARYNX CANCER

O'Sullivan et al. reported the results of a large retrospective review which identified oropharyngeal tumors that could be spared by contralateral ENI.[67] Two hundred twenty-eight patients with tonsillar carcinomas were treated with ipsilateral radiotherapy at Princess Margaret Hospital. Eligible patients typically had T1 or T2 tumors (191 T1–2, 30 T3, 7 T4) with N0 (133 N0, 35 N1, 27 N2–3) disease. Radiation was typically delivered with wedged pair Cobalt beams and ipsilateral low anterior neck field delivering 50 Gy in 4 weeks to the primary volume. At a median follow-up of 5.7 years, the 3-year local control rate was 77%, regional control 80%, and cause-specific survival 76%. Contralateral neck failure occurred in 3% (8/228). All patients with T1 lesions or N0 neck status had 100% contralateral neck control.

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**TABLE 14.4A Consensus Guidelines for Target Delineation of Nodal Levels in the Elective Treated Neck**

| Level | Cranial | Caudal | Anterior | Posterior | Lateral | Medial |
|---|---|---|---|---|---|---|
| IA | Geniohyoid muscles | Hyoid bone | Symphysis menti | Hyoid bone | Medial edge of anterior belly of digastric | Midline |
| IB | Mylohyoid muscles cranial edge of SMG | Hyoid bone | Symphysis menti | Posterior border of SMG | Medial border of mandible | Lateral edge of anterior belly of digastric |
| IIA | Inferior border of lateral process of C1 | Inferior edge of hyoid | Posterior bord of SMG | Posterior edge of IJV | Medial edge of SCM | Medial border of ICA |
| IIB | (As IIa) | Inferior edge of hyoid | Posterior edge of IJV | Posterior border of SCM | Medial edge of SCM | Medial edge of ICA/deep cervical muscles |
| III | Inferior edge of hyoid | Inferior edge of cricoid | Anterior edge of SCM | Posterior edge of SCM | Medial edge of SCM | Medial ICA/deep cervical muscles |
| IV | Inferior edge of cricoid | 2 cm superior to SCL joint | Anterior edge of SCM | Posterior edge of SCM | Medial edge of SCM | Medial ICA/deep cervical muscles |
| Va | Superior edge of hyoid | Inferior edge of cricoid | Posterior edge of SCM | Anterior border of trapezius | Platysma | Paraspinal muscles |
| Vb | Inferior edge cricoid | Transverse cervical vessels | Posterior edge of SCM | Anterior border of trapezius | Platysma | Paraspinal muscles |
| VI | Inferior border of thyroid | Manubrium | Platysma | Common carotid artery | SCM | trachea |
| Retropharyngeal | Skull base | Top of hyoid bone | Pharyngeal constrictor muscles | Prevertebral fascia | Medial border of carotid artery | Midline |
| Retrostyloid | Jugular foramen | Inferior border of lateral process of C1 | Paraphageal space | Vertebral body/ skull base | Parotid space | Lateral edge of RP nodes |
| Supraclavicular | Lower border IV/Vb | Sternoclavicular joint | Skin/SCM/ clavicle | Anterior edge of postscalenus muscles | Lateral edge of posteriorscalenus muscles | Trachea/thyroid gland |

**TABLE 14.4B Guidelines for Neck Treatment in Patients with Head and Neck Squamous Cell Carcinomas: Echelons of Lymph Nodes to Be Treated**

| Primary Tumor Site | Stage N0–N1 | Stage N2–3 |
|---|---|---|
| Oral cavity | I, II, III, and IV (for anterior tongue tumors only) | I, II, III, IV, and V (may omit if only levels I–III are involved) |
| Oropharynx | II, III, IV, and retropharyngeal node | I, II, III, IV, V, and retropharyngeal nodes |
| Hypopharynx | II,[a] III, IV, and VI (for esophageal extension only) | I, II, III, IV, V, retropharyngeal nodes, and VI (for esophageal extension only) |
| Larynx[b] | II,[a] III, IV, and VI (for transglottic and subglottic) | I, II, III, IV, V, and VI (for transglottic and subglottic tumors) |

[a]May exclude level IIb for N0 patients.

[b]Excludes T1 N0 glottic carcinomas.

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Patients with a 10% or greater risk of contralateral neck failure included those with T3 lesions, lesions involving the medial one-third of the hemi-soft palate, tumors invading the middle third of the ipsilateral base of tongue, and patients with N1 disease. In the presence of ipsilateral node metastases, the risk for contralateral neck failure was 9.5%, 14%, and 21% (all crude rates) for involvement of the soft palate, the base of tongue, and both structures, respectively. However, the authors appropriately note the limitations of these observations as they included patients with uncontrolled primaries and involved a total of only eight patients with contralateral neck failures. Despite this, the report provides confidence in the selection of patients with T1 N0 tonsil carcinomas (as well as selected patients with more advanced disease) for only ipsilateral ENI. Similar observations were also reported by Jackson et al. further supporting these observations.[70]

## ELECTIVE NODAL IRRADIATION FOR MAXILLARY SINUS CANCER

Traditionally, ENI has not been routinely considered for maxillary sinus carcinomas due to the low incidence of nodal disease at presentation. However, several investigators have suggested a benefit of ENI for locally advanced N0 squamous cell carcinoma of the maxilla.[71–74] Le et al. reported a retrospective review of 97 patients with maxillary sinus carcinoma treated with primary radiotherapy or postoperative radiation at UCSF and Stanford.[73] Squamous cell histology was the most common with 60% (58/97), followed by adenoid cystic carcinoma in 20% (19/97) and undifferentiated carcinoma in 16% (16/97). Eighty-nine patients had T3–4 lesions with T2 in eight patients whereas 11% (11/97) presented clinically with nodal disease. Of these 11, one was treated with combined neck dissection and post-op radiation whereas 10 were treated with primary radiation to a median dose of 63 Gy. Of the 86 clinically node-negative patients, 25 patients received ENI (median dose 50 Gy) to the bilateral upper neck nodes. The 5-year actuarial risk for nodal relapse was 0% in patients receiving ENI and 20% for those not receiving ENI. The most common site of nodal relapse was in the ipsilateral level I and II nodal groups with a small number of regional failures in the ipsilateral parotid and upper level V nodes and no instance of failure at level III/IV or supraclavicular nodes. There was no association between primary recurrence and risk for neck failure. However, on multivariate analysis, there was significant association between neck failure and incidence of distant metastasis with higher risk after neck recurrence compared to those regional controlled (82% vs. 19%, $p = 0.02$). The influence of selection bias with regard to these results is unclear. However, it is likely to have biased against the efficacy of ENI because those patients receiving ENI were likely to have had more advanced disease. Only 1 of 10 patients with neck relapse was salvaged. Of greater significance was the observation that the 5-year actuarial risk for DM was 29% for patients with neck control and 81% for patients with neck failure. Multivariate analysis demonstrated that T stage, N stage, and regional nodal control (HR = 4.5, $p = 0.006$) independently influenced this risk. The 5-year survival was 37% and 0% for patients with neck control and neck relapse, respectively ($p = 0.3$). Late complications arising from neck irradiation occurred in 1 of 36 patients who developed ipsilateral brachial plexopathy and severe neck fibrosis. In light of the relapse pattern, the investigators concluded that ipsilateral ENI to only the upper neck (levels I and II) be considered for patients with T3 and T4 N0 squamous cell carcinoma of the maxillary sinus. Similar conclusions were reached by other investigators.[23,25]

## MANAGEMENT OF THE CLINICALLY NODE-POSITIVE NECK (N+)

Management of the clinical positive neck is controversial with a wide variety of approaches that mirrors the complexity and competing regimens established to treat the primary site. These include neck dissection followed by postoperative radiation; definitive concurrent chemoradiation, radiation, or concurrent chemoradiation followed by planned or salvage neck dissection; and induction chemotherapy followed by neck dissection before or after radiation. Refinements in the radicality of neck dissection (radical vs. modified vs. selective vs. super selective neck dissection) and the identification of patients at high risk for recurrence, development of consensus guidelines in nodal target delineation for intensity-modulated treated patients, radiation dosing, and fractionation as well as integration of chemotherapy have been issues that have been explored to maximize regional control and preserve quality of life and function. The manner in which the primary site is managed guides treatment of the neck. Thus, relevant considerations in the decision include the resectability of the primary and neck disease, the functional morbidity incurred by surgery or radiation at the primary site, and the appropriateness of the primary lesion for potential organ-preserving therapy with either radiation alone or in combination with chemotherapy. When unresectable disease exists, the use of chemoradiation strategies has largely been favored. Although the optimal chemoradiotherapy regimen for both organ preservation and unresectable disease remains to be defined, the bulk of the data favor concurrent chemoradiation whereas more recent data point to possible additional benefit of induction chemotherapy or to integration of biologic therapies. Following these therapeutic considerations for the primary lesion, the principal issue with regard to neck management has been the necessity of adjuvant postoperative radiotherapy/chemoradiation or postradiotherapy/chemoradiation neck dissection.

### Surgery and Postoperative Radiation

Surgery and postoperative radiation remains a common strategy for regional management especially for the majority of resectable oral cavity tumors and many locally advanced but resectable HNSCC such as bulky or cartilage invasive hypopharynx or larynx cancers. More recently with early and intermediate stage oropharynx cancer, transoral robotic surgery is used increasingly followed by neck dissection. Historically, radical neck dissection alone had been the mainstay of regional treatment with radical extirpation of the neck nodes and adjacent nonlymphatic structures with significant functional and cosmetic morbidity as described by Crile in 1903[75,76] and reintroduced in the 1950s by Martin.[77] However, it was well recognized that recurrence in the neck after radical neck dissection carried an ominous prognosis.[78] Large series evaluating risk factors for recurrence after neck dissection have been reported. Of these, the most consistently reported risk factor for recurrence is extracapsular extension (ECE). Snow et al. reported one of the first important large institutional experience using pathologic factors to predict risk of recurrence. In a series of 405 patients, he reported that the presence of extracapsular extension of nodal disease was the single most important predictive factor on multivariate analysis for neck recurrence and poor survival.[79] Furthermore, he noted that although there was a relationship between node diameter and fixation with ECE as >75% of nodes >3 cm and 70% with fixation had ECE, these parameters themselves were not sufficient as 20% of nodes <1 cm had ECE and 30% with nodal fixation had no ECE.[79] Carter et al. reported an extensive analysis of 250 radical neck specimens and their clinical significance.[80] Both the presence and the extent of

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ECE was found to be the most important factor predicting for neck relapse with a distinction between macroscopic and microscopic ECE emphasized with the former having a worse prognosis.[80] Others have verified such findings.[80–82] and reported other poor prognostic pathologic factors including lymphvascular invasion,[1] perineural invasion,[83] number of nodes involved,[79,84] as well as nodal level involved.[64,84–88] Risk factors for recurrence based on findings from primary site include most importantly the status of the resection margins[89–92] as well as the primary tumor site origin.[93,94]

Postoperative head and neck radiation therapy was pioneered by Fletcher, who laid down the principles of treatment fields and time-dose factors.[95] He demonstrated that 50 Gy offered excellent control rates as elective treatment but greater doses were needed to control high-risk disease in a postoperative setting.[90] Moreover, he reported the importance of comprehensive treatment of the entire neck and primary site either as adjuvant or as salvage for gross residual disease given that localized radiation was associated with high rates of locoregional failure including contralateral neck compared to comprehensive radiation of the primary and whole neck (locoregional failure 73% vs. 58%, respectively).[95] Thus, the majority of studies in the postoperative setting have evaluated the benefit of radiation as a locoregional treatment for indications based on high-risk features from either the primary site or neck.

Postoperative radiation (PORT) appears to benefit patients with extracapsular extension compared to resection alone. In a retrospective review of 405 patients treated at the Netherlands Cancer Institute, Bartelink et al. reported that PORT decreased recurrence and improved survival compared to surgery alone in the cohort of patients with ECE but no preoperative fixation of lymph nodes.[96] Similarly, Huang et al. reported superior survival rates in a retrospective review of a more homogeneous cohort of 125 patients with high-risk features (ECE or positive resection margin) treated with either surgery and PORT or surgery alone.[48] Factors demonstrated to independently influence survival included the use of PORT ($p = 0.0001$) and the number of lymph nodes with ECE ($p = 0.0001$).[97] Despite the use of PORT, the number of lymph nodes with ECE remained significant attesting to the adverse influence of this pathologic feature. This study is significant because the two study populations resulted from the management bias of the operating surgeons to prefer or not to prefer PORT. This clearly defined treatment choice limits the selection bias that often confounds retrospective analyses. Others have reported the locoregional benefit of PORT in patients with multiple positive nodes.[98–100]

Postoperative radiation has consistently been shown to decrease locoregional failure[53,64,85,87,101] but its impact on survival is less conclusive as some retrospective studies report a survival benefit whereas others report only an alteration in failure pattern toward distant metastasis but no survival benefit.[85,102,103] Mishra et al. reported on the randomization of 140 patients with stages III and IV (T3–T4, N0–N2B) buccal mucosa carcinoma to PORT (mean dose 60 Gy) or observation following surgical resection.[104] A significant improvement in the DFS was observed in favor of PORT (68% vs. 8%, $p < 0.005$) after a minimum follow-up of 36 months. This observation is noteworthy given the selection bias against the PORT arm that resulted from a biased randomization process due to surgeon preference, yielding a greater proportion of advanced node-positive disease in the PORT arm. Kokal et al. reported the preliminary results of a potentially underpowered randomized trial of 51 patients with stage III and IV squamous cell carcinoma arising from the oral cavity, the larynx, and the pharynx treated with surgery or surgery and adjuvant PORT (50 Gy).[105] The study excluded randomizing patients in the postoperative setting if the resection margins were positive or there was clinical evidence of nodal metastases, hence largely evaluating the role of PORT for pathologic nodal metastases. A median follow-up of 30 months was reported. No differences in locoregional control in the primary site and ipsilateral neck was observed (22% vs. 26%) in the surgery alone versus postoperative radiation group. However, fewer contralateral undissected neck recurrences (5.3% vs. 14.8%, crude rates) and fewer DM (5.3% vs. 14.8%, crude rates) were observed in favor of the cohort receiving PORT. This resulted in a nonsignificant difference in the actuarial relapse rate and 3-year OS rate (37% vs. 68%, $p = 0.16$ and 58.5% vs. 46.5%, $p = 0.31$, respectively) in favor of the irradiated group.

A matched pair analysis of patients treated at the Mayo clinic demonstrated a benefit of postoperative radiation in dissected patients.[106] Matched pair analysis was drawn from two pools of patients. One consisted of 95 consecutively treated patients undergoing neck dissection and postoperative radiation therapy (bilateral neck irradiation; median dose 56 Gy) treated from 1974 to 1990. The other cohort consisted of 284 patients treated by neck dissection only between 1970 and 1980. Patients were matched by nodal stage, age, gender, number of nodes involved >4, desmoplastic nodal pattern, which had been highly predictive for neck recurrence at this institution. A total of 56 matched pairs were compared. The relative risk (RR) for recurrence on the unilaterally dissected side, any neck recurrence, cancer-related death and death from any cause were 5.82, 4.72, 2.21, and 1.67 in the surgery alone arm compared to those receiving postoperative radiation. Although extracapsular extension was not specifically studied, the authors reported a high correlation between desmoplastic nodal pattern and ECE, suggesting the growth pattern may be a reasonable surrogate for ECE. With regard to absolute outcomes in the 95 patients receiving radiation therapy, the regional failure was 26% at a median follow-up of 4.5 years whereas the 5-year disease-specific survival and OS were 64% and 39%, respectively, consistent with other postoperative experiences. Frank et al. also reported an improvement in both OS and DFS in a retrospective comparative review of 110 patients with carcinoma of the hypopharynx treated with either surgery alone or followed by PORT.[107] Despite the presence of more advanced disease, the cohort receiving PORT was demonstrated to have a superior locoregional relapse rate (14% vs. 57%, $p < 0.0001$), DFS, and adjusted 5-year survival (48% vs. 18%, $p = 0.029$). Treatment with PORT was an independent prognostic factor in multivariate analysis for both DFS ($p = 0.0009$) and OS ($p = 0.0289$).

Several retrospective studies have reported the effectiveness of achieving neck control by nodal stage, and selected reports from large U.S. centers are illustrated in Table 14.5.[64] Conventional postoperative radiation offers excellent control in N1 patients, acceptable results in the N2 neck and suboptimal outcomes after N3 treatment. Vikram reported improved regional control after postoperative radiation in patients with one or multiple nodal stations involved and emphasized the importance of minimizing treatment delay.[101] A series of 114 patients treated with surgery and postoperative radiation were compared to historic control treated with similar surgical techniques (radical neck dissection). Seventeen percent were found to have nodal metastasis at one level whereas 66% had disease at multiple nodal levels. Patients were treated with postoperative doses of 50 to 60 Gy over 5 to 6 weeks. The crude regional failure rate among patients with positive nodal disease treated with postoperative radiation was 10%. Compared to patients treated with surgery alone, the regional failure rate after postoperative radiation was decreased whether disease was localized at a single nodal level (regional failure 16% vs. 36.5%) or if multiple levels of nodes were positive (13% vs. 72%) and also appeared better than another cohort treated with preoperative radiation to a dose of 20 Gy (regional failure 28% [single nodal level] and 37% [multiple nodal levels]). Regional

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**TABLE 14.5 Single-Institution Series of Radical Neck Dissection and Postoperative Radiation–Neck Control by N Stage**

| Institution | Primary Site | N1 | N2 | N3 |
|---|---|---|---|---|
| MDAC[64] | OPX,LX,HYPX | 100% (21/21) | 100% (45/45) | 75% (21/28) |
| UFla[152] | OPX,LX,HPX,OC | 91% (10/11) | 82% (54/66) | 61% (14/23) |
| MSKCC[92] | OPX,OC | 94% (30/32) | 78% (29/37) | 20%(1/5) |

MDAC, Mental Disability Advocacy Centre; OPX, oropharynx; LX, larynx; HPX, hypopharynx; OC, oral cavity; UFLA, University of Florida; MSKCC, Memorial Sloan-Kettering Cancer Center.

failure was greater in patients starting radiation 6 weeks postoperatively compared to those starting radiation within 6 weeks (2% vs. 15%, $p < 0.02$). This time interval of >6 weeks negatively impacted on regional control whether single-level nodal involvement (regional failure 33% vs. 0%) or multiple levels of nodes were involved (27% vs. 3%). Others have also demonstrated the importance of minimizing the total treatment package time.[108–110]

## Unilateral Postoperative Radiation Therapy in Oral Cavity Cancer

Vergeer reported the experience of treating 123 oral cavity cancer patients with lateralized tumors who underwent resection and unilateral postoperative radiation. A lateralized tumor was defined as >1 cm from midline. Patients were treated to the primary tumor bed in all cases, which included the ipsilateral neck in 90%. Tumors involved the oral cavity primarily including the gingival, the oral tongue, the floor of mouth, the buccal mucosa, and the floor of mouth in 104 patients with T1–4 and node-positive disease in 62%. The median total doses to the primary site involved nodal station, and elective nodal areas were 63 Gy, 66 Gy, and 46 to 50 Gy, electively. At a minimum follow-up of 5 years, a total of seven patients failed contralaterally with a 5-year actuarial failure rate of 8%. The risk of contralateral nodal failure rate was related to the pretreatment nodal stage ($p = 0.008$) and occurred in 1%, 12%, and 27% in patients with pN0, pN1–N2a, and pN2b, respectively. Of the seven contralateral nodal failures, five were salvaged with neck dissection. The presence of extracapsular extension was of borderline significance ($p = 0.06$) for increased risk of contralateral nodal failure (14% vs. 6%, $p = 0.081$). The benefit of unilateral radiation therapy was the low rate of morbidity. At 5 years, the incidence of cumulative RTOG chronic grade 2 to 4 xerostomia was 20%, grade 3 mucosal complications 9%, grade 3 to 4 bone complication 17%, and grade 3 to 4 fibrosis 23%.

## Special Issues Regarding a Solitary Node

In patients with a single histologically positive node without extracapsular spread, the regional recurrence rate may not warrant radiation therapy. In the study by Carter et al., where ECE is present in a solitary lymph node, the 3-year neck relapse rate was found to be 25%.[80] Where ECE is absent, Barkley et al. noted neck relapse in 5 of 47 (11%) patients with N1 disease treated with surgery alone compared with a comparable retrospective cohort of 21 patients that received PORT with no neck relapse observed.[64] Hence, neck irradiation is commonly recommended in the setting of ECE, reserving neck observation where no ECE is present and the patient is likely to remain compliant to a course of close observation. After SND without radiation, the regional recurrence rates ranges from 4% to 10% and did not appeared to be improved with the addition of radiation. However, others note the poor outcomes after recurrence in a dissected neck and favor treatment.[53,98,111–114]

For patients having undergone a local excision of a solitary node, the adequacy of radiotherapy in the management of a neck with potentially a higher burden of residual microscopic disease has been reported.[115,116] Mack et al. reported on 41 patients referred for irradiation following excision of a solitary neck metastasis with no gross residual disease.[116] The N stage was Nx ($n = 7$ patients), N1 ($n = 15$ patients), N2A ($n = 18$ patients), and N3A ($n = 1$ patient). Neck irradiation was administered with doses ranging from 5,485 cGy to 8,100 cGy (median dose, 6,675 cGy). A planned neck dissection was administered in two patients. Actuarial neck control was 95% at both 5 and 10 years. Distant metastasis was observed in 0 of 36 patients with disease controlled above the clavicles versus 3 of 5 patients with relapse above the clavicles. Hence, this report would support the efficacy of postexcision radiotherapy to the neck for most patients presenting with solitary N1 or N2A disease without an increased risk for distant metastasis. The efficacy of postexcision radiotherapy for N3A disease is unclear given the higher risk for residual microscopic disease in the neck. A neck dissection would appear to be warranted. Ellis et al. confirm that the potential adverse effects of violating the neck with an open neck biopsy, on both the probability of neck control and the risk for distant metastasis, could not be demonstrated in a regression analysis when radiotherapy was subsequently delivered to the neck.[117] In a separate report from the same institution, Parsons et al. also reported on the neck control rates following an open neck node biopsy resulting in patients with or without gross residual disease.[115] Gross residual neck disease remained in 55 patients. A neck control rate of 64% was observed when the neck treatment was predominantly with radiotherapy alone. The subsequent consistent addition of a planned neck dissection improved the neck control rates. For N1 to N2 disease, the neck control rate was 65% with irradiation alone and for N2 disease 86% with the addition of a neck dissection. For N3A disease, the neck control rate increased from 29% (2/7) to 63% (5/8) supporting the need for a neck dissection where the burden of residual microscopic disease is increased.

## HPV and Need for Completion Neck Dissection in a Violated Neck

Loyo reported on 94 patients treated at Johns Hopkins University or University of Pittsburgh who had an open cervical biopsy and managed with either completion neck dissection ($n = 53$) or chemoradiation ($n = 41$). Oropharynx comprised 84% of patients (79/94) and were HPV positive in 87% (55/63). Patients treated with neck dissection had a lower proportion of HPV negative patients (3.7% vs. 14.6%, $p = 0.009$) compared to those managed nonoperatively. Regional failure rate was similar 2/53 versus 2/41 in patients managed surgically or with radiation, respectively. There appeared to be no difference in 5-year disease-specific survival (82% vs. 85%, $p = 0.58$) or DFS (82% vs. 70%) in those managed with completion neck dissection versus nonoperative management.

## Pre- versus Postoperative Radiation Therapy

The sequencing of radiation therapy either before or after definitive resection was explored in the Radiation Therapy Oncology Group (RTOG) trial 73-03 involving 320 patients of primarily

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stage III/IV patients.[93] Patients with larynx or hypopharynx cancer undergoing radical surgery ($n$ = 211) were randomized to receive 50 Gy preoperatively or 60 Gy postoperatively whereas patients with oral cavity/oropharynx were randomized to three arms: pre- or postoperative radiation or a third arm of definitive radiation therapy (65–70 Gy) only. Results were reported at a median follow-up of 5 years. Of the 277 patients treated with radical resection, postoperative radiation was superior to preoperative radiation in increasing locoregional control (65% vs. 48%, $p$ = 0.04) and trended toward improved OS (38% vs. 33%, $p$ = 0.10). Among the 43 oral cavity/oropharynx treated with definitive radiation therapy, locoregional control was lower compared to those undergoing resection and pre-op or post-op radiation (38% vs. 43% vs. 52%, respectively) but not significantly different likely due to small numbers of patients. Survival was similar (33% vs. 30% vs. 36%, respectively). The rates of severe surgical or radiation complications requiring hospitalization occurred in 15% to 20% and was not significantly different. Thus, this trial appeared confirmed that postoperative radiation is the best treatment sequence for patients undergoing radical resection of the primary site.

## Dose Escalation in Postoperative Radiation

Retrospective studies have demonstrated the importance of dose escalation to overcome the greater risk for recurrence for close or positive margins.[89,90,92] The value of dose escalation with postoperative radiation was explored in a prospective, randomized trial reported by Peters stratifying 302 radically resected patients as low, intermediate, or high risk for locoregional recurrence based on an empirically derived scoring system evaluating margin status, stage, and pathologic factors.[118] Patients were randomized to four dose levels at 52.2 Gy, 57.6 Gy, 63 Gy, and 68.4 Gy to the resection bed whereas 54 Gy was delivered to nonsurgically treated areas of potential subclinical disease. Analysis of 240 patients at a median follow-up of 45 months failed to validate the scoring system but did show that ECE was the overriding risk factor for locoregional recurrence (30% vs. 19%, $p$ = 0.04). For the 110 patients with ECE, a dose of 63 Gy was superior compared to <57.6 Gy (locoregional recurrence 26% vs. 48%, respectively) but there was no further benefit at 68.4 Gy (locoregional recurrence 28%) and more complications. There did not appear to be a comparable increased risk for neck relapses (neck control: <54 Gy, 89%; 57.6 Gy, 86%; 63 Gy, 89%). For patients stratified to the high-risk group, there did not appear to be any significant benefit with regard to neck control rates (84% vs. 77%) when the 63 Gy dose level was compared with the 68.4 Gy dose level. Although these observations may reflect an underpowered analysis, it has been concluded that a dose of at least 63 Gy is warranted to postoperative sites at greatest risk. The study did show that the presence of two or more risk factors predicted a high risk for failure. These factors included the presence of a primary oral cavity site, close or positive surgical resection margins, perineural invasion, two or more metastatic lymph nodes, node diameter >3 cm, a treatment delay to PORT >6 weeks, and a Zubrod performance status of >2. Based on this trial, minimum doses of 57.6 Gy are recommended to the whole operative bed with boost to 63 Gy to areas at high risk, especially where ECE is present.

## Altered Fractionated Postoperative Radiation

The value of accelerated postoperative radiation to decrease the total treatment package time was demonstrated in a follow-up multi-institutional randomized trial reported by Ang et al.[110] Patients were stratified by risk according to the risk factors identified in the aforementioned study. Patients with no adverse pathologic factors were deemed low risk and not given PORT. Patients with one pathologic risk factor were deemed intermediate risk and treated with conventional fractionated radiation to a dose of 57.6 Gy in 6.5 weeks. Those with ECE or the presence of >2 risk factors were deemed high risk and treated with high-dose conventional radiation to 63 Gy/7 weeks or to accelerated radiation by delayed concomitant boost to 63 Gy/5 weeks. At a median follow-up of 59 months, locoregional control was excellent for low-risk patient who were observed and intermediate-risk patients (5-year actuarial LRC 90% vs. 94%, respectively). High-risk patients had a 5-year actuarial LRC and survival rate of 68% and 42%, respectively. Within this cohort, patients undergoing accelerated postoperative radiation had a nonsignificant improvement in LRC ($p$ = 0.11) and survival ($p$ = 0.08). The value of accelerated treatment was based on the ability to keep the treatment package time to 11 weeks or less as patients who were started with a 7-week conventional course of radiation within 4 weeks of surgery did as well as the accelerated radiation group. These results confirmed that in the absence of adverse pathologic factors, as studied, low-risk patients do not require PORT. In contrast, high-risk patients need a shortened treatment package time.

## Post-op Chemoradiation for High-Risk Disease

***Sequential Post-op Chemoradiation.*** The role of chemotherapy has been integrated into locoregional management due to the poor survival outcomes (30%–40%), potential for improved locoregional control from 70% to 80% and distant metastasis in 20% after standard therapies. The concept of synergistic effect of cisplatin-based chemotherapy and radiation has been reviewed.[119]

The NCI-sponsored Head and Neck Contracts Program multi-institutional phase III trial was conducted between 1978 and 1982 in 462 patients with resectable stage III/IV cancers of oral cavity/larynx/hypopharynx testing the possible benefit of either induction or adjuvant chemotherapy in patients receiving conventional postoperative radiation.[120] Patients were randomized to three arms: (a) standard resection and postoperative radiation, (b) induction cisplatin/bleomycin for one cycle followed by standard therapy, or (c) therapy as outlined in (b) followed by maintenance cisplatin chemotherapy for 6 months. Radical neck dissection was performed in node-positive patients. Radiation therapy was delivered with conventional technique to final doses of 60 to 70 Gy for any residual disease. There was no differences in postoperative surgical complications or delays in initiating radiation therapy in chemotherapy patients compared to standard therapy patients. No differences in acute or late radiation toxicities could be detected with the addition of chemotherapy. At a median follow-up of 61 months, the incidence of DM was significantly decreased in patients receiving maintenance chemotherapy (9% vs. 19% vs. 19%, $p$ = 0.025 and 0.021, respectively) compared to the standard and induction chemotherapy patients. The difference in distant metastasis was even more remarkable given that 45% randomized to the maintenance arm did not receive any chemotherapy due primarily to patient refusal, cancer recurrence, or death whereas only 9% received all six cycles. No difference in locoregional control was noted. Overall or DFS in maintenance chemotherapy patients was not statistically significantly increased compared to standard and induction arms (OS: 45% vs. 35% vs. 37%, respectively) and (DFS: 64% vs. 55% vs. 49%, respectively). However, adjuvant chemotherapy is not routinely recommended given the poor compliance and lack of evidence of survival benefit in large meta-analysis.[2–5,121]

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Intergroup-0034 randomized 442 patients to standard surgery and radiation therapy versus surgery followed by CDDP/5FU chemotherapy for three cycles then postoperative radiation.[121] Only patients with negative margins were entered and then stratified according to low or high risk. High-risk patients included those with close surgical margins (<5 mm), extracapsular extension or *in situ* disease at the margins. For all patients, there was no difference in locoregional control, disease-free survival, or OS. The incidence of first failure in the neck (10% vs. 5%, $p = 0.03$) and DM (23% vs. 15%, $p = 0.03$) was lower in the chemotherapy arm. However, among patients with high-risk disease, there was a suggestion that chemotherapy did decrease locoregional failure (28% vs. 34%, $p = 0.07$) and improve OS (50% vs. 39%, $p = 0.06$).[121]

***Concurrent Post-op Chemoradiation.*** Based on the Intergroup-0034 study, a high-risk group was identified that might benefit from chemotherapy. The concept of combining chemotherapy concurrent with radiation to provide synergistic benefit and spatial cooperation (radiation to cover locoregional disease and chemotherapy to address systemic micrometastasis) had been proposed and tested in multiple trials using single or polychemotherapy regimens in the definitive setting. Subsequent large meta-analyses demonstrated that the benefit of chemotherapy on survival and locoregional control was largely derived when combined concurrently. Although multiple chemotherapy regimens had been studied, the most consistent to offer a benefit was single-agent cisplatin.

Two landmark studies were organized independently in Europe (EORTC 22931) and in the United States (RTOG 95-01).[122,123] Both tested whether the addition of three cycles of high-dose cisplatin concurrent with conventionally fractionated postoperative radiation could benefit patients at high-risk for recurrence. The dose of cisplatin was 100 mg/m$^2$ every 3 weeks while the dose of radiation in the RTOG study was 60 to 66 Gy and 66 Gy in the European Organization for Research and Treatment of Cancer (EORTC) trial. Definition of high risk included extracapsular extension and positive margins in both studies; however, each study had other nonoverlapping eligibility criteria including multiple nodes in RTOG 95-01 and lymphvascular invasion, perineural invasion, stage III/IV disease, or level IV or V nodal involvement in oral cavity/oropharynx primaries in EORTC 22931. The primary endpoint in the RTOG trial was locoregional control whereas progression-free survival was the primary objective in the EORTC study. Table 14.6 compares the patient characteristics and outcomes of both trials. Oropharynx cancers comprised a greater proportion of patients (42% vs. 30%) in the RTOG study whereas the EORTC study had more hypopharynx cancer (20% vs. 10%). More N2/3 patients were entered in the RTOG study (94% vs. 57%). The incidence of ECE was similar between the two studies (RTOG: 53% vs. EORTC: 57%), but more positive margins were noted in the EORTC study (29% vs. 10%). Also, the majority of patients in the EORTC study received 66 Gy whereas only about a tenth of patients in the RTOG study did so. At a median follow-up of 60 months in the EORTC study and 46 months in the RTOG, the addition of chemotherapy improved the primary endpoints. Both studies showed about a 9% to 13% improvement in loco-regional and DFS, with no difference in incidence of distant metastasis. OS was statistically improved in the EORTC study with a 13% absolute improvement at 5 years and trended toward significance in the RTOG trial with a 9% absolute 4-year increase.

**TABLE 14.6 Comparison of Phase III Postoperative Chemoradiation versus Radiation**

| | RTOG95-01 | EORTC22931 |
|---|---|---|
| Number of patients | 459 | 334 |
| **Pt characteristic** | | |
| OPX/OC/LX/HPX | 42%/27%/21%/10% | 30%/26%/22%/20% |
| % T3–4 | 61% | 66% |
| % N2–3 | 94% | 57% |
| **High-risk criteria** | | |
| Percentage with ECE-margin | 49% | 41% |
| Percentage with positive margins negative ECE | 6% | 13% |
| Percentage with ECE and positive margins | 4% | 16% |
| Percentage with ECE and/or positive margins | 59% | 70% |
| RT: percentage receiving 66 Gy | 13% | 91% |
| >Grade 3 acute toxicity (CT/RT vs. RT) | 77% vs. 34% ($p < 0.0001$) | 44% vs. 21% ($p = 0.001$) |
| All late toxicity (CT/RT vs. RT) | 21% vs. 17% ($p = 0.29$) | 38% vs. 41% ($p = 0.25$) |
| Median follow-up | 46 mo | 60 mo |
| **Outcomes(CT/RT vs. RT)** | | |
| Locoregional failure | 3 yr: 22% vs. 33% ($p = 0.01$) | 5 yr: 18% vs. 31% ($p = 0.007$) |
| Disease-free survival | 3 yr: 47% vs. 36% ($p = 0.04$) | 5 yr: 47% vs. 36% ($p = 0.04$) |
| Overall survival | 3 yr: 56% vs. 47% ($p = 0.09$) | 5 yr: 53% vs. 40% ($p = 0.02$) |
| Distant metastases | 3 yr: 20% vs. 23% ($p = 0.46$) | 5 yr: 21% vs. 24% ($p = 0.61$) |

OPX, oropharynx; OC, oral cavity; LX, larynx; HPX, hypopharynx; ECE, extracapsular extension; CT, chemotheraphy; RT, radiation therapy.

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A pooled analysis of the two studies was reported by Bernier et al.[124] For all 750 patients, the chemoradiation group had improved locoregional control (hazard ratio [HR] = 0.581), DFS (HR = 0.772), and OS (HR = 0.776) compared to radiation-only patients. Among the 479 patients with either ECE or positive margins, the benefit of concurrent chemoradiation was even larger for all three endpoints: LRC (HR = 0.524), DFS (HR = 0.695, $p = 0.0$), and OS (HR = 0.702, $p = 0.0$). However, chemoradiation showed no benefit in RTOG patients with multiple nodes in any of the 3 endpoints and trended toward a locoregional control advantage (HR = 0.42, $p = 0.10$) and OS benefit (HR = 0.75, $p = 0.06$) in the EORTC patients who qualified based on the other criteria without ECE or positive margin. Because of the small number in the latter group of EORTC patients ($n = 101$) having a wide variety of eligibility criteria with only a trend toward improved outcomes, no definitive conclusions could be drawn about the addition of chemotherapy in patients with these criteria.

In summary, the use of PORT remains an important component in the management of locally advanced resectable HSNCC with pathologic high-risk features for relapse. Of these, the presence of nodal ECE is a dominant factor influencing the risk for regional relapse. There is persuasive retrospective and compelling level I evidence supporting the use of concurrent chemotherapy with PORT to reduce locoregional relapse and improve survival. Patients undergoing surgical resection, in which PORT is deemed to be likely, should be jointly evaluated prior to surgery to minimize treatment delay. Standard PORT remains with a daily fractionated schedule to at least one dose of 60 to 66 Gy to high-risk areas with the use of accelerated schedules or concurrent chemotherapy remaining promising but requiring further study.

## Primary Radiation Treatment of the Node-Positive Neck

The management of nodal metastases with primary radiation therapy has been recognized as an alternative treatment to surgery for small solitary nodes, but for increasing size and number of nodal metastases, surgery has been traditionally integrated due to the concern that such metastases are more radioresistant. With the emergence of more intensive chemotherapy and radiation therapy regimens to treat the majority of cancers of the pharyngolarynx, the effectiveness of primary radiation to control neck disease has been reevaluated. Fletcher recognized that nodal radiocurability was inversely related to the size of the metastases and the need to deliver higher doses to achieve radiocurability.[58] Certainly for N1 disease, primary radiation therapy alone offers excellent control, but is suboptimal for N2–3 disease. Traditionally, the combination of radiation and neck dissection has yielded the optimal regional control in the N2–3 patients. Improvements in locoregional control with the addition of concurrent chemotherapy, altered fractionated radiation and radiation techniques such as intensity modulated radiation and brachytherapy as well as improvement in imaging to detect residual disease has challenged this paradigm. Increasingly, it has been argued that a planned neck dissection may not be required in patients in whom a complete clinical response has been achieved after more intensive radiation-based regimens primarily with concurrent chemoradiation.[125] Better functional and anatomic imaging posttreatment has improved the selection of who may be spared a neck dissection.

***Radiation Therapy Alone.*** Thariat reported the MDAC experience of 880 node-positive patients who were treated with definitive radiation therapy either with conventional or accelerated radiation by delayed concomitant boost fractionation. Concurrent chemotherapy was given in 19% of patients. Nodal stage was 21% N1, 71% N2, and 6% N3. Primary sites were 77% oropharynx, 14% larynx, and 9% hypopharynx. CT was performed 4 to 8 weeks after radiotherapy. Forty-three percent (377/880) achieved a complete response (CR) and were observed. Of those with less than a CR, 53% (268/503) underwent neck dissection at median time of 9 weeks after radiotherapy. Pathologic residual disease remained in 30%. At a median follow-up of 51 months, regional failure for the entire group was 12% and among those with a CR, partial response (PR), and neck dissection, PR without neck dissection was 8%, 10%, and 24%, respectively. Isolated regional failure was 4%. Multivariate analysis showed lower risk for patients with oropharynx primary (HR 0.47, $p < 0.001$) and those with complete pathologic response (HR 0.10, $p < 0.001$), while N3 status (HR 3.97, $p < 0.001$), T3–4 tumors (HR 2.16, $p < 0.001$), those with less than a CR (HR 2.61, $p < 0.001$) were at higher risk.

In a retrospective review of 110 patients, in whom primary lesions were controlled, Mendenhall et al. demonstrated an inverse relationship between the size of the lymph node and its subsequent control rate after definitive radiation therapy.[126] For lymph nodes 1.5 to 2 cm, 2.5 to 3 cm, 3.5 to 6 cm, >7 cm, the regional control rates were 88%, 74%, 70%, and 0%, respectively. These authors also demonstrated a marked influence of treatment time and total dose for lymph nodes 2.5 to 6 cm, implying that a more accelerated schedule may be particularly important for regional control. In a follow-up retrospective review, Mendenhall et al. confirmed a high regional control rate of 92% in an updated cohort of patients with a single lymph node <3 cm treated with daily fractionated radiotherapy alone.[127] There was no apparent difference in regional control when compared with a cohort of patients treated with radiation and a planned neck dissection (91%) confirming the adequacy of radiotherapy alone for N1 disease.

The Institute Gustave Roussy reported the largest experience using definitive radiation therapy for the treatment of large nodal disease.[49,128–130] Bataini and Bernier reported on the impact of nodal regression and regional control probability on 708 node-positive oropharynx or pharyngolarynx cancers treated with definitive radiation therapy with doses >55 Gy (two-thirds received >70 Gy) using accelerated radiation (6-week treatment duration) fractionation and cobalt shrinking field technique.[128] Measurement of maximal nodal diameter was made at the completion of radiation as well as 2, 4, and 6 months after radiation. At the completion of the radiotherapy, one-third (247/759) of metastatic nodes had demonstrated a CR. With further follow-up, 72% (546/759), 77% (586/759), and 79% (597/759) of lymph nodes had demonstrated a CR at 2, 4, and 6 months, respectively. The mean time to CR for lymph nodes <3 cm, 3 to 6 cm, and >6 cm was 40, 51, and 62 days, respectively. The probability of obtaining a nodal CR was dependent on initial maximal nodal diameter. At 2 months, 83% of nodes <3 cm, 63% of nodes 3 to 6 cm and 45% of nodes >6 cm achieved a CR. By 6 months, the CR rates were 90%, 80%, and 55%, respectively. However, if a CR had been attained, the risk for regional failure rate was 8%, independent of the initial nodal size. Regional control for all patients with lymph nodes <3 cm, 3 to 6 cm, and >6 cm was 90%, 85%, and approximately 75%, respectively. A dose–response relationship was observed with a dose of 65 Gy, 70 to 75 Gy, and 75 Gy recommended for lymph nodes <3 cm, 3 to 6 cm, and >6 cm, respectively.[129] If residual disease persisted at 4 and 6 months, the chance for regional failure was 50% and 75%, respectively. The chance for obtaining CR was associated with site of tumor origin. The probability of complete nodal response at the end of radiation was worse for the 239 pharyngolarynx patients compared to the 469 oropharynx patients (22% vs. 40%, $p < 0.0001$). The estimated rate of regional control was 90% in nodes <3 cm with 65 Gy, 85% nodes 3 to 6 cm treated with 70 to 75 Gy and 75% for nodes >6 cm treated with 75 Gy. With regard to DFS, nodal size >6 cm, involvement of mid- or lower jugular nodes, or

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involvement of posterior cervical nodes with upper jugular nodes fixation of a single node prognosed a worse DFS. Moderate to severe complications were reported in 9% of patients (crude) with 3% of patients with complications related to neck irradiation.[129] The majority of these complications were noted to be cervical fibrosis associated with entrapment and paralysis of the hypoglossal nerve.[129] Others also reported >RTOG grade 2 fibrosis in 22% of patients treated with definitive radiation[94] and caution treatment of nodes extending into the low neck due to the risk for brachial plexopathy and severe fibrosis.[131]

An analysis by Prada Gomez et al. is relevant in providing insight into the factors influencing the radiocurability of lymph nodes describing selection criteria for patients requiring a neck dissection.[132] They reported a multivariate analysis for regional control rates in a large cohort of 313 patients treated predominantly with daily fractionated radiotherapy. A wide range of dose was delivered between 50 and 80 Gy. Significant independent factors included lymph node response to radiation ($p = 0.0000$), lymph node size ($p = 0.0000$), radiotherapy dose ($p = 0.0037$), control of the primary lesion ($p = 0.0015$), and treatment of recurrent nodal metastases following prior definitive surgery ($p = 0.0286$). With the primary controlled, regional control for lymph nodes <3 cm and for nodes >3 cm was 89% and 32%, respectively.

Bartelink demonstrated that the regression rate of nodal metastases during radiation was prognostic in a cohort of 27 patients treated to 70 Gy in 7 weeks using bi-dimensional measurements of index lymph nodes.[133] Only 1 of 12 patients with a fast regression rate (defined by a nodal volume halving time of 20 days during radiation therapy) developed a neck recurrence. In contrast, neck recurrence was significantly greater (7 of 15 patients) with a slower regression rate. Furthermore, the prognostic distinction could be made as early as day 28 after the start of the radiotherapy. In a larger study of 233 patients with nodal disease treated with primary radiation therapy, Bartelink et al. also demonstrated that persistent disease at 6 weeks post radiation corresponds with an increased risk for regional recurrence. Large nodal diameter, fixation, and multiple nodes were the main risk factors for persistent disease.[134]

***Altered Fractionated Radiation.*** The value of altered fractionated radiation has been demonstrated to improve locoregional control in stage III/IV head and neck cancers.[7–10] Altered fractionation regimens proven to increase locoregional control compared to conventional fractionation include hyperfractionated radiation which allows dose escalation typically to 77 to 80 Gy, accelerated radiation by delayed concomitant boost which attempts to overcome on treatment tumor repopulation as well as the DAHANCA regimen of six conventional treatments per week.[9] Furthermore, of these regimens, meta-analysis further show an apparent survival benefit from hyperfractionated radiation.[10]

Peters reported on 100 node-positive oropharyngeal carcinoma patients treated with accelerated radiation by delayed concomitant boost technique.[131] Seventy-five had definitive radiation therapy to the nodal region with 13 having residual disease requiring neck dissection whereas the other 62 had CR and were observed. The probability of achieving a CR after definitive radiotherapy was inversely related to maximal diameter of the involved node, as 12/13 patients with residual disease had tumor >3 cm. However, as reported by Bataini,[130] if a CR was achieved, the initial maximal nodal diameter did not impact on regional control (87% if initial tumor diameter was <3 cm vs. 85% if tumor diameter was >3 cm). The other 25 patients underwent excisional biopsy ($n = 8$) and neck dissection ($n = 17$) prior to radiotherapy. N stage for all patients were as follows: N1, $n = 35$; N2a, $n = 20$; N2b, $n = 18$; N2c, $n = 13$; and N3, $n = 14$. Radiation dose to gross disease was 72 Gy, and six patients received induction cisplatin and 5FU. At a median follow-up of 39 months, regional control was 87% (13/100). Among the 62 who attained a CR after definitive radiation therapy, the crude regional failure was 11% (7/62) and isolated regional failure in 5% (3/62). In the subgroup of complete responders, there was no difference in regional control between lymph nodes <3 cm and those >3 cm. Neck failure was greater in nodes >3 cm demonstrating an incomplete response. For the 13 patients achieving less than a CR and proceeding to resection, the regional failure was 0%. Among the 25 patients treated with neck surgery initially prior to radiotherapy, the regional failure was 24% (6/25). Regional failure was higher in patients who also had local failure versus those who had primary local control (33% [5/15] vs. 9% [8/85], respectively). Surgical salvage was attempted in 7 of 13 patients with regional failure and successful in one. With regard to toxicity, RTOG grade >3 fibrosis occurred in 22% of the definitively treated radiation patients and in 27% of patients treated with neck surgery and radiation. No difference was reported if surgery was added. However, if the initial nodal size was >6 cm, the risk of severe fibrosis was 40% versus 24% if the initial nodal diameter was 3 to 6 cm.

Parsons et al. reported the impact of the hyperfractionated radiotherapy studied on regional control rates censoring for primary failures due to the possibility of reseeding.[135] In this retrospective review, a small subgroup of patients with advanced neck disease (based on the 1983 American Joint Committee on Cancer system) did not receive a planned neck dissection as per specific departmental policies. For patients with solitary large nodal metastases (N2A and N3A) treated with radiation and a neck dissection (17 patients) or definitive hyperfractionated radiotherapy (9 patients), the 5-year actuarial regional control rate was 74% versus 41% ($p = 0.036$), respectively. The proportion of patients with N2A and N3A was noted to be virtually identical between these two patient cohorts. Similar observations were noted when comparing patients with multiple advanced neck nodes (N2B and N3B) with 5-year actuarial regional control rates of 85% (39 patients) and 68% (43 patients) ($p = 0.03$) for patients treated with a planned neck dissection or definitive radiotherapy, respectively. Wound complications in patients undergoing neck dissection occurred in 6/58 patients consisting of wound separation, flap necrosis. No carotid rupture or fatal complications were noted. The authors noted reservations regarding the use of high-dose definitive radiotherapy for large-volume N2 to N3 neck disease due to inferior regional control rates and increased neck fibrosis with increased surgical wound complications.

In summary, treatment of N2–3 disease with altered fractionated radiation therapy results in CR rates of 65% to 80%, with regional failure in 10% to 20% despite CR. Neck dissection was performed in 20% to 35% who achieved less than a CR after patients received full-dose radiation therapy. The incidence of complications from definitive radiation therapy appeared to be increased fibrosis especially for large nodes as well as increased wound complications if neck dissection is required for persistent disease. For patients attaining a CR, it remains unclear if a neck dissection can further reduce the risk for regional relapse, and the risk for surgical complications may offset any additional benefit that may exist.[136] Several investigators have advocated salvage neck dissections based on nodal response to definitive radiotherapy.[125,131] Daily fractionated radiotherapy to definitive doses appears sufficient for nodal masses <3 cm. When considering primary regional irradiation for bulky nodal disease, it is important to select patients in whom the primary lesion has a high probability of control to definitive irradiation. It is important to balance this strategy with the increased neck fibrosis that is particularly problematic when irradiating large neck volumes and in critical locations where entrapment and paralysis of the brachial plexus and CN XII may be of concern.

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## Radiation Therapy with Planned Neck Dissection

Multiple series have consistently reported efficacy of a planned neck dissection for advanced neck disease treated in conjunction with moderate doses of radiation therapy.[137–144] In general, high regional control rates have been reported with high rates of positive pathologic neck specimens suggesting therapeutic benefit. Typically, positive neck specimens have been seen in 30% to 50% of cases. One of the earliest reports, using low-dose preoperative radiation therapy (20 Gy), to decrease neck recurrence was reported by Strong.[85,145] However, this was shown to be ineffective by Ogura and this low-dose approach has largely been abandoned.[146] MacComb and Fletcher[147] introduced the concept of moderate doses of radiotherapy combined with a planned neck dissection that was further supported by Barkley et al.[64] This combined modality approach further evolved to treat N2 and N3 disease.

Several groups have reported excellent regional control outcomes after conventional doses of preoperative radiation therapy followed by planned neck dissection. Mendenhall et al.[127] reported that the addition of a neck dissection appeared to increase the regional control rate in patients with multiple nodes. These investigators also demonstrated that the risk for post–neck dissection wound complications was increased when maximum subcutaneous doses >60 Gy were delivered (17% vs. 6%) with a suggestion that most of the increased complications occurred when the neck dissection was performed >6 weeks after radiotherapy (29% vs. 14%). Further analysis noted a dose-dependent relationship for neck dissection wound complications for doses 45 to 90 Gy.[148] Currently, 60 Gy is delivered to nodal metastases with a planned neck dissection.

Lee et al. reported on a cohort of 58 patients with base of tongue carcinoma treated uniformly with 60 Gy delivered to palpable nodal disease followed by a planned neck dissection for all patients with N1 to N3 neck disease.[137] All patients had base of tongue cancers with N1 disease in 24, N2 in 25, and N3 in 7. As a brachytherapy implant was used to boost the primary, the use of a neck dissection was incorporated during the general anesthesia required for the implant. Pathologic residual disease was noted in 30%. At a median follow-up of 36 months, 5-year actuarial regional control rate of 96% was observed. In contrast, an actuarial regional control rate of 86% was noted in a cohort of patients treated with radiotherapy alone to the neck before the institutional policy of planned neck dissections was employed. All patients undergoing planned neck dissection were controlled while 1 of 7 who had a CR after induction chemotherapy recurred after radiation without neck dissection. It is also noteworthy that a clinical CR (cCR) lacked sufficient predictive power for a pathologic CR. Discordant results were observed with not only patients with cCRs demonstrating persistent pathologic disease but also patients with clinical PRs having a negative pathologic specimen. Hence, the authors concluded that despite the potential of overtreatment in possibly 70% of treated patients, systematic planned neck dissection was recommended given the favorable therapeutic ratio. Other comparable retrospective series reporting the results of comparable strategies in the treatment of base of tongue carcinomas have demonstrated high regional control rates.[149–151]

The University of Florida has advocated the use of planned neck dissection after external beam radiotherapy (EBRT) especially for patients with N2–3 neck disease.[152] In comparing 5-year neck control of 196 treated with radiation alone compared to 144 heminecks treated with combined surgery plus neck dissection, patients with N2b or N3 disease had better regional control with neck dissection added (regional failure 9% vs. 30% for N2b, $p < 0.01$; 31% vs. 67% for N3, $p < 0.01$) but not patients with N2a disease (regional failure 32% vs. 21%, $p = 0.6$). The authors recommended tailoring of preoperative dosing depending on size and location of node as well as fixation. Thus, 50 Gy was advised for mobile nodes 3 to 4 cm, 60 Gy for nodes up to 5 to 6 cm and fixed nodes while 70 to 75 Gy was recommended for nodes 7 to 8 cm.

## Neck Dissection Prior to Radiation Therapy

Byers et al. have reported on the results of initial neck dissection prior to a definitive course of radiotherapy to the primary site that included postoperative neck radiotherapy.[153] Typically, this strategy was undertaken to minimize the overall treatment time for early primary lesions with advanced resectable unilateral nodal disease where a general anesthetic was thought to be required for dental extractions with the advantage of avoiding a second anesthetic. These investigators demonstrated that the success of this strategy necessitated meticulous attention and skill to minimize any delay >2 weeks to start radiotherapy. In patients with a delay >14 days, OS was decreased (82% vs. 38%, $p = 0.010$). More than half (20/35) experienced such treatment delay for unclear reasons. The regional failure rates were not reported with this approach. Smeele reported on 35 patients with N2–3 neck disease who underwent neck dissection then definitive radiation therapy to the primary site. The mean interval between neck dissection and radiation therapy was 35 days. Overall locoregional control was 43% at 2 years with regional failure in 20% (7/35). Disease-specific survival was 49% at 2 years.

Although the sequencing of a planned neck dissection after definitive radiotherapy is not without disadvantages, the use of an up-front neck dissection does not appear to provide any significant benefit, and this strategy poses the potential for altered lymphatics and a necessity to irradiate the surgical scar and drainage sites with increased irradiated normal tissues.

## Primary Chemoradiation

Given the success of organ-preservation approaches, definitive chemoradiation for the node-positive neck has become increasingly popular with neck dissection either as a planned procedure or reserved for salvage of persistent/recurrent disease. For N2–3 disease, the integration of planned neck dissection was thought to yield optimal regional control. However, with intensive regimens of concurrent chemoradiation as well as induction chemotherapy, high rates of CR can be confirmed with anatomic and functional imaging. With careful surveillance, regional control comparable to patients treated with planned neck dissection after chemoradiation. Patients who are found to have residual pathologic residual disease on neck dissection after chemoradiation have worse survival, locoregional, and particular higher risk for distant metastasis. However, the benefit of additional therapy remains to be established in this setting.

## Planned Neck Dissection after Concurrent CT/RT

Following paradigms combining radiation followed by neck dissection especially for N2/3 disease, numerous series have reported excellent regional control for N2/3 patients treated with concurrent chemoradiation with planned neck dissection.[130,133–140] The bulk of the data are derived from single institution series with some data from randomized studies. In the majority of these series, planned neck dissection after initial definitive treatment to the primary site results in regional control rates of 93% to 99%, with pathological residual disease of 20% to 40% (Table 14.7).

Stenson et al. reported on 69 of 237 patients treated with concurrent chemoradiation undergoing a planned neck dissection for N2 or N3 neck disease or for residual adenopathy.[154] SND was performed in >82% of patients with radical or modified radical in the rest. Of the 63 patients evaluable radiographically

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**TABLE 14.7 Chemoradiation and Planned Neck Dissection for N2/3 Neck**

| | Number of Patients | Median Follow-up (mo) | Pathologic Residual (%) | Regional Failure (%) | Toxicity |
|---|---|---|---|---|---|
| Sewall et al. (2007)[210] | 93 (chemotherapy in 43 patients) | 28 mo | 28% | 7% | 10% (chyle leaks, abscess, hematoma, wound dehiscence) |
| McHam et al. (2003)[157] | 76 | NS | 33% | 7% | NS |
| Stenson et al. (2006)[209] | 69 (91) | 30 mo (mean follow-up) | 35% | 1.4% | 10% wound complications. 6% required additional surgery (chyle leak, seroma, accessory nerve transaction, Horner's syndrome) |
| Argiris et al. (2004)[155] | 61 | 4.6 yr | 31% | 1% | — |
| Brizel et al. (2004)[158] | 52 | 48 mo | 35% | 2% | 8% (wound dehiscence and vagal injury) |
| Frank et al. (2005)[160] | 39 | 24 mo | 35% | 3% | 5% (chyle leak and wound dehiscence) |
| Lavertu et al. (1997)[156] | 35 | 36 mo | 34% | 3% | — |
| Robbins et al. (2005)[159] | 35 | 36 mo | 43% | 3% | 17% chyle fistula, flap necrosis, wound breakdown and hematoma |
| Ahmed et al. (2000)[249] | 19 (all N3) | 15 mo | 26% | 0% | NS |

after chemoradiation, 48% had a CR (30/63). Pathologic residual disease persisted in 35% of the neck specimens (N2: 36%, N3: 50%, $p = 0.09$). No significant relationship could be detected between radiologic CR or PR with residual microscopic disease. The negative predictive value (NPV) of a radiographic CR was 0.77 (23/30) and the positive predictive value (PPV) of a radiographic PR was 0.39 (13/33). At a median follow-up of 30 months, the regional failure was 1.4% (1/69).

In a follow-up report with more patients, Argiris reported on 131 N2/3 patients treated with concurrent chemoradiation consisting of hyperfractionated radiation using 5FU/hydroxyurea on an alternate-week schedule with radiotherapy plus cisplatin or paclitaxel.[155] Thirty-nine were observed and compared to 92 N2/3 patients treated similarly who underwent neck dissection. The decision to proceed with neck dissection was based on institutional bias in this multicenter study. At a median follow-up of 4.6 years, the actuarial 5-year regional failure rate was 18% in those patients observed versus 1% in those undergoing neck dissection ($p = 0.0007$). Among the 30 patients who had a CR and were observed, the actuarial regional failure rate was 8%. Evaluating all patients having achieved a CR ($n = 92$), the addition of neck dissection did not improve OS (53% vs. 49%, $p = 0.95$) or regional failure (2% vs. 8%, $p = 0.21$). Among the 34 patients having a PR, the addition of a neck dissection did improve survival (68% vs. 12%, $p = 0.0003$) and decreased regional failure (0% vs. 74%, $p = 0.0002$). Among the 104 N2 patients, the addition of a neck dissection decreased regional failure (2% vs. 18%, $p = 0.004$) with no statistically significant improvement in 5-year OS (59% vs. 45%, $p = 0.19$) compared to those observed without neck dissection. Similarly, among the 27 N3 patients, the addition of neck dissection decreased regional failure (0% vs. 14%, $p = 0.09$) with no obvious statistically significant improvement in OS (55% vs. 29%, $p = 0.10$). However, there was a progression-free survival in N3 patients after neck dissection (79% vs. 36%, $p = 0.04$) but not for N2 patients (72% vs. 70%, $p = 0.78$). Based on these findings, the authors conclude that neck dissection may be omitted in N2 patients attaining a cCR but should be planned for N3 patients.[155]

Lavertu et al. reported on the comparative results of neck management resulting from a randomized trial of concurrent cisplatin and 5FU (two cycles) and conventionally fractionated radiotherapy versus conventional radiotherapy alone.[156] Treatment response was assessed at both the primary and the neck after 50 to 55 Gy, with nonresponders (<50% response) and those with disease progression, proceeding to surgery. Otherwise, radiotherapy continued to 65 to 72 Gy followed by a planned neck dissection after evaluation at 4 to 6 weeks for residual disease or for N2 and N3 disease regardless of the response. The addition of chemotherapy was observed to increase the cCR rates in the neck compared with treatment with radiotherapy alone. Among N2–3 patient, the CR rate was 64% (30/47). Thirty-five patients with N2–3 neck disease had neck dissection (18 with a cCR and 17 with less than a CR) whereas 12 were observed after achieving a CR. Regional failure occurred in 3% (1/35). In comparison, 25% of 12 patients ($n = 3$) who were observed after achieving a CR in the neck recurred regionally. None of these latter three were salvageable. Despite observing no significant differences in survival for a planned neck dissection (which likely reflected an underpowered analysis), these investigators advocate a planned neck dissection for N2 and N3 disease irrespective of treatment response and for persistent adenopathy.

A follow-up study was reported from the Cleveland Clinic of 109 N2/3 patients treated with concurrent 5 Fluorouracil/Cisplatin (5FU-CDDP) with either conventional or hyperfractionated radiation.[157] Sixty percent (65/109) achieved a cCR. The probability of attaining a cCR was dependent on maximal node diameter (cCR: diameter <3 cm: 76% [19/25] vs. diameter >3 cm 55% [46/84], $p = 0.06$) as well as N stage (cCR: N2 66% [53/80] vs. 41% N3 [12/29], $p = 0.019$). Among patients who underwent neck dissection (32 with cCR and 44 with <cCR), the regional failure was 6.5% compared to 12% (4/33) who were observed after attaining a cCR. The clinical status of the neck had an NPV of 0.75 and

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PPV of 0.39. The authors conclude that the clinical status is not a useful tool to determine in which patients to omit SND.

Brizel reported a survival advantage in patients undergoing neck dissection based on 108 patients treated with hyperfractionated radiation and concurrent cisplatin/5FU.[158] Sixty-five underwent planned MRND whereas 43 were observed. Thirty patients had N1 disease whereas 78 were N2–3. Patients were assessed for clinical response by physical exam and CT scan. Of the 13 N1 patients undergoing neck dissection, 12 had a cCR prior to surgery whereas one had less than a CR. For these patients, the NPV was 92% after CR and PPV of residual nodal mass of 100%. Among N2–3 patients, 16 had a CR and were observed, 10 had progressive disease outside of the neck and did not proceed to neck surgery, and 52 proceeded to neck dissection. The NPV for CR and PPV for residual nodal abnormality for N2–3 patients was 74% and 44%, respectively. At a median follow-up of 4 years, patients with N2–3 neck and complete CR who underwent neck dissection had better 4-year DFS (75% vs. 52%, $p = 0.08$), lower regional failure (2% vs. 19%), fewer distant metastasis (10% vs. 31%), and increased OS (77% vs. 50%, $p = 0.04$) compared to N2–3 patients with CR who were observed. Neck dissection showed no survival benefit in N1 patients. The authors hypothesize that the survival benefit of neck dissection in N2/3 patients may be related to a smaller proportion of patients failing regionally (2% vs. 19%) and distantly (10% vs. 31%) in those patients undergoing neck dissection. Serious morbidity attributable to ND occurred in none of the N1 patients and 8% of the N2–3 patients including two with wound dehiscence and two with vagal nerve injury. Brizel reported accuracy of 60% between clinical response and pathologic findings in 52 patients treated with chemoradiation followed by planned neck dissection.

***Planned Neck Dissection after CT/RT for N3 Neck.*** Smyth reported on the University of North Carolina experience for 100 patients with N3 neck disease evaluated retrospectively treated over a 20-year period from 1989 to 2009.[158a] Tumor sites included oropharynx in 53 patients, hypopharynx or larynx in 22 patients, and oral cavity in 8 patients. Seventy-six patients received definitive chemoradiation versus 24 undergoing up-front resection. Patients were well balanced with regard to age, sex, and nodal size whereas chemoradiation patients had a greater proportion of T3/4 disease (54% vs. 25%). Reflecting the changing practice patterns toward definitive chemoradiation, surgically treated patients had longer follow-up (9.5 vs. 1.6 years). Twenty-two percent had evidence of unresectable disease characterized by carotid encasement or invasion of the deep muscles and treated with chemoradiation. Patients treated with primary resection were compared to those treated with primary chemoradiation, and those treated with definitive resection appeared to have a better OS (5-year 68% vs. 32%) and DFS (64% vs. 32%). If unresectable patients were excluded, a trend toward survival benefit was maintained with surgery ($p = 0.07$ for OS and $p = 0.08$ for DFS). Patients with nonoropharyngeal primary cancers ($n = 46$) appeared to have a survival benefit with definitive neck dissection over chemoradiation (5-year OS 58% vs. 15%, $p = 0.02$ and 5-year DFS 58% vs. 10%, $p = 0.01$) but no statistical difference was seen among oropharyngeal carcinomas (5-year OS 80% vs. 46%, $p = 0.3$ and 5-year DFS 70 vs. 49%, $p = 0.5$).

Of the 76 patients treated with chemoradiation, 30% ($n = 22$) attained a CR, 53% ($n = 40$) had a PR, whereas 8% had stable disease and 8% had unknown outcome. Neck failure occurred in 4% (1/24) of dissected neck and 9% (4/44) of nondissected necks.

Postchemoradiation neck dissection did not change survival in patients with N3 disease. The authors recommended resection for nonoropharyngeal primary sites.

Based on these results, planned neck dissection after chemoradiation has also been advocated for regionally advanced neck disease given consistently excellent regional control as well as the low probability of successful salvage (14%–22%) of subsequent neck relapses.[126,131] However, opponents of such a systematic approach for N2/3 patients claims that neck dissection adds morbidity with marginal gain in regional control or survival especially since nearly two-thirds will have pathologically negative specimens.[125,136,139,143]

## Salvage Neck Dissection for PR after Chemoradiation for N3

Igidbashian reported on 70 N3 patients treated with concurrent chemoradiation with imaging at 6 to 8 weeks to evaluate patients for salvage neck dissection for a PR. CT criteria of CR was derived from their larger experience for node-positive patients, nodal response >90% shrinkage and/or nodes <1 cm. Eighty percent of patients had oropharynx primary sites. Overall, the CR rate was 37% (26/70) and these patients were observed except for two who underwent neck dissection. Of the 63% ($n = 44$) of patients with PR, 31 underwent neck dissection whereas 13 were unable to proceed to neck dissection due to disease progression ($n = 7$) or on treatment mortality ($n = 2$) or patient refusal ($n = 4$). At a median follow-up of 3.5 years, N3 patient observed after CR to chemoradiation had worse DFS compared to those who had a PR followed by salvage neck dissection (2-year DFS 63% vs. 85%, $p = 0.04$) because of higher rate of distant metastasis (33% vs. 7%, $p = 0.06$). OS at 2 years was not significantly worse (63% vs. 79%, $p = 0.26$).

## Extent of Neck Dissection after Chemoradiation

SND after chemoradiation represents the standard of care when integrated as a planned procedure typically within 6 to 8 weeks after chemoradiation. Compared to radical neck dissection, similar excellent regional control and lower morbidity are attained with SND even with bulky N2 or N3 disease. In only about one-third of patients undergoing planned neck dissection will residual viable pathologic nodal disease be found.

Multiple publications have shown that an SND after chemoradiation is adequate allowing lower wound complications and shoulder dysfunction with sparing of the spinal accessory nerve. Boyd showed that a low level of persistent nodal disease in level I and V existed in 28 patients treated with comprehensive neck dissection with only one patient with disease at level V, suggesting a level II to IV resection is adequate. Robbins suggest that radiation therapy is adequate to control disease in noninvolved nodal stations.[159] Multiple institutions have shown high rates of regional control after SND.[154,160,161]

## Super Selective Neck Dissection after PR with CT Evidence of One Nodal Station

Given that SND yields less wound complications and shoulder dysfunction, efforts to limit morbidity even further have brought into question whether even more targeted surgery at greatest risk for residual disease can further decrease morbidity without sacrificing regional control. Specifically, sparing levels IV and V are of particular interest. Inoue reported better functional outcomes and decreased pain when levels IV and V are not included in the neck dissection.[162]

Robbins' advocated the use of a super selective neck dissection confined to two nodal levels if residual lymphadenopathy is found on imaging at only one nodal level. He reported on 177 patients treated with concurrent chemoradiation using intra-arterial cisplatin. Tumor sites were as follows: oropharynx, 46%; hypopharynx, 22%; larynx, 15%; and oral cavity, 11%. Response

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was evaluated by CT of the neck, 6 weeks after treatment. CR in the neck was noted in 50%. Among the 89 patients with PR, 73 had evidence of residual adenopathy in one neck level. Of these 73 patients, 54 patients underwent 57 neck dissection whereas 19 were unable to proceed to neck dissection due to unresectable local disease ($n = 6$), distant metastasis ($n = 4$), death ($n = 3$), or noncompliance ($n = 3$). The majority had SND encompassing at least three nodal levels. Prior to treatment, 29 heminecks were deemed by CT imaging to have disease at one nodal level, 23 at two nodal levels, 4 at three nodal levels, and 1 at four nodal levels. Fifty-two of 54 had disease involving one level at the nodal stations predicted on the posttreatment neck CT whereas 2 patients had disease beyond the predicted nodal level with 1 at a contiguous nodal level and 1 at a noncontiguous nodal level. Thus, of the 54 patients with evidence of a single residual node, 53 would have disease encompassed by a super selective neck dissection of two nodal levels.[163]

Yeung also reported the benefit of using postradiation treatment CT to tailor neck dissection. CT response at 4 weeks after radiation therapy was correlated with pathologic findings on with neck dissection done at a median 7 weeks after treatment. Radiographic CR was defined as a node <1.5 cm without filling defects or calcifications. Sixty-one of 211 node-positive heminecks showed a CR at the initially involved nodal levels but underwent neck dissection with inclusion of the initially involved nodal station. Pathologic residual disease was found in 3 of 61 heminecks. When all 211 heminecks were examined by nodal level specifically, the NPV of the CT was 95% or greater for all nodal levels I to V. The authors conclude that there is a 5% risk of leaving disease behind if the initially involved nodes that have CR are left undissected.[164]

Cannady reported a retrospective single institution study of 241 N2/3 patients 329 node-positive necks treated with chemoradiation at the Cleveland Clinic. N3 comprised about 26% (63/241) of patients. Oropharynx comprised 68% of patients with 11% larynx and 12% hypopharynx. The primary site had to be in CR as an inclusion criteria. The complete clinical response was 65% (210/329) as defined by a negative physical exam and imaging with CT and/or PET after chemoradiation. Neck dissection was performed at a median of 10 weeks in 31% (65/210) of patients with complete clinical response and 81% in patients with a partial nodal response (96/119). Pathologic residual disease was found in 14% of those with a complete clinical response versus 40% in those with PR ($p < 0.01$). In analyzing the 47 necks with residual nodal disease, 72% had disease present in the originally positive node and 98% had disease at the original level or 1 distal level. Only one patient had disease beyond one distal level at level V. Regional failure occurred in 6.6% of patients (16/241) and was higher in patients with partial clinical response (9% vs. 3.4%, $p = 0.04$) and those with residual pathologic nodal disease ($p < 0.01$) as well as those with primary site recurrences ($p < 0.01$). Isolated regional failure occurred in 3.6% ($n = 10$) patients with primary site controlled and none were successfully salvaged with all dying with uncontrolled neck disease. No significant difference was noted based on neck dissection types. Distant metastasis occurred in 26% of patient with residual pathologic disease compared to 13% in those with complete pathologic response ($p < 0.05$). Neck dissection did not improve 5-year OS in those who achieved a complete clinical response compared to those who were observed (79% vs. 78%).[165]

## Role of Planned Neck Dissection for Patients with a CR to Chemoradiotherapy

There is no controversy regarding the role of a salvage neck dissection in patients who undergo primary radiation or chemoradiation and have a PR. Unquestionably, these patient require a surgical salvage whether it be a radical, modified radical, or selective neck dissection. Additionally, it is commonly accepted that a planned neck dissection is not required in low volume (N1) disease. The controversy that exists surrounds the role of a planned versus a salvage neck dissection in high volume (N2 or greater) disease who achieve a complete clinical response after radiation or chemoradiation. There are many centers worldwide that perform a planned neck dissection for N2 disease or greater regardless of the clinical response. Many feel that the high pathologic positivity rate (30%–40%) in postchemoradiation neck dissection specimens justifies a planned neck dissection regardless of the clinical response.[166,167] However, although pathologic positivity predicts for increased risk of both locoregional and distant failure, it is controversial whether patients attaining a CR after radiation or chemoradiation will have any added benefit from a neck dissection.[168]

The concept of withholding a planned neck dissection in patients who undergo a complete clinical response began in the early 1990s and has been steadily gaining momentum. In the early studies, complete regression of palpable disease was used to withhold a planned neck dissection. In these studies, regional failure was below 10%.[169–174] Posttreatment imaging has become increasingly utilized as a method to assess for PR or CR in addition to physical examination. The use of a posttreatment CT scan has become the most commonly utilized method of determining a patient's response to treatment. Retrospective studies examining locoregional failure rates range from 0% to 8%.[175–180] In 2008, Corry et al. published their study of 102 patients treated with chemoradiation for HNSCC with N2–N3 disease. They found that none of their patients who had a complete clinical response developed isolated regional recurrences and therefore concluded that a planned neck dissection was not justified in this subset of patients.[175]

More recently, with advent of more sophisticated imaging techniques such as FDG-PET/CT imaging, the role of the planned neck dissection has become even more questionable. PET-CT imaging has been shown to have an excellent and highly reliable NPV after a CR to chemoradiation.[181–185] This allows for an even higher level of comfort after a CR.

## MORBIDITY AFTER NECK DISSECTION

The main complication of a planned neck dissection is the increased risk for wound healing especially with the addition of concurrent chemotherapy. Interestingly, the data do not appear to show the risk to be unacceptably increased. Definitive doses of radiation, which are higher than the doses given when there is a plan for a staged neck dissection, appear to increase the risk for complications even more. Strategic planning to minimize the dose delivered to the neck and to ensure that the neck dissection is not unduly delayed will minimize the risk.

Davidson reported on 34 patients who underwent planned neck dissection after radiation therapy or chemoradiation.[136] Patients were treated with a mean preoperative dose of 58 Gy (50–80 Gy) and 37% ($n = 15$) patients received chemotherapy. Fifty-eight percent underwent radical neck dissection and 42% were treated with a supraomohyoid or MRND. The total complication rate was 45% with wound complications (skin necrosis, facial edema, chyle leak, seroma, nerve injury) in 24% ($n = 8$) and systemic (aspiration, urinary retention) in 21% ($n = 7$). Doses of 70 Gy or greater appeared to increase wound complications (42% vs. 14%, $p = 0.09$) and skin necrosis (33% vs. 0%, $p = 0.005$) when compared to those receiving lower doses.

Lavertu reported a comparison of 54 patients who underwent a neck dissection after radiation ($n = 30$) or chemoradiation ($n = 24$).[186] The patients had been gleaned from the phase III

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trial comparing radiation therapy alone versus concurrent chemoradiation. More patients in the chemoradiotherapy group were a higher neck stage (62% N2b–N3 vs. 43% N2b–N3) compared to the RT alone group. Selective, modified radical, and bilateral neck dissections were performed in 0, 15, and 4 patients, respectively, in the chemoradiation group whereas the corresponding numbers in the radiation-only group were 2, 16, and 0, respectively. Neck dissections were performed at a median of 7 to 8 weeks after radiation. Patients in the chemoradiation group had more wound complications with an increase in skin incision breakdown (33% vs. 7%). Overall, there were no major differences in overall complications (33% vs. 29%, $p = 0.68$) or major complications (0% vs. 7%) in the chemoradiation versus radiation-only group. No differences were noted in length of hospital stay, operative blood loss, or time between radiation and surgery. Thus, the addition of chemotherapy to radiation did appear to impair wound healing but not overall complications. Lavertu further reported that salvage ND performed later than 12 weeks after radiation was associated with an increased rate of major surgical complication compared with planned ND within 4 to 12 weeks (20% vs. 3.4%, $p = 0.04$) and overall complications (60% vs. 31%, $p = 0.04$).[186]

Stenson reported on the toxicity of 69 patients with node-positive disease treated with concurrent chemoradiation followed by SND ($n = 56$) or modified/radical neck dissection ($n = 13$). Two patients had N1 disease, 47 with N2, and 20 with N3 disease. CT was done usually 4 weeks after chemoradiation. Thirty patients had a radiographic CR, 33 had a PR, and 6 did not have imaging reported. Surgery was performed within 5 to 17 weeks after chemoradiation. Patients were followed for a mean of 30 months. Wound complications occurred in 10% (7/69) with four requiring surgical intervention requiring ultimate closure. Another 16% (11/69) had other complications including need for tracheotomy ($n = 7$), cranial nerve palsy ($n = 3$), and hypocalcemia ($n = 1$). No chylous fistula for flap necrosis was reported.

Ahlberg reported on 108 patients undergoing either supraomohyoid ($n = 25$) or MRND ($n = 83$) and adjuvant radiation and compared them to 98 patients treated with radiation without neck dissection. Patients were followed for 1-year prospectively to evaluate swallowing, trismus, cervical range of motion, and shoulder disability and underwent early rehabilitation. Among the 108 neck dissection patients, 75 underwent radiation followed by neck dissection and 33 received postoperative radiation. More patients in the postoperative radiation group underwent supraomahyoid dissection (16/33) compared to those treated with preoperative radiation (9/75). Patients treated with postoperative radiation had a higher incidence of swallowing disorders compared to the preoperative group (45% [15/33] vs. 20% [15/75], $p = 0.032$). The incidence of shoulder disability was 18% with no statistically significant difference between MRND and supraomohyoid (20% vs. 8%, $p = 0.23$). MRND caused reduced cervical range of motion at 2 and 12 months after surgery and decreased mouth opening at 2 months.[187]

## COMPLICATIONS BASED ON DOSE AND INTERVAL TO SURGERY

The University of Florida reviewed their experience of 205 patients treated with planned unilateral neck dissection. Radical neck dissection was performed in three-fourths (159/205). Twenty-seven wound complications occurred within 6 months of surgery. Patients receiving increasing dose to the neck trended toward a higher risk of complications while interval between radiation and surgery did not. Patients who received a total of <60 Gy had a 3% complication rate (1/34) versus 10% (15/147) in those receiving >60 Gy. The incidence by dose groups was 6% (45–60 Gy), 13% (60–75 Gy), and 17% (75–90 Gy) and trended toward significance ($p = 0.08$).[148]

Chepeha compared shoulder function in 54 patients undergoing 64 neck dissections comprised of 32 MRND with spinal accessory nerve sparing and 32 patients with SND. Patients were followed with the constant's shoulder scale and variables evaluated to predict for shoulder dysfunction included type of neck dissection, tumor stage, site, age, weight, radiation therapy, time from surgery, and handedness. Patients receiving MRND had significantly worse shoulder function and those undergoing radiotherapy trended toward worse function, but patients who were heavier did significantly better. However, Goguen reported that in 105 patients undergoing postchemoradiation neck dissection, the complication rate was related to the type of neck dissection performed rather than timing of neck dissection.

## DYSPHAGIA AFTER NECK MANAGEMENT

Dysphagia after multidisciplinary management of the neck concurrent chemoradiation is significant. Radiation dose, larynx/hypopharynx primary site, advanced age, female sex as well as neck dissection have been found to increase the risk for long-term dysphagia and risk for feeding-tube dependence. Retrospective review of 199 patients at the Cleveland clinic demonstrated that 21% of patients developed strictures requiring dilation. Risk factors associated with stricture formation included twice-a-day fractionation, primary tumor of the hypopharynx, and female gender (Lee, 2006).[187a] University of Florida reported similar risk factors for chronic feeding tube placement in 934 patients treated with definitive radiotherapy included hypopharynx, RT dose, and female sex.

Machtay reported on 230 stage III/IV patients treated with concurrent chemoradiation on three RTOG trials evaluating factors associated with severe late toxicity. A total of 479 were enrolled in the studies and 136 were excluded because of locoregional failure or death, 100 excluded because of severe laryngopharynx baseline dysfunction, and 13 were excluded because of missing data. Twenty percent (47/230) underwent posttreatment neck dissection with similar proportion regardless of primary site (oral cavity/oropharynx 22% vs. 19% of larynx/hypopharynx). Grade 3 and 4 late toxicity was common, occurring in 43% of patients. On multivariate analysis, patients with older age (OR 1.05, $p = 0.001$), neck dissection (OR 2.39, $p = 0.18$), advanced T stage (OR 3.07, $p = 0.0036$), and larynx/hypopharynx primary site (OR 4.17, $p = 0.0041$) were significant variable correlating with developing severe late toxicity. Among those undergoing neck dissection versus those not undergoing neck surgery, the crude rate of severe late toxicity was higher (55% versus 40%). The data were a retrospective analysis, and those undergoing neck dissection may have had a selection bias for worse neck disease since >50% had N2/3. Nevertheless, the author hypothesize that neck dissection could impair swallowing dysfunction because of increased fibrosis and impaired mobility of laryngopharynx.

Lango reported on 67 patients with node-positive disease treated with primary radiation or chemoradiation at Fox Chase. Thirty-four patients were observed whereas 33 had a comprehensive neck dissection at a median time of 6 weeks after treatment. The two groups were well balanced with regard to those undergoing concurrent chemoradiation, T and N stages whereas patients undergoing neck dissection were younger (56 vs. 62 years, $p = 0.011$), more likely to have a stricture present (6% vs. 1%, $p = 0.054$), and less likely to have a tonsil primary (7% vs. 17%, $p = 0.54$ with similar rates of larynx/hypopharynx primary sites 12% vs. 9%). Minimum follow-up was 24 months. On multivariate analysis, the authors reported a significant

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association with posttreatment neck dissection with feeding-tube dependence with an RR of 4.74 at 18 months and higher risk at 24 months (RR = 7.66). If patients with strictures were excluded from analysis, the RR for feeding-tube dependence was 5.49 at 18 months (40% vs. 2%, $p = 0.02$) and 11.28 at 2 years (40% vs. 1%, $p = 0.005$) after neck dissection. No increased risk for feeding-tube dependence was noted at 1 year with RR of 1.19 (29% vs. 24% $p = 0.658$). Other risk factors predictive for feeding-tube dependence included pretreatment weight loss ($p = 0.04$) and advanced age ($p = 0.03$).

## NECK CONTROL AFTER PRIMARY CHEMORADIATION WITHOUT PLANNED NECK DISSECTION IN NODE-POSITIVE PATIENTS

Given that pathologic CR is noted in about two-thirds of patients undergoing planned neck dissection after radiation or chemoradiation, multiple institutions have reported low rates of overall regional and isolated regional failure with observation in complete responders. Attaining imaging confirmed CR for N1 disease is high occurring in >80% while for N2 patients it is achieved in 60% to 80% and modest for N3 patients, successful in about 40% (Table 14.8). Aside from N stage, factors which improve the chance for a CR, include the use of induction and concurrent chemotherapy, higher radiotherapy dose, HPV status, and oropharyngeal primary site.

Forest reported on neck control after definitive concurrent chemoradiation in 184 patients with 13% N1, 72% N2, and 15% N3 with oropharynx in 73%, larynx 13%, and hypopharynx 6%. Patients were evaluated with CT at 6 to 8 weeks after treatment. Complete clinical radiographic response was defined as a node <1 cm with well-defined borders and no focal abnormalities (no necrosis) or nodal shrinkage >90% compared to initial CT. Salvage neck dissection was performed in patients with persistent disease at 6 to 12 weeks after treatment. Of the 184 patients, radiographic CR was 68% and the rate of CR related to the size of nodal such that nodes <3 cm, 3 to 6 cm, and >6 cm had a CR rate of 83%, 66%, and 43%, respectively. One hundred twenty-six patients attained a CR and were observed except in 3 patients who underwent neck dissection. Fifty-eight patients had a PR and 45 underwent neck dissection with 9 patients refusing surgery and 4 with disease progression. Regional failure among the 123 CR patients was 5% (6/123) and only 1 of 6 could be salvaged. Among the PR patients undergoing neck dissection, regional failure was 7% and 40% had pathologic residual nodal disease. No obvious difference was noted in regional failures between patients obtaining a CR who were observed versus patients undergoing neck dissection after a PR whether they were 3 to 6 cm (7% vs. 4%) or >6 cm (9% vs. 8%), respectively.

**TABLE 14.8 Complete Response after Chemoradiation Based on Initial N Stage**

| | Getec ($n = 103$) | Smyth ($n = 100$) | Igidbashian ($n = 70$) | Corry ($n = 102$) | Clavel ($n = 369$) |
|---|---|---|---|---|---|
| N1 | 86% | | | | 83% |
| N2a | 90% | | | | 66% |
| N2b | 50% | | | 63% (all N2) | 72% |
| N2c | 60% | | | | 80% |
| N3 | 45% | 30% | 37% | 40% | 45% |

Corry reported regional control of 102 N2–3 patients treated with definitive concurrent chemoradiation with neck dissection reserved for salvage on the Trans Tasman Radiation Oncology group Study 98-02. Oropharynx comprised the majority of patients (78/102) with hypopharynx in 15/102 and larynx 6/102. N2 constituted 82/102 and N3 20/102. CR was determined based on physical exam and CT of the neck 12 weeks after chemoradiation. The CR rate was defined as <1 cm without focal abnormalities. CR was achieved in 60/102 for all patients and was 63% of N2 and 40% for N3 disease. Median follow-up was 4.3 years. Among patients with complete nodal response, the regional failure was 8% with no isolated regional failures.[188]

Several other groups reported a low incidence of isolated failure after radiologic CR[189] and Groupe d'Étude des Tumeurs de la Tête Et du Cou (GETTEC).[190] Lambrecht evaluated 368 patients treated with definitive radiotherapy, with 37% receiving concurrent chemotherapy. At a median follow-up of 34 months, 3-year regional failure was 20%. Crude data showed that 41 patients developed neck failure (11%) of the 368 but only 11 (3%) were isolated failures. At 3 years, nodal control for N1, N2a, N2b–c and N3 patients was 84%, 83%, 70%, and 67%, respectively.

Yovino reported on 120 patients with node-positive disease treated with definitive chemoradiation to the neck. CT was performed 8 weeks after treatment with a CR defined as tumor <1.5 cm without focal necrosis. Seventy-six percent (91/120) achieved a CR. At a median follow-up of 30 months, regional failure occurred in 3% (3/90) patients with 2% isolated regional failure. Among partial responders who proceeded to neck dissection, regional failure was 4/29 patients.[189]

Dequanter reported on 28 patients with N2/3 disease treated with primary chemoradiation without planned neck dissection.[191] Patients received conventionally fractionated radiation to a dose of 65 to 70 Gy with concurrent high-dose cisplatin or induction 5FU/cisplatin. Twenty-five had a clinical and radiographic CR and were observed while 3 had residual clinical disease and underwent neck dissection. Of the 25 who were observed, 20% developed a regional recurrence at a median follow-up of 11 months with 2 of 5 also having primary recurrence. None were salvageable and all died of progressive disease. Among the three patients undergoing neck dissection, all were regionally controlled at a median follow-up of 36 months.

Grabenhauer reported on 97 patients who had cCR at the primary site after chemoradiation.[192] Forty-one refused neck dissection and 56 patients proceeded to neck dissection. However, 22% who refused neck dissection were N0 versus 3% in the patients who underwent neck surgery whereas there were 22% more N2b/2c patients in those undergoing neck dissection. Pathologic residual disease was seen in 17% undergoing neck surgery. At a median follow-up of 37 months, no difference in 5-year regional failure in those observed versus undergoing neck dissection (15% vs. 20%, respectively) or OS (42% vs. 44%).The highest neck recurrence rates in those observed were among those with multiple nodes and hypopharynx primary. Wound healing complications occurred in 10% and dysphagia requiring PEG dependence was worse in patients undergoing neck surgery versus observation (21% vs. 12%). The authors recommend neck dissection in those patients with CR at the primary site who have multiple residual nodes or a hypopharynx primary.

Lau reported on 56 N2/3 patients treated with definitive concurrent chemoradiation to the neck. N2 patients comprised 91% and 9% were N3. Oropharynx patients comprised 59% with larynx in 15%, hypopharynx in 11%, and unknown primary

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in 15%. CR was assessed primarily by physical exam with imaging in 31%. The CR rate was 85% (46/54). Of the eight patients with <CR, salvage neck dissection was performed in three all of which were pathologically negative whereas four patients were inoperable due to persistent disease at the primary site or developed disease distantly ($n = 1$) and one patient was medically inoperable. At a median follow-up of 35 months, regional failure for the entire group was 15%, occurring in 9% in those with a CR versus 63% in those with <CR ($p < 0.001$). Regional failure among CR patients occurred at median time of 15 months (7–24 months). OS for the entire group was 82% at 2 years whereas patients with a CR had a higher 2-year OS (92% vs. 25%, $p < 0.001$) compared with those who had <CR. Two-year survival was similar among patients who had a neck dissection versus those who did not (82% vs. 75% $p = 0.28$).

The GETTEC group reported on 103 stage III/IV node-positive patients treated with definitive chemoradiation consisting of cis- or carboplatin with or without 5FU. Sixty-nine patients had N2 disease whereas 14 had N1 and 20 with N3. Oropharynx was the most common site in 67 patients with hypopharynx primaries in 14 and oral cavity in 12.

CR was defined by disappearance of detectable disease by physical exam and CT scan done at a mean time of 3 months after chemoradiation (1–4 months) and was achieved in 61% of all patients and were 86%, 90%, 50%, 60%, and 45% for N1, N2a, N2b, N2c, and N3, respectively. Among the 39% patients achieving a PR, 70% (28/ 40) proceeded to salvage neck dissection and found to have pathologic disease in 50%. The 2-year regional failure was 18% for the entire cohort and 8%, 29%, and 42% in those patients achieving a CR, PR with salvage neck dissection or PR without surgery. At a median follow-up of 30 months, the DFS and OS were similar between those who were observed after CR or those who had PR. Although regional failure was decreased, salvage neck dissection did not appear to improve survival in patients achieving a PR but may be related to a high pathologic nodal residual disease rate in those undergoing neck dissection.

## Salvage Neck Dissection for Residual Nodes after Induction Chemotherapy

Induction chemotherapy has been employed as a strategy to select for favorable responsive tumors that may be appropriately treated with organ-preserving primary radiation. Although meta-analysis of large groups of patients have demonstrated minimal survival benefit of induction chemotherapy compared to concurrent chemoradiation, new induction trials combining a taxane with cisplatin/5FU have demonstrated promising survival benefit and have renewed interest in this form of therapy.[12,13] The benefit of the addition of neck dissection in this setting has not been reported. The evidence suggesting a benefit of withholding a neck dissection if a CR is obtained after induction chemotherapy is derived from older induction chemotherapy regimens based on cisplatin and 5FU.

Wolf reported on a subset of 46 patients with N2/3 disease randomized to the organ preservation arm on the VA Cooperative Larynx Study.[193] Patients received induction 5FU/CDDP followed by definitive radiation therapy to the primary and involved neck nodes (66–75 Gy). Among those patients undergoing organ preservation, 74% had a major response (CR in 39% [18/46] and PR in 35% [16/46]) after induction chemotherapy and then proceeded to definitive radiation therapy. Salvage neck dissection was required in 5 of 18 patients with nodal CR and 19 of 28 with nodal PR. Twelve of the 46 patients died of uncontrolled neck with a higher rate of neck failure in patients with PR than CR (53% [10/19] vs. 11% [2/18]). Patients achieving a CR had better DFS compared to those with less than a CR (67% vs. 33%, $p = 0.014$). Wolfe and Fisher recommended neck dissection after induction chemotherapy and before radiation therapy would improve survival in patients with partial nodal responses.

A subsequent study reported by this group on 39 node-positive patient undergoing early neck dissection before radiation if a less than a CR was obtained after induction chemotherapy.[194] Patients received three cycles of induction 5FU/carboplatin/leucovorin. A nodal CR was obtained in 49% of all patients (19/39) and was higher for N1 patients compared to N2–3 (80% [8/10] in N1, 39% [9/23] in N2, and 33% [2/6] in N3 patients). Fifty-one percent had less than a nodal CR and underwent neck dissection before radiation therapy whereas those with a nodal CR proceeded to radiation therapy without planned neck dissection. At a median follow-up of 26 months, patients undergoing up-front neck dissection had a regional failure of 21% compared to 15% in those achieving a CR after induction chemotherapy who were observed. Of the N3 patients with less than a CR undergoing neck dissection, regional failure was 80%. There was no difference in DFS or OS between the two groups. Thus, results appeared to favor the use of early neck dissection in patients having a PR after induction chemotherapy.

Similarly, Armstrong reported outcomes in 53 node-positive patients treated with cisplatin-based induction chemotherapy followed by radiation only or neck dissection.[195] Major response in the neck after induction chemotherapy occurred in 66% (CR in 24 and PR in 11). Of these 35 patients, 22 (17 CR, 5 PR patients) were treated with definitive radiation alone (mean dose 66 Gy), 10 patients (6 CR, 4 PR) underwent neck dissection (9 prior to radiation therapy), and 3 had no further neck therapy. More patients in the radiation-therapy-alone arm were staged as N1 compared to the neck-dissection group (41% vs. 0%, $p = 0.02$). At a median follow-up of 25 months, regional control was better in those undergoing radiation therapy than patients undergoing neck dissection plus radiotherapy (regional control of 91% vs. 70%, $p = 0.40$). Regional control was 94% (16/17) in those obtaining a CR and 80% in those having a PR (4/5). No difference in survival was observed between the definitive radiation therapy versus neck dissection group (3-year OS 43% vs. 53%, respectively). Clark reported that 23 patients with N2–3 neck disease who had a CR after induction chemotherapy followed by radiotherapy also had excellent regional control of 87% (20/23). Patients who had a PR to chemotherapy followed by definitive radiation therapy had regional control of 33% (15/40).

Leon reported on 65 patients with residual nodal disease after induction chemotherapy who underwent either neck dissection followed by definitive radiation therapy to the primary site or upfront radiation therapy followed by planned neck dissection.[196] Two hundred eleven node-positive patients received three courses of CDDP/5FU and CR was obtained in 41% and PR in 46%. The neck stage (1987AJCC) predicted response to chemotherapy as CR was noted in 54% of N1, 41% of N2, and 15% of N3 patients ($p < 0.0001$). Except for two patients, all patients achieving CR received radiation therapy alone to a dose of 65 to 70 Gy to the primary and involved nodes. Among those with less than a CR, 65 patients underwent resection and radiation therapy whereas 64 received definitive radiation therapy alone. Patients with N2–3 disease with less than a CR and undergoing resection ($n = 46$) had better regional control (70% vs. 32%, $p = 0.001$) compared to those with less than a CR treated with radiation therapy alone ($n = 38$). The addition of surgery for all N stages improved regional control in patients not achieving a CR after induction chemotherapy as follows: N1, 79% versus 65%, $p > 0.05$; N2, 80% versus 36%, $p = 0.02$; and N3, 57% versus 23%, $p = 0.05$. The timing of neck dissection either before or after radiation therapy had no impact on regional control, 73% versus 75%, respectively ($p > 0.05$).

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Soltys reported on 90 patients with N2/3 disease treated with induction chemotherapy followed by concurrent chemoradiation. Patients were imaged by CT or MRI after 5 weeks into radiation treatment to determine who should proceed to planned neck dissection. Patients who had nodal disease >1 cm proceeded to planned neck dissection whereas those with a CR were observed. By this criteria, 62% (56/90) attained a CR of whom 48 observed and 8 underwent neck dissection with no residual disease found. Among the 48 CR patients, 10% (5/48) failed regionally with isolated regional failure of 2% (1/48). Thirty-four patients (38%) had a PR and 30 underwent planned neck dissection whereas 4 developed progressive disease. Pathologic residual disease was found in 47% (14/30). Those with pathologic residual disease had a higher relapse rate (50% [7/14] compared to 13% [1/16]) with those with no residual disease. Among the 30 patients with PR undergoing neck dissection, the neck failure rate was 12% (4/34) with 1 isolated regional failure. Nineteen patients had N3 disease and 53% (10/19) achieved a CR and were observed with no regional failures. At a median follow-up of 5 years, the regional failure rates among patients with CR, those with PR with no residual pathologic disease and those with PR but with residual nodal disease were 10%, 7%, and 22%, respectively, but not statistically significant. Corresponding 5-year DFS was 53%, 75%, and 42% ($p = 0.04$), respectively, and 5-year OS was 68%, 81%, and 48% ($p = 0.012$), respectively. Thus, pathologic confirmed CR was associated with higher survival compared to those with a cCR. Regarding regional control, planned neck dissection of all patients would have yielded a potential benefit in only 2% (2/90).

Paccagnella reported a phase II randomized study of induction TPF × 3 cycles followed by concurrent chemoradiation versus concurrent chemoradiation alone. One hundred one stage III/IV patients were randomized with 66% N2/3 disease in the concurrent chemoradiation arm versus 64% N2/3 in the induction arm. Imaging was performed 6 to 8 weeks after chemoradiation. CR after chemoradiation was doubled in the induction arm (50% vs. 21%, $p = 0.004$). Surgery for residual neck disease was higher in the concurrent chemoradiation arm versus the induction arm (34% [18/47] vs. 10.8% [5/46], $p = 0.012$). At a median follow-up of 42 months, no difference in median OS was noted between the two groups (40 vs. 33 months, $p = 0.268$).[197]

Thus, it appears that induction chemotherapy increases CR rates in patients treated with concurrent chemoradiation and those achieving a CR may be observed. Those with less than a CR clearly benefit from a planned neck dissection. There appears to be no difference whether the neck dissection is performed before or after radiation therapy, but should be incorporated as a planned procedure rather than as salvage. Whether these data are relevant in patients achieving a PR after induction chemotherapy followed by concurrent chemoradiation is unknown.

## Role of Imaging to Confirm CR after Definitive Chemoradiation

Determining which patients have achieved a CR after definitive chemoradiation of a node-positive neck is challenging, but progress has been made using imaging to identify such patients in a timely manner so that surgical salvage may be performed without undue morbidity. Clearly, a discordance exists between physical exam and imaging with standard CT with regard to pathologic findings seen on neck dissection. False negatives after a complete clinical response is seen in 20% to 40%, whereas false positives are noted in 60% with a clinical PR.[155]

***Computed Tomography.*** Multiple investigators have proposed radiographic parameters of CT scans done 4 to 8 weeks after treatment which correlate highly with pathologic CR or high rates of long-term regional control.

The University of Florida reported the radiographic–pathologic correlation between pre–neck dissection CT scans performed at 4 weeks post radiation treatment to the pathologic findings of neck dissection in 211 patients.[198] The study cohort were culled from 550 patients who were LN positive and treated with definitive radiation to the primary site (62% oropharynx, 16% hypopharynx, and 13% larynx). One-fourth received induction or concurrent chemotherapy, and planned neck dissection was performed in 341 patients within 8 weeks of completion of radiation. Of these 341 patients, 211 had CT scans at 4 weeks available for review. The radiographic characteristics with highest predictive value for a pathologic CR were absence of node >1.5 cm and no focally abnormal node (focal lucency, focal enhancement, or focal calcification). If these conditions were satisfied, the NPV was 94%. About 29% (61/211) of patients met these criteria. Of these 61, 29 proceeded to neck dissection and showed residual disease in 6% (2/29). Regional failure was 0% in these patients. The other 32 who did not undergo neck dissection and the regional failure rate was 3%.

Greven reported on 103 patients with node-positive disease with disease as follows N1 26 whereas 77 had N2/3 (N2a, 4; N2b/c, 65; and N3, 8) patients. Concurrent chemoradiation was delivered to 58 patients whereas 45 were treated with radiation alone. Seventy-seven patients had a posttreatment CT scan at a median of 4 weeks after treatment (range 2–24 weeks) whereas 24 were observed without scan. Radiographic CR was defined as <1.5 cm without necrosis. An rCR was attained of 49 of 103 patients, 50% of N1 and 47% of N2/3 patients attained an rCR. Posttreatment neck dissection was performed in 13 of N1 patients (50%) and 29 (38%) of N2/3 patients. Patients with rCR had higher neck control compared to those with rPR (95% vs. 85%). Ten patients of 49 with rCR underwent neck dissection with residual nodal disease in 60%. However, neck control was not improved in patients with rCR undergoing neck dissection versus none (97% vs. 89%, respectively, $p = 0.24$). In contrast, among rPR patients, nodal control was higher in those patients undergoing neck dissection (94% vs. 73%, $p = 0.14$) but with no difference in DFS. No improvement in DFS was noted in patients undergoing neck dissection in either those with rCR (50% vs. 87%, $p = 0.01$) or rPR (67% vs. 62%, $p = 0.93$), respectively.

Clavel reported on the Montreal experience evaluating the role of CT scan to monitor patients after definitive chemoradiation in 369 node-positive patients with 13% N1, 72% N2, and 15% N3 and oropharynx in 77%, larynx in 10%, and hypopharynx in 5%. Concurrent chemoradiation consisted of 5FU with either carbo- or cisplatin and in about one-third IMRT was delivered. CT was performed about 6 to 8 weeks after chemoradiation. CT parameters associated with a high rate of CR was a >80% decrease in the initial nodal volume from initial CT (NPV 100) and nodal size <1.5 cm without focal heterogeneity (NPV 86%). Overall, 71% of the group achieved a CR with N1, N2a, N2b, N2c, and N3 achieving a cR in 83%, 66%, 72%, 80%, and 45%, respectively. Among the 29% ($n = 106$) who achieved a PR, neck dissection was performed in 96 patients while 10 were observed. Neck dissection was performed at about 8 to 12 weeks after CT/RT and consisted primarily of selective neck in 55% and modified radical in 27%. Pathologic nodal disease was noted in 40%. Median follow-up was 44 months. Regional failure was 9%. Patients who achieved a CR or underwent neck dissection after PR had a regional failure of 4%. Among the PR patients, neck dissection appeared to increase regional control (50%–92%), DFS (40%–78%), and OS (40%–80%). Among 16 patients failing regionally, only 2 were salvaged.

Thus, it appears that CT characteristics of nodal size <1.5 cm without focal abnormality and nodal shrinkage >80% are important early predictors of CR but it should be noted that reliance of CT will not capture all patients who are successfully controlled regionally with definitive chemoradiation.

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***Functional Imaging with FDG PET/CT.*** The incorporation of PET/CT imaging in the posttreatment assessment of node-positive patients treated with chemoradiation has been well established to improve clinical-pathologic concordance compared to CT such that better selection is possible for those who may avoid neck dissection[152,153,159–163] (Table 14.9). In that regard, several studies have demonstrated the critical importance of timing of the PET in relation to the end of treatment to achieve maximal accuracy.

Greven reported on 45 patients followed with serial PET scans as well as either MRI or CT at 1, 4, 12, and 24 months after radiation therapy.[199] At 1 month, 36 patients had surveillance PET of whom 25 were reported as PET negative, but 7 had subsequent positive biopsies 3 to 12 months after radiation, 6 were positive on PET and confirmed on biopsy, 5 PETs were reported as equivocal but positive on biopsy in 4. Thus, at 1 month, the NPV was 72% (18/25) whereas the PPV was 100% (6/6). At 4 months, the NPV was 100% (18/18) with a PPV of 86% (6/7). The NPV remained at 100% at 12 and 24 months post treatment. Other groups reported the NPV ranging from 97% to 100% when a PET scan is done after 3 months.[152,161] The NPV was poor when a PET/CT was done at 1 month.

Timing of the PET/CT at 2 months after chemoradiation yield conflicting data regarding its NPV. Some have shown modest NPV whereas others have demonstrated high NPV. PET/CT at 6 to 8 weeks after chemoradiation was evaluated in 31 patients. Patients were treated on the RADPLAT regimen of high-dose targeted intra-arterial cisplatin during radiation therapy. N2/3 comprised 16/31 and 16% (5/31) were N1 and oropharynx were present in 58% while oral cavity, larynx, and hypopharynx each comprised about 10%. Patients were observed if a complete clinical response was achieved. Neck dissection were performed as salvage treatment for clinically suspicious residual disease based on imaging and physical exam. Median follow-up was 24 months. For the 21 N1–3 patients, 3 patients had persistent FDG uptake with confirmation of residual disease on neck dissection and thus the PPV was 100% but due the limited sample size, the authors opted to report the PPV of 75% or greater to account for the next collected event assuming it was positive. They reported an NPV of 94%. For the primary site, the PPV was lower at 31% with similar NPV (92%). Chen also reported a high NPV when PET/CT is done at 2 months. Thirty patients with node-positive disease underwent PET/CT and contrast enhanced CT at about 7 ± 4.4 weeks (range 2–24 weeks) after treatment. Pathologic residual disease was noted in 28%. All patients were oropharynx or unknown primary and 25 were N2/3. The PPV for the neck was 36% for PET/CT but the NPV was 100%.[200]

In contrast, Gourin reported on 32 N2/3 patients treated with concurrent chemoradiation with PET/CT at 8 to 11 weeks after chemoradiation and planned neck dissection.[201] N3 comprised 6 of the 32 with oropharynx in 25/32, larynx in 5, and hypopharynx in 2. PET/CT was positive in 63% (20/32); however, pathology was positive in 31% ($n = 10$), six of whom had a positive PET and four with a negative PET, yielding a PPV of 30% (6/20) and NPV of 67% (8/12). Thus, authors conclude that PET/CT at 8 to 11 weeks is a poor predictor for patient needing neck dissection.

Similarly, Waldron reported a prospective trial to evaluate the benefit of PET/CT to predict need for neck dissection after definitive radiation therapy in 399 patients with N2–3 disease. CT and PET/CT at a mean of 9.2 weeks (8–10 weeks) following definitive RT with or without chemotherapy. Patients with residual nodes >1 cm underwent neck dissection. Sites of disease were primarily oropharynx (75%) but also oral cavity (8%), hypopharynx (8%), and unknown primary (14%). N2 disease comprised 90% and N3 10%. A total of 152 neck dissections were performed and 201 necks were observed. Three hundred twenty-five patients were followed for at least 18 months. PET/CT sensitivity was significantly lower than CT (53% vs. 94%). The regional failure rate was 4% in those who were observed. The NPV was 73% and PPV was 44%.[202]

***PET/CT 3 Months after Chemoradiation.*** Consistently, PET/CT 3 months or later after treatment yields high rates of NPV >95% and improved rates of PPV. A prospective trial correlated PET with pathologic findings in 23 patients with N2b or greater disease (70% oropharynx) treated with concurrent chemoradiation in 87% (20/23).[203] PET scans were done at a median time 13.3 weeks (6.3–26.1 weeks). Seventeen patients underwent neck dissection (1 patient bilateral) and 6 patients with residual nodes >1 cm underwent fine-needle aspiration (FNA). Pathology showed 19 negative nodes and 5 neck with residual disease. Using a maximum standardized uptake value (SUV) of 3.0 or greater as positive, 8 of 24 necks were considered positive and 16 negative. Of the 8 PET positive necks, 5 were positive and all 16 PET negative were pathologically negative. The NPV was 100% and PPV was 63%. Therefore, the group recommends PET to be done at 3 months after radiation and defined a negative PET as having an SUV <3.0.[153]

A follow-up prospective study validated the use of PET/CT to select patients who may have omission of neck dissection after definitive radiation.[204] Ninety patients with N2/3 neck disease (N2a: 12%; N2b: 43%; N2c: 31%; N3: 13%) with 71% oropharynx were evaluated using PET/CT to evaluate the need for neck dissection after definitive treatment to the involved nodes and primary site. IMRT was used to deliver 70 to 74 Gy to involved neck nodes defined as those >1 cm, exhibiting focal necrosis or having abnormal PET uptake. Cisplatin chemotherapy was given in 74 patients (73 concurrent). Sixteen patients had residual nodal

**TABLE 14.9 Clinical Pathologic Correlation after Definitive Chemoradiation for N2–3 Neck Incorporating PET**

| | Number of Patients | Median Time of PET after RT (Range) | NPV | PPV | Regional Control |
|---|---|---|---|---|---|
| Yao et al. (2007)[203] | 23 | 3 mo | 100% | 63% | |
| Yao et al. (2005)[254] | 53 | 3 mo (5–29 wk) | 100% | 43% | 100% |
| Yao et al. (2007)[204] | 79 | 3 mo | 99% | 67% | 99% |
| Greven et al. (2001)[199] | 25 | 1 mo | 72% | 100% | |
| | 18 | 4 mo | 100% | 86% | |
| | 14 | 12 mo | 100% | | |
| | 15 | 24 mo | 100% | | |
| Porceddu et al. (2005)[205] | 39 | 3 mo (8–32 wk) | 97% | 71% | 96% |
| Rogers et al. (2004)[255] | 12 | 1 mo | 14% | 100% | |
| Lowe et al. (2000)[256] | 21 | 2 mo | 86% | | |

NPV, negative predictive value, PPV, positive predictive value.

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disease after treatment, of which 13 had neck dissection while 2 refused and 1 had distant metastasis. Seventy-four patients were observed without neck dissection. All had negative CT scans and 64 had negative PET scans done at 3 months. Among the observed patients, at a median follow-up of 29 months, regional failure occurred in 1 patient for a regional failure of 1% and a corresponding NPV of 98% (1/63) for PET scans at 3 months. Of the 13 patients undergoing neck dissection, 43% were pathologic positive and thus the PPV was 62%. For all 90 patients, the 3-year regional failure was 5% and local control 96%. The incidence of distant metastasis was 20% and OS was 68%.

The role of PET in the management of neck nodes was reported in 53 patients with N2a disease or greater.[205] The N staging was as follows: N2a = 3, N2b = 25, N2c = 15, N3 = 8, N2 (nasopharyngeal) = 2. All patients had CR of the primary site after treatment with definitive radiation therapy with or without chemotherapy. PET scans were done at median time of 15 weeks posttreatment (5 to 29 weeks). Seventy heminecks were evaluated with bilateral neck performed in 17 patients. No residual lymphadenopathy was noted on CT scan and negative PET were seen in 42 heminecks, and all were observed without neck dissection. Residual lymphadenopathy with positive PET was seen in seven heminecks and all were evaluated pathologically, six undergoing neck dissection and one having an FNA. Three contained residual neck disease and four pathologically negative. Residual lymphadenopathy with negative PET was noted in 21 heminecks. Neck dissection was performed in four at the discretion of the clinician. All four were pathologically negative. At a median follow-up of 26 months, no regional failure was identified nor were there any local failures. The NPV of PET was 100% and PPV 43%. The authors conclude that a patient with no residual lymphadenopathy and negative PET at 12 weeks after definitive radiation therapy warrants observation.

Rabelais reported on 52 node-positive patients managed with concurrent chemoradiation. Approximately, 62% were N2 with 27% N1, 56% were oropharynx, and 33% larynx cancers. PET/CT was done at a median time of 12 weeks after chemoradiation. Ten patients were PET/CT positive in the neck. Five were followed due to patient refusal or medically inoperable. Two of the five had residual palpable lymphadenopathy. All five were followed by serial PET/CT and became pet negative without obvious neck recurrence at 1-year follow-up. Three patients underwent neck dissection with 2 of 3 positive for residual disease. Two patients had disease documented in the neck on FNA and the other developed metastatic disease. Eleven patients had palpable lymphadenopathy at the end of treatment with 5 having PET/CT positivity and 6 negative. Among those that were PET/CT positive with palpable nodes, three were confirmed pathologically and two patients were followed by serial PET/CT without evidence of recurrence. Among the six patients that were PET/CT negative with residual nodal disease, two had neck dissection that showed no residual cancer while four were followed serially without evidence of neck recurrence. The PPV was 42% and NPV was 100%.

Loo reported on 34 N2 patients treated with induction chemotherapy followed by radiotherapy (with concurrent chemotherapy in 79%). Oropharynx comprised 82% (28/34) of patients. Patients underwent PET/CT 3 months after radiation therapy. PET/CT was positive in the neck in 1 of 34 patients, and salvage neck dissection showed no residual disease. The neck was observed if PET/CT was negative. At a median follow-up of 39 months, no regional failures were reported with five recurrence (two distant metastasis and three local failure/persistent disease).[206]

Wang reported on 44 patients treated with induction chemotherapy followed by concurrent chemoradiation. Tumor sites comprised hypopharynx in 45%, oropharynx in 39%, and larynx in 9%. PET scans without CT were performed at a minimum of 12 weeks and median 16 weeks post chemoradiation. All patients had CT scans done at 2 months post chemoradiation and residual nodal disease defined as positive if 1 cm or greater. Seventy-five percentage of patients had N2/3 disease. Neck dissection or FNA evaluation was performed in patients with residual nodal masses or FDG avid disease. Patients with CR on exam and PET were observed. Fourteen patients had residual palpable nodal disease and 9 of them were FDG avid and confirmed on pathologic evaluation whereas 5 were negative on PET and 2 were confirmed as negative on neck dissection and 3 showed no evidence of regional recurrence at 6 months. The PPV and NPV were 100% in patient with residual nodal masses. Of 30 heminecks without palpable residual nodal disease, 2 had a positive FDG scan, both of whom had neck dissection with pathologic confirmation in 1 patient; thus the PPV was 50% and NPV was 100%. For distant metastasis, the PPV was 83% and NPV was 100% whereas for the primary site the PPV was 79% and NPV was 100%. In contrast for CT scans done at 2 months, the PPV was 64% and NPV was 97%. Interpretation of the PET and CT scans were done independently.

Thus, current studies suggest that PET scan at 3 months may offer the best test to monitor patients who are observed after a cCR. The promising results of PET need confirmation at multiple centers and longer follow-up with standardization of PET guidelines. The ability of PET to select out patients at risk for distant metastasis is an important area to be addressed as even the Yao study revealed a rate of metastasis of 20%. Moreover, the role of CT to assess cCR as well as the role of limited surgery (excision of initially involved nodes vs. more extensive surgery with SND) to evaluate patients with clinical PR remain to be defined. A randomized study comparing planned neck dissection to neck dissection only in patients with a positive PET scan after chemoradiation is underway in the United Kingdom.[207]

***Value of PET beyond CT.*** Some have questioned the added value of PET over CT. Tan reported the Cleveland Clinic experience among 48 patients who underwent PET/CT or PET and CT at median 2.5 months (1.1–5.3 months) after chemoradiation (cisplatin/5FU). Ninety-three percent were node positive with 28% having N1, 50% having N2, and 15% having N3 disease with planned neck dissection in the majority of patients ($n = 27$) and salvage neck dissection in 5 patients. Pathologic residual disease was noted in 5/33 and 3/5, respectively. PET and CT were analyzed separately as well as clinical examination to determine the ability to predict for residual nodal disease. PET was called positive if any signal was detected in the node and CT was positive if nodes were >1 cm, contrast enhancing, or centrally necrotic. PET on its own was not able to predict for those with residual nodes but CT and clinical examination were able to. PET and CT, clinical exam and CT, or clinical exam and PET yielded accuracies of 87%, 79%, and 90%, respectively, with NPV of 95%, 94%, and 93%, respectively, and PPV of 20%, 25%, and 33%, respectively. In the setting of a positive CT and or clinical exam, 8 of 11 patients with residual neck disease or neck recurrence was detected. Among the three other patients with persistent or recurrent disease, only one was detected after 45 PETs were performed whereas two would have been missed. The authors question the added utility of PET scan despite such a low threshold for calling the PET positive.

The added benefit of PET over CT at 8 weeks postradiation treatment may be restricted to poor-risk patients. PET and CT was performed for 98 patients at a median time of 8 weeks (5–12 weeks), the majority of whom were nonsmoking males with stage IV oropharyngeal cancer. Seventy-eight patients received chemotherapy. Twenty-two patients underwent planned or salvage neck dissection at median time of 12 weeks after treatment. At a median follow-up of 23 months, the 2-year loco-regional

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control was 88%, OS 91%, and disease-specific survival 90%. For all patients, PET did not add to the accuracy of CT scan nor did it appear to improve the NPV for the primary site (96% vs. 97%, respectively) or node (96% vs. 98%, respectively) or for PPV (58% vs. 50% for the primary site and 27% vs. 23% for nodal site). However, if patients were stratified at low versus high risk for recurrence by T0–2 vs. 3–4, N0–2a vs. N2b–3), primary site (oropharynx vs. nonoropharynx), smoking (user vs. nonuser), HPV status, overall stage, PET did increase the PPV over CT alone from 38% to 75% for nodes and from 71% to 100% for the primary site. This increase in PPV appeared to be strongest in those stratified by risk by HPV status such that HPV-negative patients benefited from PET. ROC analysis showed the a threshold SUV max of 2.8 was the best predictor of failure for nodes and 6.5 for the primary site.

Ong reported on the MSKCC experience and demonstrated that the value of PET was to increase the PPV and accuracy of CT findings after chemoradiation treatment node-positive patients. PET/CT was done at a median time of 12 weeks (8–27 weeks) CT criteria for CR was defined as nodes <1 cm. Sixty-five patients with 84 node-positive necks were evaluated with N1 in 17% (14/65), N2 in 75% (49/65), and N3 in 3% (2/65). Oropharynx comprised 75% of patients (49/65) with larynx in nine and hypopharynx in seven patients. Neck dissection was performed in 17 patients based on N2–3 status, physical exam, and imaging results. Among 84 heminecks, CR by the CT component of the PET/CT was 65% (55/85) with CR by N stage as follows: N1, 93% (13/14); N2, 65% (42/65); and N3, 50% (1/2). Among the patients attaining CR, the PET was positive in 5% (3/55), one of which was a true positive. Among the 35% ($n = 29$) not attaining a CR, PET was positive in 34% (10/29). NPV with CT alone was 96%. PET decreased the false-positive rate of CT imaging from 23% to 10%. PET/CT done >12 weeks after chemoradiation had a higher PPV (67% vs. 14%) compared to those done from 8 to 12 weeks. NPV was 94% and 100% at those time periods, respectively. Accuracy increased from 77% to 95% if performed >12 weeks. The authors recommend observation for patients attaining CR by both CT and PET criteria and neck dissection in patients that were positive on both imaging modality. For patients either that are PET positive CT negative or PET negative CT positive, observation or neck dissection should be considered.[208]

## Planned Neck Dissection versus Primary Chemoradiation Alone for N2/3 Disease?

In summary, among N2–3 patients, regional control with the addition of a planned neck dissection appears to improve control by about 5% to 15% as regional failure occur in 1% to 7% (see Tables 14.6 and 14.10) while neck failure occurs in 8% to 25% in patients who achieve a CR and are observed after concurrent chemoradiation without planned neck dissection. For N2/3 patients treated with definitive concurrent chemoradiation, the regional CR rate was 40% to 80% after definitive concurrent chemoradiation regimens.[155,156,158] Thus, approximately 20% to 60% may have received definitive doses without the benefit of being spared neck dissection. Consequently, they are at risk for increased wound complications after exposure to higher doses compared to those treated with reduced dose radiation in conjunction with planned neck dissection. However, it may also be argued that definitive treatment spared 40% to 80% of patients a neck dissection and its consequent morbidity. Whether this translates into improved survival is not clear based on current data.[155,158] The dilemma highlights the importance of selecting patients with nodal disease that have a high probability of attaining CR and also the need for posttreatment evaluations that can confirm a CR or residual disease with high accuracy. Patients

**TABLE 14.10 Regional Control after Definitive Radiation or Chemoradiation for Node-Positive Disease**

| | Number of Patients | Regimen | Median Follow-up (mo) | PET | Regional Failure |
|---|---|---|---|---|---|
| **RT alone** | | | | | |
| Peters et al. (1996)[131] | 62 | Delayed concomitant boost | 39 mo | No | 11% |
| Chan et al. (2001)[250] | 80 | CF or split course accelerated RT | 4 yr (mean follow-up) | No | 20% |
| Bataini et al. (1987)[128] | | | | | |
| Node<3 cm | 467 | Accelerated RT | NS | No | 10% |
| Node 3–6 cm | 141 | Accelerated RT | | No | 15% |
| Node > 6 cm | 67 | Accelerated RT | | No | 25% |
| **CT/RT** | | | | | |
| Calais et al. (1999)[251] | 108 | Concurrent RT + 5FU/carboplatin | 35 mo | No | 19% |
| Sanguinetti et al. (1999)[252] | 43 | Alternating CT/RT 60 Gy | 16 mo | No | 44% |
| Grabenbauer et al. (2003)[192] | 41 | Alternating CT/RT | 37 mo | No | 15% |
| Argiris et al. (2004)[155] | 39 | Concurrent CT/RT | 55 mo | No | 18% |
| Dequanter et al. (2006)[191] | 25 | Induction or concurrent CT/RT | 11 mo | No | 20% |
| de Arruda et al. (2006)[253] | 50 | CDDP + IMRT | 18 mo | No | 12% |
| Porceddu et al. (2005)[205] | 39 | RT or concurrent CT/RT | 34 mo | Yes | 4% |
| Yao et al. (2004)[204] | 79 | CDDP + IMRT | 29 mo | Yes | 1% |
| Yovino et al. (2010)[189] | 72 | Platinum CT/RT | 36 mo | Yes | 6% |

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with N1–2 disease may be the best candidates for omission of neck dissection, whereas N3 or bulky disease extending into the low neck may best be treated with planned neck dissection.

## HPV Status and Need for Planned Neck Dissection

The University of Virginia reported their experience of 69 oropharyngeal cancer patients with node-positive disease. Nodal staging was N1 in 26%, N2a in 8.7%, N2b in 42%, N2c in 20%, and N3 in 3%. Sixty-eight percent were p16+. Patients in the p16+ group had an equal distribution of tonsil/base of tongue subsites whereas those that were p16- had more tonsil/base of tongue subsites (64% vs. 27%). HPV-positive patients had a greater incidence of contralateral nodes (28% vs. 5%, chi sq. $p$ = .09) with more advanced nodal N2c–N3 stage (32% vs. 5%) in p16-negative patients. No difference was reported in presence of radiographic extracapsular spread, overall stage, and T stage. Two-thirds of patients in both groups underwent posttreatment neck dissection. Patients in the P16+ group had chemoradiation (64% vs. 32%, $p$ = 0.01). Neck dissection was performed if N2–3, evidence of radiographic extracapsular disease was present pretreatment, or residual disease was seen on imaging post treatment. Forty-seven underwent a planned neck dissection. Among those undergoing neck dissection, pathologic residual disease was found in 18% versus 50%, $p$ = 0.02 of p16+ versus p16− patients, respectively, corresponding to an odd ratio for residual neck disease of 4.57.

Neck dissection complication rates occurred in 40% of patients and consisted of shoulder weakness, perioral weakness, wound infection/dishiscence, chyle leak, chronic pain, and seroma. No difference was noted based on p16 status. Complications resolved in all patients who underwent nonradical neck dissection. Of note, except for one, all patients with p16+ tumors with residual viable tumor were smokers/drinkers and who showed residual disease on imaging. The authors proposed an algorithm to consider neck dissection based on presence of radiographic evidence of extracapsular extension, residual disease on imaging, smoking, and alcohol status.

## Prognostic Implication of Pathologic Residual Disease on Neck Dissection After Chemoradiation

Pathologic residual disease is found in one-third of neck specimens in N2/3 patients treated with concurrent chemoradiation followed by neck dissection. Multiple reports indicate that such residual disease prognoses an adverse outcome with authors reporting various endpoints (Table 14.11). Lavertu demonstrated that patients with pathologic residual disease had worse survival compared to pathologically negative patients (50% [6/12] vs. 83% [4/23], $p$ = 0.03).[156] Stenson also reported that among the 58 patients with pathologic CR, the 3-year OS was 72% compared to 36% in 15 patients with residual neck disease ($p$ = 0.008).[154] In a separate study, Stenson reported a dose–response relationship between the incidence of pathologic residual disease and radiation dose to the neck.[209] Patients were treated on three sequential protocols in which radiation dose to gross disease was kept at 75 Gy whereas dose to the high- and low-risk areas were reduced from 60 Gy → 54 Gy → 51 Gy and 45 Gy → 39 Gy → 36 Gy, respectively. Pathologic residual disease occurred in 6%, 14%, and 33% in patients receiving the standard high, intermediate, and low doses, respectively ($p$ = 0.013). Sewall reported an increased risk for regional failure with residual neck disease. Regional failure was 13% (4/30) versus 1% (1/77) in patients with or without pathologic residual disease, respectively. Newkirk reported that in 33 patients treated with radiation ($n$ = 20) or chemoradiation ($n$ = 13) pathologic residual disease corresponded with an increased risk for local recurrence (33% vs. 0%, $p$ = 0.013) compared to those patients with a pathologic CR.[210] Pathologic residual disease status did not impact OS, distant metastasis, or regional control. No mention is made about whether the presence of residual neck disease had any different

**TABLE 14.11 Prognostic Implication of Pathologic Residual Disease on Neck Dissection after Chemoradiation**

| Author | Number of Patients | Pathologic Residual Disease (%) | Survival (pLN+ vs. pCR) | Distant Metastasis (pLN+ vs. pCR) | Regional Failure (pLN+ vs. pCR) | Local Recurrence (pLN+ vs pCR) |
|---|---|---|---|---|---|---|
| Sewall et al. (2007)[210] | 107 | 28% | | | 13% vs. 1% | |
| Hu et al. (2007)[211] | 82 | 29% | DFS: 47% vs. 85% $p$ = 0.013 | 41% vs. 11% $p$ = 0.011 | 14% vs. 4%, $p$ = 0.376 | |
| McHam et al. (2003)[157] | 76 | 33% | | | 20% vs. 0% $p$ < 0.001 | |
| Stenson et al. (2006)[209] | 73 | 21% | 3 yr OS: 36% vs. 72% $p$ = 0.008 | | | |
| Argiris et al. (2004)[155] | 61 | 31% | 5 yr PFS:62% vs. 80% $p$ = 0.11 | | | |
| Ganley[210a] | 56 | 33% | 49% vs. 93 ($p$ = 0.005) | 42% vs. 8% | 16% vs. 5% | 26% vs. 11% |
| Lavertu et al. (1997)[156] | 35 | 34% | 50% vs. 83% ($p$ = 0.03) | | | |
| Newkirk et al. (2001)[141] | 33 (39% received concurrent CT/RT) | 45% | | | | 33% vs. 0% |

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prognostic implication in chemotherapy versus the nonchemotherapy treated patients.

Hu reported that the presence of residual pathologic nodal disease in a planned neck dissection predicts an increased risk for distant metastatic disease and worse DFS in 82 patients with N2/3 necks. Patients were treated with chemotherapy and a reduced dose of 60 Gy to involved nodes whereas the primary site was treated with definitive dose of 70 Gy with conventional or accelerated radiation by delayed concomitant boost.[211] Concurrent chemotherapy consisted primarily of high-dose cisplatin (100 mg/m$^2$ q 3 weeks for 2–3 cycles). A planned neck dissection was performed within 6–8 weeks upon completion of chemoradiation. Ninety-nine planned neck dissections were performed in 82 patients. The initial N stage were as follows: N2a, 5; N2b, 34; N2c, 22; and N3, 16. Pathologic residual disease was detected in 29% of neck specimens. The incidence of pathologic residual disease did not appear to correlate with initial neck stage and was as follows: N2a, 60%; N2b, 19%; N2c, 42%; and N3, 33%. Median follow-up was 2 years. For all patients, the 2-year estimate of regional failure was 4% and the incidence of 2-year DM was 11% with 2-year OS of 91%. The incidence of DM correlated with initial N stage (N2a: 0%; N2b: 7%, N2c: 28%, and N3: 42%) and the presence of pathologic residual disease (3-year DM: 11% vs. 41%, if pCR vs. pathologic residual disease). Patients with a pathologic residual disease had worse DFS than did patients with pathologic CR (3-year DFS: 47% vs. 85%, $p = 0.013$).

Ganley reported on 56 patients with node-positive disease treated with concurrent chemoradiation who underwent planned or salvage neck comprehensive neck dissection. Oropharynx comprised 71%, larynx 20%, and hypopharynx 9% with N1 11%, N2 78%, and N3 11%. Twenty-one percent had a CR. Fifty-four percent underwent resection 6 to 12 weeks after radiation whereas 39% had >12-week interval. Thirty-three percent (19/56) had pathologically confirmed viable tumor with a higher rate on partial versus complete responders (42% vs. 25%, $p = 0.1$). No correlation with pathologic residual disease and time interval between radiation and neck surgery (36%, 33%, and 25% at >12 weeks, 6–12 weeks, and <6 weeks, respectively). Patients with viable tumor had worse overall and recurrence-free survival (49% vs. 93%, $p = 0.005$ and 40% vs. 75%, $p = 0.004$, respectively). Failure occurred in 63% (12/19) of patients with residual viable tumor with regional failure in three, local failure in five, and distant failure in eight. Failure in the patient with no viable tumor was 16% (6/37) with local failure in four, regional failure in two, and distant metastasis in three.

Dagum reported on a series of 41 patients with node-positive disease undergoing organ-preservation therapy with induction cisplatin/5FU followed by concurrent chemoradiation consisting of 5FU/CDDP with radiation for organ preservation.[212] Seventy-eight percent had N2/3 disease (32/41). Patient with pathologic residual disease had worse survival with a trend toward increased regional and distant failure compared to those with no residual disease. Patients with pathologic residual disease also had worse survival compared to complete responders to chemotherapy and radiotherapy who were observed.

Consistently, the presence of pathologic residual disease predicts worse outcomes at multiple endpoints and is a likely indication of the responsiveness of the tumor to a particular chemoradiation regimen. This not only is important in close monitoring for locoregional recurrence, but also may predict the potential of the particular chemotherapy regimen to decrease distant metastasis, which is likely to occur in at least 20% to 25% of all N2/3 patients. It has been shown that as locoregional control rates improve, the dominant pattern of failure is that of distant metastasis.[213] Whether the presence of residual disease may select out a patient population for additional systemic chemotherapy or biologic treatment or close monitoring remains an area of future investigation.

## Posttreatment Surveillance Regimen

The surveillance of patients after combined chemoradiation remains controversial with respect to the timing and type of imaging modality which is used to follow these patients. It is generally accepted for the first 8 weeks after treatment, all imaging studies should be withheld to allow for resolution of inflammation and resolution of persistent disease which is in the process of regressing. It is at about the 8-to-12-week period that imaging can be performed and interpreted with some reliability. Imaging that relies on anatomic morphology such as MRI and CT scans can be performed at 8 to 12 weeks and if there is any doubt, the findings can be repeated serially at 3-month intervals. PET-CT is the imaging modality of choice because it not only examines for anatomic abnormalities but also examines for metabolic activity. The fusion of metabolic imaging with its anatomic correlate has a very high NPV making it an extremely valuable tool in surveying patients who have been treated with combined chemoradiation. The ideal timing of a baseline exam is at 12 weeks after the completion of therapy.[214] Repeat imaging is performed at 6-month intervals.

## Postoperative Chemoradiation

***Role of Neck Dissection in trans oral robotic surgery (TORS).*** One of the difficulties with treating carcinomas of the oropharynx (base of tongue, tonsil, pharynx, soft palate) is the surgical access to these areas. In the not-so-distant past, the only way to surgically access these areas was to perform a large open procedure, which often required a mandibulotomy and mandibular swing. This approach was difficult and highly morbid, and hence, as chemoradiation became increasingly more effective, it rapidly became the standard of care for treating carcinomas of this part of the head and neck. Recently, transoral robotic surgery has become an important new addition to the treatment algorithm for cancers of the oropharynx. The robotic arms and high-powered three-dimensional visualization have enabled surgeons to now access remote parts of the upper aerodigestive tract (oropharynx and hypopharynx) without the need the mandibular swings and tracheostomies.

TORS is an effective treatment approach to the primary tumor but one must also manage the cervical lymphatics. The neck can be managed concomitantly with the TORS procedure or in a staged fashion. Many surgeons are currently staging the neck dissections in an attempt to reduce the incidence of salivary fistula formation.[215] The neck dissections can then be performed 2 to 4 weeks after the TORS procedure. Recently, Moore et al. published their experience with 148 consecutive TORS procedures with synchronous neck dissection for oropharyngeal SCCa.[216] Although 42 of the 148 patients were identified as having intraoperative oropharyngeal–cervical communication, they were all managed with primary closure, local tissue advancement, fibrin glue application, and cervical drain placement. Six of the 42 (4%) patients developed a pharyngocutanous fistula, which were all managed conservatively. None of the patients experienced a delay in the initiation of adjuvant therapy. Boudreaux et al. also reported nine cases of robotic-assisted oropharyngectomy with synchronous neck dissection with no patients developing a postoperative pharyngocutaneous fistula.[217] Genden et al. reported their experience with 15 patients who underwent TORS with a concomitant neck dissection and found that 1 patient had an intraoperative communication with the neck, which was closed with a local muscle flap, and no patients developed a postoperative pharyngocutaneous fistula.[218] Although TORS is relatively new and the decision to perform the neck dissection simultaneously or in a staged fashion has not been resolved, it seems that both approaches are reasonable and neither approach significantly delays adjuvant therapy. Regardless of the timing of the neck dissection, it seems

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to be universally accepted by the head and neck surgery community, which is actively performing TORS, that a neck dissection should be performed for N0 and N+ necks. The information from the neck dissection specimen can be very important in deciding on the role and form of adjuvant therapy.

## Role of IMRT in the Management of the Neck

With increased ability to deliver highly conformal therapy, defining nodal levels at risk is crucial and has significant implications for long-term functional outcomes particularly swallowing and xerostomia. Conformal therapy allows sparing of parotids either by constraining dose to the superficial parotid lobe or by allowing differential coverage of nodal levels whereby the high level II/retrostyloid/junctional nodes are spared on a clinically negative contralateral neck.

With the advent of conformal therapy using IMRT, the identification of gross and nodal stations at risk for subclinical disease are crucial in designing the optimal treatment. Target delineation is challenging as the rationale for treatment is based on surgical data; however, the landmarks used are radiographic ones that do not use the exact surgical landmarks identified on neck dissection. Several groups have attempted to correlate radiographic boundaries with anatomic outlines defining the nodal stations reported by Robbins representing the American Academy of Otolaryngology (AAO).[51,60,62,63] These groups have also defined nodal stations not precisely defined by the AAO such as the retropharyngeal and supraclavicular nodes. Consensus guidelines have been achieved for necks that are to be treated electively, therapeutically, and postoperatively.[219,220]

Consensus boundaries for the clinically negative neck are delineated in Table 14.04a and Figure 14-1. The jugular nodes are defined by their relation to the internal jugular vein with the superior border in a node-negative neck defined by the posterior belly of the digastric muscle crossing the jugular vein or the inferior border of the C1 transverse process. In node-positive necks, coverage of the high jugular nodes are added, which incorporates the retrostyloid nodes above the digastric muscle and lie in the carotid space in front of the internal carotid artery/internal jugular vein up to the jugular foramen.[219] The hyoid bone, cricoids cartilage, sternocleidomastoid muscular, jugular vein, and submandibular gland represent important landmarks defining the jugular nodal stations. The trapezius muscle is critical for delineation of level V and the mandible and tongue muscles define level I nodes. The retropharyngeal nodes are divided into medial and lateral chains and are defined by the medial border of the carotid artery, the skull base, and the top of the hyoid bone.

The primary difference between node positive and node negative is coverage of the retrostyloid space cranially and the supraclavicular fossa caudally.[219] If extracapsular extension is demonstrated radiographically or pathologically, coverage of the adjacent muscles (e.g., sternocleidomastoid muscle) is included with a 1-cm margin based on pathologic data demonstrating that >95% of all extracapsular disease is encompassed within 1 cm of the involved nodal capsule[221] (see Fig. 14-1). Positive nodes at the junction of two nodal levels should include both nodal levels in the target. In the postoperative setting, the surgical bed should be included especially in the presence of extracapsular extension where tumor spillage into the tumor bed is possible. For positive nodes in the pharyngeal tumors, the retropharyngeal nodes should be included. The retropharyngeal nodes are divided into medial and lateral chains, the lateral nodes also called the nodes of Rouviere. Since the lateral retropharyngeal nodes are involved first, it is reasonable to exclude the medial retropharyngeal nodes in an attempt to partially spare the superior and middle constrictor muscles which may reduce long-term dysphagia.

Consensus guidelines regarding delineation of neck node levels have been reached for the node-negative, node-positive, and postoperative neck. In outlining tumors based on the nodal levels defined by the 2002 American Academy of Otolaryngology–Head and Neck Surgery consensus reported by Robbins et al.,[61] Som translated the anatomic boundaries to identifiable landmarks based on CT imaging.[63]

Several single-institution studies have reported outcomes in head and neck cancer treated with definitive and postoperative radiation.[14,60,222,223] Eisbruch reported the importance of covering retropharyngeal nodes to the skull base rather than to C1.[223] Thorstad reported the importance of avoidance of underdosage of nodes near the deep lobe of the parotid gland, which is intentionally dose constrained. Also, others have reported marginal recurrence at the match line and low-neck fields.[224] Levandag reported on 57 patients whose necks were treated with 3D conformal therapy using a defined CT-based neck nodal delineation system defined by the Rotterdam group.[60] Forty-six received definitive radiation to the primary site of whom 13 received definitive radiation to 15 node-positive necks and 11 underwent preoperative radiation for a node-positive neck. The group consisted of 81 node-negative necks and 26 node-positive necks. Node-positive patients were treated to 70 Gy and node-negative and preoperative node-positive neck received 46 Gy. Primary sites were primarily larynx ($n$ = 29), oropharynx ($n$ = 24), and also hypopharynx ($n$ = 7) as well as one oral cavity patient. At a median follow-up of 29 months, the regional failure rate was 8.6% (4/46) with a 3-year actuarial estimate of 10%. All four failures occurred in supraglottic larynx patients, and all occurred in contralateral initial N0 necks.

## Management of Recurrent Neck Disease

Recurrent squamous cell carcinoma in the neck is difficult to manage for multiple reasons. A complete or comprehensive removal of the nodal disease is not always possible due to extracapsular extension into vital structures such as the carotid artery or fixation to deep tissues such as the prevertebral fascia. Additionally, prior surgery and radiation therapy can result in severe fibrosis making the surgical dissection extremely difficult and often impossible to perform a definitive resection of all gross and microscopic disease. Moreover, recurrent disease to the neck is associated with a high risk for DM and treatment resistance due to prior multimodality therapy. Given the morbidity of uncontrolled regional disease, palliative treatment should be considered.

In a retrospective analysis of 139 patients with neck disease treated with prior radiotherapy at the University of Florida, Mendenhall et al. note that the majority of patients failing in the neck did not undergo an attempt for salvage due to unresectable disease at the primary site or the presence of DM.[126] In total, only nine patients underwent an attempted salvage. Although the details were not provided, of 25 patients failing in a solitary lymph node, 6 underwent attempted salvage with only 2 being successful. A follow-up study reported the outcomes on 51 patients who failed regionally after primary radiotherapy.[225] These patients represented 14% of 356 patients treated with primary radiation therapy without neck dissection. Nodal recurrence occurred at a median time of 5.4 months after radiation. One-third ($n$ = 18) were candidates for salvage treatment as the other patients were unresectable, medically unfit, or had distant metastasis. Of these, 14 underwent salvage neck dissection. Complications included soft tissue necrosis in four patients, vocal paralysis in two, separation of the flap in one, chylous fistula in one, and hemorrhage in one. One of 14 was salvaged with long-term neck control. For the entire group who were eligible for salvage surgery, the 5-year regional control was 9% and absolute survival was 10%.

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In an update, Liauw reported on 54 regional failures in 550 node-positive patients treated with definitive radiotherapy. Isolated regional failure occurred in 13 patients, 11 of whom had previous neck dissection and 2 without neck dissection. Nine patients underwent attempted surgical salvage with or without reirradiation therapy. Four of nine patients were successfully salvaged with one salvaged with surgery alone, one undergoing $^{125}$I brachytherapy with surgery, and one retreated to a total dose of 70 Gy. Three of nine patients experienced wound breakdown. For the entire group, the 5-year OS was 25% and regional control was 28%.

Similarly, Peters et al. describe only one of seven attempted salvage neck surgeries being successful.[131] Bernier reported on 116 patients with isolated nodal failures from a group of 1,646 patients treated with primary radiation at the Institute Curie.[129] Of these, only 14 had salvage neck dissection. Salvage was successful in only one for an overall success rate of 1% (1/116).

Despite dismal salvage rates, several retrospective series report on the efficacy of using interstitial brachytherapy implant or intraoperative radiation therapy in combination with salvage neck dissection, typically in necks previously irradiated and dissected. Often, these series mix primary and neck recurrences and treatment of nonrecurrent lesions, reflecting the heterogeneous spectrum of neck recurrence scenarios.[226–229] Despite the heterogeniety, the treatment strategy of combining salvage surgery with brachytherapy or IORT does appear afford meaningful control of neck relapses. Although no comparative studies have been reported, efficacy has been inferred based on clinical experience expecting further neck relapse within the first 1 to 2 years with the majority of patients receiving an implant showing at least a delay to progression.[228] Although a brachytherapy implant permits sufficient cytotoxic doses to be delivered at a defined volume that limits the risk for complications, the risk for wound complications may be further reduced by a planned coordinated introduction of nonirradiated tissue flaps. Both pedicle myocutaneous flaps[230] and microvascular free flaps have been described.[231] In turn, the introduction of nonirradiated skin and soft tissue further serves to minimize the risk for carotid exposure and rupture and may facilitate further external beam irradiation to be delivered. Typically, low dose rate implants used either iodine-125 ($^{125}$I) (Fig. 14-4) or $^{192}$Ir (Fig. 14-5). The former is typically used as a permanent interstitial implant with advantages of reduced radiation exposure. The latter is advantageous as it provides more generous coverage of the tumor bed, has the ability to after load providing an opportunity for dosimetric optimization, and permits sufficient wound fibrogenesis minimizing the risk for wound dehiscence.[232] In general, control rates of approximately 40% to 80% have been reported with complication rates of 20% to 50%. Hence, patient selection is particularly important for this indication.

Chen et al. reported on 24 patients with advanced recurrent HNSCC, using salvage surgery and $^{125}$I implantation delivering a minimum dose of 100 Gy to the tumor bed with a pedicle myocutaneous flap covering the carotid artery.[233] Neck failure was the sole or at least one component of the relapse in 19 patients. Local disease control was 42%. Two-year overall and cause-specific survivals were 29% and 50%, respectively, with a major complication rate of 21% and an overall complication rate of 50%. Two patients developed carotid rupture but in the presence of further neck recurrent disease.

Park et al. reported on 39 $^{125}$I implants in 35 patients with extensive recurrent HNSCC following salvage surgery with indications of either a close or positive resection margin.[234] The neck was implanted in 44% of the cases. The average dose delivered was 82.8 Gy. The 5-year local control rate, DFS, and OS were 29%, 41%, and 29%, respectively. Significant complications occurred in 36% of all cases. Major complications included flap

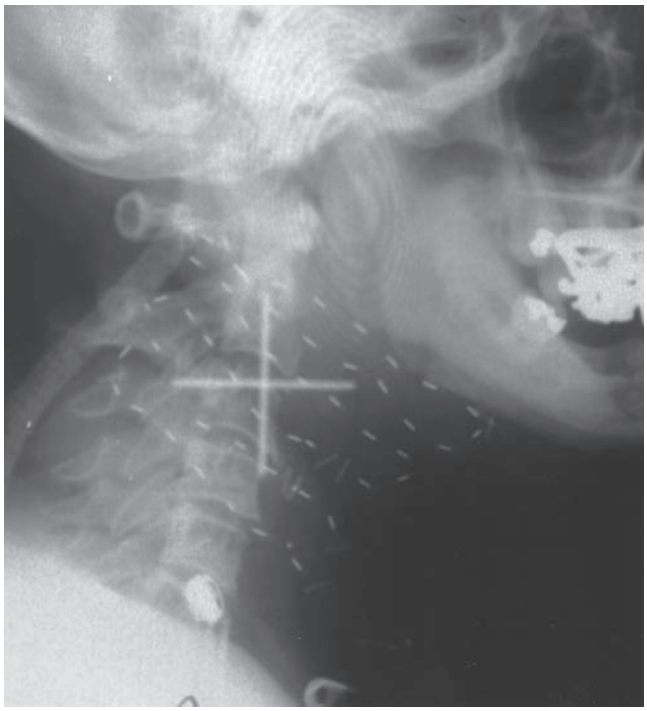


**FIGURE 14-4.** Permanent iodine-125 implant in the neck of a patient with recurrent disease in the neck following complete surgical resection.



**FIGURE 14-5.** Temporary iridium-192 implant in the neck of a patient with recurrent disease in the neck following complete surgical resection and reconstruction with a pedicled pectoralis major flap.

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necrosis in 26%, fistula formation in 8%, carotid rupture in 5%, osteoradionecrosis in 3%, and death due to sepsis in 3%. Two patients experienced a carotid rupture that occurred in the context of recurrent neck disease.

Vikram et al. reported on 21 patients with recurrent HNSCC.[228] Neck implantation was the most common indication in eight patients (38%). All gross tumor could not be removed in 15 patients, whereas satisfactory margins could not be obtained in 6. In 11 patients, a temporary implant of $^{192}$Ir (median dose 48 Gy in 6 days) was used with a permanent $^{125}$I implant used in the remaining patients. The actuarial 2-year local control and survival rate was 81% and 55%, respectively. Complications developed in four patients (19%) and proved fatal in one patient.

Fee et al. reported on 29 patients with large masses attached to the carotid artery undergoing surgical resection with preservation of the artery and intraoperative $^{125}$I with an absorbable suture.[226] Nine patients with gross residual disease that was implanted were excluded from analysis with four of the nine recurring in the implanted volume. All nine patients died within 12 months. Eighteen patients (64%) were treated for recurrent neoplasms with neck masses >4 cm, having failed prior surgery or radiation. A mean dose of 163 Gy was delivered to the implant volume over 1 year for this cohort. With a minimum follow-up of 1 year, 76% of patients were disease-free in the implant volume and 62% were disease-free in the entire neck for the entire group. Mean survival was 15 months (2–50 months) in the primary group and 12 months (4–26 months) in the recurrent group. Neck recurrence occurred in 39% of those treated for recurrent disease with 22% occurring within the implant. DM occurred in 39% of those treated for recurrent disease. The overall and major complication rate was 41% and 28%, respectively. Two carotid rupture complications were noted again in the context of recurrent neck disease.

Paryani et al. reported on 38 patients with locally advanced head and neck cancer attached to the carotid artery treated with resection and $^{125}$I Vicryl suture implant.[229] Most patients had neck masses that were >6 cm without clinically evident DM. Twenty-six patients (68%) had recurrent disease. For the cohort with recurrent disease, local control within the implant volume was observed in 81%. Distant relapses were also observed in 50% of patients treated for recurrent disease. Mean survival was 9 months. The overall complication rate was 26% with most complications involving wound breakdown or flap necrosis. Once again, three patients developed a carotid rupture in the context of biopsy-proven recurrent disease.

## Intraoperative Radiation Therapy

Intraoperative radiation therapy (IORT) has recently become an important option in the treatment of recurrent head and neck cancer. IORT is delivered to the location of the tumor recurrence at the time of surgery and the surrounding vital structures are shielded or displaced during irradiation while allowing for maximal exposure of the tumor bed to the radiation. IORT can be used as standalone treatment or in conjunction with additional external beam radiation therapy. It offers the possibility for full-course reirradiation in safe and effective manner. It is most commonly delivered using electrons or with high dose rate $^{192}$Ir applicators (Fig. 14-6).[235–241]

To date, multiple single-institution retrospective series have been reported with heterogeneous patient and tumor selection criteria, the extent of surgical resection, and the volume of intraoperative irradiation limiting. Complete surgical resection with a negative microscopic margin remains the most important determinant for neck control and survival.[235,236,239] Doses ranging from 10 to 30 Gy or 7 to 20 Gy have been delivered as the sole

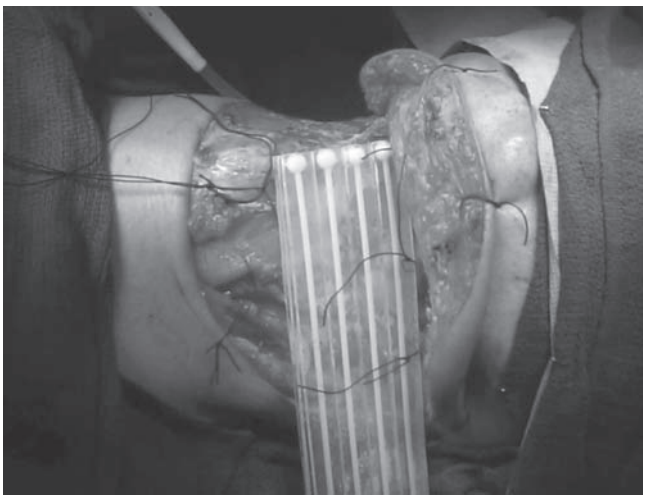


**FIGURE 14-6.** Intraoperative high-dose rate brachytherapy to the neck in a patient with recurrent neck disease following complete surgical resection.

treatment or when combined with repeat external beam radiotherapy, respectively. Complications appear to be acceptable and may include wound complications, peripheral neuropathy, osteoradionecrosis (~5%), and carotid rupture (<5%) that also appear to be related to progressive or recurrent disease. This technique is particularly attractive for several conceptual reasons: (a) high doses of radiation can be delivered with high accuracy with shielding or displacement of nearby tissue, (b) it is delivered before the onset of tumor repopulation and surgical bed hypoxia, and (c) it can be combined with a reduced dose of external beam radiation therapy. The radiobiology of large single doses of radiotherapy may be particularly advantageous in overcoming radioresistant recurrent disease.

In 2011, Zeidan et al. published their experience with 231 patients with advanced cervical nodal disease who underwent a neck dissection and IORT with electron therapy. In this report, the patients included had prior external beam radiation therapy, were at high risk for residual gross or microscopic disease within the neck, or had advanced nodal disease (N3). One hundred ninety-eight of the 231 patients presented for salvage therapy with 88% having received previous external beam radiation. A median dose of 20 Gy (range 10–25 Gy) was delivered using electrons (most commonly 5 MeV). The median cone size is 6.4 cm. Fifty patients received additional external beam radiotherapy (median dose 45 Gy). Ninety-nine patients received chemotherapy. The median follow-up was 1 year. The OS and recurrence-free survival were 26% and 49%, respectively, at 5 years. Negative prognostic factors for survival were carotid artery involvement, perineural, or dermal invasion. Complications occurred in 27% of all patients and included vascular complications in 23, pharyngocutaneous fistula in 20, wound dehiscence in 20, peripheral neuropathy in 7, and osteoradionecrosis with two flap necrosis in 8.

IORT using the high-dose rate $^{192}$Ir applicator was used in the salvage of 35 patients with isolated neck recurrences (see Fig. 14-6). The primary sites were the oropharynx (34%), the oral cavity (24%), and the larynx (21%) in the majority of cases, and 91% of patients received previous external beam radiotherapy. The major histology was squamous cell cancer (94%) and three-fourths of patients were male. Median IORT field size was 6.4 × 5.4 cm, and mean dose delivered was 13.5 Gy (range 10–17.5 Gy).

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Twenty-three had flap reconstructions, primarily rotational pectoral flaps (91%). More than half of the patients received (19/35) additional external beam radiation (median dose 45 Gy), and 26% received additional chemotherapy concurrent with radiation. At a mean follow-up of 20 months, the 1-year in-field control was 64% with higher rate in patients achieving negative margins (70% vs. 48%, $p = 0.44$) compared to those with microscopic positive margins. Among patients with positive margins, those receiving additional external beam radiotherapy had higher in-field control (100% vs. 44% $p = 0.035$) compared to those treated with IORT alone. In-field control translated into improved survival at 1 (100% vs. 73%, $p < 0.001$) and 2 years (100% vs. 25%, $p < 0.001$). Toxicity included one patients with vagal neuropathy and another patient with wound breakdown at 2 years.

In summary, the use of either brachytherapy or intraoperative techniques may afford a meaningful delay in the time to progression or salvage of neck relapses. Although no studies with quality-of-life end points or comparative analysis have been performed to validate the observations noted in retrospective reviews, in light of the morbidity associated with neck recurrences, its application in selected patients may be appropriate

## Future Directions

Significant improvements have been made in locoregional control with multidisciplinary treatment combining concurrent chemoradiation and surgery for patients with locoregionally advanced disease. Despite such aggressive treatment, locoregional failure or distant metastatic rates remain at 20% to 25%. Efforts to better select patients for further therapy will be important to tailor therapy appropriately. To that end, PET done at 3 months after chemoradiation appears to be promising in selecting patients who may be spared neck dissection; however, PET may not be able to predict those at risk for distant metastasis. Other imaging studies such as dynamic contrast-enhanced MRI to detect a hypoxic component may be able to detect a group of patients at higher risk for radioresistance and persistence of disease. Pathologic evaluation remains an important manner to assess risk. Limited excision of initially involved nodes may offer the best compromise between morbidity of surgery and the prognostic pathologic information gained. Biologic markers such as the epidermal growth factor may tailor therapy to determine which patients may have more aggressive disease that is radioresistant.[242] As an anti-EGFR therapy, the value of C225 in the management of the neck remains to be defined. The roles of induction and adjuvant chemotherapy are currently being reexplored as promising results have been reported with taxane-based regimens. Induction chemotherapy followed by concurrent chemoradiation may yield even higher pathologic CR rates in the neck than are obtained with current regimens, which would further select out patients likely to be cured from their head and neck cancer. Patients with residual neck disease may be candidates for further therapy. The RTOG is testing the benefit of postoperative chemotherapy within 2 weeks following surgery to minimize the delay between surgery and the onset of therapy. Integration of other biologics including antiangiogenic agents such as avastin may possibly decrease the incidence of distant metastasis. Just as modifications of neck dissection procedures has led to less radical surgery and better function, the selective delivery of radiation therapy to nodal stations at highest risk is now possible with conformal techniques such as IMRT which may better spare patients long-term morbidity.

With rapid advances occurring in genetic analysis, considerable progress has been made in the genetic deciphering of head and neck cancer. In 2005, Ferris et al. used quantitative reverse transcription polymerase chain reaction (QRT-PCR) to identify four makers that discriminated between lymph nodes harboring metastatic disease and lymph nodes which did not harbor metastatic disease.[243] The accuracy was reported to be >97%. The markers utilized in this report were pemphigus vulgaris antigen (PVA, aka desmoglein-3), squamous cell carcinoma antigen (SCCA1/2, neutral and acidic forms), parathyroid hormone–related protein (PTHrP), and tumor-associated calcium signal transducer (TACSTDI, aka epithelial cell adhesion molecule [EPCAM]). PVA was reported to discriminate between malignant and benign lymph nodes with 100% accuracy. This report suggested that it may be possible to use QRT-PCR analysis for PVA analysis to stage cervical lymph nodes in HNSCC. In 2011, Ferris et al. reported the use of this technology to perform rapid and intraoperative genetic evaluation of sentinel lymph nodes in HNSCC with QRT-PCR.[244] They reported the completion of the genetic analysis in <30 minutes.

Another approach which has been reported is to analyze the primary tumor genetic properties. It has been shown that the presence of a local recurrence can be predicted based upon the genetic expression in the primary tumor.[245] It has also been shown that the presence of a regional recurrence can be predicted based upon the genetic expression of the primary tumor.[246–248] Microarray technology has allowed for the rapid detection of multiple genetic markers in the primary tumor and the neck metastases and comparison. These studies suggest that the metastatic potential of a cancer can be deciphered from the primary tumor gene expression pattern.

A very powerful adjunct to the surgical management of the neck is the sentinel lymph node biopsy using lymphoscintigraphy. Morton et al. pioneered this technique for use in detecting the lymphatic spread of melanoma. Nuclear radiography is used to identify the primary, secondary, and tertiary lymph node basins as well as the "sentinel" lymph node within the lymph node basin. This technique provides the surgeon with the ability to try and stage the clinically occult neck. Pitman et al. of the University of Pittsburgh have explored the idea of identifying the sentinel lymph node in the primary lymph node drainage basins from known HNSCC primary neoplasms. By identifying the sentinel lymph node, the investigators were able to stage the N0 neck in a minimally invasive manner and then make recommendations for the elective neck therapy with this information. Sentinel lymph node biopsy in HNSCC is probably best considered an investigational technique—as such, it has not yet achieved the status of "standard of care" for the treatment of head and neck carcinoma patients.

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# PART B:
# Radiologic Imaging Considerations

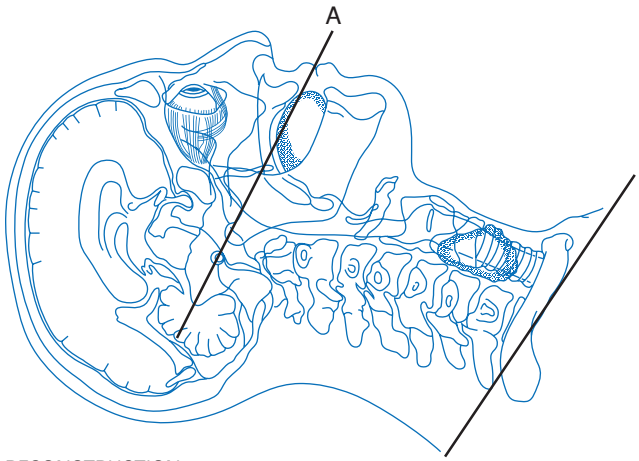
Jeffrey A. Bennett

Imaging of the neck is performed in addition to the physical exam, both as part of the initial staging of head and neck cancer and in posttreatment surveillance. It is helpful for confirmation of a clinical N0 neck, to assess nonpalpable areas of the neck such as the retropharyngeal region, and to evaluate the extent of palpable adenopathy. Prognostic information can be gained from the size of a nodal mass and the presence of extracapsular spread of tumor beyond the lymph node capsule, with associated possible invasion of muscles and vessels. Contrast-enhanced CT and contrast-enhanced MRI are the primary tools used to assess for the presence of tumor metastases in cervical lymph nodes. Ultrasound is used mostly for image-guided biopsy of a suspicious node. Suggested CT and MRI protocols are given in Figures 14-7 and 14-8.

FDG-PET can also be used to show physiological activity in lymph nodes, but its role in initial staging of head and neck cancer is still to be determined. Several studies have investigated the value of PET scanning for lymph node status in initial staging,[1–6] with a range of sensitivity from 47% to 100% and a range of specificity from 87% to 100%. Its negative predictive value is approximately 90%.[7] Its main limitation is the detection of small, < 7 mm positive nodes which is a problem given that > 40% of metastatic lymph nodes are < 7 mm in diameter.[8] Recent PET research has looked at standard uptake values (SUV) in positive lymph nodes as a prognostic factor, with one study[9] showing a higher SUV in nodes with extracapsular extension versus nodes without extracapsular extension, 11.0 versus 5.0. Higher SUV values in nodes were also shown to be predictive of distant failure at 1-year follow-up.

CT has been shown to be slightly superior to MR for the detection of metastatic deposits in lymph nodes.[8] Both CT and MRI require intravenous contrast for lymph node detection. Slice thickness should be no < 3 mm for CT and 4 mm for MRI. Multiplanar reformation of thin-section CT data can be helpful for problem solving, for example in showing a preserved fatty hilum in a folded lymph node. Criteria for calling a node positive include size, shape, enhancement pattern, and evaluation of the lymph node capsule.[10] Size, traditionally measured as the greatest diameter in the axial plane, is one feature looked at and is certainly helpful in assessing the typically uniformly enhancing lymph nodes seen in lymphoma. The availability of multiplanar reformats in CT and imaging in multiple planes with MRI allows

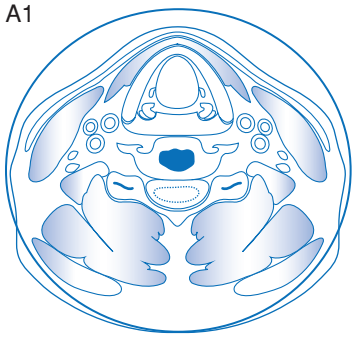
ACQUISITION




| | | |
|---|---|---|
| | Patient Position | Supine<br>Chin slightly elevated |
| | Contrast | Adult: 100 mL<br>Child: 1 mL/pound |
| | Injection Rate | Adult: 1 mL/sec; 60 sec delay<br>Child: Begin scan at 80% of contrast injection |
| | Respiration | Quiet, NO swallowing |
| | Volume Acquisition Specs | Appropriate to achieve images as specified in following reconstruction tables.<br>Head FOV. |
| A | Begin | Mid oral cavity |
| | End | Lung apices |

RECONSTRUCTION

A1



| | | |
|---|---|---|
| A1 | Algorithm | Soft tissue |
| | Thickness | 2.5 mm |
| | Spacing | 2.5 mm |
| | F.O.V | Approx. 160–190 |

**FIGURE 14-7.** Protocol for CT scan of the neck with intravenous contrast.

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| Acquisition | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Plane | Sagittal | Axial | Axial | Axial |
| Sequence | T1 | T1 | T2-FSE | T1 |
| Contrast | None | None | None | Gd |
| Thickness/spacing | 4/1 mm | 4/0 mm | 4/0 mm | 4/0 mm |
| FOV | 24 cm | 16 cm | 16 cm | 16 cm |

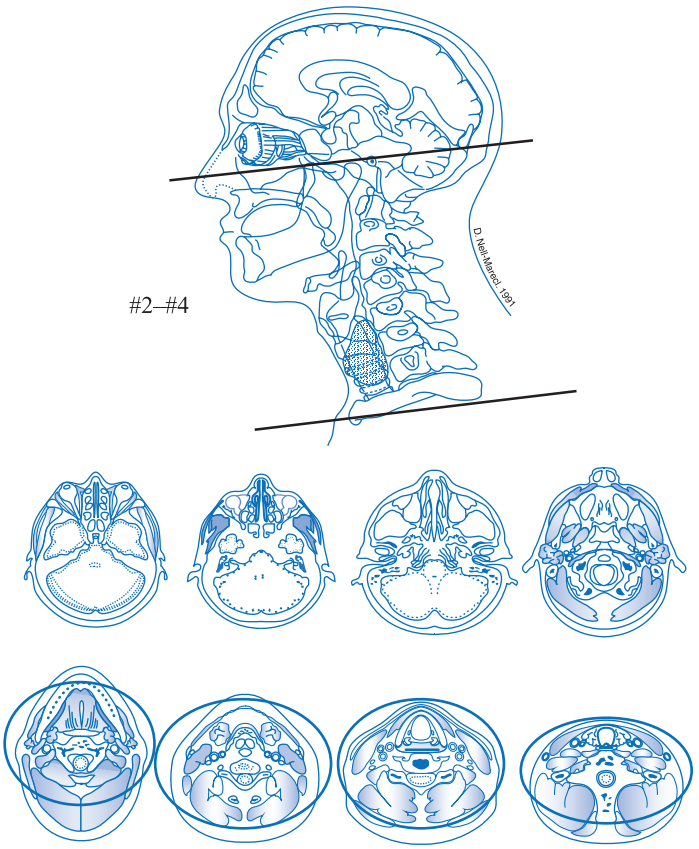



**FIGURE 14-8.** Protocol for MRI of the neck.

*Source:* Reprinted from Mancuso AA, Hanafee WN. *Head and Neck Radiology.* Philadelphia, PA: Lippincott Williams & Wilkins; 2011:2242, with permission.

a better visualization of the entire lymph node. Studies have not been performed to assess the sensitivity and specificity for metastatic head and neck cancer using the greatest diameter of a lymph node in any plane or the lymph node volume, which can be obtained easily with currently available software. Shape can be helpful, as lymph nodes filled with tumor tend to become more spherical. The enhancement pattern is probably the most useful feature. Nodes positive for squamous cell cancer have internal filling defects (Figs. 14-9 and 14-10), even when they are very small.

Sometimes, lymph nodes containing cancer can become quite necrotic (Fig. 14-11). Occasionally, these cystic nodes can be mistaken for branchial cleft cysts. Since branchial cleft cysts usually present in childhood, these cystic lesions seen in older patients must be assumed to be metastatic nodes and should be biopsied. In the author's experience, these often turn out to be metastatic nodes from HPV-positive primaries (Fig. 14-12).

Extracapsular tumor spread is a feature that has prognostic implications. This finding is made when the border of the lymph node becomes indistinct and there is infiltration of the surrounding fat. This feature can result in invasion of adjacent structures such as the sternocleidomastoid muscle or carotid artery, possibly making the tumor unresectable. Carotid artery fixation is assumed

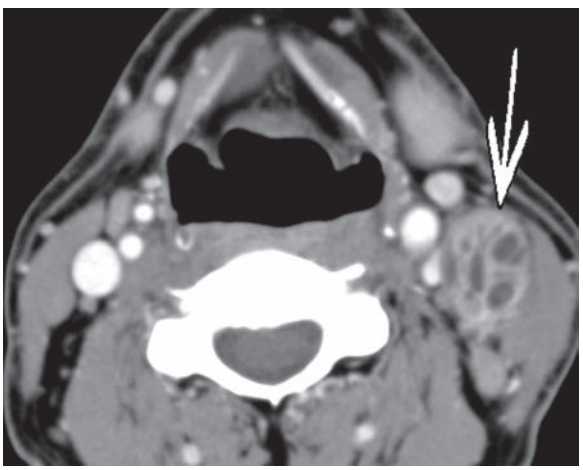


**FIGURE 14-9.** Axial CT scan with contrast shows a metastatic squamous cell carcinoma positive level III lymph node (*arrow*) showing a typical enhancement pattern of multiple filling defects.

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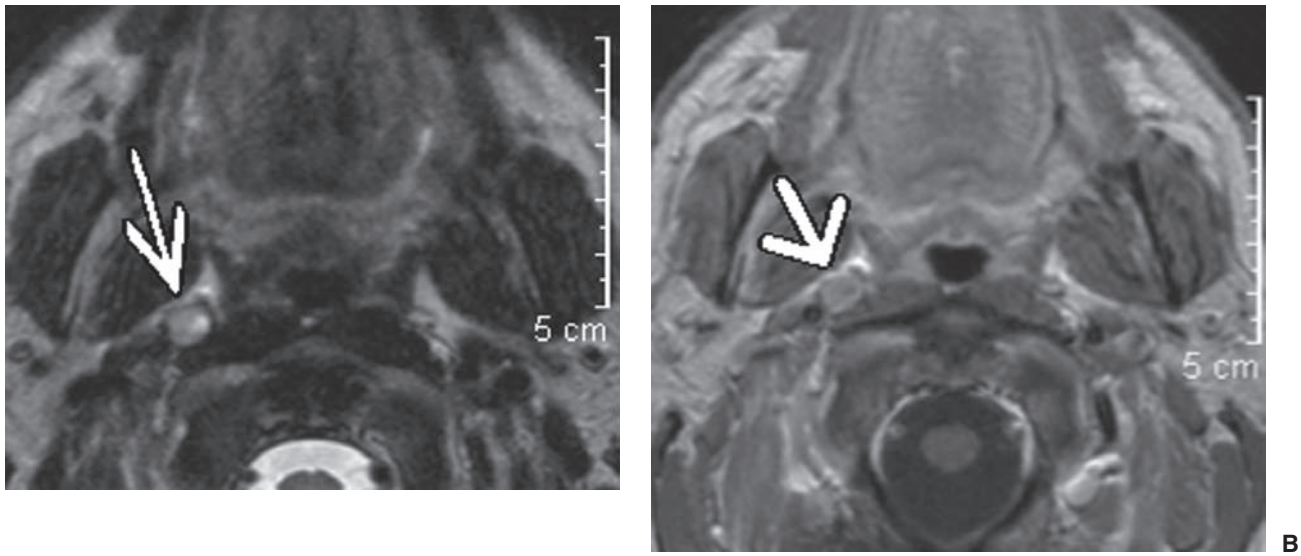



**FIGURE 14-10.** Axial T2-weighted MRI (**A**) and axial T1-weighted post gadolinium MRI (**B**) show a right retropharyngeal lymph node (*arrow*) positive for tumor in this patient with a nasal cavity primary squamous cell carcinoma. Note the high T2 signal likely representing necrosis and corresponding filling defects in its enhancement pattern.

when the tumor surrounds the carotid artery by >270 degrees (Fig. 14-13). Tumor invasion of the dermal lymphatics generally carries a poor prognosis. This is detected by skin thickening and infiltration of the subcutaneous fat (Fig. 14-14). Often focal necrotic nodules will also be present in the thickened skin.

Imaging of the neck, especially with contrast-enhanced CT, is frequently done to assess treatment response to chemoradiotherapy prior to surgery. This imaging is often performed as soon as 4 weeks post radiation. At this time point, FDG-PET would produce too many false positives from granulation tissue, and therefore CT criteria predictive of response has been generated. Labadie et al.[11] determined that a >90% reduction in the volume of a metastatic node following combined therapy compared to a pretreatment study predicted eradication of tumor within the node. Ojiri et al.[12] suggested that a neck dissection might not be necessary if the lymph nodes on the postradiation CT scan were <15 mm, free of significant internal focal low attenuation or calcification, and without imaging evidence of extracapsular spread (Fig. 14-15).

Studies have shown the value of FDG-PET when performed 3 to 4 months post radiation therapy. Two studies[13,14] showed that FDG-PET had a negative predictive value of 100% and 97% when

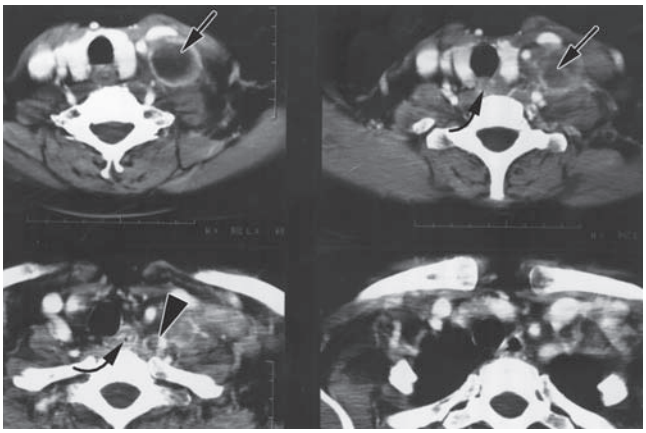


**FIGURE 14-11.** Virchow lymph node. Enhanced serial axial computed tomographic images through the lower neck. A necrotic lymph node at the left venous angle (*arrows*) and a smaller pathologic lymph node (*arrowhead*) due to a clinically occult primary squamous cancer of the esophagus (*curved arrow*) are shown.

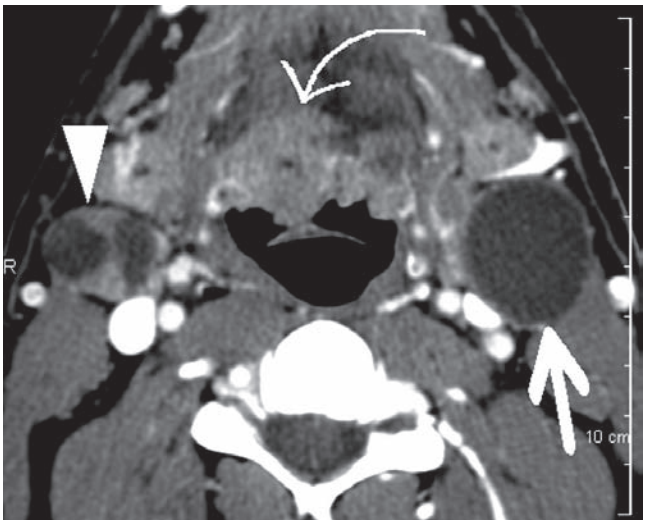



**FIGURE 14-12.** Carotid artery encasement by tumor. Axial contrast enhanced CT scan showing an almost completely cystic lymph node on the left (*arrow*) and more typically enhancing level II lymph node on the right (*arrowhead*), both positive for tumor in this patient with a primary HPV-positive tongue base squamous cell carcinoma (*curved arrow*).

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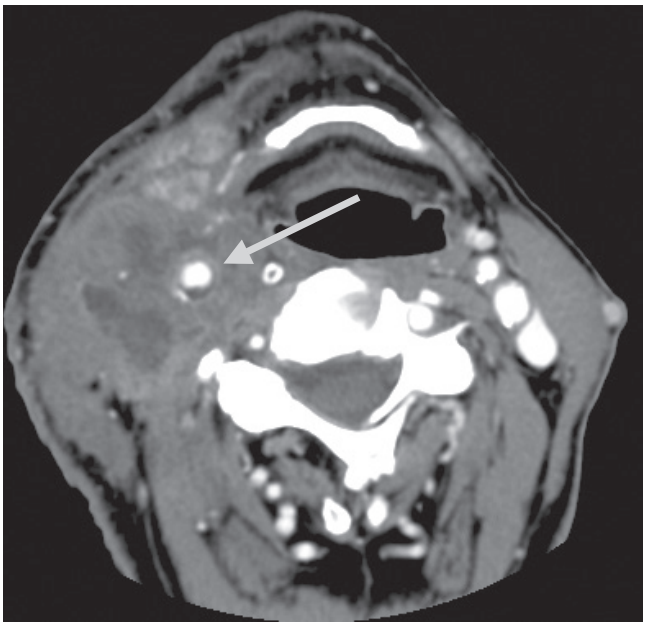


**FIGURE 14-13.** Carotid artery encasement by tumor. Axial contrast-enhanced CT shows a large tumor that completely surrounds the carotid artery indicating encasement (*arrow*). The generally agreed imaging criterion for carotid artery encasement is that the tumor must surround the carotid artery by 270 degrees. Tumors that abut or surround the carotid artery <270 degrees suggest that the tumor may be focally adherent to the carotid artery. CT, computed tomography.

performed 3 to 4 months post treatment. In most institutions, PET-CT is the preferred modality for head and neck cancer follow-up surveillance studies 4 months or greater post treatment. This is true as well for the postsurgical neck, where distortion of normal anatomy, flaps, and scarring result in challenges in interpretation

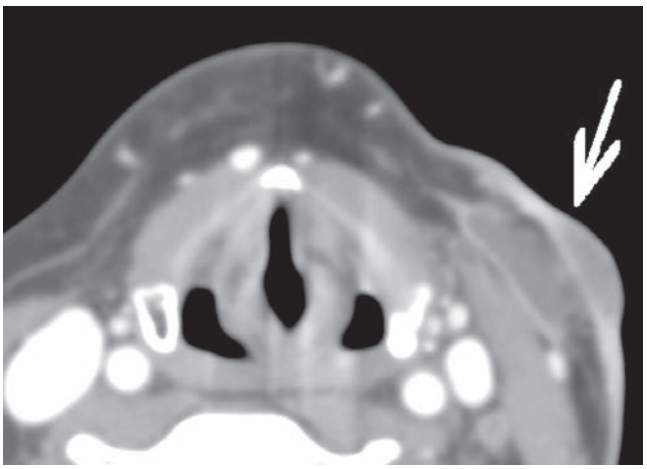


**FIGURE 14-14.** Axial contrast-enhanced CT scan showing invasion of the dermal lymphatics. Notice the skin thickening with a focal necrotic nodule located within the skin *(arrow)*. The subcuateous fat has been infiltrated with tumor.

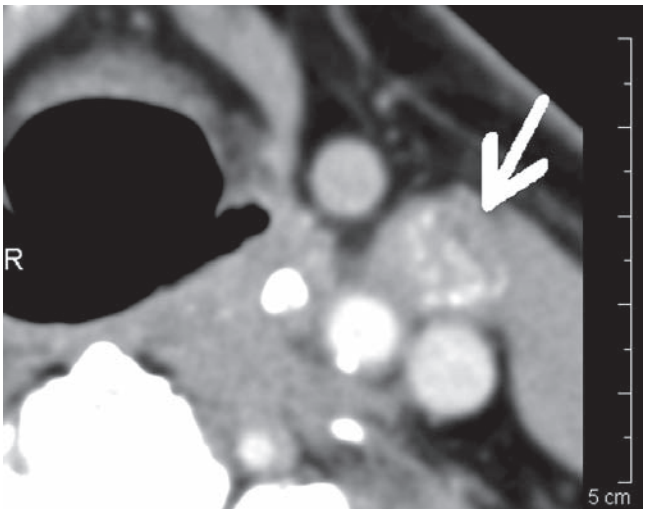



**FIGURE 14-15.** Axial contrast-enhanced CT scan obtained 4 weeks following completion of radiation therapy shows residual enhancement and calcification within a left level II lymph node (*arrow*). These imaging findings suggest the presence of residual tumor in the node and a neck dissection was recommended.

of conventional imaging studies. FDG-PET scans can be helpful to guide biopsy at sites of suspected tumor recurrence.

Diffusion-weighted MR sequences are being used more to differentiate benign from malignant neck nodes.[15] A low apparent diffusion coefficient (ADC) within a node suggests the presence of tumor compared to normal lymph nodes. Nodes that are responding to radiation therapy also have been shown to have an increasing ADC value.[16] Dynamic susceptibility-weighted contrast-enhanced MR perfusion imaging is also being studied as a promising tool to differentiate benign from malignant lymph nodes. Malignant nodes have been shown to have statistically more dynamic susceptibility contrast.[17]

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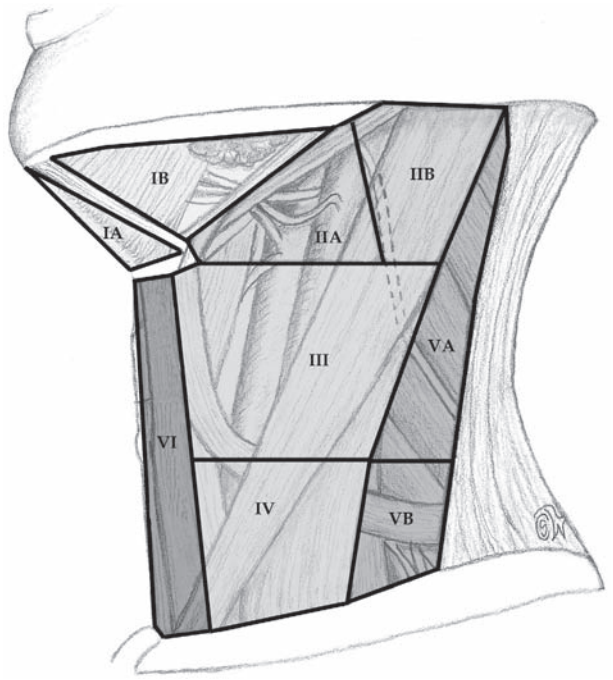
# PART C:
# Surgical Technique

Akash Anand, M. Boyd Gillespie, and Terry A. Day

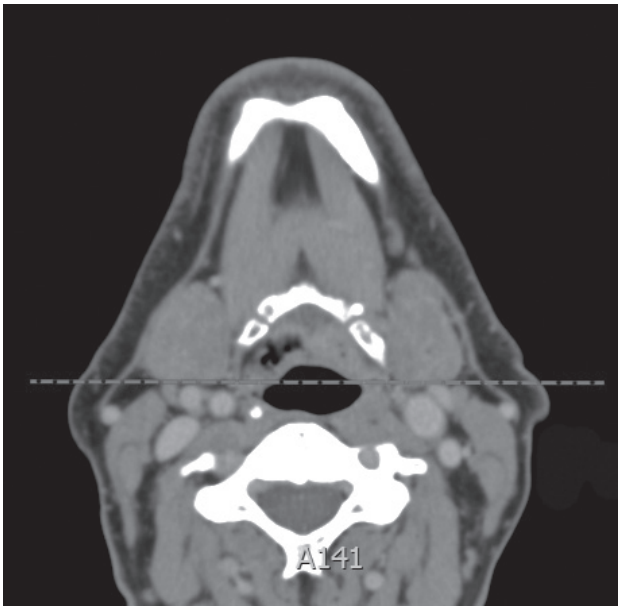
## INTRODUCTION

This section describes the various types of neck dissections and their standardized descriptions, along with the indications and risks for each when applied to squamous cell carcinoma of the upper aerodigestive tract, melanoma, salivary gland malignancies, and thyroid carcinoma, respectively. Particular detail is provided for the most commonly performed neck dissections by the authors, which includes selective neck dissections (SNDs).

Neck dissection for head and neck squamous cell carcinoma is generally performed based upon (a) location of clinically evident nodal metastases and (b) the likelihood of occult metastatic disease in the various nodal levels based on primary site.[1–4] (Fig. 14-16 depicts the clinical and radiographic boundaries of



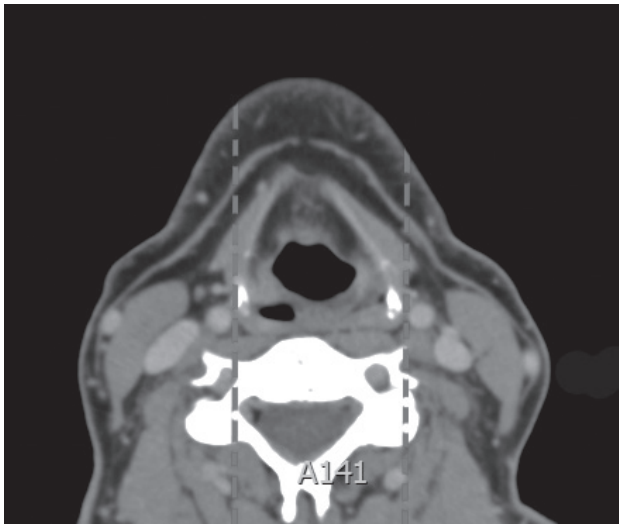

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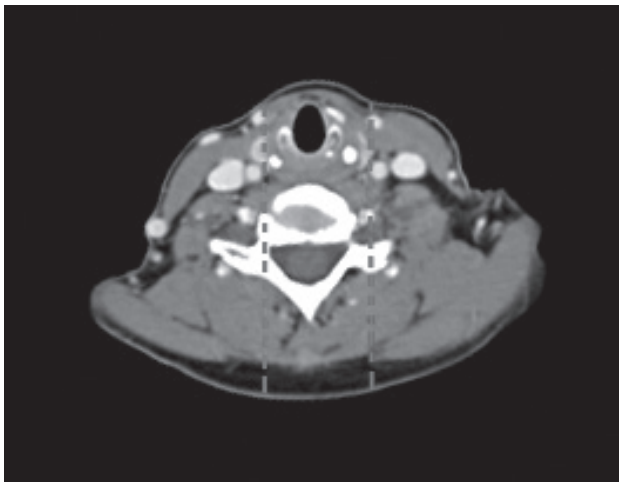

B

**FIGURE 14-16.** **A:** Clinical boundaries of the levels of the neck. **B:** Radiographic boundaries between IB and IIA are marked by a "vertical" line marked by the posterior edge of the submandibular gland.[5] For demonstrative purposes, this is shown as dashed lines on an axial CT. **C:** Radiographic boundaries between levels III and VI are marked by a vertical line at the medial border of the common carotids.[5] **D:** Radiographic boundaries between levels IV and VI are marked by a vertical line at the medial border of the common carotid arteries.

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C



D

**FIGURE 14-16.** *Continued*

the nodal levels of the neck.[5]) Based upon these factors, the authors generalize that at a minimum, when indicated, the follow lymph node levels should be considered for neck dissection and/or radiation therapy for selected sites:

- Oral cavity: Levels I, II, III, and possibly IV (Fig. 14-17)
- Oropharynx: Levels II, III, and IV (Fig. 14-18)
- Hypopharynx: Levels II, III, and IV (Fig. 14-18)
- Larynx: Levels II, III, IV, and possibly VI

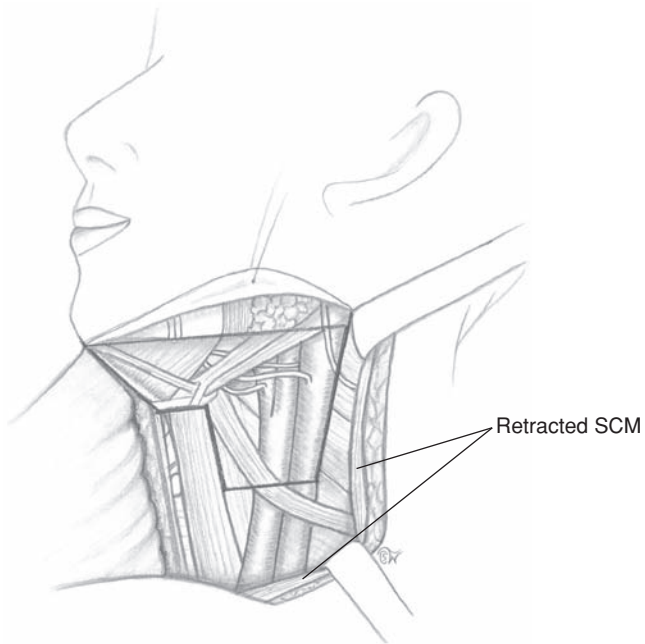



**FIGURE 14-17.** Sentinel node dissection I to III. (All contributions to the jugular vein are not shown.)

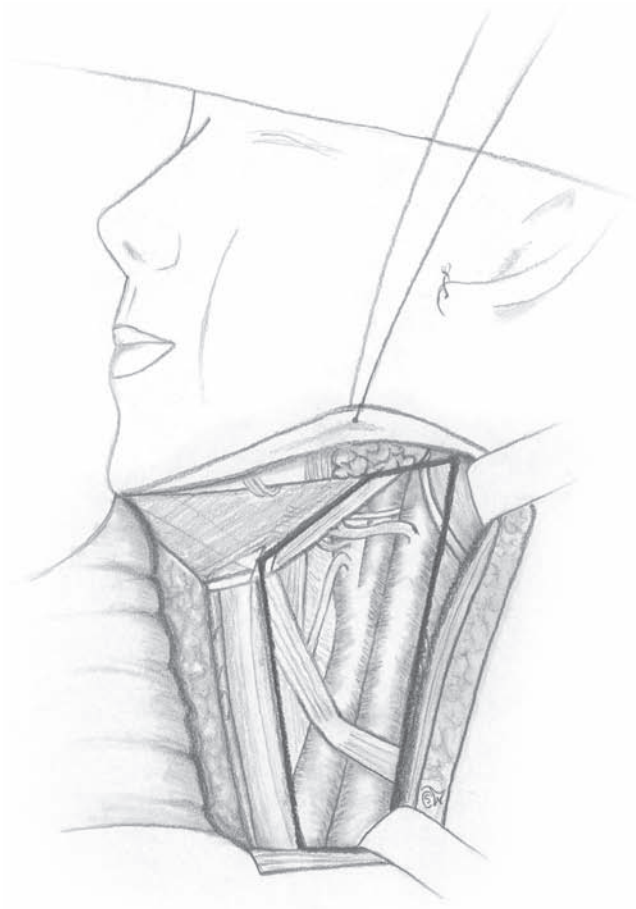


**FIGURE 14-18.** Sentinel node dissection II to IV. (All contributions to the jugular vein are not shown.)

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# SURGICAL TECHNIQUES

## Selective Neck Dissection (Levels I, II, III, IV)

By far, the most common neck dissection performed today is the SND, in which only the nodal levels that are clinically positive, or have a significant possibility of harboring metastatic disease for a given primary site, are removed.[6,7] The main advantage of this is a reduction in the morbidity that is associated with more extensive neck dissections.[8,9] Of course, clinical judgment should always be used, and any levels clinically involved with disease should be addressed regardless of the primary site.

In cases where surgery is the primary modality of treatment and nodal disease is clinically present, or in cases where nodal disease is clinically present after the completion of nonsurgical treatment, it is accepted that a neck dissection that includes the positive nodes should be performed. A remaining controversy exists in the management of the N0 neck and in the postchemoradiation neck mass. Each subsite deserves separate consideration of these issues, taking into consideration the tendency of that particular site to harbor occult metastatic disease.

Though the entire field of study with regard to neck dissections is deficient in the number of prospective trials that have addressed the benefits of different types of neck dissections for different levels of disease, several retrospective studies have shown a survival benefit with elective neck dissection for patients who have oral cavity disease that is staged T2–T4N0 or is ≥4 mm in thickness, especially in the subsites of the maxillary gingiva, alveolus, or hard palate,[10–15] though there have also been contrary reports.[16,17] It is well known that regional recurrences in oral cavity cancers have a dismal chance of successful salvage, however, and at present, this knowledge seems to have led many surgeons to err on the side of caution and perform SNDs on early-staged cN0 oral cavity patients.

The SND that is most commonly used for oral cavity carcinoma includes removal of levels I, II, and III (Fig. 14-17), and consideration should be given to removal of facial lymph nodes when evidence of malignancy or enlarged nodes of this region is present. Additional indications for this procedure may include lip carcinoma, submandibular gland malignancy, and melanoma of the cheek, the lips, and adjacent areas. This technique is not sufficient or indicated for oropharyngeal, laryngeal, or hypopharyngeal malignancy.

The techniques described herein will include removal of levels I, II, and III, and implies that SND is separate from primary site resection. When the neck dissection and primary site are addressed at the same time, it is important to modify the technique slightly to confirm mobilization and preservation of vital structures while removing all tumor en bloc when possible.

***Neck Incision Planning.*** The neck incision is usually marked and placed in a horizontal skin crease approximately two-finger breadths inferior to the mandible, but in a location adequate to expose the necessary lymph node levels. The neck incision is typically marked in a horizontal skin crease and may require an incision approximately 6 cm in length, although many surgeons continue to utilize an extension of the posterior aspect upward near the mastoid tip, and the anterior incision may continue across midline. The incision for most neck dissections can be limited to a horizontal incision in a skin crease, unless circumstances warrant an extension across midline, or extension of a vertical limb inferiorly for a radical neck dissection (RND), or superiorly, to include parotidectomy or extended neck dissection.

***Incision.*** The authors advocate using a 15-blade scalpel for the skin incision and electocautery for the remainder of the procedure. The skin incision should be carried through the subcutaneous tissue to expose the platysma muscle. At this point, the electrocautery is used to divide the platysma muscle in an avascular plane. The platysma is dehiscent at the anterior and posterior edge of the incision, forcing the surgeon to be aware that the external jugular vein and greater auricular nerve will be exposed deep to the subcutaneous fat overlying the sternocleidomastoid muscle (SCM). These two structures are commonly preserved and provide excellent landmarks for the posterosuperior flap elevation.

***Flap Elevation.*** Typically, double-pronged skin retractors are used by the assistant to retract the superior and inferior skin/platysma flap for elevation by the surgeon. The electrocautery is used to perform the flap elevation with adequate retraction and tension applied by the assistant. The superior flap is elevated to the level of the inferior border of the mandible, whereas the inferior flap is elevated to the level of the clavicle. Paralytic agents are avoided during this portion of the procedure to allow for identification and atraumatic dissection superiorly near the marginal mandibular branch of the facial nerve. Injury to the marginal mandibular branch of the facial nerve can cause smile asymmetry secondary to decreased innervation of the depressor anguli oris and depressor labii inferioris muscles.[18] If level I dissection is indicated, the marginal mandibular nerve is isolated, exposed, and retracted to remove level IB and lymphatics around these branches. If not, the fascia at the level of the hyoid bone or digastric muscle can be incised and mobilized to avoid injury to the marginal mandibular branch and expose the digastric muscle. Several small vessels are ligated with ligaclips, entering the skin flap during elevation, while electrocautery provides hemostasis for the other areas. During the superior flap dissection, the external jugular vein and greater auricular nerve can be dissected and isolated for preservation and form the deep extent of flap elevation.

***Approach to Lymphatic Structures.*** Once the flaps are elevated and the fascia overlying the lymph node levels to be removed is exposed, the skin is retracted with elastic self-retaining skin hook retractors in four quadrants to allow the surgeon and assistant hands-free retraction and dissection of the lymphatics. It is important to note that if nodal disease is present or involving structures, the technique will require modification to avoid entering lymph nodes or their extracapsular component, and these areas should be removed "en bloc."

***Lymphatic Dissection.*** The initial incision in the fascia is placed at the anterior border of the external jugular vein, the greater auricular nerve, and the SCM interface, and this fascia is then grasped with Allis forceps, thus providing tension and exposure to the anterior border of the SCM and levels II to IV. Using Babcock forceps on the SCM and Allis forceps on the lymphatics, the fascia and the lymphatics of levels II to IV are then freed from the anterior and deep aspect of the SCM, rounding the deep aspect of the SCM toward the deep and posterior border where cervical rootlets can then be exposed. It is crucial at this juncture to be aware that there is often a confluence of the greater auricular branch, and cervical branches 2 and 3, along with a communicating branch to the spinal accessory nerve that do not present themselves except near the posterior border of the SCM. After the skin flaps are elevated, the anterior and posterior border of the digastric muscle is exposed along with the SCM, the greater auricular nerve, the external jugular vein, and the omohyoid muscle, which are all preserved when oncologically indicated. The skin, muscles, and surrounding tissues can be retracted throughout the case with elastic self-retaining retractors. We will briefly separate the dissection of levels II, III, and IV to incorporate unique challenges of the anatomy of each level.

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*Level I.* See Radical Neck Dissection.

*Level II.* As the undersurface of the SCM is freed from the overlying fascia in level II, the spinal accessory nerve is identified and retracted carefully with a vein retractor. A reliable landmark for identification of the spinal accessory nerve is the presence of a vein that crosses approximately 2 mm superficial to it. Utilization of this landmark can help to avoid inadvertent spinal accessory nerve injury.[19] Iatrogenic injury to the spinal accessory nerve is repaired utilizing primary neurorrhaphy or cable grafting with the greater auricular nerve. The surrounding lymphatics are separated from the nerve and its affiliated branches to the cervical rootlets and the greater auricular nerve. If level IIB requires removal, the spinal accessory nerve is circumferentially mobilized and may be further retracted with an army-navy retractor to reach the posterior border of the SCM. At this level, no landmarks exist to specify that the junction of level IIB and VA has been reached, and thus cautery is used to dissect deeply perpendicular to the exposure to reach the floor of the neck where the splenius capitus and the levator scapulae muscles are exposed. A cranio-caudal incision in the deep fascia overlying these muscles exposes the muscle, and this fascia is then grasped with an Allis retractor, and cautery is then used to elevate the remaining lymphatic tissue anteriorly toward level IIA. At this point, the levator scapulae and the anterior scalene muscles come into view, while fascia is preserved over the anterior scalene to preserve the phrenic nerve. Visualization, palpation, and alternating anterior/posterior views are necessary to preserve and confirm the location of the spinal accessory nerve, the internal jugular vein, the internal carotid artery, and the vagus nerve. When the lymphatics are freed from the floor of the neck musculature toward the great vessels, an army-navy retractor is placed under the digastric muscle, thus exposing the internal jugular vein and possibly the external carotid artery. This "corner" of level IIA formed by the digastric muscle, the jugular vein/the carotid artery, and floor of the neck is one of the highest risk areas for jugular vein or carotid injury, and "folding" of the vein is commonly unnoticed, resulting in a small opening requiring repair. If an entry into the jugular vein or the carotid artery is present, meticulous care and exposure is indicated with suturing with a 6-0 Prolene when necessary. The lymphatics are then carefully elevated from the carotid fascia, the jugular vein, and the vagus nerve while ligating the occipital artery branch when necessary with ligaclips. Using a 15-blade scalpel, the lymphatics are freed from the adventitia of the internal jugular vein anteriorly, then diving deep between the facial vein branch and the internal jugular vein to remove this "facial pocket" and deeper bed of lymphatics of level IIA. When levels IIA and IIB are mobilized, they are removed and sent separately to pathology when oncologically sound, dividing at the inferior border of the hyoid bone.

*Level III.* Level III is performed posteriorly in a similar fashion without concern for the spinal accessory nerve. However, 2 to 3 cervical rootlets may be exposed here and preserved, while they are followed anteriorly toward the floor of the neck, staying superficial to the deep cervical fascia overlying the phrenic nerve. Dissection continues similarly to level II, toward the carotid fascia with a 15-blade scalpel used to mobilize the lymphatics from this fascia and the jugular vein, while preserving the fascia over the carotid and the vagus nerve if possible. Care is taken anteriorly in level III to preserve the superior thyroid artery and vein, the ansa hypoglossi nerve, and an occasional connection of the facial vein and the anterior jugular system. Once the omohyoid is reached, the specimen is sent to pathology.

*Level IV.* Level IV is performed in a somewhat different fashion than both levels II and III. The surgeon moves to the head of the bed, while the assistant places a large self-retaining elastic retractor under the omohyoid and the SCM or an army-navy when necessary. The surgeon uses an Allis clamp to grasp the bulky lymphatics and the electrocautery to free the lymphatics using retraction to expose the jugular vein, the transverse cervical vessels, and the thoracic duct. This lymphatic group has a more extensive quantity of fat that separates easily and can be difficult to grasp and retract. When the clavicle is reached, the lymphatics are passed off the table.At this time, irrigation is used throughout the wound, and an assessment for all vital structures is confirmed. Any bleeding is controlled with bipolar cautery. Any remaining lymphatics are removed and a drain is placed as necessary. The wound is then closed with resorbable 3-0 Vicryl undyed sutures for platysma and subcutaneous closure followed by a 5-0 Monocryl for skin closure.

Specific care is taken to avoid injury to the deep cervical fascia and the thoracic duct during the deep level IV dissection, as rates of chyle leak during neck dissection have been reported to be as high as 6%.[20] The thoracic duct enters level IV and travels anterolaterally to empty into the region before the junction of the subclavian and internal jugular veins. Meticulous dissection and a bloodless field can provide the operative surgeon with the ability to visualize this structure and ligate or avoid it as needed. After removal of the level IV lymphatics, a valsalva is provided by anesthesia to examine for any chyle in the wound. The intraoperative identification of a chyle leak requires immediate ligation and/or sealing with fibrin glue.[21]

## Radical Neck Dissection

Although rarely necessary in 2012, the RND will now be described to afford a shortened version of the modified radical neck dissection (MRND) technique, which utilizes a combination of the SND techniques and the RND techniques. A hockey stick incision is made through the skin via a natural skin crease, from the midline to the mastoid tip, allowing dissection through the subcutaneous tissue up to the superficial cervical fascia. The authors have modified the original descriptions and now avoid any inferiorly based "limb" from the horizontal incision as this "trifurcation" is often met with significant scarring, dehiscence, and poor cosmesis. Incising this fascial layer reveals the platysma, which is then incised allowing the raising of superior and inferior subplatysmal skin flaps. The skin flaps are elevated to the body of the mandible superiorly, the clavicle inferiorly, the sternohyoid medially, and the trapezius posteriorly, thereby effectively exposing the anterior and posterior cervical triangles.

The description herein will reveal an "en bloc" RND technique to highlight the difference from an SND. Thus, the only boundaries of a true RND are the mandible superiorly, the mastoid tip, the trapezius muscle, the clavicle, the strap muscles, and the contralateral anterior belly of the digastric muscle (Fig. 14-19). The deep boundaries of the RND include the muscular "floor" of the neck with preservation of the phrenic nerve, the brachial plexus, the sympathetic trunk, the carotid artery, and the vagus nerve.

We will use a "clockwise" approach to a left RND.

Dissection begins at level I by identifying the marginal branch of the facial nerve and mobilizing it superiorly to expose the mandible deep to the nerve. Monopolar cautery is then utilized to release the fibrofatty tissue of the submandibular triangle at its corner between the mandible and the anterior belly of the digastric, to include level IA and IB with the floor of mylohyoid, digastric, hypoglossal, and lingual nerves preserved. This is reflected medial to laterally until the mylohyoid muscle is appreciated, at which point an army-navy retractor is placed to elevate this muscle and gain access to the sublingual compartment. Blunt Kittner dissection is then utilized to visualize the hypoglossal

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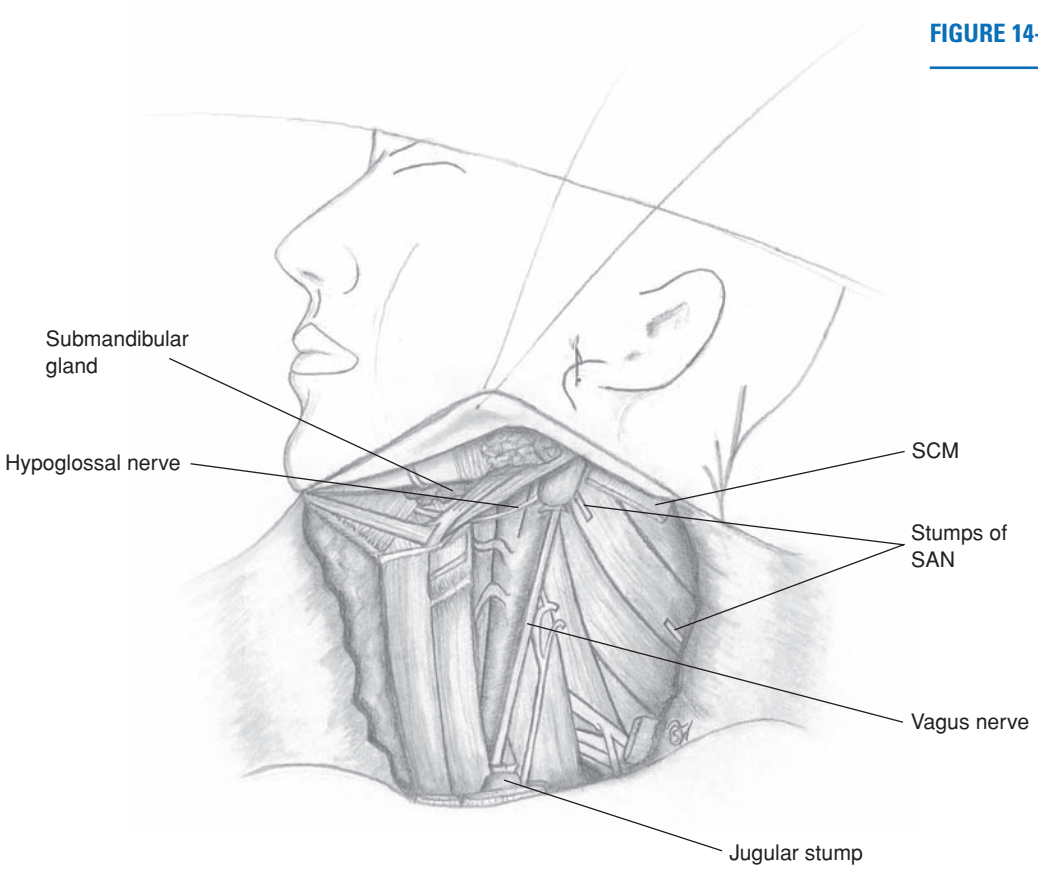



**FIGURE 14-19.** Radical neck dissection.

and lingual nerves. The submandibular duct and ganglion are identified and ligated. Following this, the facial artery is appreciated superficially as it exits the gland and crosses over the mandible. The artery is ligated as it exits the gland superficially if necessary, or preserved for microvascular anastomosis if a free tissue transfer is planned for reconstruction. The facial vein is also appreciated, and its anterior and posterior divisions noted as it passes over the submandibular gland. At this point, the specimen is reflected inferiorly, connecting it to the fascia of the digastric muscle.

Monopolar cautery is then continued with dissection through the fibrofatty tissue overlying the posterior belly of the digastric. This separates the inferior aspect of the parotid gland from the neck dissection specimen and allows dissection to proceed to the superior aspect of the SCM as it inserts onto the mastoid. The SCM is released at this superior attachment and reflected inferiorly. Blunt finger insertion deep to the released head of the SCM is utilized to develop a plane between the musculature of the posterior triangle (the splenius capitis and the levator scapula) and the overlying fibrofatty tissue. This tissue is then grasped with a series of Allis clamps and incised back to the anterior border of the trapezius. This release occurs in a posterior-superior to posterior-inferior fashion. During this turn, the spinal accessory nerve is encountered as it travels through the posterior triangle toward the trapezius muscle. It is transected and included in the specimen. After completing this turn, the specimen is reflected in a lateral to medial fashion with continued blunt finger dissection utilized to further define the muscular floor, with special attention paid to the brachial plexus as it exits between the anterior and middle scalene muscles, and the phrenic nerve, as it runs along the anterior scalene muscle. Preservation of these structures is accomplished by their direct identification. Continued lateral to medial dissection along the inferior aspect of the posterior triangle is continued, with visualization of the posterior belly of the omohyoid muscle. The transverse cervical artery and vein are also encountered and ligated for hemostasis if necessary.

The sternal and clavicular attachments of the SCM are soon encountered during this dissection, and blunt finger palpation is utilized to define its deep extent, followed by monopolar cauterization to release both ligaments. When releasing the SCM, it is important to denote the anterior belly of the omohyoid muscle deep to your dissection, in order to be sure the carotid sheath is not in danger of injury. After transecting the SCM, the omohyoid is then transected in order to gain access to the lymphatic tissue in the deep floor of the anterior cervical triangle. The circumferential "superficial" margins around the RND are now complete, and it is time to elevate the specimen from the "floor."

Beginning posteriorly at the trapezius, the lymphofatty tissue is elevated from the muscular floor posterior to anterior, and the cervical rootlets are identified in the deep neck floor and divided prior to the approach to the carotid sheath. Thus, level V is elevated and levels II, III, and IV are now being elevated from the phrenic nerve, the vagus nerve, and the carotid artery deep to the jugular vein, which is included in the specimen. At this point, the specimen is returned to its anatomic position and the carotid sheath identified deep to the transected omohyoid. It is incised, and identification of the internal jugular vein, the carotid artery, and the vagus nerve is carried out. Inferior dissection is carried out with blunt finger dissection, utilizing cold steel or cautery to open up the overlying fascia. This then proceeds superiorly, allowing the surgeon to extend deep to the posterior belly of the digastric. An army-navy retractor is utilized to retract upward the posterior belly of the digastric, thereby bringing into view the hypoglossal nerve as it runs superficial to the internal and

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the external carotid arteries and deep to the jugular vein. The internal jugular vein is ligated at its superior location, depending on tumor location, and the spinal accessory nerve is sacrificed as well. The inferior aspect of the internal jugular vein is also ligated, its exact location depending on tumor location. The authors typically use two separate zero silk sutures to ligate the vein, although large ligaclips and other suture techniques are acceptable.

At this point, the specimen is rotated laterally to medially and reflected off the fascia overlying the carotid artery, with care taken to preserve the cervical sympathetic chain and the vagus nerve. It is then rolled onto the fascia overlying the strap muscles and is subsequently removed in an en bloc fashion utilizing monopolar cautery.

Following this, the surgical bed is copiously irrigated and suction drains are placed. The skin flaps are returned to their anatomic positions, and interrupted 3-0 vicryl suture is utilized to reapproximate the platysma, followed by either staple or suture closure of the skin layer, depending on surgeon preference.

Care must be taken during ligation of the internal jugular vein as the vagus and the hypoglossal nerves are susceptible to iatrogenic injury during this period. During both superior and inferior ligation of the internal jugular vein, the vagus nerve must be identified within the carotid sheath, otherwise inadvertent cross-clamping of this structure may occur. Furthermore, during superior ligation of the internal jugular vein and its tributaries, identification of the hypoglossal nerve juxtaposed with the ranine plexus of veins is crucial to avoid injury to the hypoglossal nerve. In the setting of iatrogenic injury, primary neurorrhaphy or cable grafting is utilized for repair.

## Modified Radical Neck Dissection

The first described attempts to reduce the morbidity associated with RND came from Bocca et al.[22] in 1967. He described what was referred to at the time as a "functional neck dissection," which is currently referred to as a "modified radical neck dissection" (MRND). This procedure, like the RND, involves the removal of nodal levels I to V, but unlike in an RND, some or all of the nonlymphatic structures that are not involved with disease are spared.

At present, there has been a shift away from the MRND toward SNDs, even in patients with more advanced nodal disease. Though the main goal is an overall reduction in operative morbidity, an additional issue playing a role in the movement away from the MRND has been the consideration of preservation of certain lymph node groups that have low risk of metastasis. One of the more frequent discussions has been whether dissection of level V is truly necessary. Several reports have demonstrated that level V is rarely involved in the absence of the involvement of other nodal levels.[23,24] The spinal accessory nerve transverses level V, and even when the nerve is grossly spared, shoulder dysfunction can still occur due to traction or devascularization during the procedure. Thus, many surgeons consider the associated shoulder morbidity too significant to warrant level V dissection when other nodal levels are negative.

Modifications on the traditional RND are made, to include preservation of either the internal jugular vein, the spinal accessory nerve, or the SCM. The surgical approach is similar to that of the RND with the following modifications. It is important to note that if nodal disease is present or involving structures, the technique will require modification to avoid entering lymph nodes or their extracapsular component, and these areas should be removed "en bloc."

***Spinal Accessory Nerve Preservation.*** During the posterior-superior to posterior-inferior turn that is made in the posterior cervical triangle along the trapezius muscle, identification of the spinal accessory nerve is essential. This nerve is not sacrificed, but rather traced from the trapezius to the posterior border of the SCM. It is then followed through the SCM and located at its anterior aspect as it descends from the jugular foramen. At this point, the nerve is elevated out of the SCM and the dissection proceeds in traditional fashion.

***Internal Jugular Vein Preservation.*** After releasing the clavicular and sternal heads of the SCM inferiorly, the omohyoid is divided and the carotid sheath is incised. Identification of the internal jugular vein, carotid artery, and vagus nerve is carried out. The en bloc specimen is rolled laterally to medially from the posterior to anterior triangle, and the cervical rootlets are identified. The lymphatic tissue in levels II, III, and IV is rolled onto the jugular vein, where it is sharply removed utilizing a 15-blade scalpel. The common facial branch of the internal jugular vein, as well as other branches, must be effectively ligated in order to achieve hemostasis and full release of the specimen from the internal jugular vein in the modified neck dissection technique, unless a microvascular anastomosis is planned and there is no adenopathy in the vicinity.

***SCM Preservation.*** After performing the level I dissection, we traditionally proceed to release the superior attachment of the SCM to the mastoid tip. However, with SCM preservation this is not performed. The fascial layer is unwrapped off the anterior border of the SCM down to the spinal accessory nerve and the cervical rootlets. At this point, attention is then paid to defining the spinal accessory nerve as it traverses the posterior triangle. If the spinal accessory nerve is also to be preserved, it is then dissected free, and the fibrofatty tissue is reflected laterally to medially and passed under the preserved SCM and removed in continuity with the lymphatic tissue of the deep anterior triangle. If the spinal accessory nerve is to be resected, then after it is identified anterior to the SCM, it is dissected through the SCM and into the posterior triangle. After clipping it as it exits the jugular foramen, and as it innervates the SCM, it is effectively free anteriorly, and it is then included with the posterior triangle specimen and rolled under the SCM, allowing it to be removed in continuity with the lymphatic tissue of the deep anterior triangle.

## Neck Dissection in Nonsquamous Cell Head and Neck Cancers

***Melanoma.*** Melanoma is one of the more common nonsquamous cell cancers in the head and neck region. It is estimated that occult metastases are present in clinically negative neck nodes in an estimated 15% to 20% of cases and can increase to 50% with increased Breslow thickness of the primary lesion.[25] Although elective neck dissection has been used for staging purposes in these patients, the morbidity associated with the procedure is high, and no clear survival benefit has been shown.[26] Sentinel node biopsy has become a more popular way of staging neck disease than a neck dissection, or a "watch and wait" policy; however, some studies have shown that even sentinel node biopsy does not confer a survival advantage in these patients.[26] An additional drawback is that it has a high rate of false-negative results; however, a positive result is highly predictive of recurrence.[27] Studies in cutaneous melanoma of the head and neck region reveal that eradication of regional nodal metastasis does not improve overall survival, but may improve locoregional control and associated morbidity.

***Salivary Gland Cancers.*** As with other head and neck cancers, cervical nodal metastasis in minor salivary gland cancers is associated with decreased survival. A study using the data in the

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SEER database was conducted in 2010 with the intent of uncovering factors that may be predictive of lymph node metastasis in these patients.[28] Multivariate analysis of 2,667 cases of minor salivary gland cancer distinguished four statistically significant factors that placed patients in "high-risk" groups for the presence or development of nodal metastasis: male sex, a T stage of 3 to 4, pharynx as a primary site, and tumor histology of either high-grade adenocarcinoma or mucoepidermoid carcinoma. Thus, treatment of clinical and potential occult nodal disease in these patients is paramount.

High rates of lymph node metastasis have also been reported in certain major salivary gland cancers, with one study showing pathologically positive nodal disease in 53% of patients.[29] More recently, a study of multiple histologic types of parotid cancer demonstrated positive neck disease in 22% of patients with low-grade tumors and 49% of patients with high-grade tumors.[30] The authors concluded that a modified RND should be performed along with parotidectomy, but further trials are needed before this recommendation can be made. In general, however, neck dissection and/or radiation therapy is often indicated when high-grade major salivary gland malignancies are diagnosed.

***Thyroid Carcinoma.*** The debate over elective neck dissection in thyroid cancer patients is complex and beyond the scope of discussion for this section. A recent meta-analysis has, however, shown that when central compartment neck dissections are performed, there is no increase in permanent morbidity associated with performing the procedure along with a planned thyroidectomy.[31] The extent of lymphadenectomy is also controversial and typically includes level VI, but additional levels should be included for clinical evidence of disease in well-differentiated thyroid carcinoma and for medullary thyroid carcinoma. The level II to V techniques are well described above and, therefore, only central compartment techniques are described herein.

## Central Compartment Neck Dissection

The central compartment is made up of lymph nodes contained between the hyoid superiorly, the inominate artery inferiorly, and the carotid arteries laterally (Fig. 14-20A and B). This area is a common site for metastatic disease from the thyroid and the larynx. This compartment is further broken down into level VI (between the hyoid bone and the sternal notch) and level VII (between the sternal notch and the inominate artery).

Dissection begins by performing a transcervical incision in a natural skin crease as one typically would for a total thyroidectomy. The incision can be extended to the medial aspect of the SCM bilaterally. Superiorly and inferiorly based subplastysmal skin flaps are then elevated to the level of the hyoid superiorly and the sternum inferiorly. Dissection through the paramedian raphe enables lateral retraction of the strap muscles. Preservation or transection of these muscles can be carried out, depending on the desired level of exposure. At this point, the carotid artery is identified bilaterally and is dissected up to the level of the hyoid superiorly and the inominate artery inferiorly. Attention is then paid to removing the prelaryngeal lymph nodes between the hyoid and the thyroid. Given their scant nature, they are easily removed, yet care must be paid to identifying the superior laryngeal nerve in the process. If the thyroid gland has been removed, there is no fascial connection between the prelaryngeal nodes and the pretracheal nodes; therefore, this specimen must be passed off separately. However, if the thyroid gland is still present, the prelaryngeal nodes can be pedicled on the thyroid and removed along with the gland.

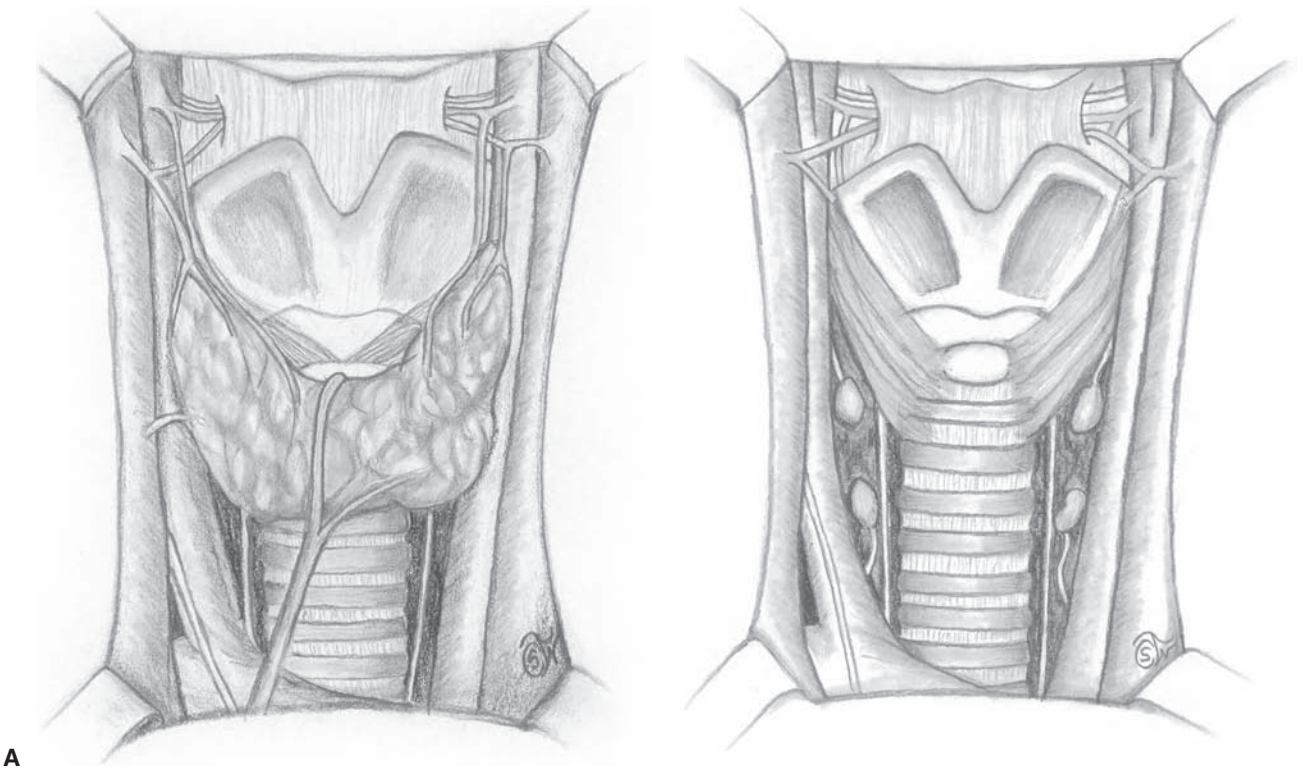


**FIGURE 14-20.** **A:** Central compartment. **B:** Central compartment after neck dissection with thyroidectomy.

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Attention is then turned to identifying the recurrent laryngeal nerves on either side. Both nerves are identified and skeletonized from their insertion into the cricothyroid joint down to the level of the inominate artery. The paratracheal lymph nodes are retracted laterally to medially off both nerves and pedicled on the pretracheal region. At this point, solely the pretracheal lymphatic tissue between the thyroid cartilage and the inominate artery remains. An Allis clamp can be utilized to grasp this tissue providing superior retraction. Direct visualization of the plane of the inominate artery is necessary to define your inferior extent. With both recurrent nerves directly visualized, resection of the pretracheal specimen can then occur. Identification of the inferior parathyroid glands may be carried out in the hopes of reimplantation; however, they are often resected en bloc with the specimen. As a result, identification of the superior parathyroid glands and their preservation is essential. The pretracheal specimen is resected and passed off in standard fashion. Meticulous hemostasis is necessary in level VII, given the nature of the tissue to retract into the mediastinum after retraction is released.

Following this, copious irrigation of the surgical bed is carried out and adequate suction drainage is applied. The skin incision is closed in the standard fashion.

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CHAPTER 15

# Metastatic Cancer of the Neck from an Unknown Primary Site

## PART A:
## General Principles and Management

Steven S. Chang and Joseph A. Califano

### INTRODUCTION

Metastatic cervical carcinoma with an unknown primary (MCCUP) represents a small proportion of all head and neck cancers. As a head and neck surgeon, the primary goal is to utilize the many diagnostic options available to determine the site of the primary. In this chapter, we will describe a thoughtful, evidence-based, and stepwise approach to the workup of the MCCUP to search for the primary tumor. We will also address the role of surgery and radiation in the management of MCCUP. Lastly, we will discuss outcomes of treatment. The various options for workup and treatment will be summarized in an algorithmic form (Fig. 15-1).

### DEFINITION

The World Health Organization (WHO) defines carcinoma of unknown primary as the histological diagnosis of metastases without diagnosis of a primary tumor, an entity that constitutes 3% of all malignant neoplasms.[1] As a distinct subgroup, MCCUP represents 2% to 9% of all head and neck cancers.[2–6]

The entity of MCCUP was first described in 1944 by Martin and Morfit[7] as metastatic disease in lymph nodes of the neck without any evidence of a primary mucosal lesion. The definition of a neck cancer of unknown primary was carefully outlined in 1957 by Comess et al.[8] and further defined by Jesse in 1966[9] at MD Anderson Cancer Center in a series of 127 patients. In 1973,[10] the same group described treatment recommendations that consisted of treatment of the ipsilateral neck along with radiation to potential mucosal sites.

Although the histological subtype of MCCUP is most commonly squamous cell carcinoma (SCC),[11] the entity actually includes all patients with unknown primary regardless of histological subtype. Some reports have noted 50% of MCCUP to be SCC and 20% to be undifferentiated.[12] Other types of malignancies, such as adenocarcinoma and melanoma rarely occur, but have a different workup, treatment, and prognosis[13,14] and therefore are not discussed in this chapter, which is focused on SCC. With that said, there are circumstances in which certain mucoepidermoid tumors (especially tongue) present as adenopathy that cytologically resembles SCC. Although unknown primary SCC of cervical lymph nodes is by far the most common subtype of unknown primary carcinoma seen by head and neck oncologists and is the focus of this chapter, one must remember that this subgroup of patients represents <10% of all unknown primary carcinomas.[15,16] The definition of unknown may change depending on the physician and the workup performed. What is unknown to a generalist may in fact be easily discoverable with a thorough head and neck examination, and what was unknown 25 years ago may now be easily discoverable by improved radiologic imaging. In those cases in which the primary tumor is not initially obvious, >50% of lesions are discovered by physical examination, computed tomography (CT), magnetic resonance imaging (MRI), and/or panendoscopy.[17] A paper from Memorial Sloan-Kettering Cancer Center showed that >50% of patients referred for treatment of unknown primary head and neck cancer had a primary lesion identified within 2 weeks of presentation.[7] A similar study from Liverpool reports that 56% of primary lesions were identified by an otolaryngologist—head and neck surgeon in cases originally thought to be of unknown primary site.[18]

Although other head and neck cancers have increased in incidence over the last 20 years, a Danish survey reports a stable incidence of 0.34 cases/100,000/year of unknown primary cervical carcinoma. It is possible, however, that an increase in the incidence of unknown primary carcinoma has been masked by improvements in detection of the primary lesion.

### OVERALL STRATEGY FOR DISCOVERY OF SITE OF PRIMARY ORIGIN

A critical component to management of MCCUP includes the search for the site of an occult primary tumor. The importance of this exercise cannot be overestimated, as different primary sites



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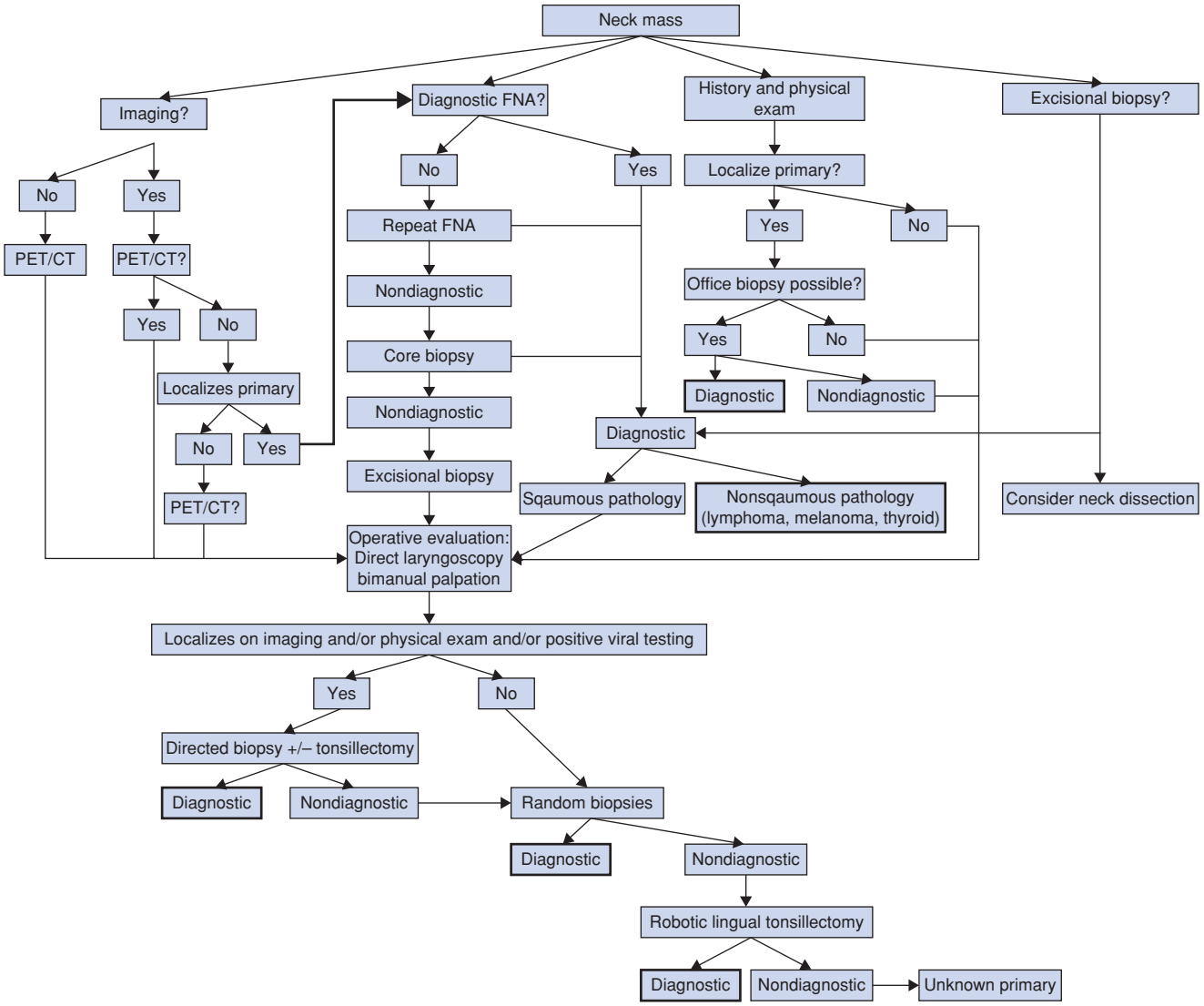



**FIGURE 15-1.** Algorithm for diagnosis and management.

have vastly different prognostic factors, staging, and therapeutic options. Failure to accurately define a primary tumor of origin may potentially result in ineffective or inappropriate therapy as well as unwanted treatment morbidity. A high premium, therefore, is placed on discovery of the site of the unknown primary.

## NATURAL HISTORY

By definition, in unknown primary cancer, the primary tumor is not evident. If left untreated, however, it becomes evident in 13% to 55% of patients after neck surgery alone.[10,19–21] When the primary does emerge, it usually enlarges, becomes macroscopic and symptomatic through locoregional progression. The emerging cancer (usually squamous carcinoma) varies in rapidity of growth, but if left untreated usually assumes aggressive locoregional progression. Locoregional control, therefore, is very important in order to achieve acceptable survival.[22]

Numerous theories attempt to explain the fact that many patients with MCCUP never develop a primary tumor even if the potential primary sites remain untreated. One possible explanation is that the neck mass is the only site of carcinoma and that no primary malignancy ever existed. A third possibility is that spontaneous regression of the primary tumor occurred after the metastatic disease had already become established. A third possibility is that the primary tumor remains viable, but quiescent, and therefore never becomes clinically or radiographically apparent.

The concept that SCC can develop spontaneously in the neck has been a topic of debate in the literature for >100 years. In 1882, Von Volkmann[7] proposed the theory that cervical squamous cell cancer can develop from a branchial cleft cyst. This is based upon the fact that branchial cleft cysts may share similar histopathologic features with metastatic SCC. Cytopathology is not always able to clearly distinguish between benign and malignant cystic squamous lesions of the neck, especially when it comes to separating benign lymphoepithelial cysts with reactive squamous atypia from well-differentiated carcinomas.[23–25] However, the preponderance of evidence argues against this theory as an explanation for cervical lymph node metastasis. One argument against this is that branchial cleft anomalies are

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in themselves rare. Because almost all patients with unknown primary SCC present with neck masses of recent onset, a large number of subclinical brachial cleft cysts would have to be present to account for the number of cases of unknown primary SCC. Therefore, on the basis of probability alone, this hypothesis is unlikely. Furthermore, with the advent of P16 and high-risk human papillomavirus (HPV) testing to define cystic, cervical nodal metastases from high-risk HPV primary oropharyngeal tumors, this dilemma has largely been resolved.[23–25]

A second possibility that would account for SCC arising solely in the neck would be if epithelial rests present in the neck, either in soft tissue or cervical lymph nodes, underwent malignant degeneration. However, there is no evidence that epithelial rests exist in the soft tissues or lymph nodes of the neck; so this does not seem to be a viable explanation for the presence of MCCUP. Occasionally, the primary tumor spontaneously regresses, presumably because of the body's natural immune process.[26] Possibly, a small primary site has expended itself during the process of metastasis or because of victory of local immune factors over alien neoplasia. Leukoplakia,[27,28] which is sometimes a precursor to invasive cancer, has been reported to regress in 37% to 44% of cases and even when dysplasia is present it has been reported to regress in 10%[29] of cases. In surgical-only treatment of unknown primary metastasis, most of the time no primary tumor develops.[30] Then, one must assume that in some of the cases where no primary tumor develops, the primary tumor has, in fact, regressed. There is also the possibility of local immunity being responsible for local tumor containment. In squamous cell cancer, different tumors possess different genetic mutations accounting for malignant degeneration. It is possible that some tumors possess mutations that allow metastasis rather than uncontrolled growth. If the metastatic disease then undergoes additional metastasis allowing for uncontrolled growth, or if the native environment of the lymph node enables uncontrolled growth of the tumor, patients could present with an undetectable microscopic primary lesion and a large cervical metastasis. Mutations that allowed degradation and migration through the basement membrane could account for such behavior. Despite the significant increase in research that has been performed on the molecular genetics of SCC, no significant data yet exist to support this theory. Although the development of the primary tumor is a major concern in patients with unknown primary cervical squamous cell cancer, the most important prognostic factor for these patients is nodal stage.

## STAGING

The staging for MCCUP follows the tumor, node, metastasis (TNM) guidelines established for other sites in the head and neck (Table 15.1). After workup, all patients by definition are classified as T0 due to the absence of an obvious primary site and N + due to the presence of nodal metastasis. Nodal staging is assigned as with other sites in the head and neck.

## CLINICAL PRESENTATION

The typical presentation of a patient with MCCUP is a unilateral painless neck mass that has enlarged over recent months. The patients usually present to a primary care physician and usually at the time of diagnosis have received several courses of antibiotics. Persistence of the painless, enlarging mass should then be evaluated by a head and neck surgeon. Studies have demonstrated that the median interval of symptom onset to accurate diagnosis by a head and neck surgeon is 3 months.[31] The median age of presentation for these patients is 55 to 65 years, although patients as young as 15 years have been reported.[32]

**TABLE 15.1 AJCC Staging for Metastatic Cervical Carcinoma with an Unknown Primary**

| | |
|---|---|
| T0 | No evidence of primary tumor |
| NX | Regional lymph nodes cannot be assessed |
| N1 | Metastasis in a single ipsilateral lymph node ≤3 cm in greatest dimension |
| N2a | Metastasis in a single ipsilateral lymph node >3 cm but not >6 cm in greatest dimension |
| N2b | Metastasis in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension |
| N2c | Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension |
| N3 | Metastasis is in a lymph node >6 cm in greatest dimension |
| M0 | No distant metastasis |
| M1 | Distant metastasis |
| MX | Distant metastasis are indeterminate |

Based on Edge SB, Byrd DR, Compton CC, et al: AJCC Staging Manual, 7th edition, New York, NY: Springer-Verlag, Inc., 2010.

The first step in the workup of a patient with unknown primary SCC is a thorough office examination with a history and physical examination. Each component of the office examination is essential to directing the operative plan to rule out a primary and determine whether the patient is a true unknown primary and thus dictates the treatment plan.

## HISTORY

Many aspects of the history can alter a head and neck's suspicion for a primary site. Historically, most patients diagnosed with head and neck squamous cell carcinoma (HNSCC) were older males with a significant tobacco and alcohol history. However, with the recent epidemic of HPV-related oropharyngeal SCC, there has been an increase in younger patients and a more even distribution among sexes. HPV-related malignancy is often a distinct entity from smoking- and alcohol-related malignancy with a different prognosis. Therefore, it is no longer safe to assume that a young female patient with a neck mass is unlikely to have a malignancy or to assume that she has a significant tobacco or alcohol history and that her prognosis is the same.

The patient's symptoms, if any, may help identify the primary site. Epistaxis, nasal obstruction, or complaints consistent with otitis media point to a nasopharyngeal primary. Complaints of otalgia, dysphagia, or dysarthria may suggest an oropharyngeal or hypopharyngeal primary lesion. Laryngeal lesions often result in voice and respiratory changes. The time course of the tumor growth can often be helpful in formulating the differential.

A careful medical history can also be very helpful. A history of previous skin cancer or immune suppression can be essential in directing the investigation for the primary. The social history can also be useful, with particular attention to tobacco use, alcohol use, sexual history,[33] ethnicity/race, foreign travel, sun exposure, and radiation exposure.

Personal and institutional review of the outside records of any ancillary testing such as imaging and pathology is strongly encouraged to ensure nothing is overlooked. When reviewing the pathology, particular attention should be paid to the histopathology

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of the tumor and HPV status. When reviewing radiology, it is important to examine the location of the metastasis and its relationship to surrounding structures. For instance, a poorly differentiated tumor with basaloid features and a large cystic level II lymph node in a young never-smoker female has a high probability of being an HPV-related tumor of the oropharynx.

Regardless of the patient's symptoms (or lack thereof), a history and physical examination by a head and neck surgeon is essential to the workup.

## PHYSICAL EXAM—NECK

### Location of Metastasis

A careful examination of the neck metastasis is essential, paying particular attention to its location and relationship to surrounding structures. The most frequent cervical metastatic site in patients with MCCUP is level II, which is the circumstance in >50% of patients.[2,31,34–36] After level II, level I and level III lymphatics are next most common. Lower neck and supraclavicular metastasis are also common and are more frequently associated with a primary site located below the clavicles.[3,24,37] Unilateral nodal involvement is the most common presentation, but bilateral nodes are seen in 10% of cases.[12,14,38] If multiple bilateral enlarged nodes are encountered, infection, lymphoma, and nasopharyngeal cancer should be placed higher in the differential diagnosis. Presentation with only a single node occurs in 44% to 52% of patients[10,38] and the median nodal size is 5 cm (2–14 cm).[12] An isolated nodal mass in the submental triangle is rarely cancer. Typically, these masses are inflammatory or related to benign salivary gland conditions. Posterior palpable nodes in a young patient are usually benign, many resulting from inflammation. By identifying the nodal stations involved and understanding patterns of lymphatic drainage with regard to primary sites, more focused diagnostic procedures and treatment strategies can be developed (Table 15.2). Therefore a thorough understanding of the anatomy of the neck is essential. Below is a description of the levels of the neck with their corresponding sites of drainage.

Level I includes the submental and the submandibular nodes. Level IA drains the floor of the mouth, the anterior tongue, the anterior inferior alveolar ridge, and the lower lip. Level IB drains the oral cavity, the anterior nasal cavity, and the soft tissue of the midface. Level II encompasses the upper internal jugular nodes. Level II nodes most commonly receive drainage from the oral cavity, the nasopharynx, the oropharynx, the larynx, the hypopharynx, and the parotid gland. Level III, which includes the middle jugular nodes, receive drainage from the oral cavity, the nasopharynx, the oropharynx, the larynx, and the hypopharynx. Level IV, which encompass the lower jugular nodes, typically receives drainage from the larynx, the hypopharynx, the thyroid, and the esophagus. Level V covers the entire posterior triangle and drains the nasopharynx, the oropharynx, and the skin of the posterior scalp. Level VI is the main drainage basin for the thyroid, the subglottic larynx, the hypopharynx, and the esophagus. Level VII overlies the tracheal esophageal grooves and the superior mediastinum from the manubrium to the superior edge of the inominate vein. The retropharyngeal nodes are not assigned a level, they drain the nasopharynx, the hypopharynx, and the larynx. The supraclavicular nodes are also not assigned a level, but are considered separately from levels I to VII. They drain from the thoracic duct on the left or the accessory thoracic duct on the right. When these nodes are present without superior neck adenopathy, the diagnostician should search for a primary site in infraclavicular or subdiaphragmatic locations. The location of the lymph nodes can help guide the search for a primary because 63% of patients with supraclavicular nodal presentation are found to have infraclavicular primaries compared to 5% of patients with jugular nodal presentation,[20] 3% to 8% of patients with unknown primary SCC to have a lung primary.[27,38–40] A study by Jones et al.[18] showed that infraclavicular primary lesions occurred in 30 of 267 patients (11%), whereas head and neck primary lesions were found in 174 of 267 patients (65%). Eighty-three percent of infraclavicular primary lesions discovered were in the lung. Fifteen of the 25 lung cancers were identified during the initial workup whereas 10 were identified during follow-up or at autopsy. These data are summarized in Table 15.2.

**TABLE 15.2 Toolbox for Possible Primary Site**

| Neck Level | First Echelon Drainage |
|---|---|
| I | Anterior oral cavity |
| | Anterior nasal cavity |
| II | Oral cavity |
| | Oropharynx |
| | Nasopharynx |
| | Larynx |
| | Hypopharynx |
| | Parotid |
| III | Oropharynx |
| | Nasopharynx |
| | Larynx |
| | Hypopharynx |
| IV | Larynx |
| | Hypopharynx |
| | Thyroid |
| | Esophagus |
| V | Nasopharynx |
| | Posterior scalp |
| Virus | Possible primary site |
| HPV | Oropharynx |
| EBV | Nasopharynx |

## PHYSICAL EXAM—PRIMARY SITE

Once the neck has been appropriately examined, we then proceed in the physical to the search for the primary tumor. A careful scalp examination is essential because skin cancers can be hidden by hair and may go unrecognized. Enlisting the consultation of a dermatologist may be helpful in this regard if the patient has many skin lesions. A careful oral cavity and pharyngeal examination is performed, looking for subtle mucosal abnormalities and focusing on areas of particular risk relative to the location of the neck mass. Areas such as the nasopharynx and the oropharynx are more likely to be the primary mucosal sites of origin in unknown primary squamous cell cancer of

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the neck and as such need special diagnostic attention. Flexible fiberoptic examination is essential to properly examine the nasopharynx and provides an excellent look at the base of tongue and the valleculla, as well as the larynx and the hypopharynx. Examination of the oropharynx, with palpation of the tonsils and the base of the tongue, is also essential. These techniques may reveal tumors not otherwise visible. The base of the tongue is an area in which the more time-honored method of a hand mirror and headlight can also provide more information than flexible fiberoptic examination. Additionally, digital palpation of the tongue is invaluable in certain tumors predisposed to submucosal spread.

## OFFICE BIOPSY AND FINE-NEEDLE BIOPSY

If a primary site is suspected, a biopsy can often be performed in the office, thereby expediting the diagnosis. Regardless of the presence or lack of a primary site, a fine-needle aspiration (FNA) of the neck mass should be performed at the outset. Depending on circumstances, it is preferable to obtain basic imaging of the head and neck before the FNA; however, it can be done before the imaging. If there is uncertainty of the diagnosis, the FNA can usually be accomplished on the initial visit to confirm the diagnosis of malignancy. If available, the use of a cytopathologist at the time of aspiration can be very helpful. A cytopathologist can ensure that an adequate cytologic sample has been obtained. In addition, if lymphoma or a nonsquamous pathology is suspected, additional material can be obtained to initiate the appropriate immunohistochemical or molecular diagnostic studies needed for the diagnosis, and, under these circumstances, the diagnostic pathway that follows is tailored differently than in epithelial cancers.

If the patient comes with a biopsy already performed, several features of the report can be helpful in directing the physical exam and possible operative examination. The degree of differentiation and gross appearance can be helpful in the investigation. For instance, if the histologic examination shows a poorly differentiated (basaloid) microscopically and grossly cystic tumor, it is highly suggestive of a HPV-positive tumor originating from the oropharynx.[41] If viral testing has not been performed at the outside institution, we suggest viral testing of the biopsy for HPV 16, P16, and Epstein-Barr virus (EBV). It has been shown that 27% to 28% of metastatic lymph nodes from an occult primary are HPV +.[41,42] Furthermore, several studies suggest that if HPV is detected in the neck metastasis, it is a reliable indicator that the origin of the tumor is in the oropharynx.[43] Therefore, viral testing can both assist in directing the surgeon's investigation for the primary site and assist in determining a patient's prognosis.

Additionally, even if a biopsy specimen shows histologic features consistent with lymphoepithelial carcinomas originating from the nasopharynx, testing for HPV and EBV is still strongly recommended because a morphologic variant of HPV-HNSCC in the nasopharynx that is microscopically indistinguishable from EBV-related carcinoma exists.[44] However, P16 immunohistochemistry is a reliable marker for separating EBV-related and HPV-related carcinomas of Waldheyer's ring.[45] It has been proposed that P16 may be a surrogate marker for HPV testing, but the authors suggest testing for both P16 and high-risk HPV. The reason is that studies have shown that P16 overexpression is not always linked to high-risk HPV integration and may be found in benign lymphoepithelial cysts. This observation limits the role of p16 staining as a surrogate marker of HPV 16 infection. P16 is therefore a useful adjunct to HPV testing in distinguishing between benign and malignant cystic squamous lesions of the neck.[23]

## IMAGING

Historically, the radiographic workup of MCCUP has consisted of CT of the head and neck and sometimes of the thorax. The goal of this study is to locate the primary site of the tumor. A report from the University of Florida showed that in 50% of patients with normal physical examinations, CT and/or MRI imaging revealed the site of origin of the primary tumor.[17] Areas of obvious or questionable radiographic abnormality can be closely examined and biopsied during subsequent panendoscopy. For this reason, all imaging studies should be obtained before panendoscopy. In addition to guiding biopsies so as to include suspicious areas, obtaining imaging before the panendoscopy is important because inflamed biopsy sites may mimic subtle tumor on imaging, particularly if positron emission tomographic (PET) scans are obtained.[46] Features of the neck metastasis on CT or MRI can also be helpful in the investigation for a primary. For instance, if the neck metastasis is cystic, it indicates strongly that the primary is a HPV-related tonsil cancer.[47]

The role of PET and/or PET/CT in the workup of patients with MCCUP has increased greatly during the last few years. A meta-analysis published in 2004 by Rushtoven et al. examined the efficacy of PET in the detection of primary tumors in patients with MCCUP.[48] In that study, PET scans had a sensitivity and specificity of 88.3% and 74.9%, respectively. In patients with MCCUP in which the CT and panendoscopic findings were negative, PET scans revealed a primary tumor in 29% to 39% of patients.[49,50] Several published studies examined the use of PET scans in the detection of distant metastasis and found that PET scans also discovered a site of distant metastasis in 11.2% of patients. PET scans also proved useful in identifying primary sites outside of the head and neck because 24.3% of primary tumors were found to be infraclavicular. PET scans localized the primary tumor in 24 of 27 patients with infraclavicular primaries.[48] PET scans, however, have a higher false-positive than false-negative rate. They tended to overread tonsillar cancers and in that particular area demonstrated a false-positive rate of 39.3%. The false-positive rate was also higher in the base of the tongue than other areas at 21.4%. PET scans, in general, are highly sensitive, although PET scans are least sensitive at the base of the tongue with the sensitivity being 81.5%, compared to 90.5% in other sites in the head and neck. The lack of sensitivity in the base of the tongue is thought to occur from the high baseline level of fluorodeoxyglucose (FDG) uptake in that area. PET scans showed the highest accuracy in tumors of the larynx and hypopharynx, with a specificity and sensitivity of 100%.[48]

PET/CT is widely available at this time, and many head and neck oncologists use this technology. Because the principles behind CT and PET scans are different, the former providing anatomic information and the latter metabolic information, a combination of the two imaging modalities have the highest yield in discovering the site of unknown primary cancers. Studies have suggested that PET/CT is superior to either PET or CT alone in the workup of head and neck cancer.[51–53] Although a positive PET scan helps guide the surgeon to a primary tumor site, a negative PET scan does not alleviate the need for a careful panendoscopy with random guided biopsies. The limitations of PET/CT are still to be fully defined, but it is well known that it is unclear how helpful this modality is in detecting nonsquamous primaries such as salivary gland and thyroid malignancies.[54] An additional benefit of PET/CT is that the recent national lung screening trial found CT scans to be superior to chest x-ray in reducing mortality from lung cancer[55] in people who are high risk for lung cancer.

Therefore, obtaining this imaging modality allows for examination of the neck metastasis features/location, search for the primary via the anatomical and metabolic modality and the

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CT can screen for a lung primary. PET/CT is an essential adjunct to the workup of a patient with the unknown primary. Fundamental to good diagnostic methodology, however, is a well-done direct examination, for which there is no technologic substitute.

## PANENDOSCOPY, BIOPYSY, AND TONSILLECTOMY—OPERATIVE MANAGEMENT

Panendoscopy under general anesthesia is an essential component of the workup of all head and neck squamous cell cancers and is especially important in the workup of MCCUP because it dictates the modality and extent of therapy. No matter how thorough a clinician is in the office, a more detailed and complete examination is possible with the patient asleep. It is difficult to determine the yield of panendoscopy in patients with MCCUP, but used in conjunction with PET/CT, studies have revealed the primary site during panendoscopy in approximately 40% to 60% of patients.[18,52,56,57] Older studies, done before the routine use of flexible fiberoptic laryngoscopy, tend to report a higher yield on panendoscopy. With that said, however, in patients with laryngeal cancer, the issues of intralaryngeal mobility and restriction of mucosal fluidity are essential; for the analysis of either of these, the visualization of the "awake" larynx in the upright patient in the office setting is essential to proper evaluation. General anesthesia and/or intubation greatly hinders this process.

With the patient under general anesthesia, careful palpation of the nasopharynx, and the oropharynx, can be performed, and this may reveal a small mass that was not appreciated in the office. Direct laryngoscopy should be done to evaluate the oral cavity, the oropharynx, the larynx, and the hypopharynx, with particular emphasis placed on an examination of the pyriform sinuses that are difficult to adequately visualize in the office.

Esophagoscopy should also be performed because the esophageal inlet is not otherwise well visualized. The use of bronchoscopy in the workup of patients with head and neck cancer is individualized and has largely been replaced by PET/CT. Lung cancer rarely presents as upper or middle jugular chain adenopathy. It can, however, present as lower jugular chain (supraclavicular or tracheoesophageal groove) adenopathy. In patients with masses in locations suspicious for a lung primary, a bronchoscopy should be performed.

If no primary site of origin is identified after a thorough direct laryngoscopy and esophagoscopy, guided mucosal biopsies should be done. Overall, the most common sites of origin of unknown primary head and neck cancer are the tonsil, the base of tongue, the nasopharynx, and the hypopharynx.[58] The use of guided mucosal biopsies of the more common sites of primary tumor location should be performed. In addition, if any of these areas was negative on clinical examination but suspicious for malignancy on imaging, that area should be biopsied carefully. A study by Lee et al. was performed in 33 patients with MCCUP in which all of these sites were analyzed, and random guided biopsies revealed the primary site in three of these patients.[59] Guided mucosal biopsies of the nasopharynx, the base of tongue, and the hypopharynx are often done using cup forceps. When biopsying the nasopharynx, it is essential to carefully examine the area being biopsied because HPV have been detected in these biopsy specimens and are thought to represent extension from oropharyngeal primaries.[45]

The tonsil, however, is a cryptic structure, and small mucosal abnormalities may be present that are not visible on either clinical examination or radiologic imaging and are not appreciated by palpation. Use of a cup forceps to sample the tonsil may result in a geographic miss of a small tumor. Because of this, the routine use of tonsillectomy is recommended for the workup of unknown primary cancer. A study of 122 patients with MCCUP by Waltonen et al. demonstrated that the overall yield of finding an occult primary carcinoma in the tonsil was 3.2% for deep tonsil biopsies versus 29.6% for tonsillectomies.[56] A study by Randall et al. was performed in 829 patients with head and neck cancer. Of the 34 patients with no identifiable tumor whose charts were available for review, 6 had the diagnosis made by tonsillectomy.[60] Lapeyre et al. performed tonsillectomy in 87 patients with unknown primary cancer, and that endeavor revealed the site of cancer in 23 patients.[61] However, the authors do not mention whether radiologic imaging was obtained, so presumably some of those cancers would have been identified without tonsillectomy if CT or PET scans had been obtained. A study by Mendenhall et al. found that tonsillectomy detected the site of the primary tumor in 10% of patients with a negative physical examination and negative radiologic imaging.[17] Additionally, two separate studies showed that if a neck node is HPV positive, it is necessary to perform palatine tonsillectomy and lingual tonsillectomy[41,62] to look for unknown primaries.

Most authors advocate ipsilateral tonsillectomy for patients with MCCUP, but some advocate bilateral tonsillectomy. A study by Koch et al. showed that of the 16 patients with unknown primary head and neck cancer whose cancer was eventually found in the tonsil, 4 patients had cancer in the contralateral tonsil.[63] A handful of other case reports demonstrating contralateral tonsil cancer in patients with unknown primary squamous cell cancer are also present in the literature.[64] There are potential advantages to bilateral tonsillectomy. In addition to the low but real possibility that cancer may be present in the contralateral tonsil, the asymmetry resulting from ipsilateral tonsillectomy may be a source of confusion in the future if the patient's care is transferred to another physician who is unsure of the details of the patient's history. The most important point to be made regarding the tonsil in the workup of MCCUP is that the standard of care for the histologic analysis of that structure is the tonsillectomy, whether unilateral or bilateral, and possible ligual tonsillectomy. With a careful history and physical examination, appropriate imaging, panendoscopy with random guided biopsies, and tonsillectomy, the site of origin can be discovered in >50% of tumors[43,52,56,57,59] that were initially classified as MCCUP. Our institutional practice is to perform directed biopsies based on the office examination, imaging studies, and pathology. If operative laryngoscopy does not yield a primary site, we proceed with bilateral tonsillectomy, robotic lingual tonsillectomy, and finally random directed biopsies, usually as a single surgical procedure with frozen section analyses if a suspected tumor is noted after tonsillectomy. Once these procedures are performed and all primary sites ruled out, we then proceed with treatment for MCCUP.

## OPEN BIOPSY

In general, open biopsy is probably overused in the workup of neck masses; however, it still can be essential in select patients. If a patient's FNA is indeterminate, and radiologic workup and panendoscopic findings are negative for cancer, an open biopsy may be required for diagnosis. Before performing such a biopsy, however, a core (or cutting) needle method can be performed. This can often yield a diagnosis even when an FNA has failed. In addition, a core needle biopsy usually does not impact future treatment, whereas an open biopsy might. One study reviewing the usefulness of core needle biopsy in 32 patients with advanced head and neck cancer obtained useful histological specimens 100% of the time.[65] Although the high yield may be somewhat optimistic, it does suggest real value to having this technique in the surgeon's armamentarium. Because of the fundamental concern about needle tract seeding, the FNA remains the standard of

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the two when possible. If all nonsurgical attempts at obtaining a diagnosis have failed, an open biopsy can be performed. Open techniques should be used with caution because of the risk of tumor spillage and disruption of fascial planes, which normally act as a barrier to tumor spread. All aspects of the surgical incision and subsequent dissection are at risk for disease recurrence and therefore require treatment. This may result in the need for more aggressive surgery or radiation to achieve disease control. If an open biopsy is performed, it is important to plan the surgical incision so that if a diagnosis of malignancy is obtained on frozen section, the procedure can be converted to a formal neck dissection without making multiple incisions or violating the basic principles of neck dissection.[66] However, if there is risk of an indeterminate frozen section, the classic technique should be modified to include the excision of the skin surrounding the biopsy site from which the tissue was removed, so that a subsequent neck dissection may be performed easily if needed. In those cases in which the initial phase of the treatment strategy is nonsurgical, that consideration of incision planning is still important; and when properly designed, it should not compromise oncologic integrity. It should be noted that the issue of open biopsy safety is associated with some controversy as to whether it has a negative effect on disease control. A study by Mcguirt et al. showed a worse outcome in patients with cervical metastasis who underwent cervical node biopsy before referral for definitive treatment of the neck.[67] These patients suffered a significant increase in the risk of recurrence in the neck and distant metastasis. A similar study from the University of Florida, on the other hand, did not show a difference in neck control, distant metastasis rate, or survival between patients who had an open cervical node biopsy before definitive treatment and those who did not.[68] A study from MD Anderson Cancer Center that reviewed 39 patients with MCCUP, who were treated with an excisional biopsy and posttreatment radiation therapy, found no recurrences in the neck. Although an open biopsy is frequently overused in the treatment of unknown primary head and neck cancer, the evidence does not necessarily confirm a negative impact on the patient's outcome.[69] It is essential that the workup, the biopsy, and the therapy be prospectively planned with the overall strategy in mind. Too often, one encounters circumstances in which a rush to biopsy and/or treatment has led to an ill-conceived treatment strategy.

## TREATMENT AND OUTCOMES

The treatment of MCCUP is controversial with regard to both the extent of radiation of the possible primary sites and what combination of surgery and radiotherapy should be used for the neck. The results of the EORTC 24001-22005 "Randomized Phase III Study on the Selection of the Target Volume in Postoperative Radiotherapy for Cervical Lymph Node Metastasis of Squamous Cell Carcinoma from an Unknown Primary"[70] was unfortunately closed due to lack of accrual. The next two sections will tackle the radiation oncologic and surgical aspects of patient care. Surgery is traditionally the performance of a comprehensive neck dissection, owing to the inability to predict the risk of uninvolved ipsilateral nodal drainage sites in MCCUP. Postoperative radiation to the involved neck and the possible mucosal sites is the standard treatment modality, and good outcomes have been achieved with minimal morbidity; patient survival is approximately 60% to 90% at 5 years with approximately 60% to 90% locoregional control at 5 years.[71–73] These data may be confounded by HPV-positive tumors which tend to have better survival.

After primary therapy, the development of the primary tumor is a major concern in patients with unknown primary cervical squamous cell cancer, and the most important prognostic factor for these patients is nodal stage. The prognosis of patients with MCCUP is similar to that of patients with known primary tumors and the same nodal stage.[2,74] Other prognostic factors include HPV status, the number of positive lymph nodes, cytologic grading, the presence of extra capsular extension, patient age, and the patients' overall performance status.[74–77] It should be noted that there is some evidence to support the fact that the emergence of a primary tumor carries a worse prognosis, with a median survival of 15 months and 5-year survival of 20%[34,78,79] of patients in that group. Whether or not this represents a biologic acceleration of the tumor is unknown. Overall, the progression of cervical lymphadenopathy inpatients with MCCUP is similar to that of patients with known primary tumors. If left untreated, nodal disease can extend through the lymph node capsule to involve adjacent structures. Such invasion can encroach on and involve the skin, the sternocleidomastoid muscle, the jugular vein, the posterior belly of the digastrics muscle, the external and the internal carotid artery, the vagus, the spinal accessory, and/or the hypoglossal nerves. Distant metastasis is associated with and proportionate to nodal stage in patients with N1 disease having a distant metastatic rate of 26% and patients with N3 disease having a distant metastatic rate of 52%.[80] The location of nodal disease also seems to correlate with distant metastasis. Patients with disease in the lower neck have a 27% rate of distant metastasis whereas in patients with disease in the upper neck, that rate is only 13%.[81] Distant metastasis and extracapsular spread decrease survival rate significantly.[75] However, tumors that are found to be HPV positive generally have a better outcome,[82] but the entity of HPV + MCCUP patients has not been studied specifically against HPV– MCCUP.

## RECURRENCE

Recurrence in patients with MCCUP is an ominous prognostic factor, as it is with most cancers of the head and neck. Recurrence in these patients can either be in the neck (either ipsilateral or contralateral) or as the development of a primary site. Additionally, patients with MCCUP can also develop second primary lesions that maybe difficult to differentiate from progression of primary tumors because by definition the primary was unknown. The management of recurrence depends both on the site of recurrence (neck vs. primary) and on the previous treatment given to that site. If disease presents in a primary site, it can represent development of the previously unknown primary or a second primary. If the patient is presenting as a recurrence, the previous treatment zones (relative to the location of the recurrence) and surgical treatment is essential to plan any further treatment. When evaluating the natural history of patients with MCCUP, it is important to distinguish the development of infraclavicular primary lesions from the development of distant metastasis. There is currently no literature to support specific treatment of MCCUP neck recurrence. Current standard of care for treatment of the recurrent neck would be to follow guidelines for a recurrent neck with a known primary. Re-irradiation with intensity-modulated radiotherapy (IMRT) and possibly concurrent chemotherapy should be considered in patients with recurrent unknown primary carcinoma although further studies are needed in this area.

## FUTURE DIRECTIONS: MOLECULAR TESTING?

In addition to continued clinical research into the outcomes of patients with MCCUP, there are also many novel methods that may be employed in the future to find the location of primary tumors and possibly assist in dictating treatment even if all mucosal biopsies are histologically negative.

Microsatellite analysis may prove useful in identifying the site of origin. Califano et al. looked at 18 patients with MCCUP. Using

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microsatellite analysis, the benign mucosal biopsies taken randomly from the typical sites (the nasopharynx, the oropharynx, and the hypopharynx) were compared with that of the neck mass.[83] Ten of the 18 patients were found to have genetic alterations in certain biopsy specimens corresponding to those found in the cervical metastasis. All patients who subsequently developed a primary tumor had similar genetic mutation in the tumor and in the original random biopsy. These mucosal sites included three cases of tonsil cancer, one of pyriform sinus cancer, three cases of base of the tongue cancer, one case of floor of the mouth cancer, one case of false vocal fold cancer, and two with combined pyriform sinus and tonsil cancer. This suggests that the mucosal sites of origin can be inferred in some patients, even if the original site is histologically negative for cancer. Although this concept is not yet employed clinically, it may play a larger role in the future.

Barker et al. performed an excellent study looking at microRNA signatures of unknown primary lesions in the head and neck. Altered microRNA (miRNA) expression alterations has been associated with head and neck cancer.[84] They used quantitative real-time polymerase chain reaction (PCR) to identify miRNA expression profiles of SCC of the tonsil, the base of tongue, and the postnasal space, as well as their corresponding metastatic lymph nodes, from six patients. Their results revealed that each cancer maintained its expression profile between the primary site and the nodal metastasis. In addition, each anatomical subsite maintained a distinct miRNA profile between individual patients. Finally, between subsites, the miRNA profiles were also distinct. This study provides an indication that miRNA expression analysis may be useful to predict the primary site of origin of metastatic disease, when the primary site remains obscure.[85]

## SUMMARY

The proper management of the unknown primary continues to evolve as our ability to isolate primaries improves. The recent identification of HPV as a risk factor for HNSCC and prognostic marker, the use of PET/CT, robotic lingual tonsillectomy, and other modalities have altered the way we investigate MCCUP. It is unclear whether the incidence of true MCCUP has decreased as a result of these innovations. A thorough and thoughtful history, physical exam, review of imaging, and pathology are required to direct surgically based investigation in the hope of defining a primary tumor site and treating the cancer appropriately. Continued translational studies that allow for better identification of primary sites will allow for de-escalation of therapy and decrease patient morbidity and mortality.

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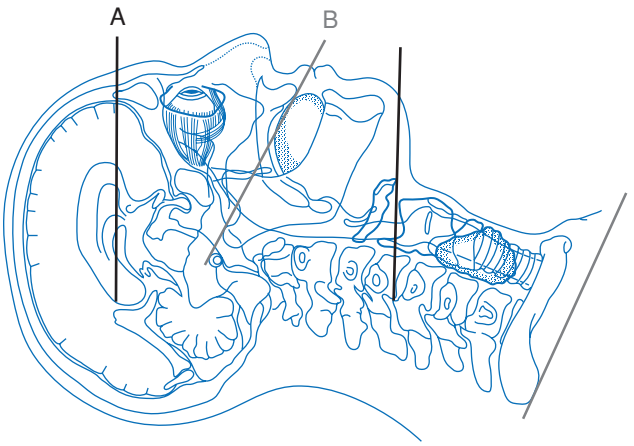

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# PART B:
# Radiologic Imaging Concerns

Jeffrey A. Bennett

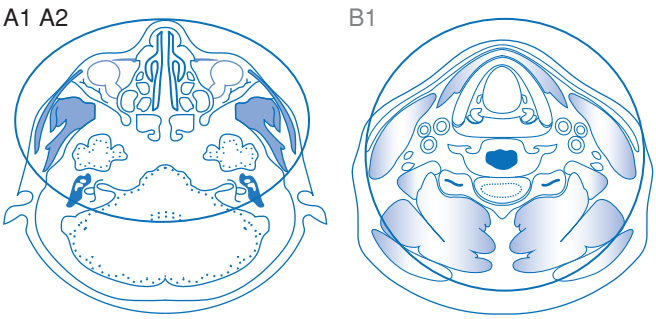
The optimal diagnostic imaging evaluation for patients presenting with cervical lymph node metastases from an unknown source is still controversial. The purpose of imaging is to help identify potential sites to pay special attention to panendoscopy with directed biopsies. Currently, it is recommended that patients receive a contrast-enhanced CT scan or MRI of the head and neck, and FDG-PET/CT should be considered.[1] Suggested CT and MRI protocols are given in Figures 15-2 and 15-3. The location of the cervical lymph nodes is important as patients with lymphadenopathy primarily in levels II and III will most often have a primary in the tonsillar fossa or the tongue base,[2] whereas patients with low neck lymphadenopathy, primarily in level IV and the supraclavicular fossa, will often have a primary tumor below the clavicles.[3] CT or MRI may identify a submucosal mass that could not be detected on physical exam or endoscopy. Alternatively, a small tumor located deep in the

ACQUISITION




| | | |
|---|---|---|
| | Patient Position | Supine<br>IOML perpendicular to the tabletop |
| | Contrast | 100 mL adult |
| | Injection Rate | 1 mL/sec; 60-sec delay |
| | Respiration | Quiet, NO swallowing |
| | Volume Acquisition Specs | Appropriate to achieve images as specified in following reconstruction table.<br>Head F.O.V. |
| A | Begin | Above frontal sinus |
| | End | Through mandible |
| B | Begin | Midoral cavity |
| | End | Apices |

RECONSTRUCTION




| | | |
|---|---|---|
| A1 | Algorithm | Soft tissue |
| | Thickness | 1.0 mm |
| | Spacing | 0.8 mm |
| | F.O.V | Approx. 170–190 |

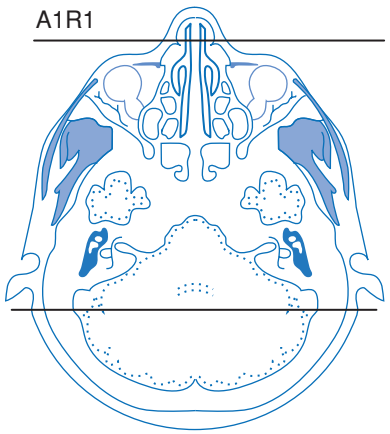
| | | |
|---|---|---|
| A2* | Algorithm | Bone |
| | Thickness | 1.0 mm |
| | Spacing | 0.8 mm |
| | F.O.V. | Approx. 170–190 |
| B1 | Algorithm | Soft tissue |
| | Thickness | 2.5 mm |
| | Spacing | 2.5 mm |
| | F.O.V. | Approx. 160–180 |

**FIGURE 15-2.** Protocol for CT scan of the maxillofacial region and neck with intravenous contrast.

*Source:* Reprinted from Mancuso AA, Hanafee WN. *Head and Neck Radiology.* Philadelphia, PA: Lippincott Williams & Wilkins; 2011:2218, with permission.

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REFORMATION




| | | |
|---|---|---|
| A1R1** | Algorithm | Soft tissue |
| | Thickness | 1.0 mm |
| | Spacing | 1.0 mm |
| | F.O.V. | Approx. 180 |
| | Plane | Coronal |
| | Begin | Frontal sinus |
| | End | Through IAC |

OTHER

- *Refer to Indications on next page.
- **Refer to Indications on next page.

**FIGURE 15-2.** *Continued*

| Acquisition | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Plane | Sagittal | Axial | Axial | Axial |
| Sequence | T1 | T1 | T2-FSE | T1 |
| Contrast | None | None | None | Gd |
| Thickness/Spacing | 3/0 mm | 4/0 mm | 4/0 mm | 4/0 mm |
| FOV | 16 cm | 16 cm | 16 cm | 16 cm |

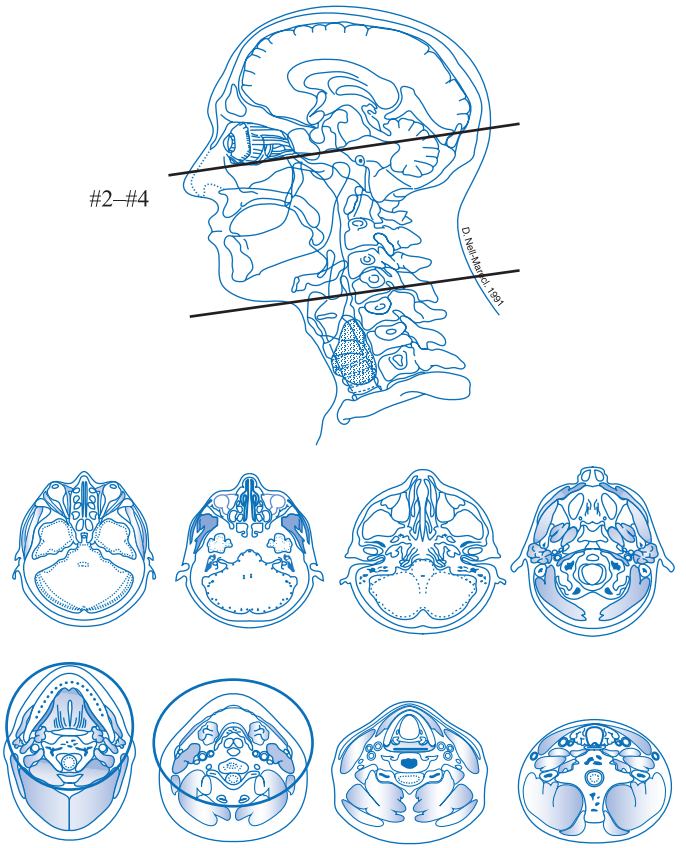



**FIGURE 15-3.** Protocol for MRI of the unknown primary.

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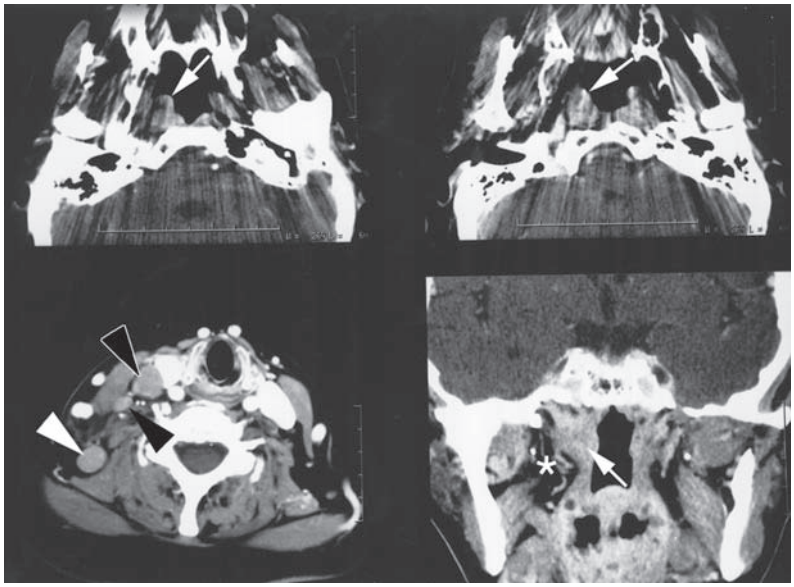


**FIGURE 15-4.** Early nasopharyngeal cancer. Enhanced axial computed tomography and direct coronal view **(bottom right)** show several pathologic right-sided neck nodes (*arrowheads*) in a patient with squamous cell carcinoma of unknown primary. Axial and coronal views show a T1-stage lesion of the right nasopharynx (*arrows*). The parapharyngeal space is normal (*asterisk*).

crypts of lymphatic tissue in the nasopharynx, the palatine tonsils, or the tongue base may produce asymmetry that could guide the endoscopist to a location to biopsy (Fig.15-4). The problem arises though, that normal lymphatic tissue is quite asymmetric, especially in the palatine tonsils and the lingual tonsil, and so a better approach is to use the asymmetry to guide a search for deep invasion into the parapharyngeal space or the tongue musculature, which is a clear sign that cancer is present (Fig. 15-5).

Several investigators have advocated for FDG-PET/CT to be performed in patients with an unknown primary tumor[4–6] and claim that this study is potentially slightly better than CT or MRI (Fig. 15-6), with the limitation of a high false-positive rate, secondary to normal tracer uptake in lymphoid tissue. A meta-analysis of the literature on the diagnostic accuracy of FDG-PET and FDG-PET/CT to detect an unknown head and neck primary was performed by Dong et al. in 2008.[7] This resulted in a pooled sensitivity of 81%, specificity of 82%, and false-positive rate of 28.6% for the tongue base. FDG-PET/CT had a higher sensitivity and specificity than did FDG-PET alone. An additional literature review by Rusthoven et al.[8] identified 16 studies in which altogether the primary site was found by FDG-PET in 74 out of 302 patients (24.5%). The sensitivity was 88.3% and specificity was 74.9%. There were 47 false-positives with rates of 39.3% for the tonsillar fossa, and 21.4% for the base of the tongue. Wong et al.[9] studied 78 patients with cervical lymphadenopathy and an unknown primary. PET/CT revealed a suspicious area in 46 of the patients (59%), and cancer was confirmed in 30 of the patients (38.5%). The sensitivity was reported as 100%, specificity 66.7%, positive predictive value 65.2%, and negative predictive value 100%. These studies contrast with that of Cianchetti et al.[1] where none of 21 patients who underwent FDG-PET or FDG-PET/CT had the primary site detected by this imaging modality.

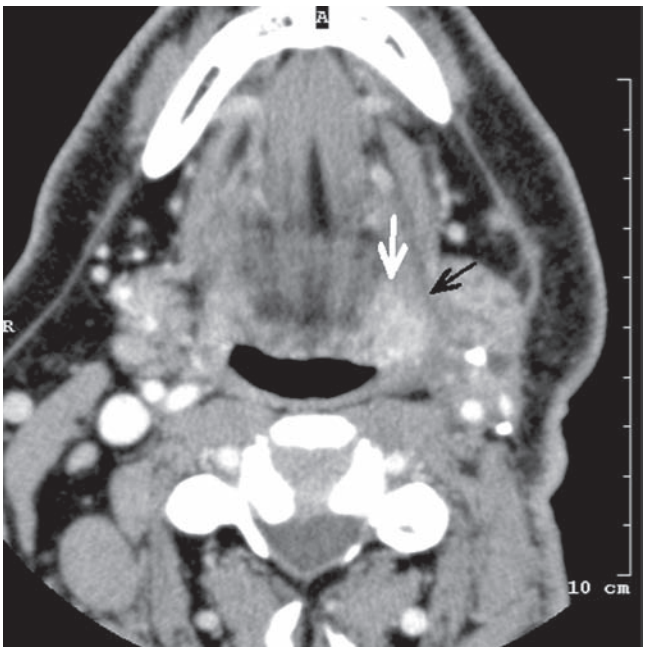



**FIGURE 15-5.** Axial contrast enhanced CT scan of a patient presenting with left level 2 lymphadenopathy and an unknown primary shows asymmetry of the lymphatic tissue at the tongue base. There is a mass in the left tongue base (*white arrow*) that has subtle penetration into the deeper soft tissue planes of the tongue. The parapharyngeal space fat is effaced on the left (*black arrow*) between the tongue base and submandibular gland compared to the right.

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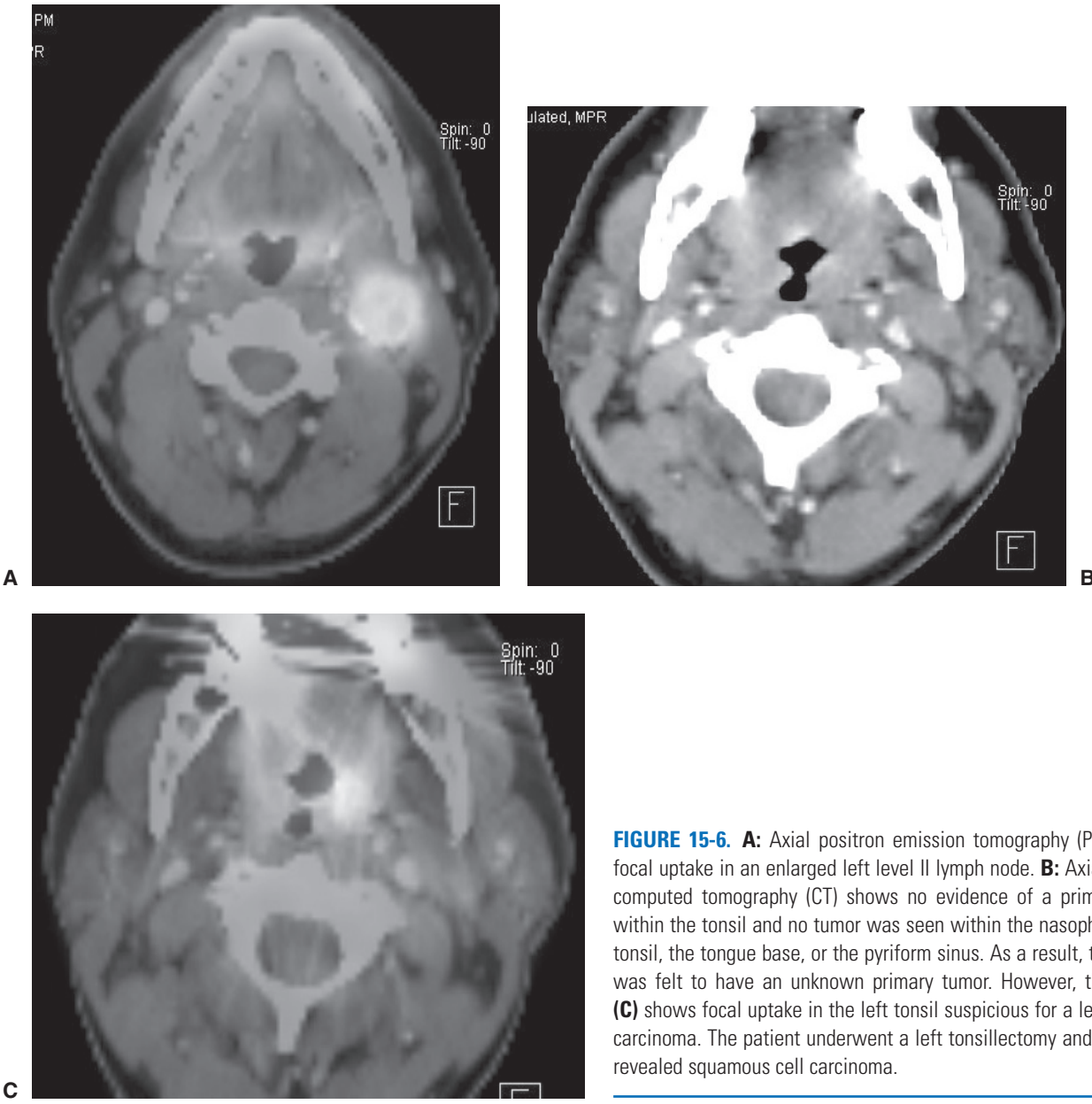



**FIGURE 15-6.** **A:** Axial positron emission tomography (PET) shows focal uptake in an enlarged left level II lymph node. **B:** Axial contrast computed tomography (CT) shows no evidence of a primary tumor within the tonsil and no tumor was seen within the nasopharynx, the tonsil, the tongue base, or the pyriform sinus. As a result, the patient was felt to have an unknown primary tumor. However, the PET/CT **(C)** shows focal uptake in the left tonsil suspicious for a left tonsillar carcinoma. The patient underwent a left tonsillectomy and pathology revealed squamous cell carcinoma.

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# PART C:
# Radiation Therapy Technique

William M. Mendenhall

The cervical lymph node area most often involved with cancer from an unknown head and neck primary site is level II. The most likely primary tumor sites are the base of the tongue and the tonsillar fossa. Accordingly, our philosophy has been to treat the unknown primary of the head and neck as if it were a T1 oropharyngeal cancer.[1] The probable primary site and the upper neck are encompassed in equally weighted parallel-opposed fields. The field borders are the thyroid notch, the posterior spinous process of C2, the floor of the sella turcica, and 2 cm anterior to the tonsillar fossa (Fig. 15-7).[2] The anterior and/or posterior borders may need to be enlarged depending on the extent of disease in the upper neck nodes. Although the likelihood of a nasopharyngeal primary is low, outside of areas where it is endemic such as Hong Kong, the risk of involved retropharyngeal nodes is relatively high, which means that part of the nasopharynx must be included in the portals.[3] Modest enlargement of the portals to include the nasopharynx with a tight margin adds little morbidity and reduces the risk of recurrence in this site. The low neck is treated with an anterior portal with a tapered midline larynx block. The lateral fields are treated once daily to 64.8 Gy in 36 fractions, with a reduction of the spinal cord at 45.0 Gy. The dose to the posterior strips may be boosted on the involved side with 8 to 10 MeV electrons after the field is reduced off the cord.

Because the occasional patient presenting with a level III node is more likely to have a hypopharyngeal or supraglottic primary cancer, these sites are included in the portals in this situation (Fig. 15-8).[2]

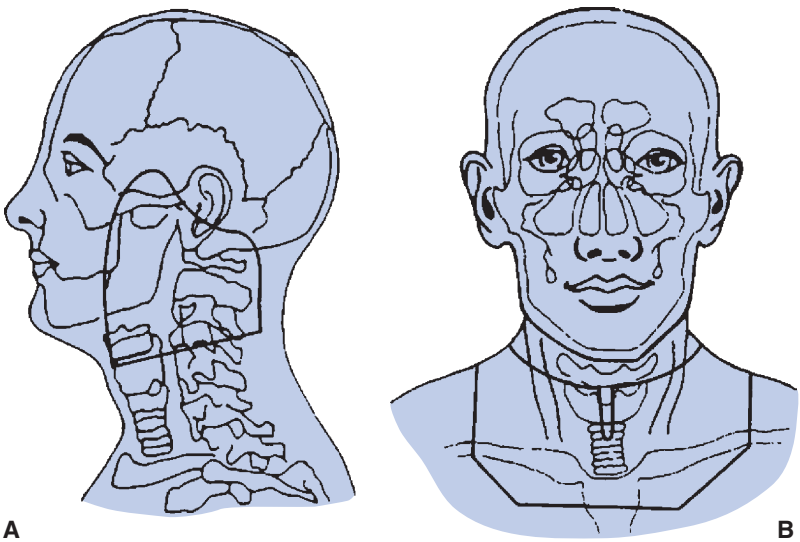



**FIGURE 15-7.** Radiation therapy portals used to treat head and neck mucosal sites and upper cervical lymph nodes **(A)** and lower cervical and supraclavicular lymph nodes **(B)**. The inferior border for lateral portals is placed at the superoanterior border of the thyroid cartilage, shielding the hypopharynx and the larynx.

*Source:* From Erkal HS, Mendenhall WM, Amdur RJ, et al. Squamous cell carcinomas metastatic to cervical lymph nodes from an unknown head and neck mucosal site treated with radiation therapy alone or in combination with neck dissection. *Int J Radiat Oncol Biol Phys.* 2001;50:55–63 (Fig. 8, p. 62), with permission.

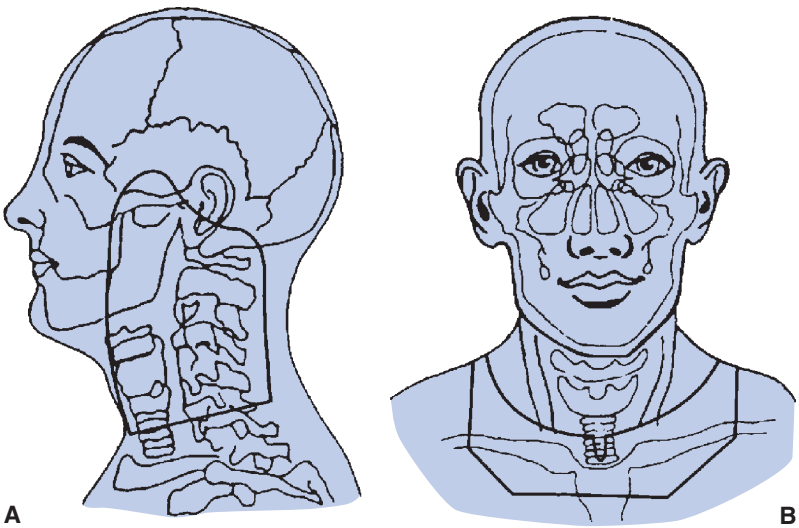



**FIGURE 15-8.** Radiation therapy portals used to treat head and neck mucosal sites and upper cervical lymph nodes **(A)** and lower cervical and supraclavicular lymph nodes **(B)**. The inferior border for lateral portals is placed 2 cm below the inferior border of the cricoid cartilage, treating the hypopharynx and the larynx.

*Source:* From Erkal HS, Mendenhall WM, Amdur RJ, et al. Squamous cell carcinomas metastatic to cervical lymph nodes from an unknown head and neck mucosal site treated with radiation therapy alone or in combination with neck dissection. *Int J Radiat Oncol Biol Phys* . 2001;50:55–63 (Fig. 8, p. 62), with permission.

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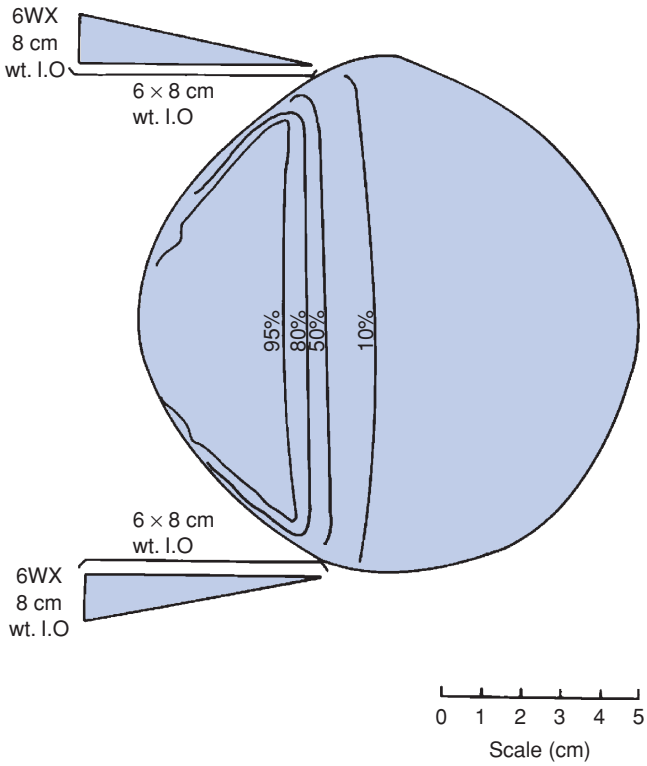



**FIGURE 15-9.** Anterior and posterior 6-MV x-ray portals used to treat the neck.

*Source:* From Million RR, Cassisi NJ, Mancuso AA. The unknown primary. In: Million RR, Cassisi NJ, eds. *Management of Head and Neck Cancer: A Multidisciplinary Approach* . 2nd ed. Philadelphia, PA: JB Lippincott Co; 1994:311–320 (Fig. 15-4D, p. 318), with permission.

It may be necessary to irradiate the positive neck nodes to a higher dose than the head and neck mucosa, depending on the extent and fixation of the nodes. In this situation, the grossly involved nodes are irradiated with anterior and posterior, 6 MV x-ray or $^{60}$Co portals, excluding the mucosa (Fig. 15-9).[4] The advantage of this technique compared with use of high-energy *en face* electrons is that some of the skin receives a lower dose, thus reducing the risk of postoperative complications if a neck dissection is to follow radiation therapy[5,6] in addition, and the spinal cord receives no exit dose. The boost may follow the treatment of the head and neck mucosa or may be given once or twice a week as a concomitant boost with a minimum 6-hour interfraction interval.

Intensity-modulated radiotherapy (IMRT) is employed primarily in patients with ipsilateral positive nodes, where it may be possible to adequately irradiate the oropharynx and nasopharynx, as well as the grossly positive nodes to 64.8 Gy at 1.8 Gy per fraction, once daily, and limit the contralateral parotid mean dose to 26.0 Gy or less.[7] The positive nodes are treated to approximately 70.0 Gy either concomitantly due to dose inhomogeneity, or as a separate boost. The low neck is treated with a separate portal, with a midline block to reduce the dose to the larynx. Clinically negative nodal areas that are electively irradiated to doses ranging from 49.5 to 54.0 Gy include ipsilateral levels IB II, III, IV, V, and the retropharyngeal nodes, as well as contralateral levels II, III, and IV.[8] An example of a patient treated with IMRT is depicted in Figure 15-10. Care must be taken to limit the dose to the anterior oral cavity, which will receive more irradiation compared with conventional field arrangements. Although it may be possible to adequately treat patients with low-volume contralateral positive nodes with IMRT, it is often difficult to achieve the goal of limiting the contralateral mean parotid dose to 26.0 Gy or less, in which case conventional fields are employed. Patients usually receive weekly concomitant cisplatin during the course of IMRT. Patients undergo a computed tomographic (CT) scan 1 month after RT to determine whether a neck dissection is indicated.[9]

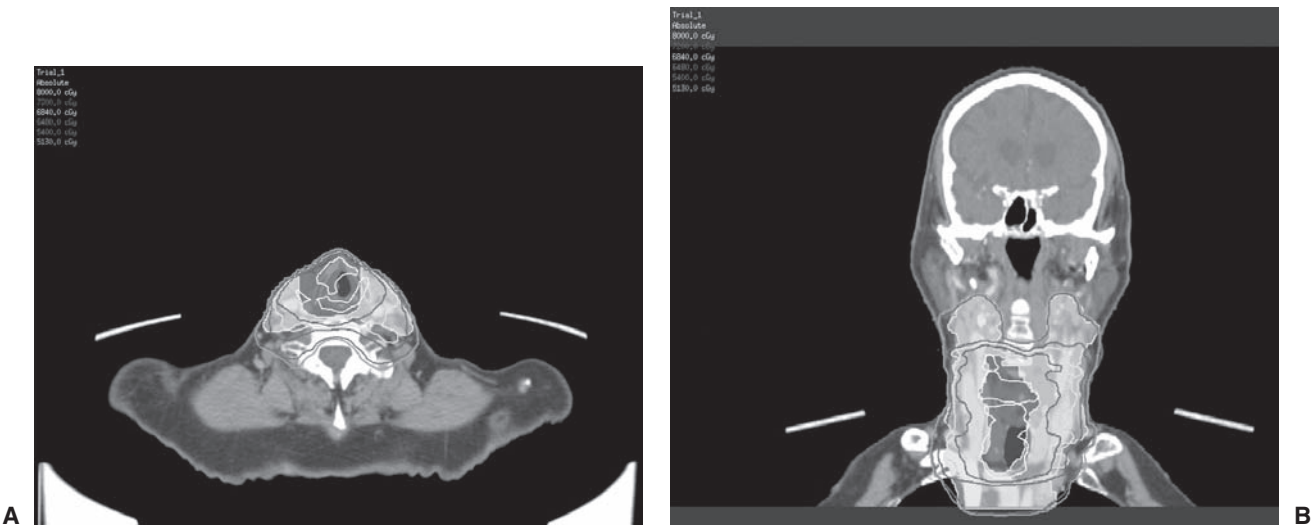



**Figure 15-10. A & B:** Patient with a T0N2B squamous cell carcinoma from an unknown primary site with left neck adenopathy. The patient is treated with IMRT with 6-MV X-rays. The oropharynx and positive nodes receive 64.8 Gy at 1.8 Gy per once-daily fraction. The gross disease is boosted to 70 Gy. The standard-risk clinical target volume (SR-CTV) receives 50 Gy. **A)** Axial contour; **B)** Sapittal contour. A PET-CT is obtained after radiotherapy and a left dissection is performed if the response is incomplete. (See color insert)

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Patients who are in poor condition, as well as those treated with palliative intent, are treated to the involved neck alone using the anterior and posterior field arrangement previously described.[10]

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CHAPTER 16

# Cancer of the Oral Cavity

## PART A:
## General Principles and Management

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### INTRODUCTION: INCIDENCE, ETIOLOGY, AND EPIDEMIOLOGY

Cancer of the oral cavity is actually a collection of distinct and overlapping disorders with differing etiology, clinical manifestation, and treatment. Tumors are most commonly categorized by anatomical location and histologic diagnosis. The quintessential oral cancer arises in an individual who has used tobacco and alcohol. These lesions tend to occur on the lateral or ventral tongue, the floor of mouth (FOM), or the alveolar ridge, most often in men between the ages of 50 and 70 years, and are differentiated squamous cell carcinomas (SCC). However, there is increasing awareness that nonsmokers also can develop oral SCC (OSCC), most often on the lateral tongue but also elsewhere including the buccal mucosa and the alveolar ridge, often in younger and older patients, including disproportionately more women. Patients with lip cancer also have distinct demographic and clinical patterns, whereas minor salivary gland cancers are much less common and occur without known risk profile. These distinct categories support the hypothesis that the underlying process of tumorigenesis is also quite different among the broad cohort of patients with oral cancer.

Oral cancer is potentially a devastating disease. At late stages, it is very difficult to control and can result in a miserable demise. Even when detected early, treatment necessarily brings collateral damage to a region of the body that has great functional importance for communication and deglutition as well as cosmetic and therefore psycho-social impact.

According to the 2012 Cancer Facts and Figures of the American Cancer Society, there will be an estimated 26,740 cases of cancer of the oral cavity including tongue, mouth, and "other" regions in the United States in 2012. One-third of these cases will arise in women. During the same year, there will be 5,520 American deaths due to these cancers. Oral cavity and oropharyngeal cancers together comprise the eighth most common cancer in American men (3% of cancers). The rate of oral cancer declined by 1% per year in American women from 2004 to 2008, and the death rate for oral cavity and oropharynx cancers has declined over 30 years by 1.2% in men and 2.2% in women. This latter statistical observation may be partly due to a proportional increase in human papillomavirus (HPV)-related oropharyngeal cancers included in data collection, a subpopulation with markedly improved response to therapy that is not seen for cancers of the oral cavity. Survival rates for African Americans with oral cancer remains well behind that of White Americans (45% 5-year survival vs. 65%).[1]

Worldwide, the American Cancer Society estimates that oral cavity cancer is the 10th most common cancer among men with 170,900 cases estimated in 2008 (the last year with data available). Most of these cases were expected to be from developing countries (107,700), and most of those cases result in cancer-related death (61,200).[2] In South Central Asia and Melanesia, oral cancer is the second most common cancer among adult males.

Using the Surveillance, Epidemiology, and End Results (SEER) database, from 1998 to 2001, Piccirillo and coauthors have calculated relative survival for patients with oral cancer. Relative survival is defined as the ratio of observed survival divided by the survival that would be expected for a cancer-free individual from the same age, gender, and racial group. These data are derived from >40,000 individuals with head and neck cancer living in 12 geographic areas of the United States including 8,637 cases of tongue cancer (base of tongue and oral tongue combined), 3,286 cases of FOM cancer, and 5,946 cases of "gum and other mouth" cancers. The 5-year relative survival rate was found to be 53.1% for tongue, 59.5% for gum, and 52.7% for FOM tumors. Broken down by gender and race, survival is slightly better for women and markedly poorer for black than for white patients in all three anatomic groups. Outcome varies with stage of cancer declining from 70% to 96% 5-year survival for stage I oral cancer to 26% to 48% for stage IV cancers (Tables 16.1). Survival for oral tongue compared to base of tongue cancer is better for small tumors (75.9% for stage I oral tongue 5-year relative survival



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**TABLE 16.1 Five-Year Relative Survival (%) of Oral Cancer from SEER Database[3]**

| | Lip | Tongue | Oral Tongue | Floor of Mouth | Gum and Other Mouth |
|---|---|---|---|---|---|
| Overall | 93.5 | 53.1 | | 52.7 | 59.5 |
| White female | 93.1 | 57.9 | | 59.3 | 66.4 |
| White male | 93.9 | 54.0 | | 53.1 | 57.3 |
| Black female | | 37.8 | | 51.5 | 60.2 |
| Black male | | 30.6 | | 32.0 | 38.1 |
| Stage I | 96.3 | 70.7 | 75.9 | 72.5 | 80.9 |
| Stage II | 82.7 | 58.6 | 57.5 | 60.1 | 62.2 |
| Stage III | 56.7 | 47.3 | 38.8 | 35.8 | 45.1 |
| Stage IV | 48.1 | 36.7 | 26.5 | 29.7 | 40.0 |

compared to 51.5% for stage I base of tongue lesions) but worse for all later stages (26.5% relative 5-year survival for stage IV oral tongue compared to 41.9% for stage IV base of tongue).[3] Survival of oral cancer patients also varies widely in different parts of the world. According to American Cancer Society Global statistics, 5-year relative survival for oral cancer patients is highest in the United States and Germany (60.7%) and lowest in Poland, Thailand, and India (36%–37%).[2]

Cancer of the lip has a distinctive demographic pattern in the United States. It affects principally white men, who account for 80% of cases in the published SEER database analysis of 12 regions.[3] Lip carcinoma accounts for roughly 12% of all noncutaneous head and neck cancers. White women make up another 17.8% with African Americans accounting for only 1.1% of cases. The vast majority of cases are diagnosed and treated at an early stage (83.2% stage I), accounting for an overall excellent outcome (93.5% relative 5-year survival). This is the lowest disease-related mortality among oral cancers. The incidence is reported to be high in Australia and New Zealand (10.2 per 100,000 men).[4] More than 90% of carcinomas of the lip involve the lower lip, attributed to sun exposure. The upper lip (2%–7%) and commissure (<1%) are less frequently involved. A variety of malignant histologies arise in the lip, most commonly basal cell and squamous cell carcinoma and less common lesions such as minor salivary gland tumors, melanoma, and sarcoma.

Cancer of the hard palate accounts for 10% of the neoplasms of the oral cavity. There is a great variety of malignant neoplasms that arise in the hard palate, including tumors of epithelial, salivary, hematopoietic, and mesenchymal tissues. SCC comprise only about 50% of these tumors. Carcinomas originating from minor salivary glands are the most common non–squamous cell malignancies in this region. Inexplicably, salivary cancers typically arise near the foramen of the descending palatine artery near the second molar tooth and the hard palate–soft palate junction. Less common malignancies presenting in the hard palate include hematologic malignancies such as lymphoma and plasmacytoma, polymorphic reticulosis (or lethal midline granuloma), Kaposi sarcoma, and mucosal melanoma.

## Risk Factors for OSCC

The use of alcohol and tobacco account for approximately 75% of all cases of OSCC worldwide.[5] It is widely agreed that tobacco plays the major role in this risk profile. Poor oral hygiene and nutritional deficits are also invoked, but because these factors often coexist with alcohol and tobacco abuse, their relative contribution is difficult to assess. In a large pooled case-control international study, smoking alone, among alcohol abstainers, was associated with a relative risk of over threefold for the development of OSCC in Europe and South America, with a somewhat lower risk estimated for persons from South Asia and North America.[6] These differences may reflect the level of carcinogens in tobacco products sold in different regions. The risk of cancer increased with exposure measured in pack years from about 1.5-fold for light smokers (<10 pack years) peaking at fourfold for those individuals who have >30 pack years of smoking. Alcohol alone in persons who do not use tobacco imparts a risk for OSCC only when a threshold of >15 units per week is reached, and then the relative risk is modest, around threefold.[7] Nonsmokers who use alcohol at this level are more prone to develop cancers of the hypopharynx and the larynx. It has long been recognized that the combined use of alcohol and tobacco in the same individual conveys a multiplied or synergistic degree of risk for OSCC.[8] The American Cancer Society reports that cigarette smoking among adults in the United States declined 50% from 1965 to 2005 (from 42% of the population to 21%) but an estimated 45 million Americans continue to smoke. The gender gap narrowed in the 1980s, and now there is a 4% difference in smoking prevelance between White men and women and a 9% difference between African American men and women. Smoking among teens has declined in the first half of the current decade, estimated at 23% in 2005.[9] The risk of cancer due to tobacco exposure is thought to decline with time. However, as there are more ex-smokers in recent years, it may be discovered that the appearance of cancers in this segment of the population has been underestimated previously. Elderly patients who have quit smoking decades earlier can develop cancer of the maxillary alveolus or buccal mucosa.[10]

The association of the use of smokeless tobacco with oral cancer is less well substantiated than that of cigarettes and alcohol use. Smokeless tobacco use causes visible changes in the oral mucosa including wrinkling with slight elevation and, in some cases, leukoplakia. However, when these areas are biopsied, histologic findings of dysplasia is unusual and somewhat more commonly seen among snuff users than with chewing tobacco use.[11] The risk of developing cancer appears to be even more remote. The use of snuff and chewing tobacco has been shown to produce alterations in cell proliferation, apoptosis, and activation of inflammatory elements which, in turn, may be linked to cancer development.[12] Typical individuals who develop oral cancer after

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smokeless tobacco do so after many decades of use, as late as their eighth decade of life.[13]

Oral submucous fibrosis in the setting of areca nut use appears to be a special case of premalignancy associated with oral cancer development. Clinically, this condition is manifested by palpable sheets of fibrous tissue in buccal and labial regions with loss of elasticity and accompanying trismus. Histologically, submucous fibrosis is diagnosed when dense, avascular collagenous connective tissue is present in affected areas together with chronic inflammation and epithelial atrophy.[14] In India, oral submucous fibrosis occurs in men five times more often than in women and affects predominantly members of lower socioeconomic classes. The use of areca nut is often combined with other potential carcinogens including snuff, alcohol, and cigarette smoking. The incidence of submucous fibrosis progressing to cancer is estimated between 2% and 7%.[15,16] The use of alcohol and tobacco-free betel quid accounts for an increase in cumulative risk of oral cavity cancer of >60% resulting in an earlier age of diagnosis than seen in nonusers.[17] Individuals of South Asian ethnicity are increasingly bringing betel-quid and areca nut use to other regions worldwide.

## OSCC in the Absence of Known Carcinogen Exposure

Americans with OSCC that have not used tobacco or alcohol (nonsmokers/nondrinkers [NS/ND]) are disproportionately women (>70% in some series). This group is also more likely to present with early-stage disease. Lateral tongue, buccal, and maxillary alveolar sites are typical.[10,18] These patients are quite concerned about why they have oral cancer, and no certain answers exist. Often, the individual patient will have a theory; dental irritation, mouthwash use, cinnamon gum use, and dietary, occupational, and environmental factors have all been suggested. Solid epidemiologic studies of this phenomenon are few, hampered by the small numbers of individuals involved. Still, the appearance of lateral tongue cancer in nonsmokers may be on the increase and constitutes a potentially very fruitful field of inquiry. Myers and others reviewed the M.D. Anderson Cancer Center experience over a 22-year period and found that the percentage of patients with tongue cancer who were <40 years of age increased from 4% in 1971 to 18% in 1993.[19] Using the SEER database, an increase of 111% of oral tongue cancer among young white women has been reported between 1975 and 2007 whereas the incidence in all other sites and subpopulations was decreasing.[20] It is intriguing that there is such site specificity in this population, predominantly affecting the lateral oral tongue on one side only. Tumors arising on the lateral tongue in NS/ND are sometimes associated with persistent hyperkeratosis to mild to moderate dysplasia in a field around the original tumor site after treatment. In these cases, return of malignancy can occur even after many years of quiescence. Tenderness to certain foods along with increased thickness and friability of lesions are bellwethers of malignant progression. In other cases, simple excision of early tongue SCC results in a nearly undetectable linear scar with no mucosal indication of persistent atypia. In these cases, disease control may be life-long.

Lichen planus (LP) is a chronic inflammatory disease that preferentially affects the buccal and lateral tongue mucosa and is seen in 1% to 2% of the adult population. It presents as a superficial, lacy leukoplakia that fluctuates in intensity in affected individuals over time. Anecdotal observation indicates that OSCC can arise within the field of LP in isolated cases. In these cases, the shallow erosive region occasionally seen in LP may develop a thickened and friable central area of red ulceration indicative of the neovascularity of malignant transformation (Fig. 16-1). The rate of malignant transformation in LP is judged to be quite low (<2%).[21]

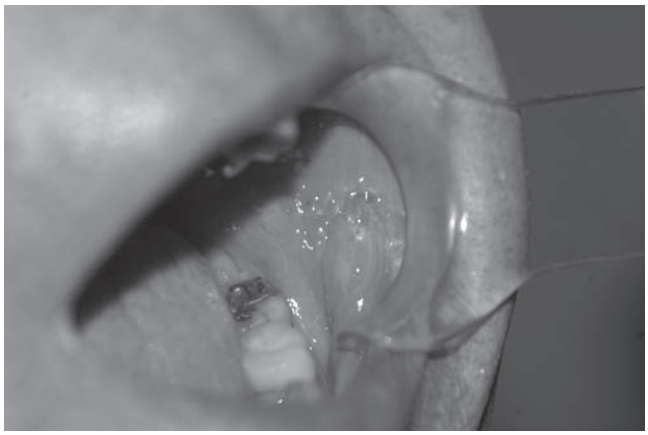


**FIGURE 16-1.** Erosive lichen planus involving the buccal mucosa.

Following the precedent of LP, an autoimmune cause has been widely postulated for the broader phenomenon of SCC in NS/NDs. Chronic inflammation causes a high rate of cell turnover and proliferation in an environment of altered cytokines and reactive oxygen species all of which may contribute to cancer initiation.[22] Alternatively, there may be some undiscovered genetic predisposition to oral tongue cancer. One example is Fanconi anemia, a rare inherited genetic condition that leads to early hematologic malignancy. Survivors of this childhood leukemia have a high risk for oral tongue cancer that also arises at a young age.[23]

OSCC is also seen in other persons who are immunosuppressed after bone marrow or other organ transplant attributed to graft versus host disease (GVHD). These cancers often arise on the alveolus, the buccal, the FOM, or the tongue mucosa.[24–25] GVHD is a severe complication of allogenic bone marrow transplantation manifesting chronic inflammation of the oral mucosa as well as the skin, the GI tract, and the liver. Whole-body irradiation for the initial malignancy may increase the risk of secondary cancer. Most second cancers following bone marrow transplantation are hematologic, although SCC is the most common form of solid tumor seen in these individuals.[24] OSCC in the setting of GVHD is not limited to the lateral tongue but can affect the dorsal tongue mucosa, the alveolar ridge, and other regions that have been affected by GVHD. These individuals are often much younger than typical OSCC patients, with lesions arising 2 to 10 years after GVHD.

Finally, there may be an undiscovered viral cause of lateral tongue cancer in NS/NDs. Although HPV is widely accepted as a causal factor for cancer arising in the lymphoepithelium of the oropharynx, its presence in lesions of the oral cavity is less common and its contribution to cancer development is controversial. When rigorous detection methods such as *in situ* hybridization (ISH) are used for HPV assessment, the rate of HPV positivity in oral cancers is small.[26] In fact, some tumors that originate in the palatine or lingual tonsil may be mislabeled as oral cavity tumors due to spread from the adjacent epicenter which may have been previously altered by diagnostic biopsy/tonsillectomy. More promiscuous detection techniques based on polymerase chain reaction (PCR) technology may overcall HPV positivity. When detected in very small amount, HPV, although present, may not play a biologically important role in tumorigenesis, bringing into question the relevance of its detection.[27] Investigators at University of North Carolina have found that 11/25 lateral tongue cancers from young patients (aged 18–39 years) had overexpression of p16(INK4a) but not HPV-16 by *in situ* hybridization. In this small series, p16 expression was associated with

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improved survival (hazard ratio [HR] = 0.23, $p$ = 0.01).[28] In a similar study, none of 32 mobile tongue cancer specimens was found to contain high-risk HPV DNA as assessed by *in situ* hybridization, although six cases had p16(INK4a) overexpression.[29] Risk factors for palate SCC include tobacco and alcohol use, including reverse chutta (cigar) smoking, although denture trauma and poor oral hygiene, as well as a history of syphilis or vitamin deficiency, are sometimes invoked.[30]

***Oral Cancer Screening.*** Over the last decade, there has been increasing attention given to the potential community health benefit of oral cancer screening. Both otolaryngologists and dental health professionals have promoted oral screening as a means to improve outcomes of oral cancer care through identification of lesions at the earliest stages. Screening pertains primarily to the oral cavity because of the accessibility of those mucosal surfaces to simple visual inspection. Evaluation elsewhere in the upper aerodigestive tract is more challenging and requires special expertise and equipment.

The Yul Brynner Society, now the Head and Neck Cancer Alliance (http://www.headandneck.org), sponsors an annual national oral cancer awareness campaign that has continued with oral cancer awareness week held each April since 1998. The public health efficacy of oral cancer screening has yet to be demonstrated. One question is who should undergo oral cancer screening. Oral cancer is relatively uncommon, and while there are well-known risk factors for the development of oral malignancy, individuals at risk are often less conscientious about maintaining good health practices and may not avail themselves of screening opportunities.[31] Finally, because of the rarity of oral cancers, few primary care dentists and physicians have seen enough oral cancer lesions to develop familiarity and expertise in early detection.

A variety of technological tools have been promoted to assist in oral screening. These tools have in common efforts to enhance visual or spectroscopic features of altered surface epithelium in cases of premalignant or malignant change. One such device, the VELscope, uses autofluorescence technology to examine the oral mucosa. A published study comparing the rate of identification of oral lesions using white light alone versus white light and autofluorescence showed a greater sensitivity for identification of premalignancy on biopsy using VELscope (100% vs. 17%) but also showed a lower specificity for VELscope (74% vs. 97%).[32] However, another study failed to show an advantage to autofluorescence over white light visualization with only 81% specificity and 50% sensitivity for autofluorescent detection of lesion compared to 98% specificity and 50% sensitivity for white light.[33] Narrow-band imaging endoscopy is another new technology that has been investigated for use in oral cancer detection. This method can be used to identify "brownish spots" within an oral cancer, a feature that may be useful for de novo cancer detection.[34] Toluidine blue staining has also been proposed as an adjunct to visual inspection for oral cancer detection. In one recent report, the sensitivity and specificity for detection of cancer or dysplasia was 65.5% and 73.3%, respectively, using toluidine blue.[35] Some dental providers now charge patients for the added evaluation using assisted devices such as VELscope. In order to address potential clinical and ethical concerns related to this practice, the American Dental Association (ADA) hosted a working group to review the evidence for device efficacy in the literature. The conclusion of the working group was "that there is insufficient evidence to determine if screening alters disease-specific mortality in asymptomatic people seeking dental care." Furthermore, the group found, "insufficient evidence that commercial devices based on autofluorescence, [or] tissue reflectance enhance visual detection beyond that achieved through a conventional visual and tactile examination."[36] It would appear that there is no substitute for a clinician being aware of the possibility of oral cancer, the degree of risk born by a particular patient, taking the time to look at the oral mucosa with a good light, knowing what makes a lesion suspicious for malignancy, and exercising appropriate vigilance to arrange a biopsy when indicated.

Another technological adjunct to oral cancer screening is the use of cytologic brush "biopsy." Oral brush biopsy with computer-assisted analysis is commercially available (OpCDx) and has been reported to have a positive predictive value of 84% and negative predictive value of 98%.[37] This may be helpful in deciding which lesions to refer for surgical biopsy. However, such surgical biopsy remains the gold standard for rigorous and accurate diagnostic assessment of the degree of cancer-associated alteration present in visible lesions of the oral mucosa. The utility of brush biopsy may vary with the degree of experience of the clinician; highly experienced observers may rightly discern degree of suspicion based on subtle aspects such as lesion friability, thickness, tenderness, or variegated coloration, which would render the additional benefit of brush cytology less necessary. The ADA notes that "there is insufficient evidence to assess the validity of transepithelial cytology of seemingly innocuous mucosal lesions," but the method can "identify dyplastic cells in lesions with a high potential for malignancy."[36] Once again, clinical judgment is a key factor in the detection of oral cancer.

## Anatomy of the Oral Cavity

The oral cavity extends from the skin-mucosal junction of the vermillion border of the lips to the oropharyngeal inlet posteriorly. The oropharyngeal–oral junction is bounded superiorly by the hard–soft palate junction, laterally by the anterior tonsillar pillar, and inferiorly by the circumvallate papillae. The lining of the oral cavity is a nonkeratinized stratified squamous epithelial mucous membrane. The submucosa is rich with minor salivary glands, with a high concentration within the hard and soft palates. The oral cavity may be divided into subsites (Fig. 16-2) including the lips, the buccal mucosa, the FOM, the retromolar trigone (RMT), the oral tongue, the hard palate, and the alveolus (maxillary and mandibular). As has been noted, the natural history characteristics of oral carcinoma vary greatly depending on the subsite in which the primary lesion is located. We will therefore consider each of these subsites separately when discussing both anatomy and the management of oral carcinoma.

*Lips.* The vermilion zone includes the red lip which extends from the fixed gingiva of the labiogingival sulcus up to the vermilion border. The surface landmarks of the lips include the labial commisure laterally, philtrum (Cupid's bow), and labial tubercle just inferior to the philtrum (upper lip).

*Buccal Mucosa.* The buccal mucosa is a smooth surface epithelium extending from the oral commissure anteriorly to the

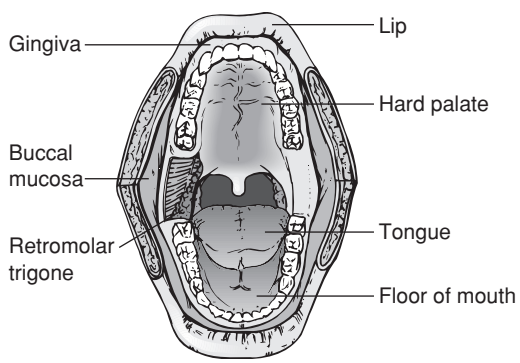



**FIGURE 16-2.** Primary sites in the oral cavity.

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retromolar gingiva posteriorly. The mucosa terminates at the gingivobuccal sulcus of both the maxillary and mandibular gingiva. Its sole landmark is the papule of Stenson's duct opposite the second maxillary molar. The buccinator muscle lies just deep to the thin mucosa with the buccal fat pad just beyond. The mucosa may be stippled with submucosal minor salivary glands manifest by cream or white colored small, slightly raised spots of approximately 2 mm diameter, called Fordyce spots.

*FOM.* Tissues of the FOM occupy a semilunar space bounded by the inner aspect of the lower alveolar ridge and the undersurface of the tongue. The transition from FOM to ventral tongue is continuous and indistinct. The posterior extent reaches the base of the anterior tonsillar pillar. The FOM is supported by a muscular sling composed of the mylohyoid, the geniohyoid, and the genioglossus muscles. The sling supports the submucosal sublingual glands, the Wharton ducts, and the minor salivary glands. The lingual and the hypoglossal nerves traverse the submucosal space of the FOM. Surface anatomy includes the lingual frenulum, the Wharton duct papillae, and the sublingual salivary ridge. Prominent veins often are visible below the mucosa as well.

*RMT.* The RMT is bounded posteromedially by the anterior tonsillar pillar, laterally by the buccal mucosa, and superiorly by the maxillary tubercle. It consists of two surfaces, one facing anteriorly just behind the third mandibular molar and the other facing medially just over the ascending ramus of the mandible. Submucosa here is very thin with bone near the surface.

*Oral Tongue.* The oral tongue comprises the anterior two thirds lying anterior to the line of circumvallate papillae. The dorsum of the tongue is covered with a thick epithelium interspersed with fungiform, filiform, and circumvallate papillae. Because of the thickness of this mucosa, it may have a wide variety of color which may change in a single individual over time. The thickness also may account for the paucity of neoplasms that arise on the tongue dorsum. The transition to the thin mucosa of the lateral tongue is relatively abrupt. However, in the posterior corner of the oral tongue, the fungiform papillae form vertical ridges which are more red in color than the lateral mucosa more anteriorly. Tongue mucosa lies directly over tongue musculature without intervening fat or salivary gland tissue. The intrinsic tongue musculature (the superior longitudinal muscle, the inferior longitudinal muscle, the transverse muscle, and the vertical muscle) make up the bulk of the freely mobile portion whereas the extrinsic tongue musculature, including the genioglossus, the hyoglossus, the styloglossus, and the palatoglossus comprise its root. The intrinsic muscles are responsible for the remarkable dexterity of the tongue, important in fine motions of articulation and bolus preparation while the extrinsic muscles elevate, depress, protrude, and retract the tongue. The muscles and their neurovascular bundles are bisected by a median raphe made of a fatty-fibrous material. The undersurface (ventral) of the tongue is lined by thin mucous membrane. The lingual frenulum serves as ventral attachment to the FOM. A deep lingual vein is often visible through the mucosa lateral to the lingual frenulum.

*Hard Palate.* The hard palate is a semilunar area bounded by the upper alveolar ridge anteriorly and laterally and the soft palate junction posteriorly. The submucosa here is tough and thick. A bony torus palatine may provide surface contour to an otherwise regular concavity. The greater palatine foramen is located in the palate bone near the second molar tooth and contains the descending palatine artery on each side that services the palate mucosa.

*Alveolar ridge.* Bony structures supporting the teeth and periodontal tissue arise from the FOM and descend from the hard palate. Here the mucosa is thin and tightly adherent to the periosteum. When teeth have been extracted, the bony elevation is often partially lost, particularly on the lower ridge. Mucosa here envelopes the neck of teeth with a small periodontal sulcus. Dental hygiene affects the quality of this mucosa with common inflammation and retraction of soft tissue from the teeth when hygiene is insufficient, and gingival hypertrophy in the setting of certain diseases and drug therapy.

The blood supply of the oral cavity is derived from branches of the paired external carotid arteries. The arterial supply of the lips is the labial arteries, which are branches of the facial artery. These paired arteries anastomose in the midline. The buccal mucosa likewise is supplied from branches of the facial artery. The lingual artery supplies the tongue, coursing deep in the extrinsic musculature below the digastric tendon and the posterior border of the hyoglossus muscle. The anterior tongue derives all of its blood supply from the lingual artery, with little contribution from the FOM mucosal vessels. The dominant blood supply of the hard palate is via the greater palatine artery and the superior alveolar arteries. Branches of the internal maxillary artery and inferior alveolar artery supply the maxillary and mandibular alveolar ridge. Branches of the facial artery supply the submandibular gland, the sublingual gland, and some of the FOM mucosa.

The oral cavity has a complex system of lymphatic drainage, supplying the first echelon basins of the submental, the submandibular, and the upper jugular systems and has recently been the subject of a review.[38] A more detailed analysis of lymphatic drainage patterns is included in the management section for each subsite.

Innervation of the oral cavity can be classified as sensory, special sense, and motor. The trigeminal nerve is the primary sensory supply of the oral cavity through its maxillary and mandibular branches. The lingual nerve (V3) supplies the sensory distribution to the anterior two thirds of the tongue and adjacent FOM. Taste fibers course with the lingual nerve after originating in the geniculate ganglion and traversing in the chorda tympani, then joining the lingual nerve. Motor control of the tongue is supplied by the hypoglossal nerve. Sensation of the lower lip and gum is provided by the mental nerve, a branch of V3. The hard palate, upper gum, and upper lip are innervated by the palatine and the labial branches of V2. The muscles of mastication are controlled by the second and third divisions of the trigeminal nerve whereas the lip and cheeks are innervated by the facial nerve.

## Natural History of Oral Cancer (Pathology, Pathogenesis, and Patterns of Spread)

***Molecular Underpinnings of Oral Cancer.*** Over the past two decades, a great deal of insight has been gained into the molecular processes that lead to the development and behavior of malignant neoplasms, including cancer of the oral cavity. It is increasingly recognized that tumor-specific genetic and epigenetic alterations affect key physiologic pathways that control functions such as cell proliferation, DNA repair, neoangiogenesis, motility, and metastasis. Genetic alterations include mutation, chromosomal rearrangement, and loss or amplification of segments of DNA while epigenetic alterations, particularly promoter hypermethylation, affect gene function through alteration of transcription. The effect of specific molecular alterations interweave in a complex manner such that a single event or intervention may have widely variable phenotypic result. Point mutation of the *p53* gene occurs in more than one half of all OSCC,[10] eliminating or reducing important cellular activities affecting cell cycle control and programmed cell death (apoptosis) in response to genotoxic stress. However, this genetic alteration alone is insufficient to account for the cancer

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phenotype, and the discovery of other genes with a substantial rate of mutation in HNSCC has not occurred. New data are emerging indicating that not all *p53* mutations have the same effect, with those that disrupt the DNA-binding domain three-dimensional configuration being associated with poorer clinical outcome.[39] Another tumor-specific target commonly affected in HNSCC is the *Rb* pathway which regulates the cell cycle. Loss of function of *Rb* and other members of this pathway including *p16* results in deregulation of cell growth and tumorigenesis. Mutations of *p16* are rare in HNSCC, but homozygous deletion occurs in >50% of cases. In another substantial group of cases, *p16* transcription is blocked by hypermethylation of the promoter region.[40]

Promoter hypermethylation is one form of epigenetic control of gene expression. Many regions of tumor-specific promoter hypermethylation have been described in HNSCC, accounting for a lack of expression of other genes with key tumor suppressor functions.[41] One distinct example is the Deleted in Colon Carcinoma (DCC) gene, frequently mutated in colon cancer, but rarely in HNSCC. Promoter hypermethylation of Deleted in Colon Carcinoma has been shown to be a frequent event in HNSCC.[42] Other key genes so altered included *MDM2*, *Interferon-alpha*, and *RAR-β*. MicroRNA, short 22-base sequences that can selectively block gene transcription, promises to provide yet another substantial mechanism for epigenetic tumor-specific alteration.

Studies of the rate and type of genetic alterations in oral premalignant lesions have helped sketch a tumor progression pathway for oral mucosal malignancy. By examining a spectrum of histologic lesions from atypia to dysplasia to carcinoma *in situ* to invasive cancer, and cataloging the molecular events present, a general pattern of accumulated alterations correlated with progressive phenotypic change has been established.[43] Some genetic alterations such as loss of *p16* expression, occur with high frequency in very early lesions such as atypia and dysplasia and do not increase greatly with further histologic progression. Other alterations only appear with substantial frequency in invasive SCC. The spectrum of genetic alterations in oral premalignant lesions may serve a prognostic role, providing evidence as to the risk of progression to invasion. Several studies have shown that loss of heterozygosity (LOH) of key gene regions including 3p, 9p, and 17p portend a significantly increased rate of progression.[44,45]

***Patterns of Spread.*** Malignant lesions of the oral mucosa arise from a region populated by clonally altered cells, a phenomenon known as *field cancerization*.[46] The involved field may be clinically apparent with regions of leukoplakia and erythroplakia, but more often it is unapparent and undetectable without sampling and sophisticated molecular methods. Enhanced visualization may be provided by supravital staining with tolonium chloride, or with measures of reflectance or absorbance of specific wavelengths of light.[47,48] The effect of field cancerization is to spawn neighboring lesions either contemporaneous to an index lesion or some time later (field recurrence). The ventral tongue and FOM are common locations for this phenomenon, presumably due to common exposure to carcinogens.

***Tumor Histology.*** By far, the majority of oral cavity cancers are OSCC. SCC arises from a series of genetic and epigenetic alterations that abrogate the function of key tumor suppressor genes at the crossroads of functional pathways.[43] The typical progression from cytologic atypia and hyperplasia to various degrees of dysplasia to *in situ* carcinoma and then invasive carcinoma may be manifest as erythroplakia, leukoplakia, or be largely unapparent. Leukoplakia, or white patch, may occur in the absence of malignant progression in the setting of local trauma or irritation. Palpable thickness, firmness, and friability (ready blushing or bleeding with manipulation) are telltale features of malignant transformation.

There are distinct patterns of tumor growth that characterize subclasses of OSCC. Verrucous change is one such variant. This

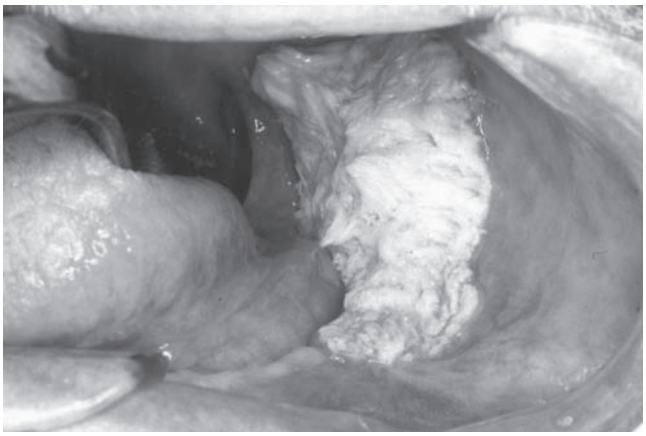


**FIGURE 16-3.** Verrucous carcinoma of the edentulous lower gum.

entity is prone to recur after excision and sometimes spreads across mucosal surfaces to involve large portions of the oral cavity. White, patchy, thickened change of the mucosa characterizes early verrucous leukoplakia. More advanced verrucous change becomes velvety and exophytic (Figs. 16-3 and 16-4). Histologically, these lesions exhibit bland cytologic change with broad pushing borders of the invasive component. This feature, together with the thick nature of advanced lesions, makes the diagnostic distinction between invasive and preinvasive verrucoid lesions difficult, with many biopsies failing to obtain full thickness of tissue that adequately demonstrates the infiltrative interface.[49]

The anatomic features of different regions within the mouth affect the pattern of tumor growth and spread. The dorsum of the tongue and the hard palate with their thick mucosa and submucosa are somewhat impervious to the development of OSCC. These regions are also located above pooled secretions which may reduce their exposure to carcinogens. Once cancer invades the intrinsic musculature of the tongue, there is no substantial barrier to its further spread between muscle fascicles. This fact makes delineation of the necessary deep boundary of resection difficult.

Detection of invasion of tumor into the mandible is important for staging and treatment planning. While cortical bone provides a substantial barrier to tumor, the lack of cortex in an empty tooth socket permits entry of invasive cancer into the marrow

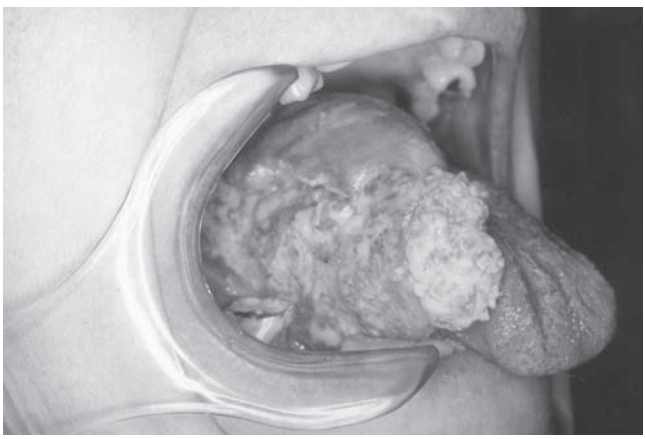


**FIGURE 16-4.** Exophytic, papillary, well-differentiated squamous cell carcinoma of the oral tongue.

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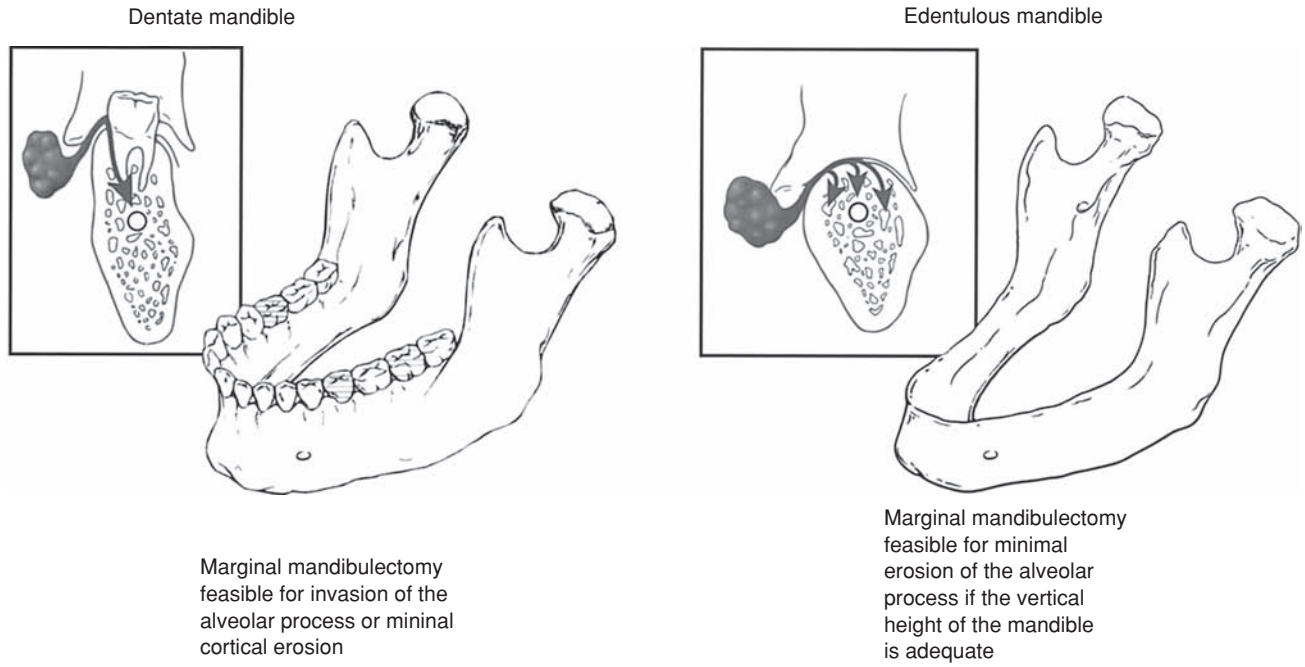



**FIGURE 16-5.** Routes of spread to mandible from oral cancer in dentate and edentulous mandible.

space and mental nerve canal. Once this has occurred, tumor can spread laterally and medially to the extent of the marrow space without obvious external evidence (Fig. 16-5).[50] Computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scanning all can help detect the presence and degree of bone invasion (Fig. 16-6).[51]




**FIGURE 16-6.** CT scan with bone windowing shows erosion of the inner cortex of the left mandible, lingual surface due to an adjacent floor of mouth tumor.

***Nonsquamous Oral Cancers.*** In addition to SCC, the oral cavity may develop minor salivary glandular carcinomas and a variety of sarcomas. Minor salivary gland tumors are malignant in the majority of cases. Specific malignant lesions include mucoepidermoid carcinoma, polymorphous low-grade adenocarcinoma, adenoid cystic, acinic cell, clear cell, and myoepithelial carcinoma, to name several. The most common location for all tumors in that series was the palate, accounting for 57% (89/156) of cases including most of the mucoepidermoid carcinomas, polymorphous low-grade adenocarcinomas, and adenoid cystic carcinomas.[52] Some of these entities have distinctive clinical presentations, such as polymorphous low-grade adenocarcinoma, which along with pleomorphic adenoma tend to arise laterally at the hard palate–soft palate junction. In a report from a single institution spanning 20 years of case accumulation, mucoepidermoid carcinoma was the most common histologic category among minor salivary gland malignancies of the oral cavity, accounting for 22% of 156 collected cases.

A wide variety of sarcomas arise within the oral cavity, although all are rare. Kaposi sarcoma is a distinctive entity typically affecting individuals with untreated human immunodeficiency virus (HIV) disease. It begins as an inflammatory, hyperplastic, angiogenic lesion. The gingiva, the palate, and the tongue are most commonly affected. HAART has reduced the rate of Kaposi sarcoma by up to 50%.[53] Osteosarcoma of the mandible and maxilla is the most common sarcoma of the oral cavity, presenting as a painless mass or accompanied by dental pain and loose teeth.[54] Other sarcomas that may appear in the oral cavity include chondrosarcoma, leiomyosarcoma, alveolar soft part sarcoma, fibrosarcoma, and liposarcoma.[55]

## Lymphatic Metastasis from Oral Cancer

Lymphatic extension from the oral cavity follows well-described patterns (Fig. 16-7). Level I nodes are the primary echelon basin for spread from the anterior FOM and the tongue tip, central lips, and mesial alveoloar surfaces of the maxilla and the mandible. Level II nodes drain the lateral FOM and the tongue. Several

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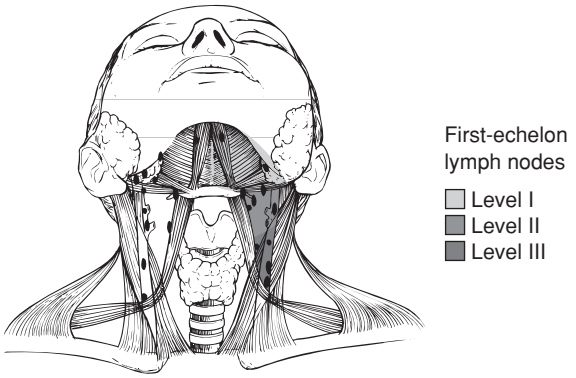



**FIGURE 16-7.** First-echelon lymph nodes at risk for metastasis from carcinoma of the oral cavity are located in the supraomohyoid triangle.

series have documented the relationship between tumor thickness of cancers of the FOM with the likelihood cervical metastasis, with tumor thickness >1.5 mm associated with an increased risk of lymph node metastasis.[56,57] Likewise, for tumors of the FOM or the oral tongue, Spiro and others, in a review of 105 patients staged N0, reported a 12% rate of regional failure with a primary tumor thickness <2 mm as opposed to a failure rate of 47% for tumors thicker than 2 mm. Clearly, those patients with clinically N0 necks with a tumor thickness >1.5 to 2 mm warrant consideration for proactive management of the neck.[58] Whereas tumor thickness has heretofore been determined by microscopic evaluation of a full-thickness tumor biopsy, intraoral ultrasound has been explored as a noninvasive alternative.[59]

Distant dissemination of OSCC is uncommon, particularly at the time of initial presentation. Spread to liver, lung, and bones does occur, more commonly in advanced cases, particularly in the setting of extensive nodal metastasis.

***Clinical Presentation.*** Oral malignancies typically present as visible lesions ranging from deep ulceration to fungating exophytic growth. They may be white or red compared to normal mucosa (Fig. 16-8). Cancers tend to be firm and thick compared to normal surrounding tissue when palpated. Malignant lesions may be painless, but more commonly are the source of deep persistent pain which may be referred to the ipsilateral ear. Bleeding is a common feature, attributed to neovascularity of malignant angiogenesis and fragility of feeding vessels. Loosened teeth or poorly fitting dentures may draw attention to alveolar ridge lesions. In some cases, a firm submandibular or upper jugular lymph node may be the presenting sign of OSCC.

## Diagnostic Evaluation and Clinical Staging

A thorough history must be obtained to initiate the workup of an oral cancer, ascertaining the time course of appearance and progression of the lesion, exposure to known risk factors and pertinent medical history. A complete head and neck exam follows with attention to the physical features of the lesion (precise location, dimension, thickness, friability) as well as screening for possible second lesions. Visualization requires good illumination, gauze, and instruments to move the lips and the tongue in order to see all surfaces thoroughly. Palpation is of great importance to detect submucosal extension and tumor thickness. Careful attention to pertinent lymph node basins in the neck follows. Bimanual palpation of the submental and submandibular regions is quite helpful to discern the presence of small but firm nodes in this region. Posteriorly positioned lesions of RMT, posterolateral tongue, or posterior FOM, because of their less accessible location in the oral cavity, are sometimes difficult to assess (Fig. 16-9). Sensory nerve distribution here is less precise making it difficult for some patients to accurately identify the source of cancer pain. Gag reflex and tongue resistance to manipulation further hinders efforts by the clinician to locate visible posterior tumor or precursor lesions on oral screening evaluations. These tumors will often remain unnoticed until the patient presents with progressive persistent pain, dysphagia and weight loss, referred otalgia, or trismus.

Assessing mandibular invasion by physical exam alone can be challenging. Involvement of the maxilla may also occur, and masticator space involvement is a particularly poor prognostic factor.[60] Physical mobility of the tumor mass relative to the mandible can be judged by bimanual manipulation which may be facilitated by general anesthesia in some cases. Imaging by CT may help to clarify the status of bony involvement. However, the sensitivity of CT for determining bony involvement is only 50%. Lane and others, in a review of patients treated for cancer of the RMT over a 14-year period, found that bony invasion was not

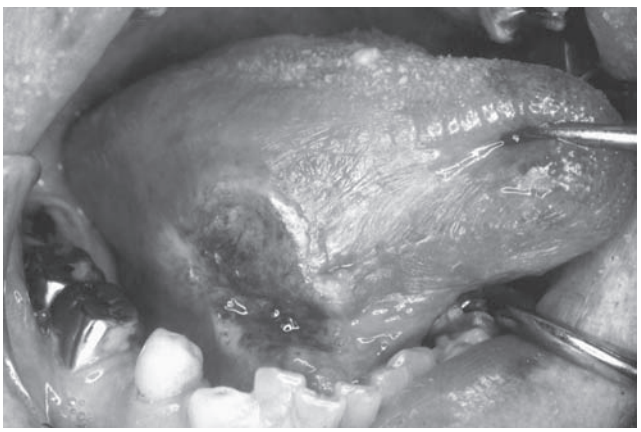


**FIGURE 16-8.** Ulcerated, flat, mostly endophytic carcinoma of the lateral border of the tongue.

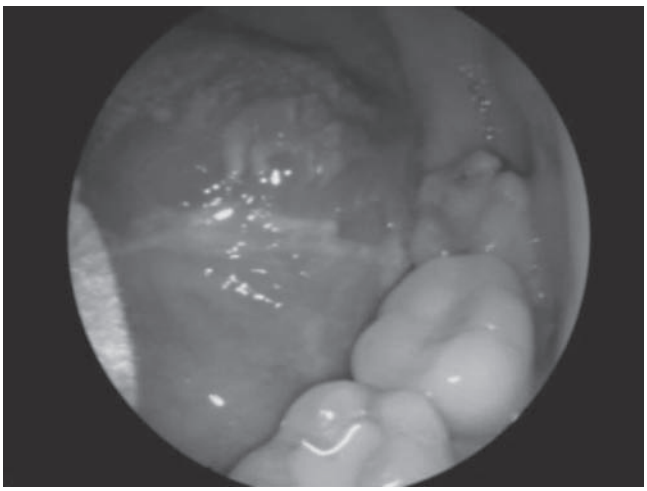


**FIGURE 16-9.** Erythroleukoplakia on the posterolateral oral tongue.

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identified correctly by radiograph in 27% of patients with preoperative CT scans.[61] The reported accuracy of MRI in detecting mandibular invasion in the literature has also been mixed.[62–64] PET scanning may help with detection of invasion in the setting of intact dentition, whereas MRI appears to be superior for detection of marrow involvement (Fig. 16-10).[51]

***Radiologic Evaluation.*** The timing and type of radiographic imaging selected for workup of oral cancer depends on several issues. Small surface lesions may not require any imaging since they will not be visible and the risk of nodal spread is small. CT, MRI, and PET scanning can help delineate the extent of larger lesions, particularly pertaining to deep tongue and mandibular invasion as well as nodal metastasis. The timing of PET scanning is particularly worthy of comment since recent biopsy may result in inflammatory metabolic activity in regional nodes rendering a false-positive uptake that could be interpreted as indicative of metastatic tumor. CT with intravenous contrast is often the first choice in this setting, as it provides excellent visualization of bone/soft tissue borders, particularly important in oral cavity lesions. Contrast enhancement is present in many tumors due to increased blood supply. MRI is the imaging modality of choice when evaluating soft tissue lesions and may be more useful for demonstrating the extent of the primary lesion. In particular, MRI provides superior imaging of lesions of the oral tongue and the tongue base. For lesions where there is a question of base of skull involvement, MRI likewise provides superior imaging.

PET with fluorodeoxyglucose (FDG) is now a standard component of the staging of head and neck cancers and in screening for second primary cancers and regional and distant metastatic disease. However, the contribution of PET imaging to the preoperative workup for staging the clinically N0 neck remains uncertain and may not be a replacement for staging neck dissection.[65,66] Schwartz and others, in a prospective series comparing pretreatment CT alone with fusion PET-CT in patients with head and neck cancer, found that PET-CT was superior in identifying regional lymph node metastasis. Although the majority of these patients had advanced-stage disease (stage III or IV), their findings provide evidence to support including functional PET imaging in the preoperative workup.[67] PET/CT scanning promises increased sensitivity for detection of distant metastatic disease over that provided by conventional CT scanning.[68] As the rate of synchronous primary cancers may range from 2.6% to 15%, a systemic workup is of importance preoperatively, particularly for patients who have been smokers. Again, the relative value of PET/CT compared to panendoscopy for detection of second primary cancers of the upper aerodigestive tract is yet to be determined.[69,70]

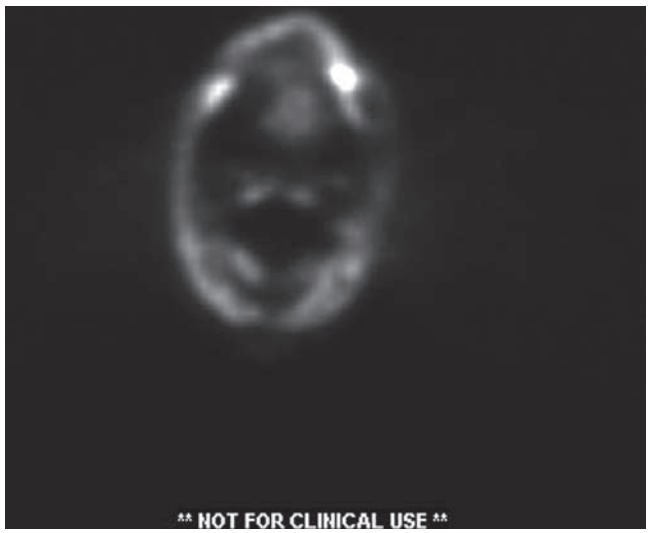



**FIGURE 16-10.** FDG-PET scan showing high metabolic uptake in the marrow space of the left hemimandible.

***Biopsy.*** An incisional biopsy to confirm the diagnosis of a suspicious lesion is mandatory. It may be necessary to sample several areas if there are regions with varying appearance. Because of the highly specialized histologic criteria for classification of the stages of oral mucosal premalignancy and the spectrum of minor salivary gland tumors, the experience of the pathologist reading the biopsy material is a key factor in proper workup. Biopsy of most sites within the oral cavity is feasible in the office under local anesthesia when the patient has even modest ability to cooperate.

***Tumor Staging.*** The stage of oral cavity cancers is based on the greatest dimension of the surface extent. A tumor may be staged T4 due to deep tongue, soft tissue, or bone invasion regardless of surface dimension (Table 16.2). Staging for nodal metastasis is identical to that of other head and neck sites. T and N stage are both excellent prognostic factors in most clinical series with good delineation between stage categories.[3,71] However, the UICC sixth edition staging categories of IVa versus IVb and T4a versus T4b did not differentiate between statistically different subpopulations in a recent report of 300 OSCC patients indicating a weakness in distinguishing between low- and high-risk advanced tumors using this schema.

# MANAGEMENT STRATEGIES

## Pretreatment Considerations

Several factors must be taken into consideration when choosing a management strategy for the patient with oral cancer. General physical health and functional status are important in determining the suitability of the patient for both surgical and nonsurgical approaches. This includes evaluating and optimizing comorbidities and the nutritional status of the patient. The patient's ability

**TABLE 16.2 T Staging of Oral Cavity Cancer**

| | |
|---|---|
| Tx | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Tis | Carcinoma *in situ* |
| T1 | Tumor ≤2 cm in greatest dimension |
| T2 | Tumor >2 cm but not >4 cm in greatest dimension |
| T3 | Tumor >4 cm in greatest dimension |
| T4 (lip) | Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, skin of face (chin, nose) |
| T4a (oral cavity) | Tumor invades adjacent structures (cortical bone, deep [extrinsic] muscle of tongue, maxillary sinus, skin of face) |
| T4b | Tumor invades masticator space, pterygoid plates, or skull base, or encases internal carotid artery |

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to undergo extensive surgery, cooperate with rehabilitation, and withstand changes in safe and efficient swallowing must be considered. The expectations of the patient for postoperative quality of life (QOL) must also be considered, particularly pertaining to cosmesis, articulation, and the ability to eat a normal diet in social situations. When tumor factors prevent adequate oral intake prior to treatment resulting in weight loss and debility, placement of a gastrostomy tube may be indicated. Several weeks of hyperalimentation are required to reverse starvation and promote anabolic enzymes needed for wound healing. An evaluation of cardiovascular health is also required for any patient undergoing surgery, particularly in cases requiring a more complex reconstruction, such as free tissue transfer. In fact, severe peripheral vascular disease may preclude microvascular reconstruction because of a lack of suitable recipient vessels in the neck.

Age alone is not considered a contraindication to surgery; however, medical comorbidities are important predictive factors for postoperative complications and overall survival, at any age.[72] In addition, longer operative times and large fluid shifts have been shown to correlate with an increased incidence of postoperative complications in head and neck cancer patients.[73] Assessing the cardiovascular fitness of patients preoperatively is essential. A thorough preoperative dental evaluation is recommended for patients undergoing treatment for oral carcinoma. For the surgical patient, this may include consultation with a prosthodontist in preparation for management of a postsurgical defect. For those patients who may require radiation therapy, an assessment of dental status with needed extractions or restorations is highly recommended prior to the initiation of radiation in order to reduce the risk of osteoradionecrosis (ORN). Furthermore, pretreatment consultation with other members of the multidisciplinary team, including speech language pathologists, medical and radiation oncologists, and social workers help prepare the patient and the caregivers for the chosen management strategy.

Finally, an understanding of the patient's social history is relevant when choosing among treatment modalities, particularly in those advanced cases where multidisciplinary support is necessary. These patients benefit from extended support from family and friends, home health care assistance, transportation resources, and help with smoking and alcohol cessation. In an analysis of 213 patients diagnosed with head and neck cancer, Chan and others demonstrated that nearly half continued to smoke after diagnosis or during treatment.[74] As patients who continue to smoke are at increased risk for second primary tumors, following through with a smoking cessation program is of paramount importance.

## Management Strategies: Selection of Treatment of the Primary Lesion

Surgery is most often the treatment modality of choice for oral cancer. This is due to a number of factors. First, most oral cancers can be reached easily for excision using a transoral approach. Second, many oral excisions can be accomplished with satisfactory retention of function including speech and deglutition. Third, maxillodental bony structures interfere with transmission of ionizing radiation complicating the delivery of primary external beam radiation. Air–tissue interfaces within the mouth and involuntary mobility of the tongue and the soft palate further challenge the delivery of therapeutic radiation. Alternative radiotherapy techniques such as the incorporation of interstitial brachytherapy have been extensively evaluated in the oral cavity and recently summarized by the European Brachytherapy Group.[75] In the absence of any randomized evidence, population-based analyses such as the Patterns of Care Study can help to direct treatment. This study reported results of 434 patients with oral tongue and FOM carcinoma clinical stages III and IV after a minimum of 2-year follow-up. Wallner et al. demonstrated that of a 120 patients treated with radiotherapy, 86% experienced an in-field relapse.[76] In contrast, 58 similar-staged patients treated with surgery and radiotherapy demonstrated an in-field relapse rate of only 27%.[76] Minor salivary gland cancers and sarcomas similarly have limited response to nonsurgical treatment. Patients with significant comorbidity unable to withstand the surgical experience may be best treated with primary radiation with the addition of chemotherapy depending on tumor and patient factors.

We will discuss the management for each subsite separately.

***Lip.*** In lesions that involve less than one-third of the lip, simple excision with primary closure offers acceptable oncologic and reconstructive results. Full-thickness excisions with margins of 8 to 10 mm are necessary. Proper alignment of the vermilion border is critical ensuring cosmesis and function. For lesions larger than one-third, but less than two-thirds the length of the lip, reconstructive options including an Abbe-Estlander "lip-switch" flap or a Karapandzic flap may be utilized. More extensive local advancement flaps including Gillies fan flaps or Bernard-Burow flaps may be employed for lesions greater than two-thirds the length of the lip. However, due to increased risk of an unacceptable cosmetic result, microstomia, and oral incompetence when advancement flaps are used for large lesions, free tissue transfer is now often chosen for reconstructing large defects (Figs. 16-11 and 16-12). To ensure oral competence after the use of an adynamic soft tissue free flap to reconstruct the lower lip, adjunctive procedures such as a fascial sling, palmaris longus sling, or temporalis muscle sling may be necessary.[77,78]

Brachytherapy can also be used effectively for lip squamous and basal cell carcinomas with local control rates >90% reported for T1–2 lower lip using both low-dose rate (LDR) implants (typically 60–68 Gy)[79–82] and high-dose rate (HDR) implants (40.5–45 Gy in 8–10 twice-daily fractions).[83] One comparative analysis based on a change in institutional practices demonstrated no significant difference in local control rates or complications between LDR-treated (median 60 Gy at 0.7 Gy/hour) and HDR-treated (median 36 Gy in 4 Gy twice daily over 5 days) patients with lip SCC.[84] Similar high local control rates (>90%) for T1–2 lesions have been reported with external beam orthovoltage radiation (median 45 Gy in 10 daily fractions).[85] Thus,



**FIGURE 16-11.** Squamous cell carcinoma recurring in reconstructed left upper lip and oral commissure after Abbe Estrandler lip switch reconstruction was performed at the time of initial tumor resection.

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**FIGURE 16-12.** Reconstruction near total left upper lip resection involving the oral commissure and buccal mucosa using radial forearm free tissue transfer and microvascular anastomosis.

alternative techniques such as external orthovoltage and HDR brachytherapy techniques offer alternative treatment options for the medically unresectable patient or for lesions where functional preservation would be sacrificed by resection. Good to excellent cosmesis and function preservation has typically been reported after radiation with severe late complications (soft tissue and bone necrosis) found in <5% of patients. These risks are reduced with the fabrication of dental lead-lined appliances.[80]

The management of the neck in patients with lip cancer can often be expectant, as regional lymph node metastases occur in only 10% of patients. Elective neck dissection is warranted for higher grade, larger (T2 or greater and for thicker lesions >1 cm) and locally recurrent lesions.[80,85,86] Regional lymph node metastases adversely affect outcome and may decrease survival by 50%. The submental and submandibular nodal basins are the primary echelon drainage pathways. However, drainage may go to the intraparotid or jugular chain lymph nodes. In addition, whereas the upper lip has ipsilateral drainage to levels I to III, the lower lip has both ipsilateral and contralateral drainage to levels I to III.

***Buccal Mucosa.*** Surgical approaches for addressing buccal carcinoma vary with the size and location of the primary lesion. Small lesions may be excised with wide margins via a transoral approach. For less accessible, more extensive lesions, an open cheek-flap approach may be necessary. Later stage lesions may involve the mandible or maxilla, necessitating marginal/segmental mandibulectomy or partial maxillectomy. Reconstructive requirements depend on the extent of resection. For small lesions, primary closure or healing by second intention may be permissible. Rotation flaps of adjacent buccal mucosa may be used to help prevent trismus due to loss of flexibility of mucosal lining. Buccal fat can also be employed to fill in a mucosal defect while serving as a scaffold for reepitheliazation.[87] Larger, deeper defects may be addressed with regional flaps such as a temporalis muscle or temporoparietal fascial flap for bulk, with a mucosal skin graft. A pectoralis myocutaneous flap may be utilized in a similar fashion. Alternatively, a folded regional fasciocutaneous flap, such as a temporalis island flap may be used for both mucosal coverage and bulk.[88] Radial forearm free tissue transfer provides reliable, thin, pliable tissue for reconstruction of major buccal defects, especially those involving through-and-through tissue loss. For defects requiring composite resection with segmental mandibulectomy, free tissue transfer with an osteocutaneous flap is necessary. In situations where branches of the facial nerve are sacrificed with the resection, facial reanimation techniques may be employed.

Nonsurgical management options may also include interstitial LDR brachytherapy especially for lesions <5 cm and <1.5 cm for which excellent local control rates have been reported.[89,90] Tumors approaching or involving mucosa of the RMT or other surfaces adjacent to bone are contraindications for consideration of a brachytherapy implant. Lapeyre et al. described significant local control advantages of a looping LDR brachytherapy technique when compared to the use of parallel wire technique (5-year local control rate of 91% vs. 58%) The preferred technique loops one of the implanted ribbon of seeds posteriorly ensuring sufficient dose delivery to the posterior extent of the tumor.[90] The striking differences in local control rates speak to the insidious risk of tumor extension posteriorly in the buccal mucosa and extension into the masticator space.

The management of the neck in these patients is predicated on the dismal prognosis for patients with regional lymph node metastasis. In the MD Anderson experience published by Diaz and others, 5-year survival declined from 70% for N0 patients to 49% for N-positive necks.[91] Elective supraomohyoid neck dissection in N0 necks may be considered in these patients with plan to extend the area of dissection if clinical nodal disease is encountered during surgery. Finally, while primary radiotherapy may be considered for select patients who are not candidates for surgical resection, treatment is often unsuccessful with recurrence rates approaching 50%.[92]

***Floor of Mouth.*** Carcinomas of the FOM are centered anteriorly or laterally under the oral tongue. Early lesions involve the mucosa and may extend to underlying submucosal structures including sublingual salivary glands. These are amenable to simple excision to clear margins. Lesions may grow deep into the musculature of the FOM, including the genioglossus, the hyoglossus, and the mylohyoid and may involve the periostium alone or the substance of the mandible. More extensive lesions require a composite resection removing involved portions of the FOM musculature, the mandible, and the oral tongue. FOM tumors have a propensity to spawn early regional lymph node metastasis. In addition, perineural invasion through the inferior alveolar nerve may facilitate the spread of tumor to the skull base.

Surgical approaches to the FOM include transoral excisions for T1–2 lesions, with primary or split-thickness skin graft closure. The transoral approach can also encompass a superior marginal mandibulectomy (Fig. 16-13). Some surgeons advocate for

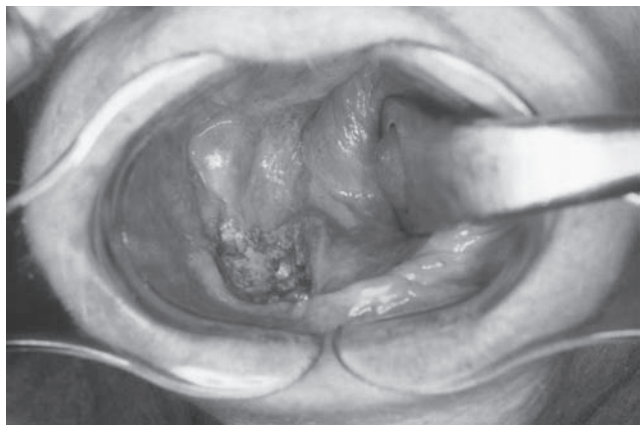


**FIGURE 16-13.** Ulcerated carcinoma of the floor of the mouth involving lower gum.

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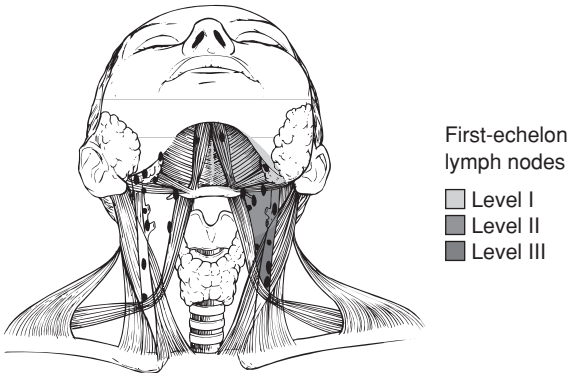



**FIGURE 16-14.** Mandibulotomy.

avoidance of the lip split, citing the ability to remove tumor and reconstruct even large defects through a transoral approach (in the absence of trismus).[93] However, in order to assure rigorous tumor resection to clear margins and facilitate accurate inset of reconstructive tissue, midline or paramedian mandibulotomy with mandibular swing provides excellent access to the FOM for more extensive lesions. We prefer to split the lip in midline and traverse around the chin pad using natural contours (Fig. 16-14). A recent study confirms a low rate of perception of disfigurement on the part of patients and associated problems with oral competency and lip sensation with the lip split approach.[94] Mandibulotomy may be fashioned to avoid injury to the mental nerve and its attachments to the lip. A step or V-shape cut provides enhanced stability for the repair with plates (Fig. 16-15). Invasive lesions require marginal mandibulectomy if there is only periosteal or superficial cortical bone involvement, or segmental mandibulectomy if there is bony invasion (Fig. 16-16).[95,96] Marginal mandibulectomy may be sagittal (inner table only), horizontal (upper portion only), or some combination. If the remaining bony bridge is thin, the placement of a reconstruction plate to reinforce it may prevent subsequent fracture. If mandibulectomy is anticipated, the mesial extent of planned resection should be

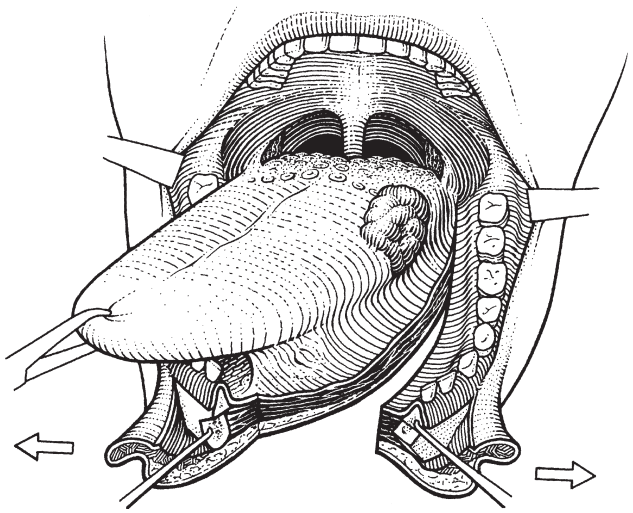


**FIGURE 16-15.** Mandibulotomy.

*Source:* From Shah JP. *Head and Neck Surgery.* 2nd ed. London, England: Mosby-Wolfe; 1996, with permission.



**FIGURE 16-16.** Segmental mandibulectomy.

*Source:* From Shah JP. *Head and Neck Surgery.* 2nd ed. London, England: Mosby-Wolfe; 1996, with permission.

the location of the entry osteotomy so as to preserve as much healthy native bone as oncologically possible. The reconstructive options for FOM defects range from split-thickness skin graft with a bolster for small lesions, to regional pedicled flaps and free tissue transfer for larger defects with soft tissue or bony defects. Regardless of the reconstructive option, obtaining a watertight seal is critical in preventing a postoperative fistula, which can lead to wound break down, as well as hardware and great vessel exposure. Recent advances in free tissue transfer include the use of two flaps simultaneously (fibula and radial forearm) for large through-and-through defects[97] and anterolateral thigh flaps particularly when more bulk is desired.[98]

For the medically unresectable FOM carcinoma, nonsurgical management with radiotherapy is an option. Institutional series have demonstrated high local control rates with the historic use of an intraoral cone technique[99] as well as interstitial brachytherapy implants for early T1–2 lesions. Implants are typically combined with external beam radiotherapy (EBRT) with long-term local control rates >80% reported.[100–103] However, an interstitial implant alone may also be used for the management of early T1–2 N0 FOM carcinomas managing the neck either with observation or neck dissection.

Reported experience suggests that when an implant is combined with EBRT, higher local control rates are observed when a significant proportion of the dose is delivered through the implant. In the Patterns of Care Study reported by Wallner et al., 41% of 73 clinical stages I and II patients treated with EBRT alone experienced an in-field relapse.[76] In contrast, 102 similar-staged patients treated with EBRT and an implant had only a 26% in-field relapse.[76] The superior local control rates when a greater proportion of dose is delivered through a brachytherapy implant has been attributed to reducing the overall treatment time possibly due to the unfavorable impact of tumor repopulation that may occur to a greater extent with fractionated EBRT.[101] For the intraoral cone technique, treatment time was also reduced using a hypofractionated schedule (typically 21–24 Gy in 3 Gy fractions). This schedule was found to be safe due to direct

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delivery of radiation to the tumor mass and the use of electrons thereby limiting the volume exposed to the larger fraction size. The use of a brachytherapy implants for the FOM (as compared to the oral tongue) appears to increase the risk of tissue necrosis, especially ORN due to the proximity of the tumor to the mandible.[103]

Management of the neck in patients with FOM cancer is critically important because of the frequency of regional lymph node metastasis at diagnosis. McGuirt and others documented a 23% rate of occult disease of 129 patients with FOM cancer over a 20-year period.[13]

***Retromolar Trigone.*** In a report from the 1980s, radiation and surgery were reported to be equivalent in the locoregional control and disease-free survival of RMT lesions.[104] A more recent retrospective report suggests the optimal management of cancer of the RMT is surgery with neoadjuvant or adjuvant radiotherapy rather than radiation alone.[105] As with other early lesions of the oral cavity, small lesions of the RMT may be addressed surgically via a transoral approach. More extensive lesions may require lateral, paramedian, or median mandibulotomy with or without marginal mandibulectomy or segmental mandibulectomy. Although marginal mandibulectomy is sufficient in selected patients with only periosteal involvement, it is generally contraindicated in patients who have been previously radiated in part because of the observation that in radiated bone, bony involvement occurs in a multifocal pattern along the cortex of the mandible, whereas in nonradiated bone, bony involvement occurs through the occlusal surface in a more focal, direct pattern.[106]

Reconstruction options for addressing RMT primary defects are numerous, including split-thickness skin grafts, local and regional flaps, as well as free tissue transfer with or without vascularized bone. Decisions regarding the particular method of reconstruction are based on the size of the defect, deficit of mandible and/or maxilla, the desirability of dental rehabilitation, and surgeon preference. The inner surface of the mandible presents a reconstructive challenge because of the thin native mucosa immediately overlying cortical bone with any remaining teeth further complicating work in the region. Bone exposure particularly in the setting of previous or future radiation puts the patient at risk for subsequent ORN.

***Oral Tongue.*** The generally accepted primary management of oral tongue carcinomas is upfront surgery. Surgical management of oral tongue carcinoma can range from local excision with margin control for T1 to a partial glossectomy for T2 lesions to a subtotal or total glossectomy for more advanced disease. Early-stage lesions are often successfully resected transorally. Median or paramedian mandibulotomy may be necessary to adequately remove later stage lesions, particularly if the FOM is involved. Large lesions limited to the tongue may be approached transcervically by detaching the tongue from the FOM and pulling it into the cervical wound, leaving the mandible intact. This approach has the advantage of reducing torque injury to the temporomandibular joint, but makes exposure for resection and closure more cumbersome. Placement of a suture for retraction of the tongue may be helpful during resection, but care must be taken not to distort the tissues to obscure palpation of deep extension during the resection. Anticipation of the location of the lingual artery with proactive management during transection of surrounding muscle may limit hemorrhage.

As with tumors in other subsites of the oral cavity, a preoperative assessment of bony involvement is critical. Criteria for performing marginal mandibulectomy or segmental mandibulectomy are the same as for other subsites of the oral cavity. Primary closure, healing by secondary intention, or closure with split-thickness skin grafts are adequate for early-stage tumors, whereas hemi- or total glossectomy defects may be best managed with free tissue transfer or regional pedicled flaps.

Early tongue carcinomas have also been treated with radiotherapy (especially with LDR brachytherapy) alone in hopes of preserving function through tissue preservation (Fig. 16-17).[76,102,103,107–112] Typically, local control rates of 85% or greater may be expected. Local control rates with brachytherapy decreased with larger T-stage disease[113] or tumor size. Suboptimal local control rates with EBRT stood in contrast to the high local control rates observed with brachytherapy implants that appeared comparable to those achieved surgically. A dose of 65 to 70 Gy at a rate of 0.3 to 0.5 Gy/hour has been recommended.[103] Alternative HDR brachytherapy schedules have been evaluated and compared to LDR schedules with (59 Gy in 6 Gy twice daily vs. 61 Gy over 5–6 days). Inferior local-control rates were observed favoring LDR schedules (T1: 85% vs. 64%; T2: 71% vs. 38%).[114] At this time, the HDR schedule for oral tongue carcinomas cannot be recommended.

As reconstructive techniques advanced, many advocated for upfront surgical resection especially for larger T-stage disease where the local control and complication rates for brachytherapy were less than ideal.[115] Nevertheless, this body of experience is important as a brachytherapy implant remains a viable consideration for the medically unresectable T1–2 tongue carcinoma patient.

Management of the neck for patients with squamous cell carcinoma of the oral tongue has generated much discussion. The neck in patients with early-stage lesions with a thickness of <2 mm can be managed expectantly. There is evidence to suggest that a supraomohyoid neck dissection of levels I to III may be insufficient in treating the N0 neck for larger tongue primaries. Byers and others demonstrated that patients may develop "skip metastases," whereby level IV may be the only involved level, or level III may be involved with no disease present in level I or II.[116] Considering these data, a selective dissection of levels I to IV may be appropriate in these patients. Finally, as primary oral tongue carcinomas close to or involving the midline have an increased risk of bilateral regional lymph node metastasis, staging neck dissections in these circumstances should address the bilateral nodal basins.

***Carcinoma of the Palate.*** Primary surgery is typically selected for most carcinomas of the hard palate. For early-stage lesions, wide local excision with 1 to 2 cm margins is sufficient, whereas larger

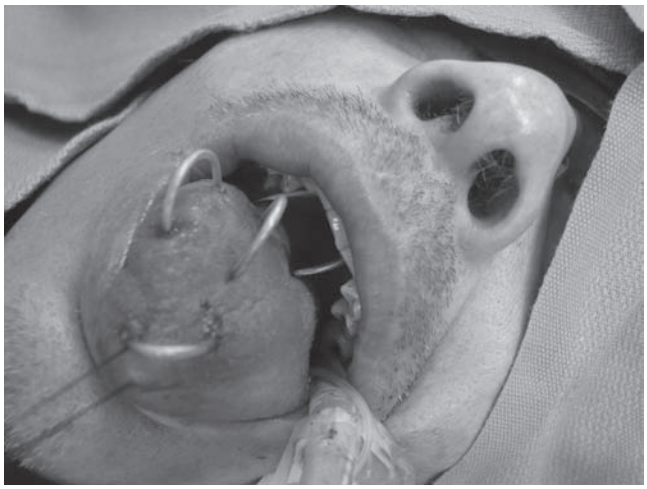


**FIGURE 16-17.** Brachytherapy catheters placed in oral tongue tumor.

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lesions often require partial or total maxillectomy with resulting through-and-through defect into the nasomaxillary cavities.

The dental prosthodontist and speech and language pathologist are essential members of the pre- and postoperative multidisciplinary team. Preoperative obturator construction can help to ensure early speech and swallowing rehabilitation. The creation of a more definitive prosthesis may be delayed until the completion of therapy, which may include adjuvant radiotherapy. Free tissue transfer has an expanding role in the reconstruction of hard-palate defects, particularly for large defects after a total maxillectomy with or without orbital exenteration for more advanced disease. Management of the N0 neck is typically expectant because of the low rate (~10%) of occult regional lymph node metastasis.

***Carcinoma of the Alveolus.*** Carcinoma of the mandibular alveolus is treated similarly to carcinoma of the RMT and FOM. These lesions often present with early mandibular involvement necessitating marginal or segmental mandibulectomy. Likewise, carcinoma of the maxillary alveolus is treated similarly to carcinoma of the hard palate. Advanced lesions may invade adjacent structures, including the nasal cavity, the paranasal sinuses, the orbit, and the skull base. Ablative surgery often results in large maxillofacial defects, necessitating complex reconstructive techniques.

Patients with alveolar lesions have a significant risk of cervical regional metastatic disease. Simentel and others, in a review of 26 patients with squamous cell carcinoma of the maxillary alveolus and hard palate over a 25-year period, found an overall incidence of cervical metastasis of 35%, with 5-year disease specific survival of 59%.[117] Lesions of the mandibular alveolus also have a significant risk for regional neck metastasis. In their review of 155 patients with carcinoma of the mandibular alveolus over a 20-year period, Eicher and others found that those patients with primary tumors that overlie the mandibular symphis, those with moderately or poorly differentiated tumors and those with those tumors having radiographic or histologic evidence of mandibular invasion are at significant risk of harboring regional metastases.[118] Treatment of the cervical lymphatics should be considered in these cases. As lesions of the maxillary alveolus drain preferentially to the jugulodigastric nodal basin, and lesions of the mandibular alveolus drain preferentially to the submandibular nodal basin, adjusted selective neck dissection may be appropriate in the elective treatment of the neck.

***Postoperative (Adjuvant) Management of Oral Carcinoma.*** Postoperative management of high-risk oral carcinoma may involve external beam radiation, interstitial brachytherapy implants, and chemoradiotherapy.[119–121] The rationale of brachytherapy implants is to irradiate the primary surgical bed only, thus reducing acute and late normal tissue toxicities. The most common indication is the presence of a close or positive surgical margin in the absence of perineural or lymphovascular invasion (LVI) in the primary site and where the neck has been found to be pathologically N0. Lapeyre et al. demonstrated that with a minimum follow-up of 36 months (mean 80 months), the 2-year actuarial local control rate using this combined strategy was 88.5%.[122] When combined with postoperative EBRT, local control rates do not appear to be compromised when the proportion of dose delivered by the implant is limited (mean EBRT 48 + 24 Gy by implant).[123]

Significant progress has been made in the development of risk-based adjuvant external postoperative radiotherapy (PORT) for oral cavity carcinomas with several randomized trials completed in the past 30 years.[124–128] The majority of patients enrolled in these randomized trials were patients with oral cavity carcinomas.[124,125] Aspects of postoperative dose,[125,128] the influence of the overall treatment time and tumor repopulation,[124] and the role of concurrent chemotherapy[126,127] have been evaluated.

The definition of a pathologic high-risk group remains a subject of much debate. There is little question that patients with (gross) extracapsular extension (ECE) and positive surgical margins constitute a high-risk population.[129] The series of randomized trials at the MD Anderson Cancer Center (MDACC) incorporated a risk definition for the endpoint of local-regional control that investigated the presence of multiple pathologic risk factors in the primary site or in the neck including perineural invasion, LVI, and the location and presence of multiple nodes in the absence of ECE. Peters et al. demonstrated that the presence of increasing number of risk factors was associated with an increasing risk of local-regional relapse. In fact, patients with four or more pathologic risk features without ECE were at a comparable risk of local-regional relapse as patients with ECE. While this empiric scoring system was demonstrated to be clinically valid, it is unable to guide a determination of whether the relapse risk is at the primary site or in the neck. For example, for a patient with N2 disease in levels II and III with perineural invasion, it is unclear if the primary site or the nodal levels are individually at a high risk for relapse. Whether they should be individually be boosted to 63 Gy (high-risk dose recommendation) as was done by Peters et al.[125] or if these anatomic sites can be treated to a minimum dose of 57.6 Gy is uncertain. This becomes a relevant consideration in the modern era of conformal radiotherapy techniques where the volume of tissues in the neck can be independently dosed.

A prospective trial reported by Ang et al. demonstrated a 5-year actuarial local-regional control rate of 90% without adjuvant therapy in the absence of pathologic risk factors (clear margins, no perineural invasion, no extranodal extension).[124] An intermediate risk group (defined by the presence of one adverse pathologic risk factor other than ECE) received PORT and had a comparable local-regional control rate to the low-risk group indirectly supporting the efficacy of adjuvant PORT.

When adverse pathologic factors predict for an increased risk of relapse, the surgical bed requires treatment with a minimum of 57.6 Gy with areas at higher risk requiring dose escalation to at least 63 Gy. Delivering doses <54 Gy to the surgical bed is associated with an increased risk of local relapse.[125] Doses >63 Gy did not further improve local-regional control rates possibly due to the adverse effects of tumor repopulation. This appears to be a particularly relevant issue in patients found to have pathologic high-risk factors for recurrence.[124] Peters et al. demonstrated an increased risk of neck relapse for patients with ECE when treated with only 57.6 versus 63 Gy (2-year actuarial neck control rates: 52% vs. 74%, respectively, $p < 0.03$).[125] Several retrospective reviews have demonstrated a reduced local relapse rate for higher total doses delivered to the site of close or positive margin disease.[130–132] In these institutional reviews, a minimum dose of 65 Gy was recommended. Thus, both the optimal radiotherapy dose to areas at higher risk for relapse and how a positive surgical margin[133] should be defined remain subjects of debate.

In the PORT study reported by Peters et al. multivariate analysis demonstrated that there was a trend for an increased risk of local-regional relapse with N2b nodal disease ($p = 0.08$).[125] Patients with N2b disease may have received a range of dose from 57.6 to 68.4 Gy raising the question of the optimal dose in this circumstance. At a minimum, 57.6 Gy in 1.8 Gy/fraction is currently recommended. However, N2b disease represents a heterogeneous cohort of patients with variable relapse risk. Within this cohort, several potential high-risk N2b disease subgroups may exist that may benefit from a higher total dose (yet to be established). For example, the presence of large number of positive nodes or the presence of nodal disease in the level IV or V region of the cervical neck may represent potential high-risk N2b disease.[127]

In the trials reported by Peters et al. and Ang et al. the prognostic influence of LVI and its implications on the radiotherapy

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dose was not evaluated. Although LVI has been correlated with local-regional relapse for oral tongue carcinoma,[134–135] its prognostic influence has not been consistently supported. In part, this may be related to the methodology used to assess LVI.[136,137] Its prognostic influence may also lose significance in multivariate models incorporating the nodal status. This has been observed in uterine cervical squamous carcinomas.[138] In a large retrospective report where all patients received a minimum of 60 Gy, LVI did not have significance on multivariate analysis.[131] Further complicating the discussion are questions of how the radiotherapy target volume should be modified by the presence of LVI if one postulates that it does have an independent effect on the risk of local relapse. Some have argued that the presence of LVI necessitates irradiation of the entire operative bed due to the potential for carcinoma cells in the intervening lymphatics between the operative bed and the adjacent nodal regions.

The recommended postoperative radiation dose range impacts not only cancer control but also side effects. Ang et al. demonstrated that with a median follow-up of 59 months, the risk of grade 3 to 4 dysphagia increased in patients receiving 63 Gy (13%–16%) compared to those receiving 57.6 Gy (4%).[124] As all patients were treated with nonconformal radiotherapy to both sides of the neck, these dose-risk levels may be ascribed to the irradiation of a large volume of the pharyngeal musculature and are consistent with other reports suggesting a possible dose threshold of 50 to 60 Gy for injury to the pharyngeal constrictor muscles and supraglottic larynx.[139]

*Post-operative Chemoradiation.* In recent years, the postoperative management of the oral carcinoma patient has been significantly influenced by the results of two large phase III randomized trials that compared PORT alone versus PORT with concurrent cisplatin.[126,127] Although oral cavity cases comprised only 24% to 30% of the patients enrolled in these two studies, the results have had a significant impact on routine practice due to the absence of any phase III studies addressing this issue specific to oral cavity carcinomas. Cooper et al. enrolled 459 patients with high-risk features including histological evidence of invasion of two or more regional lymph nodes, ECE, and microscopically involved mucosal surgical margins. The patients treated with concurrent cisplatin and radiation had improved local-regional control rates (HR = 0.61; 95% CI, 0.41–0.91; $p$ = 0.01) and disease-free survival rates (HR = 0.78; 95% CI, 0.61–0.99; $p$ = 0.04) compared to the radiation-alone arm. However, there was no difference in overall survival (HR = 0.84; 95% CI, 0.65–1.09; $p$ = 0.19).

The study by Bernier et al. enrolled 334 patients with the high-risk features defined as pT3 or pT4 (except pT3 N0 of the larynx), pT1/2 with N2/3 disease, ECE, positive resection margins, perineural involvement, or vascular tumor embolism.[127] In addition, involvement of level IV or V lymph nodes in oral cavity or oropharynx tumors were also defined as a high-risk factors. High-risk patients received either radiation alone or radiation with cisplatin. The results demonstrated that both progression-free survival (HR = 0.75; 95% CI, 0.56–0.99; $p$ = 0.04) and overall survival rates (HR = 0.70; 95% CI, 0.52–0.95; $p$ = 0.02) were higher in the cisplatin and radiation arm compared to the radiation-alone arm.

When these two studies were combined in a summary analysis, only patients with ECE and positive margins had clear benefit from the addition of cisplatin.[140] Based on these data, patients with oral cavity cancers are currently treated with postoperative cisplatin and radiation when these pathological features are present. Whether or not patients with close surgical margins, however defined, should receive concurrent cisplatin remains a subject of controversy. Further straining the general application of the study findings is the question of the effect of microscopic ECE.[141] Recently, Ghadjar et al. reported the results of a retrospective analysis of 74 head and neck carcinomas (27% of the oral cavity site) evaluating the adverse prognostic influence of microscopic ECE controlling for nodal size.[142] For several endpoints including regional relapse-free survival, distant metastases-free survival and overall survival, the presence of at least one node <7 mm in diameter with microscopic ECE was significantly associated with an adverse outcome. Moreover, when prognostic significance of the number of nodes with microscopic ECE <7 mm in size was considered, increasing number of lymph nodes (i.e., 2 or more compared to one compared to no lymph nodes) was also associated with adverse outcomes for all of the endpoints noted above. Thus, these findings would suggest that at least for the small lymph node showing microscopic ECE, tumor biology rather than physical size of the lymph node may be most relevant and should still warrant consideration of high-risk designation and the administration of concurrent cisplatin. It has also been suggested that the relationship between the extent of ECE and the lymph node size that has been well described in head and neck carcinomas in general may not be valid for oral cavity carcinomas.[143,144] Radiotherapy target volumes need to be as generous as possible in regions of oral cavity carcinomas with nodal ECE for appropriate target coverage. The treatment algorithm (Fig. 16-18) summarizes the options for overall management of oral cancer.

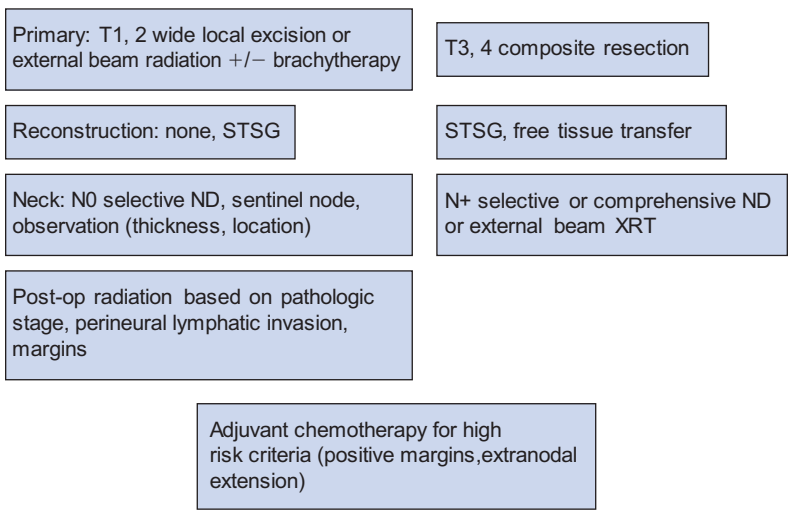



**FIGURE 16-18.** Algorithm for the treatment of cancer of the oral cavity. ND, neck dissection; STSG, split-thickness skin graft; XRT, x-ray therapy.

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## Alternative Treatment Modalities for Oral Cancer

***Photodynamic Therapy.*** Photodynamic therapy (PDT) involves the administration of photosensitizers (PS) that may be preferentially concentrated in both tumor cells and in the extratumoral compartment especially the tumor vasculature. Photoactivation occurs with exposure to wavelength-specific light typically administered with laser light generating localized oxidative stress (typically singlet oxygen). For many of the PS that have been evaluated clinically, this process is oxygen dependent. The depth of clinical activity for the PS activation is typically limited to several millimeters although the application of brachytherapy techniques to administer an interstitial PDT implants offer treatment of larger tumor volumes.

In the oral cavity, PDT for both premalignant dysplasia and for invasive carcinomas has been evaluated. The main attraction with PDT as a therapeutic modality is the ability to offer wide-field superficial mucosal ablative therapy given the challenges that often exist in defining the peripheral extent of lesions in the oral cavity. Although effectiveness for dysplasia has been reported based on complete response rates >80% for various PSs, long-term control rates are a significant limitation.[145] Similarly, the ability for PDT and many other therapeutic modalities to influence the risk of malignant transformation remains to be established.

PDT has also been used for oral cancer. A series of 38 patients with oral lesions of the tongue, the FOM, and the buccal regions, stage T1/T2 N0 was treated. PDT was repeated after a 6- to 7-month period after initial treatment if necessary. The majority of subjects (26/38) had a complete response with a 5-year survival of 84.2%. The authors contend that the morbidity of PDT treatment is less than that of surgery, radiation, and chemoradiotherapy.[146] In another European report, 170 patients treated with PDT were reported to show an overall response rate of 90.7% with a complete response rate of 70.8%.[147]

Chemoradiation as primary therapy for oral cancer. In the past 30 years, nonsurgical management of head and neck cancer has been developed seeking functional preservation, particularly in the oropharynx and larynx. Randomized chemoradiation trials were spawned by the suboptimal results observed with EBRT alone including in the management of oral tongue carcinomas. Although surgical management has been successful for local control, surgical resection for more advanced T-stage disease begins to raise issues of loss of function in the patient.

The question of whether concurrent chemoradiation or induction chemotherapy may have a role in the management of resectable oral cavity carcinomas remains largely unexplored. Several institutions have published their experience investigating concurrent chemoradiation demonstrating that this approach may have efficacy.

Investigators at the University of Chicago have recently reported their experience in treating advanced oral cavity tumors with nonsurgical primary strategies involving chemotherapy and radiation in a manner analogous to organ preservation practiced commonly for oropharyngeal and laryngeal lesions. They report results of 21 patients with tumors of the tongue, the FOM, the RMT, and the palate, stages III and IV. Treatment involved various regimens, most commonly combination chemotherapy involving 5-fluorouracil (5FU), hydroxyurea, and twice-daily radiation using intensity-modulated methodology. Two-year disease-free survival was 90%, and 5-year disease free survival was 71% with three cases of ORN. The authors conclude that this chemoradiotherapy approach is promising with acceptable toxicity.[148] The same group led a four institution phase II study involving 39 patients with T4 oral cavity tumors treated with primary chemoradiotherapy. The 5-year progression-free survival was 51% with 69% of those with bone involvement demonstrating no relapse, although there were seven cases of ORN.[149] A report of experience with intra-arterial platinum-based chemoradiotherapy in Japan showed a 51% 3-year local control rate of 68.6% for early lesions and 53.9% for more advanced lesions.[150]

For patients with locally advanced unresectable oral cavity cancer, sequential induction chemotherapy followed by concurrent chemoradiation may have a role. Again, current induction chemotherapy data are not specific to oral cavity cancer comprising only ~15% to 20% of the study populations; however, it is a valid option for selected patients with good performance status. Currently, the most utilized regimen is a three-drug combination of cisplatin, docetaxel, and 5FU (TPF) followed by concurrent carboplatin and radiation.[151] Determination of the most appropriate patient population and identification of the optimal regimen for the induction chemotherapy are still under debate.

# OUTCOMES AND RESULTS

## Quality of Life

QOL considerations for oral cancer survivors are important in deciding among treatment modalities. In recent years, QOL research has matured with the development of assessment tools that have been validated in research studies. The University of Washington Quality of Life Scale (UW-QOL) remains the most commonly used QOL assessment.[152] This tool is a questionnaire, covering topics such as pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder problems, taste, saliva, mood, anxiety, and "global" QOL. Other validated questionnaires, including the EORTC QLQ-H&N 35 and FACT-HNS, use similar methods.[153,154]

Chandu and others reviewed the literature regarding factors affecting QOL in oral cancer patients, including age, gender, site of tumor in the oral cavity, tumor size and stage, marital status, and income.[155] They found that older patients consistently reported better QOL scores than did younger patients. Whereas male patients were found to have more problems with mental illness, alcoholism, and malnutrition,[156] female patients have worse pretreatment QOL scores and greater functional posttreatment impairments.[157] With regard to oral cavity subsites and tumor characteristics, patients with more posterior tumors have worse QOL scores, whereas increasing size and stage are found to correlate with worse QOL scores. Finally, the social history of the patient is particularly relevant in QOL assessments. de Graeff and others found marital status to be independently associated with locoregional control and disease-free survival in patients with head and neck cancer, with unmarried patients at significantly increased risk. They also found family income to have no association with the outcome.[158]

Outcomes analyses of treatment modalities provide useful information in pretreatment planning as well. More extensive surgical resections and reconstructions are typically associated with poorer QOL scores. Long-term percutaneous endoscopic gastrostomy (PEG) tube dependence is associated with poorer QOL scores, adversely affecting family life, intimate relationships, social activities, and hobbies.[159] Finally, adjuvant radiotherapy has been found to adversely affect QOL scores in those patients who receive upfront surgery.[160]

## Results of Treatment

Locoregional disease control and survival for oral cancer varies with tumor site and stage, as well as patient comorbidity. In general, patients with stage I disease have approximately an 80% likelihood of successful treatment whereas those with stage IV tumors have less than a 40% 5-year disease-free survival.[161,3]

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Specific information regarding outcome for various tumor sites and stages are the substance of many published reports and are beyond the scope of this chapter. A few examples follow.

In the largest published series of previously untreated patients with SCC of the buccal mucosa in North America or Europe, Diaz and others found patients with T1, T2, T3, and T4 disease to have a 5-year survival of 78%, 66%, 62%, and 50%, respectively.[91] Other series demonstrate similar survival for patients with advanced-stage disease managed with surgery and adjuvant radiation. In their series of 57 patients treated with surgery and adjuvant radiation, Fang and others demonstrated a 3-year overall survival of 64%.[162] In these patients managed with combined therapy, however, surgical salvage for patients with locoregional recurrence is less successful than is primary treatment. The Oregon Health and Science University has reported that salvage surgery does increase survival after oral cancer recurrence, whereas radiation and chemotherapy did not show a benefit for recurrent disease treatment.[163]

Obtaining local control in patients with FOM cancer is often challenging. In a review of 280 patients with FOM cancer over a 24-year period, Sessions and others demonstrated that recurrence at the primary site (41%) was the most common cause of treatment failure. Their series included patients treated with a variety of modalities, including local resection alone, composite resection with neck dissection, radiation therapy alone, local resection with radiation, and composite resection with radiation. For all patients, the overall disease-free survival was 56%, with death due to tumor in 44%. The most important prognostic factors in their series included clear margins on resection, early tumor stage, and a lack of regional lymph node metastasis. The rate of second primary lesions in this series was 20%, emphasizing the importance of staging endoscopy and/or PET-CT in the management of patients with FOM cancer.[164] Furthermore, microscopic cut-through of tumor on the first resection attempt (positive first frozen section) has been shown to portend poorer outcome even if subsequent resection clears the margin.[165] This finding suggests that a more insidious growth pattern that cannot be accurately discerned by physical findings (visual and palpable) at the time of resection is indicative of a generally aggressive tumor phenotype.

# COMPLICATIONS

## Surgical Complications

Immediate surgical complications of oral cancer resection include infection, hemorrhage, aspiration, and cardiovascular events. Later, wound breakdown, flap loss, and fistula may occur. The oral phase of deglutition is often adversely affected by surgery of the oral tongue and/or the FOM. Scarring of the residual tongue to the FOM or the mandibular alveolus limits its excursion, making formation and transfer of the food bolus difficult. Particulate foods such as rice are most troublesome. Lack of tongue sensation due to lingual nerve damage further compromises the ability of patients to accurately find food particles within the oral sulcus. Weakness of tongue motion may also occur with damage or loss of one or both hypoglossal nerves. Loss of teeth and lip function can contribute to oral motor problems by reducing oral competence with accompanying drooling. Split-thickness skin graft or free tissue transfer of thin, pliable skin (radial forearm) are designed to help prevent ankylosis of the residual tongue.

## Complications of Radiation

Immediate complications of radiation with or without chemotherapy include mucositis and subsequent fungal superinfection with dysphagia and odynophagia. Acute or early complications of radiation therapy include those which occur within the first few weeks of a standard course of therapy and persist for some weeks or months after the completion of treatment. As the effects of external beam radiation therapy are cumulative, many patients may not begin to experience any significant side effects of therapy until threshold doses for normal tissue damage are reached during the treatment course. These side effects include changes to skin and soft tissue; mucosal changes; alteration in quality, quantity, and consistency of saliva; and changes in taste. Late complications of radiation therapy are those that occur months to years after the completion of therapy and tend to be chronic in nature. Some late effects of radiation therapy are the result of persistence or progression of some of the acute complications of treatment. These complications include permanent xerostomia, dental caries and deterioration, skin and soft tissue fibrosis, damage to bone, tongue mobility, and oral excursion adversely affecting eating, swallowing, oral hygiene, and articulation.

Xerostomia, or dry mouth, underlies many of these conditions. Damage to minor and major salivary glands by therapeutic doses of radiation is the primary cause of xerostomia. Surgical ligation of ducts or removal of major salivary glands may also contribute to the condition. The advent of highly conformal radiation delivery utilizing intensity-modulated radiation therapy (IMRT) can spare salivary function in major glands that can be excluded from the field.[166] Brachytherapy can deliver high-dose radiation to local tissues with minimal impact on surrounding salivary glands. Use of brachytherapy in combination with external beam radiation therapy to complete the dose to the primary site may help reduce xerostomia.

The effects of xerostomia are several. Dry mouth is uncomfortable, one of the major complaints of oral cancer patients, adversely affecting QOL. Patients complain of disrupted sleep, often awakening to drink water to reduce the discomfort. Lack of saliva also has a negative impact on eating, as saliva is required for the first phases of digestion and the production of a soft, lubricated, and cohesive bolus for transport through the mouth and pharynx. Furthermore, saliva is important for dental health, and its absence contributes to the likelihood of enamel loss and eventual dental deterioration. Treatment of xerostomia is often inadequate to reverse all of these problems. There are a variety of proprietary products available without prescription intended to provide relief of dry mouth. In the authors' experience, none of these is widely endorsed by affected patients. Two alpha-adrenergic agonists are available as prescription drugs (Salagen and Evoxac). These medications stimulate residual salivary glands to produce saliva. The side effects of both are unacceptable to some patients, chief among these is diffuse sweating. Some patients find the sweating to be transient and the benefit of increased saliva helpful enough to endure this inconvenience. The alpha adrenergics cannot be used in patients with rapid heart arrhythmias or glaucoma. Amifostine, tested for use during radiation to spare salivary function, has not gained widespread use due to being limited by substantial side effects.[167]

Associated with lack of saliva is loss of taste (hypogeusia) resulting from radiation therapy. This condition is most difficult during radiation and in the first months that follow. Some patients then regain all taste, but most continue to find that many foods no longer have the same appeal as before treatment. Lack of taste, together with mucositis which accompanies radiation and chemotherapy, accounts for substantial weight loss in many patients undergoing treatment for advanced oral cancer.

Skin changes as a result of radiation therapy usually begin to manifest as early as the second or third week of the treatment course and include a stepwise progression from mild erythema to moist desquamation. Radiation induced dermatitis has been somewhat minimized in the contemporary era with the broad implementation of megavoltage (mV) linear accelerators over

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older lower energy treatment units. Megavoltage radiation offers the advantage of skin sparing by depositing dose below the skin surface. In contrast, lower energy radiation sources deposit significantly higher dose at the skin surface in order to achieve the desired dose to the target lesion. The advent of intensity-modulated radiation therapy–based treatment delivery, however, may undermine the skin-sparing effect of mV radiation sources because intensity-modulated radiation therapy employs dose delivery by hundreds of tangential beamlets which serve to increase the overall dose deposition to skin.[168] Early dermatitis can be managed with various water-based topical preparations which serve to hydrate the skin. Hydrogel dressings in combination with water-based emoillents and topical antibiotics are used in the management of higher grades of dermatitis.

Trismus, or inability to open the mouth, occurs in many oral cancer patients. The pterygoid muscles located lateral to the soft palate and the tonsil folds are the jaw-opening muscles. Surgical or radiation-induced scarring causes irreversible stiffness. Another cause of trismus is soft tissue scarring of the oral commissures and buccal mucosa. Physical therapy is of some variable help to reverse or prevent trismus. Commercial devices such as Therabite and Dynasplint are available as adjunctive tools for physical therapy (PT) treatment of trismus. Inability to open the mouth limits the types of food that can be ingested, as well as access to the mouth for dental hygiene and care and surveillance for recurrent cancer.

Dental complications of oral cancer treatment have already been mentioned as a result of lack of saliva. Loss of tongue function can also adversely affect dental function in that the tongue pressure on teeth helps maintain their position. After total glossectomy, an inward displacement of mandibular teeth is commonly seen. Direct impact by radiation to dental tissue and supportive bone further compromises dental health. Small vessel damage caused by radiation results in a loss of resistance of these tissues to infection and other stress.

Small vessel damage in bone is also the prevailing explanation for the phenomenon of ORN, which can complicate oral cancer treatment. Damage to the blood supply of the mandible and supportive mucosa by surgery and radiation results in risk of bone exposure, infection, necrosis, and eventual pathologic fracture. The best treatment of ORN is prevention. Maintenance of some saliva production is helpful. Meticulous attention to dental care and hygiene before and during radiation is key. Teeth that are tenuous before beginning radiation should be removed. Enhanced fluoride treatment is also useful. Minor ORN may be managed by debridement with removal of devitalized bone, together with good oral hygiene. More substantial ORN is often treated with hyperbaric oxygen (HBO) although the ability of hyperbaric oxygen to reverse full-fledged ORN is doubtful.[169] Hyperbaric oxygen is often used in combination with more aggressive surgical debridement. Full-fledged ORN with pathologic fracture may require resection of mandible with extensive reconstruction with vascularized bone such as with a fibular microvascular free flap.[170]

In addition to the risk of ORN, there are other problems with the mandible that can occur after oral cancer surgery, particularly when mandibulotomy is required for access to the oral cavity. Repair of the osteotomy site with internal fixation plates is typically required, and there can be problems with screw loosening either because of cortical bone resorption over time or improperly placed hardware. Infection and exposure of the plate follow. Modern design of low-profile plates with locking-head screws reduces the risk of plate-related complications in the authors' experience. A stair-step osteotomy helps with mandibular stability and may also help prevent complications.[171]

As in late damage to bone, changes in microvasculature from surgery and radiation therapy also contribute to skin and soft tissue fibrosis. Such changes may be more pronounced in patients with underlying vasculopathy.[172] Edema, secondary to lymph node dissection, also plays a role in mediating the development of fibrosis in the postoperative neck. Limited data on the use of adjuvant pentoxifylline and tocopherol have shown promise in the treatment of radiation-induced fibrosis.[173,174] The major complication risks associated with brachytherapy implants is an increased risk of soft tissue necrosis (STN) especially with the implantation of larger T stages and the risk of ORN (grade 3: ~5%)[109,175] especially for tongue implants placed juxtaposed to the mandible without the fabrication of a dental spacer.[176] Other brachytherapy-related risk factors for soft tissue necrosis or ORN identified on multivariate analysis include the total dose prescribed (>80 Gy) and the dose rate (>0.7 Gy/hour).[177]

All of the conditions that affect oral feeding also impact articulation. Although even hemiglossectomy patients can speak with sufficient clarity for most daily needs, most patients undergoing treatment of cancer of the oral cavity notice at least some articulatory sequelae. The assistance of a speech-language pathologist can ameliorate these problems. Patients are encouraged to slow the rate of speaking, overemphasize the production of some sounds, and substitute others with compensatory movements. Oral prosthedontists can assist some individuals through the fabrication of partial or full dentures with regions built up to fill in regions of soft tissue loss.

Maxillectomy with resulting communication between oral cavity and sinonasal chambers presents its own problems with speech and swallowing. Loss of food and liquid into the nasal cavity is irritative and inefficient. Speech is also affected by the loss of palatal tissue resulting in hypernasality and difficulty in producing consonants such as "d" and "t." In most cases, these problems are adequately addressed by a well-formed, well-fitted maxillary obturator. Retention of the obturator may be problematic, particularly in cases requiring resection of more than half of the hard palate and alveolus. Indwelling implants in remaining bone may be required for satisfactory fixation of the prosthesis.

## Management of Recurrence

Oral cancer survivors should be followed sequentially in surveillance clinic. PET and CT scanning together with serial oral examination by a head and neck oncologist are the mainstays of early detection of recurrence, which in turn is key to optimizing the chance for meaningful intervention. Oral screening should be performed frequently in the first 2 years after treatment (q 1–3 months) when the likelihood of recurrence is highest. When oral cancer recurs after initial treatment, the options available depend on the location and extent of the disease and details pertaining to the prior treatment. Sequelae of previous treatment may make early detection of recurrence challenging, with tumor often growing unnoticed deep into the tongue or the FOM tissues. Generally, radiation therapy is provided to the maximum lifetime tolerance of normal tissues when initially given, so that re-irradiation is hazardous and remains controversial. Brachytherapy boost to local recurrence may be tolerated, but full external beam re-irradiation risks bone exposure and loss, skin breakdown and subsequent wound-management problems, as well as further deterioration of speech and swallowing function. Repeat resection of oral tissues presents advanced challenges for reconstruction and restoration of function. In general, revision surgery of tongue recurrences necessitates wide removal of residual tongue tissue even to the extent of total glossectomy. After radiation and chemotherapy, persistent cancer may extend in lymphatics beneath the mucosa in a pattern that is not detectable until frozen section margins are taken. Salvage surgery necessitates back-up plans for intraoperative management due

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to uncertainty of extent of disease. Recurrence along the alveolar surface after prior marginal mandibulectomy typically necessitates a full-segmental mandibulectomy as tumor has free access to the marrow space.

Regional recurrence is generally managed with neck dissection if this has not been done previously. However, after prior neck treatment, neck surgery is difficult, and tumor may invade vital structures such as the carotid artery and cranial nerves. Prior surgical or radiation treatment of the neck also may alter lymphatic flow and the pattern of nodal metastasis putting at risk more distal nodal basins.

Distant metastasis (lung, liver, bone) is managed only symptomatically or with palliative chemotherapy. Generally, if chemotherapy has already been used in an earlier phase of treatment, it is assumed that the surviving tumor is now resistant to those agents. Therefore, alternative drugs are used for recurrence. Given the limited scope of effective agents for OSCC (platinum, taxanes, epidermal growth factor receptor [EGFR] inhibitors, antimetabolites), the options for treating distant disease recurrence are often quite limited.

## FUTURE DIRECTIONS

Early detection of oral cancer is a fundamental goal for successful management. Intense attention is being given to oral screening within the dental community. Laboratory advances may also provide important tools for oral cancer detection. Genetic alterations can serve as markers for tumor detection and surveillance. Easy access to the oral cavity through rinses and swabs makes oral cancer an ideal target for molecular detection. Numerous epigenetic, genetic, and protein markers have been demonstrated in saliva and oral rinse specimens.[178,179] Preliminary data indicate the utility of this approach in early detection of oral cancer, but the application of these pilot studies in clinical practice will require rigorous demonstration of adequate positive and negative predictive value. De novo detection of cancer in an at-risk population is particularly daunting as the number of potential markers is high, but the identification of highly specific markers is elusive.

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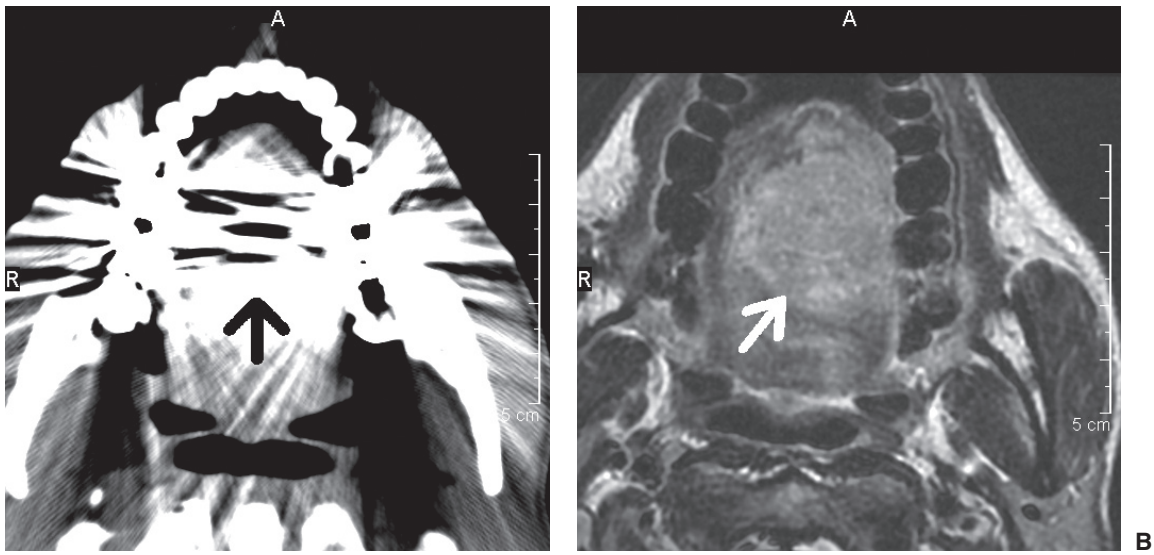
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# PART B:
# Radiologic Imaging Concerns

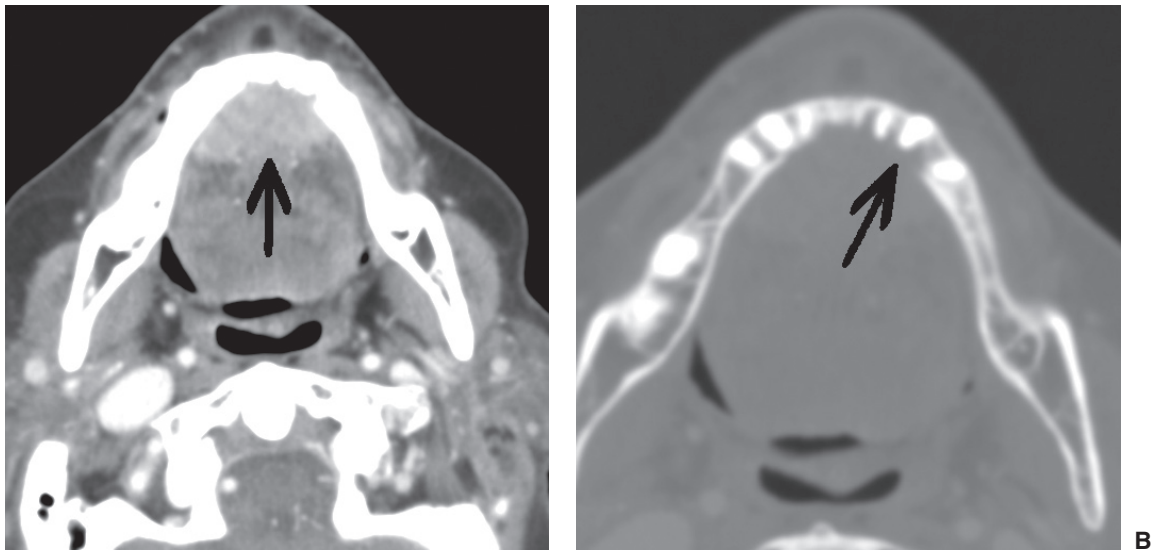
Jeffrey A. Bennett

The greatest difficulty encountered with imaging of the oral cavity is artifact created by dental hardware and fillings (Fig. 16-19). CT is particularly susceptible to this beam hardening artifact which is why two separate CT acquisitions are typically obtained at different angles in an attempt to maximize soft tissue visualization. Dental artifact is less of a problem with MRI, which can generate exquisite soft tissue detail in multiple planes. The coronal is particularly useful for visualization of pathology in the oral cavity. Very thin-section CT with bone algorithm and multiplanar reformats are excellent for the detection of subtle cortical erosions caused by tumors[1] (Fig. 16-20). MRI may have a slight advantage for visualization of bone marrow infiltration




A B

**FIGURE 16-19.** Axial CT scan through the oral cavity **(A)** is severely limited by beam hardening artifact caused by dental fillings *(black arrow)*. The soft tissue of the oral tongue cannot be evaluated. Axial T1-weighted post gadolinium MRI **(B)** in the same patient shows an oral tongue enhancing squamous cell carcinoma *(white arrow)* and does not suffer from the same limitations as CT.



A B

**FIGURE 16-20.** Axial contrast-enhanced CT scan with soft tissue windowing **(A)** shows an enhancing squamous cell cancer filling the anterior floor of the mouth *(arrow)*. The same image with bone algorithm **(B)** shows erosion of the lingual place of the mandible *(arrow)* from tumor invasion into the bone.

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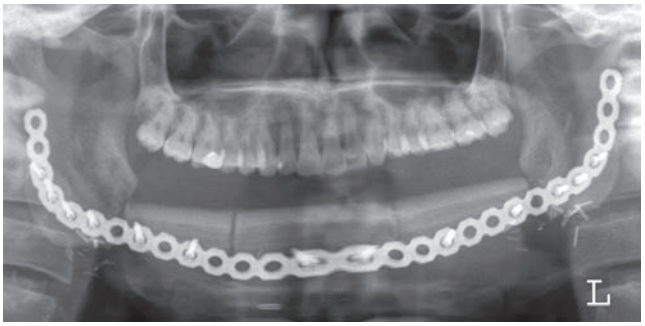


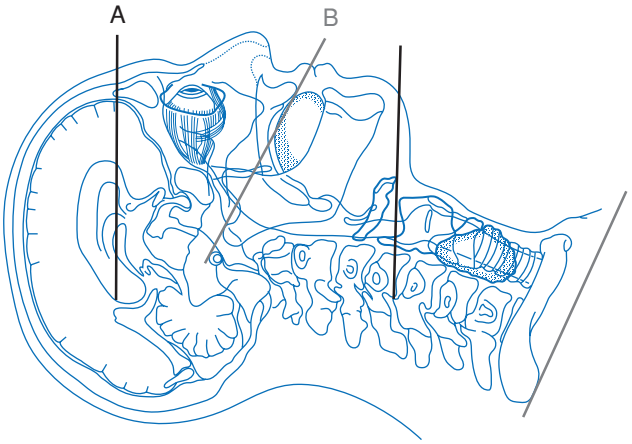
**FIGURE 16-21.** Panoramic radiograph is useful to assess the integrity of mandibular construct.

by tumor, but PET/CT can also detect this finding.[2] Panoramic radiographs and spot-occlusal radiographs are used particularly by dentists for the evaluation of the alveolus, teeth, and fixation plates (Fig. 16-21). Additional FDG-PET parameters are being investigated as potential markers for prognostic information and survival. These include the metabolic tumor volume and total glycolytic activity.[3] The most appropriate threshold values for these variables still need to be validated. Suggested CT and MRI imaging protocols are given in Figures 16-22 and 16-23.

## ORAL TONGUE

An important observation to make on images of oral tongue lesions is whether the lesion crosses the midline lingual septum (Fig. 16-24). This affects the type of glossectomy that can be

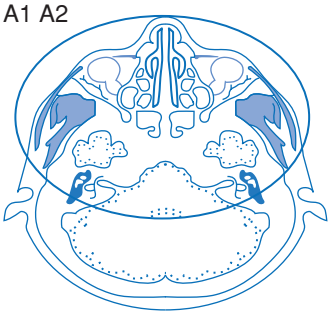
ACQUISITION



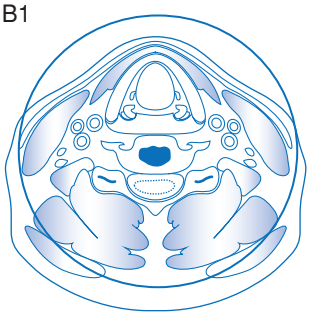

| | | |
|---|---|---|
| | Patient Position | Supine<br>IOML perpendicular to the tabletop |
| | Contrast | 100 mL adult |
| | Injection Rate | 1 mL/s; 60 s delay |
| | Respiration | Quiet, NO swallowing |
| | Volume Acquisition Specs | Appropriate to achieve images as specified in following reconstruction tables.<br>Head FOV. |
| A | Begin | Above frontal sinus |
| | End | Through mandible |
| B | Begin | Mid oral cavity |
| | End | Apices |

RECONSTRUCTION

A1 A2



B1



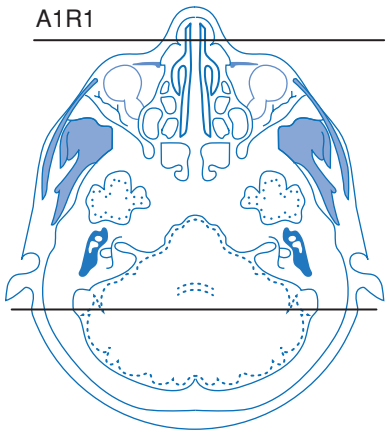
| | | |
|---|---|---|
| A1 | Algorithm | Soft tissue |
| | Thickness | 1.0 mm |
| | Spacing | 0.8 mm |
| | FOV | Approx. 170–190 |

| | | |
|---|---|---|
| A2 | Algorithm | Bone |
| | Thickness | 1.0 mm |
| | Spacing | 0.8 mm |
| | FOV | Approx. 170–190 |
| B1 | Algorithm | Soft tissue |
| | Thickness | 2.5 mm |
| | Spacing | 2.5 mm |
| | FOV | Approx. 160–180 |

**FIGURE 16-22.** Protocol for CT scan of the maxillofacial region and neck with intravenous contrast.

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| | | |
|---|---|---|
| A1R1 | Algorithm | Soft tissue |
| | Thickness | 1.0 mm |
| | Spacing | 1.0 mm |
| | FOV | Approx. 180 |
| | Plane | Coronal |
| | Begin | Frontal sinus |
| | End | Through IAC |

**FIGURE 16-22.** *Continued*

| Acquisition | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Plane | Sagittal | Axial | Axial | Axial | Coronal | Coronal |
| Sequence | T1 | T1 | T2-FSE | T1 | T1 | T2-FSE |
| Contrast | None | None | None | Gd | Gd | Gd |
| SLT/SP | 4/0 mm | 3/0 mm | 3/0 mm | 3/0 mm | 3/0 mm | 3/0 mm |
| Matrix size | — | — | — | — | — | — |
| FOV | 16 cm | 16 cm | 16 cm | 20 cm | 16 cm | 16 cm |

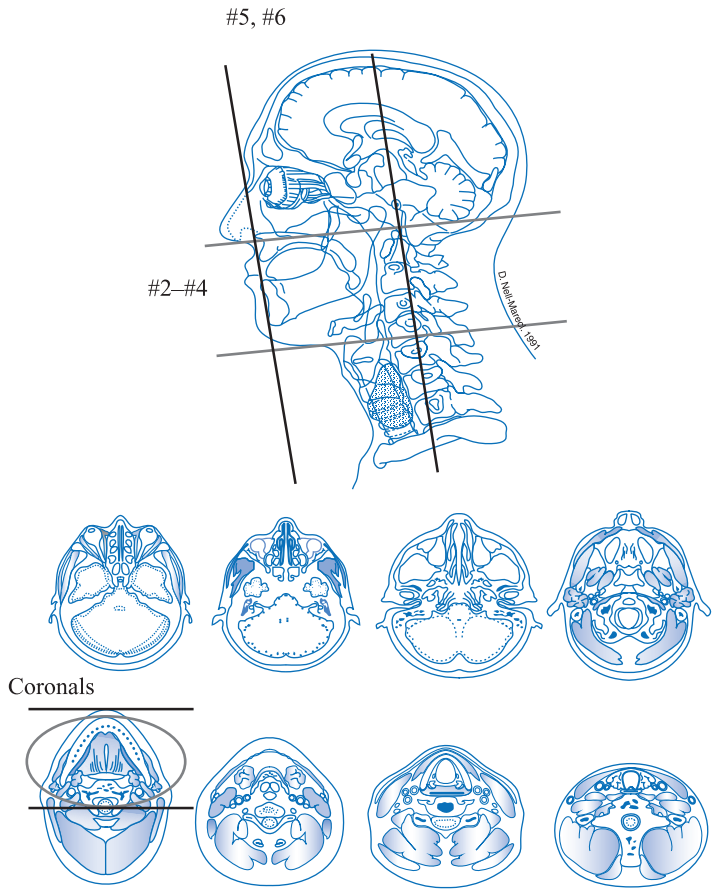



**FIGURE 16-23.** Protocol for MRI of the oral cavity.

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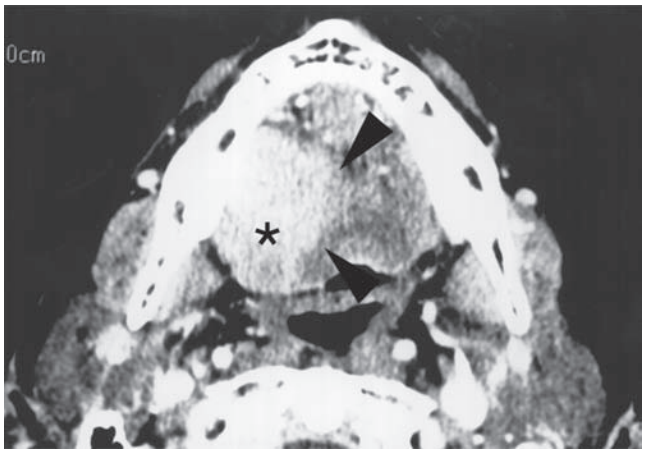



**FIGURE 16-24.** Advanced oral tongue cancer. Enhanced axial computed tomogram of large oral tongue cancer *(asterisk)* involving the midline *(arrowheads)*.

performed. Extension into the floor of the mouth can be documented clearly with coronal CT reformatted images or coronal MRI (Fig. 16-25). Posttreatment imaging can be very helpful to evaluate lesions that cannot be directly visualized underneath the surface of flaps or underneath fibrosed scar tissue. FDG-PET can be particularly useful in these cases (Fig. 16-26).

## GINGIVA

Evaluation of the alveolus for carcinoma of the gingiva is rarely performed for early disease, but is routinely performed for more advanced disease, especially for the maxillary alveolus (Fig. 16-27) and for the retromolar trigone (Fig. 16-28). The appearance of the alveolar ridge can often look irregular, especially

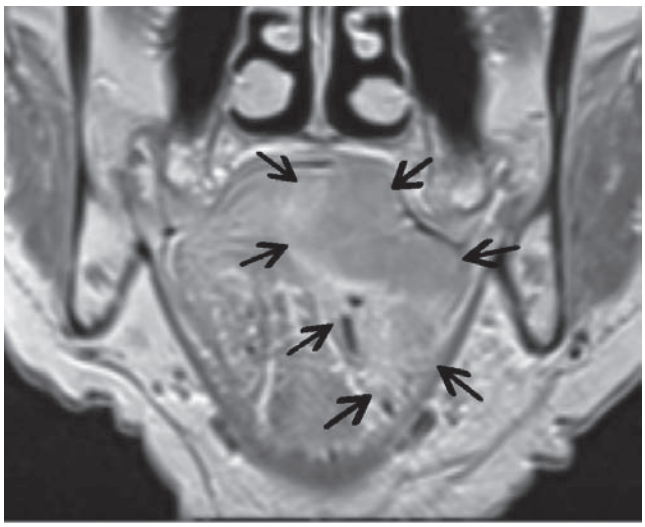


**FIGURE 16-25.** Coronal T1-weighted contrast-enhanced MRI demonstrates an infiltrating heterogeneously enhancing oral tongue mass outlined by arrows which extends into the floor of the mouth.

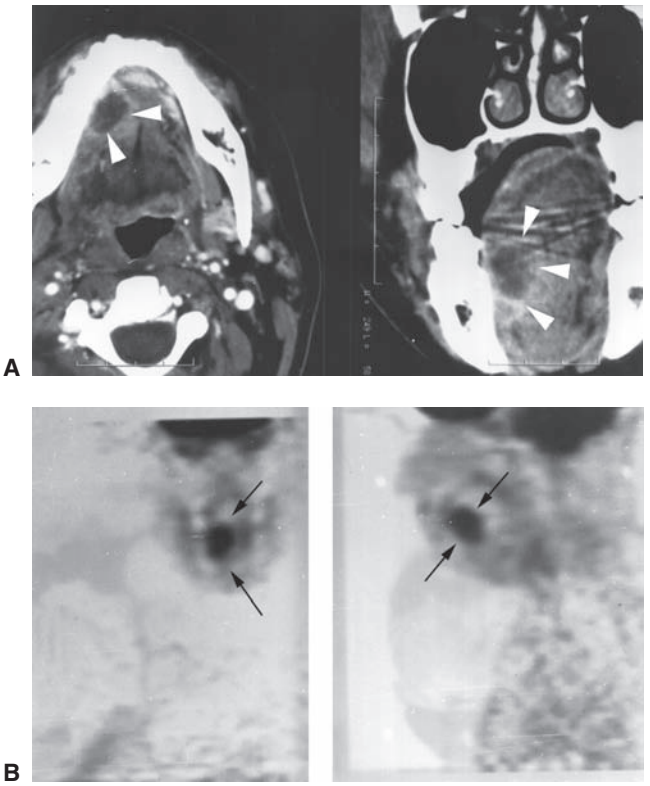



**FIGURE 16-26.** Correlation between modalities. **A:** Contrast-enhanced computed tomography in axial **(left)** and coronal **(right)** planes show necrotic process *(arrowheads)* thought clinically to be treatment-related induration. **B:** A fluorodeoxyglucose positron emission tomography scan in coronal **(left)** and sagittal **(right)** plane excludes necrosis and confirms tumor recurrence *(arrows)*.

in patients with recent tooth extractions or in edentulous patients, and this can be a limitation when trying to determine the extent of bony involvement of cancer. MRI has been shown to be relatively insensitive to bony invasion related to gingival lesions.[4] Both cone beam CT and standard CT are quite helpful to determine the proximity of a mass to the alveolar canal. In the maxilla, the extent of involvement of the maxillary sinus antrum can be seen best on coronal views (Fig. 16-27). Extension to the floor of the mouth, gingivobuccal sulcus, and posterior extension to the pterygoid processes can all be demonstrated on both MRI and CT.

## FLOOR OF MOUTH

When evaluating lesions of the floor of the mouth, posterior extension to the lingual neurovascular bundle should be commented on.[5] Invasion through the mylohyoid muscle into the submandibular space can be seen (Fig. 16-29). Submandibular gland invasion should also be differentiated from obstruction of Wharton duct.

## PALATE

The palate is best imaged in the coronal plane, where tumor invasion of bone and extension into the nasal cavity can be documented. Accurate pretreatment estimation of the extent of

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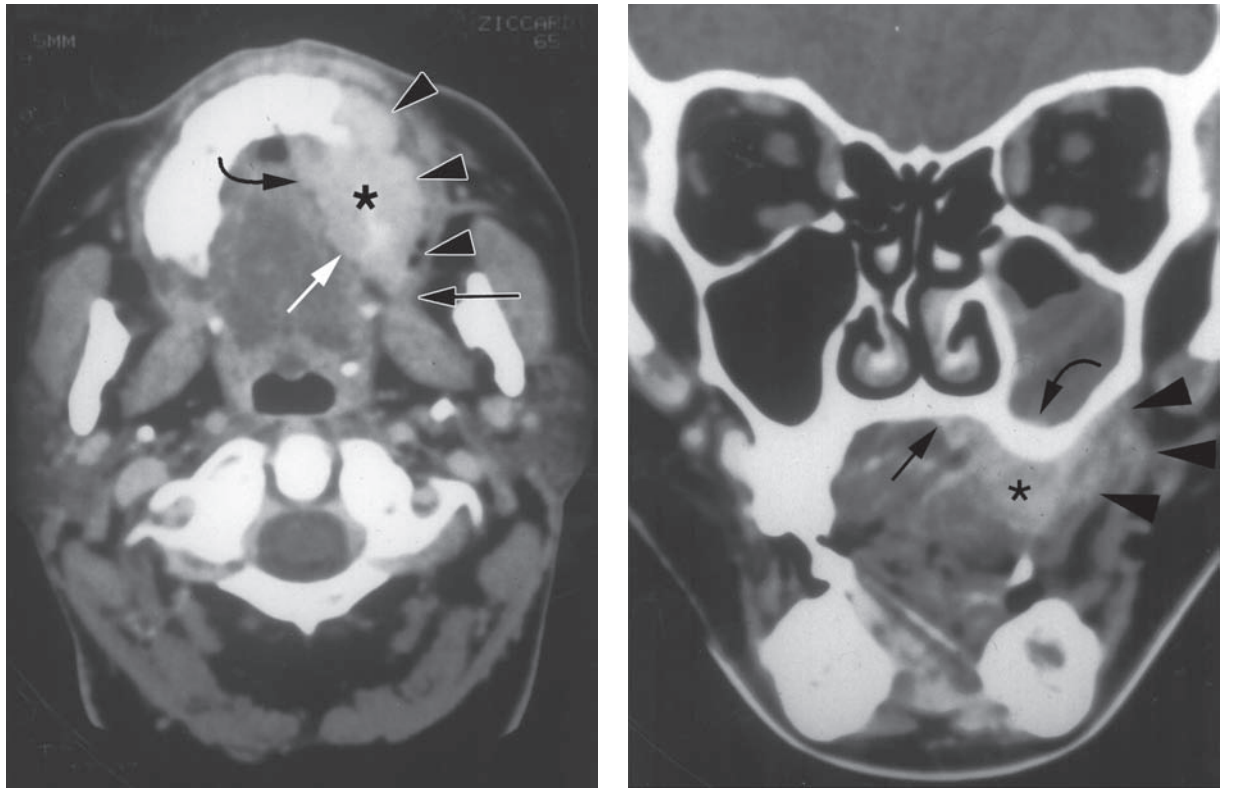



**FIGURE 16-27.** Advanced gingival cancer. Enhanced **(A)** axial and **(B)** direct coronal computed tomographic views of a large squamous cell cancer *(asterisk)* of the maxillary alveolus, with medial *(arrow)* and lateral *(arrowheads)* extent well outlined. Early antral invasion *(curved arrow)* surrounded by reactive secretions. Note preserved pterygomaxillary raphe *(long arrow)*.

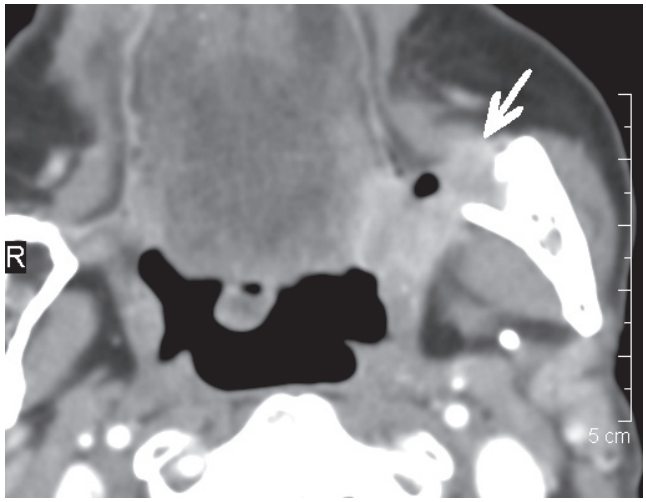



**FIGURE 16-28.** Axial contrast-enhanced CT shows an enhancing recurrent retromolar trigone squamous cell carcinoma *(arrow)*, which invades the ascending ramus of the mandible and extends to the glossotonsillar sulcus and to the anterior tonsillar pillar.

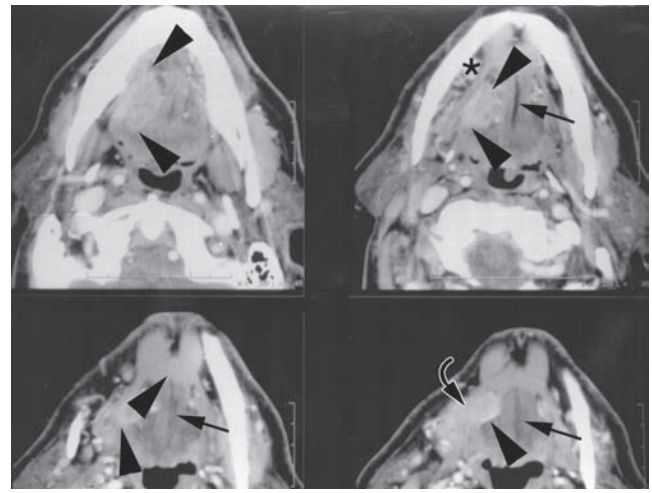


**FIGURE 16-29.** Floor of mouth cancer. Serial enhanced axial computed tomographic images through the oral cavity show an enhancing lesion *(arrowheads)*. Note preservation of the lingual septum *(arrows)* despite the invasion of the tongue. Extension through the mylohyoid muscle *(curved arrow)* into the submental compartment and suspicious lymph node *(asterisk)*.

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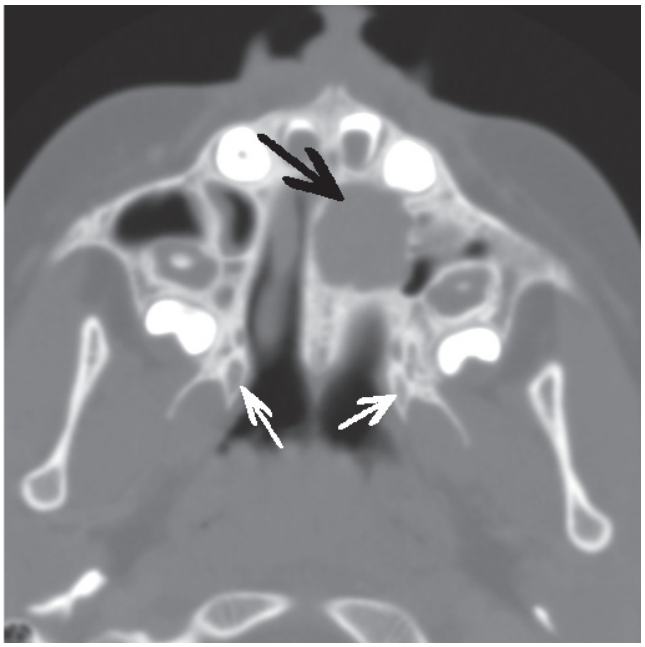


**FIGURE 16-30.** Axial CT scan at the level of the hard palate shows a lytic bone lesion in a 6-year-old *(black arrow)*. Notice the position of the greater palatine foramina *(white arrows)* at the base of the pterygoid plates. These serve as pathways of perineural spread of disease along V2 to the pterygopalatine fossa.

disease allows for early prosthesis planning and rehabilitation efforts. Careful evaluation of the palatine foramina (Fig. 16-30) and pterygopalatine fossa (Fig. 16-31) should be performed to evaluate for perineural spread of disease.

## BUCCAL MUCOSA

Imaging of the buccal mucosa is difficult as it is collapsed against the teeth. Imaging with the cheeks distended, either with gauze or air (puffed cheek imaging) may be helpful. Fortunately, imaging is rarely needed for small lesions arising on the buccal mucosa.

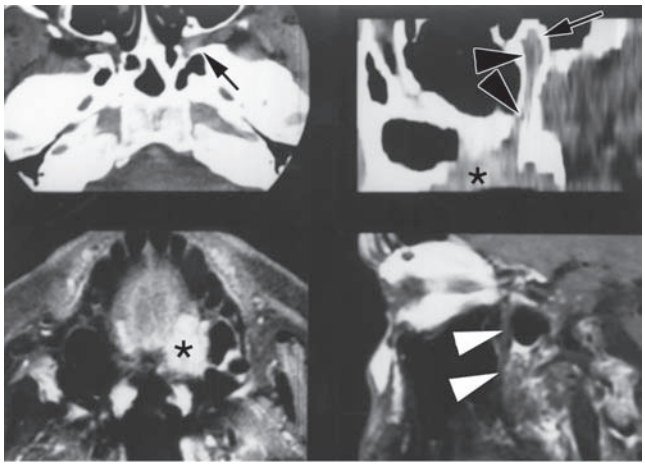


**FIGURE 16-31.** Neurotropic palate cancer. **(Clockwise from top left)** Enhanced axial computed tomogram (CT) of pterygopalatine fossa, parasagittal reformatted CT, and corresponding sagittal and axial magnetic resonance imaging (MRI) show the unanticipated extension to pterygopalatine fossa *(arrow)* along palatine canal *(arrowheads)* from the small posterior hard palate primary tumor *(asterisk)*, which is better seen on MRI than on CT.

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4. Nagata Y, Ohba T, Tahara T, et al. Advanced imaging of carcinoma of the mandibular gingiva. *Dentomaxillofac Radiol*. 1997;26(3):192–194.
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# PART C:
# Radiation Therapy Technique

Louis B. Harrison, Rudolph Woode, James Dolan, and Kenneth Hu

The most common sites treated with radiation therapy include the lip, the floor of the mouth, and the oral tongue. Lesions of the buccal mucosa, retromolar trigone are treated with techniques similar to those used for the tonsil, which are discussed in Chapter 17C. For oral cavity tumors, primary surgery is the most common approach. Radiation therapy is generally used as an adjuvant treatment in the postoperative setting. Primary RT can be used in certain situations, and brachytherapy is an important component.

Lesions of the upper lip are uncommon; the treatment techniques described hereafter apply primarily to the lower lip, but can be modified to treat the upper lip. Patients with superficial, well-differentiated squamous cell carcinoma of the lip have a low risk of cancer in the neck nodes and may be irradiated with brachytherapy alone or external beam irradiation alone. A short course of external beam irradiation precedes the interstitial implant, if the lesion is too thick to be adequately encompassed in a single-plane implant ( > 1 cm). External beam

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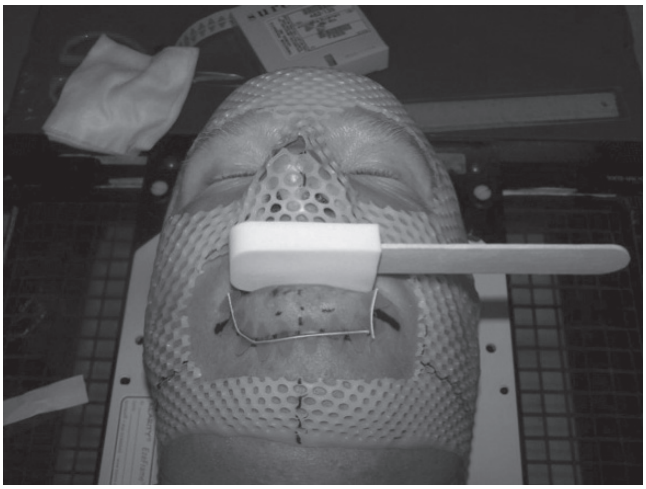
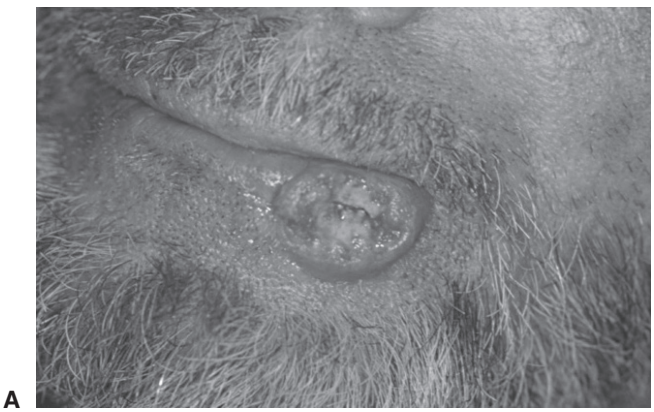


**FIGURE 16-32.** Patient has a multifocal squamous cell cancer of the lower lip. The treatment is electron beam RT to a total of 6,000 cGy in 6 weeks. 6 MeV electrons were used. Wire is seen to demarcate the field size, giving about 1.5 cm margin around the lesion. A bite block separates the lower lip from the upper lip, thus protecting the upper lip and adding to the consistency of the daily setup.

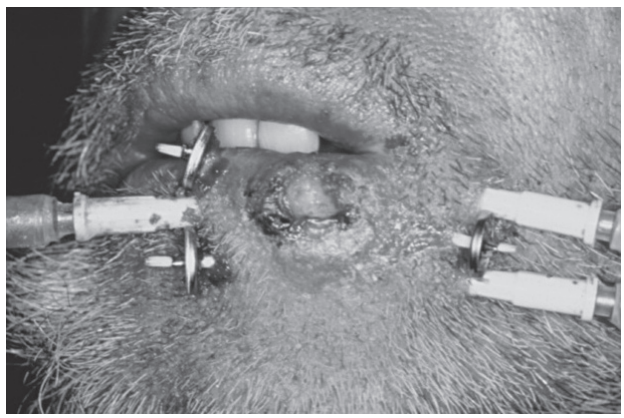
irradiation is usually done with local electron field, although photons can sometimes be used. Figure 16-32 shows a patient with squamous cell cancer of the lower lip, and the field setup for electrons.

Interstitial irradiation may be accomplished with iridium-192 ($^{192}$Ir) using the plastic tube technique. These procedures can usually be done under local anesthesia. Figure 16-33 shows a patient who had an $^{192}$Ir implant for a squamous cell cancer of the lower lip.

Small cancers of the floor of the mouth or the oral tongue can be treated with an interstitial implant alone. This is usually accomplished with an $^{192}$Ir implant afterloaded into plastic tubes. This is done under general anesthesia, in the operating room. Sometimes, a tracheostomy is performed, as a temporary protection of the airway, especially if the posterior portion of the oral tongue is involved. The tracheostomy protects the airway in the advent of the tongue swelling or bleeding. The afterloading catheters are implanted using a looping technique. The catheters enter and exit via the submental approach. Figure 16-34 shows an intraoperative photograph of an oral tongue implant and highlights the looping technique. Figure 16-35 shows AP and lateral images of an oral tongue implant, with isodose curves.



A



B



C

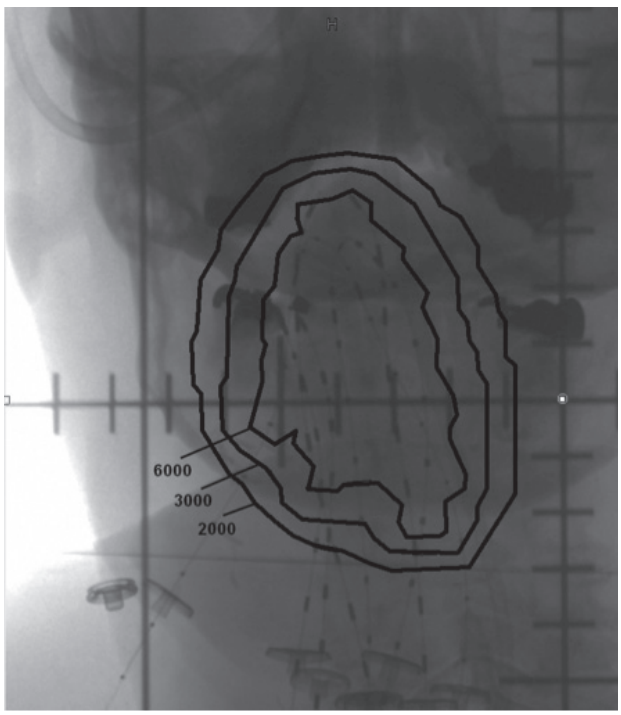
**FIGURE 16-33.** Patient had a 2.5-cm squamous cell cancer of the left side of the lower lip, near the lip commissure. Radiation was selected as the primary treatment due to the enhanced functional and cosmetic result in this particular case, given location near commissure. **A:** The lesion is seen. **B:** Patient had implantation of $^{192}$Ir via afterloading angiocatheters. A single plane implant was used and the catheters were 1 cm apart. A total of 6,000 cGy in 6 days was delivered. This photograph was taken on Day 6, just after source removal. The lesion has already regressed. **C:** Six months after implant. Patient has no evidence of disease. (See color insert.)

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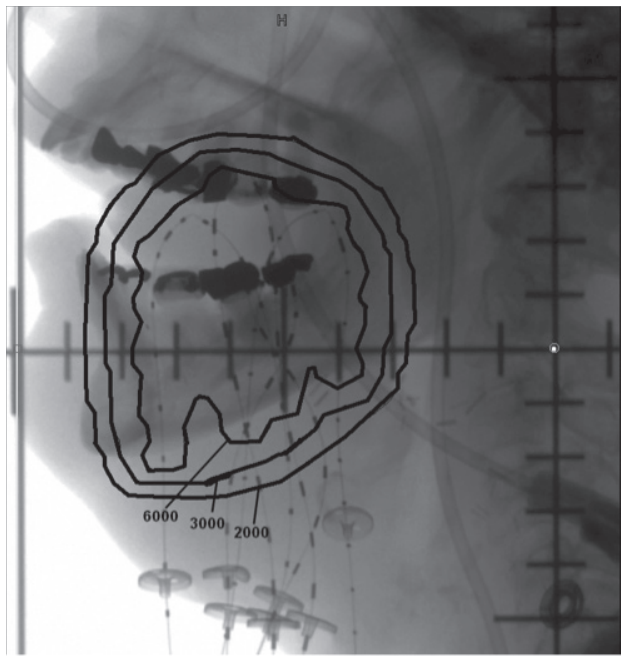


**FIGURE 16-34.** This patient had a squamous cell cancer involving the left side of the oral tongue, T2N0M0. There is irregularity and mass effect shown along the lateral aspect of the tongue and a small mucosal ulceration along the midtongue. A series of looping catheters were implanted, and the area received 6,500 cGy over 6.5 days. The patient is an attorney, so speech articulation was a key ingredient to his choice of radiation therapy. He remains free of disease for >15 years from treatment.

External beam RT techniques are similar for oral cavity sites as for other head and neck sites. Since most patients receive primary surgical treatment, especially for more advanced lesions, the main role of RT is the postoperative setting. The main reason to employ IMRT would be to provide relative sparing of key normal organs such as the parotid glands, the pharyngeal constrictor muscles, and the spinal cord. Figure 16-36 shows a clinical example of a patient with an oral tongue cancer metastatic to the neck. The contours as well as the isodose distribution are shown. Figure 16-37 shows the dose–volume histogram. This technique is similar for oral tongue, floor of the mouth, or even gingival cancer.




A




B

**FIGURE 16-35.** This patient had a T2N0 squamous cell cancer of the right side of the oral tongue. She underwent an $^{192}$Ir implant similar to Figure 16-34. She received 6,000 cGy in 6.5 days. The dummy seeds are visualized. **A:** AP radiograph showing the looping catheters with the 6,000 cGy isodose line encompassing the tumor, plus 2 cm margin, on clinical assessment. The 3,000 and 2,000 lines are also shown. **B:** Lateral radiograph showing the looping catheters as well as the 6,000, 3,000, and 2,000 isodose lines.

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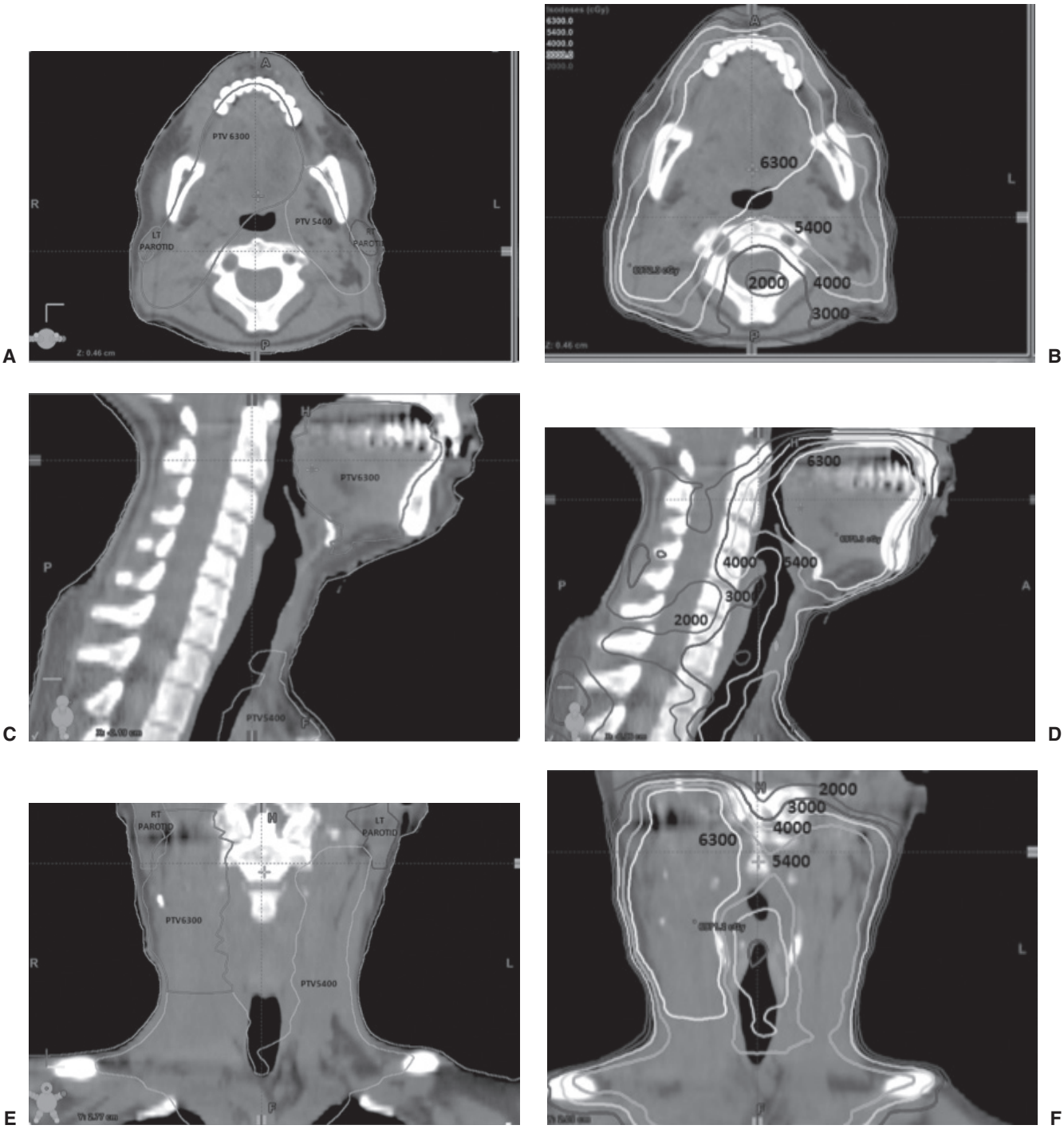



**FIGURE 16-36.** This patient had a T3N2BM0 squamous cell cancer of the right side of the oral tongue. She underwent a major glossectomy, radial forearm free-flap reconstruction, and a right neck dissection. The pathology revealed squamous cell carcinoma, moderate differentiated, with close margins and perineural invasion. The right neck revealed 4 of 26 positive nodes, all at level 2, with extracapsular spread. With these findings, the patient was treated with postoperative concomitant chemotherapy and radiation therapy, using IMRT. **A:** Axial CT for treatment planning showing the PTV63 covering the primary site bed and the right neck. PTV 63 receives 6,300 cGy in 7 weeks. The PTV54 shows the left neck which is clinically negative, but which receives elective IMRT consisting of 5,400 cGy in 6 weeks. Efforts are made to protect the left parotid gland. The right parotid gland is impossible to protect, given the extent of nodal involvement of the right level 2. **B:** Same axial CT slice as **(A)**. For ease in visual display, the contours have been removed, but the isodose curves for 6,300, 5,400, 4,000, 3,000, and 2,000 cGy are shown. **C:** Midsagittal display showing PTV63 encompassing the entire tongue bed. **D:** Same midsagittal CT slice as **C.** For ease in visual display, the contours have been removed, but the isodose curves for 6,300, 5,400, 4,000, 3,000, and 2,000 cGy are shown. Note the relative protection of the posterior pharyngeal wall. **E:** Coronal CT display showing PTV 63 and PTV 54. PTV 63 encompasses the right upper neck levels 2 and 3 in this display. The PTV 54 encompasses the right lower neck as well as the entire left neck. Note the sparing of the left (contralateral parotid gland). **F:** Same coronal CT display as **E**. As in prior figures, the contours are removed and the isodose lines are shown. (See color insert for Parts **D–F**.)



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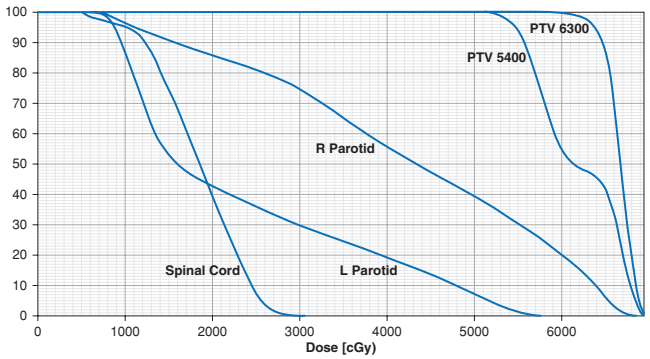



**FIGURE 16-37.** This is the dose-volume histogram for the same patient in Figure 16-36. This patient was treated with a nine-field IMRT plan.

# PART D: Surgical Technique

Charles S. Coffey and Terry A. Day

The location and behavior of oral cavity (OC) cancers make surgery the treatment of choice in the majority of cases. Many lesions can be accessed transorally without major perturbation of the surrounding uninvolved structures, resulting in improved cosmesis and satisfactory preservation of functions such as speech, chewing, and deglutition. Radiation therapy, although effective in the treatment of other head and neck sites, is hindered by the bony structures of the OC, air–tissue interfaces, and involuntary mobility of the tongue and the floor of mouth (FOM). Additionally, oral squamous cell carcinoma (SCC), minor salivary gland tumors, and sarcomas are associated with a more limited response to nonsurgical treatment. The methods of surgical approach to the OC are discussed below.

## TRANSORAL/PERORAL APPROACH

Many tumors of the OC are readily accessible for excision via a transoral approach, without the need for external incisions, or extensive dissection to achieve adequate exposure. This is particularly true for many early-stage (T1 or T2) lesions of the lip, the buccal mucosa, the anterior tongue, the FOM, or the alveolus. Transoral exposure may be maximized by use of a variety of devices, including circumferential cheek retractors, dental bite blocks, self-retaining mouth gags, or various handheld retractors for the tongue and the buccal mucosa. Exposure, access, and safety are improved when nasotracheal intubation is employed, permitting access without hindrance by the endotracheal tube in the OC. When monopolar electrocautery is employed, guarded cautery tips and coated or nonferrous retractors should be used to minimize the risk of injury to the lips and the oral commissure. Heavy suture, tongue retractors, or a penetrating clamp may be used to retract the tongue and provide additional exposure to the posterolateral tongue and the FOM. When limited transoral resection is combined with surgical management of the neck, care should be taken to avoid communication of the oral and the neck wounds when possible to minimize the risk of fistula formation. However, such concerns must always be secondary to oncologic considerations and achieving the exposure necessary for appropriate tumor extirpation. When tumors of the OC extend into the oropharynx, additional technology can afford improved visualization with transoral robotic surgery using three-dimensional visualization and robotic instruments. Transoral laser surgery has also been recommended for tumors of the OC and the oropharynx. When the transoral approach is employed, a separate neck incision and neck dissection is performed, avoiding entry into the OC whenever possible.

## COMBINED TRANSORAL/TRANSCERVICAL APPROACHES TO THE ORAL CAVITY

Achieving adequate exposure of large (T3 or T4) or deeply invasive lesions of the anterior OC may not be possible via a strictly transoral approach. In combination with surgical management of the neck, variations of either the mandibular lingual release or the "visor" approach allow excellent access to the OC through exposure via the neck.[1,2] In most cases, an upper neck dissection is performed prior to the combined approach to allow exposure of the external carotid branches, the lingual and the hypoglossal nerves, and the suprahyoid muscles.

A broad horizontal incision in a cervical skin crease is initially performed. An apron flap that is elevated to the inferior border of the mandible can be utilized in a unilateral fashion for the mandible/OC or bilaterally when large defects, anterior FOM/mandible, and bilateral tumors are treated. The unilateral approach is usually intended for lateral mandibular body, retromolar trigone, lateral FOM, or lateral tongue defects. An important consideration when elevating the subplatysmal flaps superiorly to and beyond the inferior border of the mandible is elevation and mobilization, with preservation of the marginal mandibular nerve. Ipsilateral or bilateral nodal contents are removed at this time, if indicated.

### Lingual Release

Lingual release refers to the separation of the lingual aspect of the mucosal surfaces from the inner aspect of the mandible 270° from the glossotonsillar sulcus on one side, anteriorly around the mandible to the contralateral glossotonsillar sulcus.[1] Although commonly bilateral, unilateral release is appropriate and feasible in certain small tongue or FOM cancers. In most cases, an upper neck dissection is performed prior to the combined approach to allow exposure of the external carotid branches, the lingual and the hypoglossal nerves, and the suprahyoid muscles.

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Once the soft tissue and muscular attachments to the mandible are released, the entire tongue and the FOM is "released" and can readily fall into the neck and be visualized and dissected via the neck incisions, rather than transorally. If mandibular resection is not planned, mandibular lingual release may be performed without dissection of the soft tissue envelope overlying the mandible (Fig. 16-38A,B). The digastric, the mylohyoid, the geniohyoid, and the genioglossus muscles are released at their anterior attachments, and subperiosteal dissection is performed along the inner cortex of the mandible. The intraoral mucosa is released at the dental mucosal junction with preservation of the interdental papillae in the dentate patient, or along the superior alveolar crest in the edentulous patient. Following mucosal release, the tongue and the FOM are delivered into the neck. If additional posterior exposure of the base of the tongue or the lateral pharynx is required, the dissection may be extended into a pharyngotomy incision.

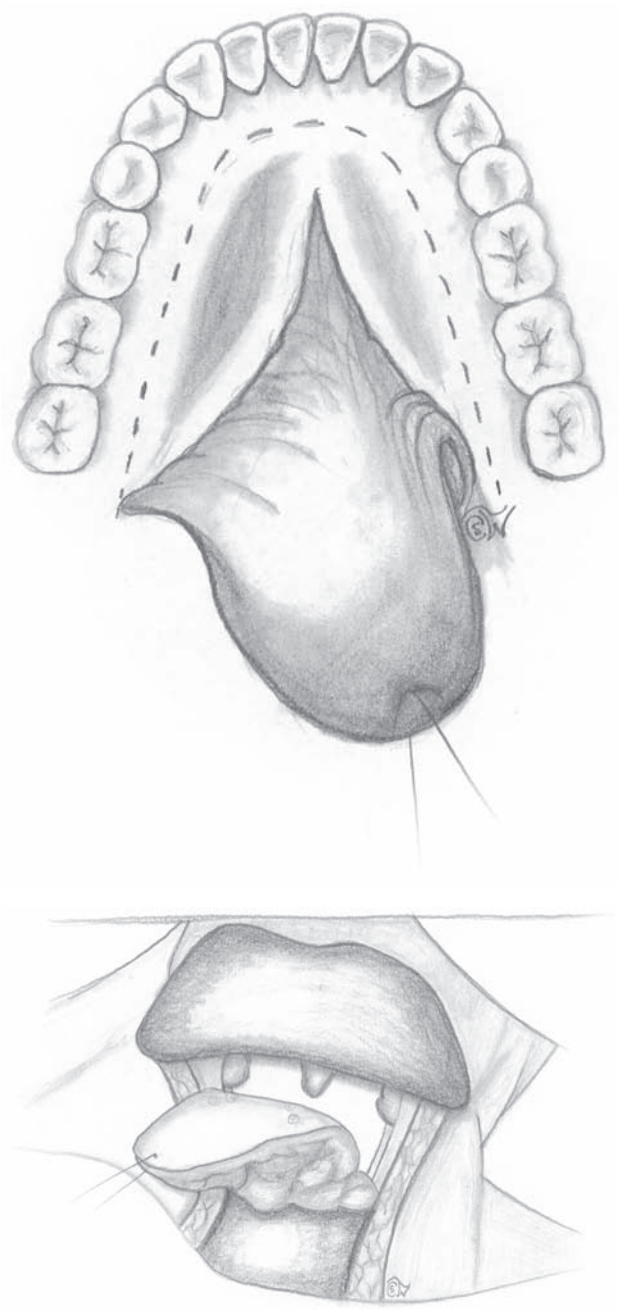


**FIGURE 16-38.** **A:** Intraoral view, lingual release. **B:** Cervical view, lingual release.

## Visor Flap for Mandibulectomy and Plating

The term "visor" is used to differentiate it from an "apron" flap, whereby visor is a bilateral neck and cheek flap elevated cephalad beyond the mandible to expose the body of the mandible bilaterally. Thus, the flap of skin can be considered a visor that nears the upper cheek and eyes. The apron flap, however, is limited in its superior extent, and thus does not reach the level of the cheek but forms an apron over the neck region. In most cases, an upper neck dissection is performed prior to the combined approach to allow exposure of the external carotid branches, the lingual and the hypoglossal nerves, and the suprahyoid muscles.

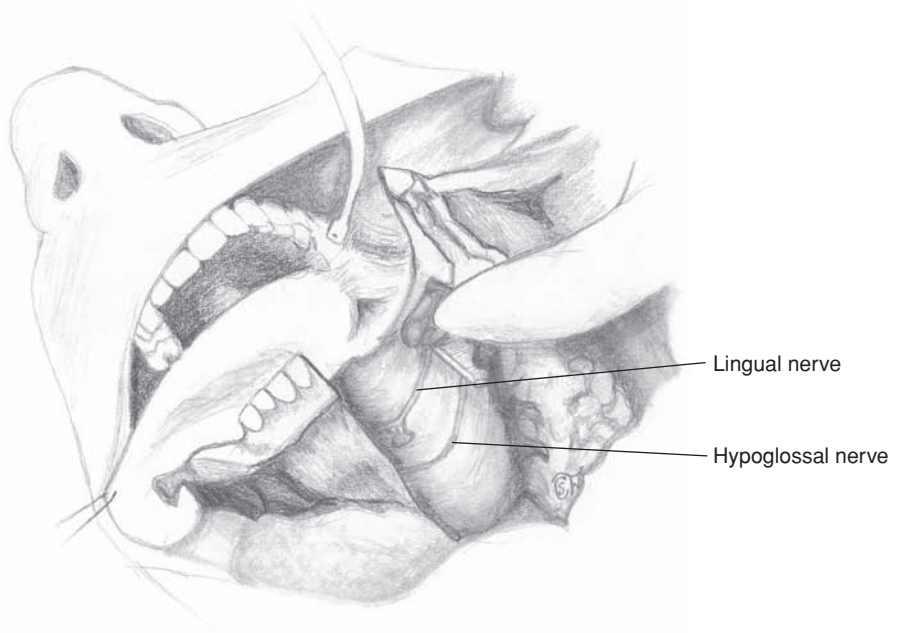
If mandibular resection is planned, a visor flap is created by subplatysmal dissection extended superiorly over the lateral surface of the mandible. This may, although not frequently, require division of bilateral mental nerves, and patients must be counseled preoperatively regarding the resulting sensory deficit. If the mandible does not require resection on one side, the mental nerve is preserved. As opposed to the "lingual" release where the incision is in the gingival or lingual aspect of the mandible, the "mandibular" release requires a releasing incision along the gingivolabial and gingivobuccal sulcus. When there is no periosteal involvement or tumor growth through the outer cortex of the mandible, the transosseous plate can be placed prior to osteotomy and removed. This may preserve occlusion and cosmesis of the mandibular contour and height. Otherwise, intermaxillary fixation may be necessary to maintain mandibular position for reconstruction. Once appropriate releasing incisions are completed, the mandible, the tongue, and the FOM are delivered into the neck. Tumor is resected with osteotomies in the bone where indicated, and margins are taken peripherally, deep, and in the neurovascular bundle and marrow of the mandible. Particular attention is paid to preservation of the lingual and the hypoglossal nerves when allowable. For large tumors of the tongue, exposure, mobilization, and ligation of the ipsilateral lingual artery in the neck prior to resection may aid hemostasis, and mobilization of the hypoglossal nerve can allow preservation of some branches when oncologically safe. Following resection, the surgical defect is appropriately reconstructed, with particular attention paid to restoring a soft tissue barrier between the OC and the neck. Native FOM musculature or myofascial tissue from the reconstruction flap should be firmly affixed to the mandible, via holes drilled into the bone, if necessary. Additional considerations would include laryngeal and/or hyoid suspension to improve postoperative swallowing function.

## Mandibular Swing Approach

The mandibular swing approach refers to a parasymphyseal or midline osteotomy and lip split, which allows the mandible and lip/cheek complex to "swing" laterally, leaving a wide open access to the OC, the retromolar trigone, the deep tongue, the oropharynx, and the parapharyngeal space without limitation by position of the lips, the cheek, or the mandible (Fig. 16-39). Such an approach may also provide access to the upper oropharynx for oral tumors extending into the soft palate, the tonsillar fossa, the glossopharyngeal sulcus, or the base of tongue. A variety of incisions for dividing the lower lip and the chin have been described, including straight line, zigzag, and chin button among others.[3,4] A visible facial scar is unavoidable, but patients who

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**FIGURE 16-39.** Mandibular swing.




have been appropriately counseled are generally not dissatisfied with the postoperative appearance.[5] The most aesthetically and functionally acceptable incisions permit precise reapproximation of the vermilion and the orbicularis muscle layer and include techniques to disrupt the linear scar and minimize contracture[6] (Fig. 16-40). The lip incision is extended along the mental crease into the neck, where it is joined to the cervical incision to allow broad surgical access. Neck dissection is generally performed at this time, not only for oncologic purposes (if indicated), but also to maximize exposure of the FOM and the posterior OC. In most cases, an upper neck dissection is performed prior to the combined approach to allow exposure of the external carotid branches, the lingual and the hypoglossal nerves, and the suprahyoid muscles. If oropharyngeal exposure is required, this may also be optimized by dissection of the lateral neck.

Subperiosteal dissection is performed around the inner and outer cortices at the planned mandibulotomy site and along the inferior and anterior surfaces where fixation hardware will be placed. Disruption of vascular supply to the mandible during these cases may be significant, and as such, the periosteum should be left in place over bone whenever possible, to preserve periosteal vascularization of the mandible. The mental nerve should be identified and preserved; this is in contrast to the mandibular swing with the visor approach, which requires division of the mental nerve at least on the ipsilateral side, as well as significant retraction on the marginal mandibular nerve. Elevation or dissection along the inner surface of the symphysis should be avoided when possible in order to minimize disruption of dense muscular attachments at the genial tubercle. Because the muscular floor comprising the oral diaphragm is preserved, this approach may offer better speech and swallowing outcomes than lingual release techniques. Multiple anterior mandibulotomy techniques have been described, including straight-line symphyseal or parasymphyseal cuts and angled cuts.[7,8] Incorporation of a step-off or angle into the mandibulotomy may improve precise reapproximation of bone if only wire fixation is planned, but it is unclear whether such techniques are as useful in the era of titanium reconstruction hardware. The authors prefer a straight vertical cut in the parasymphyseal region. This minimizes risk of injury to intact dental roots and avoids detachment of the ipsilateral genioglossus and the geniohyoid muscles from the genial tubercle, thus minimizing disruption of the oral diaphragm. Of note, neither type of cut, fixation type, or irradiation (pre- or postoperative) has been shown to significantly affect rates of nonunion.[9,10] In the dentate patient, mandibular reconstruction plates are contoured and predrilled prior to mandibulotomy to optimize restoration of dental occlusion. No such preparation is required in the edentulous patient. A powered side cutter, sagittal, or reciprocating saw may be used. Following mandibulotomy, the FOM mucosa is released at the dental mucosal junction, and the mandible is laterally retracted. A mucosal incision is extended from the alveolus to the margin of planned tumor resection, and the resection is performed. If the lingual and hypoglossal nerves have been exposed in the neck, they may be further dissected into the FOM and free of the tumor, if possible. As with the release approaches, attachments of the remaining FOM to the mandible should be restored during the course of reconstruction. The risk of postoperative fistula and oral incompetence may be higher with a mandibulotomy approach compared with a delivery approach, and this approach should be avoided for patients with an atrophic mandible due to the increased risk of nonunion or fracture.[6] During closure, it is wise to "overlap" any osteotomies with gingival mucosa or flap reconstruction to avoid the suture line being directly in line with the osteotomy.

## Mandibulectomy

Careful preoperative clinical and radiographic assessment of the mandible is critical in the evaluation of OC cancer. Lesions in direct proximity to the mandible, or those exhibiting only superficial cortical invasion may be managed with marginal mandibulectomy in select cases. Edentulous patients with significant loss of vertical mandibular height are poor candidates for marginal mandibulectomy due to the high risk for pathologic fracture, particularly in the postirradiation setting. Such patients should receive segmental resection. When moderate mandibular atrophy is present, but marginal resection is deemed feasible, placement of rigid internal fixation may reinforce the mandible and limit the risk of postoperative fracture. Segmental mandibulectomy is indicated in the setting of extensive cortical or cancellous invasion,

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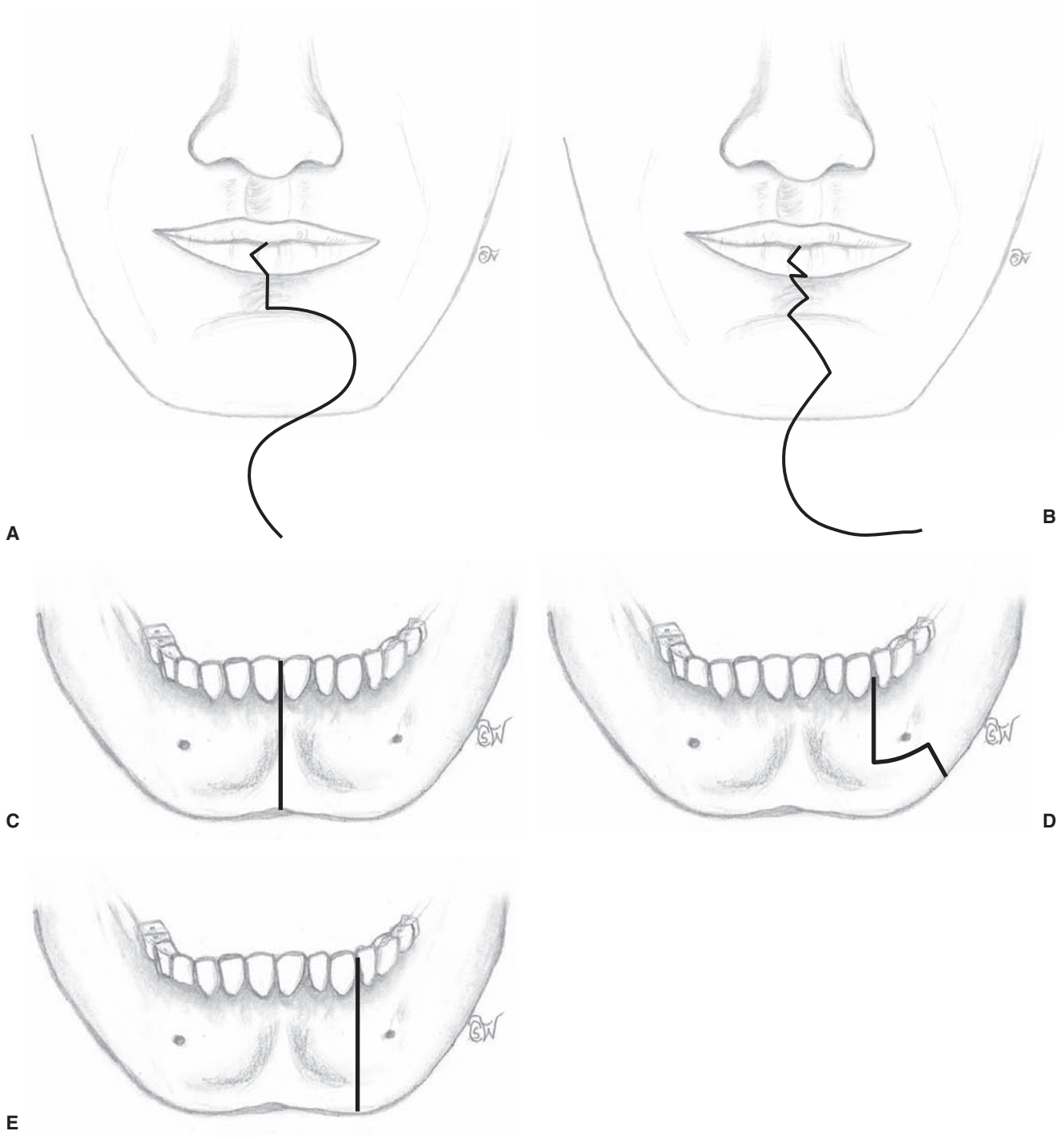



**FIGURE 16-40.** Designing lip-split incision and mandibulotomy. **A:** Broken line at vermilion and chin skin—improves precise approximation and hides scar; follows mental crease. **B:** Mucosal flap along vermilion—breaks up any straight lines into chin and maximizes precise approximation. **C:** Midline bone cut—minimizes risk of injury to dental roots, requires precise reduction and fixation with plating hardware. **D:** Parasymphseal mandibulotomy—may improve reduction and minimize risk of nonunion but confers increased risk to dental roots. **E:** Parasymphyseal straight cut, improved ease of plating because the genial tubercle is avoided; lateral position allows preservation of all attachments of geniohyoid and genioglossus while minimizing any disturbance of the oral diaphragm. This may decrease risk of fistula.

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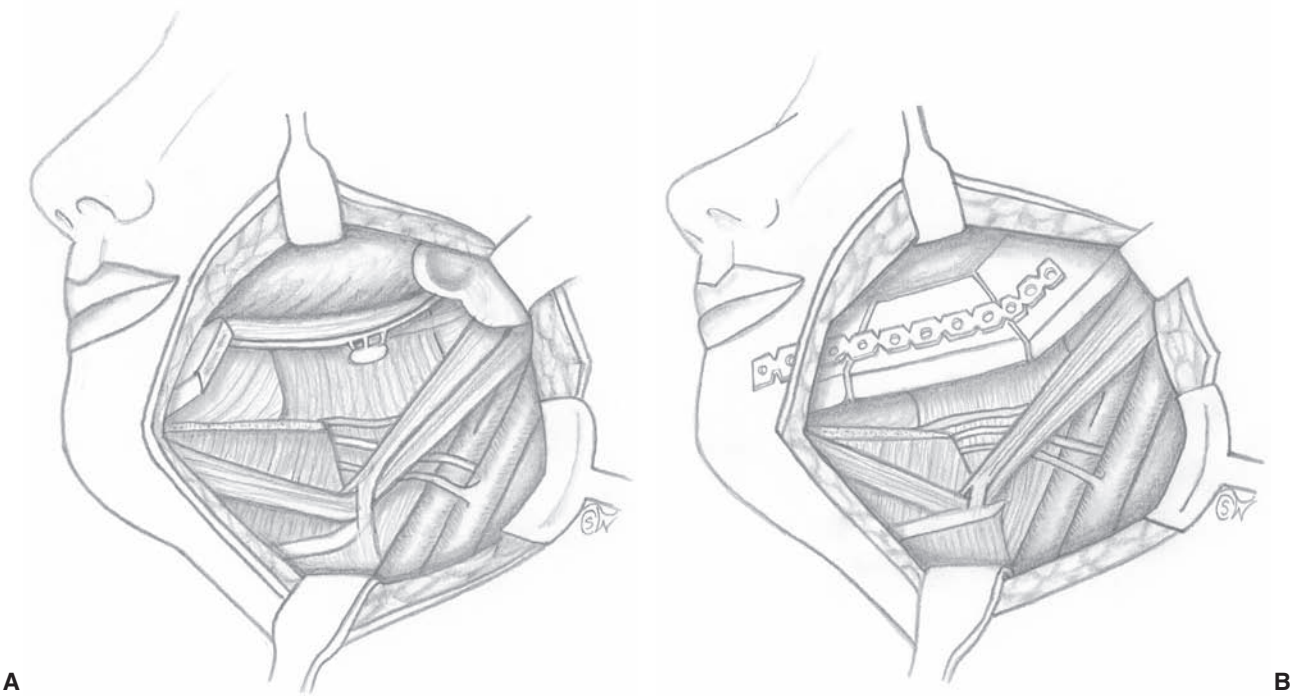



**FIGURE 16-41.** **A** and **B:** Segmental mandibulectomy with fibula osteocutaneous free flap reconstruction.

primary or metastatic bone tumor, or invasion of the marrow space, inferior alveolar nerve, or canal (Fig. 16-41).

Adequate exposure is critical, regardless of whether marginal or segmental resection is planned. An exclusively transoral approach with marginal mandibulectomy may be successful for the occasional early-stage lesion, which abuts the periosteum, but does not grossly invade the cortex. In most cases requiring mandibular resection, however, more extensive access must be achieved either via a lip-splitting incision or transcervical approach as described above. Very select low-grade lesions limited to the mandible may be amenable to marginal resection via a relatively small transoral or cervical incision. Larger lesions that are limited to the mandible may permit segmental resection via a similarly small incision. Caution is urged, however, as the degree and duration of superior retraction of the soft tissue envelope, which is required by such an approach, puts the marginal mandibular nerve at high risk of retraction injury. A lip-split or visor flap minimizes such risk. Once adequate exposure is achieved, proximal and distal mandibulectomy sites are scored with a saw blade and any necessary dental extractions are performed. In the dentate patient, an appropriate reconstruction plate is selected and precontoured to span the anticipated defect, with at least three holes predrilled on each side of the defect. In instances where tumor significantly deforms the outer contour of the mandible and precludes accurate molding of hardware, it may be necessary to estimate the desired contour when shaping the plate. Alternately, there are commercially available three-dimensional models based upon preoperative imaging, which may be customized and altered to assist with reconstruction planning. For lesions posterior to the mental foramen requiring resection of the posterior mandibular body or retromolar trigone, it may be necessary to extend a vertical cut from the mandibular angle to the sigmoid notch. This allows removal of the anterior ramus and coronoid process, while preserving the condyle and a length of posterior ramus sufficient to affix reconstruction hardware. It should be noted that aggressive attempts to preserve the condyle in such cases may be associated with an increased risk of local recurrence, and resection of the condyle and ramus without mandibular reconstruction must be favored if there is concern about achieving adequate margin status otherwise.[11] Although it is useful to delineate the intraoral mucosal margins prior to segmental mandibulectomy, performing bone cuts early in the resection will greatly improve exposure and facilitate the remainder of the soft tissue dissection. Dissection over the lateral surface of the mandible in a subperiosteal plane is usually sufficient for lesions that are limited to the medial or superior aspect of the bone. However, if tumor extends onto the buccal surface of the mandible or into the gingivobuccal surface, the margin of resection must include a cuff of overlying unaffected soft tissue.

## Reconstruction

Although beyond the scope of this chapter, suffice it to say that optimal outcomes in function and cosmesis mandate appropriate reconstruction. Additionally, free tissue transfer has permitted larger surgical resections and margins around tumors with improved cosmetic and functional results, thus obviating the need to be conservative around certain areas and risk close or positive margins. In general, the authors advocate fibula osteocutaneous free flaps when feasible for mandible defects with single soft tissue layer reconstruction (mucosa or skin), while utilizing scapula/parascapular osteocutaneous flaps for mandible *and* two-layer soft tissue defects (i.e., mucosa *and* skin). For soft tissue reconstruction, primary closure, secondary intention healing, and allograft are employed commonly for early T1 and T2 cancers. However, the area and volume of the defect is important, although previously operated or radiated patients may require vascularized free tissue transfer including the radial forearm, the anterolateral thigh, and others.

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## Site-specific Considerations

***Lip.*** In lesions that involve less than one-third of the lip, simple excision with primary closure offers acceptable oncologic and reconstructive results. Full-thickness excisions with margins of 8 to 10 mm are necessary.[12] Proper alignment of the vermilion border and the orbicularis muscle layer reconstruction is critical in ensuring long-term cosmesis and function; precise marking with prolene sutures prior to incision may aid in reapproximation. For lesions larger than one-third, but less than two-thirds of the length of the lip, reconstructive options including an Abbe-Estlander "lip-switch" flap, or a Karapandzic flap may be utilized. As the risk of an unacceptable cosmetic result, microstomia, and oral incompetence increases when advancement flaps are used for large lesions, free tissue transfer is often used for reconstructing large defects. To ensure oral competence after the use of an adynamic soft tissue free flap to reconstruct the lower lip, adjunctive procedures such as a fascial sling, palmaris longus sling, or temporalis tendon transfer may be necessary.

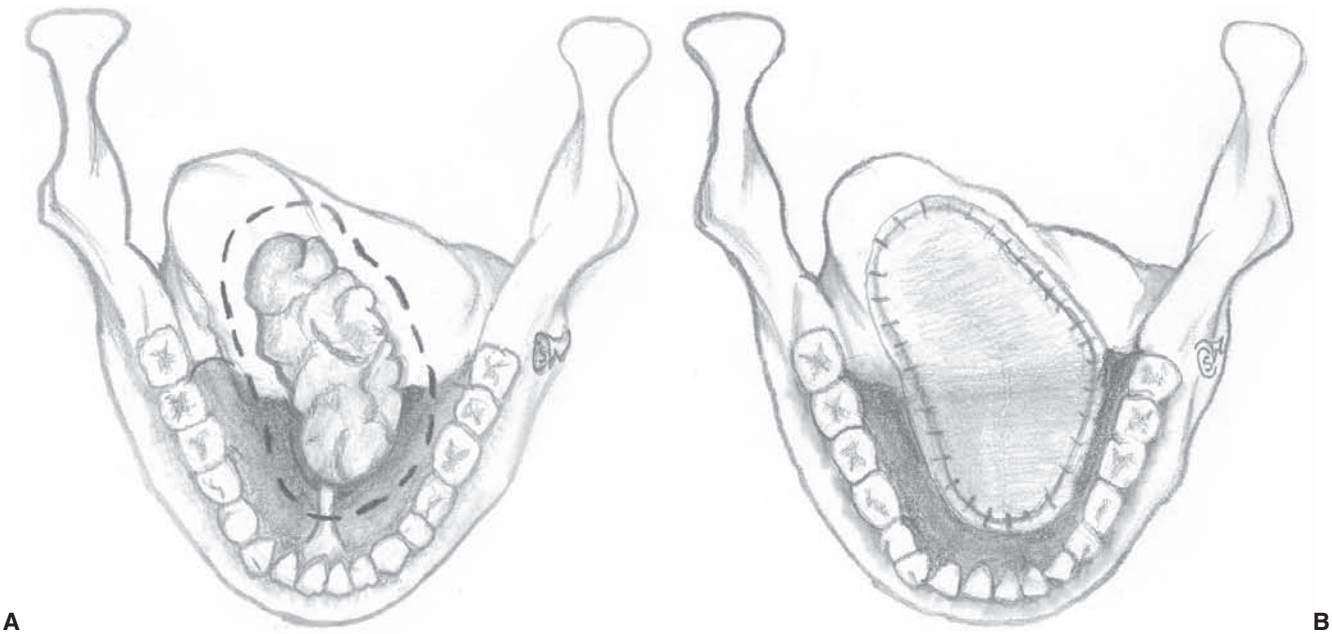
***Buccal Mucosa.*** Surgical approaches for addressing buccal carcinoma vary by the size and location of the primary lesion. These are commonly superficial, though involvement of the buccinator muscle or extension into Stenson duct may require the surgeon to consider a cheek skin or preauricular incision to assure margin clearance superficially and into the parotid. From a reconstructive perspective, a mucosal cheek flap is often used for small lesions. Contracture should be anticipated for larger lesions, and a skin graft, acellular dermal graft, or mucosal flap should be used to help prevent this. For larger defects, a radial forearm free flap may be particularly well suited for reconstruction in this region as it provides reliable, thin, and pliable tissue.

***Floor of Mouth.*** Early-stage lesions in this area may be amenable to transoral excision with primary closure or a split-thickness skin graft (Fig. 16-42), while more extensive lesions often require a composite resection involving the FOM musculature, the mandible, and the oral tongue. It is important to realize the possibility of extension into the Wharton duct, the lingual nerve, and the sublingual gland in these tumors. Reconstruction should be aimed at preserving tongue mobility and reducing mandibular/dental exposure or fistula.

***Retromolar Trigone.*** For larger RMT lesions, access to the area can be achieved through a submandibular incision as opposed to a lip-splitting incision. If the mandible is found to be involved with tumor, a marginal mandibulectomy is considered acceptable, unless the mandible has previously been irradiated or there is obvious cortical erosion. In the previously irradiated mandible, more widespread involvement is typically present, making a marginal mandibulectomy a poor choice for successful management of disease. Inner table mandibulectomies are not feasible in the RMT under any circumstances due to the thinness of the mandible in the area. If there is gross invasion of the mandible, a unilateral apron flap is considered appropriate in order to expose the medial pterygoid and masseter, which also may be involved. Appropriate mandibular release and plating can then be performed via a combined transoral/transcervical exposure. Reconstruction of lateral defects often requires vascularized tissue with scapula, fibular, or forearm osteocutaneous flaps.

***Oral Tongue.*** Depending upon the extent of the primary oral tongue lesion, surgical management can range from a partial or hemiglossectomy in T1/T2 lesions (Fig. 16-43) to a near total or total glossectomy with mandibulectomy in some T3/T4 lesions.[13] Defect closure must provide adequate mobility of the tongue to limit tethering to the FOM or gingiva. For small defects, allograft, secondary intention healing, or primary closure is reasonable if tongue mobility is not compromised. A radial forearm or anterolateral thigh free tissue transfer is often chosen for use in subtotal glossectomy defects for this reason.

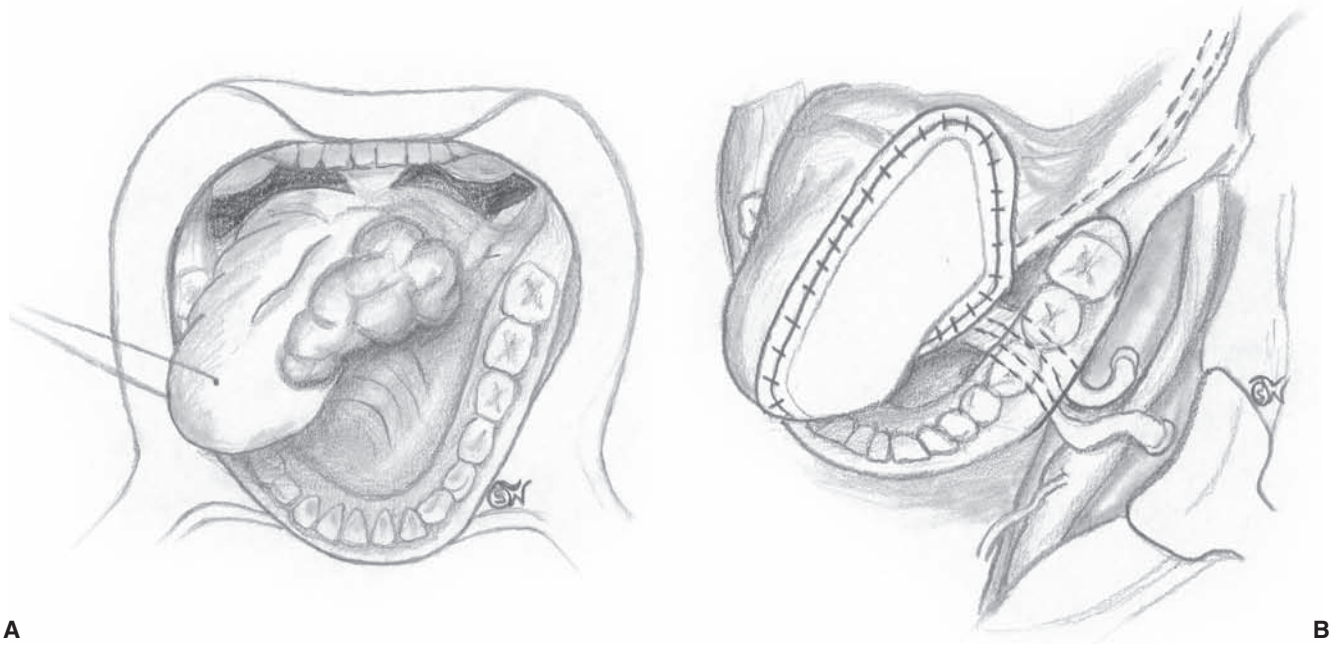
***Palate.*** For early-stage lesions of the hard palate, wide local excision with 1- to 2-cm margins is sufficient, whereas larger lesions often require a total or partial maxillectomy. The removal of early lesions often can be performed transorally, while moderate size tumors and those extending to the infraorbital foramen or pterygoid region may require a sublabial approach. Early-stage



A B

**FIGURE 16-42.** Resection of FOM tumor with skin graft or allograft reconstruction.

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A B

**FIGURE 16-43.** Hemiglossectomy with microvascular anastomosis.

malignancies of this area include low-grade polymorphous adenocarcinoma, which may or may not require bony palate resection, and thus oronasal or oromaxillary communication. Inferior maxillectomy is appropriate for small lesions limited to the alveolar ridge and hard palate. More extensive disease requires total maxillectomy, for which a lateral rhinotomy and upper lip-splitting incision generally provide adequate exposure. For smaller defects, placement of an obturator with or without osseointegrated implants is an effective means to restore oral–nasal separation and allow for fitting of dentures. However, large defects may realize improved speech, oral competence, and cosmesis with free fibula, scapula, or forearm osteocutaneous flaps.

***Alveolus.*** Carcinoma of the mandibular alveolus is treated similarly to carcinoma of the RMT and the FOM. These lesions often present with early mandibular involvement necessitating marginal or segmental mandibulectomy. Likewise, carcinoma of the maxillary alveolus is treated similarly to carcinoma of the hard palate. Advanced lesions may invade adjacent structures, including the nasal cavity, the paranasal sinuses, the orbit, and the skull base. Ablative surgery often results in large maxillofacial defects, necessitating complex reconstructive techniques.

## SUMMARY

Technical considerations and practical aspects of the surgical approach to OC cancer encompass functional, cosmetic, and oncologic principles. Oncologically, addressing the neck and the primary separately or in continuity should afford adequate exposure for margin clearance, appropriate preservation of vital noninvolved structures, and indicated lymphadenectomy. Cosmetically, mandibular contour, neuromuscular function, and limitation of unnecessary incisions are of primary concern. Functionally, preservation of soft palate and tongue function and mobility, dental occlusion, mandibular continuity, avoiding orocutaneous fistula formation, and laryngeal suspension will address the majority of functional deficits from oral cancer surgery. Surgeons should be prepared to utilize the various weapons in their head and neck oncologic armamentarium to improve locoregional control, survival, and function.

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CHAPTER 17

# Cancer of the Oropharynx

## PART A:
## General Principles and Management

Waleed F. Mourad, Kenneth S. Hu, Walter H. Choi, Bruce Culliney, Zujun Li, Adam S. Jacobson, and Louis B. Harrison

### INTRODUCTION

Oropharynx cancer (OPC) is a common manifestation for squamous cell carcinoma of the head and neck (SCCHN), and most OPC is caused by the human papillomavirus (HPV).[1] The estimated incidence of pharyngeal cancers in the United States for 2011 was 13,580 new cases and 2,430 deaths.[2] There is increasing incidence of OPC despite the decline in the overall incidence of SCCHN.[1] Current estimates suggest that by the year 2020, the annual number of HPV-positive OPC will exceed the annual number of HPV-positive uterine cervix carcinomas and there will be >15,000 cases of HPV-positive OPC per year by 2030.[1]

OPC typically involves patients in their fifth through seventh decades of life. Due to the increasing association with HPV, younger patients are being diagnosed. Men are afflicted 3 to 5 times more often than women.[2] Investigators have reported that the increase in OPC is exclusively in the base of tongue (BOT) and tonsil and that HPV/p16 accounts for approximately 70% to 90% of OPC-SCCHN.[1,3–5] Furthermore, HPV-positive OPC patients are often middle-aged (40–59 years) white men, of higher socioeconomic status, nonsmokers, and nondrinkers, but with a higher number of oral sexual partners.[1,6–15]

A history of tobacco or alcohol use can also be associated with other metachronous or synchronous tumors of the upper aerodigestive tract. Thus, tobacco and alcohol abuse still represent significant risk factors for the development of OPC and other cancers of the head and neck.[16,17] Other risk factors for OPC may include[18]

1. a diet poor in fruits and vegetables[19]
2. the consumption of maté, a stimulant beverage commonly consumed in South America[20]
3. the chewing of betel quid, a stimulant preparation commonly used in parts of Asia.[21]

Historically, the prognosis for OPC depends upon the location of the primary tumor and the stage at presentation. Studies have shown that HPV-positive OPC have more favorable prognosis, with approximately two times better 5- and 10-year overall survival (OS) compared with HPV-negative patients.[1] Likewise, recent oncologic and functional outcome data have shown superior results in HPV/p16-positive OPC patients. Of note, the significant improvement in the OS was mainly seen in patients with tonsil and BOT cancer, without obvious survival improvement in other SCCHN sites.[22] Interestingly, the survival for African Americans patients with OPC has not shown such improvement. This is attributed to the difference in OPC origin (smoking induced among African Americans vs. HPV induced among Caucasians).[10,23]

The leading cause of death in OPC and SCCHN patients is loco-regional recurrence (LRR). However, advances in radiation therapy (RT) as well as concomitant chemotherapy and RT (chemo-RT) have improved loco-regional control (LRC) rates, even for advanced-stage disease. There has also been a growing interest in the role of minimally invasive surgery (MIS) including transoral lateral oropharyngectomy (TLO), transoral laser microsurgery (TLM), and transoral robotic surgery (TORS) in the otolaryngology community.[24–29] Their application to OPC management is being actively explored. Thus, the treatment strategies for these patients are numerous, and advances in organ preservation with attention to quality of life (QOL) remain the major focus of clinical research investigations.

### ANATOMY OF THE OROPHARYNX

The pharynx is divided into the nasopharynx, the oropharynx, and the hypopharynx (Fig. 17-1). The oropharynx is located between the soft palate superiorly and the hyoid bone



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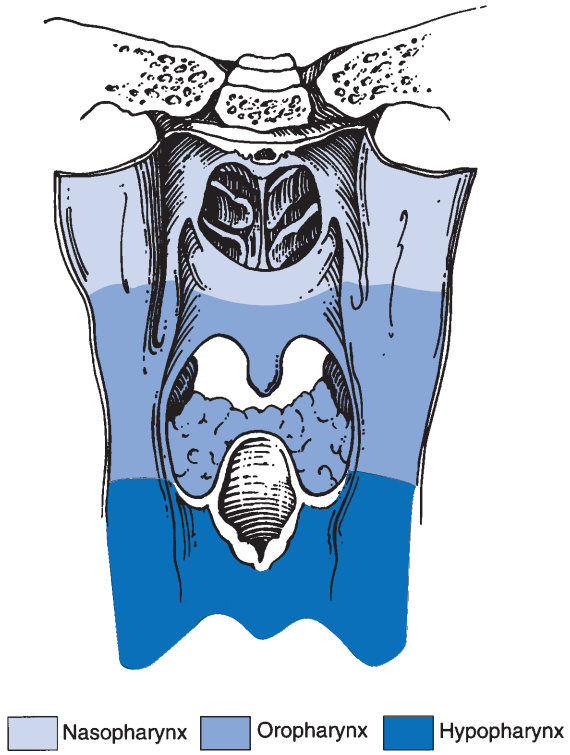



**FIGURE 17-1.** Regions of the pharynx.

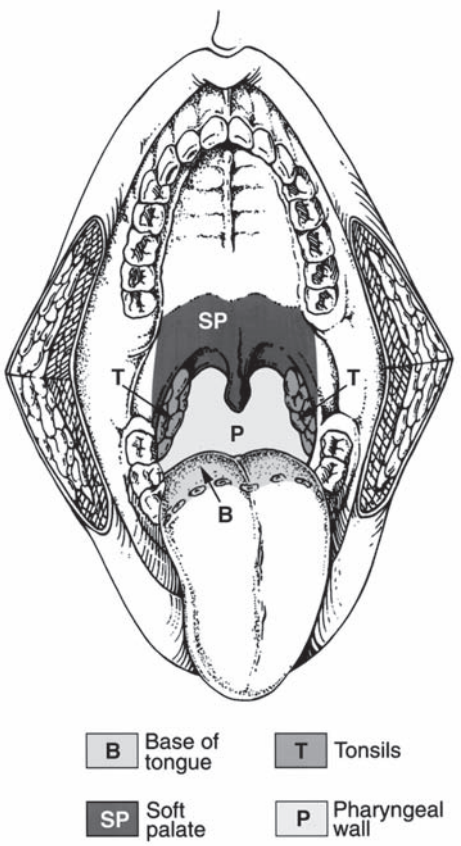



**FIGURE 17-2.** Topographic surface anatomy of the oropharynx; view from oral cavity.

inferiorly. It is continuous with the oral cavity anteriorly and communicates with the nasopharynx above and the supraglottic larynx and the hypopharynx below. Within the oropharynx are four different sites: soft palate, tonsillar region (fossa and pillars), BOT, and posterior and lateral oropharyngeal wall between the nasopharynx and the pharyngoepiglottic fold (Fig. 17-2).

## Soft Palate

The soft palate includes the uvula and incompletely separates the oral cavity and oropharynx from the nasopharynx. It is continuous laterally with the tonsillar pillars and attaches anteriorly to the hard palate. It forms both the roof of the oropharynx and the floor of the nasopharynx. The soft palate demarcates the oral cavity from the oropharynx as well as the oropharynx from the nasopharynx. Tumors arising from the oropharyngeal surface are far more common than are those arising from the nasopharyngeal surface. The authors have never actually seen a tumor arising from the nasopharyngeal surface.

## Tonsillar Region

The palatine (or faucial) tonsils, located posteriorly on the lateral wall of the oropharynx, are almond-shaped structures of largely lymphoid tissue embedded in a fibrous capsule. The tonsillar fossa, which encases the palatine tonsil, is bounded by an anterior and posterior portion, commonly called the pillars. These contain the palatoglossus and the palatopharyngeus muscles, respectively, and converge superiorly to join with the soft palate. The medial portion of the fossa becomes the glossotonsillar sulcus.

## Base of Tongue

The BOT is the tissue that extends inferiorly from the circumvallate papillae to the vallecula (base of the epiglottis) and encompasses the pharyngoepiglottic and the glossoepiglottic folds. Laterally, it extends to the glossotonsillar sulcus. The tongue musculature is composed of the genioglossus, the styloglossus, the palatoglossus, and the hyoglossus muscles. The blood supply is identical to that of the oral tongue. Motor innervation of the muscles of the tongue is through the hypoglossal nerve (XII), except for the palatoglossal muscle, which is innervated by the pharyngeal branch of the vagus nerve (X). In the BOT, both taste and general sensations are innervated by the glossopharyngeal nerve (IX).

## Pharyngeal Wall

The posterior pharyngeal wall starts at the inferior aspect of the nasopharynx, in the region of the soft palate, and extends to the level of the epiglottis inferiorly. It comprises the posterolateral surfaces of the oropharynx. The pharyngeal constrictor muscles constitute the framework of the pharyngeal wall. The wall is related to the second and third cervical vertebrae and contains the mucosa, the submucosa, the pharyngobasilar fascia, the underlying superior constrictor muscle, and the buccopharyngeal fascia. The lateral aspect of the pharyngeal wall is continuous with the pharyngoepiglottic fold and continues into the lateral aspect of the pyriform sinus. Nerve supply is from cranial nerves IX and X. The pharyngeal wall is rich in lymphatics, the primary drainage being directed to the retropharyngeal (RP) nodes and levels II and III.

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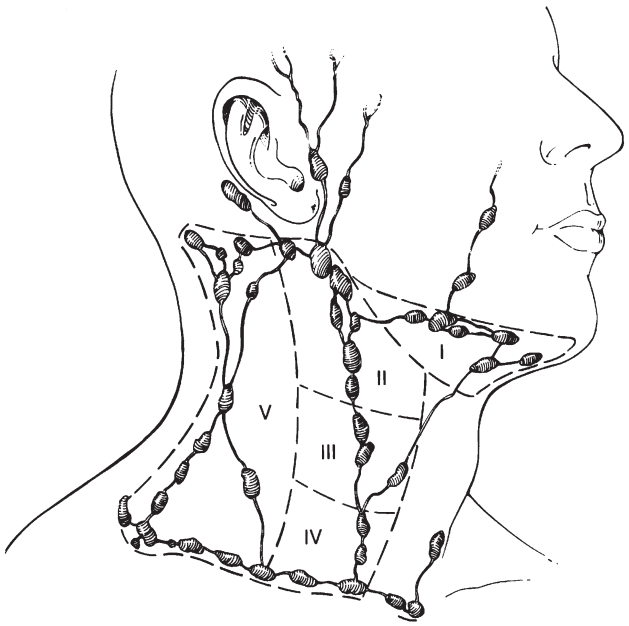



**FIGURE 17-3.** Anatomic lymph node levels of the neck.

## Lymphatics of the Oropharynx

The lymphatic drainage of the neck was described by Rouviere in 1938 and has been refined by others.[30–32] The lymph node groups are described by clinical levels I to V as depicted in Fig. 17-3.

The primary drainage of the oropharynx is to the jugulodigastric (level II) node(s) located in the upper deep jugular chain. The tonsillar region, pharyngeal portion of the soft palate, the lateral and posterior oropharyngeal walls, and the BOT are also drained by the RP and parapharyngeal nodes. These nodes are located in the RP and parapharyngeal space that is closely related to cranial nerves IX through XII, the internal jugular vein, and the internal carotid artery at the base of skull. The RP lymph nodes are subdivided into lateral (Rouviere) and medial nodal chains.[33–35] The lateral nodes lie posterolateral to the nasopharynx and the oropharynx, just medial to the internal carotid artery. The parapharyngeal lymph nodes are also known as the junctional nodes, owing to the junction of the spinal accessory (level V) and the upper internal jugular lymphatic chains.

The probability of lymphatic metastasis is related to size and location of the primary tumor within the oropharynx. The order of progression of lymph node metastases usually proceeds superiorly, from the high cervical first-echelon nodes (level II) inferiorly to the midcervical and lower cervical nodes (levels III and IV). Skip metastasis can occur in which a particular lymph node level is bypassed, but this is very unusual. Candela et al. evaluated 333 previously untreated patients with SCC of the oropharynx or the hypopharynx to ascertain the prevalence of neck node metastases by neck level. The patients underwent classic radical neck dissections. Isolated skip metastases outside of level II, III, or IV occurred in only one patient (0.3%). Otherwise, level I or V involvement was always associated with nodal metastases at other levels.[36] Metastases to the RP nodes are most commonly associated with cancers of the nasopharynx and the pharyngeal wall,[37–40] but can also occur from other subsites, particularly with advanced disease.[40–42] Notably, these metastases occur primarily along the lateral RP nodal chains. Involvement of the medial chain is extremely rare.[30,38,40]

In 1994, Hasegawa and Matsuura reported on a series of 24 patients with advanced carcinoma of the oropharynx and the hypopharynx treated with surgery and RP node dissection up to the base of the skull. This was followed by postoperative RT (PORT) of 50 Gy to RP space if nodes were pathologically involved. A total of 50% (12 of 24) of the patients had positive RP nodes: 1 of 5 (20%) with pathologic N0 neck and 12 of 19 (63%) with pathologic N-positive neck. More specifically, RP node positivity was established histopathologically in 36% (4 of 11 patients) and 61.5% (8 of 13 patients), respectively.[43] In a retrospective study of 774 patients with SCC of the nasopharynx, the oropharynx, the hypopharynx, and the supraglottis, using CT scans for RP nodes evaluation, McLaughlin et al. found an overall incidence of radiologically positive RP nodes in 9% of the patients. The highest incidence was seen in patients with cancer of the nasopharynx (74%) and the pharyngeal walls (19%). They also noted that in patients with advanced cancer of the oropharyngeal walls and the hypopharynx, the incidence of radiologically positive RP nodes was higher in patients with positive cervical nodes than in those with an N0 neck (pharyngeal wall: N+ 21%, N0 16%; hypopharynx: N+ 9%, N0 0%).[38]

Shimizu et al. reported a rate of 13% of RP node metastases for OPC. They found that the risk was higher for patients with posterior and lateral pharyngeal wall cancers (29% for lateral and posterior wall vs. 0% for others sites).[44]

Dirix et al. reported a rate of RP nodal metastases of 16% in a series of 208 patients with OPC after evaluation of pretreatment CT scans. Patients with RP nodal metastases had significantly more regional recurrences (45% vs. 10%). RP nodal involvement independently predicted the likelihood of regional recurrence in multivariate analysis ($p = 0.01$). Furthermore, disease-specific survival (DSS) was significantly lower in the RP node-positive group (38% vs. 58%).[45]

Bussels et al. analyzed the same population of 208 patients with OPC. They reported RP node involvement in 23% of those patients with nodal disease in other neck levels. More frequently, the RP nodes were involved in the case of posterior pharyngeal wall (5 of 13 = 38%) and soft palate primaries (5 of 9 = 56%). Ipsilateral involvement of level II and contralateral involvement of level III predicted for involvement of the ipsilateral RP nodes on multivariate analysis ($p < 0.05$). A solitary ipsilateral RP node was present in 3 (9%) of 34 patients with RP nodes. Two of these three patients had a primary posterior pharyngeal wall tumor. No patients presented with a solitary contralateral RP node.[46]

Yoshimoto et al. reported their series of 84 patients with BOT cancer. Two patients had RP node metastases at the time of diagnosis and two more developed recurrent cancer in the RP node. Three of these four patients had a tumor extending to the lateral pharyngeal wall. They found that the incidence of contralateral or RP node metastasis was low if the tumor neither crossed the midline nor infiltrated the lateral wall.[47]

Chan et al. retrospectively reviewed the 18F-FDG PET-CT studies of 244 patients with SCC of the oro- and the hypopharynx. RP node involvement was identified in 17%.[48]

It is clear from the data that inclusion of the lateral RP nodes is an important part of the treatment. This is especially true for patients with cervical node metastases, but it is also potentially important for patients with N0 necks.

Tumors located in the midline (the BOT, the soft palate, and the posterior pharyngeal wall) exhibit a higher propensity for bilateral nodal metastases. The probability of cervical node metastases, as demonstrated by clinical and radiological examinations of the soft palate, the tonsillar fossa, the BOT, and the oropharyngeal wall, is shown in Tables 17.1 through 17.3.[41,49,50]

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**TABLE 17.1 Percentage Incidence of Cervical Lymph Node Metastasis as Determined by Clinical Examination**

| Location | N0 | N1 | N2 |
|---|---|---|---|
| **Oropharyngeal wall** | | | |
| T1 | 75 | 0 | 25 |
| T2 | 70 | 10 | 20 |
| T3 | 33 | 23 | 45 |
| T4 | 24 | 24 | 52 |
| **Soft palate** | | | |
| T1 | 92 | 0 | 8 |
| T2 | 64 | 12 | 25 |
| T3 | 35 | 26 | 39 |
| T4 | 33 | 11 | 56 |
| **Tonsillar fossa** | | | |
| T1 | 30 | 41 | 30 |
| T2 | 33 | 14 | 54 |
| T3 | 30 | 18 | 52 |
| T4 | 11 | 13 | 77 |
| **Base of tongue** | | | |
| T1 | 30 | 15 | 55 |
| T2 | 29 | 15 | 57 |
| T3 | 26 | 23 | 52 |
| T4 | 16 | 9 | 76 |

*Source:* From Lindberg R. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. *Cancer.* 1972;29:1446–1449, with permission.

**TABLE 17.2 Defining the Risk of Involvement for Each Neck Nodal Level in Patients with Early T-Stage/Node-Positive Human Papillomavirus–related Oropharyngeal Carcinoma**

| Neck Level | Pathologically Involved | Risk of Involvement When Negative on CT |
|---|---|---|
| IB | 8.4% | 2.8% |
| II | 89.4% | 72% |
| III | 38.3% | 16% |
| IV | 20% | 7% |
| V | 2.6% | 0.8% |

*Source:* From Sanguineti G, Gunn GB, Parker BC, et al. Weekly dose-volume parameters of mucosa and constrictor muscles predict the use of percutaneous endoscopic gastrostomy during exclusive intensity-modulated radiotherapy for oropharyngeal cancer. *Int J Radiat Oncol Biol Phys.* 2011;79:52–59, with permission.

**TABLE 17.3 Percentage Incidence of Cervical Lymph Node Metastasis in Soft Palate Cancer**

| Nodal Group | Ipsilateral (%) | Contralateral (%) |
|---|---|---|
| I | 9 | 6 |
| II | 86 | 29 |
| III | 26 | 6 |
| IV | 6 | 0 |
| V | 0 | 3 |
| Supraclavicular | 0 | 0 |
| **Tonsillar fossa** | | |
| I | 16 | 3 |
| II | 97 | 13 |
| III | 24 | 3 |
| IV | 13 | 2 |
| V | 23 | 7 |
| Supraclavicular | 0 | 0 |
| **Base of tongue** | | |
| I | 8 | 1 |
| II | 88 | 31 |
| III | 40 | 7 |
| IV | 9 | 3 |
| V | 12 | 2 |
| Supraclavicular | 4 | 1 |

*Source:* From Mukherji SK, Armao D, Joshi VM. Cervical nodal metastases in squamous cell carcinoma of the head and neck: what to expect. *Head Neck.* 2001;23:995–1005, with permission.

## PATHOLOGY

More than 90% of tumors of the oropharynx are SCC, the remainder being malignant melanomas, minor salivary gland tumors, sarcomas, plasmacytomas, lymphomas, and other rare tumors.[51] Benign and malignant tumors that can be found in the oropharynx are listed in Table 17.4.

### Clinical Presentation, Pathogenesis, and Patterns of Spread

Patients with OPC are frequently asymptomatic until their primary tumors reach a significant size or metastasize to a lymph node in the neck. The usual complaints consist of vague discomfort or irritation, or a mass in the neck. The manifestation of symptoms depends upon the location of the primary tumor. Some tumors are visualized easily, but others can be insidious and are only found by careful examination of all the mucosal surfaces of the oropharynx. Pain can be a presenting complaint, which can be attributed either to deep infiltration of tumor or to referred pain. The following sections list some of the possible clinical scenarios based on the site of the primary tumor.

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**TABLE 17.4 Differential Diagnosis of an Oropharyngeal Mass**

| Malignant | Benign |
|---|---|
| Squamous cell carcinoma | Papilloma |
| Minor salivary gland tumor | Retention cyst |
| Lymphoma | Fibroma |
| Sarcoma | Lipoma |
| Melanoma | Hemangioma |
| Plasmacytoma | Lymphangioma |
| Other | Neuroma |

***Soft Palate.*** Tumors of the soft palate are almost exclusively found on the oropharyngeal as opposed to the nasopharyngeal surface (Fig. 17-4). Tumors can extend to involve the tonsillar pillars and the BOT. Occasionally, these lesions may extend laterally and superiorly as far as the nasopharynx. Involvement of the palatine nerve can result in tumor tracking along this pathway, with extension to the skull base. Lymphatic involvement is primarily to level II. Lesions of the midline and the uvula can result in bilateral nodal metastases more frequently than do lateralized lesions. The RP nodes are also at risk.[52]

***Tonsil.*** The tonsil is the most common location for a primary tumor of the oropharynx. Common presenting symptoms are ipsilateral referred otalgia, odynophagia, or sensation of a lump or foreign body in the throat. Lesions involving the anterior tonsillar pillar can appear as areas of dysplasia, inflammation, or a superficial spreading or exophytic lesion. Frequently, these lesions become endophytic, ulcerate, and can spread laterally to the buccal mucosa and directly to the retromolar trigone (Fig. 17-5). Inferior extension to the BOT can occur. Perez et al. reported that 60% of tonsil cancers involved the soft palate and 55% extended into the BOT.[53] Superior extension can even involve the hard palate. Medial extension can involve the oral tongue. The close proximity of the anterior tonsillar pillar to the mandible places the periosteum and the bone at risk for tumor involvement in advanced cases. Posterior and superior extension with destruction of the tonsillar pillars can lead to involvement of the pterygoid muscles, with subsequent trismus and pain. The lymphatic drainage is primarily to level II but can also involve RP nodes, as previously discussed. Patients with neck node involvement are at higher risk for RP node metastases.[38]

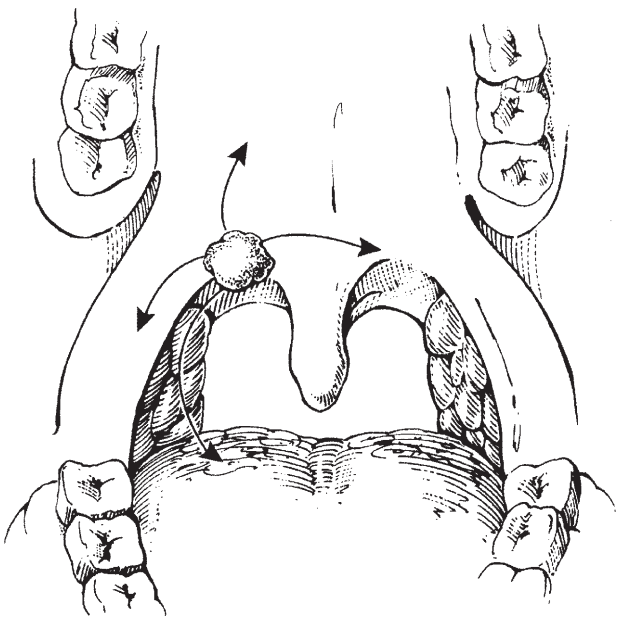


**FIGURE 17-4.** Patterns of tumor spread in soft palate.

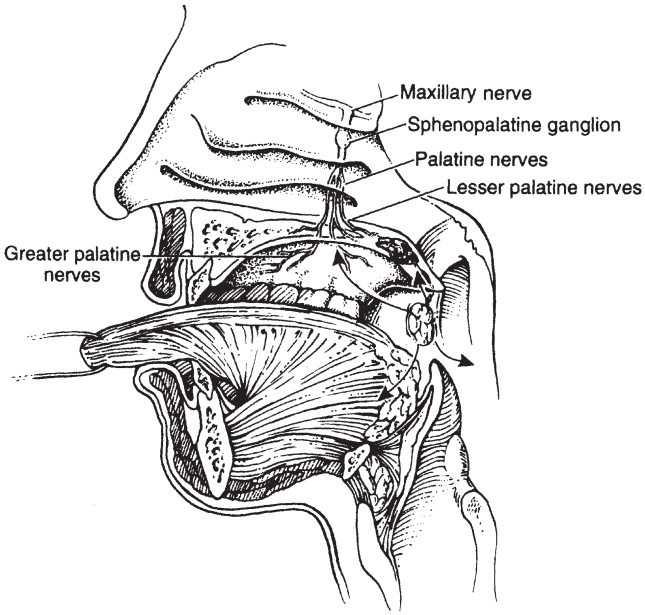



**FIGURE 17-5.** Patterns of spread of tonsillar carcinoma.

Tumors of the tonsillar fossa (in contrast to those of the tonsillar pillar) are either exophytic or ulcerative and present in more advanced stages than do tumors of the pillars or soft palate. Approximately 75% of patients will present with stage III or IV disease, for which the patterns of extension are similar to those of the tonsillar pillar. In addition, lateral extension can involve the parapharyngeal space toward the base of skull, causing neurologic signs and symptoms. Tumors of the posterior tonsillar pillar can extend inferiorly and involve the pharyngoepiglottic fold and the posterior aspect of the thyroid cartilage.

The probability of clinical lymph node involvement is greater with tumors of the tonsillar fossa in contrast to that of the tonsillar pillar. The lymphatic drainage depends upon the location of the primary tumor. Lindberg describes nodal metastases in 76% of patients with tonsillar fossa tumors.[41] The most common nodal group was level II. Contralateral lymph nodes were detected in 11% of patients. In contrast, tumors of the anterior tonsillar pillar or retromolar trigone region have an incidence of ipsilateral lymph node metastases of 45%, level II being the most common node-bearing region. Contralateral adenopathy was present in only 5% of patients. The issue of ipsilateral versus bilateral neck metastasis is discussed later in this chapter.

***Base of Tongue.*** Squamous cell carcinoma of the BOT is highly insidious. The BOT is almost devoid of pain fibers. Frequently, these tumors are asymptomatic until they have progressed significantly. Patients with cancers of the BOT often present with neck node metastases, only to be found to have a BOT lesion upon full evaluation. Visualization of this area on physical examination can be difficult, and a lesion can be often missed.[54]

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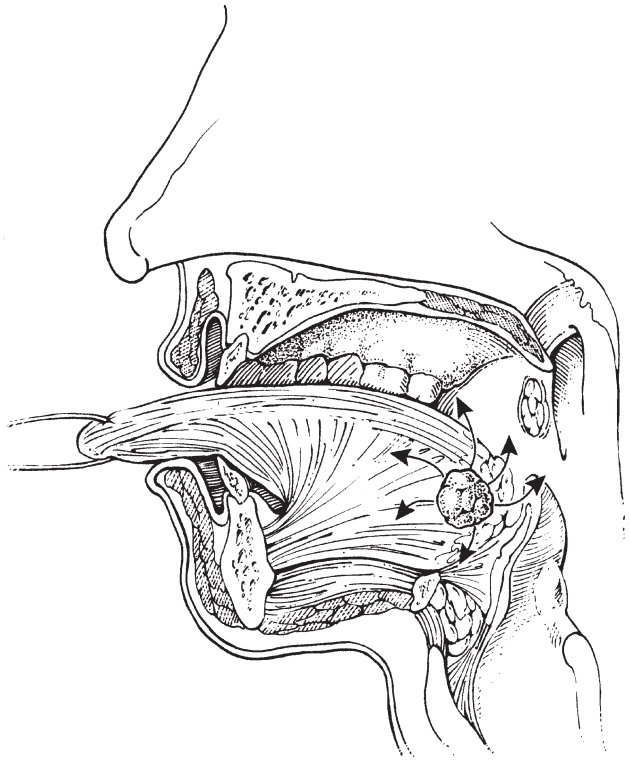


**FIGURE 17-6.** Patterns of spread of base of tongue cancer.

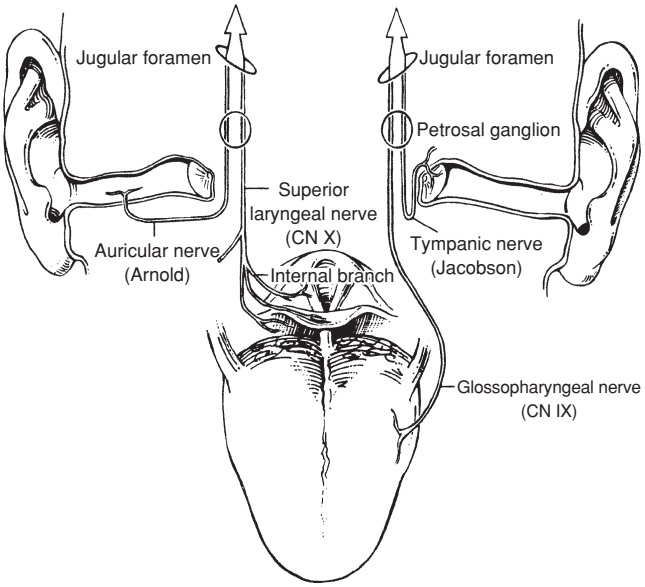



**FIGURE 17-7.** Neural pathways of referred otalgia. For pain sensed in the front of the helix and tragus, the skin of the anterior wall of the external auditory canal, the tympanic membrane, and the temple, pain is referred through the auriculotemporal nerve, which joins the lingual nerve, where the two become the mandibular nerve and enter the foramen ovale. The sensation of deep ear pain is through the tympanic nerve (Jacobson), which joins the glossopharyngeal nerve (cranial nerve IX) as the two traverse the jugular foramen. These general somatic afferent fibers innervate the base of tongue, the inner surface of the tympanic membrane, and the upper pharynx. For pain sensed in the back of the pinna, the posterior wall of the external auditory canal, and the external surface of the tympanic membrane, pain is referred through the auricular nerve (Arnold), which joins the superior laryngeal nerve (cranial nerve X), which in turn innervates the larynx, the pharynx, and the epiglottis as it traverses the jugular foramen.

Patients may experience the sensation of a mass or discomfort in the throat, with bleeding and pain at later stages. Patients might also experience difficulty with speech and swallowing. Occasionally, referred otalgia is the first symptom.

Extension anteriorly can involve the oral tongue, superior and lateral extension can involve the tonsil, and inferior extension can involve the vallecula, the epiglottis, and the preepiglottic space (Fig. 17-6). Locally advanced BOT tumors can infiltrate the deep muscle and cause fixation. Larynx and hypopharynx involvement can occur with advanced, inferior extension.

Lymph node metastasis is common, owing to the rich lymphatic drainage of the BOT. The most common first-echelon nodal region is level II, though involvement of levels III and IV is also seen. Approximately 70% of patients or more will present with ipsilateral metastases, and 10% to 20% will present with bilateral nodal metastases.[41]

***Pharyngeal Wall.*** Tumors of the pharyngeal wall are generally diagnosed in an advanced stage due to the silent location in which they develop. Symptoms can include pain and bleeding and a mass in the neck. Disease involvement can extend to the nasopharynx superiorly, the prevertebral fascia posteriorly, and the pyriform sinuses and the hypopharyngeal wall inferiorly. Clinically palpable cervical lymph node metastases are present in 25% of patients with T1 lesions, 30% of those with T2 lesions, 66% of patients with T3 lesions, and >75% of patients with T4 disease. Because most pharyngeal wall tumors extend past the midline, bilateral cervical metastases are common. RP nodes are also at great risk.[38]

***Referred Otalgia.*** Referred otalgia can be one of the first symptoms that a patient experiences with a mass in the oropharynx. The pathway for this referred pain is mediated by cranial nerves IX and X. The pathophysiology for otalgia is demonstrated in Figure 17-7.

## Diagnostic Evaluation

***History.*** The history should be part of a comprehensive evaluation of any patient with head and neck cancer. Patients can present with sore throat, odynophagia, otalgia, foreign body sensation in the throat, or a neck mass. If the history strongly reveals tobacco and alcohol use, efforts should be made to determine whether the patient is an alcoholic and continues to smoke. Alcoholic smokers are at risk for other chronic diseases of the heart, lungs, peripheral vascular system, liver, kidneys, and may present with signs of malnutrition. Before the institution of any therapeutic modality, the pathology material should be evaluated for HPV/p16 tumor status. All patients should cease alcohol and tobacco use. It may be necessary to guide the patient toward cessation programs. Clearly, those who discontinue smoking will better tolerate treatment and obtain a better result.[55]

***Physical Examination.*** The details of the physical examination are discussed in Chapter 1. Specific aspects of the physical examination should include evaluation of the lesion (exophytic or infiltrative), tongue mobility, and palatal motion. Fixation of the tongue will result in incomplete protrusion or deviation of the tongue to the side of tumor involvement. For tumors of

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the tonsil or the lateral pharyngeal wall, the examiner should test for anesthesia in the distribution of the ipsilateral mandibular nerve (V3). Any abnormality might suggest involvement of the inferior alveolar nerve in its pathway as it courses through the mandible or the base of skull and may direct the appropriate imaging study.[56] Because the tonsil is adjacent to the ascending ramus of the mandible, the BOT, and the parapharyngeal space, tumors may extend into these areas. This can often be detected by palpation. Indirect mirror examination and flexible endoscopy are important parts of the physical examination. It is useful to take a photograph or extensively diagram the physical findings in every patient. This can include a videotape. Such records are an excellent means of documenting the physical findings and of comparing future examination results to the initial presentation. In selected cases, an examination under anesthesia is recommended as a mean of obtaining information that is not completely accessible during office examination.

***Initial Workup and Radiographic Evaluation.*** In addition to a history and physical examination, a complete blood cell count and metabolic profile are recommended. Biopsy of a suspicious lesion is necessary to confirm the diagnosis.[57] The overwhelming majority of patients will also undergo PET-CT imaging as a key part of the staging evaluation. PET-CT may remove the need for a chest x-ray in many patients. See Chapter 4 for further discussion of general principles of head and neck imaging.

***Staging.*** The current staging criteria for tumors of the oropharynx, as defined by the American Joint Committee on Cancer (AJCC),[58] are listed in Table 17.5. This is a clinical staging system and not a pathologic staging system. If radiographic information reveals a discrepancy from clinical staging, this should be noted. Current staging allows the radiographic findings to factor into the clinical staging designation.

***Dental Evaluation and Prophylaxis.*** Treatment of OPC can result in a number of temporary and permanent effects on dental hygiene. Radiation-related xerostomia places dentulous patients at increased risk for dental caries, owing to the reduction in salivary flow, pH alteration, and proliferation of bacteria. A complete dental evaluation should be performed before any therapy is undertaken. See Chapter 9 for further discussion of dental oncology and maxillofacial prosthetics.

## Prognostic Factors

Traditionally, OPC prognostic factors for LRC, disease-free survival (DFS), or OS included TNM classification, location of the tumor, gender, age, and performance status.[59,60] As previously mentioned, in the current era, the impact of smoking and HPV/p16 tumoral positivity on OPC oncologic and functional outcomes has evolved remarkably.[61] A recent SEER analysis showed that the overall 5- and 10-year OS were approximately two times

**TABLE 17.5 American Joint Committee on Cancer (AJCC) Classification of Oropharyngeal Cancer**

| Primary tumor (T) | Stage | | | |
|---|---|---|---|---|
| T1: Tumor ≤2 cm in greatest dimension | **Stage 0** | Tis | N0 | M0 |
| T2: Tumor >2 cm by not >4 cm in greatest dimension | **Stage I** | T1 | N0 | M0 |
| T3: Tumor >4 cm in greatest dimension or extension to lingual surface of epiglottis | **Stage II** | T1 | N0 | M0 |
| T4A: Moderately advanced local disease; Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible* | | | | |
| * Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of larynx. | | | | |
| T4B: Very advanced local disease: Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery | | | | |
| **Regional lymph nodes (N)** | | | | |
| Nx: Regional lymph nodes cannot be assessed | | | | |
| * Metastases at Level VII are considered regional lymph node metastases. | | | | |
| N0: No regional lymph node metastasis | **Stage III** | T3 | N0 | M0 |
| N1: Metastasis in a single ipsilateral node, ≤3 cm | | T1–3 | N1 | M0 |
| N2A: Metastasis in a single ipsilateral node, >3 cm but ≤6 cm | **Stage IVA** | T4A | N0–2 | M0 |
| N2B: Metastasis in multiple ipsilateral nodes, >3 cm but ≤6 cm | | T1–3 | N2 | M0 |
| N2C: Metastasis in bilateral or contralateral lymph nodes, none >6 cm | **Stage IVB** | Any T | N3 | M0 |
| N3: Metastasis in lymph node >6 cm | | T4B | Any N | M0 |
| **Distant metastasis (M)** | | | | |
| M0: No distant metastasis present | | | | |
| M1: Distant metastasis present | **Stage IVC** | Any T | Any N | M1 |

*Source:* From Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJC cancer staging manual and the future of TNM. *Ann Surg Oncol.* 2010;17:1471–1474, with permission.

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better for those patients with HPV-positive disease regardless of the treatment modality.[1] Although HPV/p16-positive patients have better outcomes than HPV/p16-negative patients, this advantage disappears in the HIV-positive population and heavy smokers. Mourad et al. reported on 73 HIV-positive patients with SCCHN, of whom 24 patients had OPC (12 of whom were HPV/p16 positive).[62] The outcomes revealed no difference between HPV/p16-positive versus HPV/p16-negative in the setting of HIV-positive patients and no advantage to chemo-RT over RT alone. These data are limited by their retrospective nature, but suggest that HIV status is an important prognostic factor.[63] Gillison et al. reported that the risk of OPC progression and death increases directly as a function of tobacco exposure at diagnosis and during therapy and is independent of tumor p16 status and treatment.[8] Smoking-induced OPC has been associated with mutated *p53*, epidermal growth factor receptor (EGFR) overexpression, and lower HPV/p16 expression.[64] Thus, given its unique prognostic significance, HPV is reviewed in detail in Chapter 12. In addition, Chapter 3 reviews all other important prognostic factors.

Chan and McBride et al. reported that active smoking during and after RT is predictive for decreased DSS, OS, progression-free survival (PFS), and distant metastasis–free survival (DMFS) rates.[65,66] In addition to smoking, anemia around the time of RT is associated with higher rates of persistent/recurrent disease,[60,67,68] and its correction may improve outcome.[69]

Multiple studies have investigated various molecular markers as potential predictive factors in patients treated definitely for OPC. Single-institution studies have reported that a high intratumoral microvessel density predicts for poorer LC and worse OS after definitive RT.[70] High Ki-67 labeling index is associated with local relapse[71] and shorter time to relapse[72] after definitive treatment. Shoushtari et al. reported that tissue microarray analysis using p16, EGFR, and HIF-1α for OPC could provide prognostic information.[73] These markers need validation in larger, multi-institutional trials.

Age is an important factor in the OPC management paradigm. Meta-analysis has shown that the effectiveness of chemo-RT and altered RT fractionation decreases with increasing age. For patients older than 70 years, there was no difference in survival for either chemo-RT or altered fractionation RT over conventional RT alone.[74–77] A similar observation regarding older patients (≥65 years) was also reported by Garden et al.[78] Likewise, Bonner et al. reported that the effectiveness of RT plus cetuximab versus RT alone decreases with the increase in age.[79,80] Recently, Michal et al. challenged the dogma that elderly patients (≥70) may not benefit from concomitant chemotherapy. They explored two cycles of concomitant cisplatin with RT. Older patients did experience greater myelosuppression and required more supportive care. However, their outcomes were the same as younger patients. Moreover, they recommended that age alone is not a contraindication to primary chemo-RT for locally advanced SCCHN.[81]

# MANAGEMENT STRATEGIES, RESULTS, AND OUTCOMES

## General Principles

Treatment decisions are always a balance between tumor control, cost-effectiveness, and QOL. The best decisions are usually made in a multidisciplinary context. It is very important to understand the goals and preferences of the patient before finalizing any recommendation. In general, early-stage disease can be treated by either RT or surgery, whereas more advanced disease introduces the potential use of chemotherapy and multimodality therapies into the discussion. RT has the advantage in many cases because it can be used as a single modality, it comprehensively treats the primary site and the neck, and it provides excellent functional outcomes. The advent of MIS, such as TORS and TLM, has augmented the role of surgery in early-stage diseases and will be discussed. For some patients, the use of TORS or TLM can reduce the need for RT, providing a trade-off, which can be attractive. Chemotherapy is generally reserved for patients with advanced disease. In the following sections, the management guidelines, outcomes, and results of OPC will be reported.

# SELECTION OF THERAPEUTIC MODALITY

## General Principles

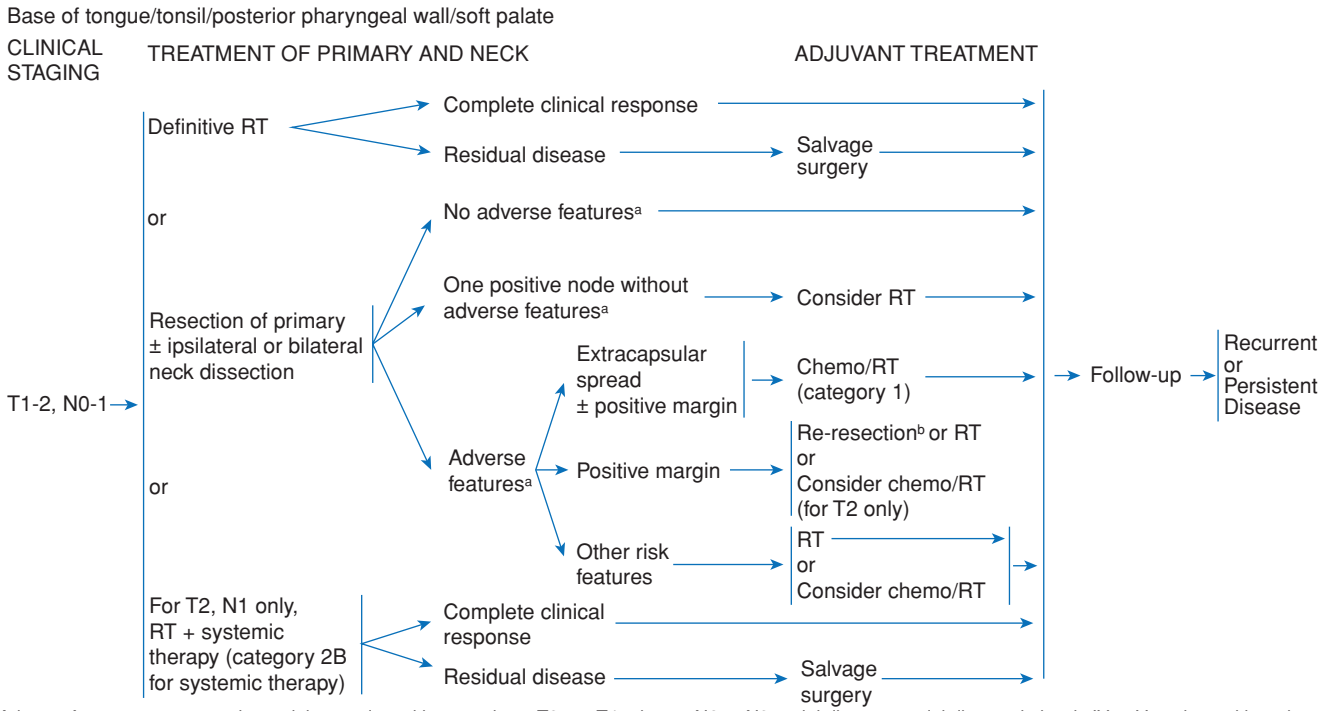
***Early-stage Disease.*** Early-stage OPCs can be treated with primary RT or primary surgery. RT is often used because it comprehensively includes the primary site, neck nodes, RP nodes, lymphatic channels in transit, and produces excellent long-term results. The increasing adoption of intensity-modulated radiotherapy (IMRT) with the addition of image-guided radiotherapy (IGRT) has led to high rates of LRC with low incidence of long-term functional morbidity.

Surgery involves the use of TLM or TORS for the primary site. This needs to be combined with a separate procedure to remove the neck nodes. Surgery may not be the only treatment needed, as patient may require additional treatment with RT, or chemo-RT, depending upon the pathologic findings in the primary tumor and the neck. Moreover, surgery generally does not address the RP nodes, which is an area at risk. Complete and multidisciplinary discussion is essential for every patient so that the best management decisions can be made. A fundamental management principle for early-stage disease is to maximize the likelihood of treatment with single-modality therapy by either RT or surgery alone. The best outcome for the patient is when one treatment modality is used. Multimodality therapy invariably increases morbidity and cost and should be unnecessary in most cases. Figure 17-8 shows the National Comprehensive Cancer Network (NCCN) 2012 guidelines for early-stage OPC treatment.

***Advanced-stage Disease.*** For patients with more advanced disease, combined therapy options are generally preferred. However, treatment needs to be individualized. See Figures 17-9 and 17-10 for the algorithm of care for advanced-stage OPC. In general, concomitant chemo-RT is the preferred management for most patients with stages III and IVA/B disease.[82,83] RT alone is often considered for certain patients, especially those with low bulk stage III lesions (i.e., T1–2N1M0).[63] Similarly, primary surgery may be used for selected patients with low bulk stage III disease (Hurtuk et al., 2012).[83a] If there are negative margins on the primary site resection, and the neck specimen is negative, surgery alone may be adequate. For other stage III patients, pathologic analysis may reveal positive nodes, inadequate margins, or other adverse features such as perineural invasion or lymphovascular invasion. This would trigger the use of PORT, or even postoperative chemo-RT, especially if the margins are positive or there is extranodal spread.[84,85]

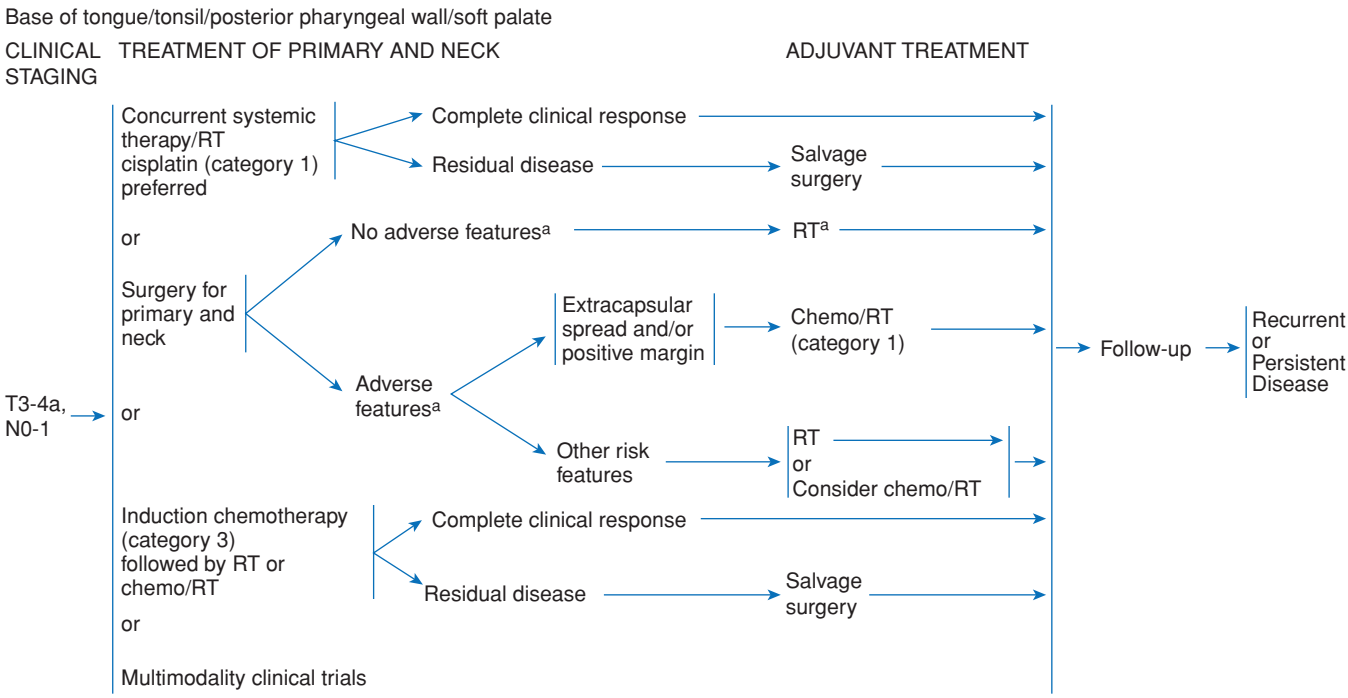
In selecting stage III patients for surgery, it is important to try to choose patients who are unlikely to have indications for chemotherapy (positive margins or extracapsular spread), to minimize treatment morbidity. If a patient turns out to need postoperative chemo-RT, then it is probably true that the patient could have been treated definitively with primary chemo-RT and the surgery has not added value to the outcome. Indeed, it may have only added cost and toxicity. On the other hand, if the pathologic findings only call for PORT alone, or no adjuvant therapy, then the surgical procedure may have saved the patient from chemotherapy or RT, thus providing a trade-off, which may

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[a]Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism.
[b]Consider re-resection to achieve negative margins, if feasible.

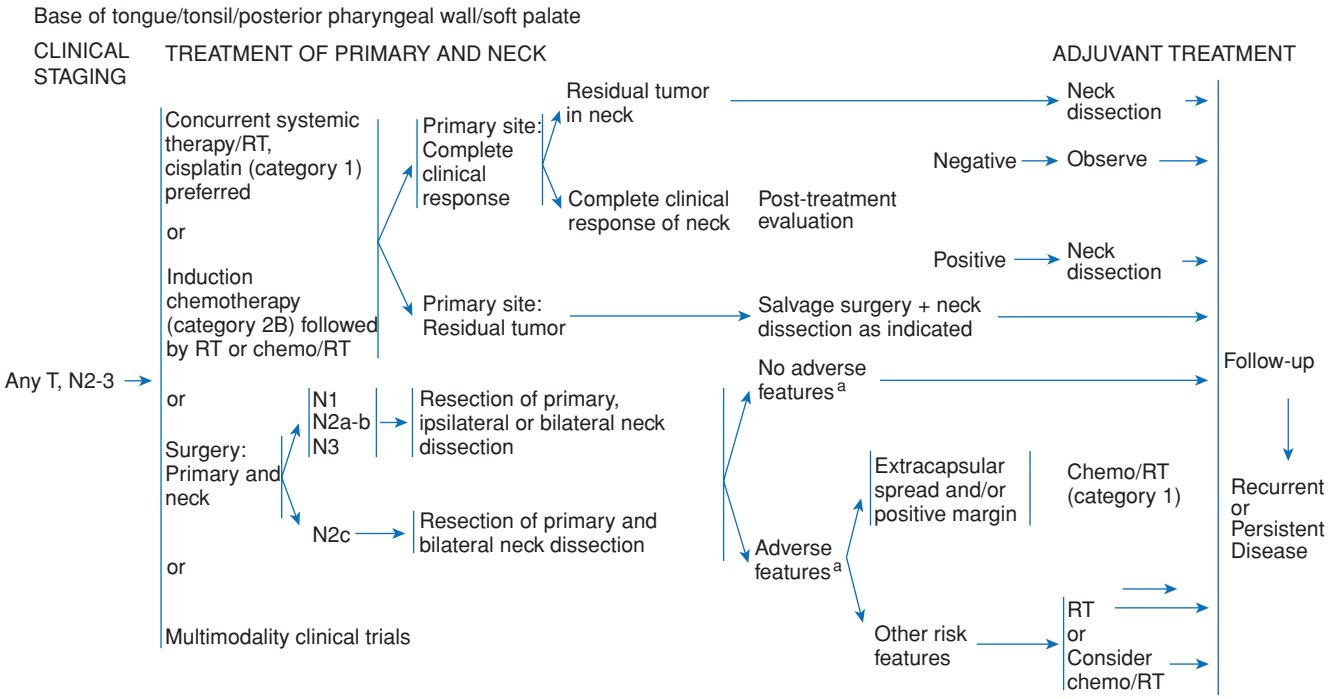
**FIGURE 17-8.** National Comprehensive Cancer Network (NCCN) 2012 guidelines for treatment of early-stage cancer of the oropharynx. All recommendations are category 2A unless otherwise indicated. NCCN believes that the best management of any cancer patient is in a clinical trial; participation in clinical trials is especially encouraged. Chemo, chemotherapy; RT, radiation therapy.
*Source:* Adapted from the NCCN Guidelines.




[a]Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism.

**FIGURE 17-9.** National Comprehensive Cancer Network (NCCN) 2012 guidelines for treatment of locally advanced cancer of thvthe best management of any cancer patient is in a clinical trial; participation in clinical trials is especially encouraged. Chemo, chemotherapy; RT, radiation therapy.
*Source:* Adapted from the NCCN Guidelines.

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[a] Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism.

**FIGURE 17-10.** National Comprehensive Cancer Network (NCCN) 2012 guidelines for treatment of regionally advanced cancer of the oropharynx. All recommendations are category 2A unless otherwise indicated. NCCN believes that the best management of any cancer patient is in a clinical trial; participation in clinical trials is especially encouraged. Chemo, chemotherapy; RT, radiation therapy. For more information, consult the specific NCCN guidelines at the website ww.nccn.org.

*Source:* Adapted from the NCCN Guidelines.

be attractive to certain patients. These complex issues require the patient to have a thorough understanding of all the options and management algorithms, so that a personalized choice can be made. Multidisciplinary evaluation and discussion is mandatory.

For stage IVA/B disease, concomitant chemo-RT is the mainstay of treatment. In general, this involves concomitant cisplatin chemotherapy with IMRT. Full-dose RT is delivered to the primary site and neck. The current paradigm calls for a PET-CT scan to be done as part of the baseline evaluation. Three months after the completion of chemo-RT, a repeat PET-CT scan is done for evaluation of response and disease status. If the scan is negative, no further treatment is needed.[86] If the scan shows residual disease in the neck, then a neck dissection (ND) is performed. If the scan is equivocal in the neck, management needs to be individualized. Some patients will get ND.[87] Others will have close follow-up to assess the evolution of the findings. Sometimes, a fine-needle aspiration can help determine whether there is residual disease warranting surgery, or whether the findings are likely benign, warranting close follow-up alone, with ND reserved for salvage. Refer to Chapters 4 and 14 for comprehensive discussion on follow-up PET-CT scan and neck management, respectively.

For patients treated with primary surgery, adjuvant RT or chemo-RT will be indicated in the overwhelming majority of cases. Therefore, it is essential to balance any potential benefit of surgery with the morbidity, given the reality that chemo-RT will be needed anyway. In selected circumstances, patients with very advanced disease at either the primary site (e.g., T4) and/or neck (e.g., N3 or low neck disease) have been treated with an induction chemotherapy approach.[68,88–93] The rationale for this sequence is related to both the aggressive nature of the systemic therapy, as well as the greater risk of distant metastases in this cohort of patients. However, results from recent clinical trials have not shown any clear benefit from induction over concomitant chemo-RT,[94,95] thereby questioning the appropriateness of induction chemotherapy outside of a clinical trial.

For stage IVC, management decisions must be individualized and will be determined by the extent of the loco-regional disease, resectability, presence and extent of distant metastases, and the performance status of the patient. Thus, careful balance of morbidity, cost, and oncologic outcome must be considered. As mentioned earlier, these complex issues require the patient to have a thorough understanding of all the options and management algorithms, so a personalized choice can be made. Multidisciplinary evaluation and discussion is mandatory.

## SITE-SPECIFIC MANAGEMENT STRATEGIES, RESULTS, AND OUTCOMES

### Soft Palate

***Early-stage Disease.*** Treatment of soft palate cancer must address the primary site as well as both sides of the neck including bilateral RP nodes.[50,96–98]

Chera et al. reported on 59 patients with SCC of the soft palate, who presented with early-stage disease. All patients underwent

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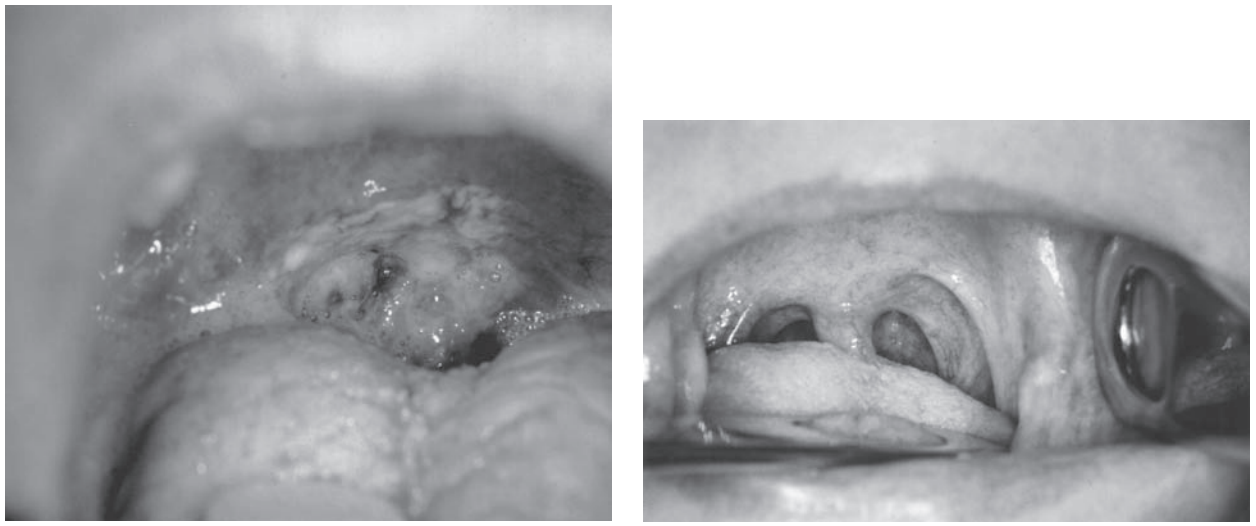



**FIGURE 17-11.** Patient with T2N0 squamous cell cancer of the soft palate before and after radiation therapy. This patient was treated with external beam radiation therapy to the primary site and both sides of the neck. The patient currently has no evidence of disease, more than 7 years after treatment.

primary RT. Stage I disease included 23 patients (16%) and stage II disease included 36 patients (25%). The 5-year initial and ultimate (i.e., after successful salvage) LRC rates for stage I were 84% and 89%, respectively. The 5-year initial and ultimate LRC rates for stage II were 85% and 88%, respectively. Specifically, the LC rates for both T1 and T2 were 90%. Nodal control rate at 5 years for N0 disease was 90%. The 5-year freedom from distant metastases rate was 95% for stage I and 97% for stage II. The 5-year DSS for stages I and II were 89% and 87%, respectively.[97] Figure 17-11 shows a T2 SCC of the soft palate before and after RT.

Iyer et al. reported on patients, with SCC of the soft palate, treated with primary surgery. With a median follow-up of 52 months, the 5-year DFS for stages I and II were 70% and 53%, respectively. Specifically, the 5-year LC for stages I and II were 85% and 84%, respectively. The 5-year regional control (RC) for stages I and II were 83% and 74%, respectively. The 5-year distant control (DC) for stages I and II were 96% and 81%, respectively. The 5-year DSS for stages I and II were 87% and 66%, respectively (Table 17.6).[98]

***Advanced-stage Disease.*** Chera et al. reported on 86 patients presented with advanced disease SCC of the soft palate. All patients underwent primary RT. Stage III disease included 23 patients (16%) and stage IVA/B diseases included 51 (35%) and 12 patients (8%), respectively. The 5-year initial and ultimate LRC rates for stage III were 66% and 96%, respectively. The 5-year initial and ultimate LRC rates for stage IVA were 85% and 88%, respectively, and for stage IVB were 43% for both. Specifically, the LC rate at 5 years was 67% for T3 and 57% for T4. Nodal control rates at 5 years were N1, 82%; N2, 68%; and N3, 71%. The 5-year rates of freedom from distant metastases were stage III, 100%; stage IVA, 93%; stage IVB, 69%; and overall, 94%. The 5-year DSS for stage III, IVA, and IVB were 88%, 57%, and 0%, respectively. In multivariate analysis, overall treatment time significantly affected local and ultimate LRC, and nodal stage significantly affected OS.[97]

Iyer et al. reported on patients with SCC of the soft palate, 81% underwent primary surgery, of whom 36% underwent surgery + PORT, and 19% underwent primary RT ± chemotherapy. With a median follow-up of 52 months, the 5-year DFS for stages III and IV were 54% and 36%, respectively. Specifically, the 5-year LC for stages III and IV were 88% and 54%, respectively. The 5-year RC for stages III and IV were 77% and 73%, respectively. The 5-year DC for stages III and IV were 72% and 83%, respectively. The 5-year DSS for stages III and IV were 64% and 55%, respectively, and for OS for stages III and IV were 55% and 37%, respectively.[98] In total, in the surgical cohort, 43% developed recurrent disease: 19% local recurrences, 20% nodal recurrences, and 12% distant

**TABLE 17.6 Five-year Oncologic Outcomes of Primary Surgery ± Postoperative Radiation Therapy in Soft Palate Cancer**

| | 5-yr Outcomes (%) | | | | | |
|---|---|---|---|---|---|---|
| **Stage** | **LC** | **RC** | **DC** | **DFS** | **OS** | **DSS** |
| **I** | 85 | 83 | 96 | 70 | 60 | 87 |
| **II** | 84 | 74 | 81 | 53 | 54 | 66 |
| **III** | 88 | 77 | 72 | 54 | 55 | 64 |
| **IV** | 54 | 73 | 83 | 36 | 37 | 55 |

DFS, disease-free survival; LC, local control; RC, regional control; DC, distant control; DSS, disease-specific survival; OS, overall survival.

*Source:* From Iyer NG, Nixon IJ, Palmer F, et al. Surgical management of squamous cell carcinoma of the soft palate: factors predictive of outcome. *Head Neck.* 2012;34:1071–1080.

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metastases. Patients with early disease ($n$ = 90) had a DSS of 79%, whereas T1–2 but with neck-positive nodes ($n$ = 22) had a DSS of 56%. For OS and DSS, N classification was predictive of outcome. For LC and DC, margin status was a significant predictor, whereas the T classification was only a significant predictor for LC.[98]

Many single institutional reports have shown relatively similar outcomes.[99–108] In the modern era, results for loco-regionally advanced OPC are often combined for all primary sites, making it very difficult to extract the specific outcomes for each anatomic subsite. Most patients have primary lesions of either the tonsil or BOT, with fewer soft palate and pharyngeal wall lesions. Refer to the sections of this chapter titled "Selection of Therapeutic Modality—General Principles" and "Management of Advanced Stage Disease—Principles of Combining Chemotherapy and Radiation Therapy" for additional data and discussion related to OPC, all sites combined. Chemo-RT is the mainstay of management of loco-regionally advanced OPC, and this is reviewed for OPC sites in the section "Management of Advanced Stage Disease—Principles of Combining Chemotherapy and Radiation Therapy."

## Pharyngeal Wall Tumors

***Early-stage Disease.*** Treatment of pharyngeal wall tumors must address the primary site and both sides of the neck, including bilateral RP nodes. Hull et al. reported on 37 patients with pharyngeal wall tumors treated with primary RT. Five-year LC rates for T1 and T2 were 93% and 82%, respectively. On multivariate analysis, factors associated with improved LRC included twice-daily fractionation ($p$ = 0.0009), stages I to II disease ($p$ = 0.0051), and oropharyngeal primary site ($p$ = 0.0193). The same group previously reported the effect of the use of once-daily versus twice-daily fractionation on LC. The LC rates for patients treated with once-daily versus twice-daily fractionation were as follows: T1—100% versus 100% and T2—67% versus 92% ($p$ = 0.0009). These investigators also examined their outcomes as a function of RT technique. They found superior outcomes when using a more modern technique where there was more generous anatomic coverage of the prevertebral area and adjacent vertebral body. The LC rate for T1 was 100%. The LC rate for T2 was 57% using older techniques versus 100% for the modern approach, emphasizing the importance of including the entire prevertebral space into the target volume.[109,110]

Mendenhall et al. recently reported the results of primary RT. The 5-year LC and ultimate LC were: T1—93% and 93%, respectively; T2—84% and 91%, respectively. Multivariate analysis revealed stages I to II tumors, female gender, and altered fractionation were associated with improved LRC. The 5-year DSS and OS were as follows: stage I—88% and 50%, respectively; stage II—89% and 57%, respectively.[111]

Spiro et al. reported on 78 patients with posterior pharyngeal wall tumors treated with primary surgery ($n$ = 60) or primary RT ($n$ = 18). Survival was greater in those with stage I and stage II tumors, but the difference was significant only in comparison to those with stage IV disease. Local recurrence occurred in 16% and 21% for stages I and II, respectively.[112]

***Advanced-stage Disease.*** Hull et al. reported the outcomes of primary RT. The 5-year LC rates for T3 and T4 tumors were 59% and 50%, respectively. The LC rates for patients treated with once-daily versus twice-daily fractionation were as follows: T3—43% versus 80%; and T4—17% versus 50% ($p$ = 0.0009). These investigators also examined their outcomes as a function of RT technique. Similar to their finding for T2 disease, they found superior outcomes when using a more modern technique where there was more generous anatomic coverage of the prevertebral area and adjacent vertebral body. The LC rate for T3 was 46% for the older technique versus 73% for the modern approach. The LC rate for T4 was 29% for the older technique versus 75% for the modern approach, emphasizing the importance of including the entire prevertebral space into the target volume.[109,110] The current practice would employ IMRT, and issues of target coverage and spinal cord protection become easier to assure.

Mendenhall et al. recently reported the results of primary RT. The 5-year LC for T3 was 60% and T4 was 44%. Multivariate analysis revealed female gender, and altered fractionation were associated with improved LRC. The 5-year DSS and OS were the following: stage III—49% and 31%, respectively, and stage IV—35% and 21%, respectively. Fatal complications occurred in nine patients (5%).[113]

Spiro et al. reported on 78 patients with posterior pharyngeal wall tumors treated with primary surgery ($n$ = 60) or primary RT ($n$ = 18). Local recurrence occurred in 37% and 63% for stage III and IV, respectively. Neck failure was noted in 21% of patients. Distant metastasis was documented in 8%.[112]

Julieron et al. reported the outcomes for primary surgery ± RT. In their hands, primary surgery followed by RT produced the best outcomes. For combined therapy, the rate of local failure (LF) was 11% and the 5-year survival rate was 35%. In the group of patients who developed LF post primary RT, the 5-year survival rate was 16%.[114] In the modern era, results for loco-regionally advanced OPC are often combined for all primary sites, making it very difficult to extract the specific outcomes for each anatomic subsite. Refer to the sections of this chapter titled "Selection of Therapeutic Modality—General Principles" and "Management of Advanced Stage Disease—Principles of Combining Chemotherapy and Radiation Therapy" for additional data and discussion related to OPC, all sites combined. Chemo-RT is the mainstay of management of loco-regionally advanced OPC, and this is reviewed for OPC sites in the section "Management of Advanced Stage Disease—Principles of Combining Chemotherapy and Radiation Therapy."

## Tonsillar Region

***Early-stage Disease.*** Treatment of tonsil cancer must address the primary site as well as the regions of the neck at risk. There is a growing body of evidence to support the strategy of unilateral treatment to the ipsilateral neck alone, including the ipsilateral, lateral RP nodes.[115–117] Unilateral treatment provides the patient with a significant QOL advantage, both with respect to acute toxicity and late functional outcomes. Lesions that approach the midline or involve the tongue base or glossotonsillar sulcus are not good candidates for unilateral treatment and should be treated to both sides of the neck. Treatment planning must ensure protection of critical normal structures, which is easily achieved with image-guided IMRT. Treatment technique will be further described in Chapter 17, Part C.

Eisbruch et al. have demonstrated that patients treated unilaterally report less xerostomia and better QOL compared to those patients treated bilaterally, even with IMRT, which spares the contralateral parotid gland.[118] However, careful patient selection is required to minimize the risk for contralateral neck failure. Multiple reports document excellent outcomes using ipsilateral neck RT.

Jackson et al. report on 178 patients receiving ipsilateral treatment for tonsillar cancers. Patients presented primarily with T1–2 (66%) and N0 (57%) disease. The rates of LRC and contralateral neck recurrence by stage were as follows: stage I—91% and 0%, respectively; stage II—74% and 2%, respectively. None of the patients with N0 disease had experienced contralateral failure. The LC rate was 84% for T1–2.[115]

O'Sullivan et al. reported on 228 tonsillar carcinomas treated with ipsilateral RT. Eighty-four percent of patients had

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T1–2 tumors of which 70% with N0. At a median follow-up of 5.7 years, none of the patients with T1 or N0 lesions had experienced contralateral neck failure. The median 3-year LC rate for stages I and II were 91% and 76%, respectively. The 3-year median ipsilateral RC for stages I and II were 98% and 91%, respectively. For the whole cohort, the 3-year cause-specific survival was 76%. The only patients subsets with significant risk of contralateral neck failure (>10%) were those with tumor involvement of the medial one-third of palate or BOT.[116]

Kagei et al. reported 32 patients with SCC of the tonsil and soft palate treated unilaterally. Each tumor did not cross midline and demonstrated no obvious contralateral disease. With a median follow-up of 3.7 years, there were no contralateral neck failures.[119]

Levendag et al. reported on 190 patients with T1–3 N0–3 SCC of the tonsil and soft palate. All patients underwent primary RT followed by surgery or brachytherapy boost (BT). The tumor control rates after BT versus surgery at 5 years were 88% versus 88% for LC; 93% versus 85% for RC; 57% versus 52% for DFS; 67% versus 57% for OS; and 5% versus 6% for RF. They concluded that there was no need to treat the contralateral neck unless the tumor extends beyond the midline of the soft palate (uvula) or beyond the lateral one-third of the ipsilateral BOT.[120]

Hu et al. performed one of the few prospective trials assessing the safety of unilateral neck treatment.[117] The eligibility criteria required patients to have primary lesions >1 cm from midline, no involvement of the BOT, and PET-CT documentation of the absence of contralateral neck metastasis. With a median follow-up of 16 months, there were no failures in the contralateral neck. These criteria seem reasonable to use in making the decision to exclude the contralateral neck.

The oncologic outcomes for early-stage tonsil cancer with primary RT have been excellent. Mendenhall reported on 503 patients with tonsillar cancer, who underwent definitive RT. Five-year rates of LC were as follows: T1—88% and T2—84%. The ultimate LC rates (after salvage surgery) at 5 years were T1—94% and T2—91%. Five-year cause-specific survivals were as follows: stage I—100% and stage II—86%.[121]

It is important to recognize that the shift of patient characteristics toward younger, healthier, nonsmoker, more favorable prognosis of the HPV-related cancer, as well as the major advances in RT delivery, have had a major impact on outcomes and QOL in the modern era. Thus, current outcomes are much better than the prior era.[61,63,122–126]

Mourad et al. reported on 79 patients with SCC of the tonsil who underwent primary RT.[127] After a median follow-up of 56 months, the 5-year local control (LC), RC, DC, and OS for stages I/II combined were all 100%.

Garden et al. reported on 777 patients with OPC. The median follow-up was 54 months. The 5-year LRC, DFS, and OS rates were 90%, 82%, and 84%, respectively. Five-year DFS was 90% in never smokers with T1–2 disease. The 5-year DFS for N0 was 92%.[128] Table 17.7 shows the excellent outcomes of OPC as reported in the English literature. It is clear that the overwhelming majority of patients with early-stage tonsil cancer achieve excellent LRC with primary RT.

Primary surgical treatment is also an option for early-stage tonsillar cancer. Most surgical series report outcomes by T and N classification and is not always possible to determine the outcomes by overall stage. Thus, there are some limitations in the interpretation of the surgical literature related to this point.

The use of primary surgery, via conventional approach, as definitive treatment for early tonsillar disease is not reported frequently. However, excellent LC rates ranging from 80% to 90% have been reported.

Moncrieff et al. retrospectively reported on 92 patients with early-stage OPC, of whom 54% had tonsillar cancer. All patients underwent primary surgery, 76% underwent ND, and 62% underwent PORT or chemo-RT. Twenty-eight percent had T1 lesions, 72% had T2 lesions, and 52% were N0. The 5-year DSS was 83% and LC rate was 87%.[129]

Walvekar et al. reported on 49 patients with early-stage OPC, of whom 53% had tonsillar cancer. All patients underwent primary surgery, 94% underwent ND, and 33% underwent PORT or chemo-RT (8%). Thirty-five percent had T1 lesions, 65% had T2 lesions, and 42% were N0. The 3-year DFS and 5-year OS was 85% and 83%, respectively.[130] Table 17.8 shows the oncologic and functional outcomes of OPC status postsurgery and microinvasive surgery (MIS), including TLO, TLM, and TORS. The vast majority of patients underwent primary surgery and ND followed by adjuvant RT or chemo-RT based upon the pathological findings. If surgery is selected as the primary treatment, MIS is the preferred surgical approach.

Laccourreye et al. reported on 166 patients with SCC of the tonsil who underwent TLO. The 5-year LC rate was 89% for T1 and 82% for T2 lesions, respectively ($p = 0.02$).[25]

There has also been a growing interest in the role of TLM and TORS in the management of OPC.[28,29,131,132]

Grant et al. reported on 69 patients with OPC, of whom 41% were tonsil cancer. All underwent primary TLM, 86% underwent ND, and 26% had adjuvant RT. With a mean follow-up of 44 months, the 5-year LRC estimate for stages I and II disease were 90% and 73%, respectively. The 5-year OS estimate was 86%.[133]

Moore et al. reported on 66 patients who underwent TORS with a minimum of 2-year follow-up. Long-term gastrostomy tube use was required in 4.5% and long-term tracheotomy in 1.5%. Three-year estimated LC and RC were 97% and 94%, respectively. Two-year DSS and DFS were 95% and 92%, respectively.[134]

One of the strongest arguments for performing TLM or TORS is the potential to avoid RT and chemotherapy in properly selected, favorable patients. If negative margins are achieved and no other poor prognostic factors are noted in the specimen (lymphovascular invasion, perineural invasion, multiple positive lymph nodes, extracapsular extension), then adjuvant therapy can potentially be deintensified or eliminated. Thus, the patient may have the personal choice of selecting an algorithm that uses surgery to avoid chemotherapy or RT, or uses RT to avoid surgery. However, it must be pointed out that surgery alone generally does not address the RP nodes, which are at risk.

It is clear that excellent outcomes should be achieved with either primary RT or primary surgery for patients with early-tonsil cancer. In the best of circumstances, patients should be treated with single modality. Because there are options, and because these options require the patient to understand their risks and benefits, multidisciplinary evaluation is mandatory.

***Advanced-stage Disease.*** In the current era, patients with loco-regionally advanced disease are still highly curable. Excellent outcomes can be achieved in stages III, IVA, and IVB.[63,126] Most patients will require multimodality therapy. Concomitant cisplatin-based chemotherapy and RT (chemo-RT) has been the mainstay of treatment.[61,77,82,83,135,136] Primary surgical treatment is also an option, but will usually require additional treatment with RT ± chemotherapy.[85,137] Patients with stage III disease can be managed by single-modality therapy of primary RT or primary surgery, but the treatment of these patients must be individualized.

Treatment of loco-regionally advanced tonsil cancer involves management of the primary site and the regions of the neck at risk. As is the case with early-stage disease, unilateral treatment may still be appropriate, even in patients with ipsilateral nodal metastases.[116] O'Sullivan et al. report the results of 228 tonsillar carcinomas. Patients with stages III and IVA/B were included.

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**TABLE 17.7 Oncologic and Functional Outcomes of OPC, Tonsil, and Base of Tongue, Treated by Primary RT**

| Study | Number of Patients | Site | RT[b] | Median Follow-up (m) | Stage III–IV (%) | Oncologic Outcome | OS% | PEG |
|---|---|---|---|---|---|---|---|---|
| Mourad (2012)[127] | 79 | Tonsil | Daily (37%, 70 Gy), 14% CRT, 49% CRT + ND | 56 | 92 | 5-yr LRC: 95%<br>5-yr LRC for stages I/II, III/IVA, and IVB: 100%, 95%, 100%<br>5-yr DM for stages I/II, III/IVA, and IVB: 0%, 7%, 33% | 80% | 4% |
| Setton (2012)[126] | 442 | Tonsil, 50%<br>BOT, 46%<br>PPW, 3%<br>Soft palate, 2% | IMRT, 70, 59.4, 54 Gy | 37 | 94 | 3-yr LC: 95%; RC: 94% | 85% | 4% |
| Eisbruch (2010)[280] | 69 | Tonsil 49%<br>BOT 39%<br>Soft palate 12% | IMRT 66/2.2, 54/1.8 Gy | 34 | 0 | 2-yr LRC: 91% | DFS 82%<br>OS 95.5% | 0 |
| Mendenhall (2006)[121] | 503 | Tonsil | Daily (25%, 70 Gy) or BID (75%, 76.8 Gy or DCB 72 Gy) N + CRT 18% | 24 | 47 | 5-yr LC: T1, 88%; T2, 84%; T3, 78%; T4, 61%<br>RC: N0, 95%; N1, 93%; N2a, 89%; N2b, 84%; N2c, 77%; N3, 66%<br>RC: 97% contralateral neck post URT | DSS:<br>Stage I, 100%<br>Stage II, 86%<br>Stage III, 84%<br>Stage IVA, 73%<br>Stage IVB, 46% | 3.6% |
| Mendenhall (2006)[281] | 333 | BOT | Daily (25%, 70 Gy) or BID (75%, 76.8 Gy or DCB 72 Gy) N + CRT 18% | 79 | 50 | 5-yr LC: T1, 98%; T2, 92%; T3, 82%; and T4, 53%<br>LRC: Stages I–II, 100%; III, 82%; IVA, 87%; and IVB, 58% | 5-yr OS and DSS:<br>Stages I–II, 67%, 91%<br>Stage III, 66%, 77%<br>Stage IVA, 67%, 84%<br>Stage IVB, 33%, 45% | 6.3% |
| Garden (2004)[78] | 299 | Tonsil, 47%<br>BOT, 40%<br>Soft palate, 7%<br>PP wall, 6% | Daily RT, 51%, 70 Gy<br>DCB, 40%, 72 Gy<br>XHF, 9%, 81.4 Gy | 82 | 100 | 5-yr LRC: 85%, DFS: 71%, DM: 19% | 2-, 5-, 10-yr OS: 80%, 64%, 50% | NR |
| Rusthoven (2009)[124] | 20 | Tonsil | URT, 70 Gy primary CRT, 60–66 for PORT | 19 | 100 | 2-yr LRC: 100%<br>2-yr DMFS and DFS: 87% and 80% | 80% | 0% |
| Chronowski (2011)[125] | 102 | Tonsil | URT | 39 | 65 | 5-yr ipsilateral LRC: 100%, 2% contralateral metastasis | 95% | 0% |
| O'Sullivan (2001)[116] | 228 | Tonsil | URT | 68 | 0% | 3-yr actuarial LC: 77%, 3.5% contralateral metastasis | 3-yr DSS: 76% | 0% |

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| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Jackson (1999)[115] | 178 | Tonsil | URT | NR | 63% | 5-yr LRC:<br>Stage I: 91%<br>Stage II: 74% and after salvage 81%<br>Stage III: 51% and after salvage 71%<br>Stage IV: 53% and after salvage 70% | 5-yr DSS: 69%<br>OS: 56% | 0% |
| Kagei (2000)[119] | 30 | Tonsil | URT, 65 Gy/26 fx, ±5–15 Gy boost | 44 | NR | 5-yr LC: 74%<br>RC: 81%<br>No contralateral neck failure | 5-yr OS: 64%<br>DSS: 79% | NR |
| Hu (2011)[117] | 22 | Tonsil | URT IMRT, 70, 63, 54 Gy | 16 | 100 | 1.5-yr LC 100%, ipsilateral RC 93%, 0% contralateral metastasis | 88 | 0% |
| Chao (2004)[282] | 74 | OPC | IMRT, 70 Gy | 33 | 93 | 4-yr LRC: 87% | 87 | NR |
| Selek (2004)[283] | 175 | Tonsil, 34%<br>Soft palate, 31%<br>BOT, 24%<br>PPW, 11% | Median, 66 Gy; CF: 49%; DCB: 42%, 10% XHF or BT boost | 76 | 0 | 5-yr LRC: 81%<br>DFS: 77%<br>5-yr ultimate LRC: 87% | 5- and 10-yr actuarial OS: 70% and 43%<br>5- and 10-yr actuarial DSS: 85% and 79% | 0% |
| de Arruda (2006)[185] | 50 | OPC | IMRT, 70, 59.4, 54 Gy | 18 | 92 | 2-yr LC: 98%<br>RC: 88% | 98 | 12% |
| Yao (2006)[284] | 66 | OPC, 11%<br>Tonsil, 47%<br>BOT, 39%<br>Soft palate, 1%<br>PPW, 2% | IMRT 70–74, 60, and 54 Gy | 27 | 92 | 3-yr LRC: 99% | OS: 78%, DFS: 64% | 15% |
| Cmelak (2007)[122] | 69 | OPC | [a]IC-CCRT, IMRT 70 Gy | 37 | 100 | 2-yr LRC: 84% | 83 | 3% |
| Garden (2007)[285] | 51 | Tonsil, 65%<br>BOT, 31%<br>OPC, 4% | IMRT 66 and 54 Gy | 45 | 84 | 2-yr LRC: 94% | 94 | 8% |
| Lawson (2008)[157] | 34 | BOT | CCRT-IMRT 70 (2.13/fx) 63(1.9/fx), 57 (1.75 Gy/fx) | 20 | 94 | 2-yr LC: 92%<br>RC: 97% | 90 | 9% |
| Sanguineti (2008)[286] | 50 | Tonsil, 68%<br>BOT, 16%<br>PPW, 4%<br>Soft palate, 12% | IMRT: CH, hypofx, AHF | 33 | 88 | 3-yr LC: 94%<br>RC:85% | NR | NR |

*(continued)*

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**TABLE 17.7 Oncologic and Functional Outcomes of OPC, Tonsil, and Base of Tongue, Treated by Primary RT (Continued)**

| Study | Number of Patients | Site | RT[b] | Median Follow-up (m) | Stage III–IV (%) | Oncologic Outcome | OS% | PEG |
|---|---|---|---|---|---|---|---|---|
| Huang (2008)[269] | 71 | OPC | IMRT-CCRT<br>70 at 2.12 Gy/fx<br>59.4 at 1.8<br>54 at 1.64 | 33 | 100 | 3-yr LRC: 94% | 83 | NR |
| Fahkry (2008)[123] | 62 | OPC | [a]IC-CCRT, IMRT 70 Gy | 39 | 100 | 2-yr LRC: 95% HPV positive<br>2-yr LRC: 67% HPV negative<br>2-yr LRC: 81% whole cohort | 95 HPV +ve<br>62 HPV –ve<br>79 All patients | NR |
| Ang (2010)[61] | 433 | OPC | | 58 | 100 | 3-yr LRC: 86% HPV positive<br>3-yr LRC: 65% HPV negative<br>3-yr LRC: 76% whole cohort | 82 HPV +ve<br>57 HPV –ve<br>70 All patients | NR |
| Daly (2010)[287] | 107<br>21% S + RT | Tonsil, 44%<br>BOT, 50%<br>PPW, 4%<br>Soft palate, 3% | IMRT 66 at 2.2 Gy/fx | 27 | 96 | 3-yr LRC: 92% | 83 | 3% |
| Garden (2011)[128] | 777 | OPC | IMRT | 54 | 89 | 5-yr LRC: 90% | 84 | NR |
| Palta (2011)[288] | 204 | OPC | CCRT, HF (64%), CF (29%), r AXF (2%) | 56 | 100 | 10- and 15-yr LRC: 80%, 70% | DFS: 72%, 63%<br>DMFS: 84%, 84%<br>OS: 47%, 26% | <10% |
| Koyfman (2011)[138] | 82 | BOT, 51%<br>Tonsil, 46%<br>OPC, 3%<br>75% HPV +ve | 3DCRT 70–74 Gy –CCRT | 26 | 100 | NR | 2-yr OS 97% | 13% |
| Greskovich (2011)[289] | 30 | OPC | IMRT-CCRT | 21 | 100 | LRC: 97%, 100% after salvage | 100% | NR |
| Chan (2011)[66]<br><br>McBride (2011)[290] | 132 | OPC 92% HPV +ve | 42% IMRT | 48 | 100 | 3-yr DMFS: 82%, LRC: 95% | DSS: 90%<br>PFS: 81%<br>OS: 84% | NR |

DFS, disease-free survival; OS, overall survival; URT, unilateral radiotherapy; OPC, oropharyngeal cancer; LC, local control; RC, regional control; LRC, loco-regional control; HPV, human papilloma virus.

[a]2 cycles of paclitaxel 175 mg/m$^2$ followed by CCRT paclitaxel 30 mg/m$^2$ IV, IMRT 70 Gy/35 fx/7 weeks, 2 Gy/fx.

[b]Doses are stated as either PTV or as a dose per fraction.

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**TABLE 17.8 Oncologic and Functional Outcomes of Oropharynx Cancer (OPC) Status Post-Surgery and Microinvasive Surgery (Mis) Including Transoral Lateral Oropharyngectomy (TLO), Transoral Laser Microsurgery (TLM), and Transoral Robotic Surgery (TORS)**

| Study | Modality | Number of Patients | TNM/ Stage | Follow-up (m) | Oncologic Outcomes | Morbidity and PEG Dependency |
|---|---|---|---|---|---|---|
| Moncrieff (2009)[129] | Surgery<br>76% ND<br>62% PORT ± chemo | 92<br>54% Tonsil, 22% BOT, 0% Soft palate, 2% Uvula, 2% PPW | T1: 28%, T2: 72%, N0: 52%, N1: 13%, N2a: 15%, N2b: 13%, N3: 7% | Not reported | 5-yr LC: 87%, LRC: 81%, DFS:73%, DSS: 83%<br>5-yr LC for PORT vs. surgery alone (93% vs. 83%) ($p = 0.27$) | Not reported |
| Walvekar (2008)[130] | Surgery<br>94% ND<br>33% PORT<br>8% CRT | 49<br>53% Tonsil<br>35% BOT<br>12% PPW | T1: 35%, T2: 65%, N0: 42%, N1: 58%<br>*Stage*<br>I: 16%<br>II: 45%<br>III: 39% | 24 (minimum) | 3-yr LRC: 71% and DFS: 85%<br>5-yr OS: 83% | 2%<br>16% mandibular resection |
| Holsinger (2005)[24] | TLO<br>78% ND<br>5% Pre-TLO RT<br>80% Induction chemo<br>29% Post-TLO RT | 191 Tonsil | T1–2: 85%<br>T3–4: 13%<br>Tx: 2%<br>N0: 51%<br>N1: 26%<br>N2: 17%<br>N3: 3%<br>Nx: 3%<br>*Stage*<br>I: 18%<br>II: 27%<br>III: 31%<br>IVA: 18%<br>IVB: 6%<br>Recurrent: 3% | Not reported | 1, 3, and 5-yr OS KM estimates were 87%, 66%, and 56% | 0%<br>3% mortality rate<br>Mean inpatient stay: 9 d |
| Laccourreye (2005)[25] | TLO<br>78% ND<br>82% Pre-TORS chemo<br>31% Post-TLO RT | 166 Tonsil | T1: 36%<br>T2: 52%<br>T3: 12%<br>N0: 51%<br>N1: 27%<br>N2: 18%<br>N3: 4% | 120 (Mean) | 1-, 5-yr KM estimates<br>OS: 88%, 58%<br>LC: 91%, 82%<br>T1 LC: 98%, 89%<br>T2 LC: 89%, 82%<br>T3 LC: 79%, 63%<br>*($p = 0.02$)* | Not reported |
| Cohen (2011)[291] | TORS<br>96% ND<br>57% Post-TORS CRT<br>28% Post-TORS RT<br>2% Post-TORS Chemo | 50<br>48% BOT<br>46% Tonsil<br>4% Soft palate<br>2% PPW<br>74% HPV +ve<br>26% HPV –ve | T1–2: 78%<br>T3: 22%<br>N0:18%<br>N1: 42%<br>N2b: 40%<br>*Stage*<br>I: 6%<br>II: 8%<br>III: 40%<br>IV: 46% | 25 (mean) HPV +ve<br>23 (mean) HPV –ve | 1 yr: 96% (45/47)<br>2 yr: 81% (25/31)<br>HPV +ve 100% LRC, 5% DM<br>HPV –ve 100% LC, 92% RC and DC<br>No SS differences in OS, DSS, and DFS | Not reported |

*(continued)*

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**TABLE 17.8 Oncologic and Functional Outcomes of Oropharynx Cancer (OPC) Status Post-Surgery and Microinvasive Surgery (Mis) Including Transoral Lateral Oropharyngectomy (TLO), Transoral Laser Microsurgery (TLM), and Transoral Robotic Surgery (TORS) (Continued)**

| Study | Modality | Number of Patients | TNM/ Stage | Follow-up (m) | Oncologic Outcomes | Morbidity and PEG Dependency |
|---|---|---|---|---|---|---|
| Weinstein (2012)[27] | TORS<br>90% ND | 30<br>47% Tonsil<br>30% BOT<br>10% GT sulcus<br>10% Soft palate<br>3% PPW | T1:30%<br>T2: 53%<br>T3: 13%<br>T4a: 3%<br>N0: 50%<br>N1: 34%<br>N2a: 3%<br>N2b: 13%<br>*Stage*<br>I: 17%<br>II: 30%<br>III: 33%<br>IV: 20% | 32 (mean) | LC: 97%<br>RC: 90%<br>DC: 100%<br>OS: 100% | 0% |
| Weinstein (2010)[292] | TORS<br>100% ND<br>57% Post-TORS CRT<br>28% Post-TORS RT<br>2% Post-TORS Chemo | 47<br>49% Tonsil<br>49% BOT<br>2% Soft palate | T1–2: 77%<br>T3–4: 23%<br>N0: 2%<br>N1: 51%<br>N2a: 2%<br>N2b: 40%<br>N2c: 4%<br>III: 51%<br>IV: 49% | 27 (mean) | TORS + ND + CRT<br>LC: 98%, RC: 96%, DC: 91%<br>Actuarial OS: 1 and 2 yr: –96% and 79%<br>Actuarial DSS: 1 and 2 yr: –98% and 90%<br>Actuarial DFS: 1 and 2 yr: –96% and 79% | 2 yr: 2.4% |
| Weinstein (2007)[293] | TORS<br>100% ND<br>56% Post-TORS CRT<br>33% Post-TORS RT<br>4% Post-TORS chemo | 27 Tonsil | T1: 19%<br>T2: 59%<br>T3: 22%<br>N0: 15%<br>N1: 48%<br>N2: 37% | 6 (minimum) | LC: 100%<br>RC: 100%<br>DC: 96% | 4% |
| White (2010)[146] | TORS<br>76% ND<br>63% PORT<br>48% Pre- or post-TORS chemo | 77 No site-specific data | T1: 38%<br>T2: 55%<br>T3–4: 7%<br>N0: 35%<br>N1: 10%<br>N2a: 14%<br>N2b: 32%<br>N2c: 8%<br>*Stage*<br>I–II 30%<br>III–IV 70% | 26 (median) | DFS: 1, 2 yr: 89%, 86% | Not reported |

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**TABLE 17.8 Oncologic and Functional Outcomes of Oropharynx Cancer (OPC) Status Post-Surgery and Microinvasive Surgery (Mis) Including Transoral Lateral Oropharyngectomy (TLO), Transoral Laser Microsurgery (TLM), and Transoral Robotic Surgery (TORS) (Continued)**

| Study | Modality | Number of Patients | TNM/ Stage | Follow-up (m) | Oncologic Outcomes | Morbidity and PEG Dependency |
|---|---|---|---|---|---|---|
| Genden (2011)[28] | TORS<br>100% ND<br>83% PORT<br>47% POcRT | 27<br>37% Tonsil<br>37% BOT<br>19% PPW + soft palate + RMT<br>7% not OPC | T1–2: 100%<br>N0: 22%<br>N1: 38%<br>N2a: 20%<br>N2b: 18%<br>N2c: 2<br>*Stage*<br>III–IV: 73% | 20 (median) | At 1.5 yr<br>LRC: 91%<br>DC: 93%<br>DFS: 78%<br>OS: 90% | At 1.5 yr 0% |
| Iseli (2009)[145] | TORS<br>22% Preoperative RT<br>41% PORT RT<br>31% Chemotherapy | 33 OPC | T1–2: 100% | 13 (mean) | Not reported | 1 yr: 9.5%<br>2 yr: 6% |
| Moore (2012)[134,149] | TORS<br>100% ND<br>16.7% surgery alone<br>21% Post-TORS RT<br>62% Post-TORS CRT | 66;<br>58% BOT<br>42% Tonsil<br>72% HPV +ve (ISH)<br>89% p16 +ve (IHC) | T1: 46%<br>T2: 39%<br>T3: 5%<br>T4a: 5%<br>Tx: 5<br>N0: 14%<br>N1: 12%<br>N2a: 12%<br>N2b: 38%<br>N2c: 12%<br>N3: 12%<br>*Stage*<br>I: 5%<br>II: 8%<br>III: 11%<br>IVA, B: 65%, 12% | 36 (mean) | 2-yr DSS and DFS: 95% and 92%<br>3-yr KM estimated LC and RC: 97% and 94%<br>4-yr DFS: 93% and 92% for tonsil and BOT.<br>HPV ($p = 0.08$)<br>DSS: 98% vs. 89% for HPV +ve vs. HPV –ve OPC,<br>DFS: 96% vs. 83% for HPV +ve vs. HPV –ve OPC.<br>HPV and Tobacco ($p = 0.3$)<br>DFS 97% vs. 92% for HPV +ve nonsmokers vs. HPV –ve smokers or HPV –ve<br>DFS 95% vs. 89% for HPV +ve nonsmokers vs. HPV +ve smokers or HPV–ve | 4.5%<br>Long-term tracheotomy in 2% |
| Dean (2010)[294] | 15 Primary TORS<br>7 Salvage TORS<br>14 Salvage open surgery | 36 BOT + Tonsil | T1-2: 100% | Not reported | Not reported | 0% TORS<br>43% after salvage open surgery |
| Aubry (2011)[148] | TORS | 9 Tonsil | *Stage*<br>I–II: 100% | 6.5 (mean) | Not reported | 12% |

*(continued)*

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**TABLE 17.8 Oncologic and Functional Outcomes of Oropharynx Cancer (OPC) Status Post-Surgery and Microinvasive Surgery (Mis) Including Transoral Lateral Oropharyngectomy (TLO), Transoral Laser Microsurgery (TLM), and Transoral Robotic Surgery (TORS) (Continued)**

| Study | Modality | Number of Patients | TNM/ Stage | Follow-up (m) | Oncologic Outcomes | Morbidity and PEG Dependency |
|---|---|---|---|---|---|---|
| Steiner (2003)[143] | TLM<br>90% ND<br>48% Post-TLM RT<br>25% Post-TLM CRT | 48 BOT | T1–2: 27%<br>T3–4: 73%<br>N0: 31%<br>N1: 19%<br>N2: 50%<br>*Stage*<br>III–IVA: 94% | 47 (median) | 5 yr<br>LC: 85%<br>DFS: 73%<br>OS: 52%<br>TLM alone: 20% LF, 28%LRF<br>TLM+ RT± chemo: 9%LF, 17% LRF | 6% |
| Rich (2009)[131] | TLM<br>99% ND<br>60% PORT<br>33% POcRT | 84<br>55% BOT<br>45% Tonsil and soft palate<br>HPV/P16 +ve 82%<br>HPV/P16 –ve 5% Unknown 13% | T1: 35%<br>T2: 39%<br>T3: 18%<br>T4: 7%<br>N0: 4%<br>N1: 14%<br>N2: 76%<br>N3: 6%<br>*Stage*<br>III: 15%<br>IV: 85% | 53 (mean)<br>49 (median) | KM estimates for<br>OS: 2, 5 yr: 94% and 88%<br>DSS: 2, 5 yr: 96% and 92%<br>DFS: 2, 5 yr: 91% and 87%<br>OS 5 yr for T3–4 (69%) vs. T1–2 (92%) $p = 0.036$<br>p16+ve OS: 5 yr 90% vs. 25% ($p < 0.0001$).<br>p16+ve DSS: 5 yr 94% vs. 50% ($p = 0.0078$) | 1 yr: 17%<br>3 yr: 4% |
| Rich (2011)[26] | TLM<br>98% ND<br>47% PORT<br>41% POcRT<br>13% Surgery alone | 118<br>51% BOT<br>49% Tonsil<br>HPV/p16 +ve 87%<br>HPV/p16 –ve 5%<br>Unknown 8% | T1: 37%<br>T2: 35%<br>T3: 20%<br>T4: 8%<br>*Stage*<br>III: 16%<br>IV: 84% | 54 (median) | Not reported | 8% overall with T4 worst outcomes ($p = 0.0023$) |
| Grant (2009)[133] | TLM<br>83% ND<br>100% No RT or CRT | 69<br>41% tonsil<br>41% BOT<br>12% PPW<br>6% Soft palate<br>1% Vallecula | T1: 36%<br>T2: 44%<br>T3: 17%<br>T4: 3%<br>N0: 46%<br>N1: 16%<br>N2a: 24%<br>N2b: 10%<br>N2c: 1%<br>N3: 3%<br>*Stage*<br>I: 17%<br>II: 19%<br>III: 28%<br>IV: 36% | 44 (mean) | 5-yr KM LRC-74%, OS-86%<br>OS: Stage I–II: 79%, III–IV: 49%–86%<br>DSS: Stage I–II: 88%, III–IV: 72%–86% | 2%<br>6% Mortality rate |

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**TABLE 17.8 Oncologic and Functional Outcomes of Oropharynx Cancer (OPC) Status Post-Surgery and Microinvasive Surgery (Mis) Including Transoral Lateral Oropharyngectomy (TLO), Transoral Laser Microsurgery (TLM), and Transoral Robotic Surgery (TORS) (Continued)**

| Study | Modality | Number of Patients | TNM/ Stage | Follow-up (m) | Oncologic Outcomes | Morbidity and PEG Dependency |
|---|---|---|---|---|---|---|
| Henstrom (2009)[144] | TLM<br>60% Post-TLM-RT<br>20% Post-TLM-chemo-RT | 20 BOT | T1: 40%<br>T2: 40%<br>T3: 5%<br>T4: 15%<br>N0: 5%<br>N1: 15%<br>N2a: 5%<br>N2b: 55%<br>N2c: 20%<br>*Stage*<br>II: 5%<br>III: 15%<br>IVA: 80% | 40 (mean)<br>38 (median) | LC: 2 yr: 84%<br>RC: 2 yr: 100%<br>DC: 2 yr: 95%<br>OS: 2 and 5 yr: 90% and 83%<br>DSS: 2 and 5 yr: 95% and 87%<br>DFS: 2 and 5 yr: 90% and 83%<br>Of note: 15% developed contralateral BOT LF | 10% |
| Haughey. (2011)[142] | TLM<br>100% ND<br>58% PORT<br>16% POcRT | 204<br>52% BOT<br>48% Tonsil and soft palate<br>HPV/P16 +ve 90%<br>HPV/P16 –ve 10% | T1: 30%<br>T2: 36%<br>T3: 22%<br>T4: 12%<br>N0: 7.5%<br>N1: 19%<br>N2: 66%<br>N3: 7.5%<br>*Stage*<br>III: 24%<br>IV: 76% | 48 (mean)<br>42 (median) | OS: 2 and 5 yr: 89% and 78%<br>DSS: 2 and 5 yr: 91% and 84%<br>DFS: 2 and 5 yr: 85% and 74%<br>TLM alone: 21% LRF + 7%DM<br>TLM + PORT: 5%LRF +6%DM<br>TLM +POcRT: 6%LRF+3%DM<br>OS: 3 and 5 yr:<br>p16+ve: 92%, 86%<br>p16–ve: 52%, 30%<br>OS SS factors:<br>low N classification ($p = 0.006$) –ve margins ($p = 0.03$)<br>HPV +ve ($p = 0.013$)<br>p16 +ve ($p < 0.0001$)<br>PORT or POcRT ($p = 0.047$) | 1 yr: 19%<br>2 yr: 9%<br>4 and 5 yr: 4% |

The vast majority of patients underwent TLM, TLO, or TORS followed by neck surgery (ND = neck dissection) and adjuvant therapy (e.g., radiation therapy [RT] or concurrent chemo-RT; CRT). BOT, base of tongue; KM, Kaplan-Meier; PPW, posterior pharyngeal wall; ISH, *in situ* hybridization; IHC, immune-histochemistry; PORT, postoperative RT; POcRT, postoperative chemo-RT; HPV, human papillomavirus; DSS, disease-specific survival; LC: local control; LRC: loco-regional control; DC: distant control; DFS: disease-free survival; OS: overall survival; LF: local failure; DM: distant metastasis; TNM: tumor, nodal, and metastasis classification; SS: statistically significant.

At a median follow-up of 5.7 years, the median 3-year LC for stages III and IVA/B were 79% and 70%, respectively. The 3-year median RC for stages III and IVA/B were 75% and 60%, respectively. Contralateral neck failure occurred in 3%.[116]

Jackson et al. report on 178 patients receiving ipsilateral treatment for tonsillar cancers. Sixty-three percent had stages III to IV disease. The rates of LRC and contralateral neck recurrence were as follows: stage III—51% and 4%; and stage IV—53% and 0%. Patients with N0 (57%) or N1 (30%) disease had contralateral failure rates of 0% and 4%, respectively. None of the 23 (13%) patients with N2–3 disease had contralateral failure.[115]

Likewise, Rusthoven et al. reported on 20 patients with well-lateralized, ipsilateral node-positive tonsil cancer, not involving midline structures (BOT or soft palate), treated with unilateral RT. Eighty percent were stage IV (N1—20%; N2a—5%; N2b—65%). None had contralateral neck failure.[124]

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Chronowski et al. reported on 102 patients with SCC of the tonsil treated with unilateral RT. Patients had TX (17%), T1 (51%), or T2 (32%) disease, with Nx (2%), N0 (32%), N1 (23%), N2a (21%), or N2b (22%) neck disease. Sixty-one patients (60%) underwent diagnostic tonsillectomy before RT. Twenty-seven patients (26%) underwent excision of a cervical lymph node or ND before RT. Median follow-up for surviving patients was 38 months. LRC at the primary site and ipsilateral neck was 100%. Two patients experienced contralateral nodal recurrence (2%). The 5-year OS and DFS rates were 95% and 96%, respectively. The 5-year freedom from contralateral nodal recurrence rate was 96%.[125]

Hu et al. reported a prospective clinical trial including 22 patients with tonsil cancer who underwent unilateral RT: stage III—41% and stage IVA—59%. Twenty patients received platinum-based chemo-RT. Eligibility criteria mandated that all patients have primary lesions >1 cm from the midline, not involving the BOT, and a negative contralateral neck on clinical examination and PET-CT scan. At a median follow-up of 20 months, no patient experienced contralateral nodal failure. The 2-year actuarial oncologic outcomes were: LC—100%, ipsilateral RC—93%, distant metastasis rate—15%, and OS—88%. No patient had more than grade 1 xerostomia or chronic dysphagia. No patient required a PEG feeding tube.[117] It is clear that unilateral RT is an option, even in patients with loco-regionally advanced disease, as long as they meet the reasonable criteria in the series above.

Mendenhall reported on 503 patients with tonsillar cancer treated with primary RT. Five-year rates of LC were as follows: T3—78% and T4—61%. The 5-year ultimate LC rates (i.e., including surgical salvage) for T3 was 82% and for T4 was 68%. Five-year DSS were as follows: III—84%, IVA—73%, and IVB—46%. Absolute OS at 5 years were as follows: III—62%, IVA—57%, and IVB—33%.[121]

Mourad et al. reported on 79 patients with SCC of the tonsil who underwent primary RT. After a median follow-up of 56 months, the 5-year LC, RC, DC, and OS by stage were as follows: stages III to IVA—98%, 96%, 95%, and 88%, respectively; stage IVB—100%, 100%, 69%, and 66%, respectively. Among stage IVB patients, DC was significantly lower ($p = 0.01$) and a trend toward lower OS was noted ($p = 0.08$).[127]

The University of Florida data have the enormous advantage of large numbers, long follow-up and treatment performed consistently by experienced head and neck radiation oncologists. However, it is important to recognize that the shift of patients' characteristics, more favorable prognosis of the HPV-related cancer in younger patients with no or minimal smoking history as well as the major advances in IMRT planning and delivery (IGRT), has made a major impact on outcomes and QOL in the modern era. Thus, current outcomes are much better than the prior era due to these improvements. Table 17.7 shows the excellent outcomes of OPC as reported in the most recent studies.

Setton et al. reported on 442 patients with OPC, who underwent primary IMRT ± concomitant cisplatin-based chemotherapy. Stages III to IVA/B formed 94% of patients. The primary tumor subsite was the tonsil in 50%, the BOT in 46%, the pharyngeal wall in 3%, and the soft palate in 2%. Median follow-up among surviving patients was 37 months. The 3-year cumulative incidence of LF, regional failure, and distant metastasis was 5.4%, 5.6%, and 12.5%, respectively. The 3-year OS rate was 85%.[126]

Toledano et al. reported the results of the GORTEC 2004–03 study, which included 208 patients with SCCHN, of whom 56% were OPC and 71% were stages III to IV. All were treated with IMRT with concomitant chemotherapy. With a median follow-up of 25 months, the 2-year LRC and OS were 86% and 87%, respectively.[136]

Garden et al. reported on 777 patients with OPC, who underwent primary IMRT ± chemotherapy. With a median follow-up of 54 months, the 5-year OS, DFS, and LRC were 84%, 82%, and 90%, respectively. The 5-year DFS by N stage were as follows: N0—75%, N1/2a—92%, N2b/2c—80%, and N3—57%. A subset analysis showed that patients with level IV disease had a 60% 5-year DFS rate due to higher rate of distant metastasis.[128]

Multiple studies have documented the improved outcomes for patients who are HPV/p16 positive. Tables 17.7 and 17.8 summarize several important trials that emphasize this finding. Even for advanced-stage patients, oncologic and functional outcomes have been excellent.[61,65,123,138,139]

The technical aspects of RT management are reviewed in Chapter 17, Part C. In summary, IMRT is the mainstay of treatment and IGRT is an important complement to IMRT. The primary site and involved nodal areas receive 70 Gy in 7 weeks. The adjacent nodal areas generally receive an intermediate dose of 60 to 63 Gy, often by a dose-painting approach. Electively treated nodal regions such as low neck, lateral RP nodes, or contralateral neck nodes, generally receive 50 to 54 Gy.

Platinum-based concomitant chemotherapy with RT is the standard chemo-RT approach. Table 17.9 outlines a variety of protocols and their outcomes. The reader is referred to the section "Management of Advanced Stage Disease—Principles of Combining Chemotherapy and Radiation Therapy" for the detailed review of chemotherapy management and outcomes. For patients who cannot receive cisplatin, alternate approaches such as carboplatin[140,141] or cetuximab[79] or even altered fractionation RT alone are considered. This is also reviewed in detail in the section "Management of Advanced Stage Disease—Principles of Combining Chemotherapy and Radiation Therapy."

The general approach to the neck involves management with primary RT or chemo-RT. A PET-CT scan is done 3 months after the completion of treatment. An ND is done if there is evidence of residual disease. Neck management is discussed in detail in Chapter 14.

Recently, there has been a growing interest in incorporating MIS into the management algorithm of locally advanced OPC. MIS includes TLO, TLM, and TORS. There are multiple reports that have shown promising oncologic and functional outcomes via this approach. Noteworthy, the vast majority of patients who underwent MIS also underwent ND, and adjuvant RT or chemo-RT. Table 17.8 shows the oncologic and functional outcomes of OPC treated via MIS approaches.

Haughey et al. reported on 204 patients with stage III/IV OPC, of whom 48% had tonsil cancer. All patients underwent TLM and ND, 74% underwent adjuvant RT, of whom 22% required chemo-RT. With a median follow-up of 42 months, the 2- and 5-year OS rates were 89% and 78%, respectively. The overall LC was 97%. Long-term PEG dependency rates at 1-, 2-, and 5-year were 19%, 9%, and 4%, respectively.[142] Similar outcomes have been reported by other investigators.[26,131,133,143,144]

Moore et al. reported on patients with stage III/IV OPC, of whom 42% had tonsillar cancer and 89% were HPV/p16 positive. All patients underwent TORS and ND, 62% underwent adjuvant chemo-RT, and 21% underwent adjuvant RT alone. With a mean follow-up of 36 months, the 2-year DFS was 94%. The 4-year estimated LC and RC were 97% and 94%, respectively. The DFS was 96% and 83% for HPV-positive versus HPV-negative tumors, respectively ($p = 0.08$). Long-term PEG dependency was 4.5%.[134] Similar outcomes have been reported by other investigators.[28,132,145–148]

The use of primary TLM or TORS has demonstrated excellent oncologic and functional outcomes with low rates of PEG dependency and high QOL scores on questionnaire assessment. Most series reporting ≥2-year PEG dependency rates below 5% to 10%.[28,132,145,149] Similarly, the rates of PEG-dependence are

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**TABLE 17.9 Outcomes of a Sampling of Prospective Randomized Studies Comparing RT Alone to Chemo-RT Using Platinum-based Chemotherapy**

| Study | Patients | Chemotherapy | RT | | ≥3 yr OS Chemo-RT vs. RT | *p*-Value |
|---|---|---|---|---|---|---|
| Jeremic (1997)[295] | 159 | Cisplatin daily: 6 mg/m$^2$ | Standard | 70 Gy@2 Gy/Fx | 32% vs. 15% | 0.011 |
| | | Carboplatin daily 25 mg/m$^2$ | Standard | | 29% vs. 15% | 0.0019 |
| Calais (1999)[140] | 226 | Carboplatin + 5-FU × 3 | Standard | 70@2 Gy/Fx | 22% vs. 16% | 0.05 |
| | | 70 mg/m$^2$/d + 5-FU 600 mg/m$^2$ × 3 CI | | | | |
| Adelstein (2003)[83] | 295 | Cisplatin × 3 D1, 22,43 = 100 mg/m$^2$ | Standard | 70@2 Gy/Fx | 37% vs. 23% | 0.014 |
| | | Cisplatin 75 mg/m$^2$ + 5-FU × 3 = 4-d 1 gm/m$^2$/d = CI/4 wk | Split course | 30 Gy 1st, 30–40 Gy 3rd cycle | 27% vs. 23% | |
| Fountzilas (2004)[296] | 124 | Cisplatin × 3 D1, 22, 43 = 100 mg/m$^2$ | Standard | 70@2 Gy/Fx | 52% vs. 17.5% | 0.0002 |
| | | Carboplatin × 3= 7 AUC on D 2, 22, 42 | Standard | | 42% vs. 17.5% | 0.001 |
| Ruo Redda (2010)[297] | 164 | Carboplatin daily every other week 45 mg/m² D1-5, weeks 1, 3, 5,7 | Standard | 70@2 Gy/Fx | 28.9% vs. 11.1% | 0.02 |
| Brizel (1998)[298] | 116 | Cisplatin 12 mg/m$^2$ D1-5 + 5-FU 600 mg/m$^2$ × 2 D1-5 weeks 1 and 6 of RT | HF | 75 Gy@1.25 Gy BID<br>70 Gy@1.25 Gy BID + chemo | 55% vs. 34% | 0.07 |
| Jeremic (2000)[299] | 130 | Cisplatin daily: 6 mg/m$^2$ | HF | 77 Gy/70Fx 35 d 7 wk | 46% vs. 25% | 0.0075 |
| Staar (2001)[141] | 240 | Carboplatin 70 mg/m$^2$ D1-5 and D29—33 + 5-FU × 2,600 mg/m$^2$ D | HF | 69.9 Gy/38D; weeks 1–3: 1.8 Gy/D, weeks 4 and 5: BID 1.8 Gy/1.5 Gy) | 25.6% vs. 15.8% | 0.0016 |
| Huguenin (2004)[300] | 224 | Cisplatin 20 mg/m$^2$ D1-5, weeks 1 and 5 | HF | BID 1.2 Gy/d, 5 d/wk, = 74.4 Gy | 59% vs. 49% | 0.147 |
| Bensadoun (2006)[301] | 171 | Cisplatin 100 mg/m$^2$ (D1, D22, D43) + 5-FU × 3 | HF | BID 1.2 Gy/d, 5 d/wk, = 80.4 Gy (OPC)<br>75.6 Gy (HPX) | 37.8% vs. 20% | 0.038 |

5-FU, 5-fluorouracil; HF, hyperfractionated; NS, nonsignificant.

very similar for patients receiving surgery versus primary chemo-RT–based management, with estimated rate of <5%.[63,126,150] The outcomes are operator dependent, whether surgery or RT, with experience being a key factor in both oncologic and functional outcomes. See Tables 17.7 and 17.8 for further details of oncologic and functional outcomes for each modality.

## Base of Tongue

***Early-stage Disease.*** Early-stage BOT cancer is successfully treated with either primary RT or primary surgery. The results are equivalent for LC and OS. It is always preferred to use single-modality treatment in order to optimize both the oncologic and the functional outcomes. Treatment of BOT cancer must address the primary site as well as both sides of the neck and bilateral RP nodes.[41,47,50] Thus, RT has the advantage of comprehensively and simultaneously treating the primary site and all nodal areas at risk.

RT alone is very effective for patients with early-stage disease. Brachytherapy boost (BT) has been used by multiple investigators as a mechanism to increase tumor dose while significantly lowering dose to the salivary glands, the constrictors muscles, the larynx, and the surrounding mucosa. Table 17.10 summarizes the LC rates for BOT cancer treated with EBRT plus BT. Although there is no prospective trial, the data using BT has been consistently excellent. Patient selection is important, and a radiation oncologist with experience in BT must perform the procedure. As always, the decision to use any specific therapeutic approach should be individualized.

Data from numerous authors have shown that the LC for early-stage disease is in the range of 80% to 100% when treated

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**TABLE 17.10 Summary of Base of Tongue Carcinoma Oncologic and Functional Outcomes Post Primary RT (External Beam RT + BT)**

| Study and Institution | No. of Patients | Median Follow-up (m) | T3–4% | Oncologic Outcome | Functional Outcome | Median RT and BT dose | Chemotherapy | ND |
|---|---|---|---|---|---|---|---|---|
| Patton (2010)[154] | 89 | 38 | 47% | 3 yr<br>LC: 97%<br>RC: 96%<br>LRC: 93%<br>DMFS: 91%<br>DFS: 88%<br>OS: 90% | PEG-dependence: 4%<br>Xerostomia 5% | EBRT: 60 Gy (45)–(72)<br>BT: 18 Gy (9–30 Gy) | 81% | 79% |
| Karakoyun-Celik (2005) MGH[302] | 40 | 56 | 53% | 5-, 10- yr<br>LC: 78%, 70%<br>DFS: 62%, 27%<br>OS: 54%, 18% | ORN 5%, Grade 2 dysphagia 5% | EBRT: 61 Gy<br>BT: 17.4 Gy | 60% | 50% |
| Harrison MSKCC (1998)[303] | 68 | 36 | 29% | 5-, 10-yr<br>LC: 89%, 89%<br>DMFS: 91% 76%<br>DFS: 80%, 67%<br>OS: 86%, 52% | ORN 3% | EBRT: 54 Gy<br>BT: 20–25 Gy (T1–2)<br>BT: 25–30 Gy (T3–4) | 13% | 100% |
| Housset (1987) University of Paris[155] | 29 | 96 | 0% all T1-2 | 5-yr<br>LC: 80%<br>OS: 30.5% | ORN 3% | EBRT: 45 Gy<br>BT: 30–35 Gy | 0% | 0% |
| Puthawala (1988) Long Beach[304] | 70 | 60 | 74% | 3-yr<br>LC: 83%<br>DFS: 67% | ORN 3% | EBRT: 45–50 Gy<br>BT: 20–25 (T1–2)<br>BT: 30–40 (T3–4) | 0% | 83% |
| Gibbs (2003) Stanford University[305] | 41 | 62 | 50 | 5-yr<br>LC: 82%<br>RC: 93%<br>OS: 66%<br>DMFS: 83% | ORN: 5%<br>STN: 7% | EBRT: 50 Gy<br>BT: 26 Gy | 7% | 56% |
| Takácsi Nagy (2004) Hungary[306] | 70 | 56 | — | 5-yr<br>LC: 60%<br>LRC: 52%<br>OS: 46% | ORN + STN = 13% | EBRT: 61 Gy<br>BT: 18 Gy | — | 32% |
| Takácsi-Nagy (2004) Hungary[306] | 37 | 51 | — | 5-yr<br>LC 60%<br>LRFS 52%<br>OS 46% | ORN + STN = 13% | EBRT: 60 Gy<br>BT: 18–28 Gy | — | 32% |
| Barrett et al. (2004) University of Cincinnati[307] | 20 | 45 | 35% | 5-yr<br>LC: 87%<br>OS: 33% | — | EBRT: 50 Gy<br>BT: 25 Gy | — | 80% |

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**TABLE 17.10 Summary of Base of Tongue Carcinoma Oncologic and Functional Outcomes Post Primary RT (External Beam RT + BT) (Continued)**

| Study and Institution | No. of Patients | Median Follow-up (m) | T3–4% | Oncologic Outcome | Functional Outcome | Median RT and BT dose | Chemotherapy | ND |
|---|---|---|---|---|---|---|---|---|
| Cano et al. (2009) University of Pittsburgh[158] | 88 | 37 | 58% | 3-yr LRC 80% DFS: 70% LC: 82% DC: 90% OS: 81% | ORN 5%, PEG-dependence 2.3% | EBRT: 62 Gy BT: 24.5 Gy | 100% | 8% |
| Crook (1988) Henri Mondor Hospital[308] | 48 | 60 | 0% | 5-yr LC: T1-85% LC: T2-71% RC: 94% DFS: 50% | ORN 6% | EBRT: 48.6 Gy BT: 32 | 0% | 27% |
| Horwitz (1996) William Beaumont[309] | 20 | 47 | 45% | 5-yr LC: 88%. After salvage: 93% | Dysphagia 10% | EBRT: 50–66.6 Gy BT: 27 Gy | — | — |

DFS, disease-free survival; OS, overall survival; BT, brachytherapy boost; RT, radiation therapy; PEG, percutaneous endoscopic gastrostomy; ORN, osteoradionecrosis; STN, soft tissue necrosis; LC, local control; LRC, loco-regional control; ND, neck dissection; FU, fluorouracil; BOT, base of tongue.

with combined RT and BT. Many centers, including our own, have used BT for patients with BOT cancers.[120,151–154] This approach has consistently yielded excellent outcomes from both the oncologic and functional prospective.[152] With the advances in RT techniques (IMRT, IGRT), changes in the patient characteristics (emergence of HPV/p16) and prognosis, it is legitimate to question whether BT should still be considered in the context of early-stage BOT cancer. There are ample reports in the literature that reveal excellent outcomes with primary RT, whether EBRT alone or EBRT with BT boost (Table 17.10). Whereas there is probably not an oncologic advantage for T1 lesions, the literature supports a potential LC advantage for T2 disease.[120,151–154] The use of BT allows considerable reduction (de-intensification) in the EBRT dose, from 70 Gy down to 50 to 54 Gy. This results in lower acute toxicity and minimal long-term swallowing dysfunction and xerostomia.[152] Of course, the use of BT involves short-term hospitalization, a temporary tracheostomy, and several days of continuous LDR-RT. This needs to be taken into account in making the best decision for the patient. A large percentage of current BOT cancer patients are healthy, young nonsmokers, who are able to tolerate this procedure well. Full informed consent is mandatory, as well as patient understanding of the options.

The authors' preferred strategy entails EBRT followed by an interstitial $^{192}$Ir implant as a boost to the BOT. The authors believe that this modality offers the greatest opportunity for excellent LC and best function results compared with either high-dose EBRT alone or to primary surgery. A BT boost to the BOT (20–30 Gy) is performed approximately 2 to 3 weeks after IMRT (50–60 Gy). The implant consists of $^{192}$Ir inserted via after-loading catheters placed with a looping technique (Fig. 17-12). As a safety precaution, a temporary tracheostomy is performed and maintained during the dwell time of the implant. A temporary nasogastric feeding tube is also used. Refer to Chapter 17, Part C, for RT techniques, where the details of contouring IMRT- and CT-based BT planning are reviewed.

Pernot et al. reported on 277 patients with SCC of BOT of whom 64% had T1–2 disease. The 5-year LC, DSS, and OS rates by T classification (T1, T2) were as follows: LC = T1—89%, T2—86%; DSS = T1—78% and T2—62%; OS = T1—62% and T2—53%. No local recurrence was detected after 3 years.[151] Multivariate analysis revealed that a treatment interval of <20 days between EBRT and BT and an overall treatment time of <55 days yielded better outcomes.[153]

While there are no randomized trials comparing BT to other approaches, there are comparative retrospective series that do compare approaches for early-stage patients. Housset et al. reported on 110 patients with early-stage BOT cancer (100% T1–2). Twenty-five percent underwent surgery and RT, 26% EBRT plus BT, and 49% underwent EBRT alone. With a median follow-up of 8 years, the LF rates were 43%, 21%, and 19% for EBRT alone, RT plus BT, and surgery plus RT, respectively.[155] The EBRT-alone patients had more favorable characteristics, highlighting the potential advantage of a BT boost in providing better oncologic outcomes. Sessions et al. reported on 262 patients with BOT cancer (26% stage I and 13% stage II), who underwent primary RT, primary surgery, or surgery plus RT. There was no significant difference in DSS or OS rates as a function of treatment modality. However, patients who underwent RT alone had improved capacity to swallow ($p = 0.001$), speak ($p = 0.01$), and work ($p = 0.001$) compared with surgery alone or surgery plus RT.[156]

MIS (TLM and TORS) has also gained interest in patients with BOT cancer. This would be especially true when surgery can be used as a single modality. As all patients with BOT cancer require treatment of the primary site, and both sides of the neck, surgical patients would require ND. A potential shortcoming of this approach related to the fact that the RP nodes are generally not addressed during these surgical procedures. This could leave the patient vulnerable to recurrence in this area. For example, Figure 17-13 shows a clinical example of RP nodal recurrence after TORS alone for BOT cancer. Thus, patient selection and

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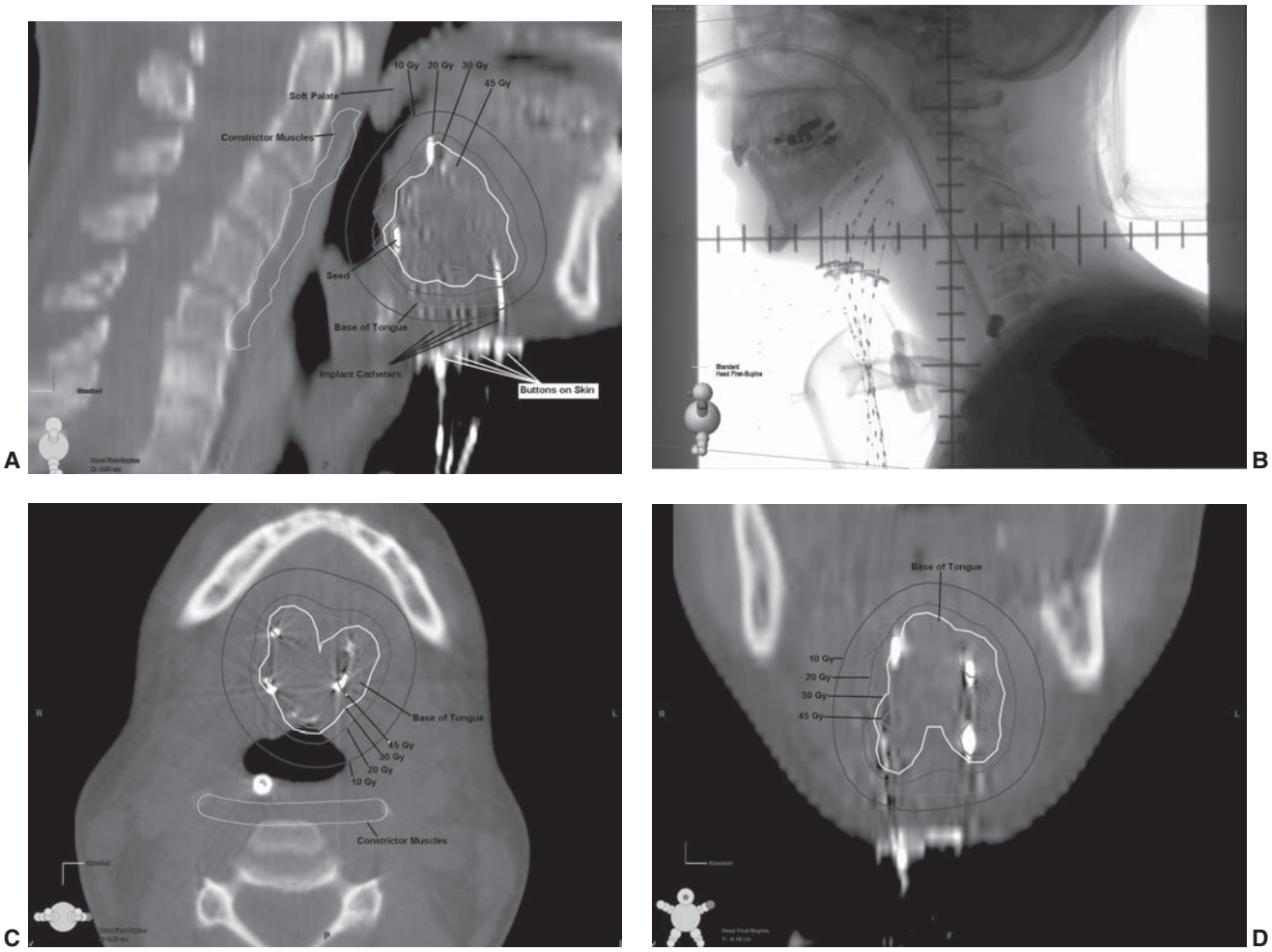
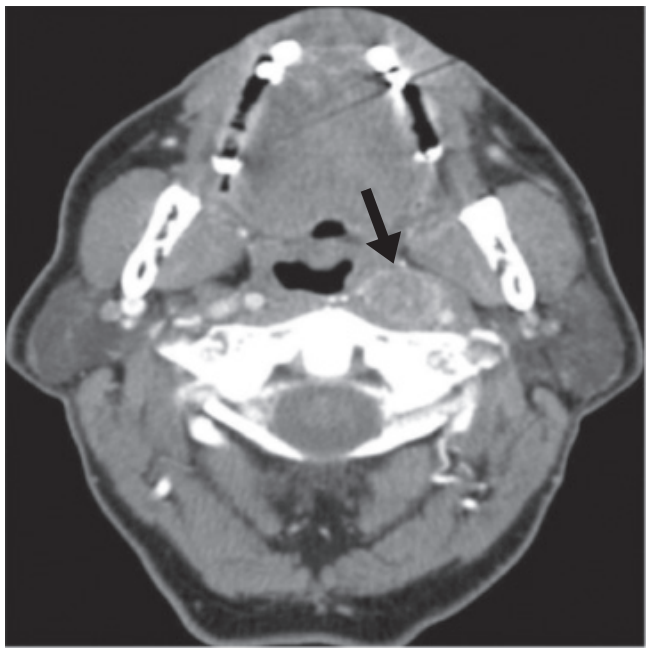



**FIGURE 17-12.** $^{192}$Ir base of tongue brachytherapy boost implant inserted via after-loading catheters placed with a looping technique. **A:** Lateral/sagittal view of the base of tongue with catheters in place which were implanted via submental approach. **B:** Lateral radiograph showing catheters as in **A**. **C:** Axial CT cut showing dosimetry. **D:** Coronal/AP view showing dosimetry.

**FIGURE 17-13.** Clinical example of retropharyngeal nodal recurrence after transoral robotic surgery alone for base of tongue cancer.

*Source:* Courtesy of Dr. Waleed Mourad.



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patient understanding of the various treatment algorithms is an absolute requirement to high-quality care.

The use of primary surgery requires a careful assessment of the resected specimen at both the primary site and the neck. Depending upon the pathologic finding, additional treatment may be indicated. Adverse pathologic features, such as inadequate surgical margins, perineural invasion, lymphovascular invasion, positive nodes, and extracapsular spread, would trigger the use of adjuvant RT or chemo-RT. One of the strongest arguments for performing TLM or TORS is the potential to avoid RT and chemotherapy in properly selected, favorable patients. If negative margins are achieved and no other poor prognostic factors are noted in the specimen, then adjuvant therapy may not be necessary. However, if the pathologic assessment triggers the need for adjuvant therapy, then the resultant management violates the principle of using single-modality therapy for early-stage disease. Thus, the patient may have the personal choice of selecting an algorithm that uses surgery to avoid chemotherapy or RT, or uses RT to avoid surgery.

It is difficult to partition the surgical data for early-stage versus advanced disease. In reality, the results of treatment are reported based upon the surgical and pathological findings rather than the clinical stage. Table 17.8 summarizes the surgical data including oncologic and functional outcomes.

Iyer et al. reported on 128 patients with SCC of the BOT, who underwent primary surgery. In the whole cohort, 16% underwent surgery only and 84% underwent surgery plus PORT. The clinical TNM classification was as follows: T1—18%, T2—41%, and N0—34%. With a median follow-up of 68 months, the 5-year DSS for surgery alone ± ND was 67%, and for surgery + ND + PORT was 100%. The 5-year DSS for T1 and T2 were 95% and 73%, respectively ($p = 0.001$). For the whole cohort, the 5-year OS and RFS rates were 60% and 61%, respectively. Multivariate analysis showed T classification is significant for local recurrence.[98]

Henstrom et al. reported on 20 patients with BOT cancer who underwent primary TLM and ND. Sixty percent underwent PORT and 20% underwent adjuvant chemo-RT. With a mean follow-up of 40 months, the 2- and 5-year OS rates were 90% and 83%, respectively. The 2- and 5-year DFS rates were 90% and 83%, respectively. The 2-year LC, RC, and DC rates were 84%, 100%, and 95%, respectively. Ten percent were PEG dependent.[144]

Moore et al. reported on patients with BOT cancer who underwent primary TORS and ND. Eighty-nine percent were HPV/p16 positive. Twenty-one percent underwent PORT and 62% underwent adjuvant chemo-RT. With a mean follow-up of 36 months, the 4-year DFS was 92%. The 4-year LC and RC were 97% and 94%, respectively. Five percent were PEG dependent.[134]

Thus, it is clear that a primary RT approach or a primary surgical approach can be used for early-stage BOT cancer. Primary RT has the advantage of being a single-modality therapy. Primary surgery is an alternative to primary RT, especially if surgery can be the only treatment. Both primary surgery and BT boost involve an inpatient hospital stay. Multidisciplinary evaluation and discussion of all treatment options is mandatory prior to embarking upon treatment and provides each patient with the best set of personalized options.

***Advanced-stage Disease.*** In the current era, patients with locoregionally advanced disease are still highly curable. Excellent outcomes can be achieved in stages III, IVA, and IVB.[126,128,154] Most patients will require multimodality therapy. Concomitant cisplatin-based chemotherapy and RT (chemo-RT) has been the mainstay of treatment.[61,77,82,83,135] Tables 17.7 and 17.9 summarizes the oncologic and functional outcomes of the concomitant chemo-RT approach.

Lawson et al. reported on 34 patients with SCC of the BOT, who underwent primary concomitant chemo-RT. Ninety-four percent were stages III to IV. With a median follow-up of 20 months, the 2-year LC and RC were 92% and 97%, respectively.[157]

Patton et al. reported on 89 patients with BOT cancer, who underwent primary concomitant chemo-RT including brachytherapy boost. Stages III and IV were 10% and 79%, respectively. TNM classification was T1—8%, T2—45%, T3—30%, T4—17%, and N2/3—80%. Patients were treated initially with EBRT to a median dose of 60 Gy followed by a brachytherapy boost (median dose = 18 Gy). Concurrent chemotherapy was given in 81%. Planned ND was performed in 79%. At a median follow-up of 38 months, 3-year LC was 97%, RC 96%, LRC 93%, DFS 88%, and OS 90%. The 3-year PEG-dependence was 4% and grade 2 xerostomia 5%.[154]

Cano et al. reported on 88 patients who underwent concurrent chemo-RT followed by BT boost. Eighty-one percent had positive nodes, 42% had T1–2, and 58% had T3–4. With a median follow-up of 3 years, the 3-year OS, LRC, and DSS rates were 81%, 80%, and 70%, respectively. The actuarial LC was 82% and DC was 90%.[158]

Platinum-based concomitant chemotherapy with RT is the standard chemo-RT approach. Table 17.9 outlines a variety of protocols and their outcomes. The reader is referred to the section "Management of Advanced Stage Disease—Principles of Combining Chemotherapy and Radiation Therapy" for the detailed review of chemotherapy management and outcomes. For patients who cannot receive cisplatin, alternate approaches such as carboplatin[140,141] or cetuximab[79] or even altered fractionation RT alone are considered. This is also reviewed in detail in the section "Management of Advanced Stage Disease—Principles of Combining Chemotherapy and Radiation Therapy."

The general approach to the neck involves management with primary RT or chemo-RT. A PET-CT scan is done 3 months after the completion of treatment. An ND is done if there is evidence of residual disease. Neck management is discussed in detail in Chapter 14.

As mentioned in the above section on the early-stage disease, surgical outcomes have generally been reported as a function of surgical and pathological findings rather in clinical stage. The data from Henstrom and Moore have already been described,[144,159] and Table 17.8 summarizes the surgical data including oncologic and functional outcomes.

Díaz Molina et al. reported on 132 patients, of whom 93% had stage III/IV BOT cancer. All patients underwent primary surgery. Stages III, IVA, and IVB were 11%, 69%, and 13%, respectively. In the whole cohort, LC was 83%, RC was 89%, LRC was 85%, and DC was 93%. The 5-year DSS was 34% and was specifically 44% for stage III, 28% for stage IVA, and 12% for IVB ($p = 0.0004$). Multivariate analysis showed N2–3 ($p = 0.016$) and T3–4 ($p = 0.04$) are associated with worse survival. Four percent were PEG dependent.[160]

Similarly, Steiner et al. reported on 48 patients who underwent primary TLM (100%), ND (90%), PORT (48%), and adjuvant chemo-RT (25%) for stage III/IV BOT cancer. With a median follow-up of 47 months, the 5-year LC, DFS, and OS rates were 85%, 73%, and 52%, respectively. The LC and LRC rates were 80% and 72% for TLM + ND, respectively. The LC and LRC rates were 91% and 83% for TLM + ND and PORT or chemo-RT, respectively.[143]

## MANAGEMENT OF ADVANCED-STAGE DISEASE—PRINCIPLES OF COMBINING CHEMOTHERAPY AND RT

The rational for combining RT and chemotherapy is multifactorial. There are the independent mechanisms of cell killing that are synergistic. Moreover, chemotherapy has the capability to

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reduce the rate of distant metastases as well as contribute to improved LRC. The latter derives from the radiosensitizing effect of drugs, such as platinum compounds.[74,161]

The role of chemotherapy in multimodality treatment for advanced-stage OPC, although firmly established, presents several unresolved issues. Concomitant platinum-based chemoradiation (chemo-RT) is a standard primary treatment for advanced-stage OPC and for postoperative high-risk patients. Recent phase III trials comparing concomitant chemo-RT versus induction chemotherapy followed by chemo-RT did not show any advantage of induction chemotherapy in advanced-stage SCCHN.[94,95]

## Concomitant Chemotherapy and RT

***Chemo-RT.*** A landmark French intergroup (GORTEC 94-01) phase III randomized trial tested 226 patients with stages III (32%) and IV (68%) OPC. Patients were randomized to 70 Gy/7 weeks RT alone or the same RT with 3 cycles of concomitant carboplatin and 5-fluorouracil (5-FU). There was no difference in the incidence of grades 3 to 4 late toxicity (56% vs. 30%, $p = 0.12$). Treatment-related mortality was 1% in the chemo-RT arm versus 0% in the RT-alone arm. At a median follow-up of 5.5 years, the 5-year LRC was 47.6% versus 24.7%, $p = 0.002$, DFS was 26.6% versus 14.6%, $p = 0.01$, and OS was 22.4% versus 15.8%, $p = 0.05$ for patients in the combined modality arm versus RT arm, respectively. However, there was no difference in the rate of distant metastases, 18% versus 17%, respectively. On multivariate analysis, pretreatment hemoglobin levels <125 g/L, stage IV disease, and RT alone were independent prognostic factors of lower survival and LRF. The approximately 20% improvement in OS and LRC argues for the utilization of concomitant chemo-RT in the context of advanced disease OPC.[140,162–164] Noteworthy, this trial did not incorporate cisplatin, which is the most effective drug.

Table 17.9 shows the outcomes of a sampling of recent prospective randomized studies comparing RT alone to chemo-RT using platinum-based chemotherapy. As can be seen, the preponderance of the evidence reveals the superiority of chemo-RT. In the current era, cisplatin-based chemo-RT is the standard of care[165] for patients who are medically suitable to receive this therapy.

The Meta-analysis of Chemotherapy on Head and Neck Cancer (MACH-NC) included 93 randomized trials and 17,346 patients. This analysis showed that concomitant chemo-RT improved OS compared with RT alone in advanced disease by 6.5% at 5 years ($p = 0.0001$). This improvement was demonstrated irrespective of RT fractionation. Platinum-based concomitant chemo-RT was the most effective combination, with an absolute survival benefit of 9% at 5 years ($p = 0.01$).[74,76]

Blanchard et al. updated the MACH-NC by tumor site. They reported that the advantage of concomitant chemo-RT was present for all tumor locations with a 5-year absolute survival benefit of approximately 8% for OPC ($p < 0.0001$).[166]

Investigators have compared the outcomes of chemo-RT using standard fractionation RT (70 Gy/7 weeks) versus altered fractionation with a variety of accelerated RT techniques, including the concomitant boost. The RTOG 0129 phase III trial compared standard RT combined with 3 cycles of cisplatin (100 mg/m$^2$ × 3 cycles) versus accelerated concomitant boost RT (72 Gy/6 weeks) with 2 cycles of cisplatin (100 mg/m$^2$ × 2 cycles). There was no difference in the 5-year OS between these two arms: 59% versus 56% ($p = 0.18$), respectively.[61] Similarly, the GORTEC 99-02 study showed no difference in OS when accelerated RT plus 2 cycles of concomitant carboplatin + 5-FU were compared with standard fractionation RT concomitant with 3 cycles of the same chemotherapy regimen.[77]

Based on the aforementioned two studies, RTOG 0129 and GORTEC 99-02, it is reasonable to conclude that 2 cycles of concomitant chemotherapy may be adequate in the setting of concomitant altered fractionation RT. Likewise, both studies suggest that altered fractionation adds no benefit over standard RT in the context of chemo-RT. The current NCCN guidelines call for the use of standard fractionation IMRT with 3 cycles of concomitant cisplatin (100 mg/m$^2$ days 1, 22, and 43).[165] However, not all patients will be able to receive all 3 cycles of cisplatin. The impact of this is unclear, and patient safety generally dictates whether all 3 cycles can be given. It seems reasonable to the authors to drop the third chemotherapy cycle if the medical condition of the patient puts him/her at higher risk of life-threatening morbidity and/or mortality.

Concomitant chemo-RT is associated with serious treatment-induced morbidity and occasional mortality. It should only be advised for medically fit patients with good performance status. It has been reported that the incidence of concomitant chemo-RT-related death in the range of 1% to 9%.[164,167–169] Treatment sequelae are reviewed in detail in an upcoming section.

The toxicity of cisplatin-based concomitant chemo-RT has led investigators to explore potentially less morbid approaches. One such approach involves the use of biological agents that target the EGFR and more recently second-generation EGFR tyrosine kinase inhibitors (TKIs).[61,79,170–172]

Bonner et al. reported the results of a multicenter phase III study. Patients with advanced-stage SCCHN were randomly assigned to RT alone ($n = 213$) or RT plus weekly cetuximab ($n = 211$) at an initial dose of 400 mg/m$^2$ followed by 250 mg/m$^2$ weekly for the duration of RT. Sixty percent of the 424 patients enrolled in the study had OPC. With a median follow-up of 54 months, the addition of cetuximab provided a statistically significant improvement in the 3-year LRC (47% vs. 34%, $p < 0.01$), PFS (42% vs. 31%, $p = 0.04$), and OS (55% vs. 45%, $p = 0.05$). The greatest survival benefit was among patients with OPC, with a median survival of 66 versus 30.3 months.[79]

Ang et al. reported the results of the RTOG 0522 phase III trial (940 patients with locally advanced SCCHN) comparing concomitant chemo-RT (2 cycles of cisplatin concomitant with accelerated RT) and the same chemo-RT plus cetuximab. The 2-year PFS and OS rates were similar for both arms (64.3% vs. 63.4% and 79.7% vs. 82.6%, respectively). Likewise, no difference was observed for loco-regional relapse (19.8% vs. 24.5%) and distant metastasis rates (12% vs. 7.6%). The incidence rates of severe mucositis and in-field skin reaction were significantly higher in the chemo-RT plus cetuximab combinations arm (43% vs. 33% and 25% vs. 15%, respectively).[173]

These trials suggest that concomitant cetuximab-RT may be an alternative to concomitant cisplatin-based chemo-RT for patients who are not fit enough for cisplatin-based chemotherapy. Also, as pointed out in Table 17.9, carboplatin-based chemotherapy is an excellent alternative for cisplatin in this cohort of patients. At the current time, it does not appear that biologic therapy adds to the outcome with concomitant cisplatin-based chemo-RT. Current trials are exploring the comparison of concomitant platinum-based chemo-RT versus concomitant RT plus biological agents (i.e., cetuximab, lapatinib, panitumumab, zalutumumab, gefitinib, erlotinib, afatinib, lapatinib, bevacizumab, and bortezomib) but the results are not yet known.[171–177]

There are patients with stages III to IV disease who are not candidates for systemic therapy and need to be treated with RT alone. In this population, it is important to utilize the most effective RT regimen. Many studies have been done that explore a variety of fractionation schemes, in an effort to assess the potential benefits of altered fractionation.

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Horiot et al. reported results of the EORTC 22791 randomized trial comparing hyperfractionated RT (HF) versus conventional fractionated RT (CF) in the treatment of 356 patients with T2–T3 N0–1 OPCs excluding the BOT. With a mean follow-up of approximately 4 years, HF improved 5-year actuarial LRC compared with CF (59% vs. 40%, respectively, $p = 0.02$) with a trend toward improved survival (38% vs. 29%, respectively, $p = 0.08$). T3 tumors benefited from HF but T2 lesions did not. The incidence of long-term grade ≥2 toxicity was no different between the two arms.[178]

RTOG conducted a landmark trial (RTOG 90-03) comparing multiple altered fractionated regimens for advanced disease SCCHN, of whom 60% was OPC. A total of 1,073 patients with were randomized to four arms: conventional fractionation, split-course accelerated fractionation (SAF), delayed concomitant boost (DCB), and HF. With a median follow-up of 23 months, the DCB and HF arms had significantly better 2-year LRC compared with CF (54.5% vs. 54.4% vs. 46%, respectively; $p = 0.05$, DCB vs. CF and $p = 0.045$, HF vs. CF) and trend toward improved DFS (39.3% vs. 37.6% vs. 31.7%, respectively; $p = 0.054$, DCB vs. CF and $p = 0.067$, DCB vs. CF) were seen in both the DCB and HF arms compared with CF. There was no difference in OS or long-term grade ≥3 toxicity.[179]

Overgaard et al. reported results of the Danish Head and Neck Cancer (DAHANCA) 6 and 7 trials, which randomized 1,476 patients with SCCHN to an accelerated versus CF protocol. Both arms were treated to a total dose of 66 to 68 Gy at 2 Gy/fraction. An oral dose of the hypoxic radiosensitizer nimorazole (1,200 mg/m$^2$) was administered with the first 30 fractions of RT. The accelerated regimen proved to be superior in terms of 5-year LC (76% vs. 64%, $p = 0.0001$), LRC (70% vs. 60%, $p = 0.0005$), and DSS (73% vs. 66%, $p = 0.01$) but without improvement in OS. Confluent mucositis was significantly higher in the accelerated group (53% vs. 33%, $p < 0.0001$), but 98% of both arms received the scheduled radiation dose. Late toxicity did not differ between the fractionation groups.[67] Several other randomized trials examining altered fractionation schemes have been reported to date, most of which also demonstrate an improvement in LC and LRC at the expense of increased acute toxicity, but without an impact on OS.[180–183]

Another issue that arises in the modern era is the role of altered fractionation schemes in the context of IMRT. Although the use of HF or accelerated treatment schedules with IMRT have been reported,[121,126,184,185] due to the expense of time and resources required with IMRT, most radiation oncologists have reverted to treating patients once a day. An alternative to twice-daily radiation is the delivery of a simultaneous integrated boost (SIB), wherein multiple targets are treated simultaneously with different prescribed doses. For example, the primary tumor and gross nodal disease may be treated to 66 Gy in 30 fractions (2.2 Gy/fraction), while at the same time, high-risk areas receive 60 Gy (2 Gy/fraction) and low-risk areas receive 54 Gy (1.8 Gy/fraction). Owing to the higher dose per fraction, however, this scheme may result in a greater risk of late morbidity.

As both the addition of concomitant chemotherapy and altered fractionated RT have been shown independently to improve outcome for patients with head and neck cancer, the present challenge is to find the optimal chemo-RT regimen(s) that offer high rates of LRC, are not unduly morbid, offer maximal preservation of organ function, and may be integrated with new biologic agents.

The RTOG (0129) has randomized patients with stages III to IV SCCHN to receive either standard RT (70 Gy/7 weeks) or accelerated RT (72 Gy/6 weeks through DCB), with both groups received concomitant cisplatin. The accelerated RT group received cisplatin 100 mg/m$^2$ on days 1 and 22, whereas the standard RT group received an additional cycle of cisplatin on day 43. The 5-year OS was 59% versus 56%, respectively, with no difference between both arms ($p = 0.18$).[61]

In conclusion, the body of data would seem to favor a generalized improvement in outcomes for loco-regionally advanced OPC with concomitant chemo-RT versus RT alone. The added toxicity of altered fractionation ± concomitant chemotherapy, and the lack of clear benefit, has led to more utilization of standard fractionation RT approaches (i.e., 1.8–2 Gy/fraction) via IMRT with concomitant chemotherapy (i.e., cisplatin 100 mg/m$^2$ days 1, 22, 43).

## Induction Chemotherapy

In most studies, the experimental rationale for induction chemotherapy has been threefold. First, systemic therapy may be used to suppress the development of distant metastatic disease in patients at high risk. Second, induction chemotherapy may help select patients for organ preservation with improved outcomes. Third, the response to induction chemotherapy may predict the oncologic outcome and may allow subsequent response stratification, intensification, or deintensification of definitive treatment. There is conflicting data on the role of induction chemotherapy in the management of locally advanced SCCHN, which will be discussed.

The major emphasis for the use of induction chemotherapy has been the exploration of this approach for patients with advanced disease, who are known to be at increased risk for distant metastases.[186] A body of literature emerged that explores a variety of induction regimens, the most notable being docetaxel plus cisplatin and 5-fluorouracil (TPF).[187] This led to the development of two pivotal studies that attempted to determine the place of induction chemotherapy in the management of patients with locally advanced disease.[94,95]

Cohen et al. reported the DeCIDE trial, where 280 patients with loco-regionally advanced disease, N2–3, were randomized to receive either induction TPF followed by concomitant chemo-RT versus concomitant chemo-RT alone. With a minimum follow-up of 24 months, there was no difference in OS between the two arms, although there was a significant difference in the cumulative incidence of distant metastasis.[94]

Haddad et al. reported the PARADIGM trial, where 140 patients with loco-regionally advanced disease were randomized to receive induction TPF followed by concomitant chemo-RT versus concomitant chemo-RT alone. There was no difference in OS or PFS.[95] In both trials, excellent OS was observed in all arms. The role of induction chemotherapy in the presence of concomitant chemo-RT remains investigational and should only be done in the context of clinical trials.

## Management of the Neck

Management of the neck is an important and complex issue in SCCHN and is discussed in detail in Chapter 14. The selection of treatment modality for the neck should be based upon the approach toward the primary tumor. In cases where surgery is the primary treatment modality, ND should be performed at the time of surgery, with the need for PORT or chemo-RT determined by pathologic findings. In OPC, however, which is most commonly treated with definitive chemo-RT, the surgical management of the neck remains a debated issue. For N0–1 patients, the probability of neck control after definitive RT or chemo-RT is very high. Therefore, patients do not require an ND unless there is evidence of persistent disease after treatment.[63,154,188] However, with increasing nodal disease, regional recurrence rates increase.[189,190] In the pre-chemo-RT era, it had long been recognized that patients treated with combined RT

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and surgery for N2–3 disease had lower neck recurrences than after either modality alone.[191,192] Historically, planned ND had been standard for patients with N2–3 disease.[87,193] However, in the current era of treatment with concomitant chemo-RT, the need for a planned ND has been questioned, particularly in the setting of a complete clinical response after definitive doses of RT.[194–196]

Historically, several investigators have advocated the incorporation of a planned ND, regardless of the response after chemo-RT,[197–203] whereas others preferred to reserve ND for those patients with clinical or radiographic evidence of residual nodal disease.[194,204–207] Recently, the use of PET-CT scans has aided in further refining the management of the neck. Liauw et al. analyzed the records of 550 patients with node-positive disease treated with RT or chemo-RT, with or without planned ND. Of 211 patients with CT scan imaging data available for review, 28% had a radiologic complete response (rCR). When correlated with the pathologic specimens, an rCR demonstrated a sensitivity of 96%, specificity of 24%, positive predictive value of 35%, and a negative predictive value of 94%. Among the 32 patients who did not undergo an ND after an rCR, the 5-year neck control rate was 97% (with salvage 100%). This was equivalent to those patients with a pathologically negative ND (5-year neck control 98%). There was no difference in cause-specific survival or OS between these groups.[208] Similarly, Yao et al. reported a series of 41 patients treated with definitive RT or chemo-RT who underwent posttreatment PET scans to assess response.[209] Patients' scans were correlated with biopsy or ND specimens. In this study, a negative PET scan (maximum standardized uptake value [SUV] < 3.0) was highly correlated with a negative pathologic examination, with a negative predictive value of 100%. Several studies support these findings, with a negative predictive value of PET scans after radiation of 83% to 97%.[210–213] Some studies, however, report significantly lower negative predictive values associated with post-RT PET scans (Rogers et al., 2004; Gourin et al., 2006).[213a,213b]

The concept of withholding planned ND in patients who experience CR to chemo-RT has continued to gain momentum over the last decade.[214] This has been extensively reviewed in Chapter 14, in the section "Role of Planned Neck Dissection for Patients with a Complete Response to Chemoradiotherapy." Corry et al. reported that all patients with N2/3 disease, who obtained a clinical and radiological CR to chemo-RT at 12 weeks post treatment, had RC, with a zero incidence of isolated neck failure, without a planned ND. These authors concluded that the use of planned ND in this patient subset cannot be justified. Hamoir et al. have recently reviewed the literature on this issue and reached a similar conclusion.[215]

It has therefore become the policy at the authors' institution to withhold ND in patients who achieve a clinical and radiologic (PET-CT) CR at 3 months after definitive chemo-RT. If clinical examination or PET-CT at 3 months post treatment suggests the possibility of residual disease in the neck, ND should be performed. Sometimes the PET-CT imaging is equivocal, and management must be individualized. In this setting, it is often helpful to perform a fine-needle aspiration biopsy from that suspicious node. ND is done if the biopsy is positive but may be withheld if the biopsy is negative. Clinical judgment should always prevail in making this decision. It is also imperative that patients are followed very carefully with frequent examinations and surveillance, especially during the first 2 years after treatment.[201]

## Postoperative RT ± Chemotherapy

In patients treated with a primary surgical approach, a careful examination of the resected specimen is essential to the determination of the need for adjuvant therapy. Chapter 1 reviews the pathologic details contained in the pathology report, and Chapter 3 reviews the important prognostic factors in detail.

The use of PORT can be triggered by findings at either the primary site or the neck. For the primary site, the key features are the tumor size, local invasiveness into adjacent structures (i.e., bone), adequacy of the resection margins, tumor grade, presence of lymphovascular and/or perineural invasion, and even tumor spillage or tumor multicentricity. Adverse features in any of these areas would trigger PORT.

Similarly, findings in the neck could trigger the use of PORT. Whereas patients with a single positive node and no extracapsular spread may not benefit from PORT, patients with multiple nodes should receive PORT and patients with positive margins and/or extracapsular spread should receive PORT with concomitant cisplatin-based chemotherapy.[216]

Several investigators examined the interval between surgery and RT. Bastit et al. reported no difference in LRC or OS in a retrospective study of 420 patients with OPCs who were treated with similar doses (59 Gy/6 weeks) either within ($n = 219$) or after 30 days ($n = 201$) of surgery.[217] However, Ang et al. report that among high-risk patients (positive margins, extracapsular nodal extension, or multiple lymph nodes), a duration of <11 weeks from the end of surgery to the end of RT resulted in better LRC ($p = 0.005$) and OS ($p = 0.03$) compared with those treated over a longer period.[218] Similarly, Rosenthal et al. reported a retrospective study on 208 patients treated with surgery and PORT (≥55 Gy) for SCCHN. With a median follow-up of 24 months, the actuarial 2-year LRC and OS were 82% and 71%, respectively. The total time from surgery to completion of RT (treatment package time) of <100 days was associated with improved LRC and OS ($p = 0.021$).[219]

The role of postoperative chemo-RT has been evaluated in locally advanced SCCHN. Two major phase III studies compared RT alone versus concomitant chemo-RT as adjuvant treatments after surgery in poor-risk SCCHN stages III to IV nonmetastatic patients. In both studies, a single-agent cisplatin, dose of 100 mg/m$^2$ on days 1, 22, and 43, was administered during PORT. Both the RTOG 9501 and the EORTC 22931 studies showed that the concomitant chemo-RT gave a significant benefit in DFS.[85,137] However, in the EORTC 22931 study, the OS showed significant improvement with chemo-RT versus PORT alone.[85] A subsequent joint analysis showed that the OS benefit of concomitant chemo-RT was significant only for patients with positive resection margins at the primary site and/or extracapsular spread in the neck.[220] These two pathological findings are the only criteria for selecting patients to treat with adjuvant concomitant chemo-RT.[220] It should be noted that combined treatment should only be delivered to patients with good performance status due to severe treatment-related toxicity. Because the aforementioned studies used high-dose cisplatin, this remains the standard regimen to be used postoperatively. However, the reported compliance analysis reveals that only 50% to 60% of patients were able to receive all three planned cycles in both studies. Recently, Cooper et al. reported the long-term follow-up of the RTOG 9501. With a median follow-up of 9.4 years, there was no significant differences in outcome However, analysis of the subgroup of patients who had either microscopically positive margins and/or extracapsular spread showed improved LRC and DFS with postoperative concomitant chemo-RT.[221] Table 17.11 shows oncologic outcomes in both RTOG 9501 and EORTC 2293.

## Recurrent Disease and Salvage

Loco-regional recurrences are seen in 15% to 50% of patients with SCCHN and this a major factor contributing to death from head and neck cancer.[137,222–227] Due to the heterogeneity of patients with loco-regional recurrence, it becomes impossible to

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**TABLE 17.11 Oncologic Outcomes in Both RTOG 9501 and EORTC 2293 for Postoperative RT ± Chemotherapy**

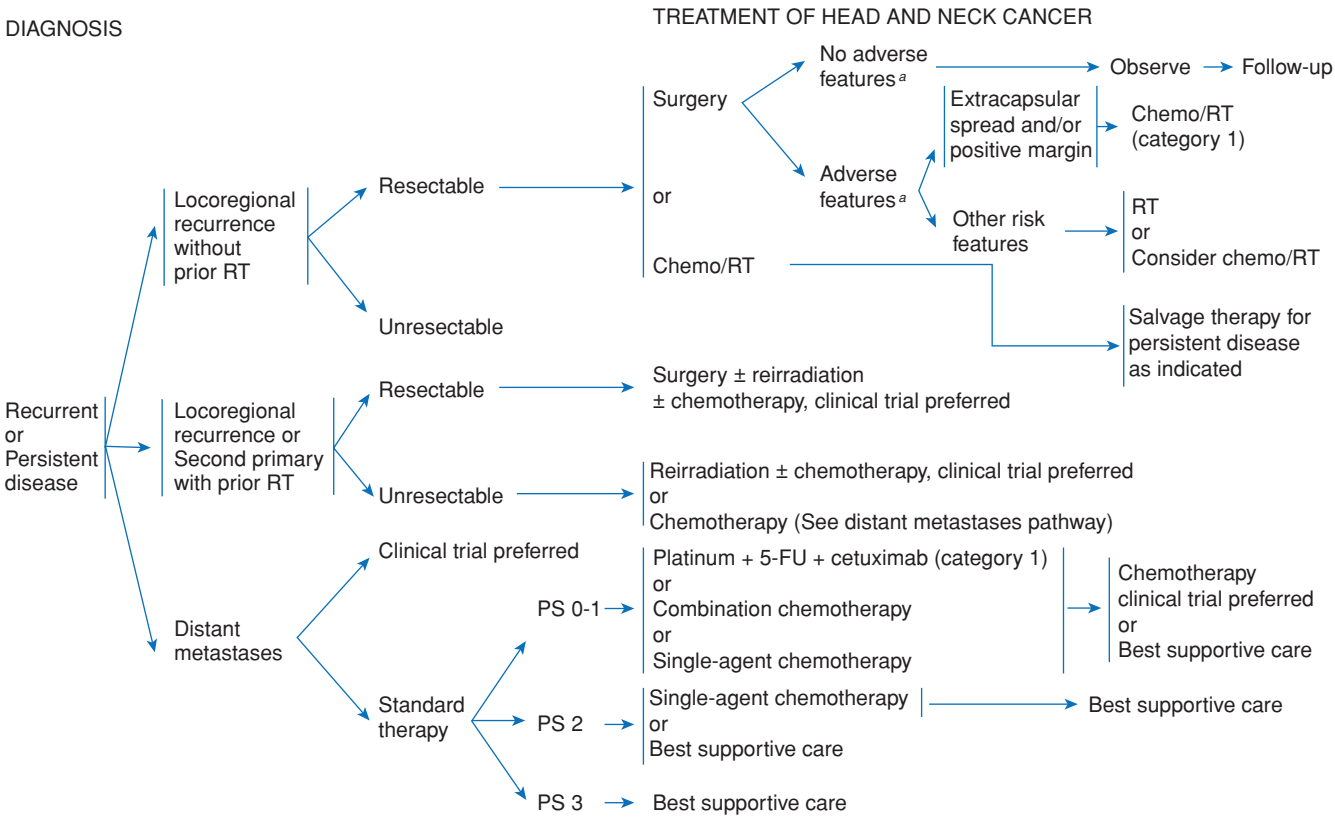
| | RTOG 9501 (Cooper, 2004)[84] | EORTC 22931 (Bernier, 2004)[85] |
|---|---|---|
| Number of patients | 459 | 334 |
| Median follow-up in months | 46 | 60 |
| RT | 60–66 Gy/6 wk | 66 Gy/6.5 wk |
| Concomitant Chemotherapy | Cisplatin 100 mg/m$^2$ D1,22,43 | |
| Received 3 cycles of cisplatin | 61% | 49% |
| LRF (CRT vs. RT) | 19% vs. 30% | 18% vs. 31% |
| DM | 21% vs. 25% | 20% vs. 23% |
| DFS* | 47% vs. 36%[a] | 47% vs. 36%[a] |
| OS | 56% vs. 47% | 53% vs. 40%[a] |

[a]Statistically significant. LRF, loco-regional failure; CRT, chemo-RT; RT, radiation therapy; DM, distant metastases; DFS, disease-free survival; OS, overall survival; D, day.

be dogmatic about treatment guidelines and approaches. A high level of individualized care is required, taking into account the disease extent, prior treatment constraints, the performance status of the patient, the ability to maintain QOL, and other appropriate factors. In general, the data support the conclusion that the best outcomes are achieved in patients who can undergo salvage resection, accompanied by re-irradiation and chemotherapy. Figure 17-14 outlines the NCCN 2012 guidelines for recurrent or persistent SCCHN.

Salama et al. reviewed the University of Chicago experience with recurrent disease and reported the best outcomes for tumor control in patients who had surgical resection, higher doses of re-irradiation, and chemotherapy.[228] Janot et al. reported a randomized trial of surgery ± chemo-RT for recurrent disease patients and reported better tumor control in those who received surgery plus chemo-RT.[229]

The restrictions imposed by prior RT have prompted the investigation of intraoperative RT (IORT) at the time of surgery, as a mechanism of safely escalating the dose of re-irradiation. Scala et al. reported on 77 patients with recurrent SCCHN, who were treated with high-dose-rate (HDR) IORT. With a median follow-up of 11 months, estimated 1-year OS was 66%, DFS 51%, in-field control (IFC) 65%, and DM 31%. Margin status impacted on IFC. In patients with negative versus positive margins, the 1-year IFC was 86% versus 56% ($p = 0.01$), respectively. The DFS was 66% versus 39% ($p = 0.05$) in patients with negative versus positive margins, respectively. Margin status did not impact upon OS or DM. Patients with IFC had improved OS.[230] Table 17.12




[a]Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism

**FIGURE 17-14.** National Comprehensive Cancer Network (NCCN) 2012 guidelines for treatment of recurrent or persistent squamous cell carcinoma of the head and neck. All recommendations are category 2A unless otherwise indicated. NCCN believes that the best management of any cancer patient is in a clinical trial; participation in clinical trials is especially encouraged. Chemo, chemotherapy; PG, performance status; RT, radiation therapy.
*Source:* Adapted from the NCCN Guidelines.

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**TABLE 17.12 A Selection of Studies That Highlight the Positive Outcomes That Can Be Achieved with Combined Surgery, RT, and Chemotherapy, Including IORT**

| Author | Institution | Number of Patients | Med F/U (mo) | IORT Dose (Gy) | LC | 2-yr OS |
|---|---|---|---|---|---|---|
| Garrett (1988)[310] | Methodist | 67 | NR | 15–20 | 75 | NR |
| Freeman (1990)[311] | Methodist | 104 | 24 (min) | 15–20 | 40 | NR |
| Rate (1991)[312] | Methodist | 47 | 14 | 15–25 | 62 | 55 |
| Cornes (1996)[313] | RMH-UK | 39 | 12 | 50 Gy/5 d | 63 | 38 |
| Coleman (1997)[314] | UCSF | 44 | 20 | 14–18 | 62 | 66 |
| Spaeth (1997)[315] | Germany | 120 | 11 | 10–20 | LC: R0-64%, R2-17% | NR |
| Toita (1994)[316] | Japan | 25 | 19 | 10–30 | 54 | 45 |
| Nag (1998)[317] | OSU | 38 | 30 | 15–20 | 4 | 21 |
| Nag (1999)[318] | OSU | 7 | 59 | 10–15 | 57 | |
| Chen (2007)[319] | UCSF | 137 | 41 | 10–18 | 67 (3 yr) | 36 (3 yr) |
| Perry (2010)[320] | MSKCC | 34 | 24 | 10–20 | 66% | 55% |
| Zeidan (2011)[321] | Stanford | 198 | 12 | 15–20 | 91% | 1, 3, 5-yr: 58%, 34%, and 26% |
| Scala (2013)[230] | BIMC | 77 | 13 | 10–17.5 | 65% | 1 yr: 66% |
| Personal-communication (2012) | MSKCC | 57 | 16 | 10–20 | 57 | 55 |

shows a selection of studies that highlight the positive outcomes that can be achieved with combined surgery, RT, and chemotherapy, including IORT, in the recurrent disease setting. Of course, as stated, treatment must be individualized.

## TREATMENT SEQUELAE AND COMPLICATIONS

Different modality treatment sequelae can be grouped into acute and late toxicities. Acute toxicity and management is discussed in detail in Chapter 10. In the current section, we present each modality late toxicity and its management.

### Surgery

Sequelae related to surgery can be clustered into intraoperative, immediate, and delayed postoperative complications. Traditionally, operative mortality for either primary tumor resection or ND has been low. Perioperative complications include infection, bleeding, nerve injury, cardiovascular, and pulmonary complications.[231,232] Delayed complications include fistula, flap loss, trismus, lymphedema, and shoulder muscle dysfunction after ND.[233,234] Locally advanced disease necessitates extensive resection that can affect speech and swallowing. Moreover, a laryngectomy may be required in very advanced disease in an effort to prevent aspiration, causing additional functional morbidity.[235]

As described in this chapter, there has been a growing interest in MIS for OPC. Currently, MIS is extensively reported within the head and neck literature, driven by the desire to offer a less morbid alternative to traditional surgery. These techniques have included TLO, TLM, and TORS, which dramatically reduce the surgical time and morbidity associated with the traditional resections.[26,28,131,132,236–239] Table 17.8 shows the oncologic and functional outcomes of several recent studies of OPC treated with either traditional surgery or MIS (i.e., TLO, TLM, and TORS). The vast majority of patients underwent TORS or TLM followed by ND and adjuvant therapy (e.g., RT or chemo-RT). In general, utilization of MIS has led to marked improvement in the QOL outcomes over traditional surgical approaches. Specifically, MIS is associated with relatively low rates of gastrostomy tube dependence and high QOL scores on questionnaire assessment.

### Radiation Therapy

The major sequelae of RT can be divided into acute and late toxicity. These depend on total dose, fraction size, prior or concomitant therapy (i.e., surgery or chemotherapy), and target volume. Refer to Chapter 10 for discussion of acute toxicity and supportive care management. The late toxicity of RT presents months to years after the completion of treatment and is often permanent. This includes xerostomia, altered taste, dysphagia, dysphonia, osteoradionecrosis, brachial plexopathy, carotid artery vasculopathy, soft tissue fibrosis, esophageal injury, hypothyroidism, and radiation-induced malignancy. Severe late toxicity is less common with current treatment techniques.

Xerostomia is the most common late toxicity of RT, which is due to loss of function of the salivary glands secondary to RT effects. Loss of saliva predisposes to mucosal fissures and ulceration. RT-induced xerostomia is dose dependent. A parotid gland mean dose of ≤26 Gy should be a planning goal if substantial sparing of the gland function is desired.[240] Moreover, mean

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doses of 40 to 50 Gy to a parotid gland typically causes >75% reduction in function.[170] There are different approaches to prevent xerostomia, including parotid-sparing IMRT, amifostine, and submandibular salivary gland transfer.

The development of IMRT and daily IGRT significantly decrease the incidence of RT-induced xerostomia. The Parotid-Sparing Intensity-Modulated Versus Conventional Radiotherapy in Head and Neck Cancer trial (PARSPORT) randomly assigned 94 patients with locally advanced SCCHN to either conventional 3D RT or IMRT. The trial utilized the Late Effects of Normal Tissues Subjective–Objective Management Analytic (LENTSOMA) subjective side-effect scale. At both 12 and 24 months, significant benefits were seen in recovery of saliva secretion with IMRT compared with conventional RT, as were clinically significant improvements in dry-mouth-specific and global QOL scores.[241] Toledano et al. reported the results of the GORTEC 2004–03 study. They utilized the RTOG-EORTC toxicity scales. At 18 months, grade ≥2 xerostomia was 16%. A mean dose to the spared parotid below 28 Gy led to significantly less grade ≥2 xerostomia (8.5% vs. 24%, $p = 0.03$). Grade ≥2 xerostomia increased by approximately 3% per Gy of mean parotid dose up to 28 Gy, and then 7% per Gy above 33 Gy.[136] Lee et al. reported that IMRT reduced severe late xerostomia from 67% to 12%.[150]

Amifostine role in preventing xerostomia is controversial. Brizel et al. randomized patients to receive RT alone or with IV amifostine before each RT dose. At 2 years, the incidence of grade ≥2 late xerostomia was improved (19% vs. 36%, $p = 0.038$).[242,243] In contrast, Buentzel et al. enrolled 132 patients in a multicenter randomized placebo-controlled study in which patient received either IV amifostine or placebo before receiving carboplatin-based chemo-RT. In this study, there was no difference in either grade ≥2 late xerostomia (37% vs. 24%, $p = 0.235$).[244] GORTEC group ran a prospective randomized study comparing IV versus subcutaneous (SC) amifostine administration. There was no difference in either compliance (70% vs. 71%) and the incidence of hypotension (3% vs. 1%). Of note, SC group had an increased incidence of rash (11% vs. 22%, $p = 0.02$) and local pain at the injection site (0% vs. 9%, $p = 0.0008$).[245]

The submandibular gland (SMG) provides approximately 70% of the unstimulated saliva. IMRT has been used to lower the RT dose to the parotid gland(s) to reduce long-term xerostomia. However, there is little experience with SMG-sparing IMRT. Mean RT doses to the SMG exceeding 39 Gy cause permanent ablation of both stimulated and unstimulated salivary flow. Attempts to do IMRT sparing SMG without impairing the oncologic outcome have been reported by many investigators.[111,246] An alternative approach to SMG sparing involves surgical transfer of the gland into the submental space before RT. Seikaly et al. reported 83% of the patients had normal salivary flow and improved swallowing outcomes.[247–249] Similarly, salivary sparing has been reported by other groups,[250,251] and in the RTOG 0244 multicenter phase II trial. Recently, Jha et al. reported that SMG transfer led to spare 74% of patients from RT-induced acute xerostomia.[252]

## Dysphagia

The development of IMRT significantly decreases the incidence of dysphagia. Eisbruch et al. reported that it is possible to reduce the mean V50 (percentage of volume receiving >50 Gy) to pharyngeal constrictors and the larynx via IMRT.[253] Setton and Lee et al. reported that IMRT reduced the PEG feeding tube rate from 21% to 3%.[126,150] Thus, RT technique is an essential ingredient to optimizing functional outcome.

The majority of patients receiving chemo-RT experience significant weight loss due to RT or chemo-RT–induced mucositis and dysphagia. Feeding tubes may limit malnutrition.[254] However, whether the prophylactic placement of feeding tubes is beneficial is controversial. A randomized study showed significantly higher QOL scores in the group who underwent prophylactic gastrostomy tube.[255] On the contrary, Chen et al. reported that due to disuse of pharyngeal musculature during RT, prophylactic gastrostomy tube placement led to increase dysphagia and ultimately higher rates of long-term gastrostomy tube dependence.[256] They retrospectively reported that prophylactic placement of a gastrostomy tube resulted in both a higher percentage of gastrostomy tube dependence at 1 year (21% vs. 0%, $p < 0.001$) and a higher rate of esophageal stricture (30% vs. 6%).[256] The importance of these issues led to the development of a specific instrument that measures the impact of gastrostomy tubes on the QOL.[257] However, the incidence of long-term gastrostomy tube dependence has declined dramatically in the recent years due to the wide use of IMRT and IGRT, with an estimated rate of <5% of patients who underwent concomitant chemo-RT.[63,126] Thus, RT technique and dose optimization have an important effect on the incidence and severity of dysphagia.

## Quality of Life

Harrison et al. retrospectively examined patients with SCC of the BOT who were treated with primary RT or primary surgery, comparing the QOL and functional outcome. Patients treated with RT had consistently better performance status and QOL scores. This was true for all early (T1–2) and advanced (T3–4) diseases. For surgery, functional status deteriorated significantly when comparing T1 to T2 and T3 to T4 lesions ($p = 0.0014$), consistent with the fact that larger tumors require more extensive surgeries.[258] In addition to QOL issues, Harrison et al. have examined the long-term socioeconomic outcomes for patients with cancer of the BOT who were treated with an organ-preservation approach. At a median follow-up of 5 years, patients' annual incomes were similar to those at the time of presentation. Of those working full-time, 72% were still in full-time work and 83% of those working part-time were in part-time work.[152,258,259]

Campbell et al. report a cohort of 111 patients who underwent surgery, RT, or surgery followed by PORT. The RT group had the least problems, followed by the surgery-only group, whereas the surgery plus RT group experienced the greatest impairment.[260]

Several investigators have studied the impact of cetuximab on QOL. No significant, incremental impact was noted for patients receiving cetuximab plus RT[79,261] or cetuximab plus chemo-RT.[262]

**Carotid artery vasculopathy** (i.e., ischemic stroke) can be a late complication of neck RT.[263–265] Multiple reports have shown that RT to the head and neck may cause carotid artery stenosis and increase the risk of ischemic stroke.[264–269] Table 17.13 summarizes recent reports on RT-induced carotid vasculopathy.

Carotid artery rupture (e.g., carotid blowout syndrome) is most common in the setting of a surgically exposed carotid artery with limited residual normal tissue to cover it, recurrent tumor, infection, or severe radiation damage.[270] Carotid blowout syndrome usually occurs proximal to the carotid bifurcation and is commonly associated with soft tissue necrosis in the neck and mucocutaneous fistulas. Powitzky et al. identified 140 patients with carotid artery events, of whom 60% had life-threatening hemorrhage that required emergency intervention.[271] Carotid blowout has been reported in the setting of recurrent disease with multiple courses of surgery, RT, and compromised wound healing.[272]

Soft tissue ulceration is an RT dose-dependent side effect that can occur anytime from 6 months to several years after RT. Usually, these ulcerations heal on their own, but it can take weeks or months. Meticulous local hygiene and pain control are the cornerstone of management. In refractory cases, hyperbaric (HBO) may be helpful in promoting healing.[273,274]

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**TABLE 17.13 Summary of Recent Reports on RT-Induced Carotid Vasculopathy**

| Author | Institution | Nature of Study | Outcome |
|---|---|---|---|
| Dorresteijn (2002)[264] | Netherlands Cancer Institute | Retrospective study of 367 patients | 14 ischemic strokes = 15-yr cumulative risk of stroke of 12% |
| Smith (2008)[268] | M.D. Anderson Cancer Center | SEER and Medicare study | 9% increase in 10 year incidence of cerebrovascular events with RT (35%) vs. surgery (26%), No significant increase with surgery and adjuvant RT |
| Huang (2008)[269] | Mt. Sinai Medical Center | SEER and Medicare study | 2.5% increase in 10-yr rate stroke incidence with RT (10%) vs. (7.5%) without RT ($p = 0.01$). No significant difference in stroke mortality |

SEER, Surveillance, Epidemiology, and End Results; RICV, radiation-induced carotidvasculopathy.

**Osteoradionecrosis** (ORN) is exposed, irradiated bone in the absence of tumor after completion of RT.[275] ORN is a spectrum of bone injury, mainly to the mandible, that ranges from bone exposure to full-blown bone necrosis. The main risk factors include the RT dose to bone,[275–277] dental extraction/trauma, and poor dental hygiene. ORN occurs in <5% of cases.[63,126,136,154,278,279] Factors that increase the risk of ORN include volume of mandible treated with RT, RT dose, dose per fraction, and poor dental hygiene. ORN is discussed in more detail in Chapter 9.

The patient's perception of the impact of illness before, during, and after treatment is a major issue. Clearly, QOL issues must factor strongly into the decision-making process and selection of the appropriate management strategy. Measurement of QOL is ongoing activity and is a key component to current research protocols. There are many head and neck cancer–specific instruments that are reliable and well validated. See Table 17.14 for QOL measurements details.

**TABLE 17.14 Quality-of-Life (QOL) Measurements in Details**

| Reference Study/ Abbreviation | | Description |
|---|---|---|
| List (1990)[322] | PSS-HN | Performance Status Scale for Head and Neck Cancer; consists of three subscales: normalcy of diet, understandability of speech, and eating in public. Scores on each subscale range from 0 to 100, with higher scores indicating better performance |
| Bjordal (1992, 1994, 1999)[323–325] | EORTC QLQ-H&N35 | European Organization for Research and Treatment of Cancer QOL Questionnaire—Head and Neck–Specific Module; can be used in conjunction with the QLQ-C30. This scale includes items assessing symptoms and side effects relevant to patients with head and neck cancer and appears to be sensitive to temporal changes before, during, and after treatment with surgery, RT, and chemotherapy |
| Browman (1993)[55] | HNRQ | Head and Neck Radiotherapy Questionnaire; a patient-rated tool that measures early treatment-related effects in patients undergoing RT for HNC. It consists of 22 questions that cover symptoms related to six domains: oral cavity, throat, skin, digestive function, energy and psychosocial function |
| Hassan (1993)[326] Rogers (1998)[327] | UW-QOL | University of Washington QOL questionnaire; a self-administered scale consisting of 15 questions assessing nine domains: pain, physical appearance, activity, recreation, employment, chewing, swallowing, speech, shoulder function, and overall QOL |
| Portenoy (1994)[328] | MSAS | Memorial Symptom Assessment Scale; a comprehensive symptom measure that records prevalence of 32 physical and psychological symptoms commonly experienced by cancer patients, symptom characteristics, and measures of symptom distress |
| List (1996)[329] | FACT-H&N | Functional Assessment of Cancer Therapy–Head and Neck; consists of the FACT-G, to which an 11-item site-specific, head and neck cancer subscale, which evaluates the unique concerns of patients with head and neck cancer such as swallowing and chewing |
| Terrell (1997)[330] | HNQOLQ | University of Michigan Head and Neck QOL Questionnaire; a 20-item that covers four major domains, namely, pain, communication, eating, and emotion |
| Trotti (1998)[331] | QOL-RTI | QOL–Radiation Therapy Instrument; specifically addresses issues related to RT in patients with head and neck cancer. This instrument evaluates the impact of treatment on mucus production, saliva, taste, cough, and local pain |

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**TABLE 17.14 Quality-of-Life (QOL) Measurements in Details (Continued)**

| | | |
|---|---|---|
| Hogikyan (1999)[332] | V-RQOL | Voice-related QOL measure; a 10-item, self-administered voice outcome measure. Scores are reported in two domains, social-emotional and physical functioning, and a total score, all ranging from 1 to 100. A higher score indicates better voice-related QOL |
| Chen (2001)[333] | MDADI | M. D. Anderson Dysphagia Inventory; a self-administered questionnaire that evaluates the impact of treatment-related dysphagia on QOL. This instrument includes global, emotional, functional, and physical subscales |
| Cella (2003)[334] | FHNSI | The FACT Head and Neck Symptom Index; a 10-item symptom index with items extracted from the FACT-H&N. The FHNSI was designed to allow rapid assessment of the most relevant disease symptoms. The FHNSI can be administered alone or scored using items embedded within the FACT-H&N (Yount et al., 2007) |
| Murphy (2010)[335] Cooperstein (2011)[336] | VHNSS | Vanderbilt Head and Neck Symptom Survey; to assess the physical and functional problems relevant to patients with head and neck cancer treated with chemo-RT. This 28-question survey has an emphasis on oral health outcomes, such as mucous production. Also, assesses other symptoms such as mucosal sensitivity, dental health, and trismus contains 50 questions and has been studied in the post-RT setting |

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# PART B:
# Radiologic Imaging Concerns

Jeffrey A. Bennett

The oropharynx provides a challenge to imaging because of its abundant lymphoid tissue, which normally enhances and has variable thickness. Small superficial mucosal tumors may not be seen on CT or MRI for this reason. Indeed, small lesions may not be seen with direct visualization if they are hiding within deep crypts in the lymphatic tissue. Therefore, tumor can only be reliably identified on imaging studies if it infiltrates into the deep soft tissue planes (Fig. 17-15). An additional challenge to CT imaging is streak artifact from dental hardware, which may necessitate changing the gantry angle to achieve adequate visualization of the entire oropharynx. Tongue motion and swallowing will degrade the images as well, which is certainly a problem for MRI, but is less of a problem with high-speed multidetector CT scanning. Suggested protocols are given in Figures 17-16 and 17-17.

Even though the superficial mucosal extent of a tumor may not be well seen with CT or MRI, both imaging modalities can readily identify invasion into the glossotonsillar sulcus, the intrinsic tongue, and the preepiglottic space (Fig. 17-18).[1] Lateral and posterior pharyngeal wall tumors can be easily overlooked radiographically, but imaging is good for assessing deep invasion into the parapharyngeal space (Figs. 17-19 and 17-20).

Soft palate tumors require coronal imaging for adequate assessment of possible bony invasion of both the hard palate and extension through the parapharyngeal space to the skull base

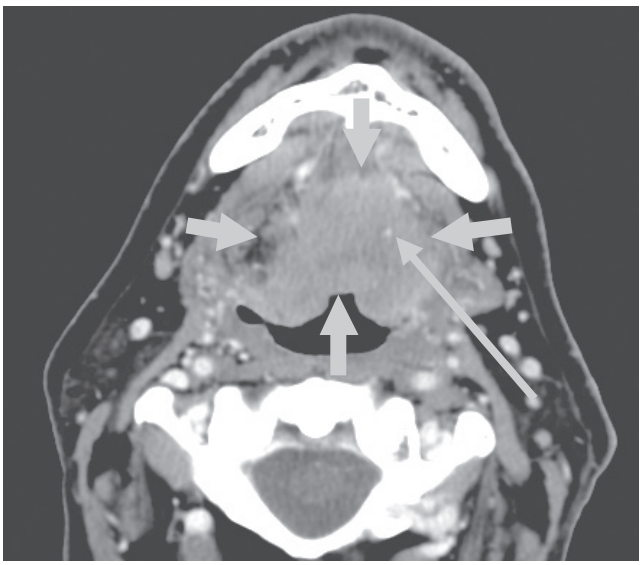
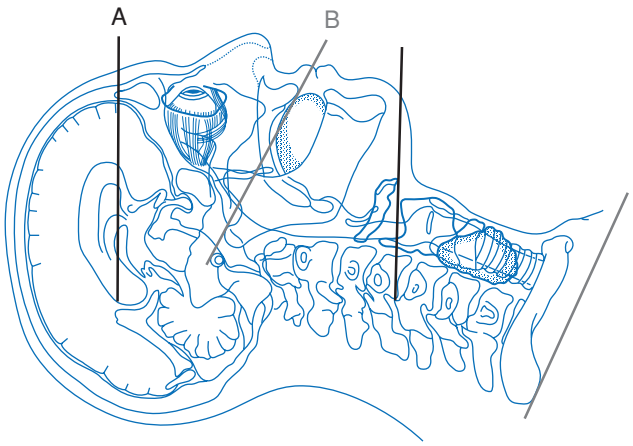


**FIGURE 17-15.** Axial contrast-enhanced computed tomography (CT) shows an aggressive tumor involving the tongue base (*short arrows*). Note that the tumor encases the lingual artery (*long arrow*).

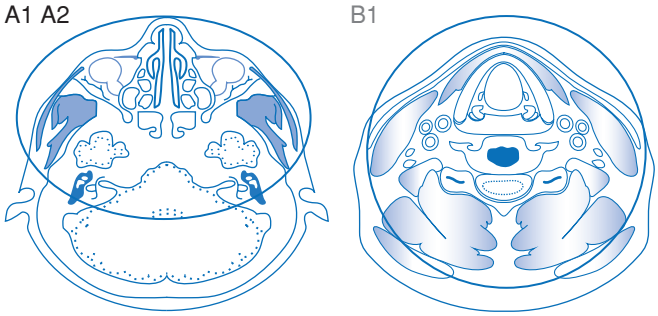
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ACQUISITION




| | | |
|---|---|---|
| | Patient Position | Supine<br>IOML perpendicular to the tabletop |
| | Contrast | 100 mL adult |
| | Injection Rate | 1 mL/sec; 60 sec delay |
| | Respiration | Quiet, NO swallowing |
| | Volume Acquisition Specs | Appropriate to achieve images as specified in following reconstruction tables.<br>Head FOV. |
| A | Begin | Above frontal sinus |
| | End | Through mandible |
| B | Begin | Mid oral cavity |
| | End | Apices |

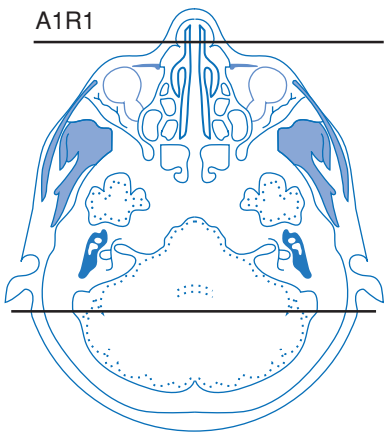
RECONSTRUCTION




| | | |
|---|---|---|
| A1 | Algorithm | Soft tissue |
| | Thickness | 1.0 mm |
| | Spacing | 0.8 mm |
| | F.O.V. | Approx. 170–190 |

| | | |
|---|---|---|
| A2 | Algorithm | Bone |
| | Thickness | 1.0 mm |
| | Spacing | 0.8 mm |
| | F.O.V. | Approx. 170–190 |
| B1 | Algorithm | Soft tissue |
| | Thickness | 2.5 mm |
| | Spacing | 2.5 mm |
| | F.O.V. | Approx. 160–180 |

REFORMATION




| | | |
|---|---|---|
| A1R1 | Algorithm | Soft tissue |
| | Thickness | 1.0 mm |
| | Spacing | 1.0 mm |
| | F.O.V. | Approx. 180 |
| | Plane | Coronal |
| | Begin | Frontal sinus |
| | End | Through IAC |

**FIGURE 17-16.** Protocol for computed tomography of the maxillofacial region and neck with intravenous contrast.

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| Acquisition | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Plane | Sagittal | Axial | Axial | Axial |
| Sequence | T1 | T1 | T2-FSE | T1 |
| Contrast | None | None | None | Gd |
| Thickness/Spacing | 3/0 mm | 4/0 mm | 4/0 mm | 4/0 mm |
| FOV | 16 cm | 16 cm | 16 cm | 16 cm |

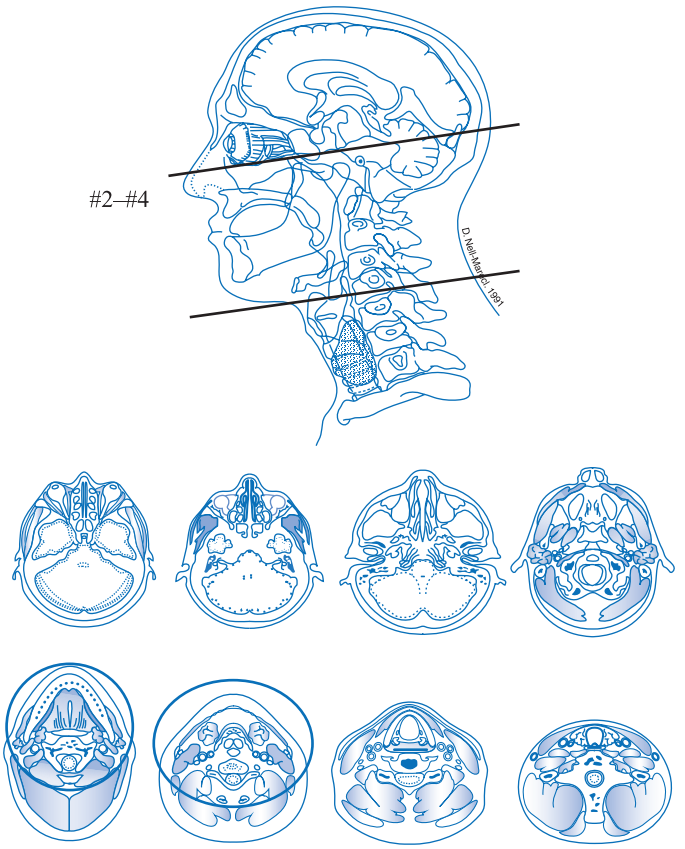
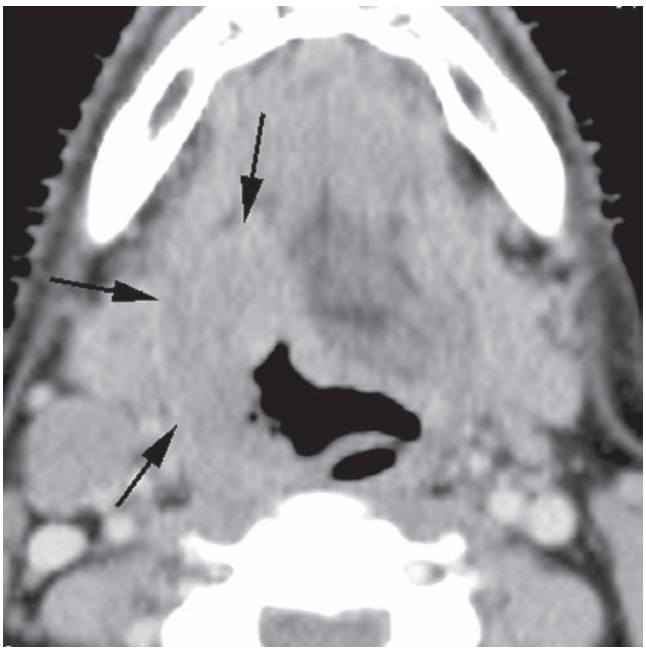



**FIGURE 17-17.** Protocol for magnetic resonance imaging of the oropharynx with intravenous contrast.

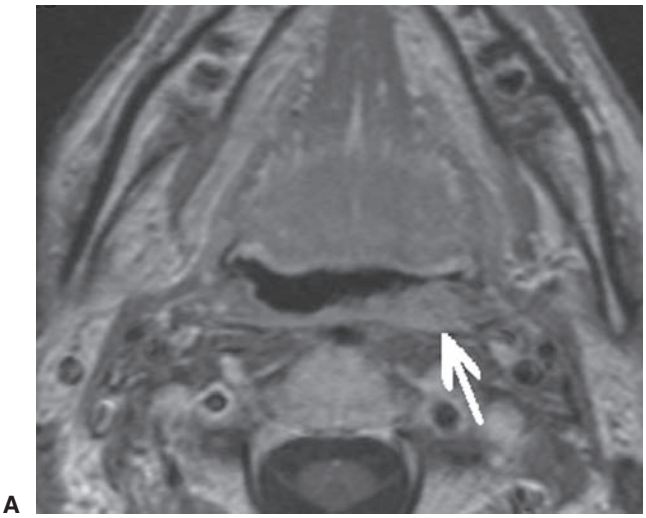
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**FIGURE 17-18.** Axial Postcontrast CT scan shows a base of tongue cancer which extends posteriorly to invade the glossotonsillar sulcus (*arrows*).

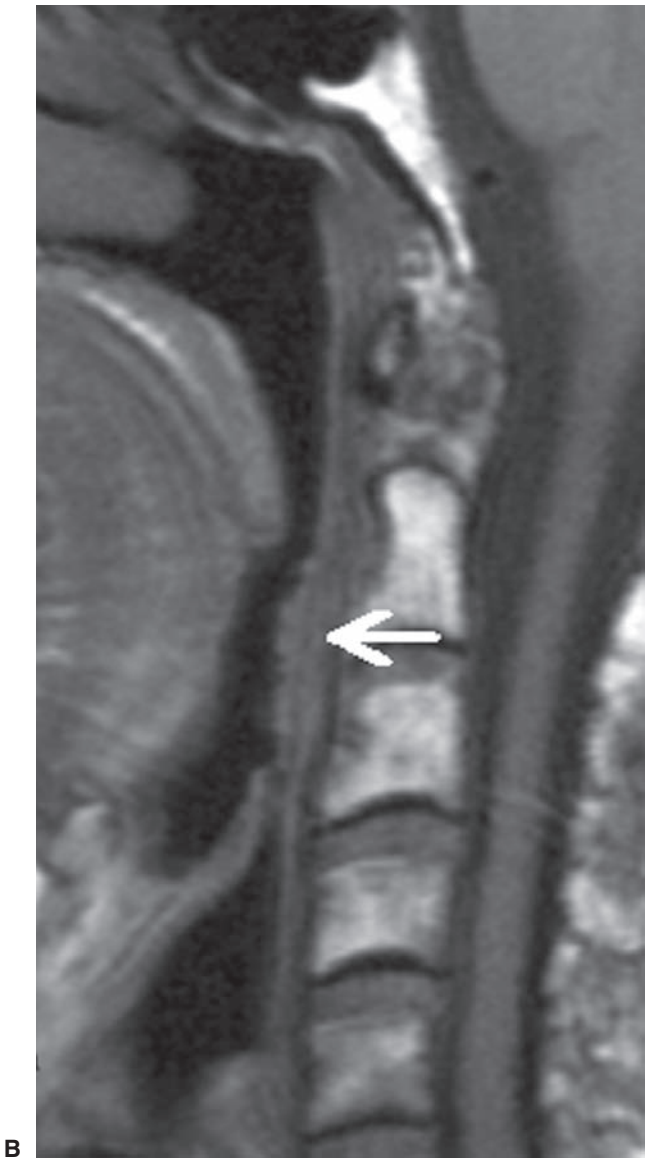




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A



B

**FIGURE 17-19.** Axial **(A)** and sagittal **(B)** T1-weighted gadolinium enhanced MR images show a relatively superficial posterior pharyngeal wall squamous cell carcinoma (arrows) which has not extended into the retropharyngeal space.

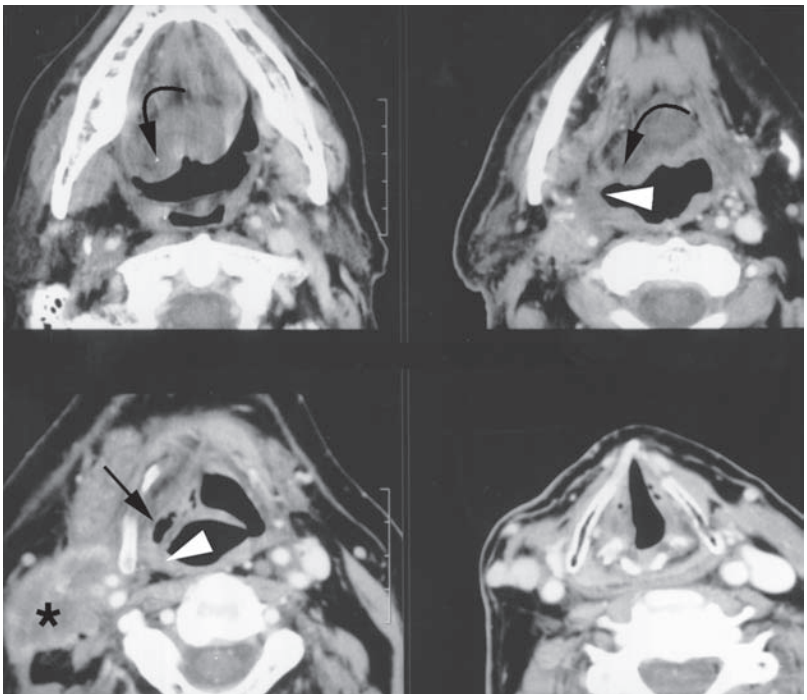


**FIGURE 17-20.** Pharyngeal wall lesion. Enhanced axial computed tomographic scan shows right lateral wall lesion (*arrowheads*) extending to vallecula (*arrow*) with necrotic ipsilateral adenopathy (*asterisk*). Note laxity of right side of base of tongue (*curved arrows*) due to recent neoplastic involvement of cranial nerve XII by matted adenopathy.



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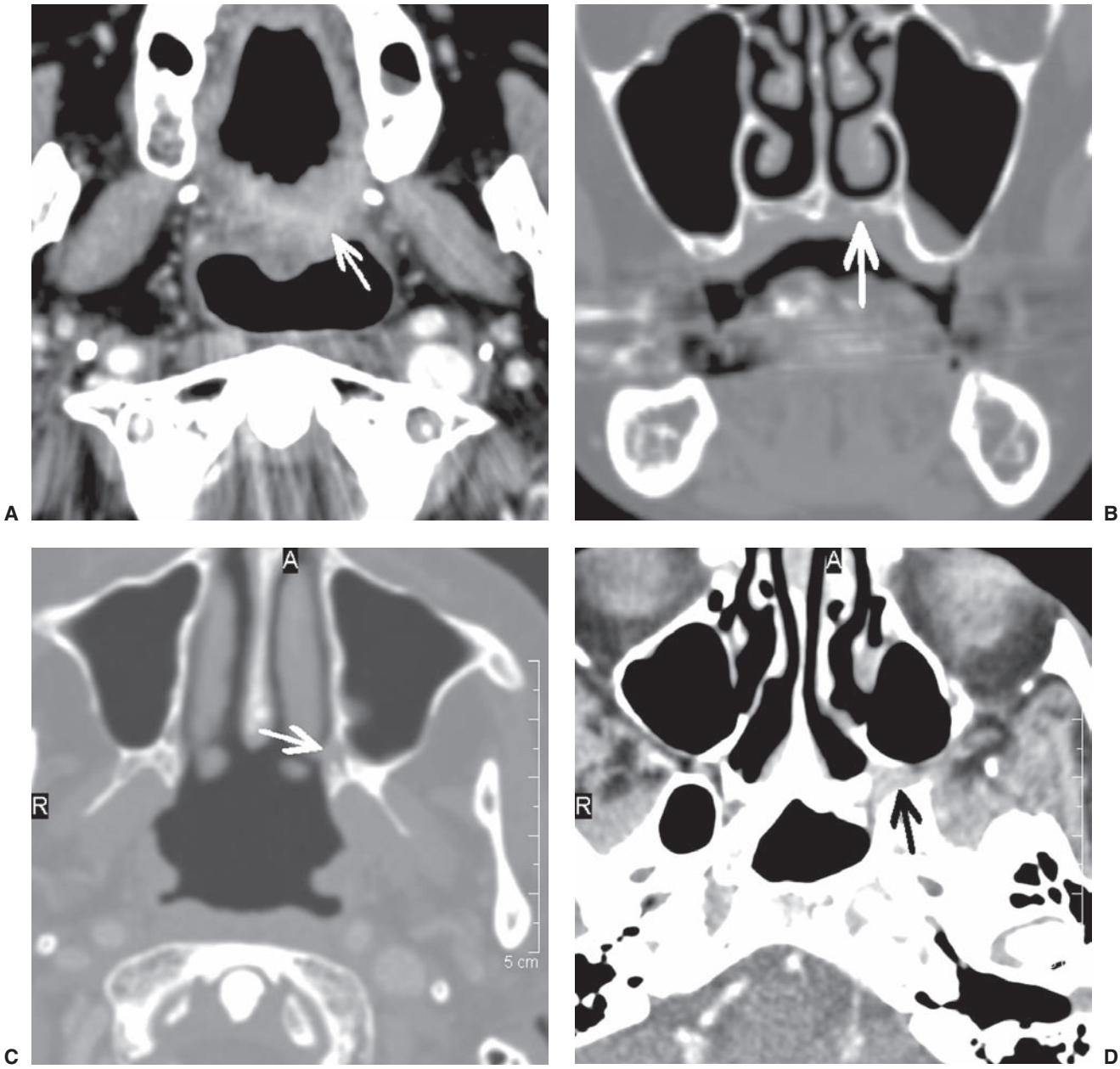



**FIGURE 17-21.** **A:** Axial contrast-enhanced CT scan shows a primary squamous cell carcinoma of the soft palate (*arrow*) on the left side. **B:** Coronal CT reformat with bone windowing shows extension to and erosion of the left side of the hard palate (*arrow*). **C:** Axial CT scan with bone windowing shows enlargement and erosion of the left palatine foramen (*arrow*) as a result of perineural spread. Compare the normal greater and lesser palatine foramina on the right side for comparison. **D:** Axial contrast enhanced CT scan shows that the tumor has spread along V2 to the left pterygopalatine fossa (*arrow*).

(Fig. 17-21). MRI may be better for visualization of tumor extending along the tensor veli palatini and the levator veli palatini muscles to the skull base.

Primary tumors of the palatine tonsils are also difficult to detect on imaging studies before there is deep invasion. Once deep tissue plane invasion is present, multiplanar CT or MRI can document extension to the palate (Fig. 17-22), the tongue base, the masticator space (Fig. 17-23), and the mandible (Fig. 17-24).

In all cases of oropharyngeal squamous cell cancer, careful evaluation of the retropharyngeal space must be made to look for lateral retropharyngeal lymph nodes (Fig. 17-25), as these cannot be detected clinically and may be excluded from limited neck dissections for clinical N0 necks.[2]

Posttreatment imaging is challenging to interpret because of altered anatomy and scarring (Fig. 17-26). FDG-PET/CT is becoming increasingly used for follow-up 3 to 4 months after

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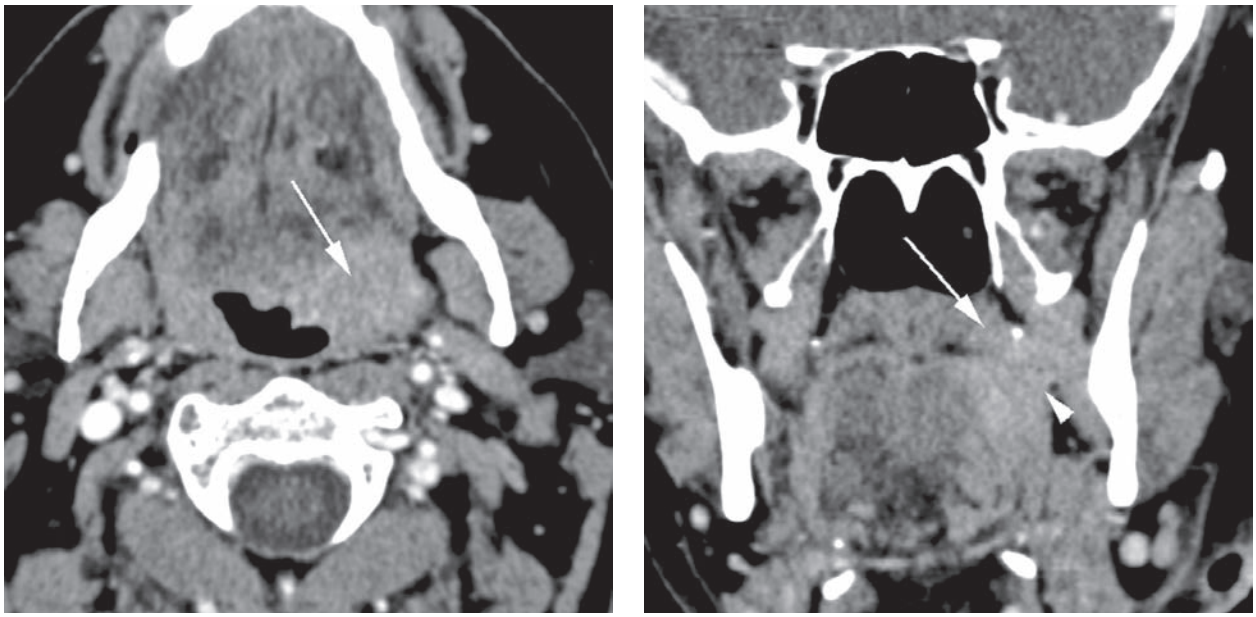



**FIGURE 17-22.** **A:** Axial contrast-enhanced CT scan shows a left tonsil infiltrating mass (*arrow*) found to be squamous cell carcinoma. **B:** Coronal reformat of the CT scan shows the tonsil mass (*arrowhead*) extending superiorly to the soft palate (*arrow*).

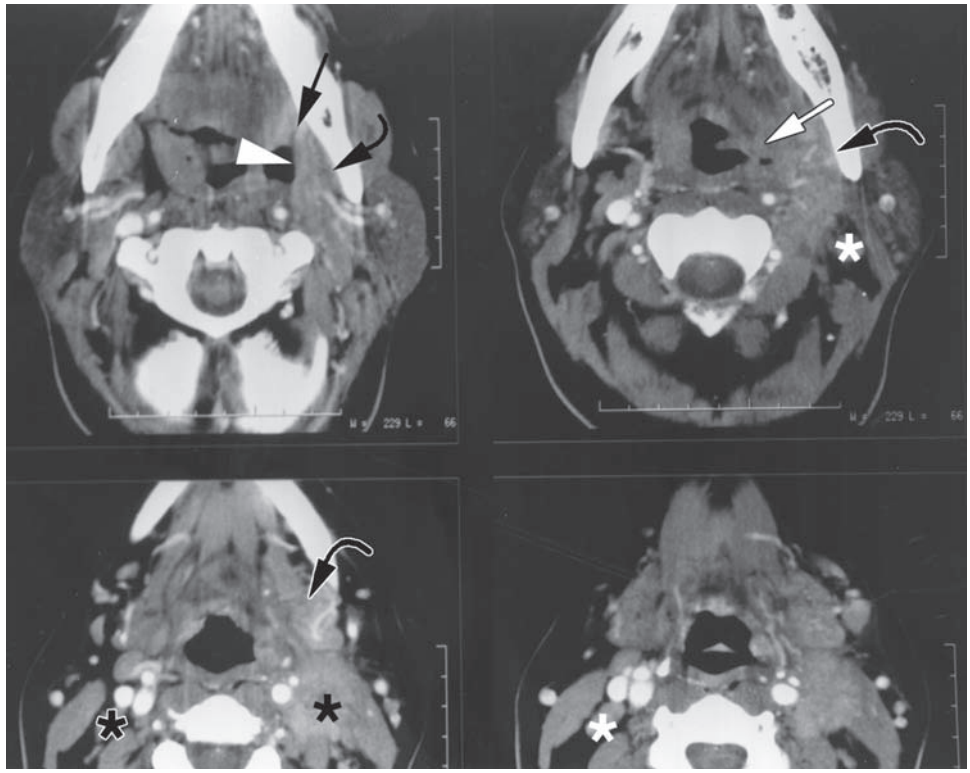


**FIGURE 17-23.** Extensive tonsillar cancer. Enhanced axial computed tomographic scan through oropharynx shows left tonsillar lefgsion (*arrows*) with extensive ulceration (*arrowhead*) approaching the mandible (*curved arrow*). Note extensive bilateral adenopathy.

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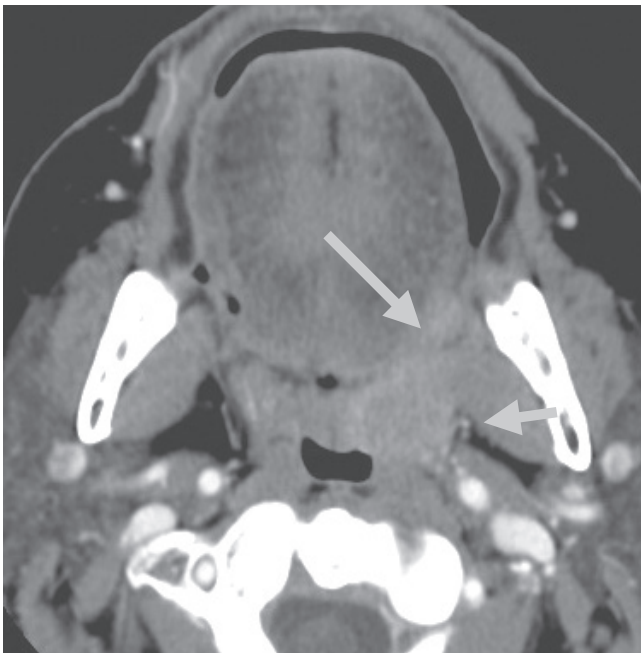


**FIGURE 17-24.** Axial contrast-enhanced computed tomographic (CT) scan shows the typical appearance of a left tonsillar carcinoma. There is deep extension into the parapharyngeal space (*short arrow*) and some anterior extension along the superior constrictor muscle (*long arrow*).

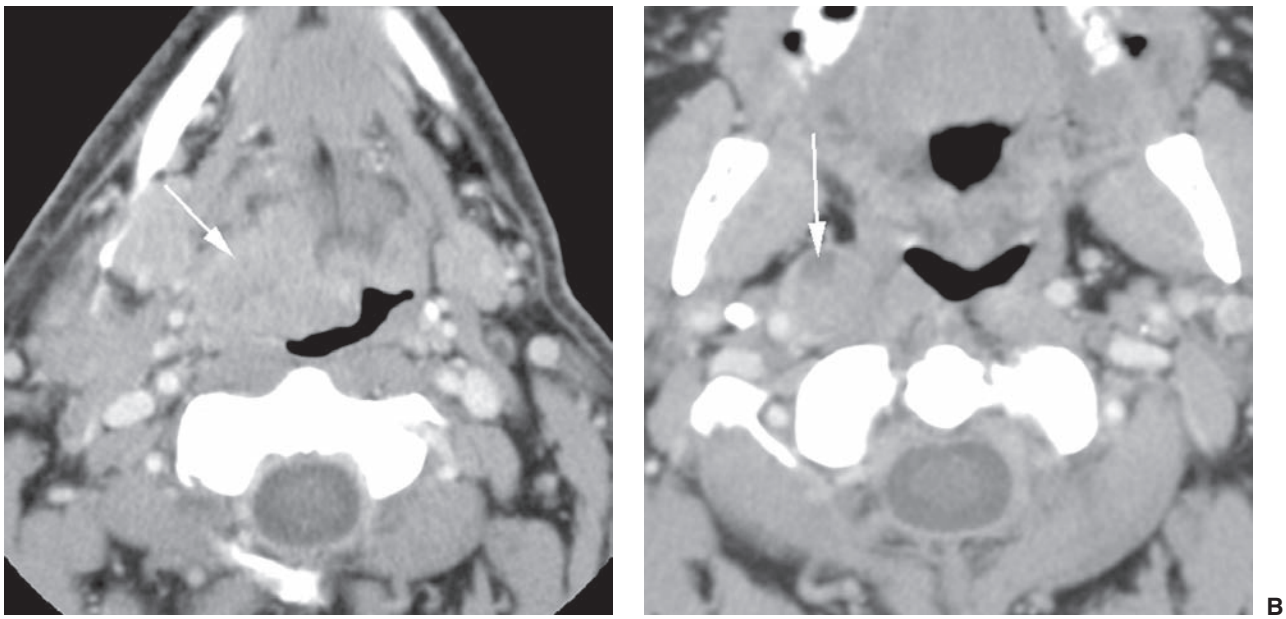


**FIGURE 17-25.** **A:** Axial contrast-enhanced CT scan shows an aggressive right tongue base squamous cell carcinoma (*arrow*). **B:** A positive right retropharyngeal lymph node is present (*arrow*).

completion of therapy. It is particularly useful because of its high negative predictive value.[3] When positive, the area with increased uptake can be biopsied to confirm recurrent tumor (Fig. 17-27). Recent studies are investigating whether higher standard uptake values (SUV) in the primary tumor or in lymph nodes have an ability to predict outcome.[4] This research may in time alter treatment regimens.

Surveillance scanning for patients with HPV-positive tumors may be different from patients with HPV-negative tumors because of their different biological behaviors, although this is still being investigated. Zhang et al.[5] found that a negative FDG PET/CT performed between 4 and 16 weeks after treatment had a 79% negative predictive value after 2 years of follow-up, indicating that those patients with a negative initial posttreatment scan were low risk for recurrence.

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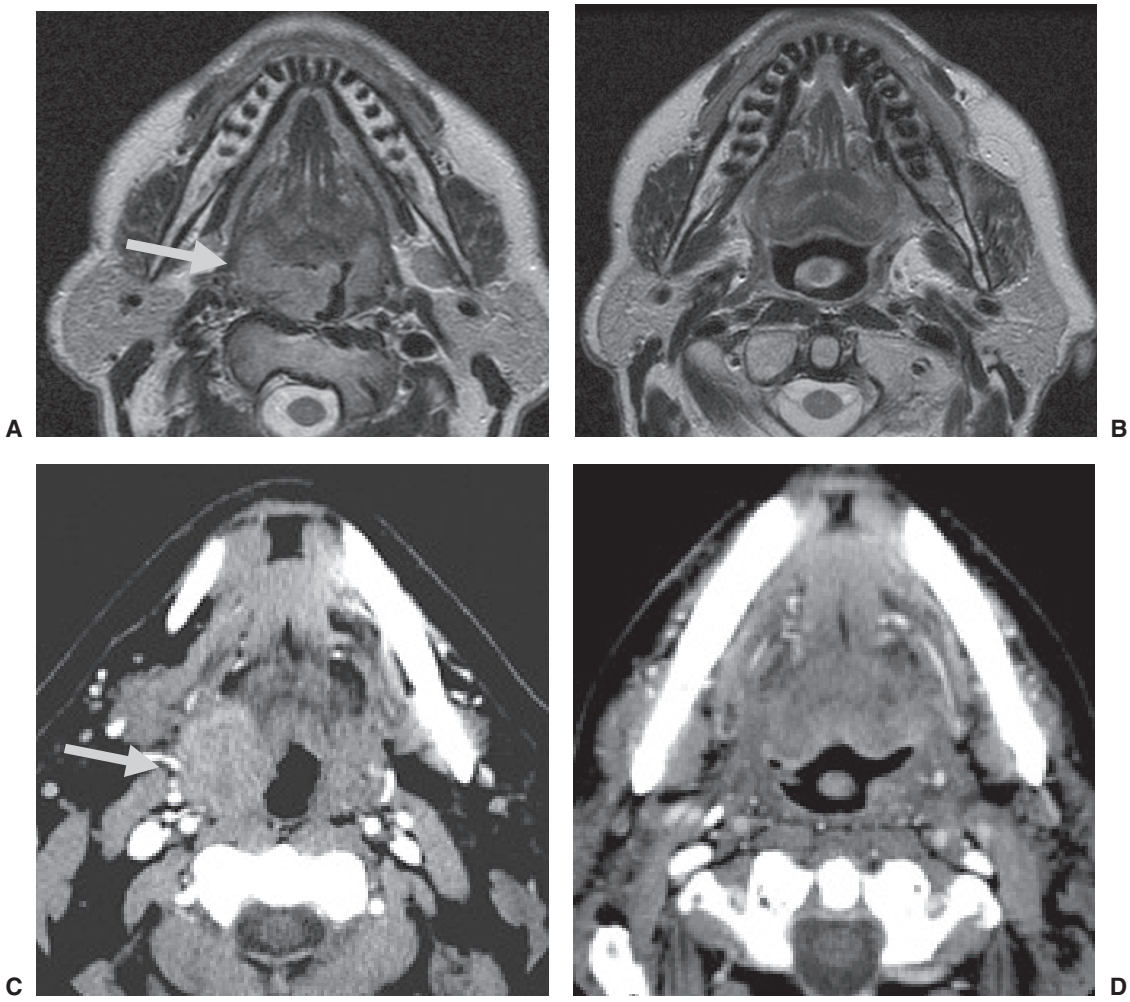



**FIGURE 17-26.** Expected posttreatment appearance: magnetic resonance (MR). **A:** Pretreatment MR shows a right tonsillar carcinoma (*arrow*). **B:** Posttreatment MR following nonsurgical organ preservation therapy (NSOPT) with combined radiation and chemotherapy shows complete response of the tumor at the primary site. **C:** Pretreatment computed tomography (CT) shows a right tonsillar carcinoma (*arrow*). **D:** Posttreatment CT following NSOPT with combined radiation and chemotherapy shows complete response of the tumor at the primary site.

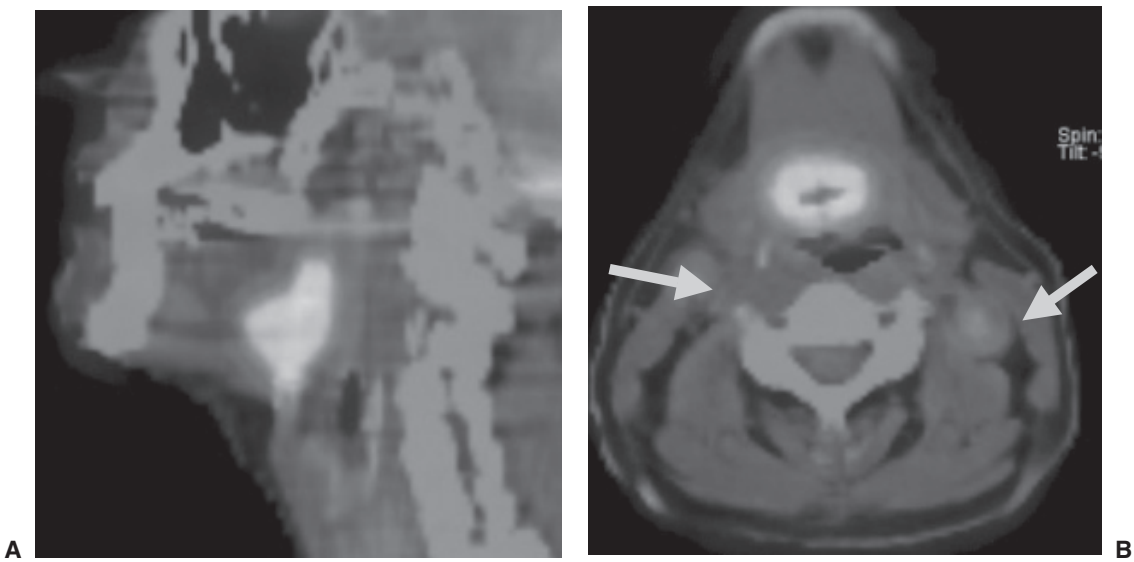



**FIGURE 17-27.** **A:** Sagittal positron emission tomography–computed tomography (PET–CT) shows intense uptake of fluorodeoxyglucose (FDG) in a tongue base carcinoma. **B:** Axial PET-CT shows the uptake of the tumor, but also demonstrates that the patient has bilateral uptake in the level II lymph nodes (*arrows*) indicative of nodal metastases.



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# PART C:
# Radiation Therapy Technique

Louis B. Harrison, James E. Dolan, Rudolph Woode, Waleed Mourad, and Kenneth S. Hu

## TONSIL

The chapter has provided extensive discussion about the relative indications for unilateral neck treatment versus bilateral neck treatment for patients with carcinoma of the tonsil. For unilateral treatment, either 3D conformal radiation therapy (3DCRT) or intensity-modulated radiation therapy (IMRT) can be used. Often, 3DCRT will allow the radiation oncologist to obtain excellent dose distribution with very acceptable normal tissue doses. The mere sparing of the contralateral neck and anatomical structures both reduces late toxicity and improves acute tolerance to treatment.

Figure 17-28 shows a patient with T2N0M0 squamous cell cancer of the left tonsil. As can be seen, excellent tumor coverage is obtained and key normal organs are well protected.

IMRT has been increasingly utilized for tonsil cancers. It is especially helpful in clinical situations where sparing of the contralateral parotid gland is appropriate or where the volume of normal tissue can be reduced with IMRT techniques. Figure 17-29 shows a patient with T1N0M0 squamous cell carcinoma of the right tonsil, treated with IMRT. The primary lesion receives the full therapeutic dose of 66 Gy in 33 fractions of 2 Gy each. The ipsilateral regional lymph nodes, including the ipsilateral lateral retropharyngeal nodes, receive elective nodal irradiation at 1.8 Gy/fraction. The contralateral neck and the contralateral parotid gland are spared. If there is a clinical indication to treat the contralateral neck electively (e.g., a primary lesion that extends within 1 cm of midline or involves the base of tongue, but the contralateral neck is clinically negative), then IMRT is used to keep the contralateral mean parotid dose ≤26 Gy (see technique for "Base of Tongue"). When IMRT is used, no bite block is used in order to maximize reproducibility and immobilization.

For patients with tonsil cancer and bilateral neck metastases, IMRT is used. The technique is similar for tonsil and base of tongue. Figure 17-30 shows a patient with cancer of the base of tongue and bilateral neck metastases. A similar technique would be used for a tonsil primary.

## BASE OF TONGUE

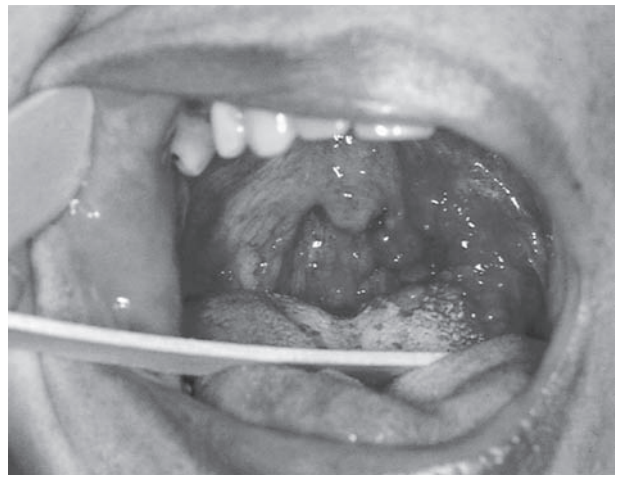
Patients with cancer of the base of tongue (Fig. 17-31) are treated to the primary site and both sides of the neck. As discussed in the chapter, authors' practice is to use an implant for the boost treatment. However, many centers do not incorporate brachytherapy and use an external beam boost.

IMRT is the standard approach for base-of-tongue cancers. Figure 17-31 shows the contours, dose distributions, and dose–volume histogram for a patient with T2N0M0 squamous cell carcinoma of the base of tongue. In this case, the primary site, as well as the bilateral neck nodes, receives 54 Gy in 30 fractions of 1.8 Gy. The contralateral parotid is relatively spared, as shown in the dose–volume histogram. However, because there are nodes near the parotid, the authors recommend caution about this. The low neck can be treated as part of the IMRT field or can be treated with a separate, anterior field, which also blocks the larynx in the upper midline. Treatment to the primary site is completed with an implant (Fig. 17-32). Figure 17-30 shows a patient with T4N2c squamous cell cancer of the base of tongue. This patient had disease extending into the upper portion of the larynx. An implant was not technically feasible, so IMRT was used for the entire course of treatment.

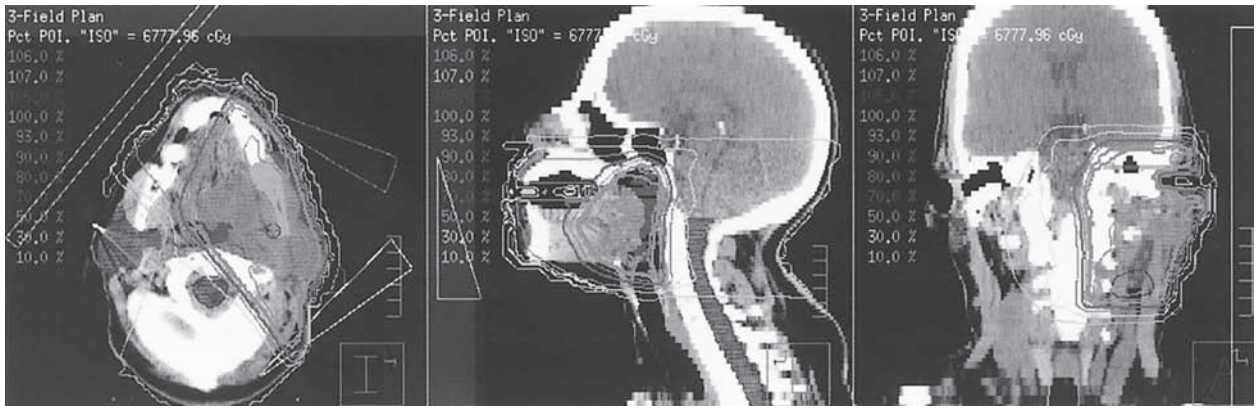
## SOFT PALATE

Patients with soft palate cancer are treated to the primary site and both sides of the neck. As with base of tongue, there are no data to support the concept of ipsilateral neck irradiation in these patients. Techniques are similar to those for base of tongue.

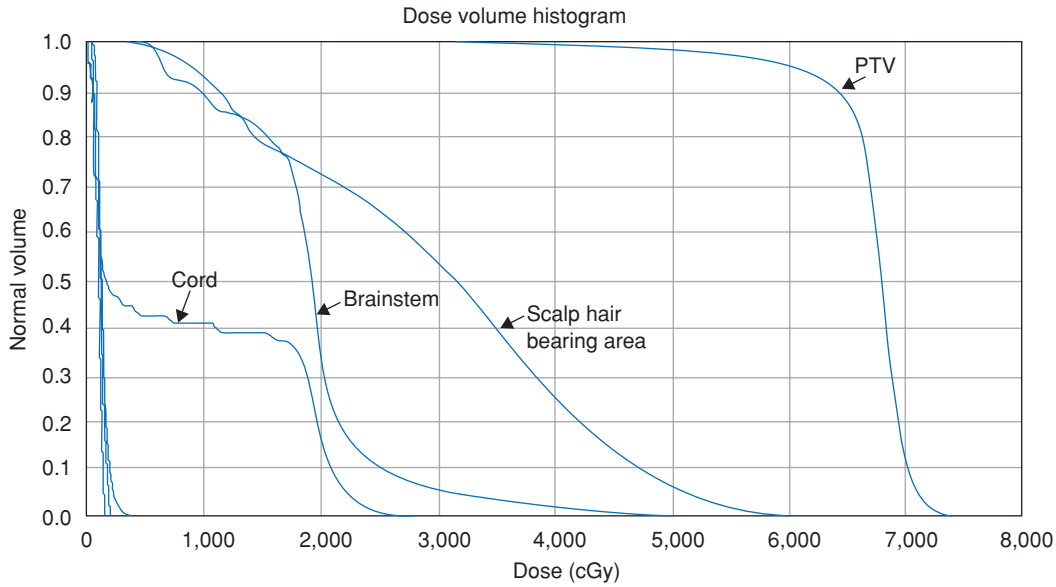
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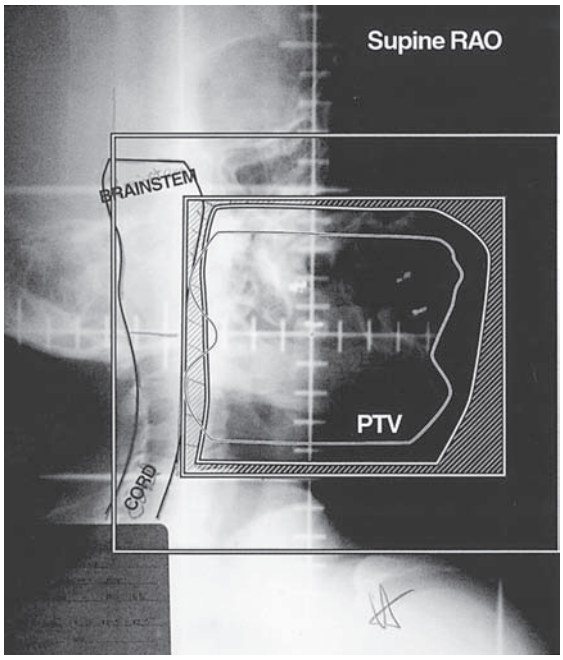



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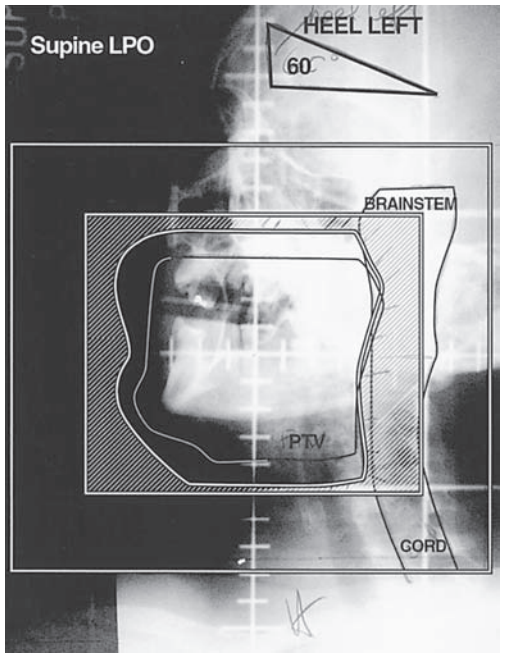
**FIGURE 17-28.** Tonsil cancer. Unilateral neck treatment technique. A patient treated with unilateral fields. This patient is a 50-year-old woman with a T2N0 squamous cell carcinoma of the left tonsil. The authors' plan is to treat this patient with definitive radiation therapy. **A:** This is a photograph of the primary lesion. It involves the tonsillar fossa, with involvement of the anterior tonsillar pillar and superficial involvement of base of tongue. **B:** This patient was treated with a three-field plan. This involves a wedged-pair plan, with a low-weighted right anterior oblique field, to help cover the tongue extension without overdosing the spinal cord. The planning tumor volume (PTV) is contoured. The primary site, extension along the soft palate, extension into the base of tongue, upper neck nodes, and retropharyngeal nodes are all included. An axial, sagittal, and coronal dose distribution shows that the PTV is well covered. The salivary gland tissue of the contralateral neck, especially the parotid gland, is well protected. **C:** Dose–volume histogram of this plan showing good coverage of the target volume and adequate protection of the surrounding normal tissue. The curves are depicting extremely low doses to the right parotid as well as the right and left retina. **D** to **F:** The simulation films showing the fields that were used. As mentioned previously, these consisted of a left anterior oblique (LAO), a left posterior oblique (LPO), and a lightly weighted right anterior oblique (RAO).



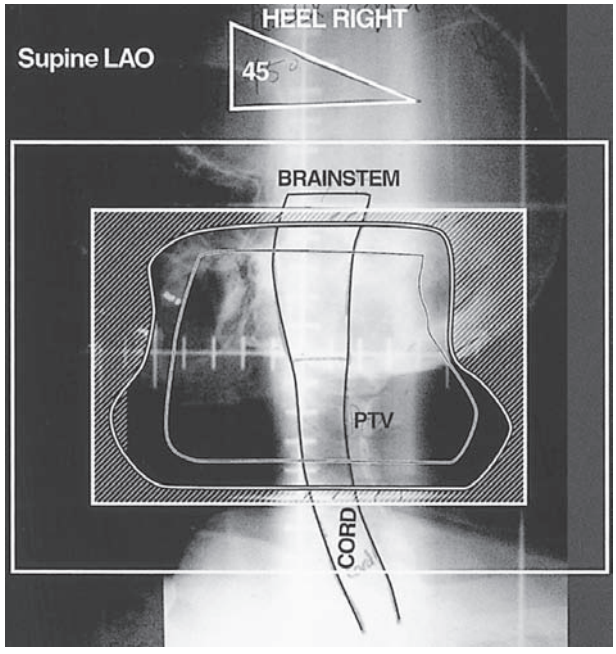
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D



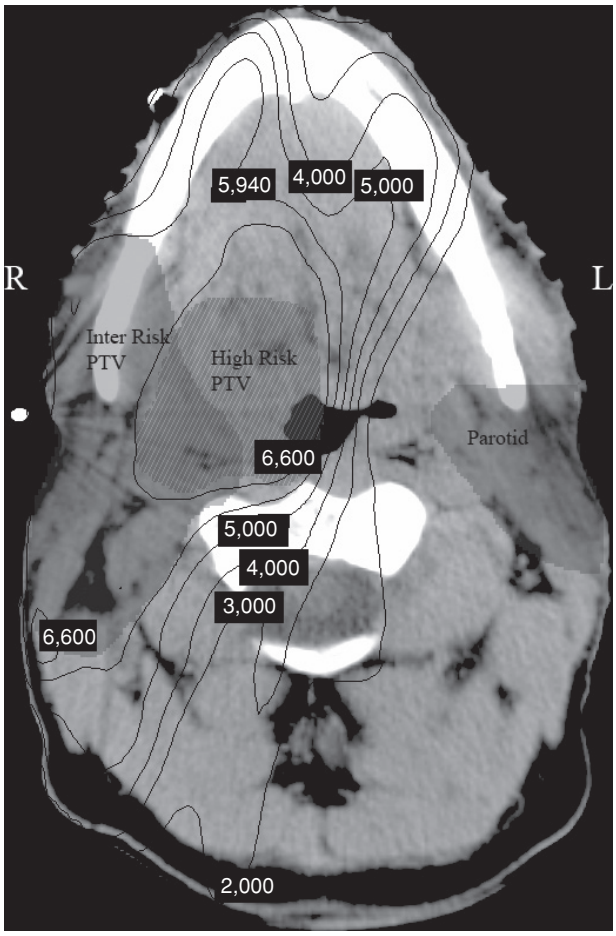

E




F

**FIGURE 17-28.** *Continued*

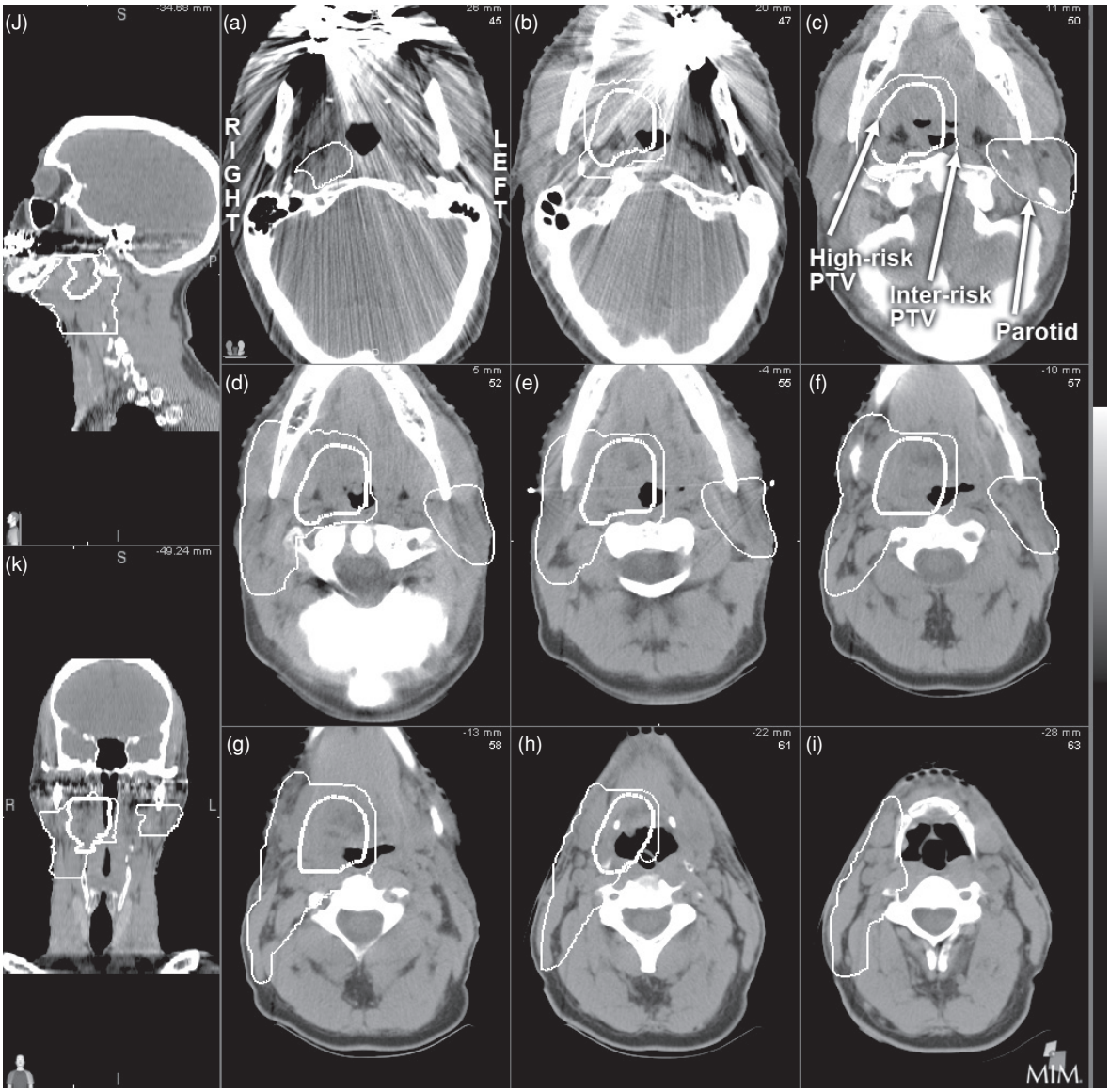
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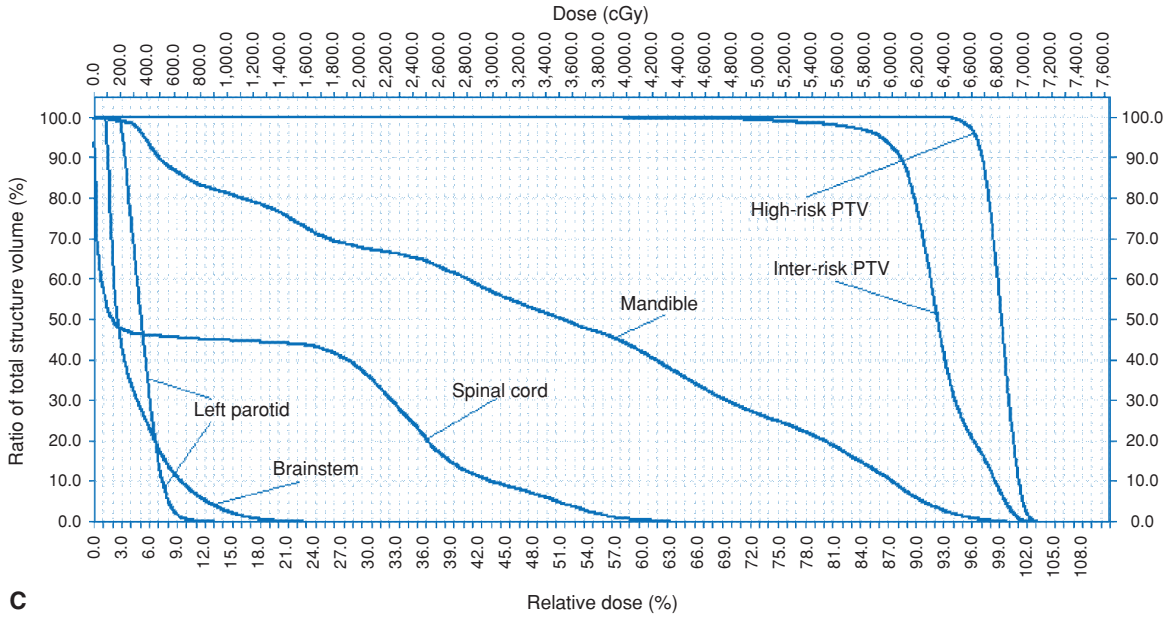

A

**FIGURE 17-29.** This patient had a T1N0M0 American Joint Committee on Cancer (AJCC) stage I squamous cell cancer of the right tonsil. The treatment plan was definitive external beam radiation therapy. The authors used intensity-modulated radiation therapy (IMRT) and did use a dose-painting technique. The high-risk PTV includes the primary site, which received 66 Gy in 2-Gy fractions over 33 fractions. The intermediate risk (interrisk) PTV includes the ipsilateral upper neck nodes and retropharyngeal nodes, as well as some additional safety margin around the primary site. This area received 1.8 Gy/fraction, so it received 59.4 Gy in total. The authors could have delivered only 54 Gy to this volume as it is treated electively. The low neck (right side only) was treated with a separate, AP field, to 50 Gy in 2 Gy fractions over 5 weeks. **A:** Isodose distribution displayed on an axial computed tomography (CT) used for treatment planning. This shows the primary site (high-risk PTV) as well as the electively treated ipsilateral regional nodes (interrisk PTV). The left (contralateral) parotid gland is spared completely. Care is taken to avoid hot spots, especially in the mandible. **B:** This figure was produced using the MIM-Vista system. It shows representative serial radiotherapy (RT) planning slices as well as representative contours.(a) Contour shows the upper limit of the ipsilateral retropharyngeal nodes. (b) Contour shows upper limit of the primary site contour, plus the added safety margin (interrisk PTV). (c) Contour shows high-risk and interrisk volumes, plus the contralateral parotid gland, which is spared. (d) Contour shows primary site (high-risk) and ipsilateral neck nodes (interrisk) as well as the spared, contralateral parotid. (e) Same as (d). (f) Same as (d). (g) Same as (d), without contralateral parotid. (h) Same as (g). (i) Inferior contour at level of hyoid bone showing the ipsilateral neck nodes contoured (interrisk PTV). (j) Midsaggital image showing the reconstructed high-risk and interrisk PTVs. (k) Coronal reconstruction showing high-risk PTV, interrisk PTV, and the left parotid gland. **C:** Dose–volume histogram. *R,* right; *L,* left.

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B




C

**FIGURE 17-29.** *Continued*



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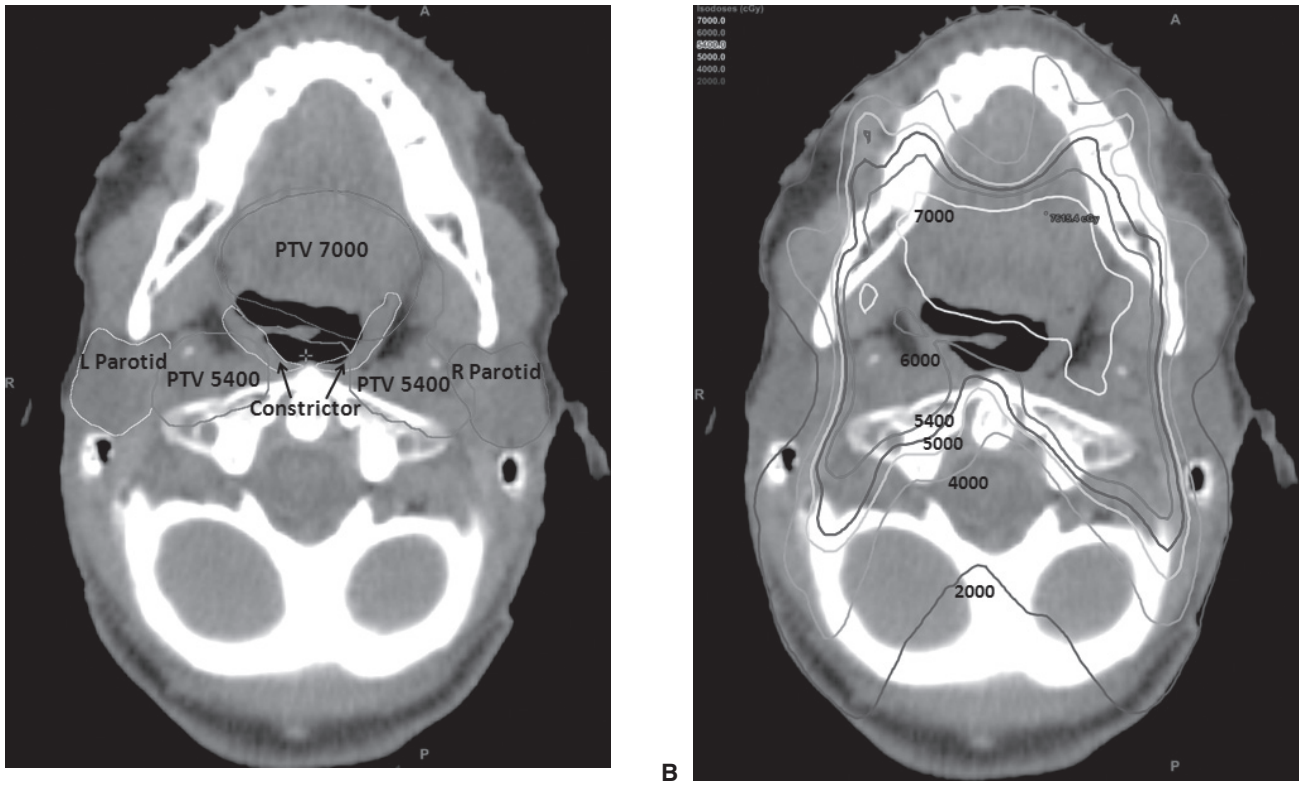
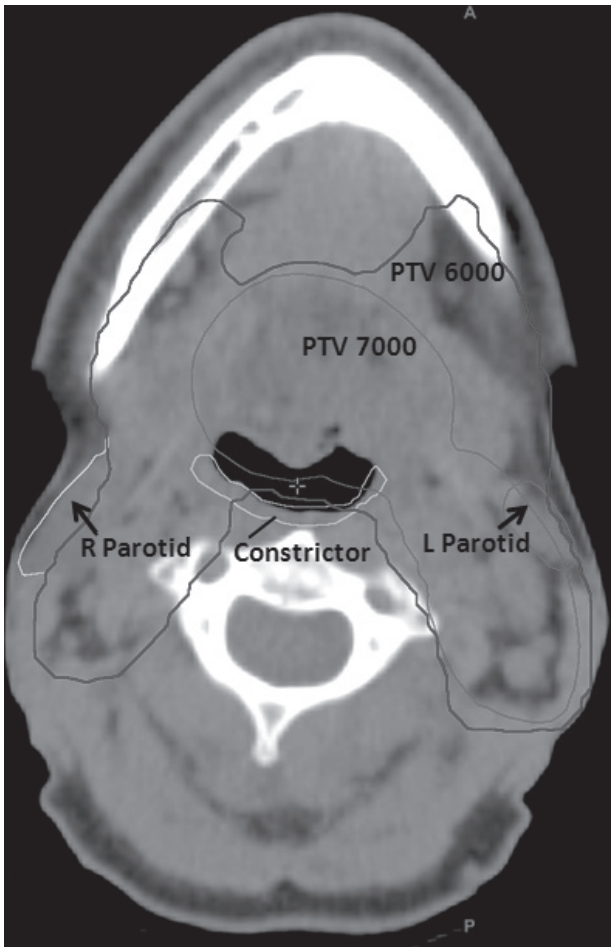
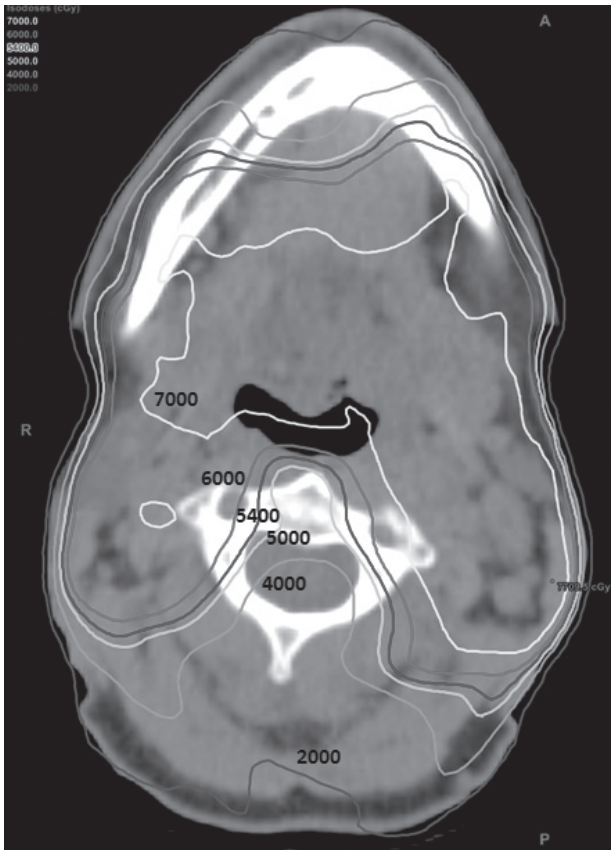



**FIGURE 17-30.** This patient had a T4N2CM0 squamous cell cancer of the base of tongue. The primary lesion involved the base of tongue at the midline, extending to both sides of the tongue base, into the vallecula, and into the upper portion of the supraglottic larynx. We treated this patient with concomitant cisplatin and IMRT. The PTV70 includes the primary site as well as the involved lymph nodes on both sides of the neck. The PTV60 includes the remaining upper neck levels II and III. The PTV54 includes bilateral retropharyngeal nodes and the bilateral lower necks. A 9-field IMRT plan was used. The patient is free of disease at 2 years. **A:** CT slice through the superior aspect of the base of tongue at level of the uvula. The PTV70 and PTV54 are identified. Also identified are the right and left parotid glands and the constrictor muscles. **B:** Same CT slice as A except that the isodose lines are shown. The PTV contours have been removed for ease in optical display. The relative sparing of the parotid glands and constrictors is evident. **C:** CT slice through the base of tongue and neck at level II. The PTV70 includes the primary site as well as the involved lymph nodes in the left level II. The PTV60 expands upon the PTV70 and includes all of levels II and III bilaterally. Small portions of the inferior aspect of both the right and left parotid glands are also shown. **D:** Same CT slice as C except that the isodose lines are shown. The PTV contours have been removed for ease in optical display. The relative sparing of the parotid glands and constrictor muscles is evident. **E:** CT slice through the hyoid bone which shows the inferior aspect of tumor as it invades the upper larynx and epiglottic. The PTV70 contours this inferior tumor extension as well as lymph node involvement of bilateral neck nodes at levels II and III. The PTV60 expands upon the PTV70 as well as including all of levels II and III bilaterally. **F:** Same CT slice as E except that the isodose lines are shown, and the PTV contours removed as in prior figures. **G:** Midsagittal slice which shows PTV70 covering the disease in the base of tongue and upper larynx. **H:** Same midsagittal contour as G with PTV70 contour removed but showing isodose display. **I:** Coronal slice showing PTV70 including involved lymph nodes on both sides of the neck, PTV60 to include entire upper neck levels II and III, and both parotid glands. **J:** Same coronal slice as I with contours removed and isodose curves displayed. **K:** Dose–volume histogram for this patient using a 9-field IMRT plan.

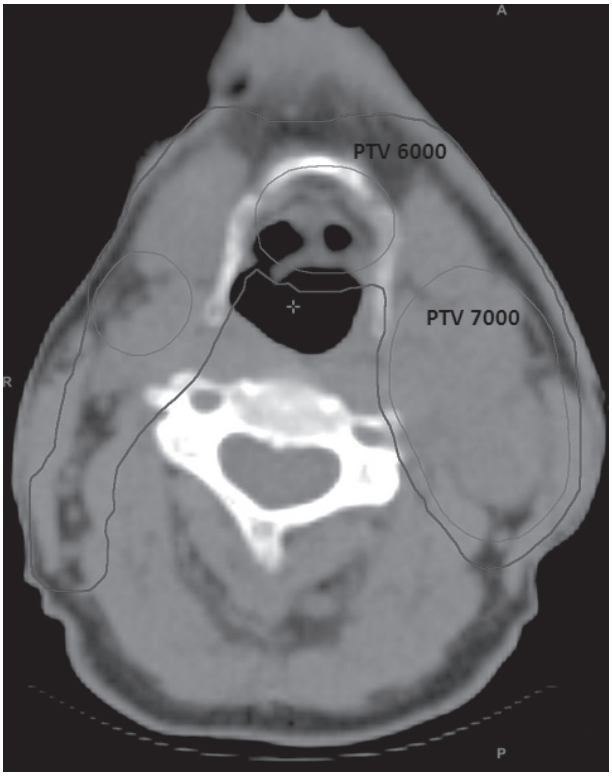
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C




D




E




F

**FIGURE 17-30.** *Continued*

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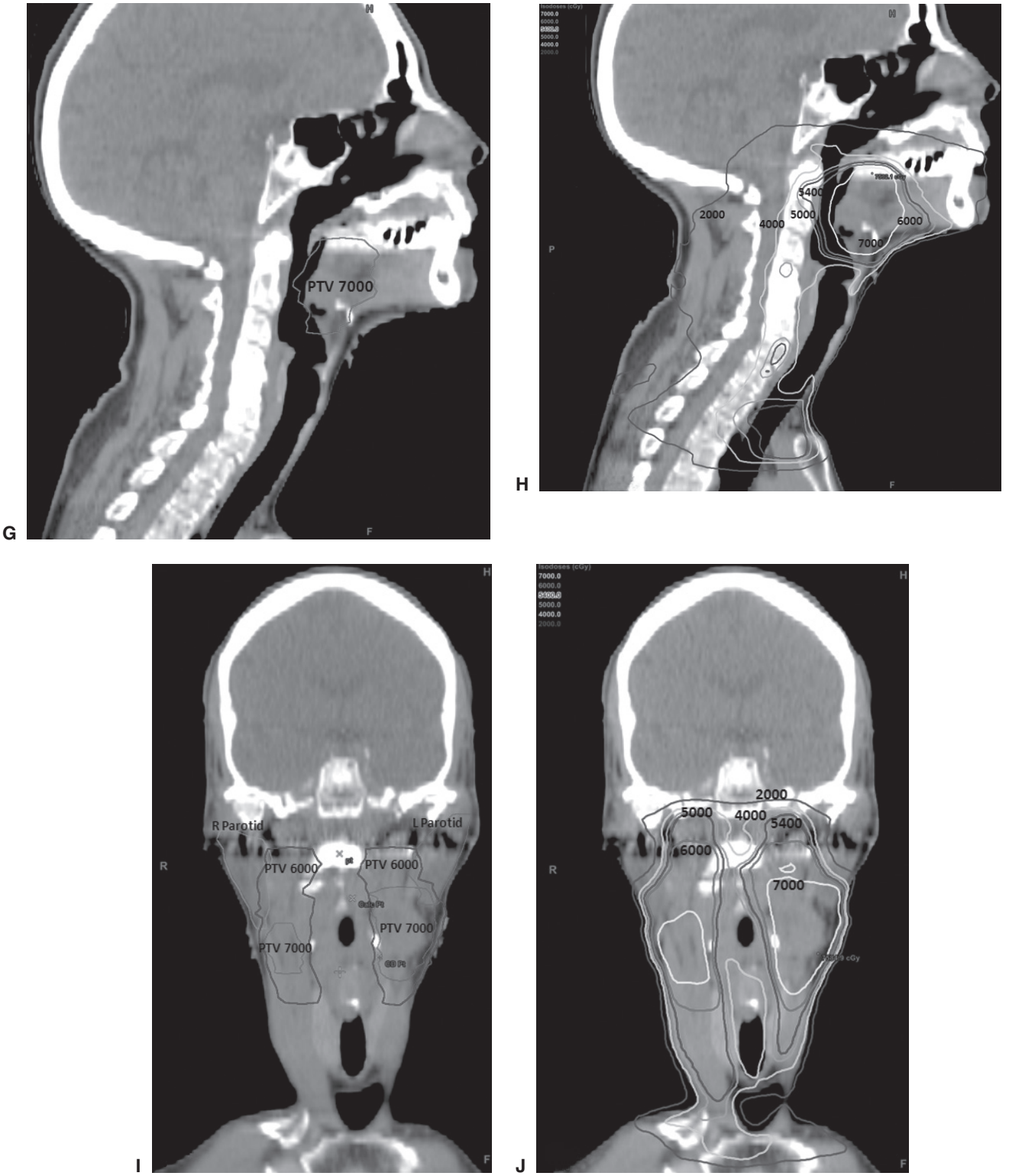
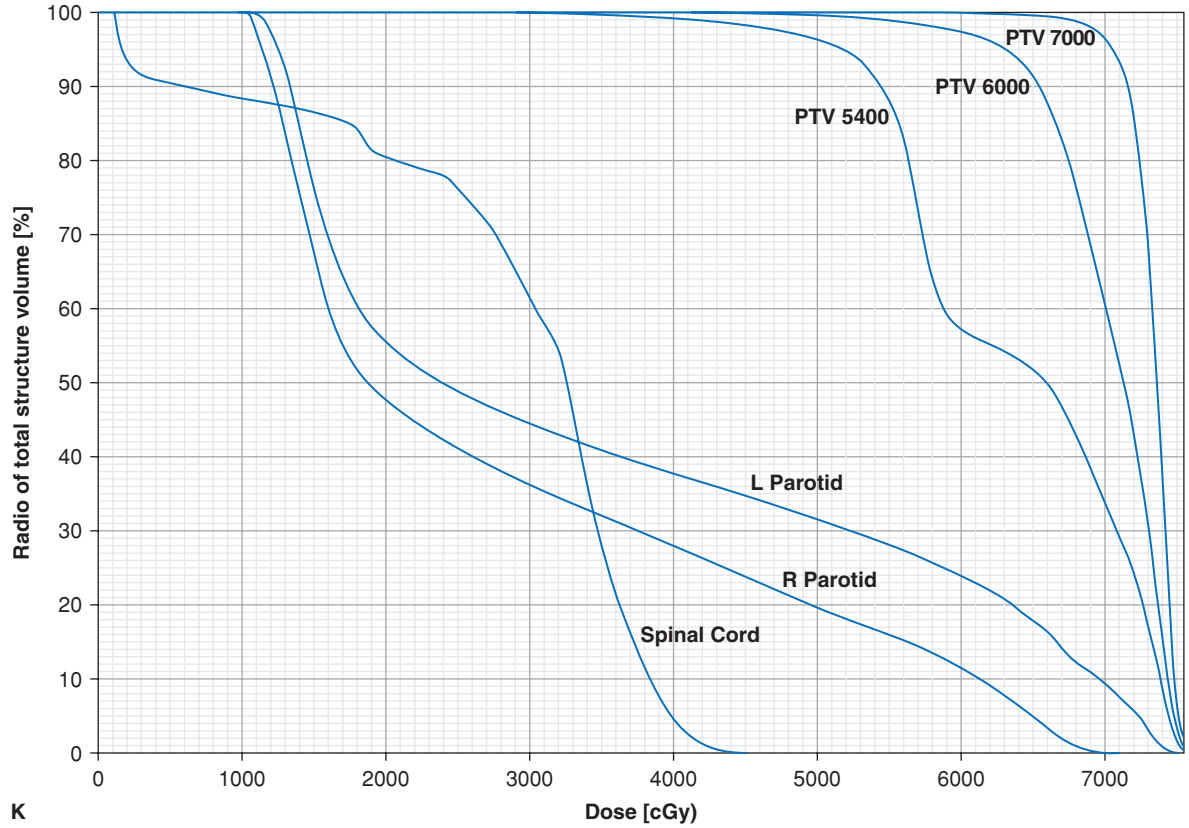


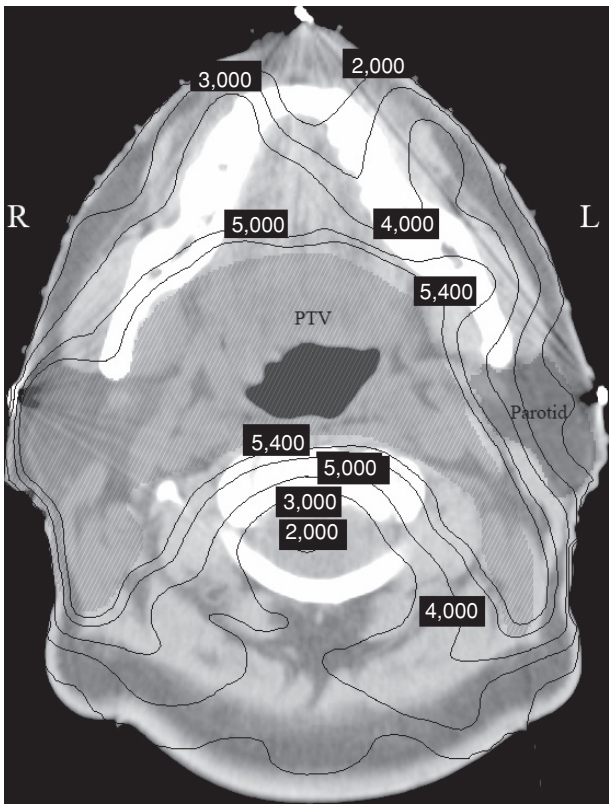

**FIGURE 17-30.** *Continued*

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K

**FIGURE 17-30.** *Continued*

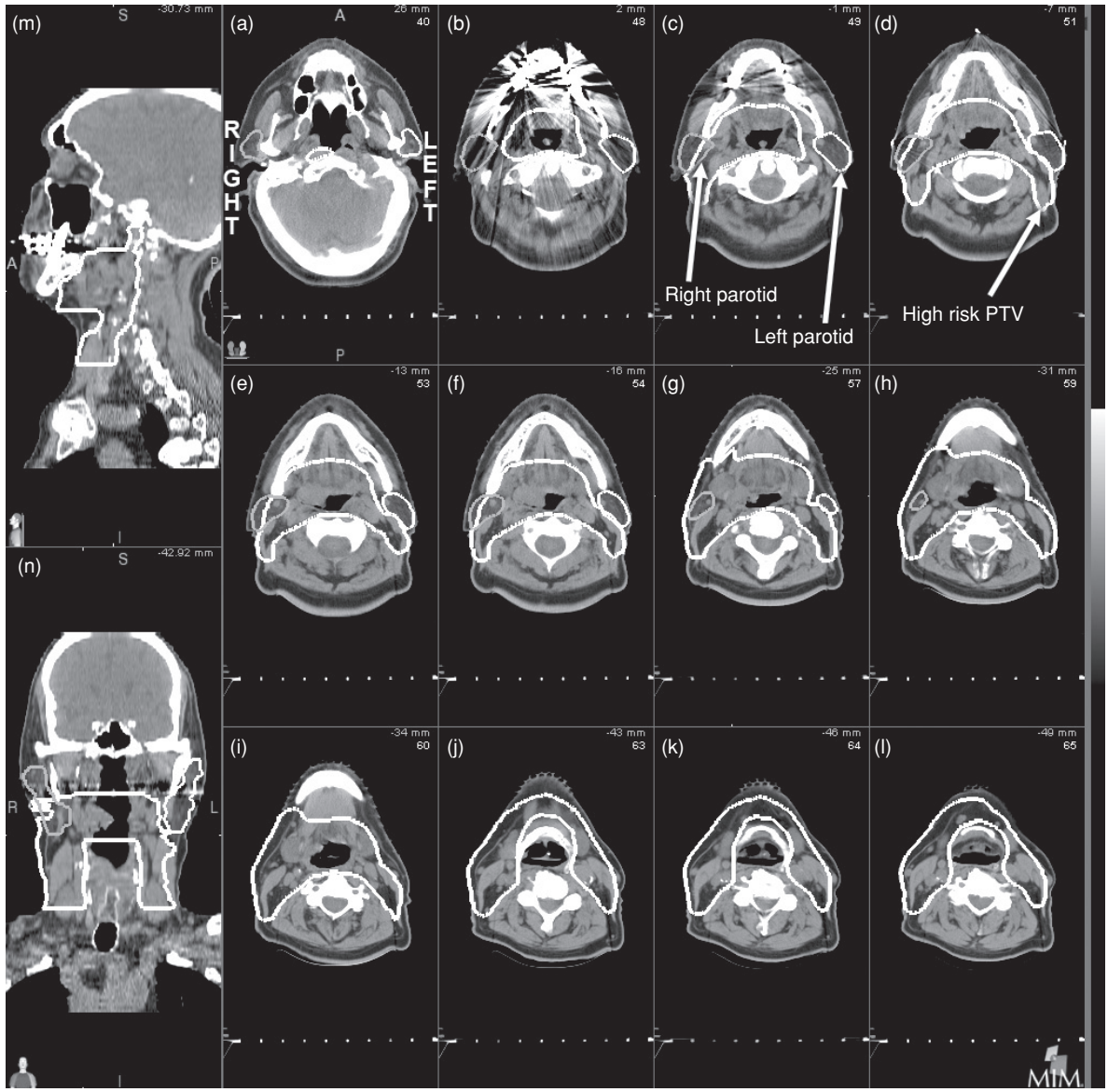



A

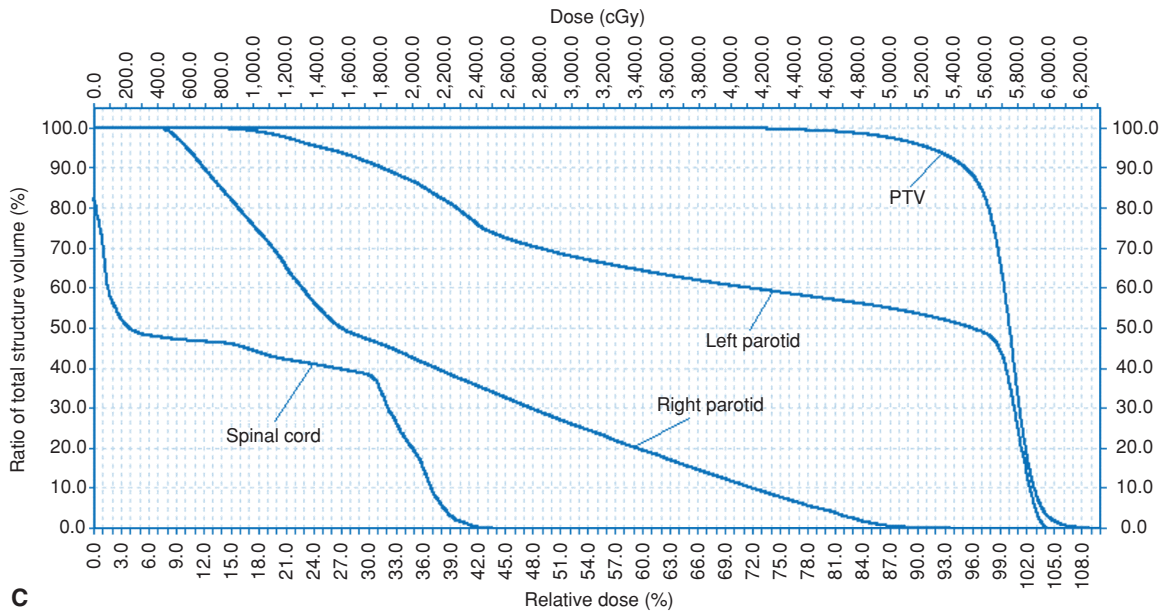
**FIGURE 17-31.** This patient had a T2N0M0 American Joint Committee on Cancer (AJCC) stage II squamous cell cancer of the right base of tongue. The treatment plan was combined external beam radiation therapy (5,400 cGy over 6 weeks to the "high-risk" PTV using intensity-modulated radiation therapy [IMRT]) followed by an interstitial iridium 92 brachytherapy boost (2,000 Gy). The high-risk PTV includes the primary site and the lymph nodes in the bilateral upper neck. The contralateral parotid gland is relatively spared. **A:** Isodose distributions displayed on an axial computed tomography (CT) used for treatment planning. This shows the primary site and bilateral upper neck nodes (PTV). There is relative sparing of the left parotid gland (parotid). Care is taken to avoid hot spots, especially in the mandible. **B:** This figure was produced using the MIM-Vista system. It shows representative serial radiotherapy (RT) planning CT slices as well as representative contours. (a) Contour shows upper limit of the retropharyngeal node contoured on the ipsilateral side and uppermost margin on parotid glands. (b) Contour covers the margin on the primary site and the retropharyngeal nodes, as well as the parotid glands. (c) Contour covers the margin on the primary site, the retropharyngeal nodes, and ipsilateral upper neck nodes. Note the sparing of the contralateral parotid. (d) Contour covers primary site, retropharyngeal nodes, and bilateral upper neck nodes, sparing contralateral parotid gland. (e) Same as (d). Note the primary tumor in the right base of tongue is enhancing. (f) Same as (e). (g) Same as (e). (h) Same as (e). This cut goes through the inferior aspect of the enhanced primary lesion in the right base of tongue. (i) Contour through the inferior aspect of the base of tongue and adjacent neck nodes on both sides. There is some sparing of the more superficial structures of the contralateral neck, mainly the structures superficial to the sternocleidomastoid muscle. (j) Midneck nodes, including crossover region anterior to the hyoid bone, are covered bilaterally. (k) Same as (j). (l) Same as (j). (m) Midsaggital cut showing high-risk PTV. (n) Coronal cut showing high-risk PTV as well as both parotid glands. **C:** Dose–volume histogram. *R*, right; *L*, left.



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B




C

**FIGURE 17-31.** *Continued*



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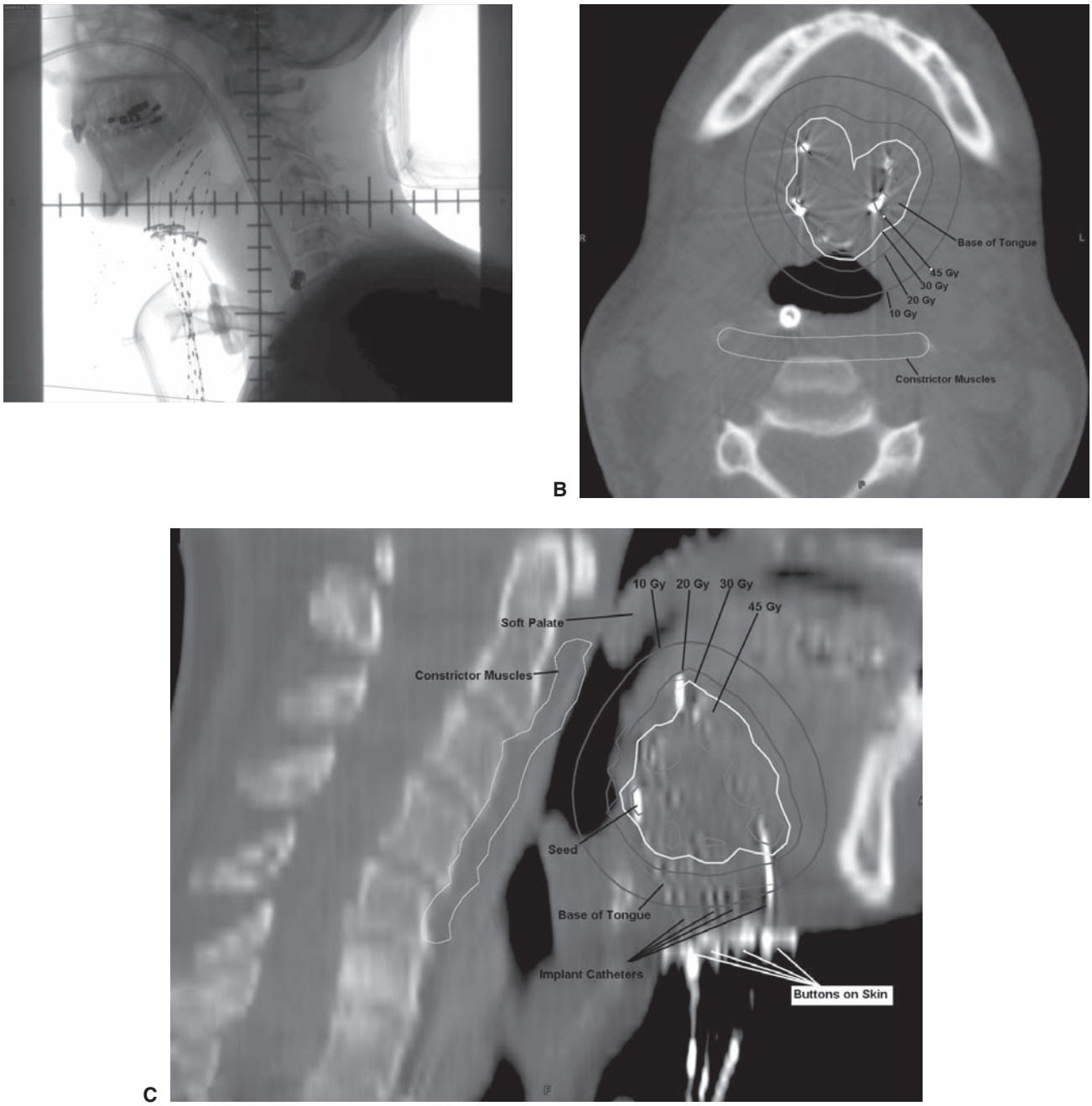



**FIGURE 17-32.** This patient had an iridium-192 ($^{192}$Ir) implant boost to the base of tongue. The patient had received intensity-modulated radiation therapy (IMRT) with concomitant chemotherapy, and the base of tongue received 5,400 cGy via IMRT. The involved lymph nodes were in the PTV70 and received 70 Gy via IMRT. This was accomplished using a dose-painting technique where the base of tongue was contoured as PTV54 and received 5,400 cGy in 6 weeks. The PTV70 received 70 Gy in 7 weeks. About 3 to 4 weeks after the completion of IMRT, the patient was brought to the operating room for the implant. **A:** Localization film showing looping implant of catheters through the base of tongue and exiting the anterior neck. **B:** CT slice through the base of tongue showing the contour of the base of tongue, the constrictor muscles, and isodose levels 3,000 cGy, 2,000 cGy, and 1,000 cGy. The dose rate is 900 cGy/day. Note the excellent sparing of the pharyngeal wall and constrictor muscles. **C:** Midsagittal CT slice showing the base of tongue, constrictor muscles, catheter loops and buttons, soft palate, and isodose levels 3,000 cGy, 2,000 cGy, and 1,000 cGy. Normal tissue sparing of the constrictor muscles, the pharyngeal wall, and the palate are nicely displayed.

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# PART D:
# Surgical Technique

Vikas Mehta, and Robert L. Ferris

## INTRODUCTION

Over the last decade, technological advances in minimally invasive, transoral surgical techniques have revolutionized the treatment paradigm for oropharyngeal neoplasms. Since the early 1990s, due to evidence extrapolated from the VA larynx and RTOG 91-11 trial[1,2] for nonsurgical larynx preservation, primary surgical therapy was reserved for small tumors (<1.5 cm) of the posterior pharyngeal wall and the tonsils, carcinomas requiring bony resection or tumors not sensitive to radiotherapy. Organ-preservation protocols demonstrated not only that patients treated with primary radiation therapy had similar survival rates to upfront surgical therapy, but also that primary surgical patients were 10 times more likely to have severe morbidity or mortality.[3] The complications from traditional surgical methods were largely due to external surgical approaches, which required opening the pharyngeal and oral contents to the neck, with the patient often needing a tracheostomy and feeding tube. The addition of a mandibulotomy and/or glossotomy further increased postoperative speech and swallowing dysfunction, as well as cosmetic deformity.

With the sharp increase in the prevalence of human papillomavirus (HPV)–associated oropharyngeal squamous cell carcinoma (OPSCC), there has been a corresponding shift in the affected population to younger, nonsmoking patients.[4] Per the current practice guidelines, these HPV-positive patients undergo intensive chemoradiotherapy (CRT) protocols, just as their HPV-negative counterparts, but with drastically improved survival. The increased risk for these younger patients of long-term sequelae such as osteoradionecrosis, progressive dysphagia, fibrosis, aspiration, and radiation-induced malignancy has led head and neck surgeons to explore minimally invasive surgical techniques to minimize the morbidity of surgical resection and reduce the need for high-dose chemoradiotherapy. Additionally, the very good survival of patients with advanced OPSCC treated with CRT can be primarily attributed to increasing rates of HPV-positive disease. A multicenter phase III trial reported 3-year overall survival (OS), disease-free survival (DFS), and loco-regional control rates of 51%, 42%, and 66%, respectively, when treated with chemoradiation.[5] When the TAX 324 study, a phase III CRT trial of 264 patients with OPSCC, was stratified by HPV status, 5-year survival was 82% for HPV+ and 35% for HPV– patients.[6]

Both transoral laser microsurgery (TLM) and transoral robotic surgery (TORS) have demonstrated excellent oncologic results with good functional outcomes for oropharyngeal tumors,[7–10] leading to a change in the National Comprehensive Cancer Network 2011 guidelines to remove primary radiation therapy as the Category 2B preferred treatment for early oropharyngeal cancer.

For advanced, high-volume, or post-CRT recurrent oropharyngeal carcinoma, surgical resection via an external approach is often required. The choice of open surgical approaches depends on the location of the tumor and degree of bony involvement. The oropharynx contains structures crucial for deglutition, respiration, and phonation. There is no one approach that allows wide exposure with minimal morbidity. The three main routes are combined transoral/transcervical, transpharyngeal, and transmandibular approaches. Each has its own risks and sequelae to these vital structures. If necessary, a maxillectomy and/or mandibulectomy can be combined with any of the three techniques. Often, oropharyngeal resections will require flap reconstruction. This chapter will address the indications, advantages and disadvantages of the transoral and external approaches.

### Minimally Invasive Transoral Approaches

Minimally invasive surgical techniques have greatly expanded the scope of the transoral approach for oropharyngeal resections. Traditionally, transoral surgery was reserved for tumors <2 cm of the tonsil, the soft palate, and the posterior pharyngeal wall. Larger neoplasms or tumors of the base of tongue were difficult to access, especially at the deep margins. The use of endoscopes greatly improved transoral visualization of the oropharynx by magnification, tissue distention, and angled optics. Additionally, advancements in laser delivery systems and the wristed technology of the DaVinci robot have allowed increased freedom of motion in previously inaccessible subsites. These innovations have enabled surgeons to remove large neoplasms from the oropharynx with excellent oncologic control and functional outcomes.

### Transoral Laser Microsurgery

Transoral laser microsurgery was first introduced by Strong and Jako in 1972.[11] Despite promising initial results, it soon fell out of favor as an oncologic treatment option due to early difficulties with exposure and en bloc removal. In 1993, Steiner revolutionized the field of minimally invasive transoral surgery by presenting an article describing results with a piecemeal resection utilizing a tumor-splitting approach.[12] The splitting of the tumor in this dimension allowed much better assessment of the deep margins (Fig. 17-33). Steiner's report was followed by a rapid influx of evidence supporting the roles of TLM in treating cancer of the upper aerodigestive tract. Recent large cohort studies and multicenter case series have reported oncologic results for laryngeal and oropharyngeal neoplasms that are comparable to nonsurgical management, with improved functional outcomes and decreased health care costs (mean cost of US$3,281 for TLM compared to US$13,825 for XRT).[10,13–17]

While most of the supporting evidence for TLM is in early glottic cancer, there has been promising results with OPSCC over the last decade. In 2003, Steiner et al. reported on a cohort of 48 patients with OPSCC treated with TLM, of which 94% were stage III/IV.[18] Twenty-three of the 48 patients required therapy for either deep extension into the tongue base or positive resection margins. The 5-year local control for all T stages was 85% with no local recurrences in the T1 or T2 group and a 20% local recurrence rate for T3/T4 tumors. OS and DFS were 52% and 73%, respectively.

In a recent, multicenter, prospective study of primary, TLM-resected, stage III/IV OPSCC, 204 patients were reported.[10] Two- and 5-year estimates demonstrated an OS of 89% and 78%, DSS of 91% and 84%, and DFS of 85% and 74%, respectively. The survival results are comparable with studies using chemoradiation as the primary treatment modality, with improved functional outcomes. A recent CRT study ($n$ = 71) by Huang et al. with 32% of the tumors staged T3 and T4, showed a 3-year OS of 83% and a loco-regional control rate of 90%.[19] In the TLM study, with

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**FIGURE 17-33.** A CT scan of a patient with a T3 tonsillar SCCA. The arrows depict the transoral laser microsurgical approach of a tumor debulking followed by radial incisions through the tumor to determine depth of resection circumferentially.

34% T3 and T4 tumors, the OS was 86% at 3 years and loco-regional control of 93%. The matched, chemoradiation group in this report had a long-term G-tube rate of 35% compared with 3.4% in the TLM study.

Studies have also indicated that TLM-based surgical treatment without adjuvant therapy can be used with excellent oncologic control for early T-stage OPSCC. In 2009, Grant et al. reported 69 cases of oropharyngeal carcinoma staged T1 to T4 (T1 = 25, T2 = 30, T3 = 12, T4 = 2) treated with TLM and a neck dissection, if indicated.[13] None of the patients received adjuvant radiation therapy, either because it was not indicated or the patient declined. Five-year OS was 86% with loco-regional control of 90% for T1 and 94% for T2. None of the T3 or T4 patients had a local recurrence. In terms of functional outcomes, none of the patients required a long-term feeding tube and 98% reported normal or near-normal swallowing, using the Salassa scale.

***Technique*** TLM is usually done with either a microscope-mounted carbon dioxide laser or a hollow-fiber carbon dioxide laser system. Exposure of the tumor is achieved with a variety of specialized endoscopes, and excision is performed either circumferentially (en bloc) or in a tumor-splitting fashion (Fig. 17-33), to ensure adequate surgical margins. Tumor mapping and margin status is typically performed using both frozen-section and permanent pathologic analysis. The reported complication rate of TLM is extremely low with the most common problem encountered being postoperative bleeding at a rate of 1.5% to 3%.[13,20] Contraindications to TLM include inadequate endoscopic access, which is unusual for oropharyngeal carcinomas, or projected unresectability because of a probable positive margin. Examples of an unresectable tumor are lateral extension of a tonsillar primary into the infratemporal fossa invading the great vessels or ventral extension of tongue base tumors into the anterior floor of mouth.

## Transoral Robotic Surgery

The first described use of robotics in head and neck surgery consisted of a robotic-assisted salivary gland resection and neck dissection in an animal model.[21] The elimination of hand tremor and superior, three-dimensional visualization were both described as significant advantages.[21] The feasibility of transoral robotic surgery was investigated at the University of Pennsylvania, first using a human cadaver,[22] followed by a supraglottic laryngectomy in a canine model.[23] Protocols were then established for positioning, use of 5-mm instruments, and hemostasis.[23,24] The first documented OPSCC TORS resection was in three patients with early T-stage, base of tongue SCCs. En bloc resection with negative margins was achieved in all three cases with no complications or change in swallowing function.[25]

In 2007, a case series of 27 patients with tonsillar SCC underwent primary resection with TORS.[26] The patients were mostly stage III/IVa.[24] Neck dissections were performed on 26 of the 27 patients with 24 of the patients having at least one positive node. The cervical lymphadenectomy was performed 1 to 3 weeks after the TORS procedure to minimize lymphedema in the oropharynx after TORS. Negative margins were achieved in all of the cases and there were no loco-regional recurrences during the 2-year study period with a minimal of 6-month follow-up. All of the patients who returned for evaluation (26 of 27) tolerated a regular diet without the need for a gastrostomy tube. Only one patient required a tracheostomy for preexisting sleep apnea, which was exacerbated by the surgical procedure.

Since 2007, several institutions have reported case series highlighting the efficacy of TORS for OPSCC.[9,27–31] These reports document excellent oncologic outcomes in patient series ranging from 20 to 47 patients. In the patient population presented by Moore et al.,[9] 12 of 45 patients (27%) were able to avoid adjuvant radiation, and at 1-year follow-up in this series, no local recurrences were detected. Weinstein et al.[31] reported a series of 47 patients with advanced OPSCC (stage III/IV). One patient had a positive margin (2%). DSS was 98% at 1 year and 90% at 2 years. Due to the TORS procedure, 18 of 47 patients (38%) avoided chemotherapy, and 5 patients (11%) did not require any adjuvant therapy. In a prospective, phase I single arm study,[32] 31 patients underwent TORS with selective neck dissection(s) (SND) with a 100% disease control rate and a 2-year PEG dependency rate of 0%. Seven patients avoided adjuvant therapy and 15 of the remaining 24 (62.5%) received radiation alone (60 Gy to the primary site and dissected neck, 54 Gy to the contralateral neck and retropharyngeal nodes) based on the lack of nodal extracapsular extension (ECE).

Functional outcome studies in OPSCC patients undergoing TORS resections have reported superior swallowing results when compared to published, organ-preservation protocols.[8,9,29,30,33,34]. In a direct comparison of TORS versus CRT with matched group of OPSCC patients at a single institution, TORS was associated with better short-term eating ability (swallowing score 72 vs. 43, $p = 0.008$), diet-tolerance (43 vs. 25, $p = 0.01$), and Functional Oral Intake Score (FOIS) (5.5 vs. 3.3, $p < 0.001$) at 2 weeks after completion of treatment.[33] At 12 months, the TORS group had returned to baseline swallowing status while diet and FOIS remained impaired in the CRT group. In a series of 45 patients, Moore et al. found that only 5 of 22 patients who had gastrostomy tubes required their use beyond 20 days and all patients had their feeding tubes removed by 4 months.[9] Dean et al. compared feeding tube dependence in patients undergoing TORS to those who had open surgery for post-CRT OPSCC failures and found that while 43% of the open salvage group were G-tube dependent at 6 months, none of the TORS patients required feeding tube supplementation. These early evaluations of the oncological and functional outcomes of TORS led to FDA approval of TORS

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for use in selected benign and malignant (T1/T2) tumors of the head and neck in December 2009.

***Technique.*** TORS is performed with exposure either using the Dingman or Feyh-Kastenbauer (FK) laryngeal retractor. Once adequate exposure is achieved, the robot is brought to the left side of the patient and the 0-degree (tonsillar fossa) or 30-degree (tongue base) binocular endoscope is positioned to allow optimal visualization of the tumor. Five-millimeter instruments are typically used with one being a grasper and the other arm holding monopolar cautery (Fig. 17-34). An assistant at the head of the bed helps with exposure, suctioning and, if necessary, hemostasis with bipolar cautery. The anatomic landmarks via a TORS approach have recently been well described for OPSCC tumors.[35] Once the tumor is removed, three-dimensional orientation of the specimen for pathologic evaluation is crucial. Reconstruction, if required, is then performed with the robot utilizing either a local flap or free tissue transfer. Most authors advocate the use of a hemostatic agent at the end of the procedure due to the difficulty in obtaining access if postoperative bleeding should occur. Fixation of the tumor to the lateral pharynx or the skull base, inadequate exposure, or presumed unresectability should discourage the surgeon from proceeding with a TORS approach.

## Traditional Transoral Excision

Proper patient selection is the most critical aspect in planning transoral excision using traditional methods. The surgeon must be able to adequately visualize the tumor through the oral cavity using a headlight throughout the procedure. This requirement effectively limits these procedures to T1/2 tumors involving the upper oropharynx: the tonsil, the soft palate, and the posterior pharyngeal wall (if the inferior aspect of the tumor does not extend beyond the tip of the epiglottis). Absolute contraindications to transoral excision include trismus, deep invasion by the tumor, and poor accessibility. These should be evaluated preoperatively through physical examination and imaging, but attachment to the deep vascular and soft tissue structures may be difficult to ascertain until the patient is under general anesthesia.



**FIGURE 17-34.** An intraoperative photo of a transoral robotic base of tongue tumor resection. A Dingman retractor is being used for exposure. The 5-mm monopolar cautery and Maryland forceps instruments are introduced into the operative field with the wristed technology allowing excellent transoral access to the oropharynx.

A high tooth profile, macroglossia, thick lips, or microstomia can all interfere with adequate exposure and are therefore relative contraindications.

Exposure of the tumor is the key step in performing a transoral excision of an OPSCC. An oral mouth gag (such as a McIver or Crowe-Davis retractor) is first inserted and suspended from a Mayo stand. If the tumor extends superiorly into the nasopharynx, red rubber catheters can be placed to retract the soft palate anteriorly and superiorly. Palpation of the tumor is then performed to assess the submucosal extent and attachment to deep structures. The tumor can be removed using either electrocautery or a handheld laser based on surgeon preference. If a handheld carbon dioxide laser is going to be utilized for resection, the use of a reinforced endotracheal tube is imperative. Usually, the initial mucosal cut is made as far posterior and inferior as possible since these areas will become difficult to visualize as the resection proceeds. Margins should be taken with at least 1 cm cuff of mucosa, and the deep margins should be checked frequently via palpation to ensure complete removal. The specimen should be oriented for pathologic analysis as a failure to orient often leads to unclear margin assessment. Finally, posterior pharyngeal wall defects can be left to heal by secondary intention after securing the edges to the prevertebral fascia or resurfaced with a split-thickness skin graft. The tonsillar fossa and soft palate can be primarily closed or left open. The reconstruction of larger defects will be discussed later in the chapter.

## Open Surgical Approaches

With increasing use of CRT and minimally invasive techniques, the need for external surgical approaches for OPSCC has steadily declined. For tumors with bony involvement or postradiation recurrences, however, an open surgical approach is often preferred, especially if microvascular reconstruction is required. The choice of open surgical technique depends on the size, location, and degree of bony involvement (Table 17.15). No external approach allows wide exposure with minimal morbidity. The transoral/transcervical, transpharyngeal, and transmandibular approaches each carries its own risk and damage to vital structures. If necessary, a maxillectomy and/or mandibulectomy can be combined with any of the three techniques.

## Transoral/Transcervical

The transoral/transcervical approach, also known as the "pull-through" procedure, involves prolapsing the contents of the oral cavity/oropharynx into the neck by releasing the oral cavity/orpharyngeal attachments to the mandible. The technique is limited to T1–3 tumor without mandibular involvement. In a series of 13 patients with OPSCC resected via this approach, the authors achieved negative margins with minimal postoperative morbidity.[36] The advantages include intact lip sensation and avoidance of a facial incision and/or mandibulotomy. Disadvantages include decreased exposure inferiorly, bilateral floor of mouth and tongue paresthesias, and communication of the oral cavity and the neck. Tumor excision begins with bilateral level I neck dissections, which helps identify the hypoglossal nerves, the lingual nerves, and the lingual arteries. Once the neurovascular structures have been isolated, the lingual mucosa of the floor of mouth is incised circumferentially taking care to leave sufficient cuff of mucosa on the mandible to facilitate closure. The lingual nerve and the sublingual gland are kept attached to the mandible. The extrinsic muscles of the tongue attached to the mandible are incised, and the tongue is delivered into the neck allowing access to the tumor.

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**TABLE 17.15 Comparison of Various Open Surgical Techniques**

| Open Surgical Approach | Indications | Advantages | Disadvantages |
|---|---|---|---|
| Transoral/transcervical ("pull-through") | T1–3 tumors of the upper posterior pharyngeal wall, the tonsil, or the soft palate | Intact lip sensation, no external facial incision, avoidance of a mandibulotomy | Decreased exposure inferiorly, bilateral floor of mouth and tongue paresthesias |
| Transhyoid pharyngotomy | T1–4 tumors of the base of tongue, the tonsil, and the low posterior pharyngeal wall | Intact lip sensation, no external facial incision, avoidance of a mandibulotomy | Swallowing impairment, poor access to tumors involving the inferior pharynx, the skull base, and the pterygoid fossa |
| Lateral pharyngotomy | T1–4 tumors of the lower lateral and the posterior pharyngeal wall | Exposure to tumors extending inferiorly to the hypopharynx | Blind entry into the pharynx, which can compromise the oncologic resection, risks of injury to the superior laryngeal nerve, the hypoglossal nerve, and the lingual artery, poor access to the superior oropharynx |
| Median mandibulotomy ("Trotter procedure") | T1–3 tumors of the base of tongue, the upper posterior pharyngeal wall, the soft palate, and the nasopharynx | Preserves lip and tongue sensation, exposure to tumors extending superiorly to the nasopharynx | Poor lateral exposure, lip-split, mandibulotomy, and tracheostomy required |
| Lateral mandibulotomy | T1–4 tumors of the tonsil, the base of tongue, and the upper posterior pharyngeal wall | Access to superolateral oropharynx | Lip, tooth, and tongue parethesia and mandibular vascular compromise |
| Mandibulectomy | T1–4 base of tongue, tonsil, upper posterior pharyngeal wall, and soft palate | Resection of advanced tumors invading the mandible | Lip, tooth, and tongue parethesia, mandibular vascular compromise, requires reconstruction |

## Transpharyngeal

***Transhyoid Pharyngotomy.*** The transhyoid approach to the oropharynx is best utilized for primary or recurrent lesions of the base of tongue, the tonsil, and the low posterior pharyngeal wall. The suprahyoid pharyngotomy can be used for any T-stage tumors in these locations, but caution should be taken when addressing T4 tonsil lesions. These advanced tumors often involve the pterygoid musculature, the skull base, and/or the mandible, and a mandibulotomy is often required for proper excision. Additionally, tumors should not involve both lingual arteries, as the maintenance of vascularized tongue base musculature is vital to the closure for this procedure. Agrawal et al. presented a series of 41 patients who underwent the transhyoid approach for OPSCC and compared outcomes to a stage-matched OPSCC group of 41 patients resected via a mandibulotomy approach.[37] Margin status (9 vs. 11 positive), survival (47% vs. 45%), and long-term gastrostomy tube dependence (18% vs. 21%) were similar between the transhyoid and the mandibulotomy procedures. The major distinction between the two came when comparing incidence of osteoradionecrosis (ORN): 2% for the transhyoid group and 17% for the mandibulotomy patients. The advantages of the transhyoid approach are the avoidance of a facial incision and mandibulotomy. Disadvantages include communication of the pharynx and the neck, swallowing impairment, and poor access to tumors involving the inferior most portion of the pharynx, the skull base, and the pterygoid fossa.

***Technique.*** The first step in the procedure is to dissect the suprahyoid musculature from the hyoid bone and release the stylomandibular ligament. The hyoid is then either retracted inferiorly or resected depending on its degree of involvement. Agrawal et al. advocate for removal of the hyoid bone as it allows for greater ease of closure through increased rotation of the tongue base. The intrinsic muscles of the tongue can then be bluntly dissected from the hyoid bone and the hyoepiglottic ligament. The condensation of fibers in this ligament, the median glossoepiglottic fold, will then be identifiable. The pharyngotomy is then performed guided by either prior endoscopy or simultaneous transoral palpation to avoid violating the tumor. The pharyngotomy can then be widened for further access (Fig. 17-35). For base of tongue carcinoma, the tongue base is grasped and pulled anteriorly through the pharyngotomy to facilitate visualization. For cancers involving the tonsillar fossa, the base of tongue and the mandible are retracted anteriorly and the carotid sheath is separated from the pharynx up to the skull base. After resection of the lesion, the hyoid bone, if present, is resuspended to the remaining tongue base musculature or the mandible. If the hyoid bone has been resected, the strap muscles should be brought up to resuspend the larynx. These closure techniques not only serve to prevent fistula formation, but are also essential for avoiding aspiration.

***Lateral Pharyngotomy.*** The lateral pharyngotomy approach is rarely used alone. It is primarily utilized for lower lateral and posterior pharyngeal wall oropharyngeal neoplasms, although

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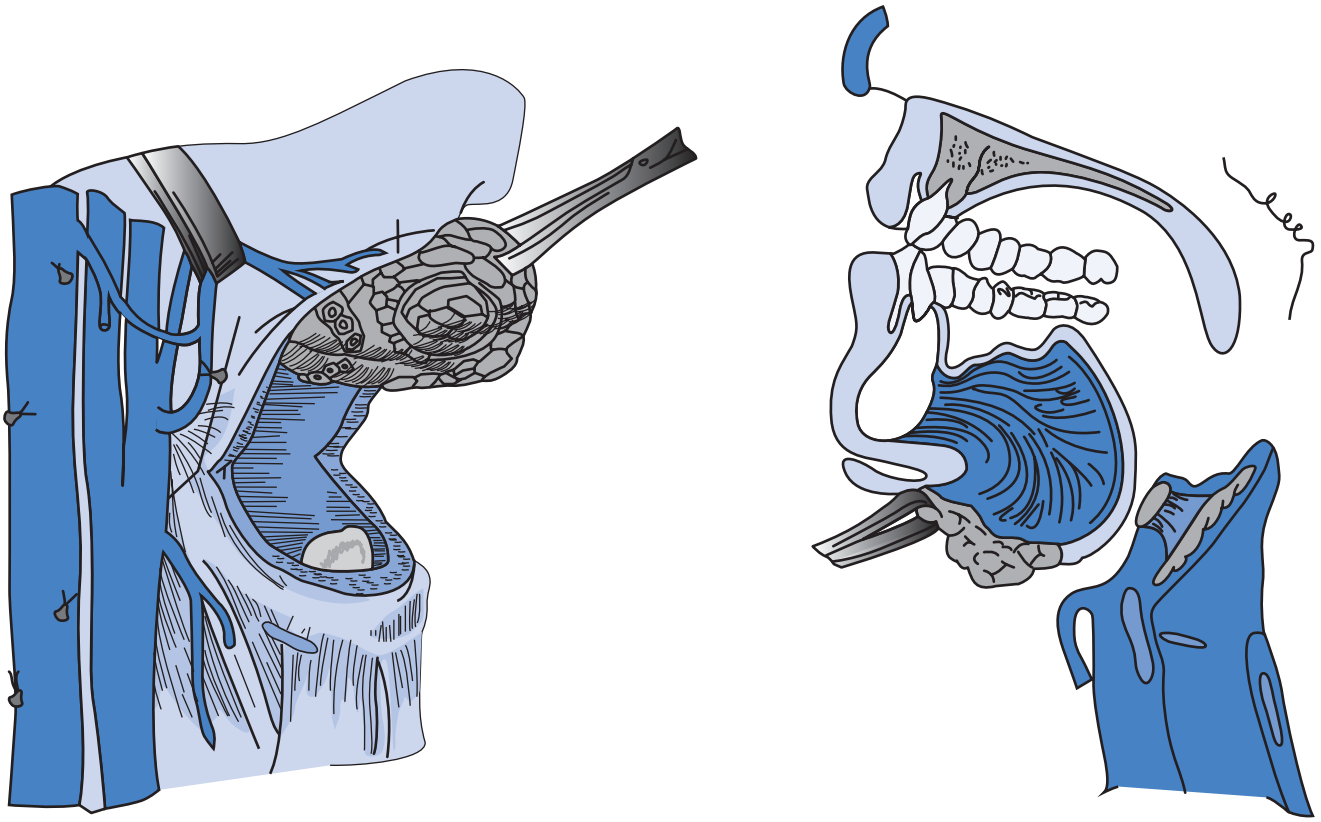


**FIGURE 17-35.** A suprahyoid pharyngotomy is depicted with retraction of the external carotid vessels. The tongue base has been grasped and delivered into the field for access to the base of tongue.

an extended lateral pharyngotomy has been described for lateral tongue base carcinomas and lesions involving the vallecula.[38] For wider exposure, the lateral pharyngotomy can be combined with a mandibulotomy or transhyoid pharyngotomy. Lesions that involve the oropharynx and spread into the hypopharynx are often amenable to resection through this approach. The major disadvantage to the lateral pharyngotomy is that it requires a blind entry into the pharynx, which can compromise the oncologic resection. Additionally, there are risks of injury to the superior laryngeal nerve, the hypoglossal nerve, and the lingual artery. Finally, lesions of the superior oropharynx are not well exposed through this approach.

***Technique.*** The procedure begins by exposing the carotid sheath and retracting its contents laterally to allow identification of the inferior constrictor muscle, as well as the superior pole of the thyroid gland and its vascular supply (Fig. 17-36). The superior laryngeal neurovascular bundle and the hypoglossal nerve are identified and preserved. The stage and site of origin of the primary cancer dictate the extent of the lateral pharyngotomy. The pharyngotomy can be extended superiorly to expose the nasopharynx or inferiorly to expose the cervical esophagus. A high pharyngotomy can be limited by the mobility of the superior laryngeal nerve and occasionally requires nerve transection for adequate exposure. The lateral third of the ipsilateral hyoid bone and the superior cornu of the thyroid cartilage can be removed and the thyrohyoid ligament can be transected in order to increase mobilization. The pharyngotomy location is identified by placing the index finger along the base of the tongue, inferior and posterior to the tonsillar fossa, and tensing the middle constrictor muscle/mucosa. Lesions extending to the superior aspect of the hypopharynx may require inferior extension of the pharyngotomy. The inferior constrictor muscle is incised over the posterior edge of the thyroid ala to expose the mucosa of the pyriform sinus, which is then dissected from the medial facet

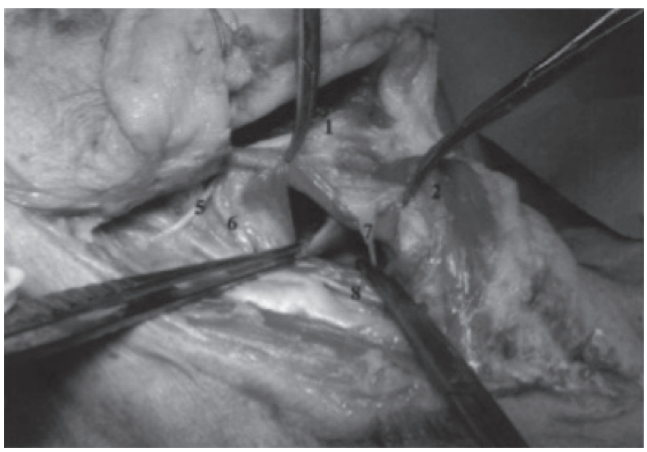



**FIGURE 17-36.** A lateral pharyngotomy has been performed with a lateral view of the epiglottis. 1, tendon of digastric muscle; 2, infrahyoid muscles transected from lateral horn of hyoid bone; 5, hypoglossal nerve; 6, lingual artery; 7, superior laryngeal nerve; 8, superior thyroid artery.

*Source:* Reprinted with permission from Laccourreye O, Seccia V, Menard M, et al. Extended lateral pharyngotomy for selected squamous cell carcinomas of the lateral tongue base. *Ann Otol Rhinol Laryngol.* 2009;118:428–434.

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of the thyroid ala. The pyriform sinus pharyngotomy is opened with the mucosa under tension. After the extirpative surgery, the pharyngotomy is repaired with a double-layer closure technique.

## Transmandibular

***Median Mandibulotomy.*** Although uncommonly utilized in the modern era, the median labio-mandibulo-glossotomy (Trotter's procedure) has been historically advocated for lesions of the base of tongue, the upper posterior pharyngeal wall, the soft palate, and the nasopharynx. The approach can be combined with a palatal split making it a good choice for tumors extending superiorly. The major advantage to the Trotter's procedure is that it preserves sensation with good functional outcome. This approach, however, is mainly reserved for midline lesions, as the exposure laterally is poor. Another disadvantage is that it requires a lip-split incision, which is often noticeable, a mandibulotomy, which increases the risk of ORN, and a tracheostomy to protect the airway due to significant tongue edema.

A midline mandibulotomy is performed by exposing the mandible via a lip-splitting incision. Soft tissue flaps are elevated to the level of the mental foramen bilaterally taking care to avoid injury to the mental nerve. The periosteum is elevated only in the area where fixation plates will be placed. Once this is done, the screw holes are predrilled to reconstitute the patient's preoperative occlusion. The mandibulotomy is performed either in the midline between the two central incisors or in the paramedian position between the lateral incisor and the canine tooth. The tongue is then incised in the midline, which is usually a fairly bloodless plane. The incision is carried as far posterior as necessary to provide exposure. After resection of the lesion the tongue is reapproximated with a layered closure and the mandible is plated.

The median mandibulotomy can also be utilized with a mandibular swing to expose lesions of the entire tongue, the soft palate, the posterior pharyngeal wall, the tonsillar fossa, the retromolar trigone, and the infratemporal fossa. After the mandible has been split, the lingual floor of mouth mucosa on the side of the lesion is incised, the mylohyoid and digastric muscles are divided, and the mandible is retracted laterally. The disadvantages of this approach include the morbidity of a mandibulotomy, loss of sensation to the lateral tongue and the floor of mouth secondary to disruption of the lingual nerve, division of the muscular attachments to the anterior and medial aspects of the mandible, and limited exposure of the inferior posterior pharyngeal wall. If necessary, a cervical pharyngotomy can be combined with this approach to provide exposure to the lower posterior wall. Even this combined exposure, however, can be limited inferiorly by the hypoglossal nerve.

***Lateral Mandibulotomy.*** A lateral mandibulotomy can be used to access lesions of the tonsil, the base of tongue, the parapharyngeal space, and the upper posterior pharyngeal wall. The mandibulotomy is usually made posterior to the mental foramen, which results in disruption of the inferior alveolar nerve and the lingual nerve. These can be reapproximated post resection. Once the mandibulotomy has been performed, the soft tissues are released medially to allow the mandible to swing laterally. In general, this approach is not commonly used due to the sacrifice of lip, tooth and tongue sensation, as well as the potential risk of compromising the mandibular blood supply. The midline mandibulotomy usually offers equal surgical exposure with far fewer morbidities.

***Mandibulectomy.*** Finally, a mandibulectomy, or composite resection, is used when tumor invades the mandible (Fig. 17-37). Advanced tumors of the tongue, the tonsil, and the soft palate may all be addressed via this approach. A lip-split incision is then performed and a cheek flap is developed. The mental nerve is sacrificed and the periosteum elevated from the level of the mental nerve to the ascending ramus. The buccal mucosa is incised posteriorly to the retromolar trigone. When elevating the posterior aspect of the cheek flap, it is important to stay close to the ramus of the mandible as a more lateral excursion can injure the facial nerve. Once the mandible has been exposed, a mandibular reconstruction plate is fashioned with holes drilled on either side of the proposed mandibulectomy. There should be room enough for three holes on either side. Once the bony cuts are made, the lesion is excised. Wound closure depends on the chosen method of reconstruction.



**FIGURE 17-37.** Intraoperative photo of a patient with recurrent right tonsillar SCCA. A mandibulectomy was performed along with a hemipharyngectomy, hemiglossectomy, and floor of mouth excision. The tumor was dissected off the carotid vasculature which can be visualized medial to the pharyngeal defect. Microvascular reconstruction was required for closure.

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## Reconstruction

The oropharynx contains structures crucial for deglutition, respiration, and phonation making it imperative but difficult to reconstruct. With the advent of microvascular free tissue transfer, the reconstructive options available have increased significantly over the last three decades. A detailed discussion of all the techniques is beyond the scope of this chapter, but a brief outline of the options, as well as their advantages and disadvantages, are described below.

For limited defects, primary closure can be attempted provided it does not impair function or place the tissues under excess tension. Healing by secondary intention has gained resurgence in popularity as more OPSCCs are being treated with minimally invasive techniques. Several authors have reported good swallowing function, even after resection of large tumors.[9,30,31,34,39–41] Shallow defects can be reliably resurfaced with a split- or full-thickness skin grafts if placed in an adequate recipient bed.[42,43] Cicatricial scarring and relief of closure tension are alleviated by the use of a dermal graft. The graft's survival can be improved by the use of a bolster dressing and by not placing it on a previously irradiated recipient site.

The more commonly used local flaps consist of tongue rotational flaps, facial artery musculomucosal flap (FAMM), and palatal island flap. The tongue rotational flap provides enough vascularized tissue to close small to medium defects. The effect on the oral swallowing phase by harvest of this flap is unpredictable thereby limiting its use. The FAMM flap was first described by Pribaz et al.[44] and has been used for medium-sized defects of the soft palate, the tonsillar fossa, and the base of tongue with good reliability.[44–46] One-third of the patients will require a second stage to decrease bulk and improve mobility, although a harvesting modification has been proposed to exclusively utilize the FAMM in a single-stage fashion.[46] The palatal island flap is an axial flap based on the greater palatine vessels. The flap is hearty, easily accessible, and not technically challenging to harvest. It has a limited arc of rotation (which can be improved by drilling out the vascular supply) and can result in oropharyngeal narrowing.

Prior to the advent of free tissue transfer, regional flaps, including the pectoralis major flap, were the primary means of reconstructing large or through-and-through defects. The bulk of this flap, however, while occasionally helpful, is not often beneficial to functional pharyngeal reconstruction. Fasciocutaneous flaps are the most widely utilized reconstructive option for large pharyngeal defects with the two most common being the radial forearm free flap (RFFF) and anterolateral thigh (ALT) free flap due to their pliability and thickness. The RFFF is the workhorse for reconstruction in the oropharynx due to its demonstrated versatility, reliability, and ease of harvest. Simultaneous harvesting can be performed, donor site morbidity is low, and sensory reinnervation using the lateral antebrachial nerve has been well established and can improve functional outcome.[47] The ALT free flap, which is based on the branches of the lateral circumflex femoral artery in a more suitable option for larger defects where more soft tissue bulk or extensive carotid artery coverage, is needed. The harvest is more challenging than the RFFF due to the small caliber of the perforating vessels, but the donor site morbidity is low, a two-team approach can be used, and sensory reinnervation is also possible.[48] Additionally, successful inset of these flaps has been described using a transoral robotic approach, thereby obviating the need for an open approach to reconstruct these defects.[49–51]

If a bony defect is present, an osseocutaneous flap is often required for functional reconstruction. The fibula free flap, introduced by Taylor in 1978, has emerged as the most commonly used bone-containing free flap in head and neck reconstruction. It provides up to 25 cm of bone, which can support osteointegrated implants, and a skin paddle up to $10 \times 20$ cm. The thin, pliable skin can also be harvested as a sensory flap. The main limitation to the use of this flap is donor site morbidity related to vascular compromise after harvest. Careful preoperative assessment is required of the tibial arterial system. The RFFF can also be harvested with radial bone, but due to the poor bone quality and donor site morbidity, an osseocutaneuous RFFF is seldom chosen. Finally, if the lower extremity vascular supply is insufficient or if an extensive, complicated soft tissue defect exists, a scapula osseocutaneous free flap can be utilized. It can provide up to 15 cm of bone stock and can also support an independently vascularized bony segment at the tip of the scapula for simultaneous maxillary reconstruction. A large fasciocutaneous skin paddle can be included for larger defects and the donor site can be closed primarily. The major disadvantages include the complexity of the subscapular system and the inability to simultaneously harvest the flap and perform the oncologic resection.

## CONCLUSION

The changing demographics and good outcome of HPV-related oropharynx cancer and advances in minimally invasive, transoral surgical techniques have significantly impacted the therapeutic options available for this malignancy. Due to the rise of HPV-associated OPSCC, which has demonstrated improved survival and treatment response to both surgical and nonsurgical modalities, the focus has shifted from being able to cure patients to doing so in a manner that best preserves their long-term function. TLM and TORS have demonstrated excellent oncologic control for oropharyngeal neoplasms with minimal deficits in functional swallowing outcomes. There still remains a role for open surgical approaches primarily for surgical salvage or advanced-stage disease not amenable to transoral surgery or CRT. The use of free tissue transfer to repair large oropharyngeal and bony defects has greatly improved the quality of life for these patients. The ability to achieve reconstruction of the defect with a minimally invasive technique and provide sensory reinnervation with free flaps, as well as avoid the long-term sequelae of organ-preservation protocols, may further increase the role of surgery for OPSCC.

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CHAPTER 18

# Cancer of the Larynx

## PART A:
## General Principles and Management

William M. Mendenhall, and John W. Werning

Cancer of the larynx represents about 0.8% of the total cancer risk in 2010 and is one of the most common head and neck cancers.[1] In 2010 in the United States, there were approximately 12,720 new cases of cancer of the larynx (10,110 men and 2,610 women) and about 3,740 deaths from laryngeal cancer.[1] Based on 1992 to 1997 US data at diagnosis, about 51% of the cases remain localized, 29% have regional spread, and 15% have distant metastases.[2] Cancer of the larynx is strongly related to cigarette smoking. The risk of tobacco-related cancers of the upper alimentary and respiratory tracts declines among ex-smokers after 5 years and is said to approach the risk of nonsmokers after 10 years of abstention.[3] The role of alcohol in inducing laryngeal cancer remains unclear.[4] Some evidence exists that heavy marijuana smoking may be associated with laryngeal cancer in young patients. The ratio of glottic to supraglottic carcinoma is approximately 3:1.

### ANATOMY

The larynx is divided into the supraglottic, glottic, and subglottic regions. The supraglottic larynx consists of the epiglottis, the false vocal cords, the ventricles, the aryepiglottic folds, and the arytenoids. The glottis includes the true vocal cords and the anterior commissure. The subglottis is located below the vocal cords (Figs. 18-1 and 18-2).[5]

The lateral line of demarcation between the glottis and supraglottis is the apex of the ventricle. The demarcation between the glottis and subglottis is ill defined, but the subglottis is considered to begin 5 mm below the free margin of the vocal cord and to end at the inferior border of the cricoid cartilage.

The vocal cords vary from 3 to 5 mm in thickness and terminate posteriorly with their attachment to the vocal process. The mucosa between the arytenoids is called the *posterior commissure*.

The outside shell of the larynx is formed by the hyoid bone, thyroid cartilage, and cricoid cartilage; the cricoid cartilage is the only complete ring. The more mobile interior framework is composed of the heart-shaped epiglottis and the arytenoid, corniculate, and cuneiform cartilages. The corniculate and cuneiform cartilages produce small, rounded bulges at the posterior end of each aryepiglottic fold.

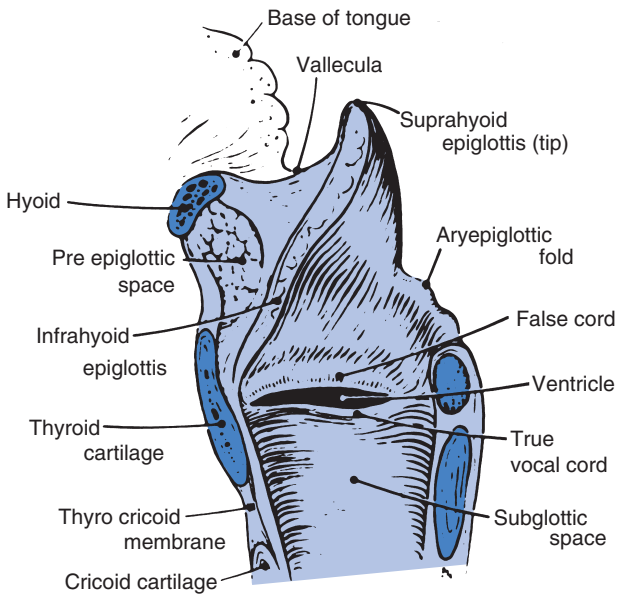



**FIGURE 18-1.** Diagrammatic sagittal section of the larynx. Note adjacency of the epiglottis to the preepiglottic space, and also note the proximity of the cephalic extent of this space to the base of the tongue. Finally, note intimate relationship of the subglottic mucosa to the cricothyroid membrane anteriorly. This is the point of exit for anterior cancers that are diverted caudally from the glottic level.

*Source:* Redrawn from Sabotta J. *Atlas der anatomie des menschen in 2 volumes.* 20th ed. Munich, Germany: Urban & Fischer Verlag; 1975 (Fig. 769), with permission.



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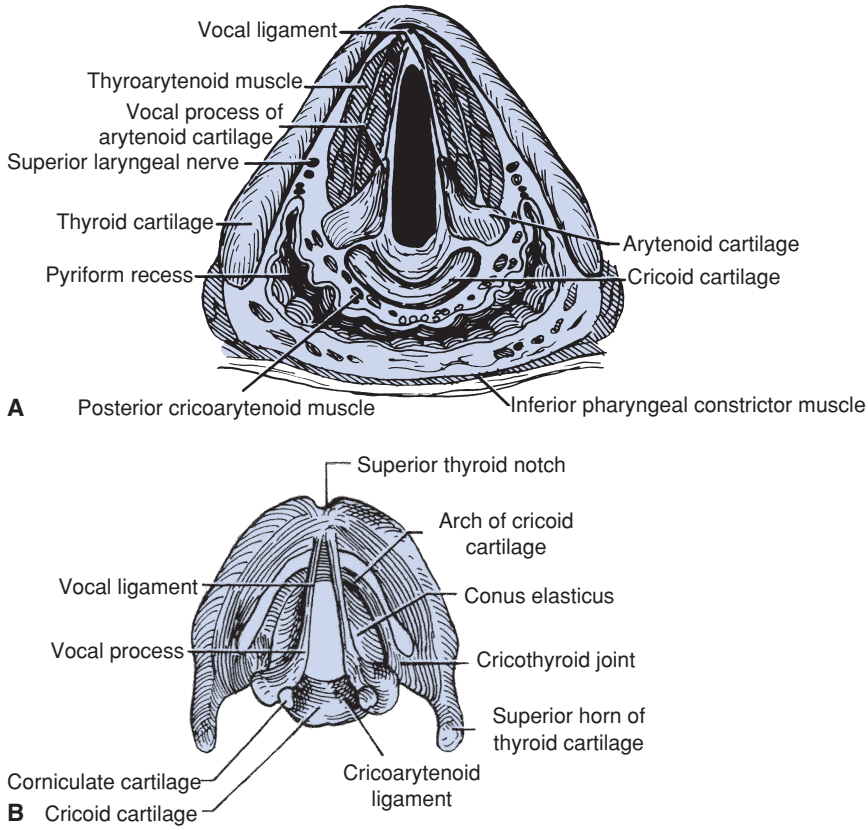



**FIGURE 18-2.** **A**: Cross-section of larynx at the level of the vocal folds. **B**: Framework of the larynx.

*Source:* Redrawn from Sabotta J. *Atlas der anatomie des menschen in 2 volumes.* 20th ed. Munich, Germany: Urban & Fischer Verlag; 1975 (**A**, Fig. 770; **B**, Fig. 761), with permission.

The thyroid and cricoid cartilages and a portion of the arytenoid cartilage are hyaline cartilage and may partially ossify with age, particularly in men. The epiglottis is elastic cartilage; ossification does not occur, and even focal calcification is rare.[6]

The external laryngeal framework is linked together by the thyrohyoid, cricothyroid, and cricotracheal ligaments or membranes (Figs. 18-3 and 18-4).[5]

The epiglottis is joined superiorly to the hyoid bone by the hyoepiglottic ligament. The epiglottis is attached to the thyroid cartilage by the thyroepiglottic ligament at a point just below the thyroid notch and above the anterior commissure. The arrangement of the ligaments that connect the cricoid and arytenoid cartilages and form the vocal ligaments, which are part of the true vocal cords, is shown in Figure 18-2B. The conus elasticus (cricovocal ligament) is the lower portion of the elastic membrane that connects the inferior framework. It connects the upper surface of the cricoid, the vocal process of the arytenoid, and the lower thyroid cartilage; its free border is thickened into the vocal ligament.

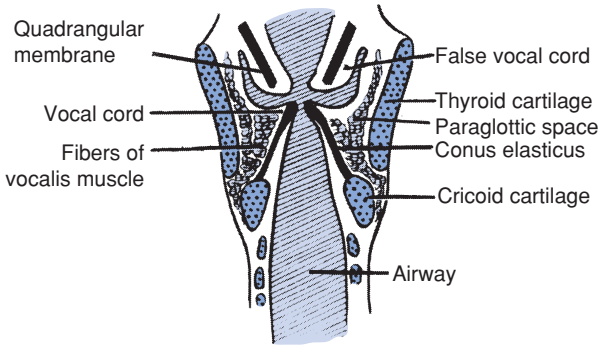



**FIGURE 18-3.** Diagram of the coronal view of the larynx. This rendition is taken through the middle one-third of the larynx, showing the fibrous barriers in both the supraglottic and the lower larynx, the intrinsic laryngeal muscles, and the thyroid and cricoid cartilages.

*Source:* Redrawn from Sabotta J. *Atlas der anatomie des menschen in 2 volumes.* 20th ed. Munich, Germany: Urban & Fischer Verlag; 1975 (Fig. 766), with permission.

The vocal ligaments and muscles attach to the vocal process of the arytenoid posteriorly and the thyroid cartilage anteriorly. The intrinsic muscles of the larynx, which primarily control the movement of the cords, are presented in Figures 18-2 and 18-3.[5] The extrinsic muscles are concerned primarily with swallowing. The cricothyroid muscle produces tension and elongation of the vocal cords and is innervated by the superior laryngeal nerve (Fig. 18-4).[5]

The preepiglottic and paraglottic fat spaces are, for practical purposes, one continuous space lying between the external framework of the thyroid cartilage and hyoid bone and the inner framework of the epiglottis and intrinsic muscles. Lam and Wong[7] showed that the thin, membranous septa located between the paraglottic and preepiglottic space are capable of holding a tumor in check to a limited degree. The space is traversed by blood vessels, lymphatic vessels, and nerves. Because few capillary lymphatics arise in this area, invasion of the fat space should only indirectly be associated with lymph node metastases. The fat space is limited by the conus elasticus inferiorly, the thyroid ala, the thyrohyoid membrane, the hyoid bone anterolaterally, the hyoepiglottic ligament superiorly, and the fascia of the intrinsic muscles on the medial side. Posteriorly, it is adjacent to the anterior wall of the pyriform sinus.

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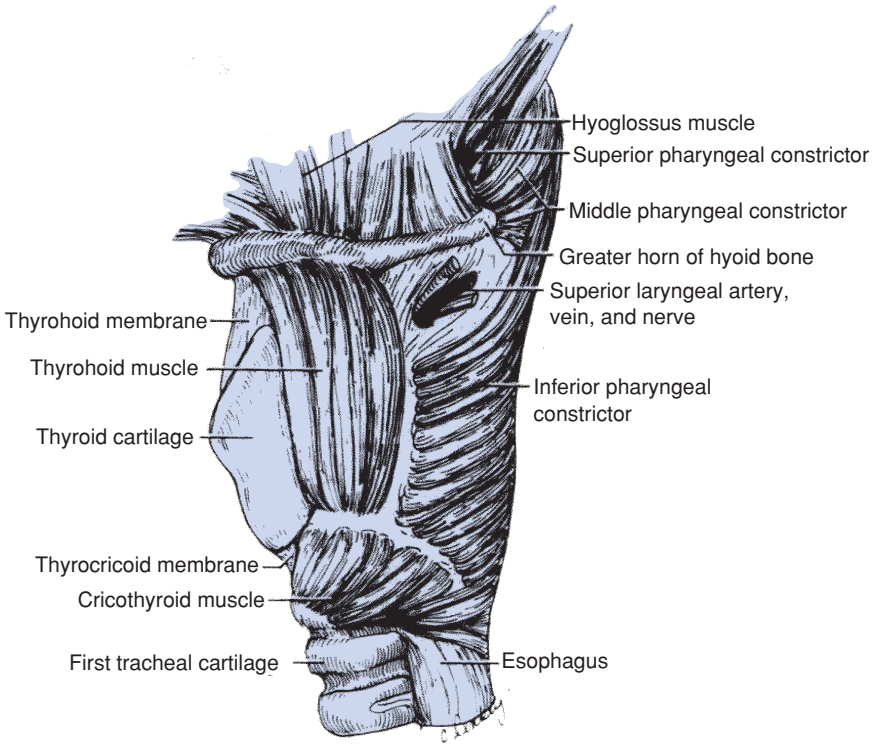



**FIGURE 18-4.** External view of the larynx.

*Source:* Redrawn from Sabotta J. *Atlas der anatomie des menschen in 2 volumes,* 20th ed. Munich, Germany: Urban & Fischer Verlag, 1975 (Fig. 744), with permission.

The laryngeal surface of the epiglottis and the free margin of the vocal cords are squamous epithelium, and the remainder is usually pseudostratified ciliated columnar epithelium. Beneath the epithelium of the free edge of the vocal cord is the lamina propria, which can be divided into three layers. There is no true submucosal layer along the free margin of the vocal fold.[8] The laryngeal arteries are branches of the superior and inferior thyroid arteries.

The intrinsic muscles of the larynx are innervated by the recurrent laryngeal nerve. The cricothyroid muscle, an intrinsic muscle responsible for tensing the vocal cords, is supplied by a branch of the superior laryngeal nerve. Isolated damage to this nerve causes a bowing of the true vocal cord; it continues to be mobile, but the voice may become hoarse.

The supraglottic structures have a rich capillary lymphatic plexus. The trunks pass through the preepiglottic space and the thyrohyoid membrane and terminate mainly in the subdigastric lymph nodes (level 2); a few drain to the middle internal jugular chain lymph nodes (level 3). There are essentially no capillary lymphatics of the true vocal cords. As a result, lymphatic spread from glottic cancer occurs only if tumor extends to supraglottic or subglottic areas. The subglottic area has relatively few capillary lymphatics. The lymphatic trunks pass through the cricothyroid membrane to the pretracheal (Delphian) lymph nodes in the region of the thyroid isthmus. The subglottic area also drains posteriorly through the cricotracheal membrane, with some trunks going to the paratracheal lymph nodes and others continuing to the inferior jugular chain (level 4).

## PATHOLOGY AND PATTERNS OF SPREAD

### Pathology

Nearly all malignant tumors of the larynx arise from the surface epithelium and therefore are squamous cell carcinoma or one of its variants. Carcinoma *in situ* occurs frequently on the vocal cords. Differentiating among dysplasia, carcinoma *in situ*, squamous cell carcinoma with microinvasion, and true invasive carcinoma is a problem that the pathologist and the clinician frequently confront. Most vocal cord carcinomas are well differentiated or moderately well differentiated. In a few cases, an apparent carcinoma and sarcoma occur together, but most of these are actually a spindle-cell carcinoma or so-called pseudosarcoma (i.e., squamous cell carcinoma with a spindle-cell stromal reaction). Verrucous carcinoma occurs in 1% to 2% of patients with carcinoma of the vocal cord. The histologic diagnosis is difficult and must correlate with the gross appearance of the lesion.

Small cell neuroendocrine carcinoma is rarely diagnosed in the supraglottic larynx, but it should be recognized because of its biologic potential for rapid growth, early dissemination, and responsiveness to chemotherapy. Minor salivary gland tumors arise from the mucous glands in the supraglottic and subglottic larynx, but they are rare.[9] Even more rare are chemodectoma, carcinoid, soft tissue sarcoma, malignant lymphoma, or plasmacytoma. Benign chondromas and osteochondromas are reported, but their malignant counterparts are rare.

### Local Spread

Although supraglottic and glottic lesions tend to remain confined to their original compartments, there is no anatomic barrier to growth from one area to the next. Glottic lesions tend to be slow growing, but as they increase in size, they extend to the supraglottic and subglottic areas. Supraglottic lesions do not often start near the vocal cords. Involvement of the cords on their external epithelial surface is a late phenomenon, but submucosal extension by way of the paraglottic area occurs earlier.

The fat space is an important avenue of submucosal tumor spread for infrahyoid epiglottis, false cord, and true vocal cord lesions. As the false cord and the true vocal cord lesions penetrate anteriorly and laterally, they encounter the tough perichondrium

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of the thyroid cartilage and may eventually be shunted by the conus elasticus (lateral cricothyroid membrane) out of the larynx via the cricothyroid space. Thyroid cartilage invasion usually occurs in the ossified section of the cartilage, commonly in the region of the anterior commissure tendon or the junction of the anterior one-fourth and the posterior three-fourths of the thyroid lamina.[10]

Fixation of the vocal cord from laryngeal cancer is usually caused by invasion or destruction of the vocal cord musculature, invasion of the cricoarytenoid muscle or joint, or, rarely, invasion of the recurrent laryngeal nerve. Perineural spread is uncommon.

## Supraglottic Larynx

***Suprahyoid Epiglottis.*** A lesion of the suprahyoid epiglottis may produce a huge exophytic mass with little tendency to destroy cartilage or spread to adjacent structures. Other lesions may infiltrate the tip and destroy cartilage. The destructive lesions tend to invade the vallecula and preepiglottic space, the lateral pharyngeal walls, and the remainder of the supraglottic larynx.

***Infrahyoid Epiglottis.*** Lesions of the infrahyoid epiglottis tend to produce irregular tumor nodules and simultaneously invade the porous epiglottic cartilage and thyroepiglottic ligament into the preepiglottic fat space and extend toward the vallecula and base of the tongue. The thick hyoepiglottic ligament is an effective tumor barrier. However, the tumor may present in the vallecula and base of tongue without involving the suprahyoid epiglottis.

Lesions of the infrahyoid epiglottis grow circumferentially to involve the false cords, aryepiglottic folds, medial wall of the pyriform sinus, and the pharyngoepiglottic fold. Invasion of the anterior commissure and cords and anterior subglottic extension usually occur only in advanced lesions. Infrahyoid epiglottic lesions that extend onto or below the vocal cords are at a high risk for thyroid cartilage invasion, even if the cords are mobile.[11]

***False Cord.*** Early false cord carcinomas, which are usually submucosal with little exophytic component, are difficult to delineate accurately. They involve the paraglottic fat space early in their development and may spread a considerable distance beneath the mucosa without producing physical signs. These carcinomas extend to the perichondrium of the thyroid cartilage quite early, but cartilage invasion is a late phenomenon. Extension to the lower portion of the infrahyoid epiglottis and invasion of the preepiglottic space are common. Submucosal extension involves the true vocal cord, which may appear normal. Vocal cord invasion is often associated with thyroid cartilage invasion. Submucosal extension to the medial wall of the pyriform sinus occurs early.

***Aryepiglottic Fold/Arytenoid.*** Early lesions of the aryepiglottic fold/arytenoid are usually exophytic. It may be difficult to decide whether the lesion started on the medial wall of the pyriform sinus or on the aryepiglottic fold. As the lesions enlarge, they extend to adjacent sites and eventually cause fixation of the larynx, which is usually a result of involvement of the cricoarytenoid muscle or joint or, rarely, invasion of the recurrent laryngeal nerve. Computed tomography (CT) may distinguish the cause of fixation. Advanced lesions invade the thyroid, the epiglottic, and the cricoid cartilages and eventually invade the pyriform sinus and postcricoid area.

## Glottic Larynx

Most lesions of the true vocal cord begin on the free margin and upper surface of the cord. When diagnosed, about two-thirds are confined to the cords, usually one cord. The anterior portion of the cord is the most common site. Anterior commissure involvement, which is common, occurs when no tumor-free cord can be seen anteriorly. Small lesions isolated to the anterior commissure account for only 1% to 2% of cases. Extension to the posterior commissure is uncommon, occurring only in advanced lesions.

Tumors at the anterior commissure may extend anteriorly via the anterior commissure tendon (Broyles' ligament)[12] into the thyroid cartilage. Kirchner,[11] using whole organ sections, showed that such extension is unusual unless the tumor extends off the vocal cord onto the base of the infrahyoid epiglottis and suggested that the tendon serves as more of a barrier than an avenue of tumor spread. Early subglottic extension is also associated with involvement of the anterior commissure, and tumor may grow through the cricothyroid membrane.

Lesions that arise on the posterior half of the vocal cord tend to extend along the submucosa toward the medial side of the vocal process and invade the cricoarytenoid joint and posterior commissure; this spread is difficult to appreciate by clinical examination.

Subglottic extension may occur by simple mucosal surface growth, but it more commonly occurs by submucosal penetration beneath the conus elasticus. One centimeter of subglottic extension anteriorly or 4 to 5 mm of subglottic extension posteriorly brings the border of the tumor to the upper margin of the cricoid, exceeding the anatomic limits for a conventional hemilaryngectomy. Lesions may spread beneath the epithelium along the length of the vocal cord within Reinke's space.[13] As vocal cord lesions enlarge, they extend to the false cord, vocal process of the arytenoid, and subglottic region. Infiltrative lesions invade the vocal ligament and muscle and eventually reach the paraglottic space and the perichondrium of the thyroid cartilage. Advanced glottic lesions eventually penetrate through the thyroid cartilage or via the cricothyroid space to enter the neck, where they may invade the thyroid gland. Lesions involving the anterior commissure often exit the larynx via the cricothyroid space after they extend subglottically.[13]

A fixed cord that is associated with a lesion having <1 cm of subglottic extension and no false cord involvement does not ordinarily indicate invasion of the thyroid cartilage.[11] If the false cord is also involved, cartilage invasion is more likely.

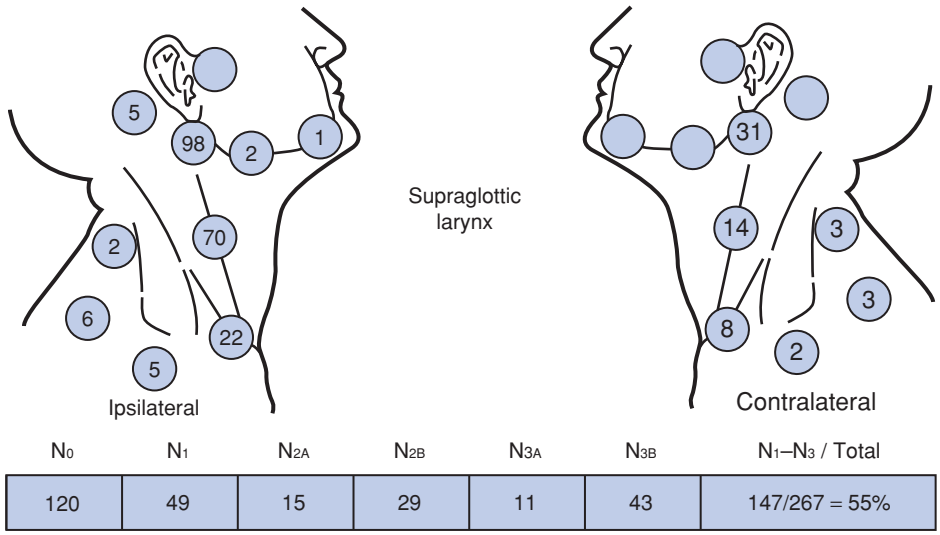
## Subglottic Larynx

Subglottic cancers are rare. Most involve the inferior surface of the vocal cords by the time they are diagnosed, so it is difficult to know whether the tumor started on the undersurface of the vocal cord or in the subglottis. Because early diagnosis is uncommon, most lesions are bilateral or circumferential at discovery. They involve the cricoid cartilages in the early stage because there is no intervening muscle layer. Partial or complete fixation of one or both cords is common; misdiagnosis or diagnostic delay is frequent.

## Lymphatic Spread

The location and stage of neck nodes detected on admission for previously untreated patients with squamous cell carcinoma of the supraglottic larynx are given in Figure 18-5.[14] The disease spreads mainly to the subdigastric nodes (level 2). The submandibular nodes (level 1b) are rarely involved, and there is only a small risk of spinal accessory lymph node (level 5) involvement. The incidence of clinically positive nodes is 55% at the time of diagnosis; 16% are bilateral.[14] Elective neck dissection shows pathologically positive nodes in 16% of cases; observation of initially node-negative necks eventually identifies the appearance of positive nodes in 33% of cases.[15,16] Spread to the pyriform sinus, the vallecula, and the base of the tongue increases the risk of

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| $N_0$ | $N_1$ | $N_{2A}$ | $N_{2B}$ | $N_{3A}$ | $N_{3B}$ | $N_1$–$N_3$ / Total |
|---|---|---|---|---|---|---|
| 120 | 49 | 15 | 29 | 11 | 43 | 147/267 = 55% |

**FIGURE 18-5.** Nodal distribution on admission, M. D. Anderson Cancer Center, 1948–1965.
*Source:* From Lindberg RD. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. *Cancer.* 1972;29: 1446–1449 (Fig. 5, p. 1449), with permission.

lymph node metastases. The risk of late-appearing contralateral lymph node metastasis is 37% if the ipsilateral neck is pathologically positive, but the risk is unrelated to whether the nodes in the ipsilateral neck were palpable before neck dissection.

In carcinoma of the vocal cord, the incidence of clinically positive lymph nodes at diagnosis approaches zero for T1 lesions and 1.7% for T2 lesions.[17] The incidence of neck metastases increases to 20% to 30% for T3 and T4 lesions. Supraglottic spread is associated with metastasis to the jugulodigastric nodes. Anterior commissure and anterior subglottic invasion are associated with involvement of the midline pretracheal lymph nodes (Delphian nodes).

Lederman[18] reported a 10% incidence of positive lymph nodes in 73 patients with subglottic carcinoma.

## CLINICAL PRESENTATION

Carcinoma arising on the true vocal cords produces hoarseness at a very early stage. Sore throat, ear pain, pain localized to the thyroid cartilage, and airway obstruction are features of advanced lesions.

Hoarseness is not a prominent symptom of cancer of the supraglottic larynx until the lesion becomes quite extensive. Pain on swallowing, usually mild, is the most frequent initial symptom, often described as a sore throat. Some patients report a sensation of a "lump in the throat." Pain is referred to the ear by way of the vagus nerve and auricular nerve of Arnold. A mass in the neck may be the first sign of a supraglottic cancer. Late symptoms include weight loss, foul breath, dysphagia, and aspiration.

## DIAGNOSTIC EVALUATION AND CLINICAL STAGING

### Physical Examination

Flexible fiberoptic endoscopes are now used routinely as a complement to the laryngeal mirror examination. The mirror gives a larger image of the larynx or the hypopharynx than that obtained by direct laryngoscopy or fiberoptic endoscopy. The mirror often provides the best view of the posterior pharyngeal wall. The flexible fiberoptic laryngoscope is inserted through the nose and is useful in more difficult cases.

Determination of the mobility of the vocal cords frequently requires multiple examinations because the subtle distinctions between mobile, partially fixed, and fixed cords are often challenging, apparently changing from examination to examination. A cord that appeared mobile to the surgeon before direct laryngoscopy may exhibit impaired motion or even fixation after biopsy. Videostroboscopy is particularly useful for assessing vocal cord mobility.

Ulceration of the infrahyoid epiglottis or fullness of the vallecula is an indirect sign of preepiglottic space invasion. Palpation of diffuse, firm fullness above the thyroid notch with widening of the space between the hyoid and the thyroid cartilage signifies invasion of the preepiglottic space. The preepiglottic fat space is a low-density area on the CT scan, and changes resulting from tumor invasion are easily seen.

Postcricoid extension may be suspected when the laryngeal click disappears on physical examination. Postcricoid tumor may cause the thyroid cartilage to protrude anteriorly, producing a fullness of the neck.

Invasion of the thyroid cartilage remains a difficult clinical diagnosis. Localized pain or tenderness to palpation or a small bulge over one ala of the thyroid cartilage is suggestive.

### Radiographic Studies

Contrast-enhanced CT scan is the method of choice for studying the larynx. The CT scan should be performed before biopsy so that abnormalities that may be caused by the biopsy are not confused with tumor. CT is preferred to magnetic resonance imaging (MRI) because the longer scanning time for MRI may result in motion artifact.[19] CT slices 1 to 2 mm thick are obtained at 1 to 2 mm intervals through the larynx and at 3 mm intervals for the remainder of the study. The gantry is angled so that the scan slices are parallel to the plane of the true vocal cords. It is also necessary to obtain a CT scan of the entire neck to detect positive, nonpalpable lymph nodes. Positive retropharyngeal nodes

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may be present at diagnosis in patients with laryngeal cancer who have advanced neck disease.[20] Retropharyngeal adenopathy is often not apparent on physical examination but is usually apparent on the CT scan.

Contrast enhancement helps to outline the blood vessels and thyroid gland. The tumor often enhances, probably because of reactive inflammatory changes. In addition to CT, MRI may be obtained to define subtle exolaryngeal spread or early cartilage destruction. The value of MRI for detecting early cartilage destruction is open to speculation. Sagittal MRI may be useful in detecting early invasion of the base of the tongue.

Positron emission tomography (PET) is not routinely obtained. It may be useful to evaluate a questionable finding on CT or MRI if that finding would alter the treatment plan. It may also be useful to determine whether or not distant metastases exist in a patient with advanced neck disease, particularly if it involves low neck below Ho's line.[21]

## Glottic Larynx

Although the CT scan does not show minimal mucosal lesions, it is excellent for determining subglottic extension and extension anterior to the anterior commissure and is used in virtually all T1 and T2 lesions for these reasons alone. CT scanning is useful in the diagnosis of moderately advanced and advanced lesions; it is excellent for demonstrating extension outside the larynx into the soft tissues of the neck and has potential for determining thyroid or cricoid cartilage invasion, which tends to occur at the edges of the cartilage rather than on the faces. Early cartilage involvement is difficult to detect with axial scans, but it may be demonstrated by coronal or sagittal scanning techniques. If the low-density plane of the paraglottic space is intact, cartilage is probably not invaded by tumor. CT is also useful for evaluating the neck. Radiographically positive adenopathy may be appreciated that would otherwise be undetectable.

## Supraglottic Larynx

The CT scan provides an excellent means for viewing the preepiglottic and paraglottic fat spaces. Soft tissue extension into the neck or base of the tongue also can be seen. The CT scan is also useful for determining extension to the subglottic areas and to evaluate the neck.[6]

## Direct Laryngoscopy

Diagnostic procedures for laryngeal cancer at the University of Florida are summarized in Figure 18-6. A CT scan is usually performed, followed by direct laryngoscopy and biopsy. The ventricles, the subglottis, the apex of the pyriform sinus, and the postcricoid area must be carefully examined because these areas are not consistently seen by indirect examinations. Fiberoptic telescopes (0 degree and 30 degrees) are introduced through the laryngoscope for inspection of these areas. Endoscopic visualization facilitates the assessment of arytenoid fixation and involvement of the laryngeal ventricle, factors which must be considered before laryngeal preservation surgery is attempted. A generous biopsy specimen is taken from the obvious lesion; additional biopsies may be obtained from suspicious areas. In cases where the lesion is limited and superficial, directed biopsies that are guided by the surface appearance of the lesion may fail to detect foci of microinvasion, resulting in sampling error; thus, excisional biopsy should be considered whenever possible. Diffuse mucosal abnormalities suspicious for premalignancy should be endoscopically excised with the $CO_2$ laser or by using cold instrument dissection

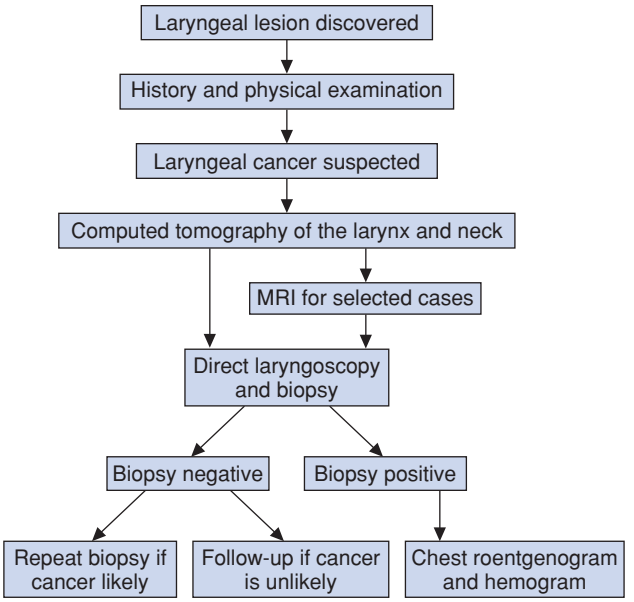



**FIGURE 18-6.** Algorithm for diagnostic evaluation of a laryngeal lesion. MRI, magnetic resonance imaging.

in lieu of crude vocal cord stripping to spare the superficial lamina propria, thereby optimizing postoperative voice quality.

## Clinical Staging

The 2010 American Joint Committee on Cancer (AJCC) staging system for laryngeal primary cancer is listed in Table 18.1.[22] T2 glottic cancers are stratified into those with normal (T2A) and impaired (T2B) vocal cord mobility. For lesions arising in the supraglottis, the sites of origin include the false cords, the aryepiglottic folds, the suprahyoid epiglottis, the infrahyoid epiglottis, the pharyngoepiglottic folds, and the arytenoids.

Only in the early T stages can one identify the specific site of origin with certainty. As the lesion enlarges, the site of origin is an educated guess based on the location of the greatest bulk of tumor. The major difference between the 1992 and 2010 staging systems is that a supraglottic cancer that invades the mucosa of the base of tongue and/or medial wall of the pyriform sinus can be staged as a T2 lesion. This has resulted in a reverse "Will Rogers effect" and negative stage migration such that the likelihood of local control for supraglottic cancer will likely be lower within each T stage while remaining the same overall. In contrast, invasion of the paraglottic space now upstages a T2 cancer to a T3. Parenthetically, we have evaluated the impact of paraglottic space invasion determined by pretreatment CT in a series of patients with T2 glottic cancers and found no significant adverse effect on local control after definitive radiotherapy (RT).[23] Additionally, T4 cancers have been stratified into T4A and T4B, which reflects the likelihood of achieving a complete resection.

# TREATMENT SELECTION: VOCAL CORD CARCINOMA

## Selection of Treatment Modality

In treating vocal cord carcinoma, the goal is cure with the best functional result and the least risk of a serious complication. Patients may be considered to be in an early group if the chance

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**TABLE 18.1 2010 American Joint Committee on Cancer Staging System for Larynx Cancer**

| Tumor Stage | Characteristics |
|---|---|
| **Supraglottis** | |
| T1 | Tumor limited to one subsite of supraglottis with normal vocal cord mobility |
| T2 | Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx |
| T3 | Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic tissues, paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex) |
| T4a | Tumor invades through the thyroid cartilage, and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus) |
| T4b | Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures |
| **Glottis** | |
| T1 | Tumor limited to vocal cord(s) (may involve anterior or posterior commissure) with normal mobility |
| T1a | Tumor limited to one vocal cord |
| T1b | Tumor involves both vocal cords |
| T2 | Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility |
| T3 | Tumor limited to the larynx with vocal cord fixation, and/or invades paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex) |
| T4a | Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus) |
| T4b | Tumor involves prevertebral space, encases carotid artery, or invades mediastinal structures |
| **Subglottis** | |
| T1 | Tumor limited to the subglottis |
| T2 | Tumor extends to vocal cord(s) with normal or impaired mobility |
| T3 | Tumor limited to larynx with vocal cord fixation |
| T4a | Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, esophagus) |
| T4b | Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures |
| **Regional Lymph Nodes (N)*** | |
| NX | Regional lymph nodes cannot be assessed N0; no regional lymph node metastasis |
| N1 | Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension |
| N2 | Metastasis in a single ipsilateral lymph node, 3–6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension |
| N2a | Metastasis in a single ipsilateral lymph node, 3–6 cm in greatest dimension |
| N2b | Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension |
| N2c | Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension |
| N3 | Metastasis in a lymph node, more than 6 cm in greatest dimension |
| **Distant Metastasis (M)** | |
| M0 | No distant metastasis |
| M1 | Distant metastasis |

**Note:* Metastases at level VII are considered regional lymph node metastases.
*Source:* American Joint Committee on Cancer. *Cancer Staging Manual.* 7th ed. New York, NY: Springer-Verlag; 2010:59–60, with permission.

of cure with larynx preservation is high, a moderately advanced group if the likelihood of local control is 60% to 70% but the chance of cure is still good, and an advanced group if the chance of cure is moderate and the likelihood of laryngeal preservation is relatively low. The early group may be treated initially by RT or, in selected cases, by partial laryngectomy. The moderately advanced group may be treated with either RT or partial laryngectomy with total laryngectomy reserved for relapse or by total laryngectomy with or without adjuvant postoperative RT. The obvious advantage of the former strategy, which we use at the University of Florida, is that there is a fairly good chance that the larynx will be preserved.[24] Although some patients may be rehabilitated with a tracheoesophageal puncture after laryngectomy, only about 20% of patients use this device long term and the majority use an electric larynx.[25] The advanced group is treated with total laryngectomy and neck dissection with or without adjuvant RT or by RT and adjuvant chemotherapy.[26] Data suggest that if patients whose tumors show a partial or complete response to two to three cycles of neoadjuvant chemotherapy are then given high-dose RT, the cure rates are comparable to those obtained with initial total laryngectomy.[27] Another less expensive and less toxic method to select patients likely to be cured by RT alone is to calculate the primary tumor volume on pretreatment CT or MR. Data indicate that primary tumor volume is inversely related to the probability of local control after irradiation.[28,29] Data indicate that whereas induction chemotherapy probably does not improve the likelihood of local–regional control and survival, concomitant chemotherapy and RT result in an improved possibility of cure compared with RT alone.[30–32] There is a subset of patients with high volume (>3.5 cc), unfavorable, advanced cancers who may be cured by chemoradiation but have a useless larynx and permanent tracheostomy and/or gastrostomy.[28] These patients are best treated with a total laryngectomy, neck dissection, and postoperative RT.

## Carcinoma *In Situ*

Lesions diagnosed as carcinoma *in situ* may sometimes be controlled by stripping the cord. However, it is difficult to exclude the possibility of microinvasion on these specimens. Recurrence is frequent, and the cord may become thickened and the voice hoarse with repeated stripping. Localized carcinoma *in situ* can also be excised using the $CO_2$ laser.

Early RT for carcinoma *in situ* often means a better chance of preserving a good voice, especially since many patients with this diagnosis eventually receive this treatment.[33]

Many patients with a diagnosis of carcinoma *in situ* have obvious lesions that probably contain invasive carcinoma. We have often proceeded with RT rather than put the patient through a repeated biopsy procedure.

## Early Vocal Cord Carcinoma

In most centers, RT is the initial treatment prescribed for T1 and T2 lesions, with surgery reserved for salvage after RT failure[34–36] (Fig. 18-7). Although hemilaryngectomy or cordectomy produces comparable cure rates for selected T1 and T2 vocal cord lesions, RT is generally preferred.[34,37] Supracricoid laryngectomy, as reported by Laccourreye et al.,[38] is a procedure designed to remove moderate-sized cancers involving the supraglottic and the glottic larynx. The larynx may be removed with preservation of the cricoid and the arytenoid with its neurovascular innervation, the defect is closed by approximating the base of the tongue to the remaining larynx. The oncologic and functional results of this procedure in selected patients are reported to be excellent. Transoral laser excision also may provide high cure rates for select patients with small, well-defined lesions limited to the mid-third of one true cord.[39–43]

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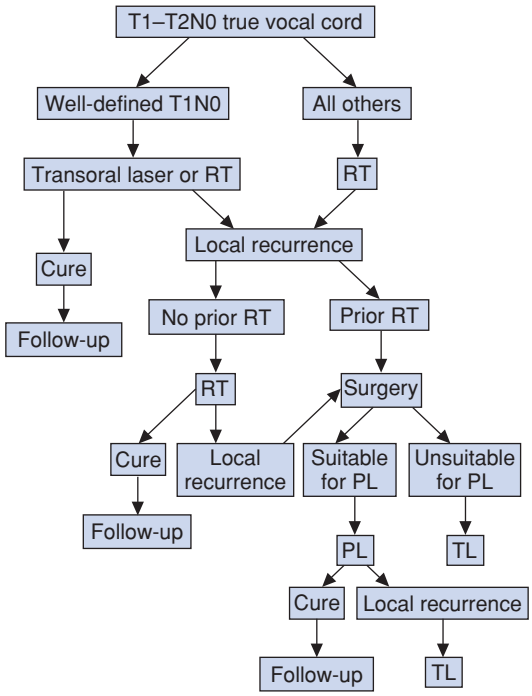



**FIGURE 18-7.** Treatment algorithm for T1–T2N0 squamous cell carcinoma of the true vocal cord. RT, radiation therapy; PL, partial laryngectomy; TL, total laryngectomy.

A small subset of transoral laser surgeons successfully use this technique in moderately advanced cancers.[34] The major advantage of RT compared with partial laryngectomy is better quality of the voice. Partial laryngectomy finds its major use as salvage surgery in suitable cases after RT failure. Even if the patient has a local recurrence after salvage partial laryngectomy, there is a third chance with total laryngectomy, which may still be successful.

Verrucous lesions have the reputation of being unresponsive to RT and, in some instances, converting into invasive, often anaplastic, metastasizing lesions. Partial laryngectomy is recommended for early verrucous carcinoma of the glottis, but RT is recommended if the alternative is total laryngectomy. We have observed typical verrucous lesions that have disappeared with RT and not recurred. O'Sullivan and associates[44] also have made this observation. Additionally, a variety of tumors that recur after unsuccessful treatment (with surgery, RT, and/or chemotherapy) are more likely to exhibit more aggressive behavior.

## Moderately Advanced Vocal Cord Cancer

Fixed-cord lesions (T3) may be subdivided into relatively favorable or unfavorable lesions. Patients with unfavorable lesions usually have extensive bilateral disease with a compromised airway and are considered to be in the advanced group. Patients with favorable T3 lesions have disease that is low volume (≤3.5 cc), confined mostly to one side of the larynx, have a good airway, and are reliable for follow-up. Some degree of supraglottic and subglottic extension usually exists. The extent of disease and tumor volume, in particular, are related to the likelihood of control after RT.[28]

The patient with a favorable lesion is advised of the alternatives of RT with surgical salvage or immediate total laryngectomy; the occasional patient may be suitable for a partial laryngectomy. Data suggest that the likelihood of local–regional control is better after some altered fractionation schedules compared with conventional once-daily RT.[32,45] Follow-up examinations are recommended every 4 to 6 weeks for the first year, every 6 to 8 weeks for the second year, every 3 months for the third year, every 6 months for the fourth and fifth years, and annually thereafter. The patient must understand that total laryngectomy may be recommended purely on clinical grounds without biopsy-proven recurrence and that the risk of laryngeal osteochondronecrosis is about 5%.

Evaluation of cord mobility after 50.4 Gy or at the end of RT has not been helpful in predicting local control.[29] Some patients in whom the vocal cord remained fixed have had local tumor control of the disease for 2 years or longer after RT.

The major difficulty in using RT for the more advanced lesions is distinguishing radiation edema from local recurrence during follow-up examinations.[46] Progressive laryngeal edema, persistent throat pain, or fixation of a previously mobile vocal cord frequently signifies recurrent disease in the larynx, although a few patients with these findings remain disease free with long-term follow-up.

Partial laryngectomy has been used by a few surgeons in the treatment of well-lateralized fixed-cord lesions. A permanent tracheostomy is usually required because a portion of the cricoid is resected, but a useful voice may be retained.[47]

## Advanced Vocal Cord Carcinoma

Advanced lesions usually show extensive subglottic and supraglottic extension, bilateral glottic involvement, and invasion of the thyroid, cricoid, and/or arytenoid cartilages.[10,48] The airway is compromised, necessitating a tracheostomy at the time of direct laryngoscopy in approximately 30% of patients. Clinically positive lymph nodes are found in about 25% to 30% of patients.

The mainstay of treatment is total laryngectomy, with or without adjuvant RT. The most frequent sites of local failure after total laryngectomy are the tracheal stoma, the base of tongue, the neck lymph nodes, and/or soft tissues of the neck. If the neck is clinically negative before surgery and if postoperative RT is planned, neck dissection may be withheld and RT may be used to treat both sides of the neck. However, in practice, most surgeons prefer to perform elective bilateral selective (levels II–IV) neck dissections in conjunction with a total laryngectomy for T3N0 or T4N0 laryngeal cancer, even if postoperative RT is planned. If the lymph nodes are clinically positive, a therapeutic neck dissection is performed at the time of laryngectomy.

The indications for postoperative RT include close or positive margins, significant subglottic extension (1 cm or more), cartilage invasion, perineural invasion, endothelial-lined space invasion, extension of the primary tumor into the soft tissues of the neck, multiple positive neck nodes, extracapsular extension, and control of subclinical disease in the opposite neck.[49,50] Preoperative RT is indicated for patients who have fixed neck nodes, have had an emergency tracheotomy through tumor, or have direct extension of tumor involving the skin.

Definitive RT is prescribed for the patient who refuses total laryngectomy or is medically unsuitable for major surgery.

As previously stated, there is evidence that two to three cycles of induction chemotherapy followed by RT in patients obtaining at least a partial response may provide a moderate likelihood of larynx preservation without compromising cure.[27] Data suggest that concomitant chemotherapy and RT is more efficacious than RT alone or induction chemotherapy followed by RT.[30,31] The optimal combination of concomitant chemotherapy and irradiation is unclear.[32]

A randomized intergroup trial (RTOG 91-11) compared three treatment arms: Arm A, three cycles of induction cisplatin and fluorouracil followed by RT in complete and partial responders; Arm B, RT and concomitant cisplatin (100 mg/m$^2$ on days 1, 22, and 43 of RT); and Arm C, once-daily RT (70 Gy in 35 fractions over 7 weeks) alone.[30] Five hundred forty-seven patients were

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randomized and followed for a median of 3.8 years; 518 patients were evaluable. The rates of larynx preservation were: Arm A, 72%; Arm B, 84%; and Arm C, 67%. The rates of larynx presentation were significantly improved for Arm B; there was no significant difference between Arm A and Arm C. The 5-year survival rates were similar for the three treatment groups: Arm A, 55%; Arm B, 54%; and Arm C, 56%. The likelihood of developing distant metastases was lower for the two groups of patients that received adjuvant chemotherapy.

# TREATMENT SELECTION: SUPRAGLOTTIC LARYNX CARCINOMA

## Selection of Treatment Modality

Patients with supraglottic laryngeal carcinoma may be considered to be in an early or favorable group suitable for RT or conservation laryngectomy or an unfavorable group often requiring total laryngectomy (Fig. 18-8).

## Early and Moderately Advanced Supraglottic Lesions

Treatment of the primary lesion for the early group is by RT or supraglottic laryngectomy, with or without adjuvant RT.[51] Transoral laser excision is effective in experienced hands for selected lesions and is currently preferred to open approaches by many surgeons.[40] Total laryngectomy is rarely indicated as the initial treatment for this group of patients and is reserved for treatment failures.

RT and partial laryngectomy are highly successful modes of therapy for early lesions.[51] Approximately 50% of supraglottic laryngectomies performed at the University of Florida have been

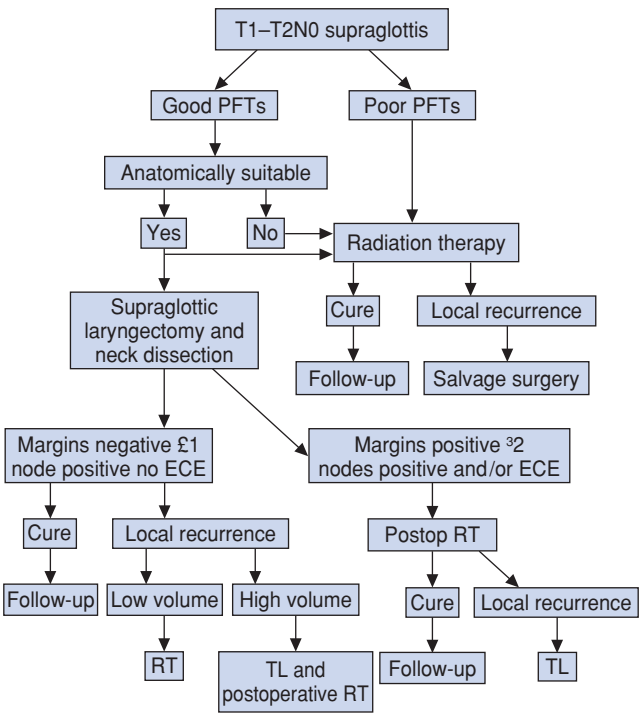



**FIGURE 18-8.** Treatment algorithm for T1–T2N0 squamous cell carcinoma of the supraglottis. PFTs, pulmonary function tests; ECE, extracapsular extension; RT, radiation therapy; TL, total laryngectomy.

followed by postoperative RT because of neck disease and, less often, positive margins.

The decision to use RT or supraglottic laryngectomy depends on several factors including the anatomic extent of the tumor, medical condition of the patient, philosophy of the attending physician(s), and the inclination of the patient and the family. Overall, about 80% of patients are treated initially by RT. Approximately half of the patients seen in our clinic whose lesions are technically suitable for a supraglottic laryngectomy are not suitable for medical reasons (e.g., inadequate pulmonary status or other major medical problems); these patients are treated with RT.

Analysis of local control by anatomic site within the supraglottic larynx shows no obvious differences in local control by RT for similarly staged lesions. Invasion of the preepiglottic space is not a contraindication to supraglottic laryngectomy or RT. Primary tumor volume based on pretreatment CT is inversely related to local tumor control after RT.[28] A large, bulky (>6 cc) infiltrative lesion, especially one with extensive preepiglottic space invasion, is a common reason to select supraglottic laryngectomy.

The status of the neck often determines the selection of treatment of the primary lesion. Patients with clinically negative neck nodes have a high risk for occult neck disease and may be treated by RT or supraglottic laryngectomy and bilateral selective neck dissections (levels II–IV).

If a patient has an early-stage primary lesion but advanced neck disease (N2b or N3), combined treatment is frequently necessary to control the neck disease.[26] In these cases, the primary lesion is usually treated by definitive RT, with surgery added to the treatment of the involved neck site(s). If the same patient were treated with supraglottic laryngectomy, neck dissection, and postoperative RT, the portals would unnecessarily cover the primary site and the neck. If the patient has early, resectable neck disease (N1 or N2a) and surgery is elected for the primary site, postoperative RT is added only because of unexpected findings (e.g., positive margins, multiple positive nodes, or extracapsular extension). Patients who have positive margins at the primary site after a partial laryngectomy should not have been treated surgically; the postoperative RT dose to the remaining larynx is likely to result in major complications requiring a permanent tracheostomy and/or gastrostomy. The usual indurations for postoperative RT are related to neck disease. The remaining larynx is treated to 55.8 Gy at 1.8 Gy per fraction and the involved neck is boosted to a higher dose as needed.[52]

## Advanced Supraglottic Lesions

Although a subset of these patients may be suitable for a supraglottic or supracricoid laryngectomy, total laryngectomy is the main surgical option. Selected advanced lesions, especially those that are mainly exophytic, may be treated by RT and concomitant chemotherapy[31] with total laryngectomy reserved for RT failures.

For patients whose primary lesion is to be treated by a total or partial laryngectomy and who have resectable neck disease, surgery is the initial treatment, and postoperative RT is added if needed. In practice, virtually all patients undergoing a total laryngectomy as the initial step in treatment have very advanced disease and require postoperative RT. If the neck disease is unresectable, preoperative RT is used. The indications for preoperative and postoperative RT have been previously outlined.

# RESULTS OF TREATMENT

## Vocal Cord Cancer

The local control and survival rates after treatment of early-stage glottic carcinoma are depicted in Tables 18.2–18.5.[34] Sengupta et al. recently reported on 37 patients treated at the University

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**TABLE 18.2 Local Control after Transoral Laser Excision For $T_{1s}$–$T_2$ Glottic Carcinoma**

| Study | Follow-up[a] | Number of Patients | Stage | Local Control (Interval) | Local Control with Larynx Preservation (Interval) | Ultimate Local Control (Interval) |
|---|---|---|---|---|---|---|
| Steiner (1993)[40] | Median, 78 mo | 159 | pTis–pT2 | 94% (NS) | 99% (NS) | — |
| Rudert and Wiener (1995)[69] | Mean, 40 mo | 8 | pTis | 100% (NS) | — | — |
| | | 88 | pT1a | 92% (NS) | | — |
| | | 10 | pT1b | 80% (NS) | | — |
| | | 8 | pT2 | 88% (NS) | | — |
| | | 114 | pTis–pT2 | — | 96% (NS) | — |
| Peretti et al. (2000)[70] | Mean, 76 mo | 21 | pTis | 81% (NS) | — | 95%[b] (5 yr) |
| | | 96 | pT1 | 82% (NS) | — | 87%[b] (5 yr) |
| | | 23 | pT2 | 74% (NS) | — | 91%[b] (5 yr) |
| | | 140 | pTis–pT2 | 80% (NS) | 97% (NS) | — |
| Spector et al. (1999)[71] | Minimum, 3 yr | 61 | T1 | 77% (NS) | 90% (NS) | 98% (NS) |
| Motta et al. (1997)[72] | Minimum, 5 yr | 321 | T1 | 82%[b] (NS) | 89%[c] (NS) | — |
| | | 158 | T2 | 60%[b] (NS) | ~67%[c] (NS) | — |
| Gallo et al. (2002)[73] | Minimum, 3 yr | 12 | Tis | 100% (NS) | 100% (NS) | — |
| | | 120 | T1a | 94% (NS) | 100% (NS) | — |
| | | 24 | T1b | 91% (NS) | 100% (NS) | — |
| Pradhan et al. (2003)[74] | Minimum, 18 mo | 52 | T1a | 90% (NS) | 94% (NS) | — |
| | | 17 | T1b | 65% (NS) | 88% (NS) | — |
| | | 13 | T2 | 77% (NS) | 92% (NS) | — |

NS, not stated.

[a] Follow-up period for total number of patients.

[b] Ultimate local control with laser alone.

[c] Local–regional control rates.

*Source:* From Mendenhall WM, Werning JW, Hinerman RW, et al. Management of T1–T2 glottic carcinomas *Cancer.* 2004;100:1786–1792, with permission.

**TABLE 18.3 Local Control after Open Partial Laryngectomy for $T_1$–$T_2$ Glottic Carcinoma**

| Study | Follow-up[a] | Number of Patients | Stage | Local Control (Interval) | Local Control with Larynx Preservation (Interval) | Ultimate Local Control (Interval) |
|---|---|---|---|---|---|---|
| Giovanni et al. (2001)[75] | NS | 62 | T1 | 100% (NS) | 100% (NS) | — |
| | | 65 | T2 | 92% (NS) | 92% (NS) | — |
| Crampette et al. (1999)[76] | Minimum, 3 yr | 18 | T1a | 100% (NS) | — | — |
| | | 40 | T1b | 95% (NS) | — | — |
| | | 23 | T2a | 83% (NS) | — | — |
| Thomas et al. (1994)[77] | Median, 6.6 yr | 159 | Tis–T1 | 93% (5 yr) | 94% (NS) | 100% (NS) |
| Laccourreye et al. (1994)[78] | Minimum, 3 yr | 295 | T1 | 89% (NS) | — | — |
| | | 90 | T2a | 74% (NS) | — | — |
| | | 31 | T2b | 68% (NS) | — | — |
| | | 416 | T1–T2b | 84% (NS) | — | 97% (NS) |
| Spector et al. (1999)[71] | Minimum, 3 yr | 404 | T1 | 92% (NS) | 93% (NS) | 99% (NS) |
| Spector et al. (1999)[79] | Minimum, 5 yr | 71 | T2 | 93% (NS) | 93% (NS) | 99% (NS) |

NS, not stated.

[a] Follow-up period for total number of patients.

*Source:* From Mendenhall WM, Werning JW, Hinerman RW, et al. Management of T1–T2 glottic carcinomas *Cancer.* 2004;100:1786–1792, with permission.



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**TABLE 18.4 Local Control after Radiotherapy for $T_{1s}$–$T_2$ Glottic Carcinoma**

| Study | Follow-up[a] | Number of Patients | Stage | Local Control (Interval) | Local Control with Larynx Preservation (Interval) | Ultimate Local Control (Interval) |
|---|---|---|---|---|---|---|
| Mendenhall et al. (2001)[35] | Minimum, 2 yr | 230 | T1a | 94% (5 yr) | 95% (5 yr) | 98% (5 yr) |
| | Median, 9.9 yr | 61 | T1b | 93% (5 yr) | 95% (5 yr) | 98% (5 yr) |
| | | 146 | T2a | 80% (5 yr) | 82% (5 yr) | 96% (5 yr) |
| | | 82 | T2b | 72% (5 yr) | 76% (5 yr) | 96% (5 yr) |
| Wang (1997)[80] | NS | 665 | T1 | 93% (5 yr) | — | — |
| | | 145 | T2a | 77% (5 yr) | — | — |
| | | 92 | T2b | 71% (5 yr) | — | — |
| Le et al. (1997)[81] | Median, 9.7 yr | 315 | T1 | 85% (5 yr) | — | 96%[b] (5 yr) |
| | | 83 | T2 | 70% (5 yr) | — | 91%[b] (5 yr) |
| Warde et al. (1998)[82] | Median, 6.8 yr | 403 | T1a | 91% (5 yr) | — | — |
| | | 46 | T1b | 82% (5 yr) | — | — |
| | | 286 | T2 | 69% (5 yr) | — | — |
| Garden et al. (2003)[83] | Median, 6.8 yr | 114 | T2a | 74% (5 yr) | — | — |
| | | 116 | T2b | 70% (5 yr) | — | — |
| | | 230 | T2 | 72% (5 yr) | — | 91% (5 yr) |

NS, not stated.

[a] Follow-up period for total number patients.

[b] Local–regional control rates.

*Source:* From Mendenhall WM, Werning JW, Hinerman RW, et al. Management of T1–T2 glottic carcinomas *Cancer.* 2004;100:1786–1792, with permission.

**TABLE 18.5 Survival Data for $T_{1s}$–$T_2$ Glottic Carcinoma**

| | | | | | Survival Rate (%) | |
|---|---|---|---|---|---|---|
| Study | Treatment | Follow-up[a] | Number of Patients | Stage | Cause-Specific Survival (Interval) | Absolute Survival (Interval) |
| Spector et al. (1999)[71] | Laser | Minimum, 3 yr | 61 | T1 | 95% (5 yr) | 84% (5 yr) |
| Steiner (1993)[40] | Laser | Median, 6.5 yr | 159 | pTis–T2 | 100% (5 yr) | 87% (5 yr) |
| Peretti et al. (2000)[70] | Laser | Mean, 6.3 yr | 140 | pTis–T2 | 98% (5 yr) | 93% (5 yr) |
| Spector et al. (1999)[71] | OPL | Minimum, 3 yr | 404 | T1 | 97% (5 yr) | 84% (5 yr) |
| Thomas et al. (1994)[77] | OPL | Median, 6.6 yr | 159 | Tis–T1 | — | 84% (5 yr) |
| Spector et al. (1999)[79] | OPL | Minimum, 5 yr | 71 | T2 | — | ~92% (5 yr) |
| Mendenhall et al. (2001)[35] | RT | Minimum, 2 yr | 230 | T1a | 98% (5 yr) | 82% (5 yr) |
| | | Median, 9.9 yr | 61 | T1b | 98% (5 yr) | 79% (5 yr) |
| | | | 146 | T2a | 95% (5 yr) | 77% (5 yr) |
| | | | 82 | T2b | 90% (5 yr) | 77% (5 yr) |
| Le et al. (1997)[81] | RT | Median, 9.7 yr | 315 | T1 | 96% (10 yr) | 65% (10 yr) |
| | | | 83 | T2 | 91% (10 yr) | 63% (10 yr) |
| Wang (1997)[80] | RT | NS | 665 | T1 | 98% (5 yr) | — |
| | | | 145 | T2a | 92% (5 yr) | — |
| | | | 92 | T2b | 84% (5 yr) | — |
| Garden et al. (2003)[83] | RT | Median, 6.8 yr | 230 | T2 | 92% (5 yr) | 73% (5 yr) |

OPL, open partial laryngectomy; RT, radiotherapy; NS, not stated.

[a] Follow-up period for total number of patients.

*Source:* From Mendenhall WM, Werning JW, Hinerman RW, et al. Management of T1–T2 glottic carcinomas *Cancer.* 2004;100:1786–1792, with permission.



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**TABLE 18.6 Stage T3 Fixed Cord Glottic Carcinoma Treated with Irradiation Alone (No Chemotherapy)**

| Investigator | Institution | Number of Patients | Minimum Follow-up (yr) | Local Control (%) | Ultimate Control after Salvage Surgery (%) |
|---|---|---|---|---|---|
| Harwood et al. (1980)[84] | Princess Margaret (Toronto) | 112 | 3 | 51 | 77 |
| Wang (1987)[85] | Mass. General (Boston) | 70 | 4 | 36 | 57 |
| Fletcher et al. (1969)[86] | M.D. Anderson (Houston) | 17 | 2 | 77 | No data |
| Skolyszewski and Reinfuss (1981)[87] | 15 European Centers | 91 | 3 | 50 | No data |
| Stewart et al. (1975)[88] | Manchester (England) | 67 | 10 | 57 | 67 |
| Mills (1979)[89] | Cape Town, South Africa | 18 | 2 | 44 | 78 |
| Mendenhall et al. (1997)[29] | U. Florida (Gainesville) | 75 | 2 | 63 | 86 |

*Source:* Modified from Parsons JT, Mendenhall WM, Mancuso AA, et al. Twice-a-day radiotherapy for T3 squamous cell carcinoma of the glottic larynx. *Head Neck.* 1989;11:123–128, with permission.

of Florida with definitive RT for carcinoma *in situ* and observed the following 5-year outcomes: local control, 91%; local control with larynx preservation, 91%; and ultimate local control, 91%.[33] Chera et al. reported on 585 patients at the University of Florida for T1 to T2N0 glottic carcinoma and observed the following 5-year local control rates: T1A1, 95%; T1B, 94%; T2A, 81%; and T2B, 74%.[36] Hinerman et al. recently reported an update of the University of Florida experience treating fixed cord T3 glottic cancers with definitive RT and reported a 5-year local control rate after RT of 63%.[24] The local control and survival rates are similar for transoral laser excision, open partial laryngectomy, and RT. Larynx preservation rates are also comparable. Voice quality depends on the amount of tissue removed with partial laryngectomy and is probably similar for patients with limited lesions treated with transoral laser resection to those undergoing RT and poorer for patients undergoing open partial laryngectomy.[34]

Foote and coworkers[53] reported on 81 patients who underwent laryngectomy for T3 cancers at the Mayo Clinic between 1970 and 1981. Seventy-five patients underwent a total laryngectomy and 6 underwent a near-total laryngectomy; 53 patients received a neck dissection. No patient underwent adjuvant RT or chemotherapy. The 5-year rates of local-regional control, cause-specific survival, and absolute survival were 74%, 74%, and 54%, respectively. The results of definitive RT for patients with fixed cord T3 glottic carcinoma are depicted in Table 18.6[54] and are similar to the surgical outcomes reported by Foote et al.[53]

The survival and control rates of patients with T3 fixed-cord lesions treated at the University of Florida are presented in Table 18.7.[55] There was no relationship between subsequent local control and whether the vocal cord remained fixed or became mobile during irradiation. The incidence of severe complications, including those after the initial treatment and any later salvage procedures, was 15% after RT alone and 15% after surgery alone or combined with adjuvant irradiation. The vocal quality varied from fair to nearly normal.

The results of treatment of T4 vocal cord carcinoma in four surgical series and two definitive RT series are summarized in Table 18.8.[56] Hinerman et al. observed an 81% 5-year local control rate in 22 selected patients with favorable T4 cancers treated with definitive RT at the University of Florida.[24] Parsons and coworkers[57] reviewed the literature and reported a local control rate of 62% in a series of 87 patients treated with RT alone for T4 glottic carcinoma.

## Supraglottic Cancer

The proportion of patients suitable for a supraglottic laryngectomy is depicted in Table 18.9.[51] Depending on the referral patterns, a modest subset of patients is suitable for this operation.

**TABLE 18.7 T3 Glottic Fixed Cord Carcinoma Treated at the University of Florida, 1965–1988: 5-Year Results**

| Parameter | Radiotherapy Alone (53 Patients) | Surgery with or without Adjuvant RT (65 Patients) |
|---|---|---|
| Local–regional control | 62% | 75% |
| Ultimate local–regional control | 84% | 82% |
| Absolute survival | 55% | 45% |
| Cause-specific survival | 75% | 71% |

RT, radiotherapy.

*Source:* Data from Mendenhall WM, Parsons JT, Stringer SP, et al. Stage T3 squamous cell carcinoma of the glottic larynx: a comparison of laryngectomy and irradiation. *Int J Radiat Oncol Biol Phys.* 1992;23:725–732, with permission.

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**TABLE 18.8 Treatment of Stage T4 Glottic Carcinomas**

| Investigator | Tumor Stage | Number of Patients | Method of Treatment | Results (NED) |
|---|---|---|---|---|
| Jesse (1975)[90] | T4N0-N+ | 48 | Laryngectomy | 54% at 4 yr |
| Ogura et al. (1975)[91] | T4N0 | 11 | Laryngectomy | 45% at 3 yr |
| Skolnik et al. (1975)[92] | T4N0 | 7 | Laryngectomy | 30% at 5 yr |
| Vermund (1970)[93] | T4N0 | 31 | Laryngectomy | 35% at 5 yr |
| Stewart and Jackson (1975)[94] | T4N0 | 13 | Radiotherapy with surgery for salvage | 38% at 5 yr |
| Harwood et al. (1981)[56] | T4N0 | 56 | Radiotherapy with surgery for salvage | 49% at 5 yr[a] |

NED, no evidence of disease

[a] Life-table method; uncorrected for deaths from intercurrent disease.

*Source:* Modified from Harwood AR, Beal FA, Cummings BJ, et al. T4N0M0 glottic cancer: an analysis of dose-time-volume. *Int J Radiat Oncol Biol Phys.* 1981;7:1507–1512, with permission.

The extent of neck disease for patients treated with either surgery or RT is shown in Table 18.10.[51] In general, patients treated with supraglottic laryngectomy appropriately have earlier stage neck disease and would be anticipated to have a lower risk of distant failure and improved survival. The local control rates after transoral laser, RT, and open supraglottic laryngectomy are summarized in Tables 18.11–18.13.[51] In general, the local control rates after transoral laser excision are fairly good for patients with T1 to T2 tumors and tend to deteriorate for those with more advanced disease. The local control rate for patients selected for open supraglottic laryngectomy are excellent. However, the incidence of severe complications tends to be higher after supraglottic laryngectomy compared with RT and transoral laser excision (Table 18.14).[51,58]

## Radiation Therapy Sequelae

The acute reactions from the treatment of early vocal cord cancer using a tumor dose of 2.25 Gy per day to administer a total dose 63 Gy (4 MV or 6 MV photons, five fractions per week) are relatively mild. During the first 2 to 3 weeks, the voice may improve as the tumor regresses. The voice generally becomes hoarse again because of RT-induced changes, even though the tumor continues to regress. A mild sore throat develops beginning at the end of the second week, but medication is usually not required. The voice begins to improve approximately 3 weeks after completion of treatment, usually reaching a plateau in 2 to 3 months. Patients with extensive lesions often recover a normal voice, although not as frequently as those with small tumors.

Edema of the larynx is the most common sequela after RT for glottic or supraglottic lesions. The rate of clearance of the edema is related to the RT dose, volume of tissue irradiated, addition of a neck dissection, continued use of alcohol and tobacco, and the

**TABLE 18.9 Proportion of Patients Suitable for Supraglottic Laryngectomy**

| Series | Number of Patients | Number and Percentage with Supraglottic Laryngectomy |
|---|---|---|
| Ogura et al. (1975)[95] | 263 | 177 (67%) |
| Lutz et al. (1990)[96] | 202 | 72 (36%) |
| Lee et al. (1990)[52] | 404 | 60 (15%) |
| Weems et al. (1987)[97] | 195 | 30 (15%) |
| Gregor et al. (1996)[98] | 89 | 26 (29%) |
| Spriano et al. (1997)[99] | 257 | 38 (14%) |

*Note:* Some figures were estimated as closely as possible to fit table format if the information was not specifically stated in the cited reference.

*Source:* Hinerman RW, Mendenhall WM, Amdur RJ, et al. Carcinoma of the supraglottic larynx: treatment results with radiotherapy alone or with planned neck dissection. *Head Neck.* 2002;24:456–467, with permission.

**TABLE 18.10 Supraglottic Carcinoma: Extent of Neck Disease Versus Treatment**

| Series | Treatment | Number of Patients | Extent of Neck Disease |
|---|---|---|---|
| Bocca (1991)[100] | SGL | 537 | 94% N0–N1 |
| Isaacs et al. (1998)[101] | SGL | 39 | 74% N0–N1 |
| Ogura et al. (1975)[91] | SGL | 177 | 77% N0 |
| Davis et al. (1991)[102] | Laser | 14 | 93% N0 |
| Zeitels et al. (1994)[103] | Laser | 45 | 100% N0 |
| Rudert et al. (1999)[104] | Laser | 34 | 82% N0–N1 |
| Ghossein et al. (1974)[105] | Radiation | 203 | 53% N0 |
| Hinerman et al. (2002)[51] | Radiation | 274 | 54% N0 |

SGL, supraglottic laryngectomy.

*Note:* Some figures were estimated as closely as possible to fit table format if the information was not specifically stated in the cited reference.

*Source:* Hinerman RW, Mendenhall WM, Amdur RJ, et al. Carcinoma of the supraglottic larynx: Treatment results with radiotherapy alone or with planned neck dissection. *Head Neck.* 2002;24:456–467, with permission.

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## TABLE 18.11 Supraglottic Larynx: Local Control after Transoral Laser Excision

| Series | Staging | Number of Patients | Percentage of Patients with T1 or T2 Tumors | Local Control | | | |
|---|---|---|---|---|---|---|---|
| | | | | T1 | T2 | T3 | T4 |
| Davis et al. (1991)[102] | P | 14 R | 57 | 100% | 100% | 50% | — |
| Steiner (1993)*[40] | P | 81 R | 72 | — | 76% | 77% | 100% |
| Zeitels et al. (1994)[103] | ND | 22 | 100 | 100% | 100% | — | — |
| Zeitels et al. (1994)[103] | ND | 23 R | 65 | 100% | 92% | 63% | — |
| Csanády et al. (1999)[106] | ND | 23 | 100 | 70%† | | — | — |
| Rudert et al. (1999)[104] | P | 34 R | 50 | 100% | 75% | 78% | 38% |

*51 glottic and 30 supraglottic.

†Overall local control rates for T1 and T2.

## TABLE 18.12 Supraglottic Larynx: Local Control after Radiotherapy

| Series | Institution | Number of Patients | T1 | T2 | T3 | T4 |
|---|---|---|---|---|---|---|
| Fletcher and Hamberger (1974)[107] | M.D. Anderson Hospital | 173 | 88% | 79% | 62% | 47% |
| Ghossein et al. (1974)[105] | Fondation Curie | 203 | 94% | 73% | 46%[a] | 52% |
| Wang and Montgomery (1991)[108] | Massachusetts General Hospital | 229 q.d. | 73% | 60% | 54% | 26% |
| | | 209 b.i.d. | 89% | 89% | 71% | 91% |
| Nakfoor et al. (1998)[109] | Massachusetts General Hospital | 164 | 96% | 86% | 76% | 43% |
| Sykes et al. (2000)[110] | Christie Hospital | 331[b] | 92%[c] | 81%[c] | 67%[c] | 73%[c] |
| Hinerman et al. (2002)[51] | University of Florida[d] | 274 | 100% | 86% | 62% | 62% |

*Note:* Some figures were estimated as closely as possible to fit table format if the information was not specifically stated in the cited reference.

[a]All had cord fixation.

[b]All N0.

[c]After 17 were salvaged by total laryngectomies.

[d]1998 AJCC staging; q.d., once a day; b.i.d., twice a day.

*Source:* Hinerman RW, Mendenhall WM, Amdur RJ, et al. Carcinoma of the supraglottic larynx: treatment results with radiotherapy alone or with planned neck dissection. *Head Neck.* 2002;24:456–467, with permission.

## TABLE 18.13 Local Control after Supraglottic Laryngectomy

| Series | Institution | Number of Patients | Patients with T1 and T2 Tumors (%) | Local Control | | | |
|---|---|---|---|---|---|---|---|
| | | | | T1 (%) | T2 (%) | T3 (%) | T4 (%) |
| Ogura et al. (1975)[95] | Washington University | 177 | 78 | — | 94[a] | | — |
| Bocca (1991)[100] | Milan University | | | | | | |
| Stage I | | 47 | 100 | 94 | — | — | — |
| Stage II | | 252 | 100 | — | 82 | — | — |
| Stage III | | 205 | 53 | — | 80[b] | — | — |
| Stage IV | | 33 | 70 | — | 67[c] | | — |
| Lee et al. (1990)[52] | M.D. Anderson Cancer Center | 60 | 58 | 100 | 100 | 100 | 100 |
| DeSanto (1990)[111] | Mayo Clinic | 70 | 100 | 100 | 100 | — | — |
| Steiniger et al. (1997)[112] | Albany Medical College | 29 | 83 | — | 97[a] | | — |

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**TABLE 18.13 Local Control after Supraglottic Laryngectomy (Continued)**

| Series | Institution | Number of Patients | Patients with T1 and T2 Tumors (%) | Local Control | | | |
|---|---|---|---|---|---|---|---|
| | | | | T1 (%) | T2 (%) | T3 (%) | T4 (%) |
| Spriano et al. (1997)[99] | Varese, Italy | 54 | 100 | 96[d] | | — | — |
| Burstein and Calcattera (1985)[113] | University of California (LA) | 40 | 58 | 100 | | 85 | 94 |
| Isaacs et al. (1998)[101] | University of Florida | 33 | 76 | 100 | | 78 | 71 |
| Lutz et al. (1990)[96] | University of Pittsburgh | 72 | No data | — | | 99 | — |

*Note:* T stages were not specified. Some figures were estimated as closely as possible to fit table format if the information was not specifically stated in the cited reference.

[a]Overall local control rates for T1–T4.

[b]Overall local control rates for T1–T3.

[c]Overall local control rates for T2–T3.

[d]Overall local control rates for T1–T2.

*Source:* Hinerman RW, Mendenhall WM, Amdur RJ, et al. Carcinoma of the supraglottic larynx: treatment results with radiotherapy alone or with planned neck dissection. *Head Neck.* 2002;24:456, with permission.

**TABLE 18.14 Supraglottic Larynx: Severe Complications According to Treatment Modality**

| Series | Institution | Number of Severe Complications |
|---|---|---|
| **Radiotherapy** | | |
| Fletcher and Hamberger (1974)[107] | M.D. Anderson Cancer Center | 10/173 (6%) |
| Ghossein et al. (1974)[105] | Fondation Curie | 8/117 (7%) |
| Nakfoor et al. (1998)[109] | Massachusetts General Hospital | 12/169 (7%) |
| Sykes et al. (2000)[110] | Christie Hospital | 7/331 (2%) |
| Hinerman et al. (2002)[51] | University of Florida | 12/274 (4%) |
| **Supraglottic laryngectomy** | | |
| Lee et al. (1991)[52] | M.D. Anderson Cancer Center | 9/63 (14%) |
| Isaacs et al. (1998)[101] | University of Florida | 14/34 (41%) |
| Burstein and Calcaterra (1985)[113] | University of California Los Angeles | 14/41 (34%) |
| Steiniger et al. (1997)[112] | Albany Medical College | 12/29 (41%) |
| Spriano et al. (1997)[99] | Varese, Italy | 13/54 (24%) |
| Gall et al. (1977)[63] | Washington University | 20/133 (15%) |
| Weber et al. (1993)[114] | University of Pittsburgh | 12/69 (17%) |
| Beckhardt et al. (1994)[115] | University of Wisconsin | 15/50 (30%) |
| **Transoral laser excision** | | |
| Rudert et al. (1999)[104] | University of Kiel, Germany | 3/34 (9%) |
| Zeitels et al. (1994)[103] | Massachusetts Eye and Ear Infirmary | 2/45 (4%) |
| Steiner (1993)*[40] | University of Gottingen, Germany | 7/240 (3%) |
| Davis et al. (1991)[102] | University of Utah, Salt Lake City | 0/14 (0%) |
| Csanády et al. (1999)[106] | Albert Szent Gyorgyi MedicalUniversity, Szeged, Hungary | 0/23 (0%) |

*Includes patients with glottic cancer.

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size and extent of the original lesion. Edema may be accentuated by a neck dissection and may require 6 to 12 months to subside.

Soft tissue necrosis leading to chondritis occurs in fewer than 1% of patients, usually in those who continue to smoke. Soft tissue and cartilage necroses mimic recurrence, with hoarseness, pain, and edema; a laryngectomy may be recommended as a last resort for fear of recurrent cancer, even though biopsy specimens show only necrosis.

Corticosteroids such as dexamethasone (Decadron) have been used to reduce RT-induced edema after recurrence has been ruled out by biopsy. If ulceration and pain occur, administration of an antibiotic such as tetracycline may help. Of 519 patients with T1N0 or T2N0 vocal cord cancer treated at the University of Florida, 5 (1%) experienced severe complications,[35] including total laryngectomy for a suspected local recurrence (1 patient), permanent tracheostomy for edema (3 patients), and a pharyngocutaneous fistula after a salvage total laryngectomy (1 patient).

In patients irradiated for supraglottic carcinoma, sore throat persist 1 to 2 months after completion of treatment. There is an associated dry mouth from RT of the salivary and parotid glands, a loss of taste, and a sensation of a lump in the throat. It is unusual for patients to require a tracheotomy before RT unless severe lymphedema develops at the time of direct laryngoscopy and biopsy. However, in patients who have recovered from the direct laryngoscopy and biopsy without obstruction, a tracheotomy has rarely been required during a course of definitive RT.

Patients treated twice a day with 1.2-Gy fractions (continuous-course technique) to a total dose of 74.4 Gy usually have more brisk acute reactions than those treated once a day with 2-Gy fractions. All patients are treated with continuous course; planned split course RT is associated with a higher risk of failure. Approximately 30% treated with twice-a-day RT require temporary gastrostomy feeding tubes because they have difficulty in swallowing.[59]

Examples of acute chondritis requiring discontinuation of treatment have not been seen, although most epiglottic lesions exhibit cartilage invasion.

The epiglottis, both suprahyoid and infrahyoid portions, remains thicker than normal for long periods of time, but this is not often associated with difficulty in swallowing, respiratory obstruction, or aspiration. The patient is cautioned to eat and drink slowly until the edema resolves. The false cord and arytenoids may develop some edema.

Lesions of the suprahyoid epiglottis frequently destroy the tip of the epiglottis, and it may require some time for the exposed cartilage to heal. Successful RT of infrahyoid epiglottis tumors is not associated with a high rate of necrosis, even though most of these lesions penetrate the porous epiglottic cartilage.

The incidence of severe late complications in 274 patients treated with RT alone or combined with neck dissection at the University of Florida was 4%.[51]

# MANAGEMENT OF RECURRENCE

## Follow-up Policy

Follow-up of patients with early lesions is planned for every 4 to 8 weeks for 2 years, every 3 months for the third year, and every 6 months for years 4 and 5, and then annually for life.

Follow-up of patients with early- and moderate-stage vocal cord or supraglottic larynx lesions treated by RT or conservative surgery is almost more important than the treatment itself because early detection of recurrence usually results in salvage that may include cure with voice preservation.[46] If recurrence is suspected but the biopsy is negative, patients are reexamined at 2- to 4-week intervals until the matter is settled. The value of follow-up positron emission tomography and CT scans for detecting early local recurrence is investigational.

The likelihood of salvage of a local-regional recurrence after total laryngectomy and adjuvant RT is very low.

An important goal of follow-up, in addition to detection of recurrent cancer and management of complications, is detection of metachronous second primary malignancy.[60] Wagenfeld and associates[61] studied 740 cases of glottic larynx cancer treated from 1965 to 1974 to determine the incidence of second respiratory tract malignancies. With a minimum follow-up of 5 years, 48 second respiratory tract malignancies occurred, although only 14 were expected. Twenty-five were in the lung, and 23 were scattered among other head and neck sites. Only 7 of the 23 second head and neck primary lesions resulted in death; these second lesions were frequently diagnosed in an early stage during routine follow-up for the glottic lesion.

Because the risk of a lethal lung primary lesion is nearly as great as that of dying of an early glottic carcinoma, it makes sense to obtain annual chest radiographs. Patients with supraglottic cancers who receive RT to the neck have a high risk of developing hypothyroidism and require monitoring of their thyroid functions every 6 to 12 months.[62]

## Glottic Larynx Carcinoma

Most recurrences appear within 18 months, but late recurrences may appear after 5 years.[63] With careful follow-up, recurrence is sometimes detected before the patient notices a return of hoarseness. There is often minimal lymphedema for 1 to 2 months after RT, which usually subsides or stabilizes. An increase in edema, particularly if associated with hoarseness or pain, suggests recurrence, even if there is no obvious tumor. Fixation of a previously mobile vocal cord usually implies local recurrence, but we have occasionally observed a patient who has experienced a fixed cord with an otherwise normal-appearing larynx and who has not shown evidence of recurrence. It may be difficult to diagnose recurrence if the tumor is submucosal. Generous deep biopsies are required. If recurrence is strongly suspected, laryngectomy may rarely be advised without biopsy-confirmed evidence of recurrence.

RT failures may be salvaged by cordectomy, hemilaryngectomy, or total laryngectomy. Biller and associates[64] reported a 78% salvage rate by hemilaryngectomy for 18 selected patients in whom irradiation failed; total laryngectomy was eventually required in two patients. Only two patients died of cancer. These investigators offered guidelines for using hemilaryngectomy: contralateral vocal cord is normal, arytenoid is not involved, subglottic extension does not exceed 5 mm, and vocal cord is not fixed. In our experience, 10 patients irradiated for T1 or T2 vocal cord cancers underwent a hemilaryngectomy following a local recurrence, and 6 were successfully salvaged.[17]

The rate of salvage by irradiation for recurrences or new tumors that appear after initial treatment by hemilaryngectomy is about 50%.[65] Patients who experience a local-regional failure after surgery and postoperative irradiation have a low chance of cure, particularly if the initial procedure was a total laryngectomy.

## Supraglottic Larynx Carcinoma

***Recurrence After Radiation Therapy.*** The overall likelihood of successful salvage after a local recurrence is about 50%; it is probably somewhat better for patients who initially have stages I to II disease.[46] Most patients require a total laryngectomy; a few

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are suitable for a voice-sparing procedure. Approximately one-third of patients sustain a major complication secondary to salvage surgery, usually related to poor wound healing.

When an isolated recurrence develops in a previously $N_0$ neck, patients have a 50% to 60% chance of cure by means of a salvage neck dissection.[66] The likelihood of salvaging a failure in a previously positive neck is remote.

The likelihood of cure after development of distant metastases is nil, and management is palliative with either supportive care or chemotherapy.

***Recurrence After Surgery.*** Patients who develop a low-volume local recurrence after a supraglottic laryngectomy may sometimes be successfully treated with RT. Patients with high-volume recurrences are best managed with a total laryngectomy and postoperative RT.

## SPECIAL ISSUES AND FUTURE DIRECTIONS

There are limited data pertaining to the use of chemotherapy alone as the initial step in treatment of patients with early-stage laryngeal cancer.[67,68] A small subset of patients may be cured with chemotherapy alone, thus sparing them the morbidity of RT and/or partial laryngectomy. A caveat is that the cure rates for patients with early-stage disease are already very high, the morbidity of chemotherapy may be more severe than that associated with conventional treatment, and >90% of patients must proceed to RT or surgery despite the chemotherapy (which probably does not enhance the likelihood of cure).

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# PART B:
# Radiologic Imaging Concerns

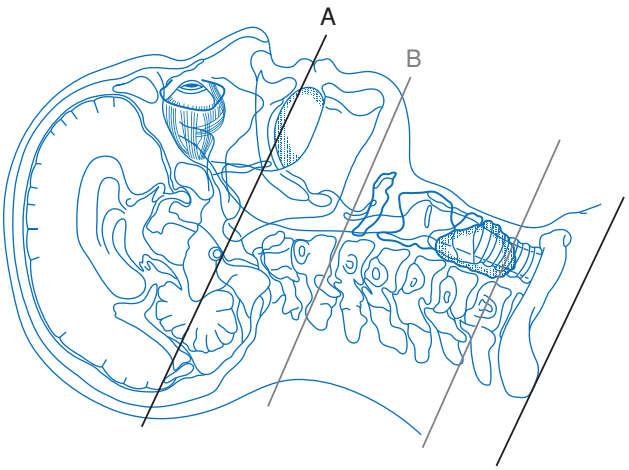
Jeffrey A. Bennett

Imaging the larynx requires high speed because of the difficulties patients have with secretions and throat discomfort, which lead to frequent swallowing, coughing, and resultant motion artifact. Therefore, computed tomography (CT) is the imaging modality of choice, especially with the newer multidetector row helical or volumetric scanners. Very thin axial sections can be obtained, down to 0.5 mm, which allow outstanding quality of sagittal and coronal reformats. The axial images should be performed parallel to the true vocal cords to allow the best view of the anterior and posterior commissures. However, this is proving to be less important now, because many PACS software packages allow reformation of the images in any plane. This data manipulation can essentially "straighten out" the patient and optimize the imaging plane, no matter how the images were acquired. The long imaging time required for magnetic resonance imaging (MRI) often results in motion-degraded images, but in cooperative patients who are able to hold very still and not swallow for extended periods of time, MRI still provides better soft tissue differentiation. Since this scenario is infrequent, MRI is mostly reserved for problem solving in more advanced transglottic tumors, such as when there is a question of tracheal or esophageal invasion. Intravenous contrast is necessary for both modalities. Suggested protocols are given in Figures 18-9 and 18-10.

No matter which imaging technique is chosen, MRI or CT, the information obtained is critical in staging.[1] Imaging frequently upgrades clinically suspected low-grade tumor based on submucosal spread deep to the mucosal lesion visualized with endoscopy. As seen elsewhere in the head and neck, visualization of fat planes is critical to image interpretation (Fig. 18-11). In the larynx, obliteration of the paraglottic fat and preepiglottic fat are signs of tumor extension. At the level of the true vocal cords, normally no fat is seen in the paraglottic space, but at the level of the false cords a clear paraglottic fat plane should be seen. The anterior commissure is very thin, and normally minimal to no soft tissue should be seen at that location. Similarly, in the subglottic region, no soft tissue should be seen in the airway inside the cricoid cartilage. Soft tissue in these locations is a sign of tumor spread. Multiplanar imaging is helpful for determining the full extent of the primary tumor (Fig. 18-12).

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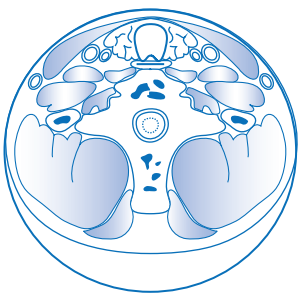
ACQUISITION




| | | |
|---|---|---|
| | Patient Position | Supine<br>Mandibular body perpendicular to tabletop |
| | Contrast | 100 mL total adult |
| | Injection Rate | 1 mL/sec |
| | Volume Acquisition Specs | Appropriate to achieve images as specified in following reconstruction tables.<br>Head FOV. |
| A | Contrast | 70 mL; 60 sec delay |
| | Respiration | Quiet, NO swallowing |
| | Begin | Mid oral cavity |
| | End | Lung apices |
| B | Contrast | 30 mL; 30 sec delay |
| | Respiration | Breath-hold, NO swallowing |
| | Begin | Hyoid |
| | End | 1 cm below bottom of cricoid |

RECONSTRUCTION

A1



B1



| | | |
|---|---|---|
| A1 | Algorithm | Soft |
| | Thickness | 2.5 mm |
| | Spacing | 2.5 mm |
| | F.O.V. | Approx. 160–180 |

| | | |
|---|---|---|
| B1 | Algorithm | Soft |
| | Thickness | 1.5 mm |
| | Spacing | 1.5 mm |
| | F.O.V. | 100 |

**FIGURE 18-9.** Protocol for CT scan of the larynx with intravenous contrast. CT, computed tomography.

*Source:* Reprinted from Mancuso AA, Hanafee WN. *Head and Neck Radiology.* Philadelphia, PA: Lippincott Williams & Wilkins; 2011:2222, with permission.

Occasionally, gross morphologic changes to the larynx such as a laryngocele are caused by a tumor. A careful search for an obstructing mass should be performed when a laryngocele is encountered (Figs. 18-13 and 18-14).

Not uncommonly, the laryngeal cartilages will be seen to be sclerotic. There is frequently irregular ossification of the laryngeal cartilage, so asymmetries cannot be assumed to be tumor invasion of the cartilage. The best way to be sure that cartilage invasion has occurred is if tumor is seen on both sides of the cartilage (Fig. 18-15). The arytenoid cartilage is frequently sclerotic. Pathologic studies have revealed a 50% likelihood of microscopic cartilage invasion in a single sclerotic cartilage directly adjacent to the tumor. There is a >90% possibility of cartilage invasion if more than two adjacent cartilages are sclerotic next to the tumor. Cartilage sclerosis has been correlated with a poorer local control rate with radiation therapy.[2] Both CT and MRI can detect cartilage sclerosis, appearing solid bright on CT and black on MRI. Initial studies reported a higher specificity for cartilage invasion with CT compared to MRI.[3] A recent study was performed[4] to investigate the accuracy of MRI in predicting thyroid cartilage invasion and found that MRI overpredicts cartilage and thyroid gland invasion.

Examples of glottic squamous cell carcinoma spreading to the supraglottis and subglottic region are given in Figures 18-16 to 18-18.

Primary supraglottic tumors are sometimes difficult to see on imaging studies if they are superficial and low volume. Direct visualization often outlines the mucosal extent of disease. Imaging studies should focus on deep extension to the preepiglottic and paraglottic spaces, as well as spread to lymph nodes. Particular attention should be paid to level VI nodes and lateral retropharyngeal nodes (Fig. 18-19).

If paratracheal lymph node metastases are present, the patient carries a worse prognosis. These nodes can be detected with

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| Acquisition | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Plane | Sagittal | Axial | Axial | Axial | Coronal (angled) |
| Sequence | T1 | T1 | T2-FSE | T1 | T1 |
| Contrast | None | None | None | Gd | Gd |
| SLT/SP | 3/0 mm | 3/0 mm | 3/0 mm | 3/0 mm | 3/0 mm |
| FOV | 16 cm | 16 cm | 16 cm | 16 cm | 16 cm |

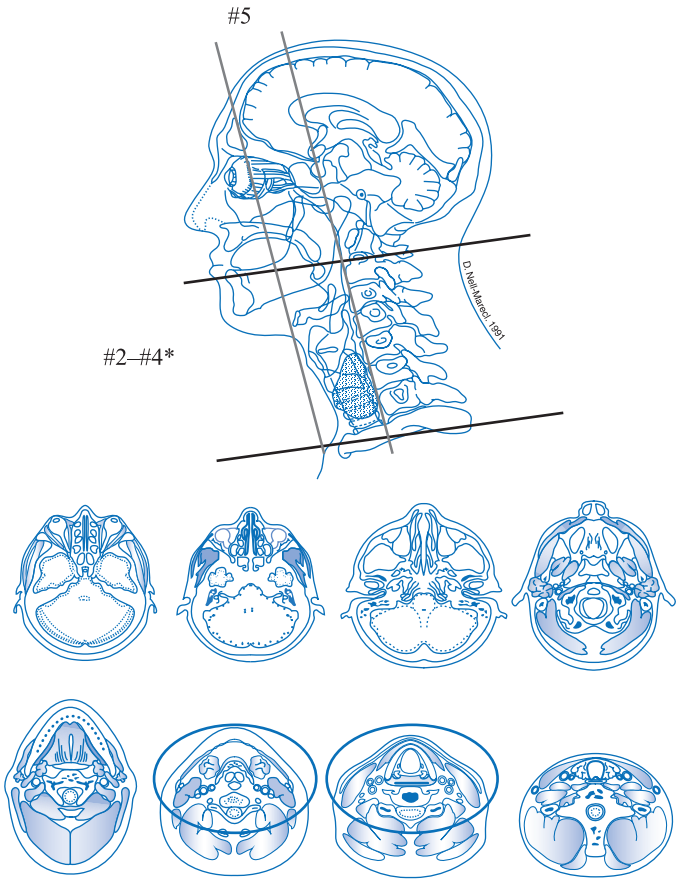



**FIGURE 18-10.** Protocol for MRI of the larynx. MRI, magnetic resonance imaging.

*Source:* Reprinted from Mancuso AA, Hanafee WN. *Head and Neck Radiology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2011:2237, with permission.

both CT and MRI. One study showed a sensitivity and specificity of 70% and 36% for CT and 50% and 71% for MRI, when the node was >5 mm in its greatest axial diameter.[5] CT perfusion may provide additional functional information regarding the presence of tumor in lymph nodes.[6]

Follow-up imaging is of limited use for treated small mucosal early lesions, unless there are clinical symptoms of tumor recurrence, although CT has been demonstrated to be able to detect treatment failure before it is clinically suspected.[7] Radiation therapy produces posttreatment changes of edema and mucosal enhancement, and so careful comparison with the pretreatment study is necessary to assess for response (Fig. 18-20). Interpreting postsurgical changes requires an understanding of what was removed and where flaps have been placed. Often mucosal and submucosal soft tissue thickening is seen after surgery, and the initial posttreatment scan serves as a baseline for future follow-up. Scar tissue generally shrinks, and enhancement reduces over time, whereas tumor grows and enhances more over time. When present, special attention should be made to sites of anastomosis of the neopharynx and along the tracheostomy.

Posttreatment cartilage necrosis can often present diagnostic difficulty (Fig. 18-21). Fragmentation of sclerotic cartilage and tunneling through osseous segments are signs of radiation necrosis. If there is an associated soft tissue mass, this raises the suspicion for necrotic tumor. In these cases, FDG PET-CT at least 3 to 4 months after treatment completion may be helpful in directing a biopsy. A negative FDG PET is very encouraging in that there is no recurrent disease.

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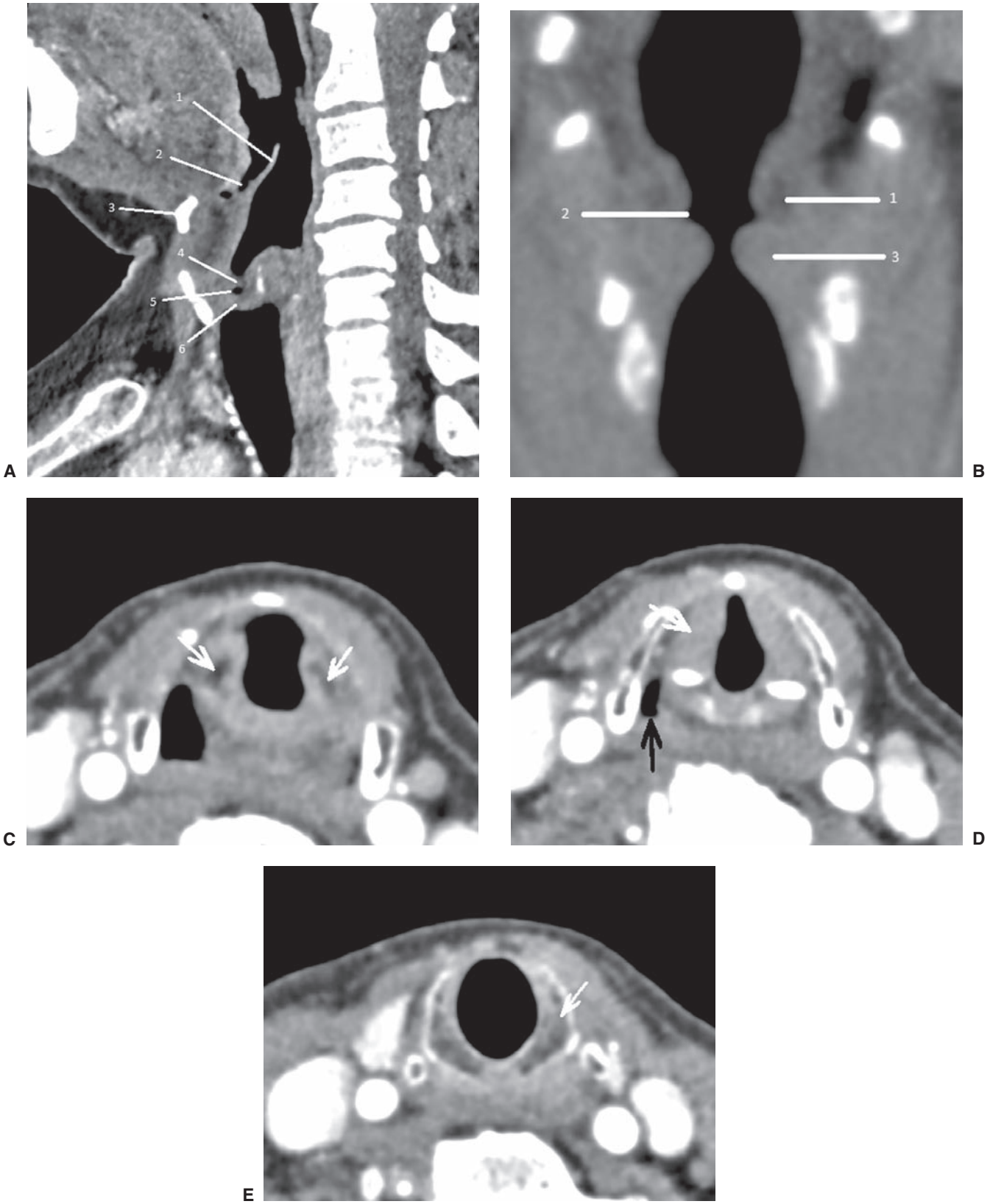



**FIGURE 18-11.** Normal larynx anatomy. **A:** Sagittal reformation of a postcontrast CT scan showing normal anatomy. 1, free margin of the epiglottis. 2, vallecula. 3, hyoid bone. 4, false cords. 5, laryngeal ventricle. 6, true cords. **B:** CT coronal reformat showing normal anatomy. 1, false cords with paraglottic fat. 2, laryngeal ventricle. 3, true cords with no paraglottic fat seen at this level. **C:** Axial postcontrast CT scan at the level of the false cords. Fat is seen in the paraglottic space (*arrows*) at this level. **D:** Axial postcontrast CT scan at the level of the true cords (*white arrow*). No paraglottic space fat is seen. Notice the apex of the piriform sinus (*black arrow*) can extend inferiorly to the level of the true cords. **E:** Axial postcontrast CT scan at the level of the cricoid cartilage (*arrow*). Notice that normally no soft tissue is seen on the luminal side of the cricoid cartilage. CT, computed tomography.



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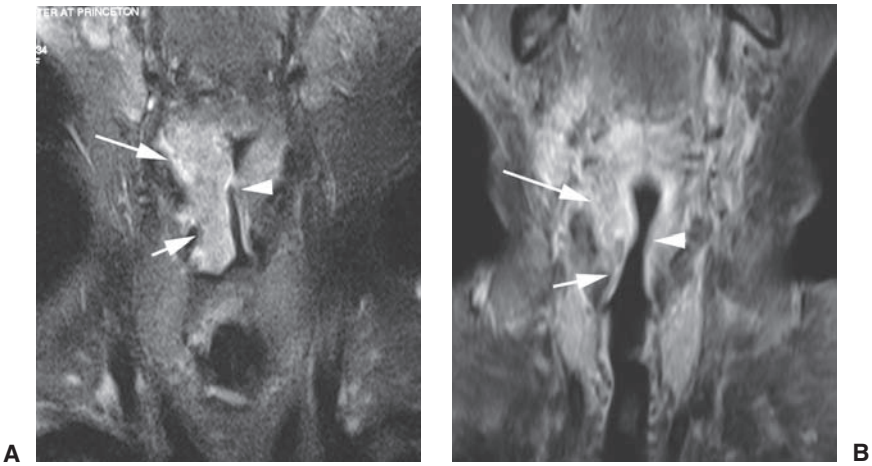


**FIGURE 18-12.** Transglottic squamous cell carcinoma treatment follow-up. **A:** Pretreatment coronal MRI with contrast shows the large transglottic mass (*long arrow*) straddling the plane of the ventricle (*arrowhead*) with extensive subglottic component (*short arrow*). **B:** Posttreatment coronal MRI with contrast shows marked reduction of subglottic component (*short arrow*). *Arrowhead* defines level of ventricle. MRI, magnetic resonance imaging.

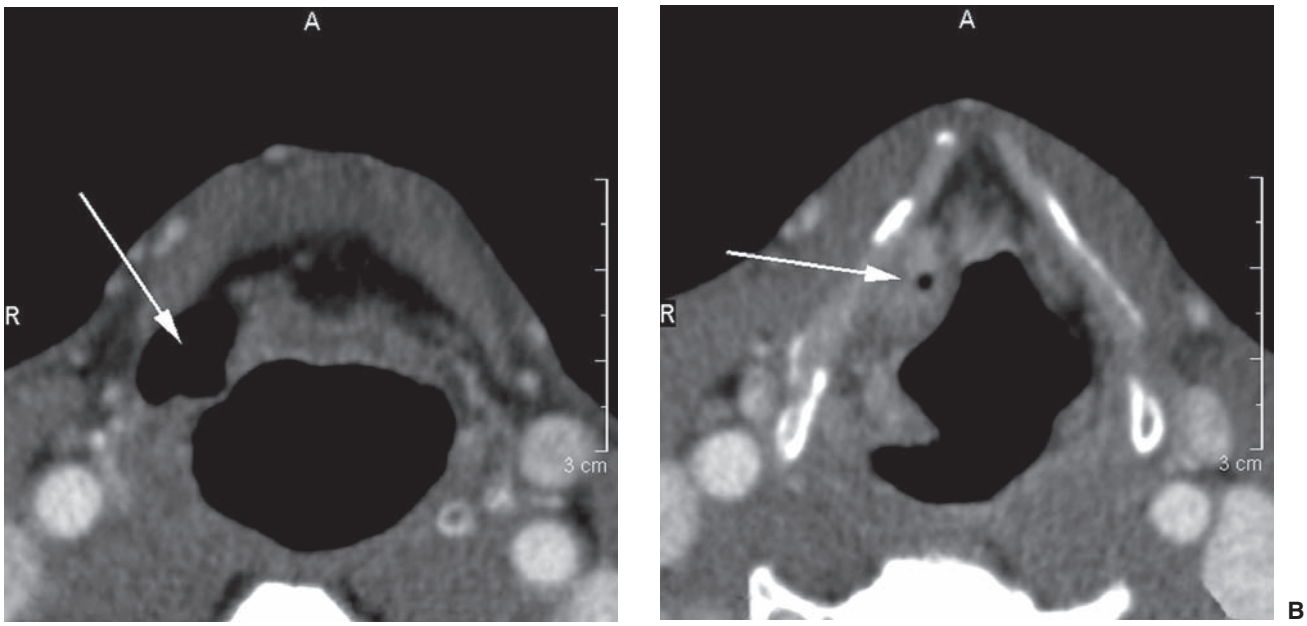



**FIGURE 18-13.** **A:** Axial contrast-enhanced CT scan shows an air-filled laryngocele on the right (*arrow*). **B:** The cause of the laryngocele is an enhancing larynx cancer (*arrow*) obstructing the laryngeal ventricle. CT, computed tomography.

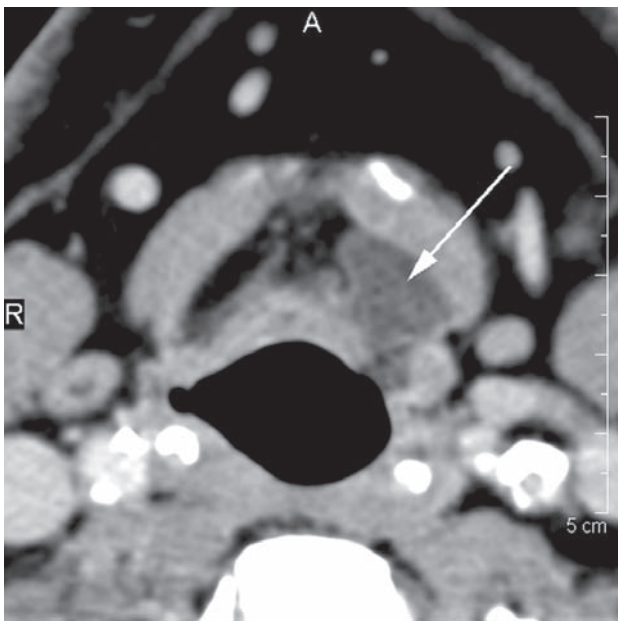
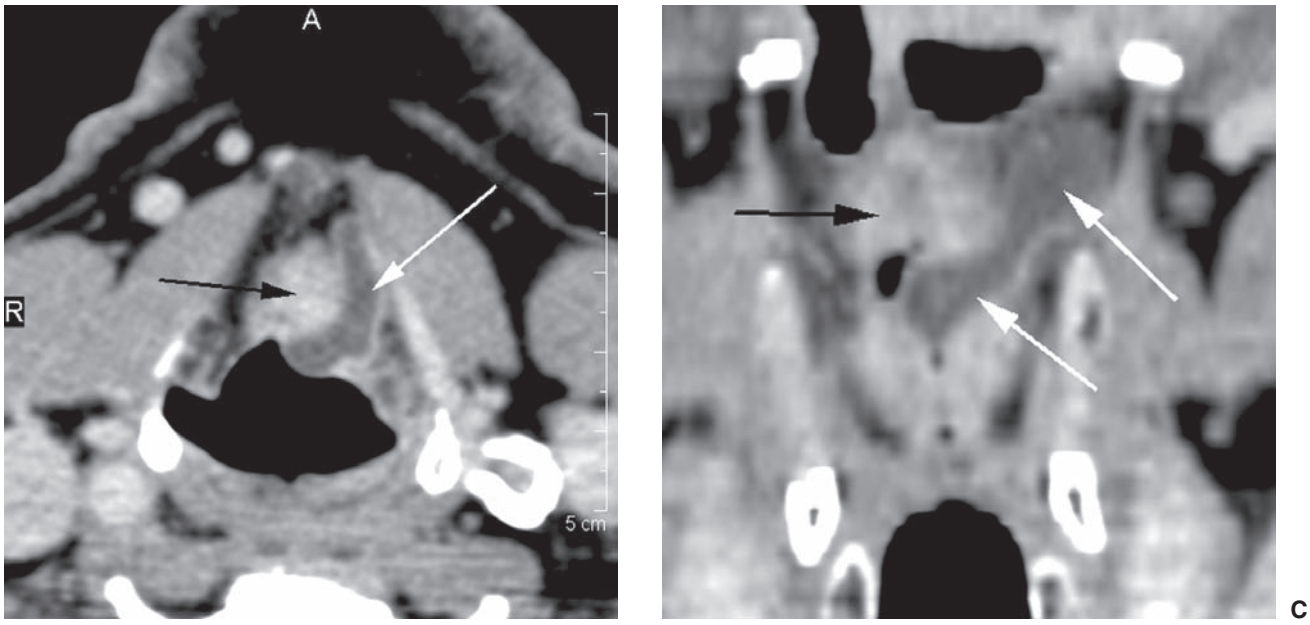



**FIGURE 18-14.** **A:** Axial contrast-enhanced CT scan shows a left-sided fluid-filled laryngocele (*arrow*). **B:** The cause of the laryngocele (*white arrow*) is shown to be an epiglottic-enhancing squamous cell carcinoma (*black arrow*). **C:** Coronal reformation of the contrast-enhanced CT scan better shows the full extent of the laryngocele (*white arrows*) and also shows the enhancing tumor (*black arrow*). CT, computed tomography.

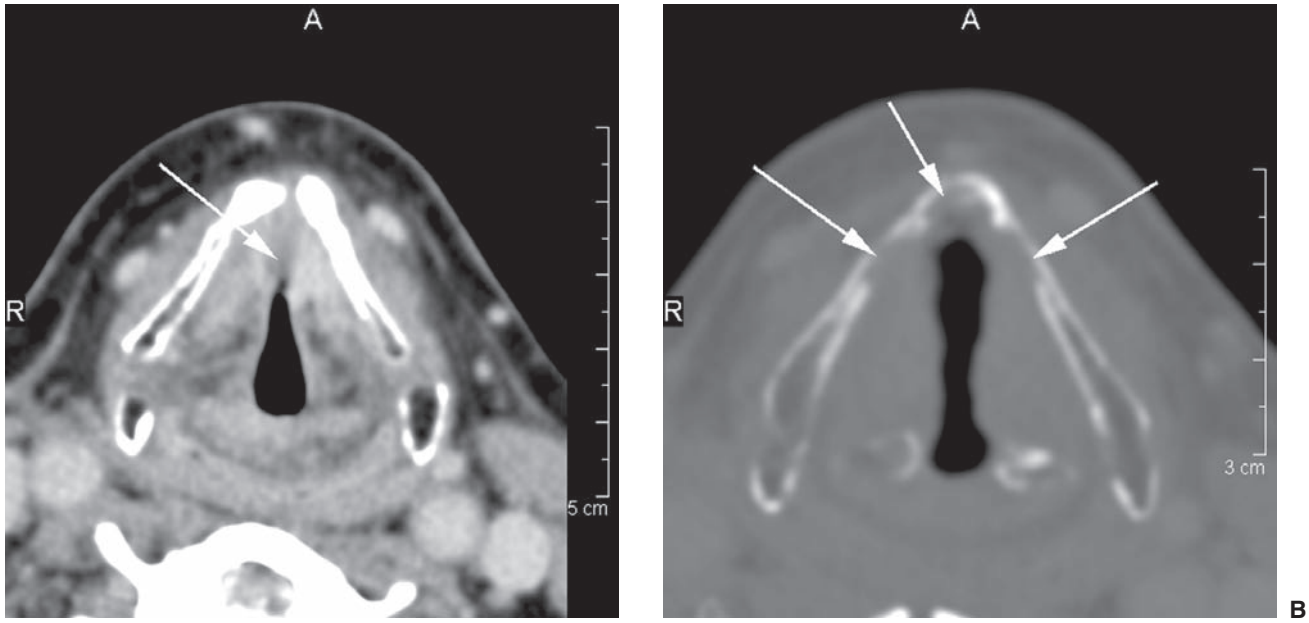


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B C

**FIGURE 18-14.** *Continued*




A B

**FIGURE 18-15.** **A:** Axial contrast-enhanced CT scan demonstrates a squamous cell carcinoma at the anterior commissure (*arrow*). **B:** Axial CT scan windowed for bone shows multifocal erosions (*arrows*) along the inner surface of the thyroid cartilage likely from tumor invasion. CT, computed tomography.

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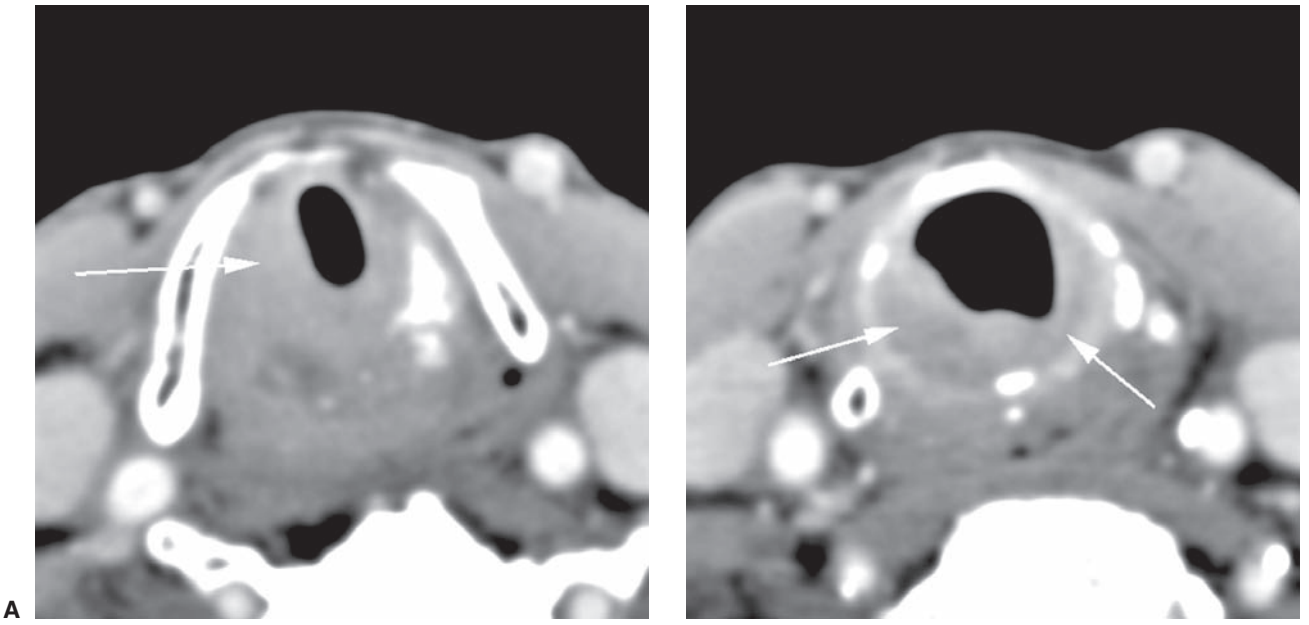


**FIGURE 18-16.** Axial postcontrast CT scan in a patient with advanced laryngeal cancer. **A:** Infiltrating tumor is seen involving the right true cord (*arrow*). **B:** There is extensive subglottic spread of cancer (*arrows*) along the mucosal surface of the cricoid. CT, computed tomography.

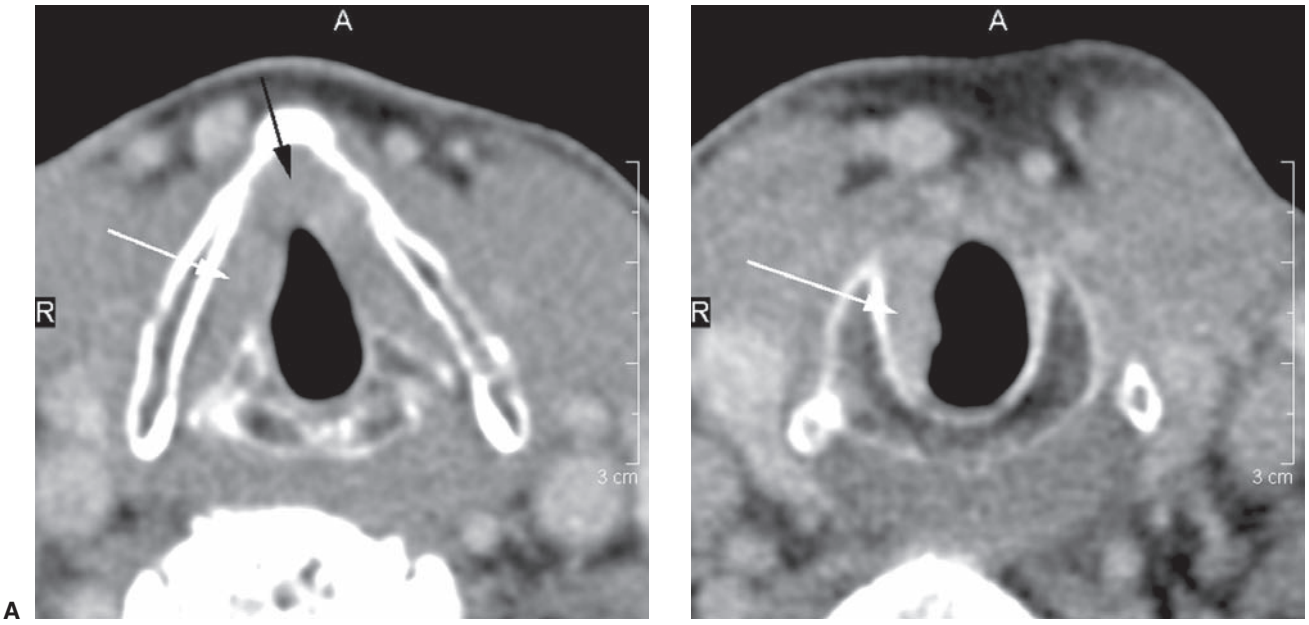



**FIGURE 18-17.** **A:** Axial postcontrast CT scan shows a subtle right true cord squamous cell carcinoma (*white arrow*) extending across the anterior commissure (*black arrow*). **B:** More caudal image in the same patient shows subglottic spread of tumor (*arrow*). CT, computed tomography.

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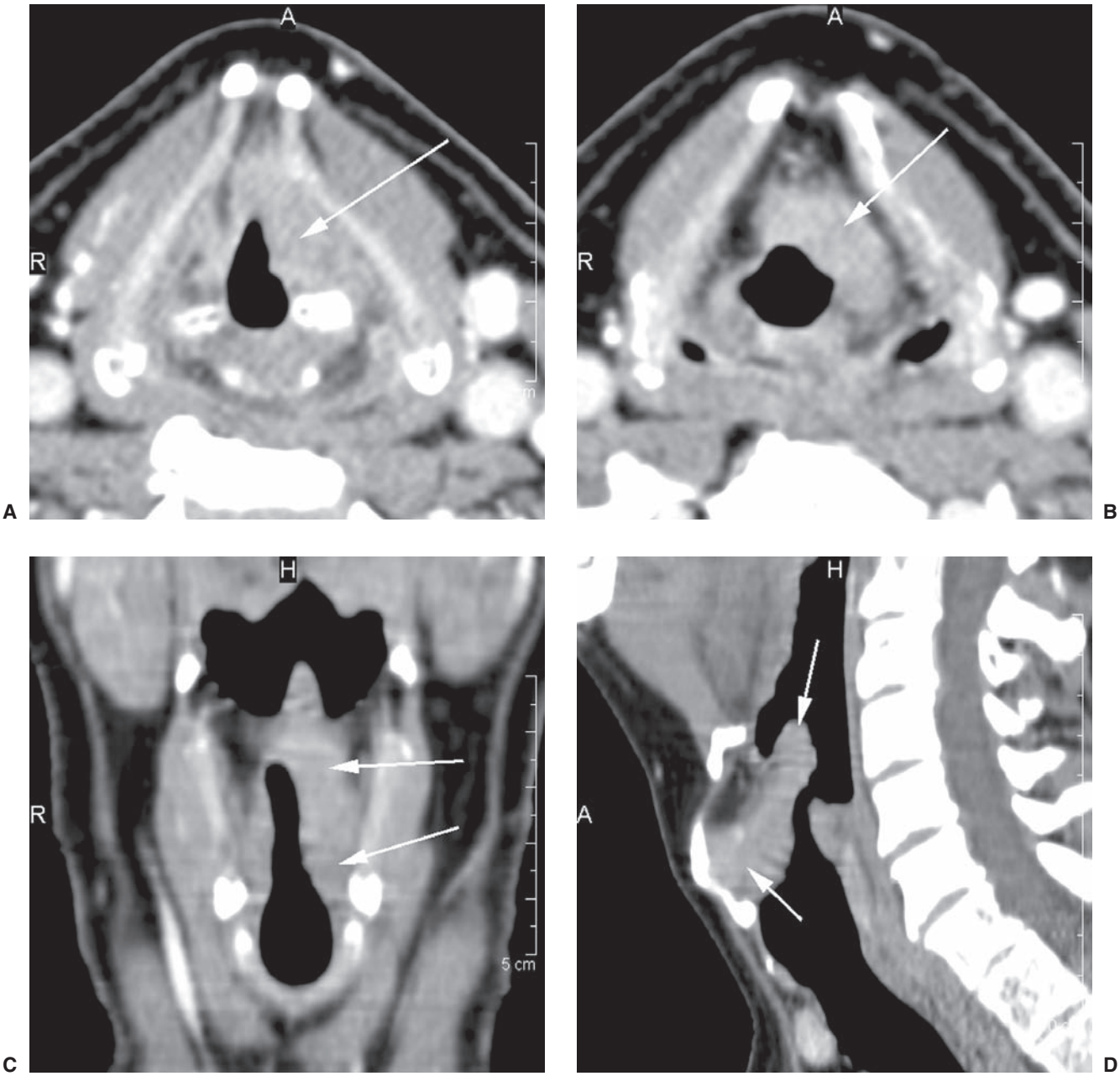



**FIGURE 18-18.** Postcontrast CT scan in a patient with laryngeal squamous cell carcinoma. **A:** Axial image shows enhancing tumor in the left true cord (*arrow*). **B:** There is extension of tumor superiorly along the mucosa to the supraglottis (*arrow*). **C:** Coronal reformat shows tumor (*arrows*) extending from the true cord to the epiglottis. **D:** Sagittal reformat shows tumor (*arrows*) extending from the glottis to the tip of the epiglottis. CT, computed tomography.

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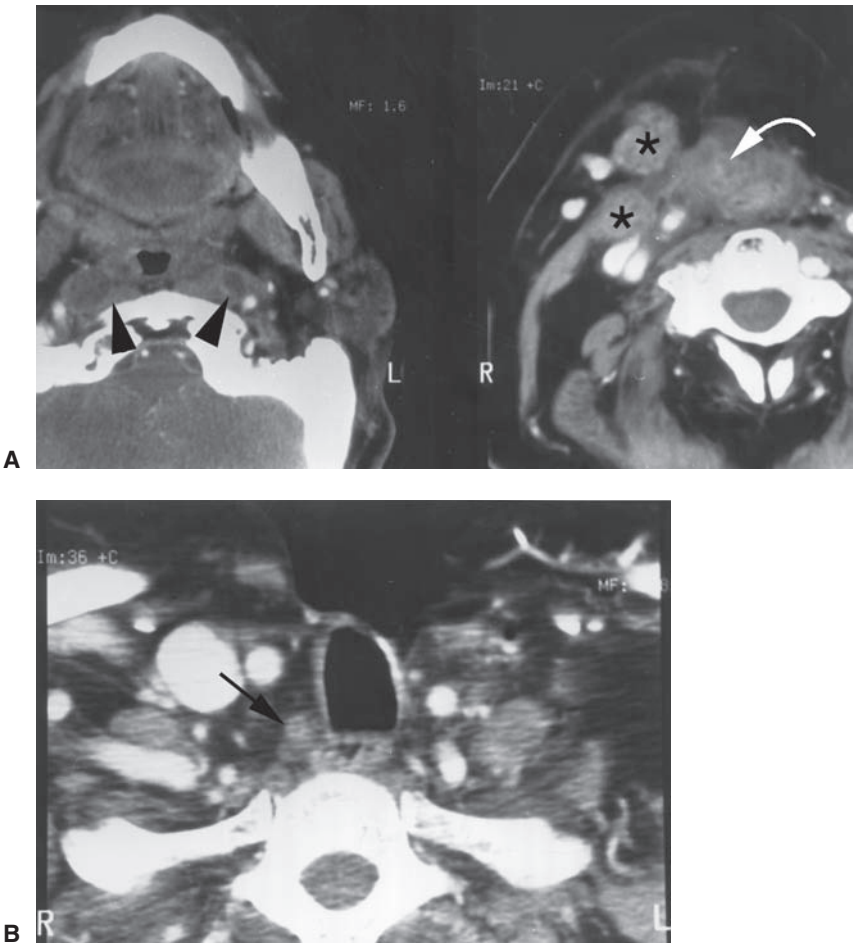



**FIGURE 18-19.** Adenopathy. Selected enhanced axial CT images in a patient with recurrence at the tongue base anastomosis (*curved arrow*). Upper neck images **(A)** show right cervical adenopathy (*asterisk*) and bilateral lateral retropharyngeal adenopathy at the C1 level (*arrowheads*). The lower image through the inlet **(B)** shows a pathologic right tracheoesophageal lymph node (*arrow*). CT, computed tomography.

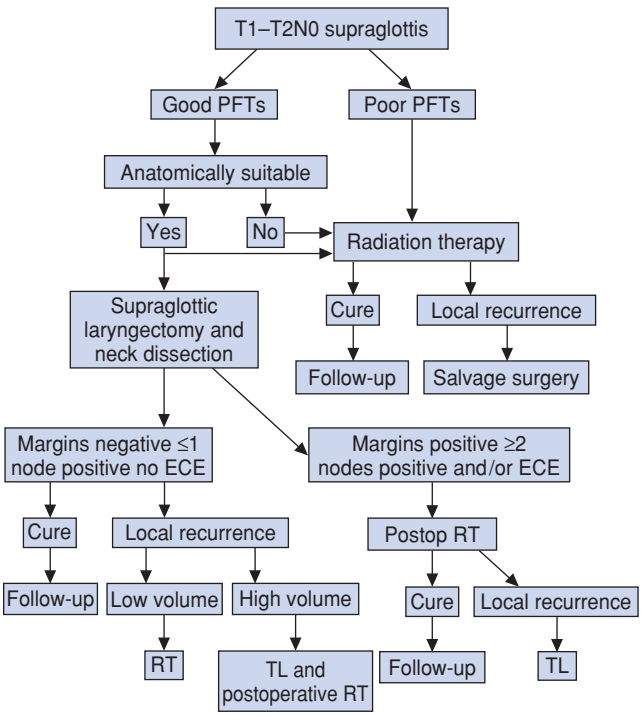



**FIGURE 18-20.** Acute treatment changes. Clockwise from top left: Enhanced thin axial CT sections of a treated T1 glottic lesion from subglottic to false cord level show edema of paraglottic space (*arrows*) and generalized increased enhancement of the mucosal surfaces at the false cord level (*arrowheads*) and hypopharynx (*curved arrow*). CT, computed tomography.

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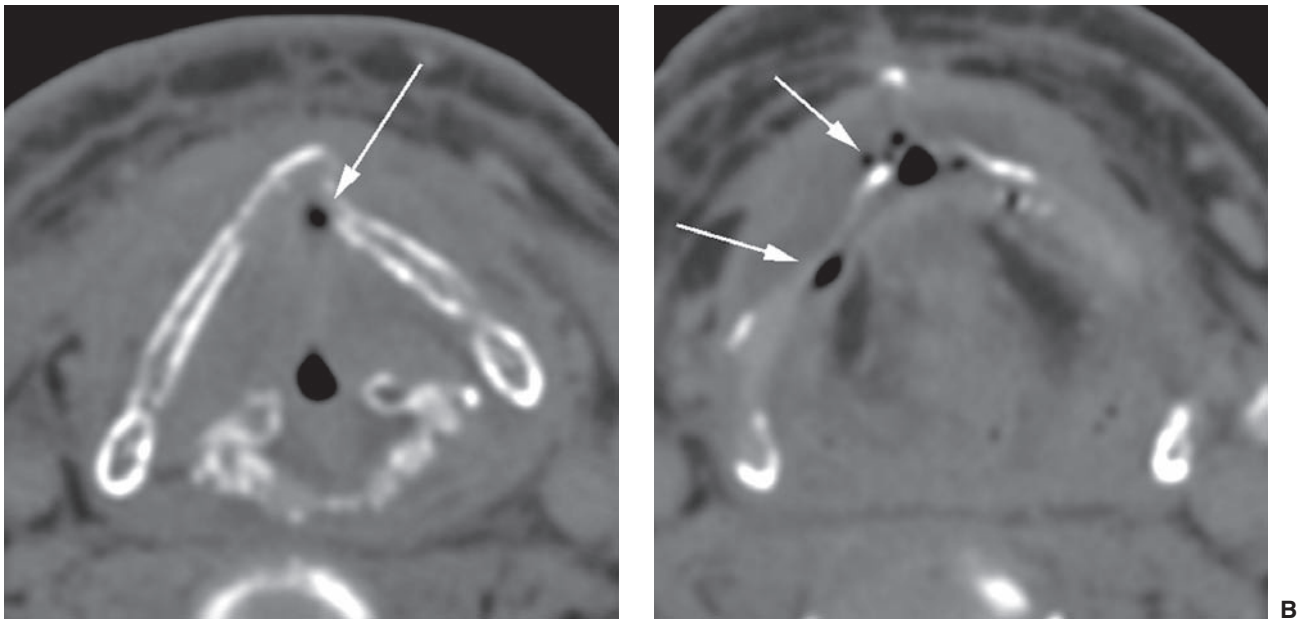


**FIGURE 18-21.** Postradiation laryngeal necrosis. **A:** Axial CT scan shows air and breakdown of the thyroid cartilage (*arrow*) representing necrosis. **B:** Air is seen along the thyrohyoid membrane (*arrows*) from necrosis. CT, computed tomography.

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# PART C:
# Radiation Therapy Technique

William M. Mendenhall

## T1N0–T2N0 GLOTTIC LARYNX

The portals used to treat T1N0 and T2N0 glottic carcinomas are limited to the primary lesion. The risk of occult disease in the neck nodes is very low, even for patients with T2B tumors, and elective neck irradiation is not indicated.

Patients may either be treated in the lateral decubitus position with the fields set up daily by the physician using the anatomic landmarks or in the supine position with aquaplast to ensure accurate repositioning. Parallel-opposed fields are used and weighted 3:2 toward the side of the cancer, if it is lateralized. Weighting the fields reduces the dose to the contralateral posterior larynx. The field borders for a T1N0 cancer involving the anterior two-thirds of the cord are the middle of the thyroid notch, the bottom of the cricoid cartilage, 1 cm posterior to the thyroid lamina, and 1.5 cm fall off anteriorly (Fig. 18-22).[1] The fields are enlarged for T2 cancers depending on the sites of disease extension. Approximately 5% of the dose may be delivered with an anterior field centered over the tumor, with the patient in the supine position, in order to reduce the dose laterally. Patients are treated with $^{60}$Co, 4 MV x-rays, or 6 MV x-rays; the dose delivered to the tumor is similar for these beams.[2] Alternatively, patients may be treated with intensity-modulated radiation therapy (IMRT) to reduce the dose to the carotid arteries and reduce the long-term risk of stroke.[3] Patients with cancers that extend anteriorly though the cricothyroid membrane into the soft tissues of the neck may be underdosed with 6 MV x-rays. However, these lesions are T4 by definition, and the treatment techniques are addressed elsewhere.

Patients with T1 or T2 vocal cord cancer treated with once-a-day fractionation at the University of Florida are irradiated with 2.25 Gy fractions to 63 Gy for T1 and T2A cancers and 65.25 Gy for T2B lesions.

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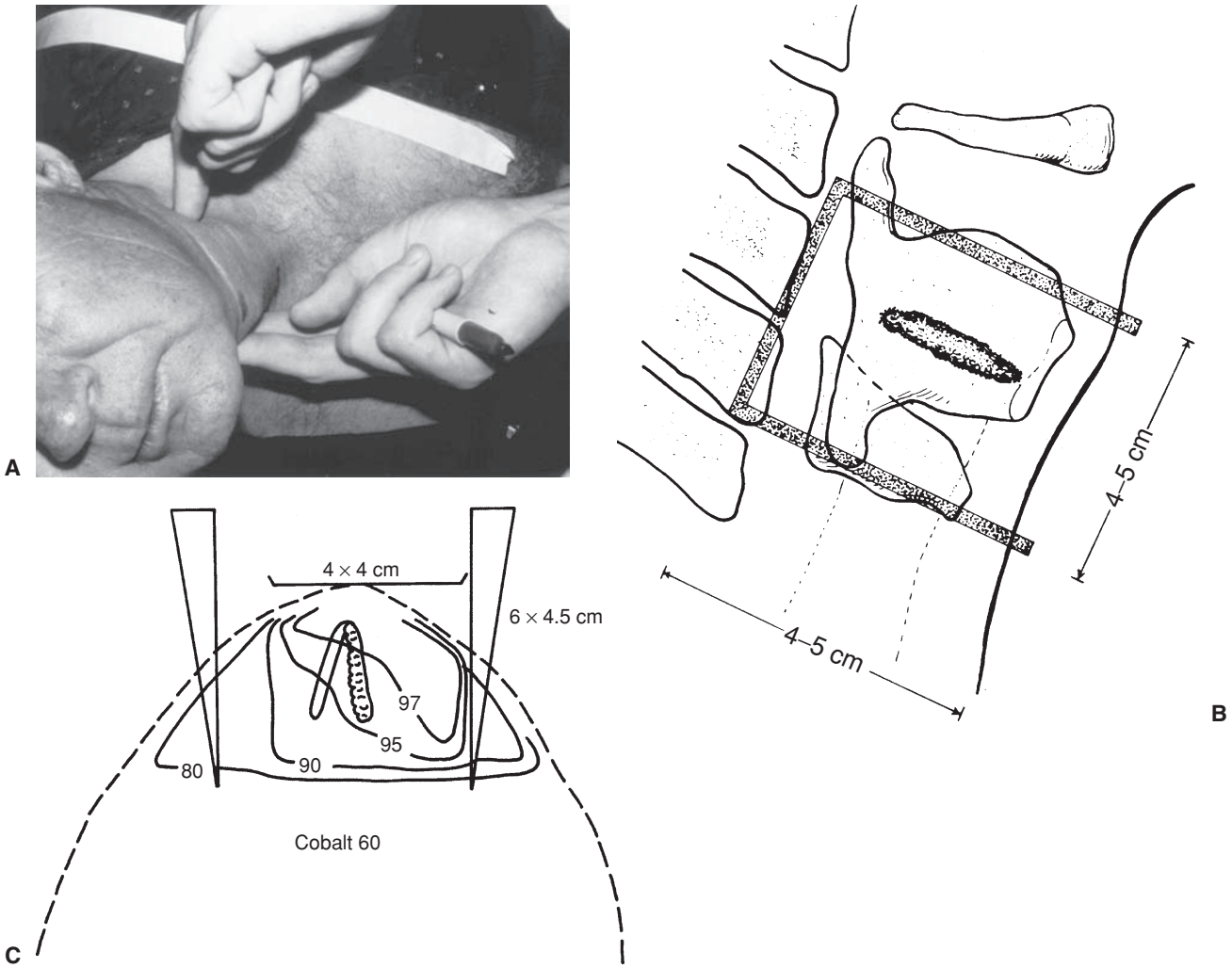



**FIGURE 18-22.** Radiation treatment technique for carcinoma of glottic larynx, stage T1–2. **A:** Patient is in lateral decubitus position. To locate the posterior border of the thyroid cartilage, fingers of one hand are positioned under the patient's neck and the larynx is lifted gently a few millimeters while the index finger of the other hand simultaneously locates the posterior edge of the thyroid lamina. **B:** For T1 cancer, the superior border of the field is usually at mid thyroid notch (height of the notch typically is approximately 1.0 cm or slightly more in male adults); for minimal lesions (e.g., carcinoma *in situ*), the bottom of the thyroid notch is chosen. If the ventricle or false vocal cords are minimally involved, the top of the notch (which corresponds to the cephalad portion of the thyroid lamina as palpated just off midline) is often selected; more advanced lesions call for greater superior coverage. If only the anterior half of the vocal cord is involved, the posterior border is placed at the back of the mid portion of the thyroid lamina. If the posterior portion of the cord is involved, the border is 1.0 cm behind the lamina. If the anterior face of the arytenoid is also involved, the posterior border is placed 1.5 cm behind the cartilage. If no subglottic extension is detected, the inferior border of the irradiation portal is at the bottom of the cricoid arch as palpated at the midline. If computed tomography demonstrates subglottic extension, the portal is adjusted accordingly. Anteriorly, beam fall off (by 1.5 cm) over patient's skin. **C:** The three-field technique (two lateral wedge fields and an anterior open field) is commonly used to treat vocal cord cancer at the University of Florida. Lateral fields are differentially weighted to involved side. The anterior field, which usually measures 4 × 4 cm, is centered approximately 0.5 cm lateral to midline in patients with one cord involved and typically delivers approximately 5% of total tumor dose (usually on last 2 treatment days) after treatment from the lateral portals is completed. The anterior portal is essentially a reduced portal that centers high dose to the tumor. The isodose line at which the dose is specified is that which covers gross disease. By appropriate field weightings, encompassing the tumor within 95% to 97% of maximum isodose line is virtually always possible.

*Source:* Parts A and C from Parsons JT, Palta JR, Mendenhall WM, et al. Head and neck cancer. In: Levitt SH, Khan FM, Potish RA, et al., eds. *Levitt and Tapley's Technological Basis of Radiation Therapy: Practical Clinical Applications*. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 1999:269–299 (Fig. 16.1A and C, p. 270); Part B from Million RR, Cassisi NJ, Mancuso AA, et al. In: Million RR, Cassisi NJ, eds. *Management of Head and Neck Cancer: A Multidisciplinary Approach*. 2nd ed. Philadelphia, PA: JB Lippincott; 1994:431–497 (Fig. 18-21, p 464.), with permission.

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## T1–T2N0 SUPRAGLOTTIC LARYNX

The risk of occult disease in the neck nodes is relatively high, even for early-stage lesions, so that the nodes at risk are treated bilaterally in conjunction with the primary malignancy. For patients with a clinically negative neck, the nodes at highest risk are those in levels II, III, and IV. Nodes in levels I, V, and VI, and the retropharyngeal lymph nodes are unlikely to harbor metastatic disease, and the fields are not enlarged to include these areas.

Patients are treated with parallel-opposed fields weighted to the side of the cancer, if it is lateralized. The fields usually extend from the bottom of the cricoid cartilage to 1 to 2 cm above the angle of the mandible, to the posterior of the spinous processes, and fall off 1.5 cm anteriorly, if the cancer extends to the anterior commissure and/or petiole. If not, a strip of anterior skin may be spared (Fig. 18-23).[4] The low internal jugular lymph nodes are included in a tight low neck field with a small, tapered, midline block (see Fig. 18-23).[4] The fields are reduced off the spinal cord at approximately 45 Gy, and a second mucosal reduction is performed at 60 Gy to encompass the initial gross disease, with a 1.5- to 2.0-cm margin.

Most patients treated at the University of Florida are currently irradiated at 1.2 Gy per fraction, continuous course, with a minimum 6-hour interfraction interval. The dose for T1 and T2 lesions is 74.4 Gy. The total doses for patients irradiated once daily at 2 Gy per fraction are 60 Gy for T1 cancers and 64 to 66 Gy for T2 cancers. All patients are treated with the continuous-course technique.[5]

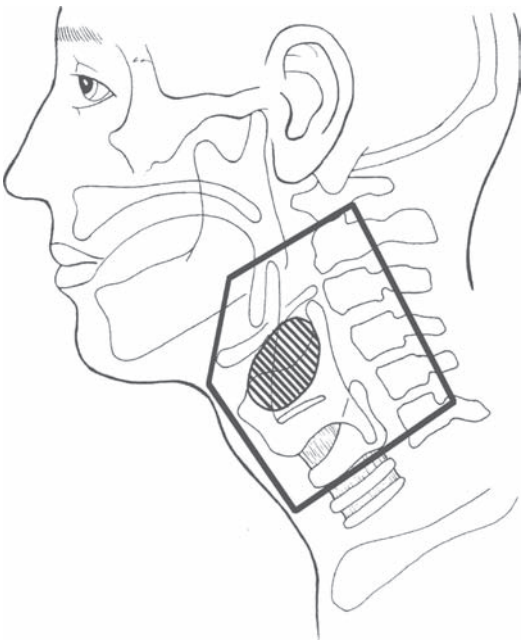


**FIGURE 18-23.** Example of a portal for a lesion of the lower epiglottis or false vocal cord and a clinically negative neck. The subdigastric nodes are included but not the junctional nodes. Depending on the anatomy and tumor extent, the anterior border may fall off (i.e., "flash") or a small strip of skin may be shielded.

*Source:* From Million RR, Cassisi NJ, Mancuso AA, et al. Management of the neck for squamous cell carcinoma. In: Million RR, Cassisi NJ, eds. *Management of Head and Neck Cancer: A Multidisciplinary Approach.* 2nd ed. Philadelphia, PA: JB Lippincott; 1994:75–143 (Fig. 6-52, p. 133), with permission.

IMRT is employed when there is a clear advantage compared with conventional field arrangements. IMRT is not employed to spare the salivary glands in patients with T1–T2N0 supraglottic carcinomas because most of the parotid glands are excluded from the initial parallel-opposed fields. The main reason to use IMRT would be to obtain an adequate inferior margin on the occasional patient with a low-lying larynx and a short neck where the inferior extent of the primary tumor cannot be included in the parallel-opposed lateral fields.

## T3–T4 GLOTTIC AND SUPRAGLOTTIC CANCERS

Patients with T3–T4 laryngeal cancers are treated with parallel-opposed portals weighted 3:2 to the side of the lesion, unless the cancer is midline or significantly crosses the midline necessitating 1:1 weighting. The initial portals extend from 2 cm above the angle of the mandible to the bottom of the cricoid cartilage, 1.5 cm anterior to the skin of the anterior neck, and to the posterior aspect of the spinous processes of the cervical vertebrae. The posterior border may be tight for patients with node-negative glottic cancer, where the risk of level V node involvement is minimal (Fig. 18-24).[6] A strip of skin may be spared for patients with supraglottic cancers depending on the anterior extent of the tumor. IMRT is usually not indicated for these patients because it is possible to exclude most of the parotid glands from the conventional fields. The fields are enlarged depending on the location of the primary tumor and neck disease. For example, the inferior edge of the field may be placed 1 to 2 cm below the bottom of the cricoid cartilage if there is subglottic extension. Because patients with positive neck nodes have an increased risk of retropharyngeal lymph node involvement, it is necessary to include the retropharyngeal lymph nodes at the level of the C1–C2 vertebral bodies in the initial portals. The fields are reduced off the spinal cord at approximately 45.0 Gy, and a second mucosal reduction usually occurs at about 60.0 Gy. If necessary, electron beam may be used to treat the posterior strip after reducing off the cord. The low neck is treated with an anterior field with a small, tapered, midline block.

Patients may be treated once daily or with an altered fractionation schedule.[7] The concomitant boost technique is currently employed at the University of Florida; gross disease receives 72.0 Gy in 42 fractions over 30 treatment days over 6 weeks, and moderate risk subclinical disease receives 49.5 to 54.0 Gy.[8] Alternatively, hyperfractionation may be employed to deliver 74.4 Gy in 62 twice-daily fractions. Clinically negative nodal regions that are treated include ipsilateral levels IB, II, III, IV, V, VI, and retropharyngeal nodes, as well as contralateral levels II, III, and IV.[8] Patients receive weekly concomitant cisplatin 30 mg/m$^2$ during the course of radiation therapy (RT). A computed tomographic (CT) scan is obtained 1 month after RT to determine whether a neck dissection is indicated.[9] An example of a patient treated with IMRT is shown in Figure 18-25.[8]

The portals used to treat patients after surgery, which would usually entail a total laryngectomy and neck dissection for patients with an advanced primary cancer are depicted in Figure 18-26.[10] The anterior field edge allows tangential irradiation of the skin of the anterior neck. The neck nodes are often positive, necessitating inclusion of the retropharyngeal and junctional nodes in the initial portals. The lower border of the lateral fields slants superiorly from anterior to posterior, and the central axis of the anterior low neck field is placed at the field junction, so

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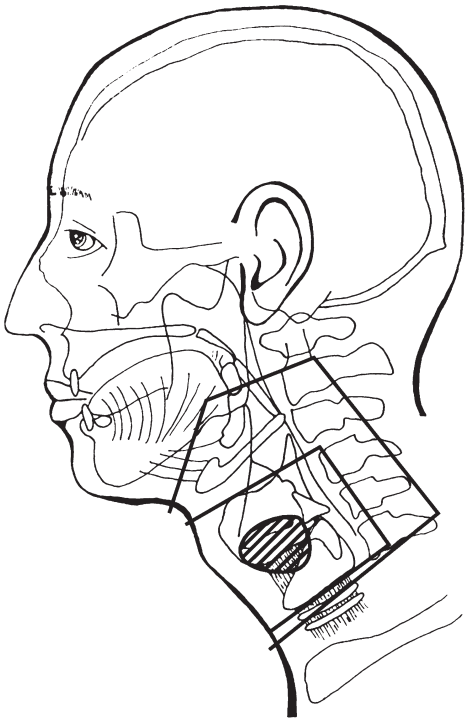


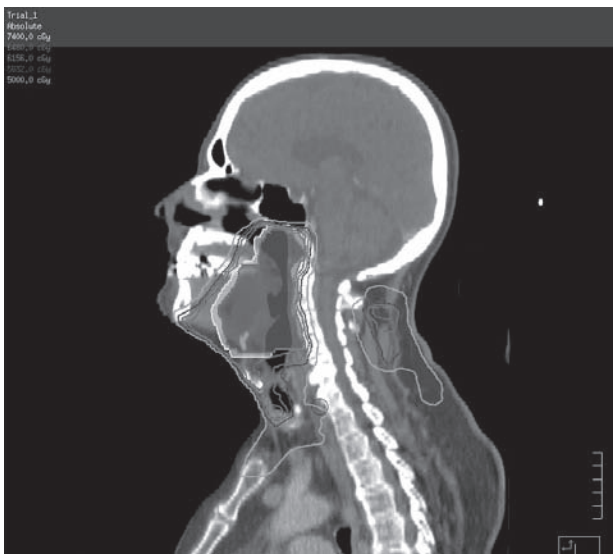
**FIGURE 18-24.** Portals for T3–4 lesions: The initial portal includes the jugulodigastric and mid jugular lymph nodes. In the N0 patient, the highest jugular lymph nodes near the base of the skull are at little risk of involvement. To ensure adequate coverage of the mid jugular lymph nodes, it is necessary to include the spinal cord in the treatment volume. The placement of the inferior border depends on the presence and degree of subglottic extension as determined by direct laryngoscopy and computed tomography and is commonly 1.0 to 2.0 cm below the inferior border of the cricoid cartilage; this line is slanted to facilitate matching with the anterior low neck portal. Anteriorly, the beam is allowed to "fall off" over the skin and subcutaneous tissues. The entire preepiglottic space is included within the initial treatment volume.

*Source:* Parsons JT, Mendenhall WM, Mancuso AA, et al. Twice-a-day radiotherapy for T3 squamous cell carcinoma of the glottic larynx. *Head Neck.* 1989;11:123–128 (Fig. 1, p. 124), with permission.

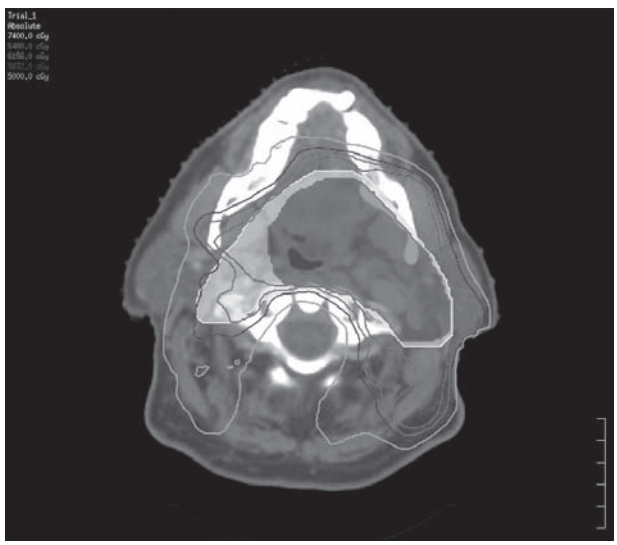
that dose to the spinal cord at the junction is low (Fig. 18-27).[11] This field-matching technique has been used for over five decades at the University of Florida, with a very low risk of radiation myelitis and a low risk of failure in the neck at the junction. Patients are treated with $^{60}$Co or 6 MV x-ray. Vaseline gauze bolus, 5 mm thick, is placed in the incision to ensure an adequate surface dose. The low neck node is given 50 Gy in 25 fractions specified at Dmax, after which the dose to the stoma may be boosted with an electron beam (usually 12 MeV), if there is subglottic extension.

IMRT may be employed postoperatively for the same indications as those used for patients treated with definitive RT. The fractionation schedule and whether concomitant chemotherapy is employed depends on the pathologic findings.

The technique employed for preoperative irradiation is the same as that used for patients treated with irradiation alone.



A



B

**Figure 18-25. A & B:** Patient with a T3N0 squamous cell carcinoma of the glottic larynx. The patient is treated with 6-MV X-rays with IMRT. The high-risk clinical target volume (HR-CTV) receives 70 Gy at 2 Gy per once-daily fraction or its equivalent using altered fractionation. The standard-risk CTV (SR-CTV) receives 54 Gy. **A)** Axilla contour; **B)** Control contour. (See color insert.)

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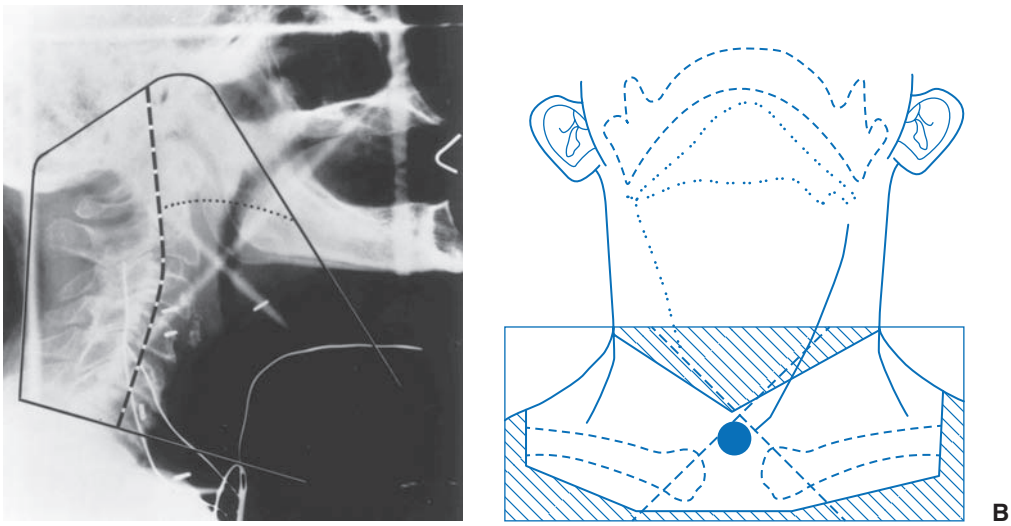



**FIGURE 18-26.** The University of Florida's three-field technique for laryngeal irradiation. **A:** Typical simulation field for laryngopharyngeal irradiation. An initial off-cord reduction executed at 50 Gy is indicated by *dashed lines*, whereas the second reduction (60 Gy) is indicated by the *dotted lines*. The slanting inferior border reduces the length of spinal cord in the primary field, avoids irradiating the shoulders, and facilitates avoidance of a field overlap with the low neck match field. **B:** Schematic diagram of the low neck field. The *solid line rectangle* represents the setting of the machine collimators, whereas the *shaded areas* represent the portions of the field that are blocked using full-height hand blocks made of Lipowitz metal. The superior border of the low neck field is common with the inferior borders of the primary fields. Because of the hand blocking of the low neck field, the superior border of the field assumes a V shape. Therefore, a short segment of the spinal cord remains untreated at the match line between fields.

*Source:* Amdur RT, Parsons JT, Mendenhall WM, et al. Postoperative irradiation for squamous cell carcinoma of the head and neck: an analysis of treatment results and complications. *Int J Radiat Oncol Biol Phys.* 1989;16:25–36 (Fig. 1, p. 27), with permission.

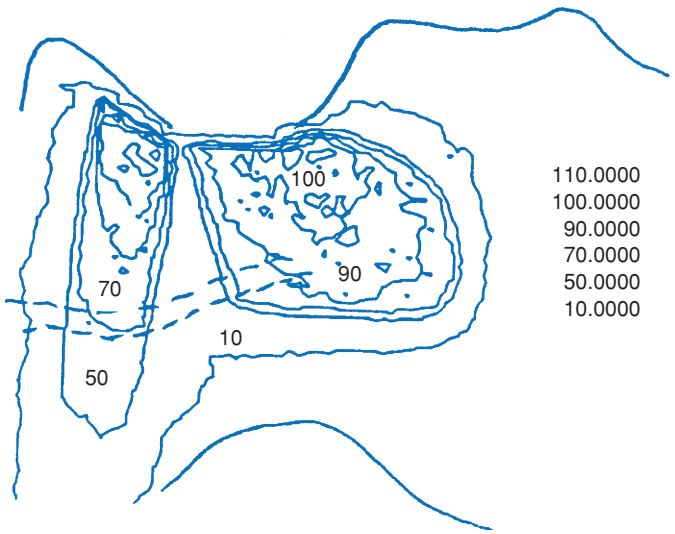



**FIGURE 18-27.** Averaged cobalt-60 ($^{60}$Co) distribution for larynx primary field with low neck match and trachea block removed. The dose distribution was obtained using a thermoluminescent detector (TLD) sheet, and the doses are normalized to the central-axis dose.

*Source:* Meeks SL, Williams RO, Bova FJ, et al. The midline dose distribution for a three-field radiotherapy technique. *Med Dosim.* 1999;24:91–98 (Fig. 8, p. 96), with permission.

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# PART D:
# Surgical Decision Making and Technique

F. Christopher Holsinger and Andrew J. McWhorter

Options for surgical treatment of early larynx cancer include open conservation laryngeal surgery (CLS) or transoral endoscopic resection, with either traditional "cold-steel" phonosurgery or transoral laser microsurgery (TLM). Although the use of open techniques has declined, the emergence of transoral endoscopic head and neck surgery (eHNS)[1] has rekindled interest in functional organ-preservation surgery of the larynx and has expanded the available multidisciplinary treatment options for patients. Chen et al.[2] recently found that among patients with early-stage cancer, those receiving primary surgery increased (from 20% in 1985 to 33% in 2007), whereas the use of RT decreased from 64% to 52%. However, for intermediate- and advanced-staged cancers, Hoffman described the opposite trend: a greater role for radiation and concurrent chemoradiation over these same decades.[3] This review of the National Cancer Database between the years 1985 and 2001 found a trend toward decreasing survival among patients with laryngeal cancer from the mid-1980s to mid-1990s. During these decades, the authors found a significant increase in chemoradiation, with a concomitant decline for the role of surgery.

Over this same time period, there has been a sea change within the field of head and neck surgery. For years, cancer surgery for tumors of the larynx has been synonymous with "total laryngectomy." However, now an array of new surgical approaches, including transoral minimally invasive surgery of the larynx, and supracricoid partial laryngectomy (SCPL) offer the potential to improve clinical outcomes, function, and quality of life.[4] Since these techniques are just now being routinely accepted and employed within the multidisciplinary paradigm, we review here the current role of surgery for patients with laryngeal cancer.

## ENDOSCOPIC RESECTION

### Vocal Stripping, Cold-Steel Resection, and Phonosurgery

Vocal cord stripping may still occasionally be performed for selected superficial, noninvasive lesions of the glottis.[5,6] In general, this previously accepted technique of vocal cord stripping has fallen out of favor due to the poor voice results that often accompanied these procedures. Early malignant tumors, and even extensive premalignant disease, may seem superficially invasive, by preoperative exam in the clinic, but in fact often have invasion of the vocal ligament.[7] Our improved understanding of the layered vocal fold from Hirano[8] and the refinement of microflap techniques have pushed this technique toward obsolescence. The stripping technique is rather imprecise in peeling away the epithelium in the layer of the superficial lamina propria. Failure to preserve this layer when possible, and in a nonuniform manner, has relegated its use to a vocal fold scar model for investigational studies. The more precise technique of microflap excision has proven to be voice preserving in many instances and successful in the treatment of precancerous lesions. Ossoff's work detailed the successful regression of preneoplastic lesions with serial microflap excision of dysplasia.[9]

***Technique.*** Rigid laryngoscopy in suspension under microscopic guidance is used for resection. Microlaryngeal instrumentation is used to sharply excise the tumor from the vocal folds. In the microflap technique, an incision is made lateral to the lesion, which is bluntly undermined and then sharply excised.

### Transoral Laser Microsurgery

In contrast to transoral cold-steel "phonosurgery," the concept of TLM encompasses the laser-based surgical resection of tumors of the larynx through the mouth. For the purposes of this chapter, we will limit this terminology to TLM of the larynx, but the technique can easily and reliably be applied to the oral cavity, oropharynx, and hypopharynx as well. TLM as a surgical approach is founded upon the historical evolution of the field of otolaryngology and reflects the practitioner's ability to look through the transoral window into the laryngopharynx and treat myriad conditions. Traditionally, TLM is done using a line-of-sight laser beam aided by a microscope. As the use of the operating microscope with the laser greatly facilitated complete tumor excision that was not possible with cold surgical techniques, advances in technology will likely continue to expand the repertoire of the TLM approach. With continued advances in lasers, robotics, and visualization technologies, TLM techniques will continue to evolve and improve.

In 1972, Jako and Strong published the first clinical experience using the carbon dioxide laser as part of transoral microsurgery for the treatment of benign and early malignant lesions of the larynx.[10] The technique was widely adopted among laryngologists, but failed to take hold within head and neck surgery. Steiner[11,12] and others in Europe developed this technique and made critical conceptual advances and improvements in instrumentation. Since then, TLM has played a much greater role within the multidisciplinary paradigm, and its use has been expanded for tumors throughout the upper aerodigestive tract and for more advanced-stage tumors.[12]

TLM may or may not entail a "piecemeal excision" of the laryngeal tumor. Small lesions can be removed *en bloc* or by dividing the tumor across its main axis. Although this approach violates Halstedian technique, advocates argue that by appreciating the unseen depth of the lesion, especially near critical and/or unique anatomy, an adequate oncologic resection can be achieved, while minimizing the sacrifice of surrounding normal structures. Using the operating room microscope, which provides magnification of 4× to 12×, the endoscopic surgeon can have significantly improved visualization and thus more detailed understanding of the interface between tumor and normal tissue.[13,14] By dividing the tumor, though, the surgeon must bear additional responsibility to provide adequate margins through close coordination with pathology—as well as close tumor surveillance postoperatively. In fact, in the largest series published on the role of margins in TLM, Jackel et al.[15] found that 30% of patients required some additional surgery for a variety of T1 to T4 tumors treated with TLM, mostly for inadequate margins on final histopathology, despite negative frozen sections. Most of these patients (82% of the re-resected specimens demonstrated no evidence of residual tumor) had similar rates of local control as those patients in whom revision was not necessary. This discordance suggests the inherent challenges associated with TLM and underscores close partnership with the surgical pathologist. However, patients with residual tumor after revision TLM showed a significant reduction in locoregional control as well as

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larynx preservation. However, in this study, overall survival was not significantly affected[15]; rather, there is a need for open surgery and salvage radiation therapy for these patients with positive re-resection margins.

Despite these concerns, TLM has outcomes comparable to open conservation surgery and radiation therapy for patients with T1 to T2 glottic cancer. Local control for T1 lesions was 77% to 92% and that for T2 tumors was 61% to 88%. After salvage therapy, an "ultimate" local control rate was well above 90% with 5-year disease-specific survival of 86% to 98%.[16–22] Authors quote high rates of overall larynx preservation, when TLM is selected as the first treatment modality with rates ranging from 90% to 99%,[16–19,21,22] although one group reported a larynx-preservation rate of 97% for T1 tumors and 82.5% for T2 lesions.[20] Critics of TLM point out that most of the literature is derived from single institutional retrospective reviews. However, there remains no NCI, or industry-funded cooperative group, or funding to support central data collection and prospective investigation.

Despite these current roadblocks to prospective clinical investigation, Hinni and his colleagues assembled in 2007 a multidisciplinary review of TLM in the treatment of advanced laryngeal cancer of stages T2 to T4. Two-year larynx preservation and local disease control rates were 92% and 82%, respectively. Five-year Kaplan-Meier estimates of overall survival were 55%, in keeping with results from the RTOG-911. A number of larger series such as this and other now appear to suggest that TLM for the treatment of larynx cancer has local control rates, and larynx preservation, on par with open approaches with better functional outcomes, and in properly selected patients on par with radiation therapy.

First and foremost, TLM represents a dramatic break from traditional compartmental or subunit surgery for the resection of laryngeal tumors. Yet this "precision medicine"[23] approach using transoral eHNS creates challenges in nomenclature and description of the TLM procedure performed. In this new approach, each endoscopic resection is personalized for the individual patient's tumor and is thus not removed in the traditional whole organ or compartmental fashion. In 2000, Remacle led the European Laryngological Society (ELS) effort to develop a classification system for the endoscopic resection of glottic cancer.[24] In this schema, endoscopic cordectomy is categorized into five types, ranging from subepithelial to anterior commissurectomy with bilateral anterior cordectomy, to "extended cordectomy," representing the full array of partial laryngectomies[24,25] (Table 18.15). In 2009, the ELS proposed a classification system for endoscopic supraglottic laryngectomy with four categories, ranging from limited excision to a lateral supraglottic laryngectomy[26] (Table 18.16).

Although TLM offers many advantages to the surgeon, there are also important limitations. First, not every patient may be a suitable candidate. Inadequate endoscopic exposure due to dental occlusal, deformity, retro- or micrognathia, or macroglossia may limit the number of patients eligible for endoscopic resection. Second, adverse tumor features, such as an endophytic growth pattern, perineural invasion, or occult extralaryngeal spread,[27,28] are associated with poor oncologic and functional outcomes. Previous radiation treatment may also be a relative contraindication. Although TLM may be effective in this setting, identification of tumor margins and prolonged mucosal healing are more difficult during endoscopic resection after radiation therapy.

Steiner et al.[29] reported on 34 patients with early- or advanced-stage recurrent glottic carcinoma after radiation therapy. Twenty-four patients (71%) were cured after one or more TLM. Patients with early-staged recurrent carcinomas had lower rates of local recurrences and salvage total laryngectomy than did patients with advanced recurrent cancers. However, in this experience, more than half of the patients required at least two TLM procedures to achieve disease control, underscoring the difficulty of this approach. Similarly, Quer et al. presented a series of patients treated with TLM for both supraglottic and glottic cancers, recurrent after radiation.[30] Although disease-free survival rate after 5 years was 100%, multiple procedures were required to achieve disease control. For these reasons, the role of TLM in the setting of surgical salvage after radiation should be carefully considered. For small limited recurrences (rT1), TLM may appear to offer good results. For more extensive recurrence after radiation, open surgery may be a better option. What is clear, though, is that TLM has its best role to play as primary, rather than salvage, therapy.

As primary treatment for laryngeal cancer, TLM is associated with several advantages in the short-term benefits (Fig. 18-28A,B). Tracheotomy is rarely needed. Swallowing dysfunction is rare, especially for patient undergoing endoscopic

**TABLE 18.15 Schema for Endoscopic Cordectomy**

| | |
|---|---|
| I | Subepithelial cordectomy |
| II | Subligamental cordectomy |
| III | Transmuscular cordectomy |
| IV | Total cordectomy |
| V | Extended cordectomy |
| | Va including contralateral vocal fold |
| | Vb including the arytenoids |
| | Vc including the ventricular fold |
| | Vd including the subglottis |
| VI | Anterior commissurectomy with bilateral anterior cordectomy[25] |

*Source:* From Remacle M, Eckel HE, Antonelli A, et al. Endoscopic cordectomy. A proposal for a classification by the Working Committee, European Laryngological Society. *Eur Arch Otorhinolaryngol.* 2000;257:227–231, with permission.

**TABLE 18.16 Classification of Endoscopic Supraglottic Laryngectomy**

| | |
|---|---|
| I | Excision of small, superficial lesions confined to single subsite of the supraglottis |
| II | Medial supraglottic laryngectomy with preservation of the preepiglottic space |
| | IIa with superior hemi-epiglottectomy |
| | IIb with total epiglottectomy |
| III | Medical supraglottic laryngectomy including the preepiglottic space |
| | IIIa with preservation of the ventricular fold |
| | IIIb with resection of the ventricular fold |
| IV | Lateral supraglottic laryngectomy |
| | IVa with resection of the ventricular fold |
| | IVa with resection of the arytenoid |

*Source:* From Remacle M, Hantzakos A, Eckel H, et al. 1, 2. Endoscopic supraglottic laryngectomy. A proposal for a classification by the working committee on nomenclature, European Laryngological Society. *Eur Arch Otorhinolaryngol.* 2009;266:993–998, with permission.

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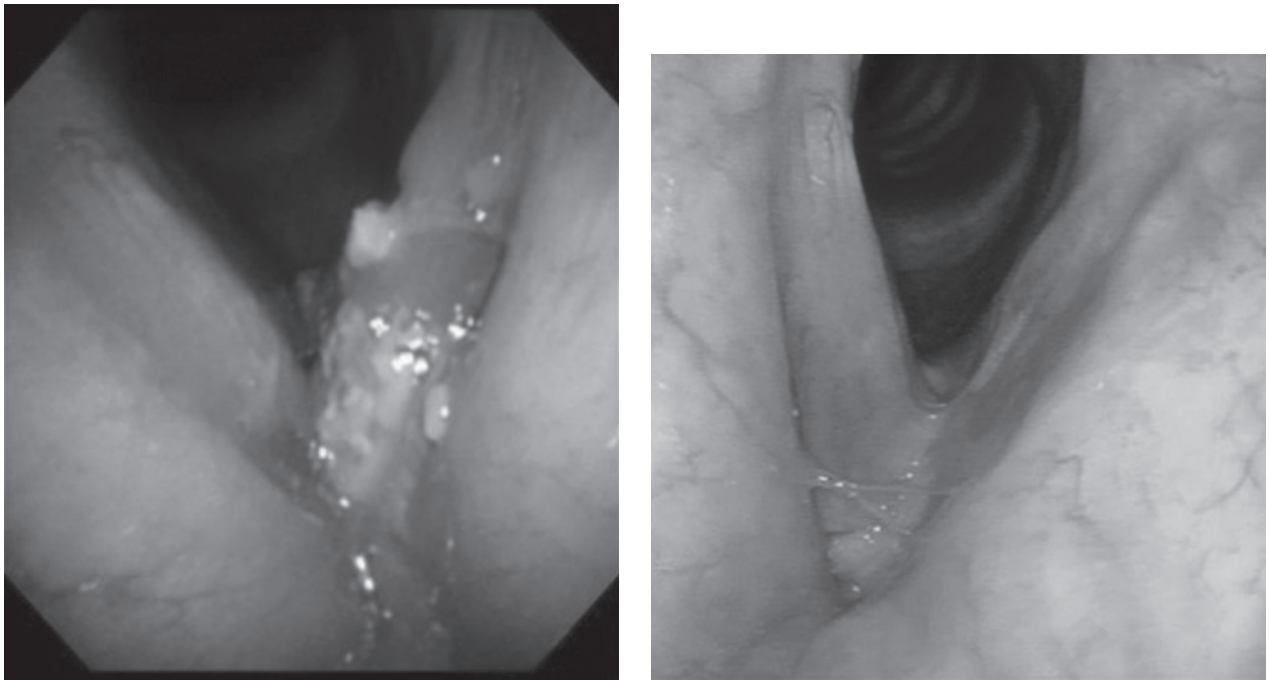


**FIGURE 18-28.** Transoral laser microsurgery for glottic laryngeal cancer. **A:** Preoperative laryngoscopy demonstrates a tumor of the left transglottic larynx in a 63-year-old male smoker with T2N0M0 squamous cell carcinoma. The tumor extends from the false cord to the subglottis. **B:** Postoperative view at 24 months.

resection for glottic cancer. These functional advantages are also associated with shorter hospital stays and lower costs of treatment.[31] In most cases, endoscopic surgery broadens the management possibilities for persistent or recurrent disease; salvage for failure after TLMs can be approached with further endoscopic, or open surgery, or with radiotherapy.[5,14]

***Technique.*** Using suspension direct microlarynoscopy, the carbon dioxide laser is used to transect the tumor to determine the depth of invasion. Using microlaryngeal instrumentation, it is then typically resected, either *en bloc*, or in the fashion proposed by Steiner,[32] maintaining orientation of the specimens removed in order to evaluate for margin status. The technique usually varies from traditional open CLS in following the tumor, rather than subscribing to the compartment resection theory of the larynx. Healing is by secondary intention, with contraction of the resected tissue, avoiding the need for reconstruction (Fig. 18-29).

## Conservation Laryngeal Surgery

CLS[33] represents a broad array of open surgical techniques, ranging from laryngofissure with cordectomy to supracricoid laryngectomy. In addition to achieving comparable rates of local control, with CLS, surgeons can achieve functional organ preservation by understanding the cricoarytenoid unit[34] (defined as arytenoid, cricoid cartilage, associated muscles, and corresponding innervation by the superior and recurrent laryngeal nerves) as the basic functional unit of the larynx, not the vocal cord alone.[33]

Rarely, laryngofissure with cordectomy may still be required, perhaps for patients with poor transoral exposure. The thyroid cartilage is divided to gain access to the endolarynx, and with wide visualization, the tumor is excised. Historically, postoperative tracheotomy was always required,[35] but Laccourreye et al. described a series of 33 patients where this was not needed: local control was 100%; 5-year survival rate 97%.[36]

Vertical partial laryngectomy (VPL), also known as hemilaryngectomy, is a time-honored approach to resecting an entire ipsilateral glottic larynx, including paraglottic space and corresponding thyroid ala, but preserving the ipsilateral arytenoid. Local control rates for T1 cancers range from 89% to 100%.[37–40] Involvement of the anterior commissure decreases local control; one study reported that anterior commissure involvement decreased local control from 93% to 75%. For tumors involving the anterior commissure or the anterior-most aspect of the contralateral vocal fold, an extended VPL or frontolateral vertical hemilaryngectomy can be done. Yet for larger T2 tumors, VPL may be less effective, with local control rates of 74% to 86%.[37–39,41] Ultimately, for preoperative decision making, T classification may be less effective than careful laryngoscopic exam: for instance, patients with significant extension to the subglottis or supraglottis, or without impaired vocal cord mobility may fare worse.

***Technique.*** Tracheotomy is performed separately from the incision for resection. The strap muscles are then reflected isolating the laryngeal cartilages. The outer perichondrium is then elevated and preserved overlying the ipsilateral thyroid cartilage. A midline vertical thyrotomy is performed, and resection is carried across the cricothyroid membrane and thyrohyoid membrane preserving the epiglottis. *En bloc* resection of the true vocal fold and paraglottic space along with thyroid cartilage is obtained. Reconstruction is performed with the preserved perichondrium and strap muscles to create a buttress for contact with the remaining contralateral vocal fold. These resections can be extended to include the contralateral true vocal fold or ipsilateral arytenoid.

In contrast to the VPL, the supraglottic laryngectomy (SGL) is also known as the "horizontal" partial laryngectomy. First performed in 1939[42] by Alonso from Uruguay,[43] SGL encompasses the resection of the entire supraglottis from hyoid to false cord, including the preepiglottic space, while preserving both true vocal cord and arytenoids. For properly selected patients, SGL

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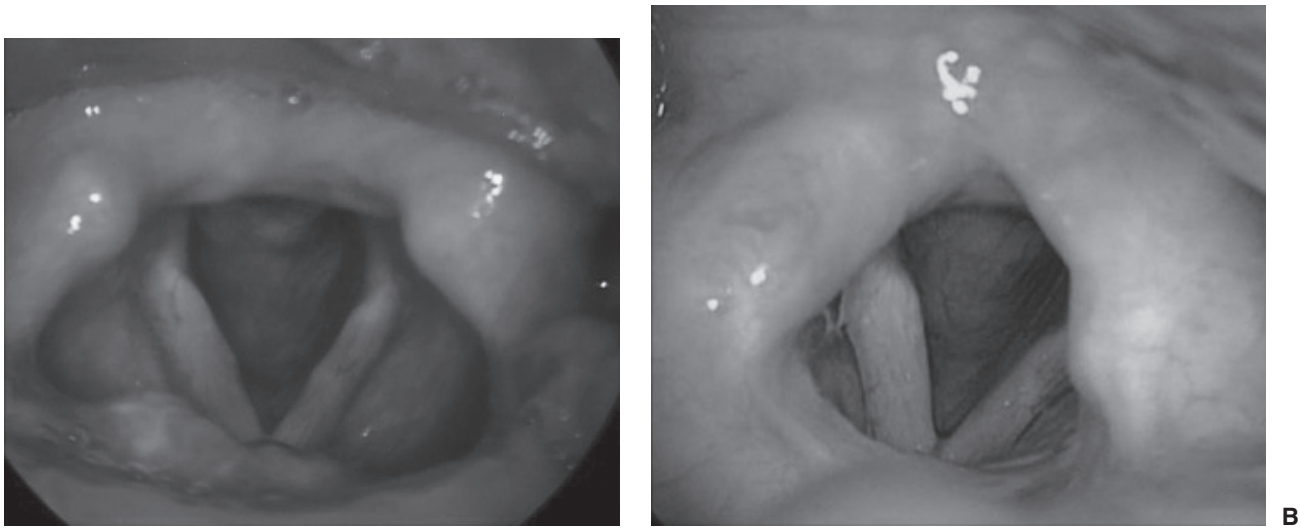



**FIGURE 18-29.** Transoral laser microsurgery for supraglottic laryngeal cancer. **A:** Preoperative laryngoscopy demonstrates a tumor of the infrahyoid supraglottic larynx in a 57-year-old female smoker with T2N0M0 squamous cell carcinoma. **B:** Postoperative view at 12 months.

achieves rates of locoregional control ranging from 92% to 100% for T1 lesions and 85% to 100% for T2 tumors.[44–47] Ogura[48] and others have described a variety of extended procedures, which range from procedures that include resection of the tongue base, arytenoids, aryepiglottic fold, or pyriform sinus. Contraindications include tumors that involve the glottis larynx, or extend to the thyroid, or cricoid cartilage invasion, tongue base, or the intrinsic deep-tongue musculature.[48,49]

***Technique.*** Tracheotomy is performed, followed by separation of the strap muscles, and isolation of the thyroid cartilage and hyoid bone. The hyoid is released from the suprahyoid musculature. The pharynx is entered in the vallecula, and the thyroid cartilage is transected immediately above the anterior commissure. Cuts are made through the apex of the ventricle, anterior to the body of the arytenoid resecting the false folds, the epiglottis, and the aryepiglottic folds, while including the preepiglottic space. Reconstruction is performed by closing the laryngeal remnant to the base of tongue and the strap muscles as a second layer of closure.

Though VPL and SGL have a long and rich history within the pantheon of CLS, the SCPL has gained popularity over the past decade. SCPL was first described in French by Majer and Rieder in 1959 while they were working in Vienna.[50] This novel approach advocated preservation of speech and swallowing via subtotal laryngectomy, by creating an impaction of the hyoid bone onto the cricoid cartilage, a "crico-hyoïdo-pexie."

Surgeons in France made critical technical refinements, namely, Labayle[51] working in Paris and J. J. Piquet working in Lille,[52] which led to wide adoption of SCPL. Laccourreye organized these disparate procedures as supracricoid partial laryngectomies and standardized their reconstructions as either cricohyoidopexy (CHP) or cricohyoidoepiglottopexy (CHEP).[53,54]

SCPL[34] involves the resection of both true and false vocal folds, the entire thyroid cartilage, both paraglottic spaces; the epiglottis may or may not be removed depending on tumoral spread. After SCPL, the laryngopharynx is reconstructed through either cricohyoidoepiglottopexy (CHEP) or a cricohyoidopexy (CHP), depending on the extent of resection (Fig. 18-30). For early- and intermediate T1–2 stage cancers, the 5-year estimates of local control range from 91% to 98%.[55,56] The most common complication is postoperative aspiration, occasionally leading to pneumonia.[57] Rates of permanent gastrostomy and/or tracheotomy are < 5% to 10%, as is postoperative mortality rate (1%–2%).[55,58] Severe postoperative morbidity usually develops when the SCPL is used as salvage therapy after radiation therapy. Although SCPL-CHEP can be used with some success after radiation therapy, good functional outcomes after radiation are more difficult to achieve when performing salvage SCPL-CHP. Much higher rates of local wound-healing complications[59] or rupture of the pexy are seen after RT.[60,61]

***Technique.*** Apron flap is elevated, and the strap muscles are divided in the midline released below the infrahyoidal and above the oblique line of the thyroid cartilage, thus isolating the hyoid, the thyroid, and the cricoid cartilages. The superior laryngeal nerves are preserved, and the thyrohyoid membrane is incised, releasing the thyroid cartilage superiorly. Inferiorly, the cricothyroid joint is disarticulated, preserving the recurrent laryngeal nerve, and the cricothyroid membrane incised releasing the thyroid cartilage inferiorly. The larynx is then entered through the vallecula or

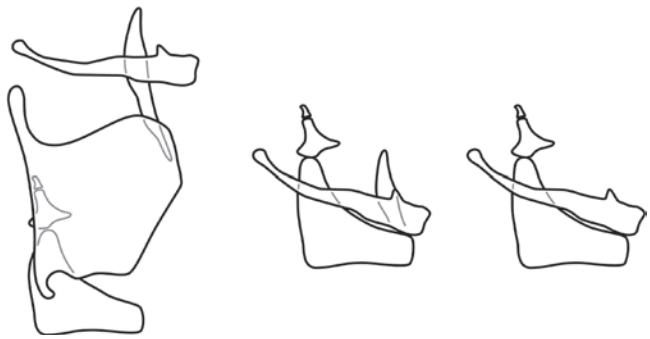


**FIGURE 18-30.** Schematic for SCL with CHEP and CHP reconstruction. A diagram indicating the extent of resection with SCL and the optimal mechanical cricohyoid impaction for reconstruction using cricohyoidopexy or cricohyoidoepiglottopexy.

*Source:* From Holsinger FC, et al. Technical refinements in the supracricoid partial laryngectomy to optimize functional outcomes. *J Am Coll Surg.* 2005;201(5):809–820, with permission.

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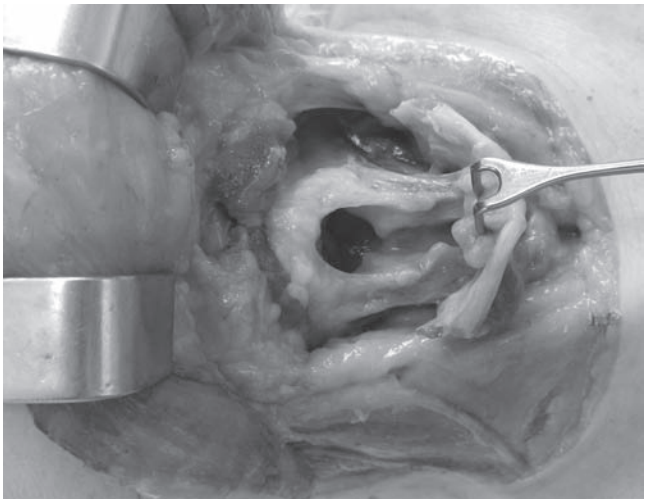


**FIGURE 18-31.** Cadaveric dissection demonstrates the arytenoid cartilages as seen from the laryngotomy in supracricoid laryngectomy.

*Source:* Courtesy of Professor Ollivier Laccourreye, Paris, France, with permission.

across the petiole of the epiglottis depending on the location of the tumor (Fig. 18-31). For supraglottic tumors, the surgeon should encompass the epiglottis and the underlying preepiglottic space within this vallecular laryngotomy incision. For glottic tumors, the surgeon can preserve the epiglottis to assist in deglutition. Posterior incisions are made at the vocal process, down along the cricoid cartilage, preserving the lateral cricoarytenoid muscle, while resecting the paraglottic space (Fig. 18-32). Reconstruction is performed by "impacting" or suturing the cricoid to the hyoid with a #1 suture. This impaction creates a neoglottis with the arytenoids to the epiglottis (CHEP) or the base of tongue (CHP) (Fig. 18-33).

## Total Laryngectomy

Total laryngectomy is the gold standard of treatment for advanced-stage laryngeal cancer. First performed successfully by Billroth in 1863 for cancer resection, it was later modified to a one-stage procedure in the 1880s by Gluck and Sorenson.[62] It is used for advanced-stage tumors of the larynx, and for both oncologic and functional surgical salvage. The role of primary therapy with total laryngectomy has long been cast in a negative light due to the necessary rerouting of the trachea, and the stigma of a permanent stoma and voice loss. Today, it is used only for advanced-stage

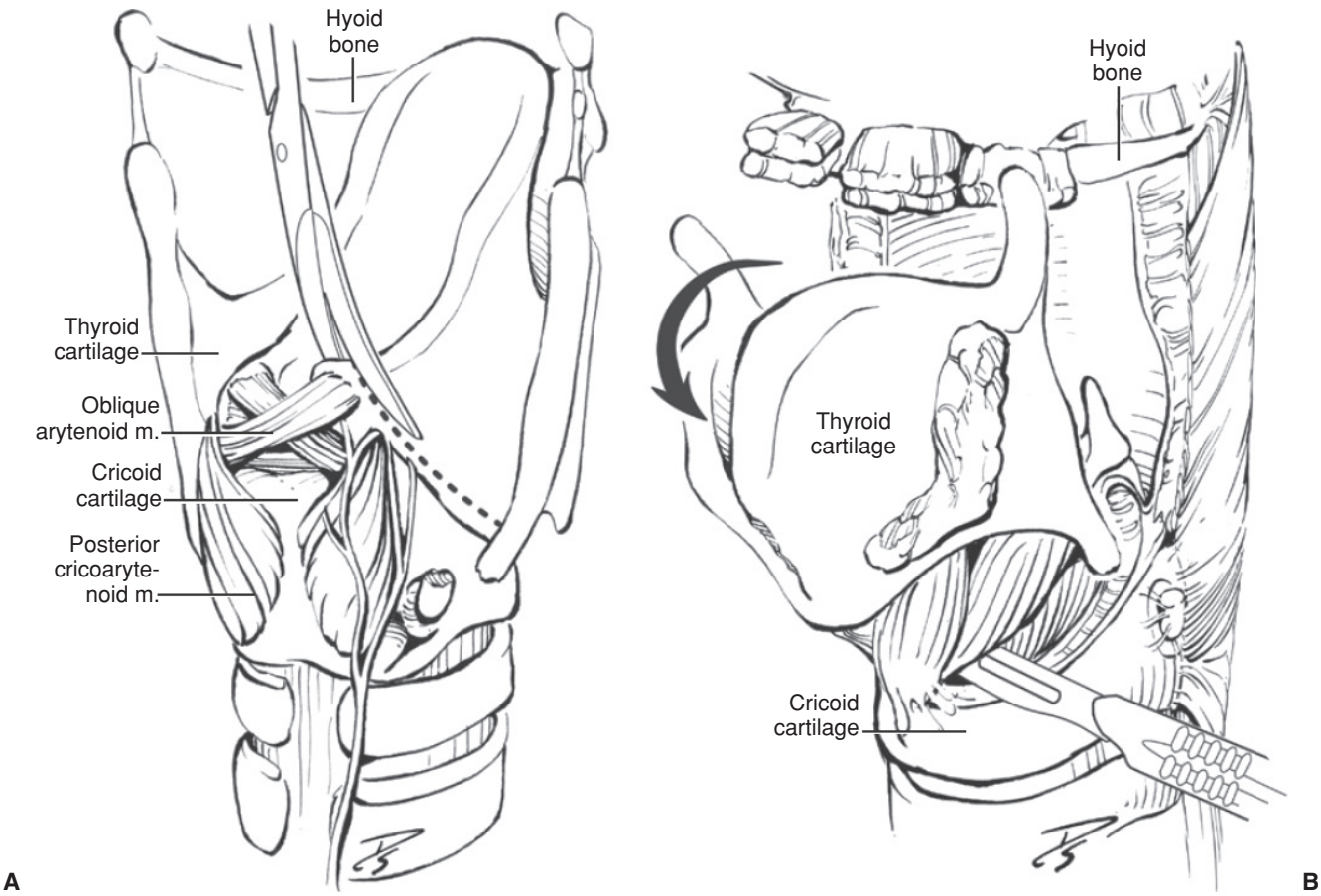



**FIGURE 18-32.** Schematic for laryngeal incisions for supracricoid laryngectomy (SCPL) for a glottic laryngeal tumor. **A:** After vallecular laryngotomy and the anterior release of the larynx, posterior incisions must be made through the base of the aryepiglottic folds, preserving the entire unaffected arytenoid cartilage, and separating the glottis with a final incision just anterior to the vocal process of the arytenoid. To clarify, the vocal cords are removed completely during SCPL. Shown here with scissors, cold-steel technique or monopolar cautery may be used. **B:** Then the remaining paraglottic space is removed with incisions placed just above the anterior border of the cricoid cartilage, hence the name of the procedure.

*Source:* From Cohen JI, Clayman GL. *Atlas of Head and Neck Surgery.* Philadelphia, PA: Elsevier; 2011 (after Fig. 36-3), with permission.

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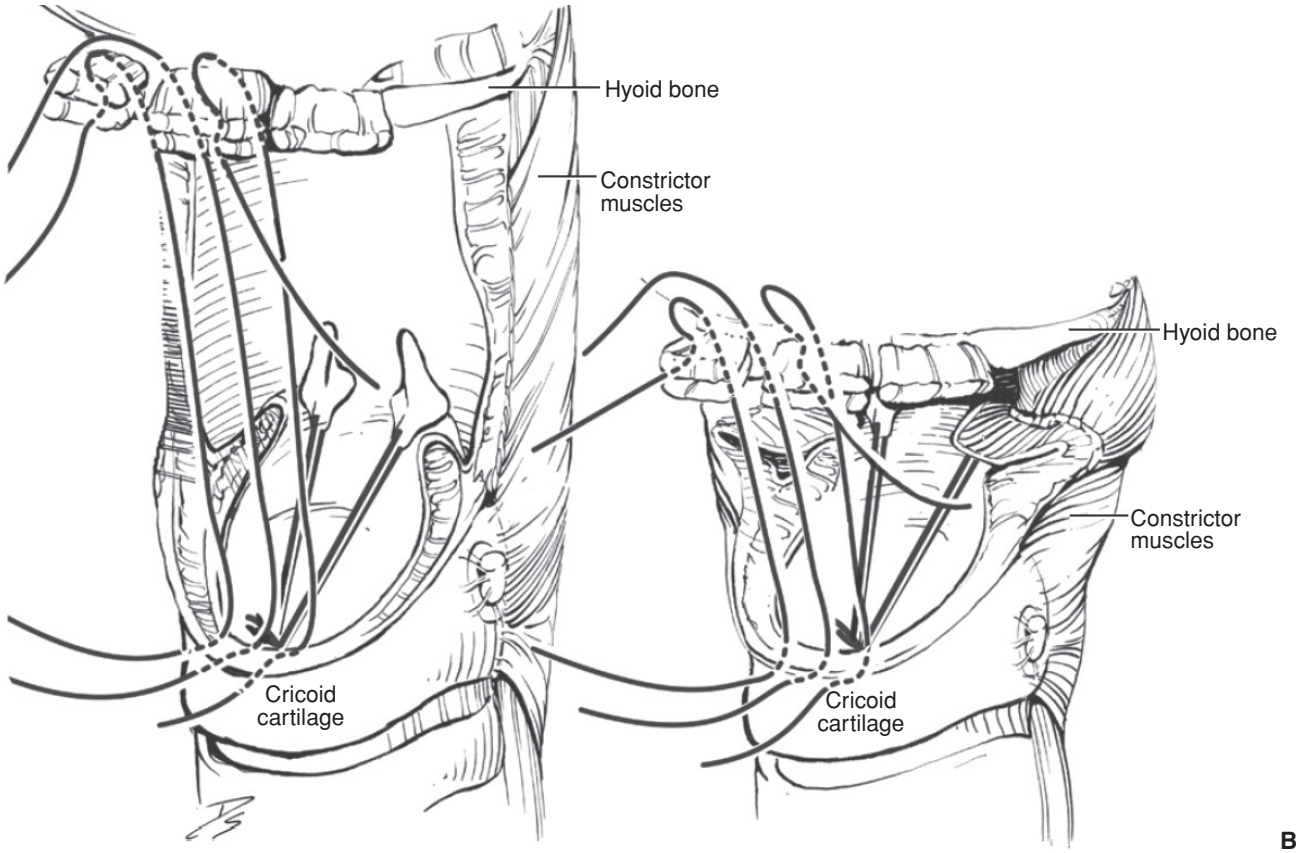



**FIGURE 18-33. A:** Three stitches are used to approximate the hyoid bone and the epiglottis (for cricohyoidoepiglottopexy) to the cricoid cartilage. Each should be placed 8 to 10 mm apart from the midline and are passed from inferior to superior submucosally. **B:** The neolaryngeal apparatus is reconstructed as these sutures are tightened in a secure "pexy" between the hyoid above and the cricoid below.

*Source:* From Cohen JI, Clayman GL. *Atlas of Head and Neck Surgery.* Philadelphia, PA: Elsevier; 2011 (after Fig. 36-6), with permission.

tumors not felt to be candidates of organ-preservation therapy, due to extensive thyroid cartilage invasion, extralaryngeal spread, or comorbidities that prevent nonsurgical therapy. Functionally, the rehabilitation of these patients has seen dramatic benefit from the extensive adoption of tracheo-esophageal speech and cricopharyngeal myotomy. Control rates for total laryngectomy are very good overall. Five-year disease-free survival for T3 glottic tumors treated with total laryngectomy range from 49% to 80%.[63–65] The 5-year overall survival is 54%.[66,67] For T4 tumors of the glottis, the 5-year overall survival after total laryngectomy ranges from 32% to 63%.[64,65,68]

Partial pharyngectomy with total laryngectomy is required for tumors with extension into the oropharynx or the hypopharynx. For small additional defect, this can be accomplished without the need for more than primary closure in reconstruction. The typical resection, however, only includes the hyoid and the laryngeal cartilages and is closed with primary reapproximation of the pharyngeal remnant on itself to create a neopharynx. Complications are most commonly wound infection and pharyngocutaneous fistula. Fistula rates can approach 50% in the postradiated patient.[69]

***Technique.*** An apron incision is made and the tracheotomy is typically delayed until the larynx is fully mobilized. The strap muscles are included in the resection, releasing the hyoid from the suprahyoid musculature. The trachea is isolated inferiorly, and the inferior constrictor is released from the thyroid cartilage bilaterally, with the thyroid gland mobilized contralaterally, and resected with the specimen for margin ipsilaterally. The pharynx is entered in the vallecula or lateral pharynx depending on the primary, and the cuts are made across the vallecula resecting the hyoid with the preepiglottic space, and all of the endolarynx with the arytenoids, the thyroid, and the cricoid cartilages. The pyriform sinuses are released from the thyroid cartilage to maximize the pharyngeal remnant for reconstruction of the neopharynx between the esophagus and the base of tongue. The inferior cuts are made through the trachea and separated through the parting wall with the esophagus (Fig. 18-34). Though still part of the ablative aspect of total laryngectomy, the surgeon must keep in mind how surgical resection anticipates alaryngeal voice restoration. Suspension of the trachea, wide maturation of the stoma, release of the sternal heads of the sternocleidomastoid muscle, cricopharyngeal/inferior constrictor myotomy, and primary tracheo-esophageal puncture all facilitate function postoperatively. The pharynx is closed on itself primarily using a running Connell stitch, ideally in a straight line, vertical closure.

## Radiation Salvage

Surgical salvage is performed for recurrent or persistent disease following organ-preservation therapy. CLS, transoral microsurgery, and total laryngectomy all have a role in posttreatment surgical salvage. Salvage surgery may also be performed to restore function due to chondroradionecrosis or severe dysphagia. Posttreatment surveillance can be challenging due to edema and mucosal

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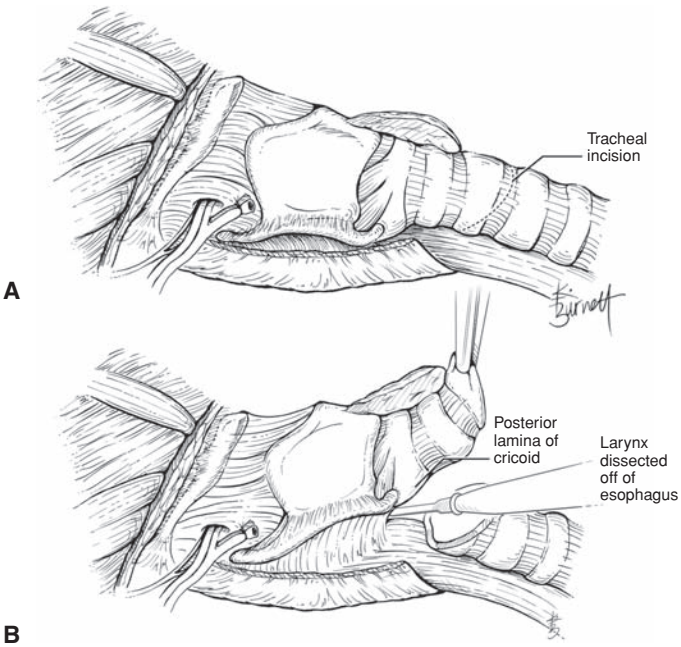



**FIGURE 18-34. A:** A gently curving tracheotomy is performed at least 1 to 2 cm below the tumor, exposing the common "parting" wall between the larynx and trachea superficially, and the posterior hypopharynx and esophagus deeply. **B:** The tracheal incision is carried through the posterior tracheal wall, and the trachea is separated from the cervical esophagus.

*Source:* From Cohen JI, Clayman GL. *Atlas of Head and Neck Surgery.* Philadelphia, PA: Elsevier; 2011 (after Fig. 37-9), with permission.

change that can mask recurrent disease. Despite close monitoring, reviews of RT failures in T1 and T2 laryngeal cancer have shown that nearly 70% of patients in whom the disease recurs require total laryngectomy as the only option for salvage treatment.[70,71]

Patient selection is critical to the successful performance on these procedures that are performed in lieu of total laryngectomy. Wound healing is prolonged in these patients, and exposed cartilage is less likely to be viable, leading to an increased incidence of wound complications and fistulae. Wider margins are required in the TLM procedures due to yet greater difficulty in determining tumor extent in the altered tissue and the opportunity for satellite lesions. Open conservation procedures have similar difficulties with decreased cartilage viability following surgery in the radiated field.

Quer et al. reported on 24 patients with recurrent supraglottic and glottic cancer who underwent salvage TLM.[30] The larynx was preserved in 18 patients (75%), and the disease-free survival rate after 5 years was 100%. Steiner et al.[29] described 34 patients with early (T1–2, $n = 21$) or advanced (T3–4, $n = 13$) recurrent glottic carcinoma after full-course RT. Twenty-four patients (71%) were cured after one or more TLM. With a median follow-up of at least 3-years, 15 (71%) of the 21 patients with early recurrent carcinomas (rT1–rT2) and 9 of the 13 patients with advanced cancer (rT3–rT4) remained disease free. Patients with early-staged recurrent carcinomas had lower rates of local recurrences and salvage laryngectomies than did patients with advanced recurrent cancers; the overall 3-year survival rate was 74%, and the 5-year survival rate was 53%.

Open conservation surgery can be even more challenging than TLM due to the wound-healing issues being compounded by the open approach. Although technically feasible, there has been less success with salvage vertical, partial, and supraglottic laryngectomy than when SCPL is performed. Laccourreye and others have successfully demonstrated the feasibility of SCPL salvage with good local control rates.[60,61] Laccourreye et al. initially reported this in 1996, with Kaplan-Meier 3-year actuarial survival and local control estimate of 83.3%.[60] Salvage total laryngectomy resulted in a 100% local control rate, while maintaining for the whole population a 75% laryngeal-preservation rate. Furthermore, these findings have been widely reproduced outside of France, with Luna Ortiz most recently finding an organ-preservation rate of 75%, and local control of 87%, with an overall 5-year survival of 50%.[72]

When patient selection precludes salvage partial larynegectomy for functional or oncologic reasons, total laryngectomy remains an excellent alternative. Again, there is a significant increase in the complication rates. Salvage total laryngectomy can also be utilized if conservation salvage efforts fail.

### Management of the Neck

New options for surgical management of the primary laryngeal tumor require us to revisit how we manage the neck. Regional lymphatic spread is uncommon for glottic cancer,[73] but is an important consideration for patients with supraglottic cancer. Even for N0 patients, 30% may occult lymphatic spread.[74] It is therefore recommended that the levels II to IV of the neck be addressed bilaterally for all supraglottic tumors, either surgically, or with postoperative radiotherapy.[75,76]

## FUNCTIONAL OUTCOMES AFTER FUNCTION-PRESERVING LARYNGEAL SURGERY

The reintroduction of surgery into the multidisciplinary paradigm, especially for early-stage disease, has introduced not only confusion and uncertainty, but also the opportunity to improve the care for patients with laryngeal cancer.

At present, there is no comparative level A evidence-based medicine comparing oncologic and functional endpoints after radiation therapy, open surgery, or transoral endoscopic surgery for laryngeal cancer. For each modality, much of the published literature is retrospective and confounded by selection bias, heterogeneity in study population, and inconsistency of outcome measures. So a consensus for how to treat the disease relies on physician preference and patient choice.

In the literature, there's a bias suggesting that radiation therapy results in better overall voice outcomes.[14] Sjogren et al. found no significant difference in posttreatment speech outcomes in T1a midcord glottic cancer treated either with laser excision or radiotherapy.[77] Voice-handicap index scores and perceptual, acoustic, aerodynamic, and stroboscopic analyses demonstrated no significant difference. Using a similar retrospective cohort design, Hirano

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et al. found an interesting discrepancy between a higher incidence of hoarseness, incomplete glottal closure, and altered vocal fold vibration with TLM, yet no difference in overall global voice function.[78] A series of additional reports demonstrate a similar equivalence in voice outcomes after either radiotherapy or laser surgery.[79,80]

Clearly though, case selection is important. For patients undergoing TLM, resections extending to or into the vocalis muscle ELS/Remacle I-c and beyond are associated with worse postoperative voice quality.[79,81,82] In view of these data, subepithelial and even subligamentous cordectomy may provide a good overall voice outcome. However, naturally, the more extensive and deep a soft tissue resection is required (> ELS/Remacle I-c), the less certain is the overall voice result. Involvement of the anterior commissure remains an issue of great interest and debate. Here also, both modalities may be associated with anterior glottis web remains, but the final impact of treatment on voice remains unknown.

For early- to intermediate-staged glottic laryngeal cancer, swallowing dysfunction is rare after TLM. For supraglottic cancers, aspiration must be expected at least in the short term.[83] However, for most patients, nasogastric tubes are usually removed within 3 weeks.[84] Without disrupting the supporting laryngeal musculature and superior laryngeal neural network, transoral endoscopic surgery is associated with a much faster return to normal deglutition, when compared to open SGL or SCPL. Sasaki et al. found that the glottic closure reflex returned within 72 hours after endoscopic SGL, compared with nearly 3 weeks for patients undergoing open SGL.[85] Similarly, after SCPL, most patients achieve full oral diets,[58,86–89] most within the first postoperative month.[58] For more advanced-stage patients, T stage and a history of previous radiotherapy were associated with the need for more long-term dysphagia, requiring gastrostomy.[83,90]

## CONCLUSION

Up-to-date multidisciplinary management of early and intermediate laryngeal cancer now includes several new surgical options.[91,92] In the absence of prospective clinical trials comparing surgery with radiotherapy to guide treatment decisions,[93] clinicians should offer the range of treatment options for patients. The largely retrospective literature suggests similar rates of local control and survival among these modalities, especially for T1 tumors.

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CHAPTER 19

# Cancers of the Hypopharynx and Cervical Esophagus

## PART A:
## General Principles and Management

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## INTRODUCTION

Cancers of the hypopharynx and the cervical esophagus share a number of overlapping features with regard to risk factors, epidemiology, management, and treatment outcomes. The anatomy of this region is served by a rich lymphatic network; therefore, presentation with nodal metastases is commonplace. In addition, patients with hypopharynx and cervical esophageal tumors frequently present with advanced-stage disease and harbor medical comorbidities that may limit the feasibility of delivering aggressive cancer care. Therefore, despite therapeutic advances in recent years, oncologic outcomes in these tumors remain relatively poor. Although organ-preservation surgery may be feasible in selected early-stage tumors, surgical management more commonly requires radical surgery such as laryngopharyngectomy or pharyngolaryngoesophagectomy. These procedures result in significant functional impairment, as well as cosmetic changes, and therefore tumors of the hypopharynx and the cervical esophagus are commonly managed with radiation or chemoradiation in an effort to control tumor while preserving organ function.

Cancers of the hypopharynx and the cervical esophagus are commonly considered together, as they share many features, and tumor frequently extends from one anatomic region into the other. Cancers of the hypopharynx accounted for 5.2% of upper aerodigestive malignancies from 2000 to 2008.[1] Similarly, cervical esophageal cancer is rare, with only 2% to 10% of esophageal carcinomas occurring in the cervical location.[2] In a recent worldwide study of >4,500 esophagectomy patients, upper esophageal tumors accounted for only 4.1% of the cohort.[3] The relative rarity of these tumors lends itself to grouping them together in order to effectively study epidemiology, management strategies, and outcomes. However, randomized control studies specific to tumors of the hypopharynx and/or the cervical esophagus are rare; studies of these cancers are often retrospective, incorporating heterogeneous management strategies spanning many years, and in some cases decades. The relative rarity of these tumors leads to a paucity of large-scale clinical trials data with which to base treatment guidelines.

Cancers of the hypopharynx and the cervical esophagus are commonly associated with tobacco use.[4,5] In addition, patients are typically elderly, with dysphagia and weight loss as a result of their tumor burden and/or a poor baseline diet.[5,6] These matters complicate management decisions and delivery of effective therapy. Given the complexity of these tumors, the surrounding structures, and frequent patient comorbidities, management of patients warrants multidisciplinary management with evaluation by head and neck, reconstructive, and thoracic surgeons, medical oncologists, radiation oncologists, speech/swallow therapists, nutritionists, and social workers. Despite advances in the treatment of hypopharyngeal and cervical esophageal cancer, the overall outcome in these patients remains poor. Efforts to improve cure rates and reduce treatment-related morbidity, including the incorporation of molecularly targeted agents, remain vital for the future.

### Incidence, Etiology, and Epidemiology

In the United States, cancer of the hypopharynx and cervical esophagus account for <10% of the tumors of the upper aerodigestive tract.[7] Approximately 1,800 cases of hypopharyngeal cancers are diagnosed each year in the United States.[8] Tumors of the cervical esophagus account for 5.3% of all esophageal cancers,[7] which equates to roughly 900 of the nearly 17,000 esophageal cancer cases per year in the United States.[9] Squamous cell carcinoma (SCC) accounts for 95% of cancers in the hypopharynx and cervical esophagus, and the causative factors for SCC in these locations are shared.

The mean age of patients presenting with hypopharyngeal cancer is 65, with three-fourth of cases occurring in men. More than 90% of patients will report a tobacco history.[10] Alcohol consumption potentiates the carcinogenic effects of cigarette smoke; in combination, heavy tobacco and alcohol users are at



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**TABLE 19.1 Odds Ratios for Oral and Pharyngeal Cancers Associated with Alcohol Consumption. Odds Ratios (or) Adjusted for Smoking, Age, and Race**

| | Males | | Females | |
|---|---|---|---|---|
| **Drinks per Week** | **OR** | **95% CI** | **OR** | **95% CI** |
| <1 | 1.0 | — | 1.0 | — |
| 1–4 | 1.2 | 0.7–2.0 | 1.2 | 0.7–1.9 |
| 5–14 | 1.7 | 1.0–2.7 | 1.3 | 0.8–2.1 |
| 15–29 | 3.3 | 2.0–5.4 | 2.3 | 1.2–4.5 |
| >30 | 8.8 | 5.4–14.3 | 9.1 | 3.9–21.0 |

*Source:* Adapted from Blot WJ, McLaughlin JK, Winn DM, et al. Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res.* 1988;48:3282–3287, with permission.

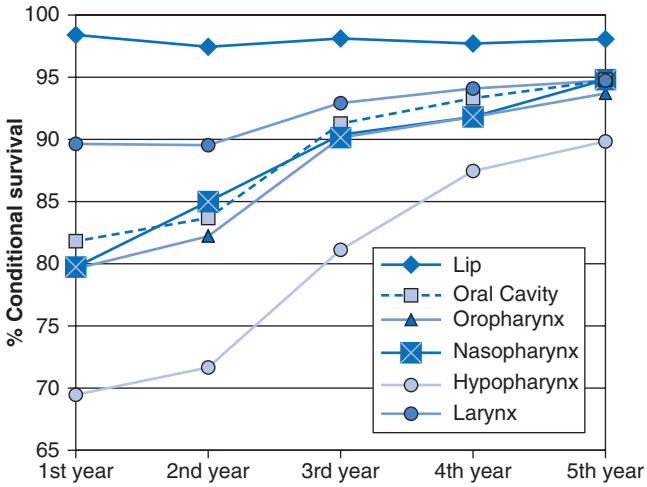



**FIGURE 19-1.** Conditional 5-year survival of head and neck cancers. A nearly 30% difference exists in survival through the first year, with hypopharynx cancers faring the poorest. Hypopharyngeal cancer patients continue to have lower rates of survival in years 2 to 5; secondary malignancies and comorbidities contribute to this phenomenon.

*Source:* Reprinted with permission from Cooper JS, Porter K, Mallin K, et al. National Cancer Database report on cancer of the head and neck: 10-year update. *Head Neck.* 2009;31:748–758.

up to 100 times elevated risk of developing tumors in the upper aerodigestive tract as compared with nonsmoking, nondrinking individuals. In addition to potentiating the effects of tobacco, a moderate to high consumption of alcohol can put nonsmoking individuals at a higher risk for hypopharyngeal and cervical esophageal cancers (Table 19.1).[7,11] Alcohol appears to have a stronger neoplastic effect in the hypopharynx than in the larynx, and dark liquor may carry a higher risk than light liquor.[12] In addition to tobacco and alcohol, gastroesophageal reflux, obesity, and achalasia can lead to higher rates of esophageal cancer.

As tobacco and alcohol are the major causative agents for tumors of the hypopharynx and cervical esophagus, field cancerization is a common phenomenon in these patients. The wide mucosal exposure to carcinogens results in a field of diseased mucosa characterized by high-grade dysplasia, giving rise to the index hypopharyngeal or cervical esophageal tumor. Therefore, these patients have high rates of synchronous and/or metachronous upper aerodigestive primary tumors. Approximately 10% of patients may be found to have synchronous primary tumors,[13] and up to 20% will develop a metachronous second primary tumor. Hypopharyngeal cancer patients have a worse overall survival than other malignancies of the head and neck due to the tendency for advanced disease at presentation.[10] In addition, even among survivors of the initial presenting lesion, survivorship is poorer in the following years; the fact that metachronous malignancies are more common in these patients than in other head and neck squamous cell carcinoma (HNSCC) patients contributes to this observation (Fig. 19-1). Counseling patients on smoking cessation can diminish treatment-related side effects, can minimize the risk of subsequent malignancies of the upper aerodigestive tract, and should be emphasized during the initial evaluation of these patients.

Occupational factors may also play a causative role in the formation of cancers of the hypopharynx and the cervical esophagus. Two European studies have shown that masons, iron workers, railway workers, cement industry workers, and rock diggers demonstrate high rates of cancer in the larynx and the pharynx,[14,15] suggesting that coal dust, steel dust, iron compounds, and fumes may contribute to carcinogenesis in these anatomic regions. In addition to occupational exposures, dietary factors can influence cancer rates in the hypopharynx and the cervical esophagus. High consumptions of salted foods and nitrosamines have been linked to esophageal SCC.[16] Although the incidence of esophageal SCC are approximately 2.5 to 5/100,000 for men in most areas of the world, rates in China, Singapore, Iran, former USSR, Chile, Brazil, Puerto Rico, Switzerland, France, and South Africa have been demonstrated to be much higher.[17] Dietary and occupational factors, as well as infection with the human papillomavirus (HPV) (see below), have been posited to account for these differences. One such example of a dietary risk for neoplasia is Plummer-Vinson syndrome, which is characterized by iron-deficiency anemia, hypopharyngeal webs, weight loss, and dysphagia. The syndrome is accompanied by an elevated risk of cancers in the postcricoid region.[7] This risk has been ameliorated by the addition of iron to flour in the northern Midwest United States and Scandinavian countries, where this syndrome was problematic.

The relationship between HPV infection and head and neck cancer has become well recognized in recent years, especially for cancers of the oropharynx. Epidemiologic studies have strongly suggested that HPV has a causative role in SCC of the base of tongue and the tonsil, with up to 60% to 70% of oropharyngeal SCC patients demonstrating evidence for HPV infection.[18] HPV positivity is a strongly positive prognostic factor in oropharyngeal SCC patients undergoing chemoradiation.[19] Whether HPV is similarly carcinogenic and/or prognostic in tumors of the hypopharynx and the cervical esophagus is less clear. Approximately 20% to 25% of hypopharynx cancer tumor specimens have detectable HPV DNA.[20,21] Additionally, the detection of antibodies against the HPV16 E6 and E7 antibodies is associated with an elevated risk of hypopharyngeal cancer,[22] suggesting a causal relationship. A large analysis of HPV rates in esophageal SCC showed the HPV can be detected by *in situ* hybridization in 23% of tumors, and in 15% by polymerase chain reaction.[17] A wide geographic variance in HPV detection was noted, with low detection rates in Europe and the United States and higher rates noted in high-risk areas for esophageal SCC such as China, Japan, and South Africa. However, while HPV-positive oropharyngeal patients are more likely to be younger and nonsmokers as compared with their

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HPV-negative counterparts, HPV-positive and HPV-negative esophageal cancer patients have been shown to have similar clinical risk factors.[23] Therefore, although current data are suggestive of a carcinogenic role for HPV in the hypopharynx and the cervical esophagus, prospective studies demonstrating that persistent HPV infections result in malignant transformation, such as those performed in uterine cervix cancer, may be necessary to confirm this suspicion.

## RELEVANT ANATOMY

The hypopharynx (sometimes referred to as the laryngopharynx) and the cervical esophagus are contiguous structures that collectively span from the hyoid bone to the thoracic inlet (Fig. 19-2). The hyoid bone demarcates the inferior border of the oropharynx, and the hypopharynx extends from the hyoid bone superiorly to the inferior border of the cricoid cartilage distally (approximately the level of the sixth cervical vertebral body). The cervical esophagus continues inferiorly from the lower edge of the cricoid cartilage to the thoracic inlet, approximated by the suprasternal notch.

The hypopharynx is composed of three primary anatomic subsites: the bilateral pyriform sinuses, the posterior pharyngeal wall, and the postcricoid region. Anteriorly, the aryepiglottic fold forms the border between the postcricoid hypopharynx and the supraglottic larynx; tumors of the aryepiglottic fold can be labeled of hypopharyngeal or of supraglottic larynx origin, depending on where the majority of the tumor bulk lies. The postcricoid region is composed of the mucosa overlying the cricoid cartilage and is bound by the posterior arytenoid cartilages and aryepiglottic folds superiorly and the cricopharyngeus inferiorly (Fig. 19-3).

The pyriform sinuses are bilateral conical structures with the open-ended bases superiorly at the level of the pharyngoepiglottic

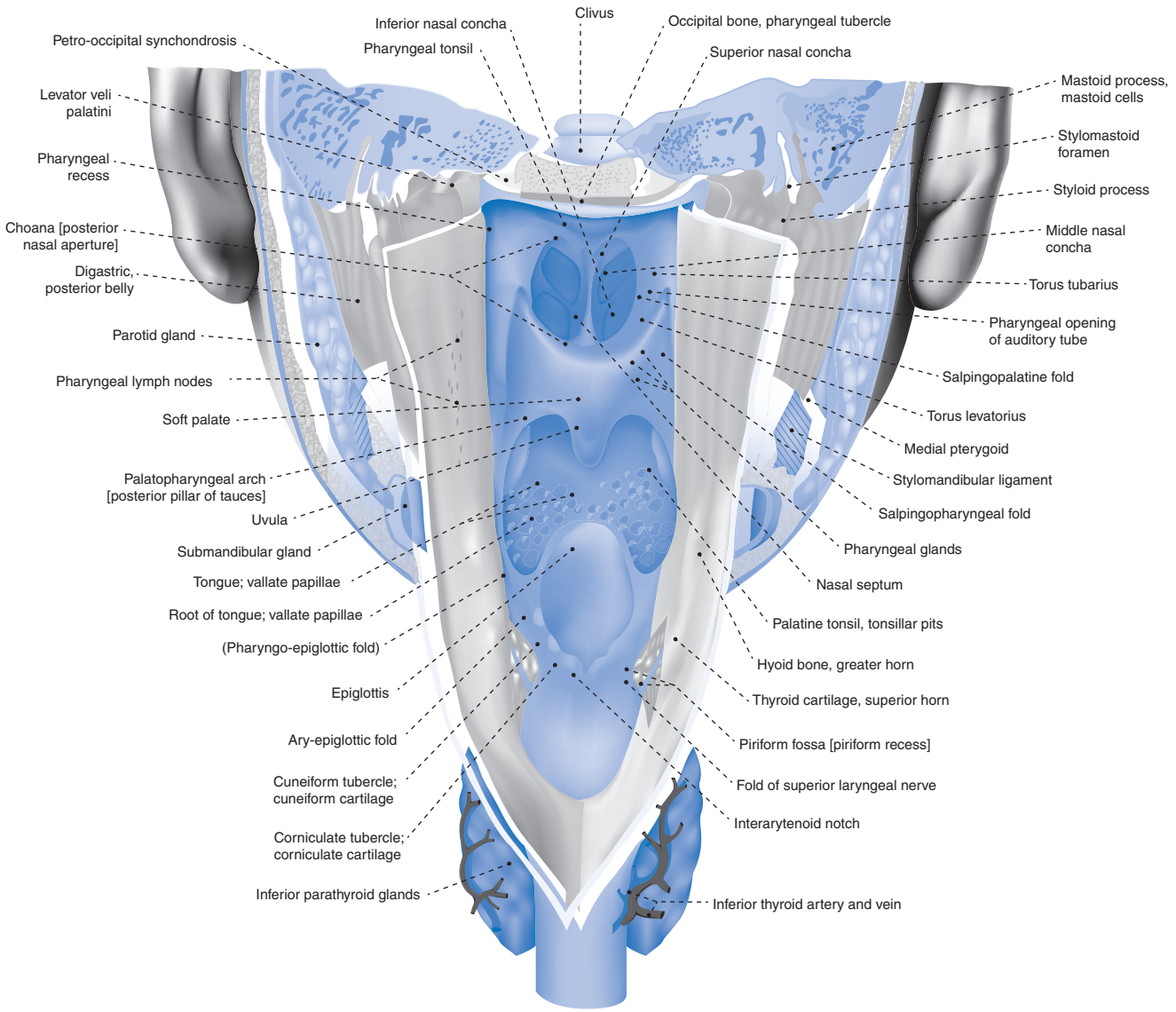



**FIGURE 19-2.** Posterior view of the larynx and hypopharynx as viewed by a posterior midline incision through the posterior pharyngeal wall, cricopharyngeus, and cervical esophagus.

*Source:* From Sobotta, Atlas der Anatomie des Menschen © Elsevier GmbH, Urban & Fischer Verlag München, with permission.

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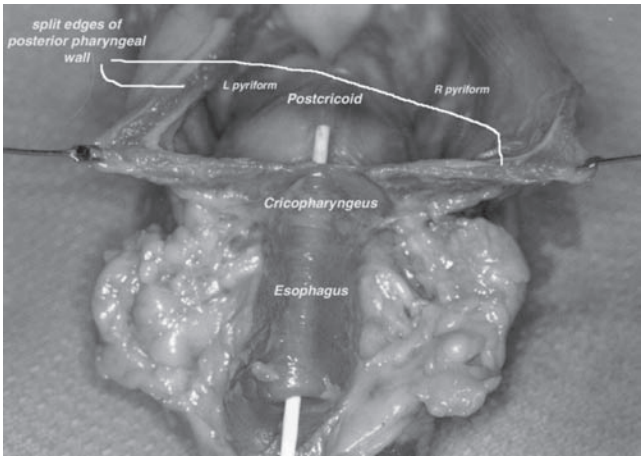



**FIGURE 19-3.** This anatomic specimen (with the posterior pharyngeal wall incised) allows a posterior view of the hypopharynx, demonstrating the three primary anatomic subsites (posterior pharyngeal wall, postcricoid region, and pyriform sinuses) of the hypopharynx.

fold, and the medial, anterior, and lateral walls narrowing inferiorly to form the apices, which extend slightly below the cricoid cartilage. The pyriform sinuses are open posteriorly and contiguous with the posterior pharyngeal walls. The internal branch of the superior laryngeal nerve pierces the thyrohyoid membrane, which surrounds the superior aspects of the pyriform sinuses laterally. Tumor involvement of the sensory component of this nerve, which synapses superiorly with the nerves of the external auditory canal in the jugular ganglion, can result in referred otalgia. The remaining sensation in this region is provided by nerve fibers of the glossopharyngeal nerve. The recurrent laryngeal nerve provides motor function to the cricopharyngeus muscle and the posterior cricoarytenoid muscles of the larynx, with remaining primary motor supply to the hypopharynx provided by the pharyngeal plexus.

The posterior pharyngeal wall is predominantly composed of squamous mucosa overlying the middle and the inferior pharyngeal constrictor muscles. The posterior pharygneal wall is separated from the prevertebral fascia by the retropharyngeal space; the mucosa overlying this region is thin and provides little barrier to direct tumor infiltration from the posterior wall to the prevertebral fascia. The distal fibers of the inferior constrictor coalesce to join the cricopharyngeus muscle, which serves as the junction between the hypopharynx and the cervical esophagus.

The cervical esophagus is lined by nonkeratinizing squamous mucosa overlying two muscular layers: an inner circular layer and an outer longitudinal layer. These muscles are striated in the upper third of the esophagus, whereas a gradual transition to smooth muscle occurs through the course of the thoracic esophagus. The cervical esophagus lies just posterior to the trachea, extending from the cricopharyngeus (C6 level) for about 4 to 5 cm to the thoracic inlet (suprasternal notch). Measured from the incisors (as commonly reported in endoscopic procedures), this ranges from 14 to 16 cm (cricopharyngeus) to approximately 20 cm. The tracheoesophageal grooves run laterally between these structures, and the recurrent laryngeal nerves and the paratracheal nodes are located in these grooves. The lateral lobes of the thyroid gland approximate the cervical esophagus and lie between the cervical esophagus medially and the carotid sheaths more laterally (Fig. 19-4). Vascular supply to the cervical esophagus is from branches of the inferior thyroid artery and veins, as well as ascending vessels along the thoracic esophagus. The sympathetic trunks and branches of the recurrent laryngeal nerves provide innervation.

There is a rich network of lymphatics that surround the hypopharynx and the cervical esophagus. From the hypopharynx, primary lymphatic drainage is to the jugulodigastric nodes (levels II–IV). Spinal accessory (level V) nodes are also at risk. Anterior lymphatic channels within the hypopharynx may drain from the pyriform sinuses directly through the thyrohyoid membrane along the path of the superior laryngeal artery. When tumors invade the posterior pharyngeal wall, lymphatic vessels passing through the inferior constrictor muscles place the retropharyngeal nodes at risk for involvement, including the most cephalad retropharyngeal nodes at the base of skull (nodes of Rouvière).

Lymphatic drainage from the cervical esophagus may mirror that of the hypopharynx and can pass superiorly toward the nodes surrounding the internal jugular vein. Lymphatics may also drain within the paratracheal and esophageal grooves to involve paratracheal lymph nodes. These lymph nodes are in the central compartment (level VI) and lie between the medial edge of the common carotid laterally, the trachea medially, inferior to the cricoid, and superior to the suprasternal notch. These paratracheal nodes are not usually included in a standard neck dissection and deserve consideration in hypopharyngeal and cervical esophageal tumors.[24] The paratracheal lymph nodes are contiguous with lymph nodes of the upper mediastinum inferiorly; the anatomic and radiographic border between these two regions is poorly defined. Nonetheless, caudal drainage from the hypopharynx and cervical esophagus can involve these lymph node basins, which may also warrant attention from surgeons and radiation oncologists.[25]

## NATURAL HISTORY, PATHOLOGY, PATHOGENESIS, AND PATTERNS OF SPREAD

### Natural History

Tumors of the hypopharynx and the cervical esophagus tend to present with advanced disease, usually including nodal metastases. A retrospective study from Washington University demonstrated that 87% of patients with pyriform sinus tumors and 82% of posterior pharyngeal wall tumors presented with either stage III or IV disease.[26] Similarly, a study of 107 patients with cervical esophageal tumors demonstrated that 79% of patients had stages III to IV disease.[27] Therefore, despite stepwise advances in the diagnosis and treatment of these tumors, outcomes remain disappointing. Hypopharynx cancers fare poorly as compared with patients with HNSCC in other tumor sites, with 5-year survival rates approximating 30% (Fig. 19-5).[8] Likewise, single institution reports have noted 5-year overall survival rates for cervical esophageal patients to range from 12% to 28%,[13,28,29] and cervical esophageal patients have demonstrably inferior outcomes to tumors located in the thoracic esophagus (Fig. 19-6).[3] A thorough understanding of the patterns of spread is essential to surgeons and oncologists in combating these aggressive tumors.

### Pathology

Historically, approximately 95% of tumors of the hypopharynx or the cervical esophagus are SCC. Recent analysis of the Surveillance, Epidemiology, and End Results (SEER) database from 2000 to 2008 support this claim, as 93.9% of hypopharynx cancers were SCC, whereas lymphoma, sarcoma, adenocarcinoma, and adenoid cystic carcinoma accounted for approximately 0.5% of cases each.[1] Similarly, the National Cancer Data Base (NCDB) Benchmark Reports evaluated 17,654 cases of hypopharyngeal cancer in the United States between the years of 2000 and 2008. More than 90% of cases were SCC.[30]

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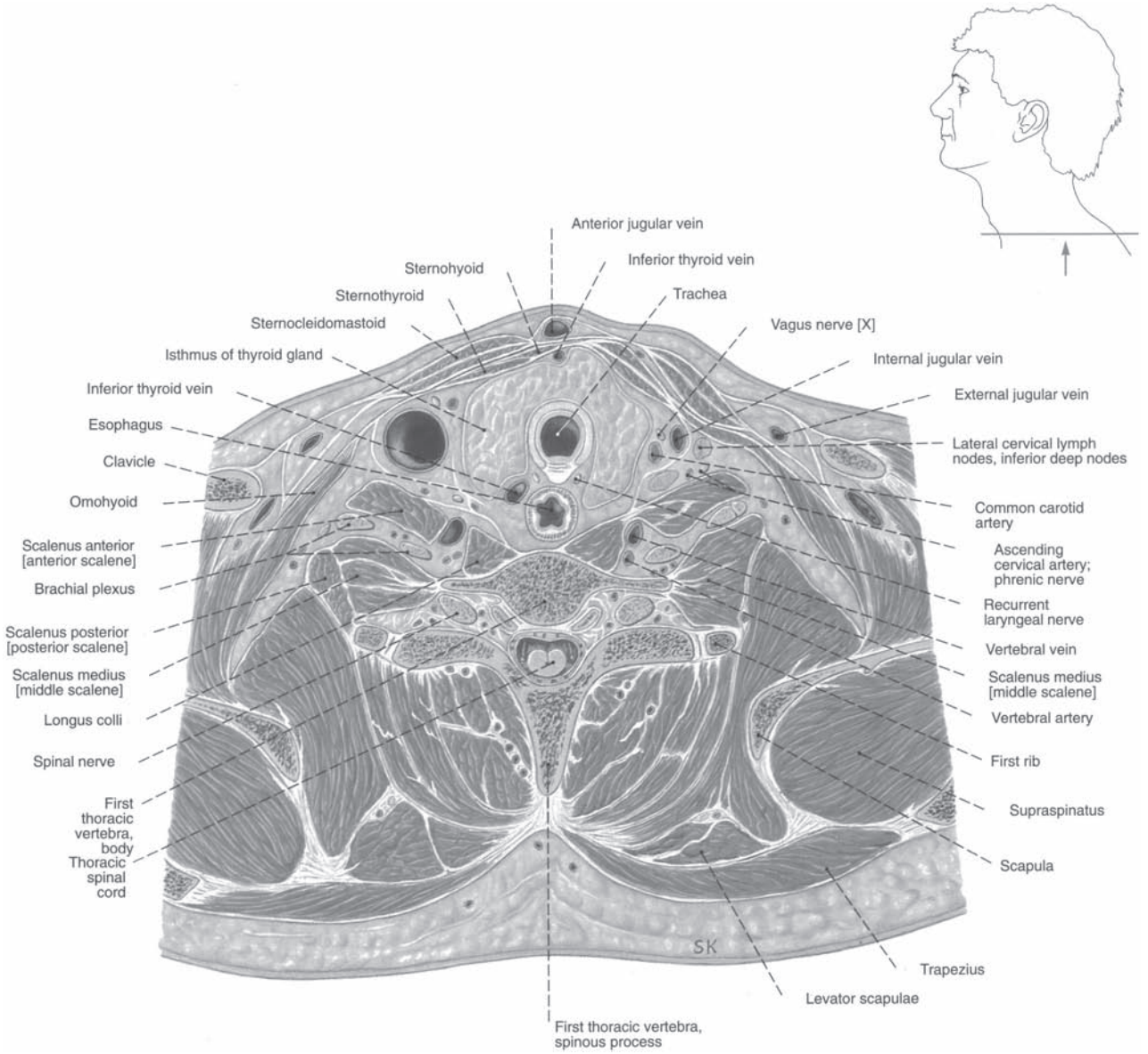



**FIGURE 19-4.** Transverse section detailing relationship of the cervical esophagus and adjacent structures at the level of the first thoracic vertebrae.

*Source:* Adapted from Sobotta, Atlas der Anatomie des Menschen © Elsevier GmbH, Urban & Fischer Verlag München, with permission.

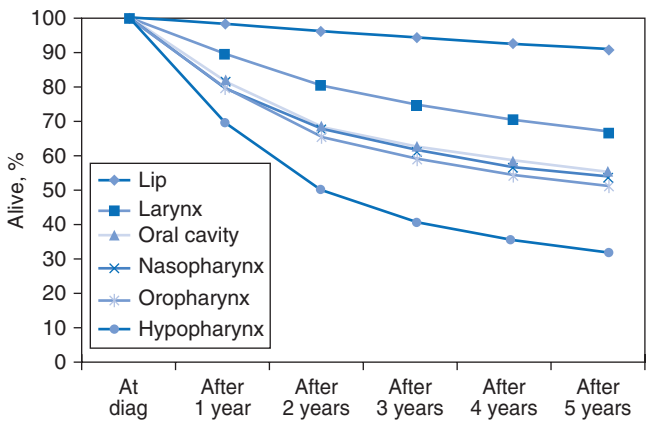



**FIGURE 19-5.** Five-year survival by mucosal site for head and neck cancers from 1990 to 1999 cases.

*Source:* Reprinted with permission from Cooper JS, Porter K, Mallin K, et al. National cancer database report on cancer of the head and neck: 10-year update. *Head Neck.* 2009;31:748–758.

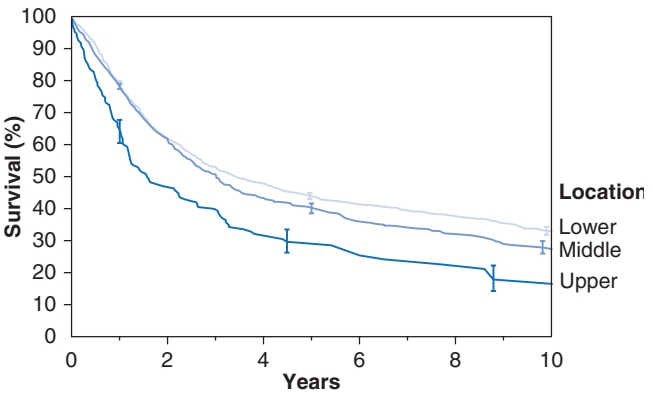



**FIGURE 19-6.** Survival according to upper extent of cancer in the esophagus.

*Source:* Reprinted with permission from Rice TW, Rusch VW, Apperson-Hansen C, et al. Worldwide esophageal cancer collaboration. *Dis Esophagus.* 2009;22:1–8.

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## Primary Tumor Location, Spread

Within the hypopharynx, tumor involvement of more than one subsite can cloud the ability of clinicians and/or radiologists to assign the tumor to a specific primary subsite. Within the Surveillance, Epidemiology, and End Results database from 2000 to 2008, 83% of tumors with known subsite arose within the pyriform sinus. The posterior pharyngeal wall accounted for 9% of primary tumors; the postcricoid was less commonly the primary site, accounting for 4% of tumors.[1] Cancers in the hypopharynx and cervical esophagus are prone to submucosal spread, though less so in the pyriform sinus than in other locations. Serial sectioning of surgical specimens has shown that 60% of hypopharynx cancers demonstrate significant subclinical spread, which can contribute to local failures following definitive management. Typical patterns of submucosal spread in such patients can include a range of 10 mm superiorly and 20 mm inferiorly.[31] Skip lesions from the hypopharynx therefore commonly involve the cervical esophagus. Cervical esophageal tumors are similarly prone to submucosal spread, especially caudally; up to 23% of cervical esophageal tumors may have clinical evidence of thoracic esophageal involvement at the time of diagnosis.[27]

Cancers originating in the pyriform sinus can infiltrate laterally to invade the posterolateral portion of the thyroid cartilage and/or the superior lobe of the thyroid gland. The medial wall is the most common site of involvement for pyriform sinus tumors, and tumor invasion in this location can result in invasion of the cricoarytenoid joint and/or muscle or the recurrent laryngeal nerve and may cause the vocal cord to become fixed. Superior extension may involve the aryepiglottic folds and arytenoids, and the paraglottic space is also at risk for involvement. Posterior pharyngeal wall extension is common as the tumor grows laterally.

Tumors primarily of the postcricoid area commonly extend inferiorly to involve the cervical esophagus, and circumferential growth frequently occurs, with invasion of the cricoid cartilage and cricoarytenoid muscle and resultant vocal cord fixation. These tumors are commonly extensive at presentation and portend a worse prognosis in comparison to tumors from other hypopharyngeal locations.[32] Tumors of the posterior pharyngeal wall tend to expand in the craniocaudal dimension, tracking submucosally in a superior fashion to the oropharynx or inferiorly to the cricopharyngeus and the cervical esophagus. Deep infiltration can involve the retropharyngeal space with access to the lymphatics in that region and subsequently into the prevertebral fascia.

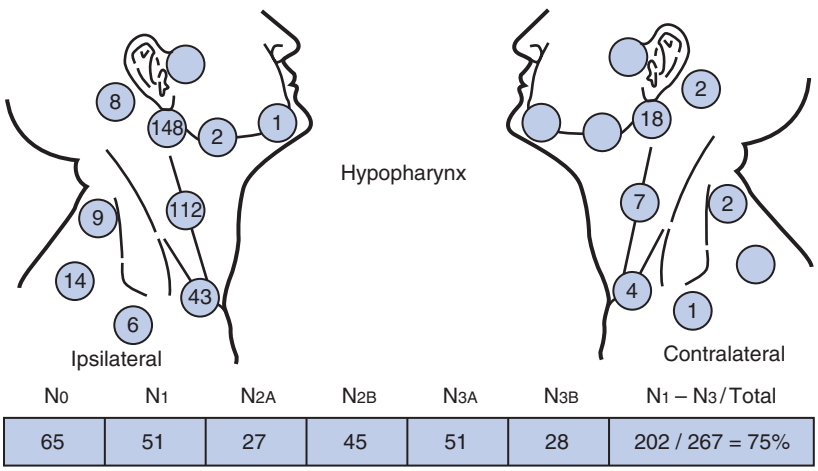
Cervical esophageal tumors commonly extend into adjacent tissues at presentation.[13] Direct anterior extension can result in tumor involvement of the trachea, and involvement of the larynx and/or recurrent laryngeal nerve may result in vocal cord paralysis in approximately 10% of patients. Lateral extension into the thyroid gland is not uncommon, and possible posterior infiltration into the prevertebral fascia warrants careful evaluation on upfront diagnostic imaging. Thus, the extensive pattern of primary tumor infiltration in hypopharyngeal and cervical esophageal tumors can present considerable challenge in the effort to achieve clear surgical margins or achieve full dosimetric coverage with radiotherapy.

## Lymphatic Spread

A rich lymphatic network surrounds the hypopharynx and the cervical esophagus, and lymph node involvement occurs in the majority of tumors by the time of diagnosis. More than 50% of patients will present with clinically positive cervical lymph nodes at diagnosis. An additional 30% to 40% of N0 necks are found to show pathologic involvement when dissected electively,[33] rendering 65% to 80% of patients ultimately node positive.

The primary lymph node drainage of the cervical esophagus is to the paratracheal lymph node bed, and surgical series consistently demonstrate these lymph nodes to be most commonly involved, with approximately 40% to 70% of cases demonstrating metastatic involvement on pathologic analysis.[13,34,35] The general lymph drainage of the cervical esophagus is directed upward, and therefore levels III and IV of the neck are at the next highest risk, with levels II and V at lower but not negligible risk. Lymph node risk is associated with the length of the primary tumor, with lesions >5 cm showing lymph node involvement in 90% of cases.[36]

In patients with hypopharyngeal cancer, 50% to 80% of patients will have metastatic lymph node involvement. Jugular chain nodes (levels II–IV) as well as the retropharyngeal nodes are all at high risk for metastatic involvement. Lymphatics from the hypopharynx can drain anteriorly along with the lymphatics of the supraglottic larynx through the thyrohyoid membrane to primarily drain into levels II and III. Posterior lymphatics more commonly drain tumors of the inferior hypopharynx, penetrate the superior constrictor muscle, and drain to the lateral retropharyngeal and the paratracheal lymph nodes. Cross-draining lymphatics are present, and bilateral cervical node metastases are common (Fig. 19-7). In addition to the jugular chain lymph nodes typically addressed during neck dissection procedures, paratracheal lymph nodes are also at risk in hypopharynx cancer, with surgical specimens demonstrating involvement in 20% to 25% of cases[37,38] and warrant surgical consideration.




| N0 | N1 | N2A | N2B | N3A | N3B | N1 – N3 / Total |
|---|---|---|---|---|---|---|
| 65 | 51 | 27 | 45 | 51 | 28 | 202 / 267 = 75% |

**FIGURE 19-7.** Nodal distribution patterns for a series of 267 patients with hypopharynx cancer as summarized by admission records at the MD Anderson Hospital.

*Source:* Redrawn with permission from Lindberg R. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. *Cancer.* 1972;29:1446–1449.

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### Distant Metastases

Cancers of the hypopharynx have higher rates of distant metastatic disease than do primary tumors of other HNSCC subsites.[39] Approximately 16% of hypopharyngeal cancer patients present with distant metastases at diagnosis.[40] Distant metastatic rates rise with time, especially in patients with residual or recurrent locoregional disease following initial therapy; rates of ultimate distant metastases have been reported up to 60% in older reports.[39] Data regarding initial metastatic presentation and ultimate metastatic risk with cervical esophageal cancer is less robust. Nonetheless, metastatic patterns of tumors from the hypopharynx and the cervical esophagus are similar, with the lung most commonly involved, followed in incidence by the mediastinal lymph nodes, the liver, and bone.

## CLINICAL PRESENTATION

Patients with cancers of the hypopharynx and the cervical esophagus initially develop nonspecific symptoms, which are commonly attributed to presumed infectious or gastrointestinal causes, leading to frequent delays in diagnosis. Therefore, the majority of patients will present with advanced local and/or regional disease. Presentations of hypopharyngeal and cervical esophageal tumors are similar, although cervical esophageal tumors tend to present earlier, as the lumen of the cervical esophagus is smaller than that of the hypopharynx. Dysphagia is the most common presenting symptom, present in up to 85% of cases, although a palpable neck mass is the most common physical finding.[13] Other common symptoms at presentation include odynophagia, weight loss, and neck pain. The majority of patients will note more than one of these symptoms by the time of diagnosis.[41] Rarely, early-stage tumors may be diagnosed in the evaluation of new-onset reflux symptoms.[10]

Other presenting symptoms can include unilateral ear pain (referred otalgia), classically seen in patients with tumors of the pyriform sinus. This results from involvement of the superior laryngeal nerve (a branch of the vagus nerve), which synapses with the auricular branch of cranial nerve X (the nerve of Arnold) in the jugular ganglion. Hoarseness can result from tumor infiltration into laryngeal structures or from involvement of the recurrent laryngeal nerve by tumors in the cervical esophagus or the postcricoid regions. Weight loss is common and is often substantial and can reflect poor nutritional status that may result from clinically significant dysphagia, alcohol dependency, and/or tumor-mediated cachexia/anorexia.

## DIAGNOSTIC EVALUATION AND CLINICAL STAGING

### Workup and Evaluation

Patients with tumors of the hypopharynx and/or the cervical esophagus should be evaluated in a multidisciplinary fashion, with input from surgeons, medical oncologists, radiation oncologists, speech-and-swallow specialists, social workers, dentists, nutritionists, and often specialists in alcohol and/or tobacco cessation. A detailed history should be elicited, with the nature and duration of symptoms documented, as well as the degree of weight loss. Assessment of dysphagia to both solids and liquids should be noted. Changes in voice quality and the complaint of referred otalgia are frequently present. Exposure in pack-years of cigarette smoking should be noted, as should the use of smokefree tobacco (chewing tobacco, snuff). Alcohol history should be elicited, with particular attention to current use, which may predispose patients to withdrawal.

The initial physical examination should indirect visualization of the full laryngopharyngeal axis. Given the high rate of second head and neck mucosal primaries, thorough attention to any other mucosal irregularities is warranted. Tumors of the pyriform sinus can be notoriously difficult to visualize; having the patients puff their cheeks (blow against closed lips) during nasopharyngolaryngoscopy can aid in visualization of the pyriform sinuses. In addition to the primary tumor (size, location, involved structures), particular attention should be paid to the mobility of the vocal cords with phonation, as this impacts tumor staging. Furthermore, the initial examination should include an assessment of dentition, particularly if (chemo)radiation is likely to be employed as a treatment modality. Unlike many tumors of the head and neck region, where indirect visualization may suffice, direct visualization under anesthesia is warranted in most tumors in these locations to fully delineate the extent of tumor spread and for biopsy confirmation of malignancy. An upfront thorough assessment of dentition allows for dental extractions, if needed, to be performed simultaneously while the patient is under anesthesia for tumor mapping under direct visualization (Table 19.2).

Physical exam should include assessment of cervical lymphadenopathy, providing a description of the size, location, number, mobility, and texture of suspicious lymph nodes. As all patients with biopsy-proven malignancies of the hypopharynx and/or the cervical esophagus warrant advanced radiographic imaging, fine-needle aspirate of enlarged lymph nodes to further confirm metastatic lymphadenopathy is rarely of value and should not be routinely performed.

Panendoscopy should be complemented by advanced imaging to assess the extent of the primary tumor and rigorously assess cervical lymph node chains for presence and/or extent of regional lymph node involvement. High-resolution computed tomography (CT) with contrast from the base of skull to below the clavicles is usually the imaging study of choice, although MRI can be utilized. A low threshold should be utilized in extending a CT through the lungs distally, as tumors of the hypopharynx and cervical esophagus have significant rates of pulmonary metastases at presentation. For the rare early-stage, lymph node–negative hypopharyngeal tumor, chest x-ray may suffice to rule out distant pulmonary metastases. Cervical esophageal tumors in particular commonly involve the lymph nodes of the upper mediastinum[25] and may have thoracic esophageal involvement,[27] and therefore CT imaging should routinely include the thorax in these patients.[18] FDG-PET (or PET-CT, with accompanying CT slice co-registration) is increasingly utilized in the upfront staging of tumors of the hypopharynx and the cervical esophagus. PET-CT allows for detection of distant metastases and provides information that may aide in the determination of lymph node malignant involvement. Furthermore, PET-CT imaging may influence radiation planning, in terms of field design and/or prescribed dose.[42] A recent prospective study of PET imaging in HNSCC tumor management included 46 patients with hypopharyngeal cancer. Therapeutic decisions were made with physicians blinded, and then unblinded, to FDG-PET imaging data. Tumor/node/metastases (TNM) staging was altered in 100 of 233 enrolled patients (43%), whereas PET altered the management of 32 patients (13.7%) (Table 19.3). This study, and similar experiences with PET imaging in HNSCC management support a role for PET-CT imaging in the upfront evaluation of patients with hypopharyngeal and cervical esophageal tumors. Worldwide, approximately 75% of oncologists utilize FDG-PET imaging in a proportion of esophageal cancer patients for staging purposes, with routine use slightly more common in North America than in Europe or Asia.[43]

Patients with cancers of the hypopharynx and/or the cervical esophagus commonly present with significant weight loss,

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**TABLE 19.2 Workup and Pretreatment Evaluation for Patients with Tumors of the Hypopharynx and Cervical Esophagus**

| | |
|---|---|
| History | – Nature/duration of symptoms<br>– Degree of weight loss<br>– Dysphagia (to solids? also to liquids?)<br>– Referred otalgia?<br>– Change in voice quality?<br>– Tobacco history (cigarettes, smoke-free)<br>– Alcohol history—current heavy use? |
| Physical examination | – Assessment of dentition (extractions necessary)<br>– Cervical lymphadenopathy description<br>– Indirect nasopharyngolaryngoscopy, with particular attention to other mucosal irregularities (second primaries) and cord mobility<br>– Examination under anesthesia for biopsy, tumor mapping, with opportunity for dental extraction simultaneously |
| Imaging | – CT with contrast (preferred) or MRI of the neck (skull base to below clavicles)<br>– CXR (early-stage HP tumors only)<br>– CT of the chest (advanced HP tumors; all CE tumors) |
| Additional specialty input | – Dental assessment<br>– Nutrition assessment; consideration of PEG tube placement<br>– Speech and swallow assessment<br>– Tobacco and alcohol cessation<br>– Social work input (transportation, finances, other support) |

often as a result of progressive tumor-associated dysphagia and odynophagia. An assessment should be made of the patient's nutritional status, with attempts to correct nutritional deficits prior to the initiation of aggressive therapy. A nutritionist should be involved as a part of the multidisciplinary team. A percutaneous enteral gastrostomy (PEG) tube is commonly utilized. In surgical patients, a PEG tube is commonly placed at the time of surgery to allow for maintenance of nutrition during the postoperative recovery period. Whether upfront PEG tube placement should occur routinely in patients planning to undergo (chemo)radiation or should happen only in patients who demonstrate significant difficulties with maintaining weight and hydration during radiation is an area of debate. Patients with tumors of the hypopharynx and cervical esophagus tend to have more dysphagia, odynophagia, and prediagnosis weight loss than other HNSCC patients. Therefore, in our experience, the benefits of prophylactic PEG tube placement in terms of improved weight preservation and maintenance of hydration appear warranted for the majority of patients. Therefore, we routinely place PEG tubes during the pretreatment evaluation phase prior to chemoradiation.

**TABLE 19.3 Impact of FDG-PET on Staging and Management in 233 HNSCC Patients**

| Endpoint | Impact of FDG-PET |
|---|---|
| Discordant TNM stage | 100/233 (43%) |
| PET accurately upstaged | 30/233 (13%) |
| PET accurately downstaged | 17/233 (7.3%) |
| PET innacurately changed stage | 13/233 (5.6%) |
| No confirmed gold standard TNM | 40/233 (17%) |
| **Impact on patient management** | |
| No significant change | 188/233 (80.7%) |
| Change within the same treatment modality | 12/233 (5.2%) |
| Change in treatment intent and/or modality | 20/233 (8.6%) |

*Source:* Adapted from Lonneux M, Hamoir M, Reychler H, et al. Positron emission tomography with [18F]fluorodeoxyglucose improves staging and patient management in patients with head and neck squamous cell carcinoma: a multicenter prospective study. *J Clin Oncol.* 2010;28:1190–1195, with permission.

In addition to input from a nutritionist, a formal evaluation by speech-and-swallow therapists before initiation of therapy to assess baseline dysphagia is valuable. If swallowing dysfunction is noted, adaptive techniques may be taught to the patient to improve caloric intake and minimize aspiration risks. Although informal bedside assessment may be performed of swallow function, a more definitive fluoroscopic barium swallow study (videopharyngogram or oro-pharyngeal motility study [OPMS]) is usually preferable. Close posttreatment surveillance with a speech-and-swallow specialist familiar with the patient is important following definitive therapy.

All patients should undergo dental evaluation, with routing cleaning and Panorex imaging to assess for periapical abscesses, unerupted third molars, or other pathology prior to initiation of therapy. For patients who receive (chemo)radiation, long-term xerostomia may result and places patients at risk for accelerated dental decay. Therefore an assessment of teeth in poor repair that may warrant extraction is warranted, especially for any teeth that

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occupy a region likely to receive high-dose radiation. Upfront removal of such teeth in poor repair is preferable to subsequent removal following radiation, as manipulation of the teeth and sockets following radiation places patients at risk for osteoradionecrosis. Dental extractions should precede radiation by 10 to 14 days to allow for adequate healing. For patients who have teeth that will remain in place through radiation should receive custom fluoride carrier trays. Long-term use following radiotherapy of fluoride can minimize dental decay in the setting of postradiotherapy xerostomia.

Patients with hypopharyngeal and cervical esophageal cancers commonly have ongoing issues with alcohol addiction and tobacco dependency. Engagement with specialists for counseling and other methods to aide tobacco and alcohol cessation can be valuable. Medications such as the nicotine patch can be prescribed by surgeons and oncologists to assist patients with tobacco cessation. Additionally, many of these patients with benefit from input from social workers, as they often face issues such as financial difficulties, lack of transportation for appointments, and limited family/social support. A case manager or social worker can help these patients navigate the medical system and cope with these concerns through their cancer management.

## Staging

In 2009, the American Joint Committee for Cancer (AJCC) updated their staging system, releasing the 7th edition.[44] While the AJCC staging system provides a platform for grouping patients, in order to help guide discussions between physicians and for assessment of outcomes, patient factors include comorbidities, age, and motivation for organ preservation must be taken into account when considering management of an individual patient. For tumors of the hypopharynx, no significant changes were instituted in the 7th edition, with the exception that tumors extending to the esophagus are now T3 (previously T4a). T1 tumors are <2 cm in greatest dimension and limited to one subsite. T2 tumors measure between 2 and 4 cm, and/or invade more than on subsite of the hypopharynx or an adjacent site. Extension to the esophagus or fixation of the hemilarynx renders a tumor T3, as does size >4 cm. Tumor that invades either the hyoid bone, the thyroid gland, the central compartment soft tissue (prelaryngeal strap muscles and subcutaneous fat), or the thyroid and/or the cricoid cartilage is deemed moderately advanced local disease (T4a). Tumors are very locally advanced (T4b) if they invade the prevertebral fascia, involve mediastinal structures, or encase a carotid artery. Nodal staging and stage grouping is identical for hypopharyngeal cancer patients as to other HNSCC sites (excluding the nasopharynx).

For tumors of the cervical esophagus, major changes were implemented between the 6th (2002) and 7th (2009) editions of the AJCC staging based on a worldwide analysis of 4,627 patients with tumors of the esophagus and esophagogastric junction treated with surgery alone.[3,45] While the previous staging system was based only on tumor/node/metastases criteria, these analyses resulted in histology, grade, and location being incorporated into the stage grouping for 7th edition. T staging of esophageal tumors is based on depth of invasion and remains largely unchanged from the 6th edition of the AJCC staging system. As the vast majority of cervical esophageal tumors are SCC, the tumor (T) and the nodal (N) definitions for esophageal SCC are depicted in Table 19.4. It should be noted that only 4.1% of the tumors comprising the data set used for derivation of this staging system were located in the upper one-third of the esophagus, which would also include upper thoracic esophageal tumors.

Tis (*in situ*) is characterized by noninvasive high-grade dysplasia. T1a tumors invade the lamina propria or muscularis mucosae, with invasion of the submucosae staged T1b. T2 tumors invade muscularis propria, whereas T3 tumors invade adventitia.

**TABLE 19.4 T and N Staging for Esophageal Squamous Cell Carcinoma**

| Tumor Level of Invasion | T Descriptor |
|---|---|
| Noninvasive, high-grade dysplasia | Tis (*in situ*) |
| Invading the lamina propria or muscularis mucosal layers | T1a |
| Involving submucosa | T1b |
| Involving the muscularis propria | T2 |
| Involving the adventitia | T3 |
| Involving the diaphragm, pleura, or pericardium (resectable) | T4a |
| Involving aorta, trachea, vertebral body, other adjacent tissues (unresectable) | T4b |
| **Metastatic Lymph Node Burden** | **N Descriptor** |
| 1–2 lymph nodes | N1 |
| 3–6 lymph nodes | N2 |
| ≥7 lymph nodes | N3 |

*Source:* Adapted from Edge SB, Byrd DR, Compton CC, et al. *AJCC Cancer Staging Handbook.* New York, NY: Springer; 2010, with permission.

T4 tumors (invading adjacent structures) were split into T4a and T4b in the 7th AJCC system. T4a tumors are resectable tumors invading the pleura, pericardium, or diaphragm. T4b tumors are unresectable, invading other structures including the aorta, the trachea, and the vertebral body.

Nodal (N) staging also changed between the 6th and 7th AJCC staging systems for esophageal tumors. Previously lymph node staging was dependent on the location of lymph nodes, with lymph nodes in the cervical, scalene, internal jugular, periesophageal, and supraclavicular regions termed "regional" for cervical esophageal tumors. Currently, metastases in 1 to 2 regional lymph nodes renders a patient N1, metastases to 3 to 6 regional lymph nodes is N2, and involvement of 7 or more regional lymph nodes is N3. Regional lymph nodes are now designated as any nodes from the cervical nodes to the celiac nodes for all esophageal cancers, whereas previously cervical lymph nodes were deemed metastatic for thoracic esophageal tumors.

Grade and location now are also incorporated into AJCC staging for esophageal SCC, impacting the stage grouping in early-stage tumors (Table 19.5). Grade that cannot be assessed (grade x) and grade 1 tumors (well-differentiated) are grouped together, whereas grade 2 (moderately differentiated), grade 3 (poorly differentiated), and undifferentiated (grouped as grade 3 squamous) are grouped together. Furthermore, anatomic location impacts stage grouping. Tumors of the cervical esophagus are defined in this system as being bordered by the hypopharynx superiorly and by the thoracic inlet (sternal notch) superiorly, or from 15 to 20 cm from the incisors by endoscopy.[45]

# MANAGEMENT STRATEGIES AND TREATMENT PLANNING GUIDELINES

Historically, surgery has been a mainstay in management of cancers of the hypopharynx and cervical esophagus. This has typically involved sacrifice of the larynx, either via laryngo-pharyngectomy

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**TABLE 19.5 Stage Grouping for Esophageal Squamous Cell Carcinoma**

| Stage | T | N | M | G | Location |
|---|---|---|---|---|---|
| 0 | Tis (HGD) | 0 | 0 | 1 | Any |
| IA | 1 | 0 | 0 | 1 | Any |
| IB | 1 | 0 | 0 | 2–3 | Any |
| | 2–3 | 0 | 0 | 1 | Lower |
| IIA | 2–3 | 0 | 0 | 1 | Upper, middle |
| | 2–3 | 0 | 0 | 2–3 | Lower |
| IIB | 2–3 | 9 | 0 | 2–3 | Upper, middle |
| | 1–2 | 1 | 0 | Any | Any |
| IIIA | 1–2 | 2 | 0 | Any | Any |
| | 3 | 1 | 0 | Any | Any |
| | 4a | 0 | 0 | Any | Any |
| IIIB | 3 | 2 | 0 | Any | Any |
| IIIC | 4a | 1–2 | 0 | Any | Any |
| | 4b | Any | 0 | Any | Any |
| | Any | 3 | 0 | Any | Any |
| IV | Any | Any | 1 | Any | Any |

*Source:* From Rice TW, Rusch VW, Ishwaran H, et al. Cancer of the esophagus and esophagogastric junction: data-driven staging for the seventh edition of the American Joint Committee on Cancer/International Union Against Cancer Cancer Staging Manuals. *Cancer.* 2010;116:3763–3773, with permission.

or pharyngolaryngoesophagectomy. However, in recent years, increasing efforts toward organ preservation have become more prevalent. As tumors of the hypopharynx and cervical esophagus tend to present with locally advanced and/or node-positive disease, these efforts at organ preservation most commonly involve chemoradiation for locally advanced disease (Fig. 19-8). However, more advanced surgical techniques may allow for organ preservation in those patients who present with early-stage disease amenable to larynx-sparing surgery. Nonetheless, radical surgery remains an important component of management and should be considered as an alternative to organ-sparing approaches, depending on the motivation of the patient for organ preservation and the patient's medical comorbidities. Active rehabilitation therapy in order to maximize eventual speech and swallow function must accompany all definitive management, regardless of the specific treatment approach. Rehabilitation and posttreatment surveillance are discussed at the end of this section.

## Hypopharyngeal Cancer Management

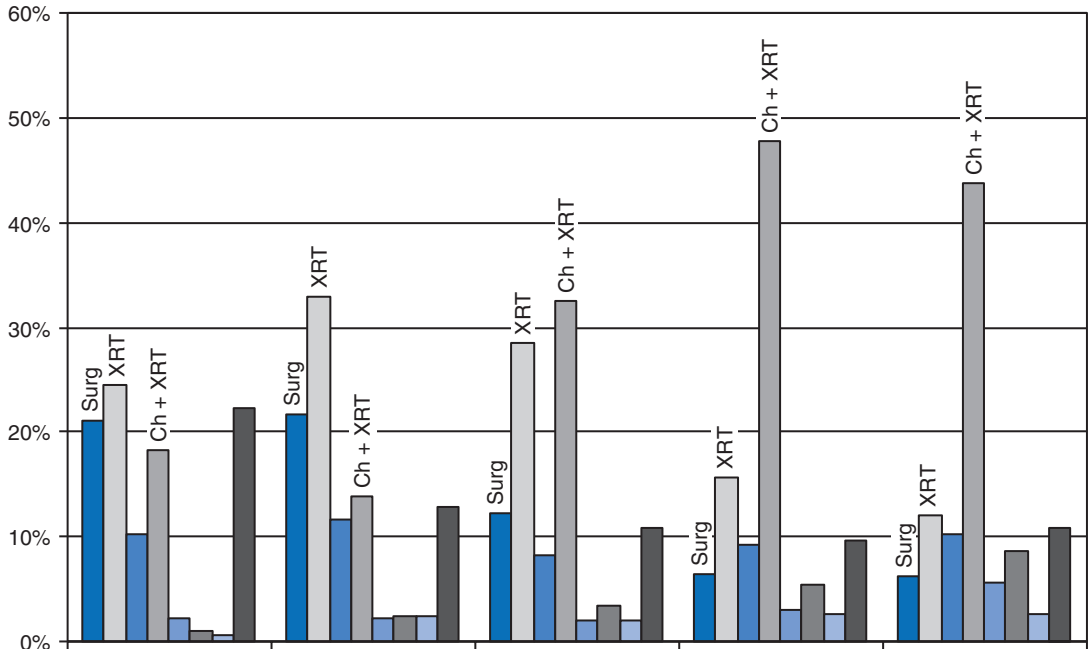
***Stages I to II Disease (T1–2, N0).*** A large analysis of 853 hypopharyngeal cancer patients revealed that approximately 84% of patients will present with either T3–4 and/or node-positive disease,[46] whereas a review of 1,210 hypopharyngeal cases diagnosed in 2003 through the NCDB identified only 150 (12.3%) of cases to be stages I to II.[30] Therefore, stages I to II hypopharyngeal cancer is a relatively rare clinical scenario. In general, curative radiation therapy is preferred as the definitive treatment approach for patients with early-stage hypopharynx tumors, as it provides a good chance for organ preservation. Alternatively, open or endoscopic surgery (partial laryngopharyngectomy) with ipsilateral or bilateral neck dissection may be performed (Table 19.6). More recently, transoral laser microsurgeries have been performed with promising results in selected early-stage lesions.

***Radiation Therapy.*** Radiation is commonly favored in stages I to II hypopharynx cancers, as surgery in this region often results in chronic aspiration due to injury/sacrifice of the superior laryngeal nerve. Additionally, given that concerning pathologic features (positive margins, node positivity, pathologic T3 or T4 status, perineural invasion, lymphovascular invasion) often prompt postoperative (chemo)radiation following surgery, definitive radiation may allow patients to forego the toxicities associated with multiple treatment modalities. However, for patients who receive definitive radiation, it is important for the head and neck surgeon to remain involved in the patient care. Endoscopic biopsy for detailed assessment of tumor extent may be necessary prior to definitive radiation, and the surgeon should remain involved in the multidisciplinary oncologic follow-up after treatment.

Radiotherapy for stages I to II hypopharygeal cancer classically consists of a 6-to-7-week course, with treatment delivered 5 days per week.[47–52] Lymphatic coverage from the skull base to the clavicle is routine for patients undergoing radiation for hypopharyngeal cancer. Conventional field design utilizes opposed lateral fields covering the primary tumor and upper neck regions matched to an anterior field covering low-neck and supraclavicular neck lymphatic regions. The superior border of the opposed lateral radiation fields should include jugular chain lymphatics to the base of skull, whereas inferiorly fields should extend to the lower aspect of the cricoid cartilage, unless more inferior coverage is mandated by extensive caudal tumor extension. Anteriorly, fields should flash skin at the level of the thyroid cartilage, and posterior borders should extend behind vertebral spinous processes, or further if needed to cover metastatic level V lymph nodes. Wedges or custom compensators should be used for the lateral fields to account for varying tissue thickness of the head and neck to maximize dose homogeneity. When the spinal cord reaches a dose of ≤45 Gy, shrinking-field techniques should be used to maintain the spinal cord dose below tolerance. Posterior neck electrons supplement dose to the posterior cervical lymph nodes, whereas 54 to 60 Gy should be delivered to the remaining lymphatics via lateral fields before final mucosal reductions are made to deliver 66 to 70 Gy to the primary tumor plus a margin (for T1 tumors) or 70 Gy for T2 tumors. Three-dimensional planning with intensity-modulated radiation therapy (IMRT) is now commonly utilized for radiotherapy in hypopharynx cancer and will be discussed further in the sections discussing management of locally advanced disease.

In patients with head and neck SCC undergoing definitive radiotherapy, rapid proliferation (repopulation) of tumor cells between radiation fractions can limit the effectiveness of radiotherapy. Intensified radiation fractionation schedules, including hyperfractionation and accelerated fractionation, have demonstrated improved local control rates for head and neck cancer patients in randomized studies. Hyperfractionation consists of twice-daily radiation treatments, separated by at least 6 hours (i.e., 1.1–1.2 Gy BID) and has shown promising results in early-stage tumors.[49,53] Accelerated fractionation (i.e., 6–7 fractions per week or concomitant boost regimens) also have shown demonstrable benefits in HNSCC radiation patients.[53–55] Recently, a meta-analysis examining multiple randomized control trials of altered fractionation versus conventional fractionation demonstrated an overall survival benefit with altered fractionation.[56] The benefit was greatest with hyperfractionation and was most pronounced in younger patients. Therefore in patients undergoing

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| | Stage 0 (N=176) | Stage I (N=1020 | Stage II (N=1849) | Stage III (N=3288) | Stage IV (N=9803) |
|---|---|---|---|---|---|
| Surg | 21% | 21.60% | 12.30% | 6.50% | 6.20% |
| XRT | 24.40% | 33% | 28.40% | 15.60% | 12% |
| S + XRT | 10.20% | 11.60% | 8.30% | 9.30% | 10.20% |
| Ch + XRT | 18.20% | 13.80% | 32.60% | 47.80% | 43.80% |
| Ch | 2.30% | 2.30% | 2.10% | 3% | 5.70% |
| S + Ch + XRT | 1.10% | 2.50% | 3.40% | 5.40% | 8.60% |
| Other | 0.60% | 2.40% | 2.10% | 2.70% | 2.70% |
| None | 22.20% | 12.80% | 10.90% | 9.60% | 10.90% |

**FIGURE 19-8.** First course of treatment for cases of hypopharyngeal cancer diagnosed in the United States from 2000 to 2008, by stage. S, surgery; XRT, radiotherapy; Ch, chemotherapy.

*Source:* From National Cancer Data Base. Commission on Cancer. American College of Surgeons. Benchmark Reports, accessed August 24, 2011, with permission.

**TABLE 19.6 General Treatment Recommendations for Hypopharyngeal Cancer**

| | |
|---|---|
| T1N0, T2N0 not requiring laryngectomy | Radiation alone *or*<br>Larynx-preserving surgery (open or endoscopic) with neck dissection ± postoperative radiation |
| T2N0 bulky and/or requiring laryngectomy | Radiation alone (consider concurrent chemotherapy) *or*<br>Laryngopharyngectomy ± postoperative radiation |
| Resectable stage III and IV with functional laryngopharynx | Concurrent chemoradiation ± selective neck dissection *or*<br>Induction chemotherapy followed by (chemo)radiation if response or surgery if no response *or*<br>Laryngopharyngectomy +postoperative (chemo)radiation |
| Stage III and IV with dysfunctional laryngopharynx[a] | Laryngopharyngectomy with postoperative (chemo)radiation (preferred) *or*<br>Induction chemotherapy followed by (chemo)radiation if response or surgery if no response *or*<br>Concurrent chemoradiation ± selective neck dissection |
| Unresectable, nonmetastatic disease | Concurrent chemoradiation ± selective neck dissection *or*<br>Induction chemotherapy followed by (chemo)radiation |

[a]Patients with bulky, destructive tumors that destroy cartilage, bone and deep soft tissue and/or severely compromise the airway are often best served with immediate surgery.



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radiation alone, especially for bulky T2N0 lesions, altered fractionation deserves consideration. Alternatively, concurrent chemotherapy may be considered for bulky T2 lesions to enhance locoregional control (see below sections for rationale).

***Larynx-preserving Surgery.*** Primary surgical management of patients with early-stage cancer of the hypopharynx is indicated in patients who refuse radiation, have had previous radiotherapy, or those patients in which organ preservation is feasible and postoperative radiation is unlikely to be used. As submucosal spread of tumor is common (making margin-negative resections difficult) and 30% to 40% of clinically N0 patients will have pathologically involved lymph nodes that may warrant postoperative radiotherapy, careful patient selection is necessary before attempting organ-preservation surgery. Additionally, adequate counseling on the possibility for adjuvant radiotherapy should be given to all early-stage hypopharyngeal cancer patients considering upfront surgical management, as a significant portion of patients will experience the side effects of both treatment modalities if upfront surgery is chosen. Additionally, the primary concern after organ-preserving surgery is dysphagia, and adjuvant radiation will commonly worsen swallow function due to radiation-induced edema and/or fibrosis. Given these considerations, all hypopharyngeal cancer patients should discuss treatment options with a multidisciplinary team of specialists before embarking on a treatment course.

Favorable areas for larynx-preserving surgeries include the upper pyriform sinus or posterior pharyngeal wall. Tumors causing impairment in vocal cord mobility, involving the pyriform apex, the postcricoid area, or the anterior wall of the pyriform sinus often require total laryngectomy, as do patients with poor lung function.[57] Cartilage invasion is also a relative contraindication to organ-conserving surgery in the hypopharynx. Supraglottic laryngectomy standardly encompasses the aryepiglottic fold and may be extended to resect the upper pyriform sinus. Small tumors of the posterior pharyngeal wall can at times be removed successfully by either an open approach or via endoscopic laser resection. If an adynamic and insensate free flap is utilized with an open approach, dysphagia (often requiring NPO status) is commonly encountered postoperatively.

Supracricoid hemilaryngopharyngectomy can be considered with selected T1–2 tumors of the aryepiglottic fold or upper pyriform sinus. Good pulmonary reserve is necessary before consideration can be given to this procedure. Free-flap reconstruction innovations may allow for retention of speech and swallow function after this procedure, despite extensive soft-tissue resection. Rigid cartilaginous support with temporo-parietal flap and radial forearm free flap can be utilized in cancers without involvement of the pyriform sinus apex or postcricoid region to retain function in selected patients.[58] Bilateral neck dissections (levels II–IV) should accompany most organ-preserving surgeries in hypopharygeal cancers; close-interval CT scan surveillance can be considered in select T1N0 patients.

Transoral methods, including transoral laser microsurgery (TLM) and transoral robotic surgery, have been recently employed in attempt to achieve margin-negative tumor resection while minimizing damage to adjacent normal tissues. With these approaches, neck dissection is often deferred until final margin analysis is performed on the primary tumor specimen, with delayed neck dissection performed if margins are negative, or more radical open surgery (or radiation ± chemotherapy) entertained when primary margins are positive. This approach may facilitate surgery without the need for tracheostomy and feeding tubes, and oncologic outcomes appear similar to open surgical approaches for appropriately selected T1–2 lesions. However, it should be noted that adjuvant (chemo)radiotherapy is utilized in the majority of T1–2 patients in reports of this approach.[59–62]

## Stages III to IVa Disease (T1–2, Node Positive, or T3-4a), Resectable

As discussed above, patients with early T-stage disease may achieve negative primary tumor margins via larynx-sparing surgical approaches. However, the presence of clinically apparent lymph node metastases at presentation suggests that adjuvant (chemo)radiation will be indicated following definitive surgical management in the vast majority of these patients (see indications in postoperative radiation section below), which can exacerbate swallowing complications of larynx-sparing surgical approaches. Patients with T3–4 hypopharyngeal tumors (and advanced T2 lesions) generally require laryngopharyngectomy for surgical management and adjuvant (chemo)radiotherapy. Therefore, given the need for radiotherapy and goals of organ preservation, definitive chemoradiotherapy is the treatment most commonly utilized in stages III to IV hypopharyngeal cancers (Fig. 19-8).[30] Induction chemotherapy can also be utilized and may be appropriate for some patients[63] prior to definitive therapy, with recent randomized trials showing benefits in terms of overall survival to three-drug induction regimens as compared with two-drug regimens.[64,65]

***Chemoradiation (± Neck Dissection).*** Desire for organ preservation in locally advanced disease is the primary indication for nonoperative management in patients who may be technically resectable. Other reasons to forego surgical management include medical comorbidities that preclude general anesthesia. Conventional radiotherapy, with or without chemotherapy, is utilized in this scenario and typically aims to deliver 70 Gy in 2 Gy daily fractions to gross disease, with 50 to 60 Gy delivered to areas at risk for microscopic disease. For patients with locally advanced hypopharyngeal cancer, three-dimensional CT-based planning has become routine. This technology allows for more accurate target volume delineation, as well as three-dimensional representations of dose distributions (Fig. 19-9).

In patients with good performance status and stages III to IV disease, concurrent systemic chemotherapy should be considered. Numerous randomized controlled trials in head and neck cancer radiotherapy have demonstrated benefits to concurrent chemotherapy,[66] and a recent meta-analysis demonstrated a 6.5% benefit in terms of overall survival with the use of concurrent radiosensitizing chemotherapy[67] (Fig. 19-10). This benefit was noted primarily in younger patients, and no benefit was demonstrated in patients above age 70; therefore, consideration to radiation alone should be given to elderly patients who are undergoing nonoperative management for locally advanced hypopharyngeal cancer. For patients who are not candidates for concurrent chemotherapy (renal insufficiency, poor performance status, elderly), altered fractionation can be considered (see above discussion in early-stage section). However, similar to analyses of concurrent chemotherapy, where a benefit was not demonstrable in patients above the age of 70, altered fractionation has not been shown to be significantly advantageous in patients above the age of 70 in meta-analysis.[56] For patients with modest performance status or the elderly, once-daily radiation schedules without concurrent chemotherapy offer a reasonable treatment option.

Molecularly targeted agents provide another alternative to concurrent chemotherapy in patients with locally advanced hypopharyngeal cancer. Inhibitors of the epidermal growth factor receptor (EGFR) such as cetuximab have the most mature clinical data supporting their use in such patients. A randomized, phase III study in advanced head and neck cancer patients (including the hypopharynx) of radiation alone versus radiation plus weekly cetuximab demonstrated a 10% overall survival benefit at 5 years for the patients treated with concurrent cetuximab.[68,69] Concurrent cisplatin exacerbates common

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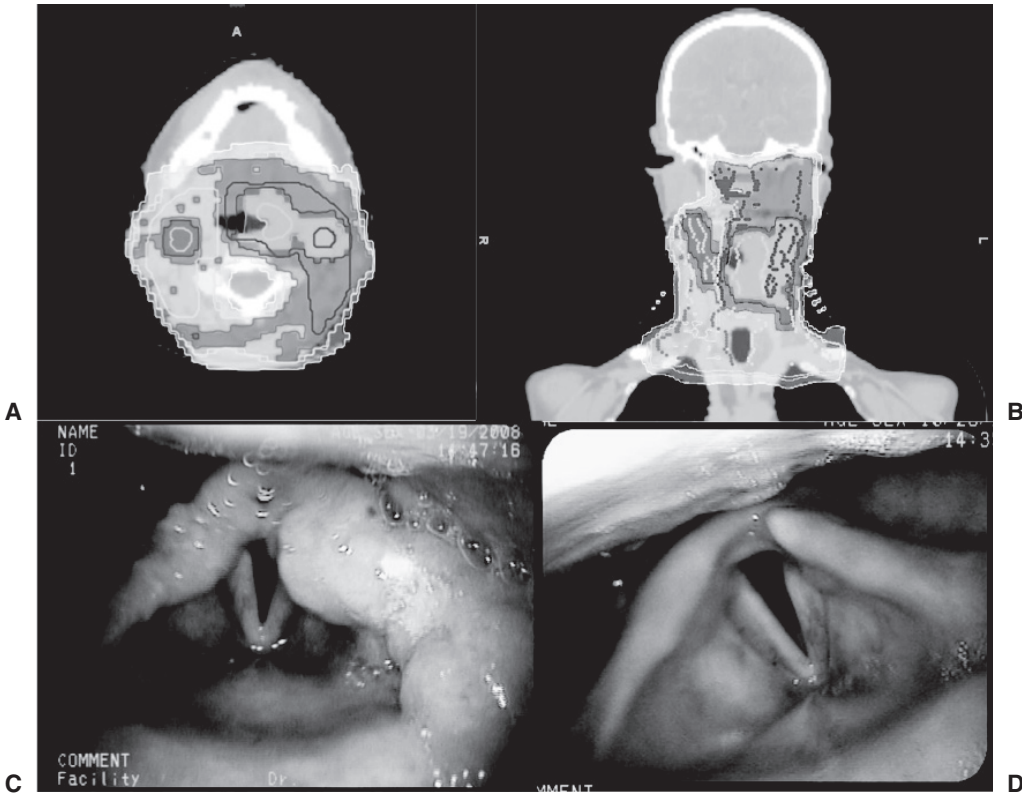
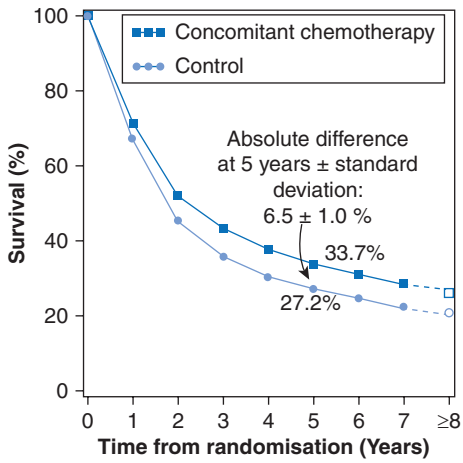



**FIGURE 19-9.** Axial (**A**) and coronal (**B**) dose distributions of a patient with a T3N2b SCC of the left pyriform sinus and aryepiglottic fold, treated with helical tomotherapy on protocol RTOG 0522. Turquoise contour represents the primary GTV, with involved left node contoured in red, both encompassed by a 70 Gy dose-cloud. Elective nodal areas received doses of 66 Gy (purple), 60 Gy (pink), and 56 Gy (yellow). Sparing of the right parotid is demonstrated on the coronal image. Panel (**C**) demonstrates the primary tumor prior to treatment via endoscopic examination, with complete response demonstrated at 3 years follow-up in panel (**D**). (See color insert.)




**Death/person-years by period**

| | Years 0–2 | Years 3–5 | Years ≥ 6 |
|---|---|---|---|
| **Control** | 2500/6298 | 672/3658 | 217/2487 |
| **Chemotherapy** | 2187/6647 | 706/4576 | 278/3194 |

**FIGURE 19-10.** Survival curves by treatment arm (meta-analysis) of patients randomized to either radiation alone, or concurrent chemoradiation.

*Source:* Used with permission from Pignon JP, le Maitre A, Maillard E, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol.* 2009;92:4–14.

radiation-induced toxicities (mucositis, dysphagia) and causes other nonoverlapping toxicities (anemia, leukopenia, renal insufficiency, ototoxicity, nausea/vomiting), thereby limiting the ability of many patients to receive concurrent cytotoxic chemotherapy. In contrast, concurrent cetuximab was not demonstrated to worsen acute radiation-induced toxicities and therefore may be tolerated by patients unable to tolerate concurrent cisplatin with radiotherapy.

IMRT is now the dominant technique for radiation delivery in locally advanced head and neck cancer. IMRT can minimize dose to normal structures and diminish toxicity; this is particularly useful to avoid excessive radiation dose to contralateral parotid glands, minimizing late radiation-induced xerostomia. The best candidates for IMRT-mediated sparing of contralateral parotid radiation are those patients in whom the bulk of disease is well lateralized, that is, T1–3 primary lesions with ≤N2b neck disease. The cephalad margin of the N0 contralateral neck radiation can often be limited to the C1–2 interspace in such patients to facilitate parotid sparing.[70] Recently, a randomized control trial demonstrated the superiority of IMRT over conventional radiotherapy for parotid sparing in locally advanced oropharyngeal and hypopharyngeal cancer patients.[71] An avoidance goal of limiting the contralateral parotid to <24 Gy was utilized in the IMRT radiation plans, and this resulted in a reduction of grade 2 or worse xerostomia at 24 months from 83% (conventional radiation) to 29% in the IMRT patients. Improved quality-of-life (QOL) scores were observed in the IMRT patients, strongly supporting the use of IMRT in locally advanced hypopharyngeal cancer patients.

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For patients undergoing primary radiation or chemoradiation, consideration should be given to postradiation neck dissection. For patients with N0–N1 necks, postradiotherapy neck dissection is rarely utilized. Many institutions utilize postradiotherapy neck dissections for patients with N2–N3 neck disease in attempt to enhance regional disease control[72,73]; in such cases, radiation dose to gross nodal disease can be limited to 60 to 63 Gy. Alternatively, gross nodal disease can be carried to 70 Gy, with neck dissection utilized only for patients with concerning imaging findings on postradiation imaging studies. Increasingly, a PET-CT scan at 10 to 12 weeks in patients with N2–N3 disease who receive 70 Gy to the gross nodal disease is used for such an assessment, as studies have demonstrated that complete clinical response by this assessment has a very high negative predictive value.[74]

***Primary Resection and Postoperative Radiation.*** Total laryngectomy and partial pharyngectomy (laryngopharyntectomy) with bilateral neck dissections was the historical mainstay of treatment for locally advanced hypopharygeal cancer. While a minority of favorable T3 hypopharynx cancers presenting in the upper portion of the pyriform sinus may permit oncologic resection via extended supraglottic laryngectomy or extended vertical partial laryngectomy with free-flap reconstruction, the vast majority of T3–4 tumors require total laryngectomy.

When laryngopharyngectomy is undertaken, efforts are made to preserve a posterior strip of the hypopharynx to form the basis of a conduit for passage of food and saliva. Primary closure (such as over a nasogastric tube) of the hypopharyngeal mucosa is now discouraged when <3 to 3.5 cm of the posterior pharyngeal wall mucosa is available to be tubed on itself. Free-flap reconstruction with a pedicled or free flap to reconstruct the anterior and lateral walls of the hypopharynx results in superior swallow function most commonly in such cases. When the entire hypopharynx must be removed for bulkier tumors, a gap exists between the oropharynx and esophagus. In these cases, radial forearm free flaps, anterolateral thigh flaps, free jejunum, or pedicled myocutaneous free flap are methods that may provide for a tubed fasciocutaneous flap to reestablish continuity of the alimentary tract.

***Postoperative Radiation.*** The majority of advanced hypopharyngeal cancers that undergo upfront surgery warrant postoperative radiation. Indications for postoperative radiation include pathologic T3–T4 tumors, N2–3 nodal disease (>1 involved lymph node), positive margins, perineural invasion, tumor emboli in adjacent vasculature, or extracapsular extension (ECE) of an involved lymph node.[75] Traditional postoperative radiation delivers 54 to 63 Gy to volumes at risk for microscopic residual disease, with areas of known ECE or margin positivity boosted to 60 to 66 Gy. Shrinking-field techniques can be used with conventional radiation field design, such that the entire cervical nodal chains bilaterally, from the base of skull to the clavicles are included. As described above, IMRT techniques are now commonly employed for postoperative radiation to reduce normal tissue toxicities.

The addition of cisplatin chemotherapy to postoperative radiation has been demonstrated to improve outcomes in high-risk patients, however, at the expense of additional toxicity. Two randomized trials, one from the European Organization Research and Treatment of Cancer (EORTC) group and another through the Radiation Therapy Oncology Group in the United States, evaluated the addition of 100 mg/m$^2$ cisplatin every 3 weeks to postoperative radiation in patients with locally advanced head and neck cancer, including hypopharyngeal cancer patients.[76,77] Although the entry criteria for the respective trials differed somewhat, a subsequently published analysis of the combined data suggested that patients with ECE and/or positive margins were most likely to benefit from the addition of chemotherapy to postoperative radiation (Fig. 19-11).[78] Given an approximate doubling of grade 3 acute adverse effects seen with the addition of concurrent chemotherapy, careful clinical judgment regarding patients most likely to benefit from this approach is necessary.

***Induction Chemotherapy and Sequential (Chemo) Radiation.*** In patients who would require total laryngectomy for adequate surgical resection, induction chemotherapy can be utilized to facilitate organ preservation in some cases. A European study for patients with advanced tumor of the hypopharynx randomized patients to primary surgical resection with total laryngectomy with postoperative radiation versus induction chemotherapy with 5-florouracil (5FU) and cisplatin followed by definitive radiation. In the patients randomized to induction chemotherapy and radiation, two-thirds of patients who survived were able to preserve their larynx, and no differences in 5- or 10-year survival or progression-free survival were noted, establishing this approach as

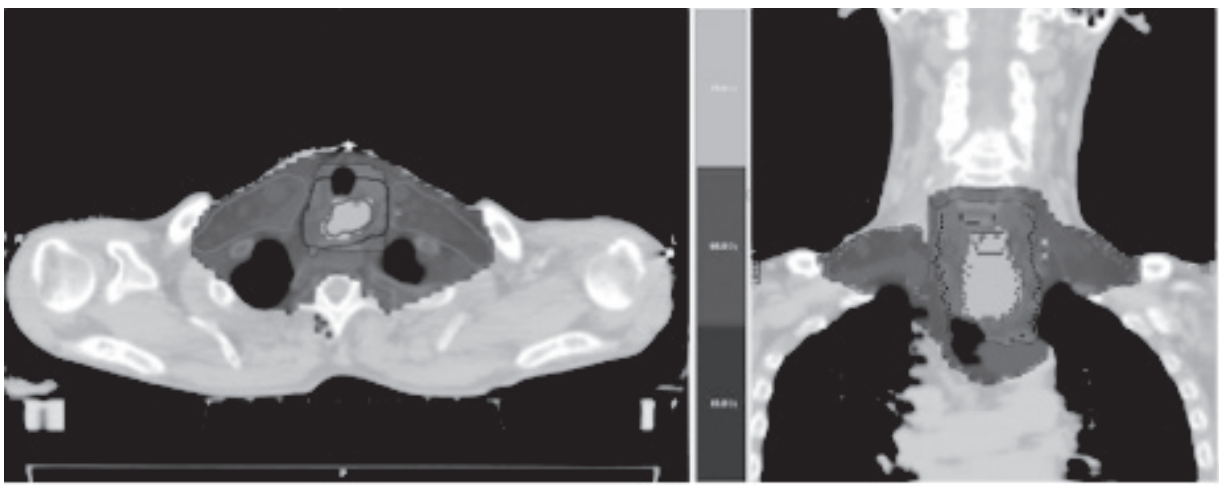



**FIGURE 19-11.** **(A)** Axial and **(B)** coronal representations of a patient with a T3N0 squamous cell carcinoma of the cervical esophagus treated with definitive chemoradiation. Helical tomotherapy was utilized to deliver 70 Gy to the primary tumor volume, 60 Gy to the high-risk clinical target volume, and 45 Gy to a prophylactic nodal volume, delivered with concurrent weekly cisplatin.

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an option for patients with advanced disease.[79] Cisplatin (P) and 5FU (F) in combination (PF) became a commonly used induction chemotherapy option.

Recently, the addition of docetaxel (T) to the backbone of cisplatin and 5FU (PF) has been studied in order to facilitate organ-preservation in patients with locally advanced cancer of the larynx or hypopharynx that would require total laryngectomy.[80] A French group randomized 213 patients to 3 cycles of induction PF or TPF. Response was assessed by laryngoscopy and CT/MRI imaging, and responders were treated with larynx-preserving (chemo)radiation, whereas nonresponders underwent laryngectomy and postoperative (chemo)radiation. TPF induction chemotherapy resulted in a higher tumor response rate (80% vs. 59%) than PF, allowing for a higher rate of laryngeal preservation (70% vs. 57%) at 3 years. Overall survival was 60% in both arms at 3 years.

***Unresectable, Nonmetastatic Disease.*** Patients with unresectable locoregional disease may warrant aggressive treatment with curative intent or may be best served by a palliative approach, with tumor burden, patient motivation, and performance status factoring into decision making. Curative-intent (chemo)radiation may be offered as above. For patients with high motivation and good performance status, induction chemotherapy followed by (chemo)radiation may be entertained. Two randomized studies have examined the addition of docetaxel (T) to the backbone of ciplatin and 5FU (PF) induction chemotherapy for patients with locally advanced, unresectable disease. TAX 323 was conducted by the EORTC and randomized such patients to induction TPF or induction PF, followed by definitive radiation alone.[65] TPF improved median overall survival as compared to PF. A similar study in the United States (TAX 324) randomized patients similarly to TPF versus PF induction chemotherapy, followed by definitive radiation with further concurrent chemotherapy (weekly carboplatin).[81] Improved overall survival was again demonstrated in the patients treated with TPF, and a subgroup analysis of patients with larynx and hypopharynx patients demonstrated improved survival as well as higher rates of laryngectomy-free survival.[82] These aggressive sequential therapy approaches may be considered in patients with good performance status, no contraindications to taxanes or platins, a high-tumor burden and/or advanced nodal disease.[63] However, these strategies are costly, toxic, and prolong the course of management. Randomized trials comparing these induction chemotherapy approaches with concurrent (chemo)radiotherapy have not yet been reported and will be important to determine the role for these regimens in the management in advanced head and neck cancer patients.

Patients with advanced disease and poor performance status who are not considered appropriate for aggressive radiation or chemoradiation can be offered palliative radiotherapy alone. Appropriate regimens include 4-5 Gy × 5 fractions over 1 to 2 weeks, which may be repeated 3 weeks later if initial tolerance is acceptable and response is seen. A comparative, nonrandomized study of palliative radiation regimens suggested that 3.7 Gy fractions twice daily × 2 consecutive days for 3 cycles every 2 to 3 weeks may offer similar palliation to other regimens, with less acute toxicity.[83]

## Cervical Esophageal Cancer Management

Large series evaluating management strategies for cervical esophageal tumors are lacking, and tumors in the cervical location comprise a small minority of cases enrolled in randomized studies evaluating management of esophageal cancers. Therefore, clear guidelines based on randomized data for management of tumors in this location do not exist. Pharyngolaryngoesophagectomy (PLE) with or without adjuvant radiotherapy has historically been the standard treatment approach for cervical esophageal tumors. However, given the impact of laryngectomy on QOL, concurrent chemoradiation with laryngeal preservation is commonly the preferred treatment approach for medically fit patients.[84] Many patients present with unresectable disease and/or metastatic disease, and aggressive treatment regimens may not be warranted in such patients.

***Resectable Disease.*** Large pattern of practice studies in the United States examining management of esophageal cancer have commonly excluded cervical tumors from their analyses.[85,86] Therefore, strong data of practice patterns in this rare tumor location are lacking, especially comparing upfront surgical treatment versus radiation approaches. However, oncologic outcomes appear to be similar between surgically treated patients and those managed with organ-sparing chemoradiation, with higher posttherapy QOL expected among the patients who can avoid pharyngolaryngoesophagectomy. When definitive radiation is delivered for curative intent, concurrent chemotherapy is indicated and is commonly utilized.[87]

***Chemoradiation.*** Practice patterns in esophageal cancer patients who are managed via nonoperative approaches have been heavily influenced by a randomized trial (RTOG 85-01) that randomized patients between dose-escalated radiation alone (64 Gy) versus chemoradiation utilizing 50 Gy with concurrent 5FU and cisplatin. Concurrent chemotherapy markedly improved the results; no 5-year survivors were seen in the radiation alone arm, whereas outcomes in the chemoradiation arm approximated surgical series (5-year survival of 26%).[88] Although cervical esophageal tumors were not enrolled, 88% of tumors in RTOG 85-01 were SCC, and therefore given the associated morbidity of operative management in cervical tumor locations, these results have been largely extrapolated to cervical esophageal tumors. Therefore, concurrent chemotherapy is most commonly employed with definitive radiation approaches for cervical esophageal tumors. Nonrandomized studies have shown survival outcomes following definitive chemoradiation in esophageal tumors to be similar to surgical series.[89–91]

Two approaches to definitive chemoradiation are commonly utilized. One approach is to treat cervical esophageal cancer with concurrent cisplatin and 5FU chemotherapy, as per RTOG 85-01. If this approach is chosen, valuable clinical trial data are available to guide radiation dosing. An intergroup phase III trial (INT 0123) randomized patients undergoing radiation with concurrent cisplatin and 5FU to a standard arm, with a dose similar to RTOG 85-01 (50.4 Gy), versus a dose-escalated arm treated with 64.8 Gy. Cervical tumors were enrolled in this study, and 86% of all tumors were SCC. Overall survival was not different between the standard arm and the dose-escalated arm (Fig. 19-12). Increased treatment-related deaths were noted in the dose-escalated arm, although this did not appear related to radiation dose as the majority of deaths on treatment in the dose-escalated arm occurred before patients received >50.4 Gy. Nonetheless, no differences were seen in cumulative local failure rates (Fig. 19-12), and therefore 50.4 Gy was felt to represent a standard dose when radiation was delivered with concurrent cisplatin and 5FU. Despite this, many current series specific to cervical esophageal tumors have reported radiation doses of 54 to 68 Gy with concurrent cisplatin and 5FU, with low rates of treatment-related mortality.[27–29,92] Although more advanced radiation delivery, including IMRT, may allow for safe dose-escalation beyond 50.4 Gy with concurrent 5FU and cisplatin, this approach should be undertaken cautiously. Alternatively, analogous to practice patterns in hypopharyngeal cancers, radiation may be delivered to doses of 60 to 70 Gy, with concurrent cisplatin chemotherapy.[28,93] A recent comparison of these two

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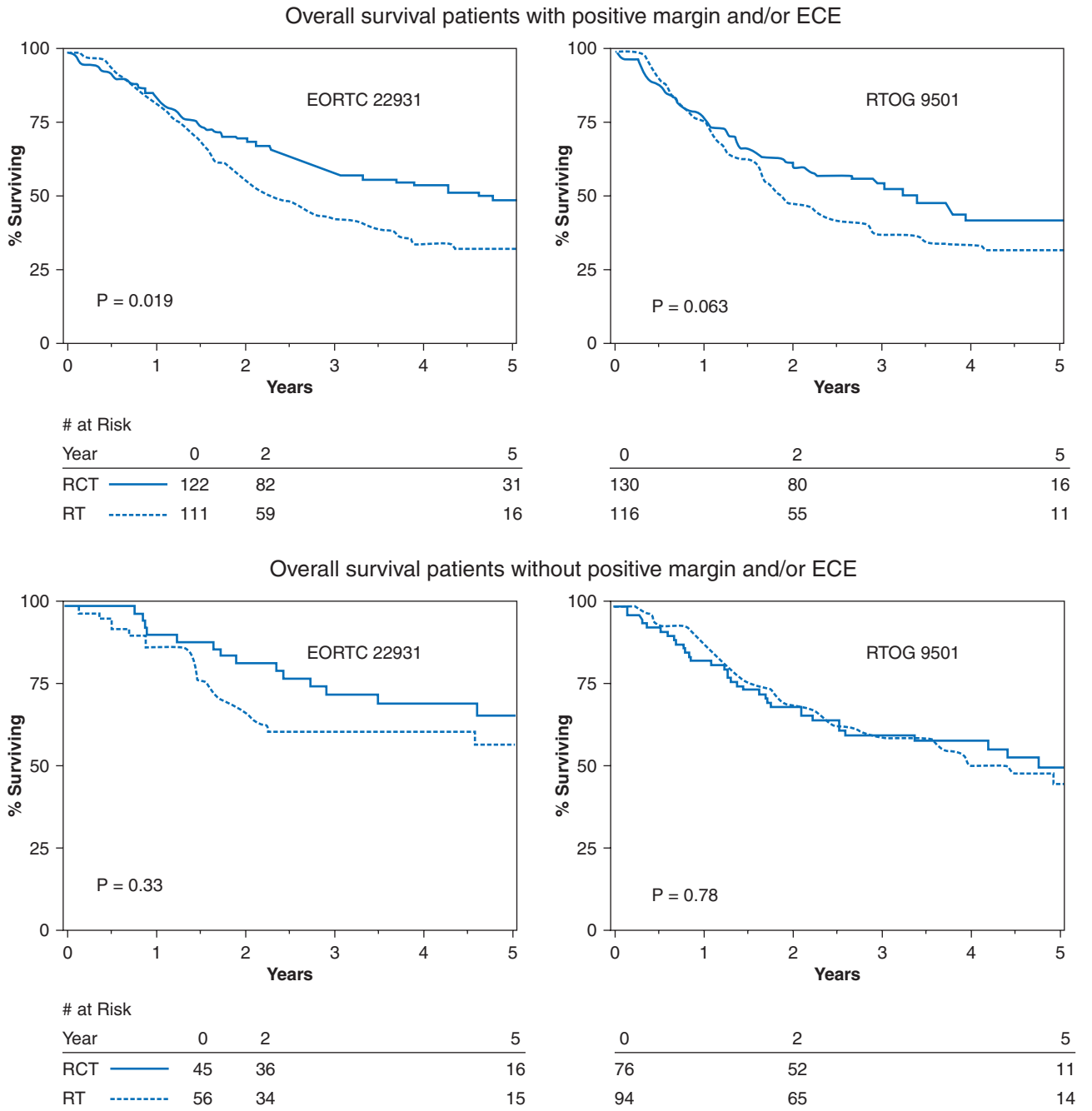



**FIGURE 19-12.** Impact of the addition of concurrent cisplatin to postoperative radiation on overall survival, according to the presence of positive margins and/or extracapsular extension (ECE).

*Source:* Redrawn with permission from Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (#9501). *Head Neck.* 2005;27:843–850.

approaches from Princess Margaret Hospital revealed similar oncologic outcomes between two cohorts of patients managed via these differing approaches.[28]

When designing radiation fields, careful review of endoscopic examinations, operative reports, and staging imaging studies is necessary. Additionally, the prospect of subclinical submucosal spread must be taken into account. Historical field design has encompassed a 5-cm margin in the cranial and caudal directions to cover possible submucosal spread,[90] with any boost dose delivered classically to a volume 2 cm above and below the gross tumor volume. More recent reports utilizing modern staging studies have limited the extent of normal-appearing esophagus and pharynx structures covered to 2 to 3 cm in the craniocaudal dimensions[27,28] (Fig. 19-13). With more advanced three-dimensional conformal techniques available in the modern era, efforts should be made to cover clinically negative bilateral supraclavicular lymph nodes and cervical neck level IV nodes, as well as the superior mediastinal (above the carina) lymph node basin with

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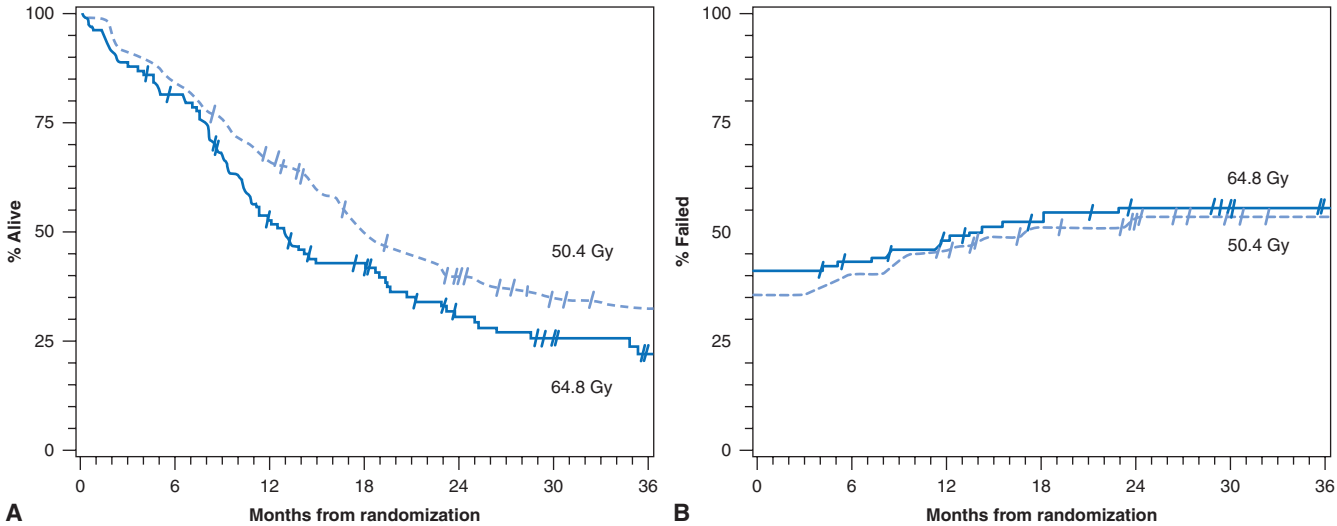



**FIGURE 19-13.** **A:** Overall survival in patients with esophageal cancer undergoing definitive chemoradiation with concurrent cisplatin and 5FU, randomized between standard dose (50.4 Gy) versus 64.8 Gy. **B:** Cumulative locoregional failure in patients with esophageal cancer undergoing definitive chemoradiation with concurrent cisplatin and 5FU, randomized between standard dose (50.4 Gy) versus 64.8 Gy.

*Source:* Redrawn with permission from Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. *J Clin Oncol*. 2002;20:1167–1174.

prophylactic doses of approximately 50 Gy. Extension of prophylactic radiation volumes in the neck should extend at least one full cervical lymph node level at any area where clinically positive lymph nodes are located. Given the proximity of vital structures such as the spinal cord, the parotids, the submandibular glands, the brachial plexus, the heart, and the lungs, IMRT has been utilized and may offer advantages in treatment of cervical esophageal tumors in terms of normal tissue toxicity avoidance.[93]

***Surgery.*** Surgical treatment for malignancy of the cervical esophagus is markedly different from those tumors located in the thoracic esophagus. Cervical esophageal resections are difficult due to the proximity of the larynx, which hinders visualization and surgical access to the tumor. It may be difficult to obtain a negative resection margin while leaving a functional larynx, even for early-stage lesions. For this reason, resections frequently require concomitant laryngectomy. Furthermore, transcervical surgical access is limited below the thoracic inlet, potentially making it impossible to resect and reconstruct the inferior limit of a tumor. For this reason, esophagectomy is frequently required. PLE was first reported in 1960 by Ong and Lee[94] and has been the mainstay of surgical management for cervical esophageal tumors, even those that appear to be early-stage disease given the tendency for submucosal spread.

In addition to having a propensity for submucosal spread, extramural extension to adjacent structures is common. One study analyzing cervical esophageal cancer patients demonstrated clinical or pathologic involvement of surrounding structures in 55% of cases,[13] including neck soft tissue, the trachea, the prevertebral fascia, and the thyroid gland. As a result, 36% of resection specimens had positive margins upon pathologic analysis, highlighting the difficulty of resection in this anatomic region.

While radical resection at the primary site in effort to achieve margin-negative resection is a difficult operation, patients also additionally require unilateral or bilateral neck lymphadenectomy to address the likelihood of microscopic nodal disease spread. The primary lymph node pathway is to the paratracheal lymph nodes, and paratracheal lymph node dissection is necessary and carries attendant risks such as hypothyroidism and hypoparathyroidism.[24] Superior mediastinal lymph node dissection is warranted, as one-third of patients will have pathologic involvement of these lymph nodes.[25] Unilateral thyroid lobectomy or total thyroidectomy is usually performed, as the gland is often invaded.[95] Immediate reconstruction of the digestive tract must also accompany the resection and can be accomplished in several ways. However, this combination of these factors leads to long and difficult operations, which are associated with substantial morbidity.

Esophagectomy is traditionally performed with abdominal and cervical exposure, with or without thoracotomy. The literature suggests that the transthoracic approach is associated with lower risk of anastomotic leak and recurrent laryngeal nerve injury and higher lymph node yield. Meanwhile, the transhiatal approach, which avoids thoracotomy, is associated with shorter procedures and fewer respiratory complications; the transhiatal approach is used more commonly than the transthoracic approach in tumors of the cervical and upper thoracic esophagus.[96] More recently, thoracoscopic and laparoscopic techniques have been applied to esophagectomy in hopes of limiting perioperative morbidity. No definitive studies exist regarding the benefits of these "minimally invasive" approaches.[97]

Resection of cervical esophageal cancers requires immediate reconstruction to restore continuity of the digestive tract. In selected cases, cervical esophageal tumors that are well below the level of the cricopharyngeus may lend themselves to larynx-sparing, limited cervical esophageal resection, and reconstruction may be accomplished with fasciocutaneous free flaps[98] or with jejunal free flaps (Fig. 19-14A).[99,100] Jejunal free flaps require harvesting a section of jejunum,[101] with end-to-end jejunostomy, which can then be anastomosed in an end-to-end fashion with any remaining proximal esophagus or in an end-to-side manner with the hypopharynx; an end-to-end anastomosis is performed distally (Fig. 19-14B). Resections that include esophagectomy are usually managed with gastric pull-up, in which the stomach is brought through the posterior mediastinum and anastomosed to the upper resection margin. Anastomotic leak is a common and

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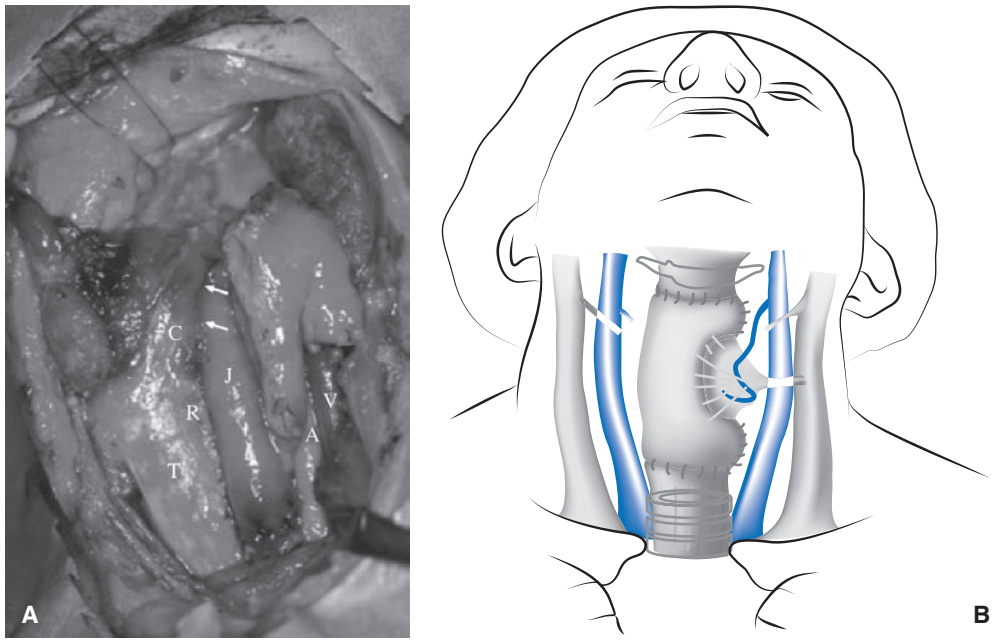



**FIGURE 19-14.** **A:** Free jv position in the left neck following larynx-preserving cervical esophagectomy. Jejuno-pharyngeal anastomosis is located at the level of the hypopharynx (*arrow*). The recurrent left laryngeal nerve is preserved. A, common carotid artery; C, cricopharyngeal muscle; J, transferred jejunal graft; R, recurrent laryngeal nerve; T, trachea; V, internal jugular vein. **B:** Diagram of free jejunal graft with end-to-end anastomosis to the cervical esophagus. End-to-end anastomosis to the superior thyroid artery and end-to-side anastomosis to the internal jugular vein is depicted.

*Source:* Reprinted with permission from Ott K, Lordick F, Molls M, et al. Limited resection and free jejunal graft interposition for squamous cell carcinoma of the cervical oesophagus. *Br J Surg.* 2009;96:258–266.

troublesome complication after gastric pull-up, occurring in almost 10% of cases in one series.[102] A pectoralis major muscle flap can be used to cover the anastomosis to mitigate against morbidity from anastomotic leak.[103] Colon transposition is an alternative to gastric pull-up for reconstruction after esophagectomy and is preferred in some centers.

Lymph node dissection is indicated in the management of carcinomas of the esophagus. The jugular chains, central cervical, and mediastinal nodes are of particular importance. Kelley et al. reported that the central cervical compartment nodes were most commonly involved at 32%, followed by the jugular chain nodes at levels 3 and 4 (18% each), in a cohort of previously untreated patients.[13] Weber et al. reported a 71% incidence of central compartment nodal metastasis in patients operated for cervical esophageal cancer.[34] They advocated removal of the nodes in continuity with the hemithyroid to ensure completeness of dissection. The superior mediastinal nodes extend from the level of the sternal notch down to the level of the carina. Metastasis to the superior mediastinal nodes was reported by Hirano et al. in 33% of patients with cervical esophageal carcinoma, which increased to 56% in patients whose tumors extended into the thoracic esophagus.[25] A substantial portion of patients in this cohort had been treated with neoadjuvant chemotherapy.

For patients who undergo upfront PLE, the use of adjuvant radiation is an area of debate. Many patients will have significant morbidities associated with PLE and will decline or not be recommended to undergo adjuvant (chemo)radiotherapy. However, some data support the use of adjuvant radiotherapy. In a large series of patients with hypopharyngeal and cervical esophageal primary tumors undergoing surgical resection, 73% of patients received adjuvant radiotherapy. Postoperative adjuvant radiotherapy was a significant beneficial factor on multivariate analysis, as was hypopharyngeal tumor location, in this series.[104] However, more recent studies have been much more selective in the use of adjuvant radiation.[27,99] Current NCCN guidelines recommend postoperative chemoradiotherapy for R1 or R2 resections, but recommend observation for all margin-negative resections.[84] More trials to address the role for adjuvant therapy in this setting are unlikely given the shift to primary nonoperative management, and therefore individual patient and tumor factors must be utilized to guide the decision for adjuvant therapy should surgery serve as the primary oncologic modality.

***Unresectable Disease, M0 or M1.*** In patients with unresectable cervical esophageal tumor without distant metastases, definitive chemoradiation is preferred, as discussed above. Patients with distant metastases have incurable disease, and systemic therapy is preferred, unless local symptoms predominate and warrant palliative radiation. Current common regimens utilized in metastatic esophageal SCC include ECF (epirubicin, cisplatin, and 5FU), a flouropyrimidine (5FU or its oral equivalent, capecitabine) plus cisplatin, a fluoropyrimidine plus oxaliplatin (or irinotecan), or a taxane (paclitaxel or docetaxel) plus cisplatin.[84] Performance status and medical comorbidities should be incorporated into decision making, as many patients may be best served by best supportive care and hospice enrollment. Only patients with excellent performance status and easy access for frequent toxicity assessment should be considered for three-drug regimens.

***Posttreatment Surveillance and Rehabilitation.*** Patients with cancers of the hypopharynx and cervical esophagus remain at high risk for locoregional and/or distant metastases following definitive treatment, regardless of whether surgery and/or radiation is used for upfront management. Therefore, close posttreatment

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surveillance is of value and typically involves head and neck surgeons and radiation oncologists in a multidisciplinary fashion.

Initially, follow-up visits for surveillance of disease recurrence should occur every 1 to 3 months for the first year, every 2 to 4 months for the second year, every 4 to 6 months for years 3 to 5, and then every 6 to 12 months thereafter.[75,84] These visits should include detailed physical exam, usually to include flexible nasopharyngoscopy. Serum TSH should be assessed every 6 to 12 months if head and neck radiation was utilized. Guidelines regarding posttreatment imaging surveillance are not well defined. However, given that the majority of locoregional tumor recurrences that are destined to occur happen in the first 2 years following therapy, serial CT imaging studies every 3 to 6 months for the first 2 years is a reasonable approach. The focus of surveillance shifts from recurrence of the initial disease to second primary development as the time from initial treatment lengthens, and while routine imaging after 2 years is likely of marginal value, it should be considered as symptoms warrant, as delayed locoregional recurrences, second primaries, and/or distant metastases are not uncommon in these patient populations.[26] Assessment of posttreatment scans in hypopharyngeal and cervical esophageal cancer patients can be difficult, as soft tissue changes following surgery and reconstruction can be difficult to distinguish from recurrent disease. Additionally, postradiation edema and fibrosis can similarly mimic recurrent disease, and therefore the involvement of experienced head and neck radiologists is highly desirable.

In addition to oncologic surveillance, management of toxicities and rehabilitation play an important role in maximizing posttreatment QOL. Utilization of a head and neck nurse coordinator or similar case manager can help patients navigate through the acute phase of their toxicities and facilitate posttreatment rehabilitation efforts.[105] Regardless of the primary treatment approach long-term speech and swallow dysfunction are likely to some degree. Early and intensive involvement of speech and swallow therapists can mitigate the impact these changes can have on QOL and help to maintain nutrition and minimize the risks for complications such as aspiration pneumonia. Additionally, many patients will find themselves able to minimize use of tobacco and/or alcohol during their acute treatment course but remain at high risk of relapse in the months and years following treatment; continued involvement of experts in tobacco and alcohol cessation, as well as routine encouragement of these efforts, is of value.

# OUTCOMES AND RESULTS

Series analyzing outcomes of hypopharyngeal and cervical esophageal cancer treatments are limited. Few randomized trials of these tumor subsites exist, and they are often included in (but form a minority of) larger cohorts of head and neck and/or esophageal tumors for enrollment in clinical trials and/or retrospective reviews. Nonetheless, it is accepted that outcomes in these tumor sites are disappointing, in part due to their tendency to present with advanced disease. Furthermore, patients presenting with these tumors often have significant medical comorbidities and socioeconomic barriers that limit aggressive oncologic treatment, further confounding comparisons of treatment approaches. Additionally, medical comorbidities and the emergence of second primary tumors cloud interpretation of published series. With these caveats, published reports of outcomes of these patients are presented.

## Hypopharyngeal Cancer

Outcomes in hypopharyngeal cancers are poor in comparison with other head and neck cancers, with 5-year overall survival rates approaching 30% (Fig. 19-5). An analysis from the NCDB of hypopharnygeal cases diagnosed in 2003 demonstrates that at 5 years stage-specific overall survival rates were 51.3% for stage I (3.0% of cases), 34.8% for stage II (9.4% of cases), 34.8% for stage III (22.3% of cases), and 19.8% for the 65.3% of cases presenting with stage IV disease (Fig. 19-15).[30] This highlights the proportion of patients presenting with advanced disease and the poor prognosis in hypopharyngeal cancer. Poor prognostic factors include increasing age, with patients above 70 faring poorly compared with younger patients,[7,106] likely reflecting poor tolerance of aggressive treatment approaches. Women may have a better outcome than men,[32,107] though this may be due to more common presentation with earlier stage disease. Furthermore, tumors of the pyriform sinus fare better than those arising on the posterior pharyngeal wall or postcricoid region.[32,107,108]

### Stages I to II Disease (T1-2, N0)

***Radiation.*** Nonoperative management is often chosen for early-stage disease (T1–2, N0). With T1N0 lesions, 5-year disease-specific survival (DSS) of approximately 90% can be expected with definitive radiation, while T2N0 lesions may expect DSS of >70%. Recent selected studies are highlighted below.

Garden et al. reported the MD Anderson experience treating T1–2 hypopharyngeal cancers from 1976 to 1992 with radiation alone, using varying fractionation schemes to deliver doses ranging from 60 to 79 Gy to the primary tumor. More than half (52%) of the patients were clinically node positive, and a portion of the node-positive patients had surgical management of neck disease prior to radiation. Actuarial local control rates for T1 lesions at 2 years were 89% and for T2 lesions were 77%. While survival was not presented by stage (including neck metastases stratification), 5-year overall survival rates were 67% for T1 lesions and 46% for T2 lesions, including the node-positive patients.

Amdur et al.[47] analyzed outcomes in 101 patients with T1–2 cancers of the pyriform sinus treated with primary radiation at the University of Florida from 1964 to 1997. Again, node-positive patients were included in the analysis, and approximately half of patients had no staging CT scan performed prior to treatment. Despite this lack of modern staging, 73% of patients were node positive. Radiation was delivered either daily at 1.7 to 2 Gy to a mean of 66.9 Gy or twice-daily at 1.2 Gy BID to a mean of 74.7 Gy. Unilateral neck dissections following radiation were utilized in 43% of patients. Local control for T1 lesions was 89%, and ultimately 95% including those who underwent salvage surgery. Local control for T2 lesions was 82% and was 91% when salvage surgery was included. DSS rates at 96% for stages I to II, 62% for stage III, 49% for stage IVa, and 33% for stage IVb. Overall survival rates were 57% for stage I, 61% for stage II, 41% for stage III, 29% for stage IVa, and 25% for stage IVb, highlighting the competing medical comorbidities in these patients.

Ten Japanese institutions reported their combined outcomes in stages I to II hypopharyngeal cancers managed with definitive radiation from 1990 to 2001.[106] Approximately half (57/115) of the patients received concurrent chemotherapy. Median total dose for T1 lesions was 63 Gy in once-daily fractions and 63.5 Gy in BID fractionation schemes, while median doses for T2 lesions were 66 Gy in once-daily fractions and 70 Gy in BID fractionation schemes. Local control with voice preservation was achieved in 34/39 (87%) patients with T1N0 disease (including seven cases successfully salvaged after local recurrence), with these patients experiencing a 5-year DSS rate of 96%. T2N0 lesions fared worse, with 56/76 (74%) experiencing local control with voice preservation, and a 5-year DSS rate of 70%. Concurrent chemotherapy was demonstrated to be a significant prognostic factor for local control on multivariate analysis, as were age <70, T1 (vs. T2) primary, and better performance status. Strikingly, 65 (57%) of patients had either synchronous or metachronous malignancies.

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Another Japanese group reported on 77 patients with stages I to II hypopharynx cancers treated with definitive radiation from 1988 to 2007.[108] Median radiation dose to the primary tumor was 66 Gy, and 66 patients (86%) had elective bilateral neck irradiation with a median dose of 40 Gy. Five-year recurrence-free survival and local control rates with laryngeal preservation were 57% and 70%, respectively. Five-year overall survival was 47%, whereas 5-year hypopharyngeal cancer specific survival was 74%. The majority of these patients (68%) were diagnosed without symptoms upon endoscopic examinations for other malignancies (most commonly esophageal cancer), and therefore nonhypopharyngeal cancer deaths were more common than hypopharyngeal cancer deaths in this series.

***Primary Surgery.*** Outcomes of patients treated surgically are difficult to summarize, as reports often include patients of widely variable stage, with differing proportions treated with larynx-sparing operations versus laryngopharyngectomy. Furthermore, endpoints between studies, use of adjuvant radiation, and time of endpoints reported vary widely between publications. Recently, TLM approaches have been used in selected hypopharyngeal cancers, with a potential for less invasive, more precise resection with lower morbidity and better QOL for surgically managed patients in comparison with open surgical approaches. Strict patient and tumor selection must be utilized, and given that margins of 15 to 20 mm are recommended for hypopharyngeal cases, TLM is not tenable in many patients, even with early T-stage lesions. Contraindications for TLM in cancers of the pyriform sinus include thyroid cartilage invasion, base of tongue and/or cervical space invasion, arytenoid involvement, and tumors crossing the posterior midline or involving the cervical esophagus.[109] Additionally, detailed knowledge of endoscopic anatomy, comfort with conventional surgery and microsurgery, and experience with the use of lasers are necessary skills for the endoscopic surgeon. TLM in combination with neck dissection and postoperative radiation as indicated can achieve results similar to (chemo)radiation in appropriately selected patients. Selected series utilizing TLM are summarized.

Steiner et al.[62] analyzed 129 patients with tumors of the pyriform sinus undergoing TLM from 1981 through 1996. Cases were pT1 in 24 patients, pT2 ($n = 74$), pT3 ($n = 17$), and pT4 ($n = 14$). The majority of patients ($n = 110$; 85%) received either a unilateral or bilateral delayed neck dissection, with 68% of cases ultimately node positive. Therefore, only 10 cases (7.7%) were stage I, 23 were stage II (18%), 26 were stage III (20%), and 70 cases (54%) were stage IV. Of the 33 stages I to II cases, only 6 (18%) received adjuvant radiation to the neck and primary, whereas 78 (81%) of the stages III to IV cases received adjuvant radiation, for indications of positive margins, ≥1 nodal metastases, or lymph nodes with ECE. The 5-year local control rate was 82% for stages I to II disease and 69% for stages III to IV patients, whereas overall neck failure rate was 14%; distant metastases developed in 14.7% of patients. Recurrence-free 5-year survival rates were 95% for stages I to II and 69% for stages III to IV, with overall survival rates at 5 years of 71% and 47%, respectively. Functional results were excellent, with all but 2 patients able to achieve oral intake, with median duration of nasogastric feedings of 7 days.

A smaller early series examining TLM in hypopharyngeal cancer reported outcomes in 29 patients.[110] Standard therapy consisted of TLM plus neck dissection and postoperative radiation. Five-year survival rates were encouraging in early-stage patients at 78%, but only 35% in the stages III to IV patients. However, functional outcomes were promising in this small series, with normal speech and swallowing reported in 100% of patients without local recurrence at 5 years.

Another German group performed TLM on 172 patients with hypopharyngeal cancers, with the vast majority ($n = 150$; 87.2%) having primaries in the pyriform sinuses.[61] Despite being candidates for TLM, only 15% of patients had stages I to II disease, whereas 85% had stages III to IV disease. Selective neck dissections were performed in 93% of patients, and 52% received postoperative radiotherapy. Five-year local control rates were 84% for pT1 tumors, 70% for pT2, 75% for pT3, and 57% for pT4a. Recurrence-free survival rates were 73% for stages I to II, 59% for stage III, and 47% for stage IVa. Second primary tumors developed in 44 patients (26%), resulting in 28 deaths. Consistent with the earlier report by Steiner, nasogastric tubes were needed by 80% of patients postoperatively, for a median of 6.5 days; only 6 patients (3.5%) required permanent gastrostomy tubes for long-term dysphagia. Postoperative edema, scar formation, or stenosis required repeat microlaryngoscopy in 6 patients (3.5%), and 7 patients required tracheotomies. Compared to radical surgery or open larynx-conserving experiences, oncologic outcomes appeared similar with lower morbidity and complication rates.

The largest reported experience of TLM in patients with only T1–2 primary tumors examined 119 patients.[60] TLM was able to achieve R0 primary resections in 101/119 (85%) of patients. The majority of patients (83.2%) received adjuvant neck dissections and/or postoperative radiotherapy. In patients with cN0 necks managed with neck dissection, 8 of 21 (38%) had occult neck disease. With a median follow-up of nearly 6 years, DSS was 83.7% in N0 neck cases, and 67.4% in node-positive cases. Tolerance of TLM in combination with adjuvant therapies was good, with permanent tracheostomy only needed in 2.5% of cases, and permanent gastrostomy tubes also needed in 2.5% of cases. Importantly, this series demonstrated the importance of negative margins, as DSS rates were significantly higher (77%) in R0 cases as compared with margin-positive cases (48%, $p < 0.001$).

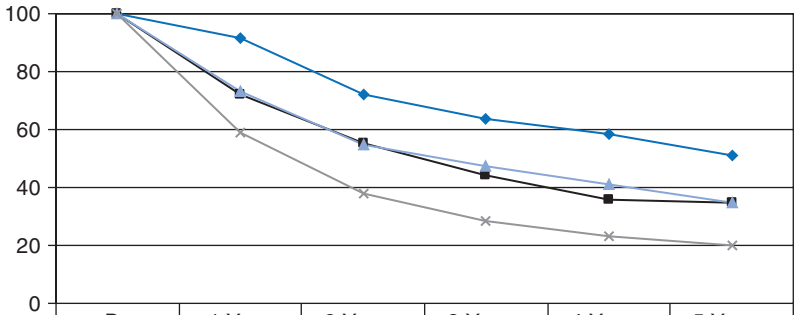
## Stages III to IV Disease

***Chemoradiation.*** Single institution reports have demonstrated that 5-year overall survival rates of approximately 35% to 45% can be achieved with concurrent chemoradiotherapy in patients with advanced hypopharyngeal cancer, with approximately two-thirds of surviving patients expected to retain a functional larynx. These rates are slightly higher than those reported in cross-sectional analysis of outcomes in the NCDB (Fig. 19-15) as patients chosen to undergo chemoradiotherapy are generally of higher performance than unselected hypopharyngeal cancer cohorts. Results from recent series utilizing modern radiation techniques and concurrent chemotherapy in patients with advanced disease are summarized.

Lee et al.[111] analyzed a group of patients with stages III and IVa–b laryngeal ($n = 20$) and hypopharyngeal cancer ($n = 11$) all treated with IMRT and concurrent platinum-based chemotherapy at Memorial Sloan Kettering Cancer Center from 2002 to 2005. All patients had PEG feeding during treatment, and PEG tubes were routinely placed prophylactically. The 2-year local progression-free survival rate for hypopharyngeal patients was 73%, and the 2-year overall survival rate in these patients was 53%. The 2-year posttreatment PEG-dependency rate was 31% in hypopharyngeal patients, higher than that observed in the laryngeal cancer patients (15%), with severe stricture and significant dysphagia contributing to this observation.

A Taiwanese group reported on 94 patients with locally advanced hypopharyngeal cancer managed either via chemoradiotherapy ($n = 30$) or surgery plus adjuvant radiation ($n = 44$) between 1995 and 2004.[112] No significant differences in T or N staging or other patient characteristics existed between the surgical or chemoradiotherapy groups. No significant differences in overall survival or disease-free survival between the two groups were observed, with 3-year overall survival rates of 39% in the chemoradiotherapy patients and 44% in the surgery plus

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| | Dx | 1 Year | 2 Years | 3 Years | 4 Years | 5 Years |
|---|---|---|---|---|---|---|
| Stage I n = 36 | 100 | 91.7 | 72.2 | 63.9 | 58.3 | 51.3 |
| Stage II n = 114 | 100 | 71.9 | 55.2 | 44.2 | 35.7 | 34.8 |
| Stage III n = 270 | 100 | 73.1 | 54.7 | 47.2 | 40.8 | 34.8 |
| Stage IV n = 790 | 100 | 59.1 | 37.7 | 28.5 | 23.3 | 19.8 |

**FIGURE 19-15.** Observed survival for hypopharyngeal cancer in the United States as calculated for new cases identified in the National Cancer Data Base in 2003. All pathologic types were included.

*Source:* Redrawn with permission from *National Cancer Data Base. Commission on Cancer. American College of Surgeons. Benchmark Reports,* accessed August 24, 2011. Staging according to 6th edition AJCC staging manual.

radiation group reported. Patients managed with surgery had a higher rate of local control, but approximately 70% of those surviving 2 years in the chemoradiotherapy arm were able to retain their larynx.

Liu et al.[113] treated 27 patients with concurrent chemoradiotherapy, with IMRT utilized in all patients. Early in the experience cisplatin days 1 and 29 with 5FU days 1 to 4 and 29 to 32 was given concurrently ($n$ = 6), but profound pharyngitis and esophagitis prompted a change to concurrent weekly cisplatin at 30 mg/m$^2$ for the latter 21 patients. The 5-year disease-free survival rate was 51%, whereas the overall survival rate was 35%, with a laryngeal preservation rate of 63%. Seven patients (26%) required a tracheostomy due to stridor with only two able to reverse to normal breathing; thus 5 of 27 (18.5%) had grade 3 laryngeal stricture. The authors concluded that IMRT with concurrent chemotherapy can attain high locoregional control rates and high functional laryngeal preservation rates, but late laryngeal stricture remains problematic.

Another Taiwanese report[114] compared outcomes in 33 patients treated with concurrent chemoradiotherapy with IMRT and outcomes of 14 patients treated with primary surgery. No patient and/or tumor factors were significantly different between the groups. The 5-year overall survival rates were not statistically different, observed at 44% for chemoradiotherapy versus 33% for those with primary surgery. Six patients in the chemoradiotherapy group underwent salvage surgery, such that 22 patients preserved a functional larynx. IMRT with concurrent chemotherapy was felt to preserve the larynx at high rates, without compromising survival as compared with primary surgical management.

***Surgery Plus Adjuvant Radiation.*** Oncologic outcomes of patients undergoing total laryngopharyngectomy plus adjuvant radiation are felt to be roughly equivalent to concurrent chemoradiation, with 5-year DSS rates of 40% to 50%. However, hypopharyngeal reconstruction presents a challenge with such approaches, and late complications and morbidity are problematic, including permanent gastrostomy tubes and significant strictures in a significant minority of patients, as well as the loss of natural voice. Thus, the use of open surgical techniques in hypopharyngeal cancer is declining.[115] Recent studies examining patients treated with primary surgery are presented, although limited by the trend toward nonoperative approaches in recent years.

A French group[104] reported on pharygolaryngectomy performed in 209 patients with either hypopharyngeal ($n$ = 131) or cervical esophageal cancers from 1982 to 1999. Methods of reconstruction to accompany pharyngolarygectomy varied; esophagectomy with pharyngogastric anastomoses were performed in 127 patients, free jejunal transfer in 77 patients, and total esophagectomy with pharyngocolic anastomoses in 5 patients. Of the hypopharyngeal patients, the vast majority were clinically T2 or T3 (85%), whereas clinical staging revealed node positivity in only 34%. Pathologic staging was not carefully reported, but ultimately 62% of patients were node positive, and 73% of patients were treated with postoperative radiotherapy. The 5-year survival rate was 29% for the hypopharyngeal cancer patients. No difference was noted between patients treated with either stomach interposition or jejunal transfer. Positive prognostic factors included R0 resection, postoperative radiotherapy utilization, and absence of surgical complications. Anastomotic leaks occurred in 47 patients (22.5%). The average time to resumption of oral feeding was 19.7 days, highlighting the severity of these operations, whereas mean hospital stay was 23.6 days. Late stricture occurred in 17 patients (8.5%).

Bova et al.[116] examined outcomes in 180 patients treated with pharyngolaryngectomy, all for hypopharyngeal cancer from 1979 to 2002. The majority (91%) had stages III to IV disease. The treatment paradigm in the reported patients was quite uniform, except that patients treated before 1990 received induction chemotherapy, but this practice was subsequently discontinued. Reconstruction involved a jejunal graft in all cases. Postoperative radiotherapy was utilized in 94% of patients, and all node-positive patients underwent neck dissections. Locoregional recurrence was low in this series at 18%, but 20% of patients developed isolated metastatic disease, whereas 16% developed second primary tumors. Therefore, the 5-year overall survival rate was 33%, whereas the DSS rate at 5 years was 52%. Functional outcomes, toxicities, and morbidity were not reported.

The experience of surgical management at Princess Margaret Hospital[117] included 66 patients treated with pharyngectomy as primary treatment. As nonsurgical management was favored at the institution, the indications for surgical treatment were

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previous head and neck irradiation ($n = 36$) or advanced primary disease ($n = 30$), where radiotherapy was felt unlikely to provide control. Five-year local and regional control rates (including salvage therapies) was 79% and 67%, respectively. The 5-year overall survival was 38%, and DSS was 45%.

## Cervical Esophageal Cancer

Pharyngolaryngoesophagectomy has traditionally served as definitive management for SCC of the cervical esophagus, but 5-year survival rates were approximately 15% utilizing this approach. Nonoperative management with chemoradiation is now commonly recommended given the substantial morbidity and poor oncologic outcomes associated with resection.[84] Outcomes of chemoradiotherapy are therefore emphasized, with 5-year overall survival rates of 25% to 40% expected in patients who are candidates for curative chemoradiation. Recent surgical series are also summarized.

***Chemoradiation.*** One of the earliest reports came from two Australian institutions, which analyzed 34 patients treated from 1991 to 1996 with chemoradiotherapy utilizing CT-based planning.[118] Shrinking-field technique was used to deliver at least 50 Gy to the tumor and draining lymph nodes, with the primary tumor receiving 61.2 Gy on average. All patients received concurrent chemotherapy, though the specific regimens were variable. Complete response rate was 91%, and ultimate local control was 88%. Actuarial 5-year survival was 55%, but no stage IV patients were included in the study, which may have contributed to these relatively good outcomes. Acute toxicity was acceptable, and late esophageal strictures were only significant (requiring dilations) in 5 patients (15%). Given these promising results, the authors concluded that concurrent chemoradiotherapy should be the preferred treatment for cancers of the cervical esophagus.

Bidoli et al.[119] reported on 106 patients with esophageal SCC treated with chemoradiotherapy. Thirty-two patients with cervical tumors were excluded from consideration of resection and were treated to 50 Gy, whereas a proportion of thoracic tumors were resected after 30 Gy. The nonsurgical patients (including the cervical tumors) had a better median survival (22 months) than the patients who underwent surgery (12 months). Of the cervical tumors, 7 of 32 (22%) required salvage surgery. The 10-year disease-free and overall survival rates for the cervical patients were 31% and 27%, respectively. The authors advocated that a nonsurgical approach should be strongly considered in patients where laryngectomy would be required given that 25% of patients achieved long-term survival with intact laryngeal function.

Subsequently, a Japanese report[120] examined 27 patients treated with definitive radiotherapy from 1988 to 2002. The mean radiation dose administered was 66 Gy, and concurrent cisplatin and 5FU was delivered in 23 (85%) of the patients. Actuarial overall survival at 5 years was 37.9%, whereas the disease-free survival rate at 5 years was only 13%, as 85% of patients ultimately experienced recurrence. Seven patients who received <60 Gy of radiation all failed locally, and 11 patients failed distantly.

MD Anderson Cancer Center reported their experience of 35 patients with SCC of the cervical or upper thoracic esophagus treated with chemoradiation, with a median dose of 50.4 Gy with concurrent 5FU-based chemotherapy. Complete response to chemoradiotherapy was documented in 63% of patients, although this rate was significantly higher in patients receiving >50 Gy (79% vs. 27%, $p = 0.003$). The 5-year rate of overall survival was 18.6%. Those with complete response had higher overall survival and cause-specific survival than those without complete response, and in patients receiving >50 Gy, 5-year overall survival was 29%. Therefore, chemoradiation with doses of 50 to 65 Gy was recommended by the authors for management of cervical esophageal cancer.

The Princess Margaret Hospital published their results of 71 patients treated with chemoradiotherapy.[28] Patients treated before 1997 to 2000 were treated with 54 Gy in 20 fractions without intentional elective nodal coverage, with concurrent cisplatin and 5FU chemotherapy. Patients treated from 2001 to 2005 were treated in a fashion more analogous to head and neck patients with elective nodal volumes treated to 50 to 56 Gy, and a boost to the gross disease to 70 Gy, delivered with concurrent cisplatin every 3 weeks. Only 50 patients were treated with curative intent, and the overall survival for this cohort was 28% at 5 years. No difference between the two treatment approaches was appreciated. Severe dysphagia requiring intervention (feeding tube, stent, or dilation) was common, afflicting 45% of the curatively treated patients.

***Surgery.*** Triboulet analyzed 78 patients who underwent pharyngolaryngectomy, with gastric replacement reconstruction used in 68 of the patients.[104] Average hospital stay for those with pharyngogastric anastomoses was 24.7 days. The majority of patients received postoperative radiotherapy, but despite these aggressive therapeutic measures, 5-year overall survival was only 14%. Pathologic T stage was shown to be prognostic, with T1 tumors showing a 33% 5-year overall survival, whereas no pT4 patients survived 5 years.

Another large series of 74 patients who underwent esophagectomy with or without laryngectomy demonstrated operative morbidity in 34% of patients, with in-hospital mortality rates of 4%.[121] The majority (80%) had tumors extending into the hypopharynx or thoracic esophagus, and 80% were stages T3 to T4. Only 16 patients (22%) received adjuvant radiation. Overall 5-year survival was 33%, with node negativity, stages I to II disease, and female gender being favorable prognostic factors. Significant complications occurred in 34% of patients, with graft necrosis in 20%. Larynx-preserving surgery was possible in only 32% of patients.

More recent studies have analyzed larynx-preserving esophagectomies for cervical tumors. Kadota et al.[99] reported outcomes in 32 patients with larynx-sparing surgery with jejunal transfer. Postoperative aspiration was absent or transient for the majority of patients, and mean time to oral intake was 12.5 days. Decannulation was achieved in all patients who underwent tracheostomy, and laryngeal function was fully preserved in all patients. Five-year disease-free survival was approximately 40%, with overall survival not reported. This approach may be utilized in patients with low cervical esophageal tumors, with more careful selection needed in patients with high tumors involving the hypopharynx.

Ott et al.[100] published results of 109 patients managed with limited resection and jejunal graft interposition from 1986 to 2006. The majority of patients (86%) received neoadjuvant chemoradiotherapy. Laryngeal preservation (complete or partial) was achieved in 85% of cases. Although the mortality rate was promising, with a 5-year survival rate of 47%, complications were high (74%), with anastamotic leak in 27% of patients, graft ischemia in 24%, and sternal osteomyelitis in 10%. Reoperation was performed in 29% of patients.

Two recent series have compared outcomes in patients managed either surgically or with primary chemoradiation. A Taiwanese study[92] examined 15 patients who underwent radical resection with reconstruction, and 14 patients receiving chemoradiotherapy from 2002 to 2007. No significant differences were noted in pretreatment patient characteristics. Surgery included bilateral neck dissections and adjuvant chemoradiation in cases of pathologic T3, N1, or M1a involvement. Chemoradiation consisted of 60 to 70 Gy with concurrent cisplatin and 5FU. Greater improvements in dysphagia scores were noted in patients undergoing surgery than patients receiving chemoradiation. Mean DSS

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times were not different in the surgical versus chemoradiation patients.

In a second, larger study, Tong et al.[27] reported outcomes in 107 patients with cervical esophageal cancer. Pharyngolaryngoesophagectomy was performed in 62 patients who had disease judged to be resectable, usually followed by adjuvant radiation. When surgery was declined or patients were too high of surgical risk, curative chemoradiation was offered to 21 patients; treatment was palliative in the remainder of patients. Of the patients receiving chemoradiation, 6 (29%) ultimately required salvage surgery. The median survival for surgical patients was 19.9 months, whereas it was 24.9 months in the chemoradiotherapy patients ($p = 0.39$). Median survival times for patients with other management strategies, including radiation alone, were all <10 months (Fig. 19-16), highlighting the dismal outcomes of patients not managed with either radical resection or chemoradiotherapy.

## Quality of Life

Treatment for hypopharyngeal and cervical esophageal tumors is accompanied by significant acute and long-term morbidity, with impact on patient appearance, speech, swallowing, and social functions. Therefore, assessment of organ preservation, functional status, and patient-assessed QOL must be considered in evaluating the overall efficacy of treatment approaches. Relatively few prospective studies with robust QOL analyses following treatment exist. In patients requiring surgery such as laryngopharyngectomy, functional deficits are predictable, whereas assessing the extent of functional organ preservation in patients undergoing either (chemo)radiation or larynx-sparing surgical procedures can be more difficult to quantitate. Regardless of the treatment approach, long-term speech and swallow rehabilitation efforts are warranted. Although data exist from some studies detailing impact of therapy on QOL in hypopharyngeal cancer patients, similar data are largely lacking for cervical esophageal patients.

A prospective study of QOL in head and neck SCC patients in Sweden demonstrates the substantial challenges for these patients. At diagnosis, hypopharyngeal cancer patients (as compared with other head and neck tumors sites) had the lowest social, emotional, and cognitive functioning, and the lowest global QOL scores.[122] When considering treatment options, the possibility of preserving laryngeal function must be considered. A controversial study by McNeil et al. administered a questionnaire to healthy subjects and found that some patients may accept a slightly lower chance for cure in favor of larynx-sparing approaches.[123]

Two recent similar studies by the same group in the Netherlands nicely demonstrate the impact of chemoradiotherapy or pharyngolaryngectomy on hypopharynx cancer patients. In the study performed in 73 patients who received chemoradiotherapy, toxicity was measured at 3, 6, 12, and 24 months after treatment.[124] QOL questionnaires were sent to long-term survivors, alive with a mean of 5 years after treatment. The mean overall score for vocal function demonstrated a mild-to-moderate voice handicap. Deficits were identified in physical, emotional, cognitive, and social functioning, with sticky saliva, weight loss, need for nutritional supplements, dry mouth, and trouble with social eating being the most problematic symptoms. These deficits demonstrate that organ preservation does not necessarily equate with preservation of high-quality organ function.

The sister study reporting on patients treated with pharyngolaryngectomy[125] demonstrated high complications rates (63% after jejunal grafts and 89% after gastric pull-up), but long-term QOL measures were good. Among the 21 patients alive at the time of the study, 14 returned QOL surveys. Satisfying scores were given for global health status and functional scales. The biggest factors negatively impacting QOL were smell and taste difficulties, speech problems, and sexuality problems.

Another recent report performed a matched-pair analysis of patients with advanced head and neck cancer undergoing operative or nonoperative management to evaluate long-term QOL.[126] Patients in the surgical arm demonstrated worse speech outcomes than those treated with chemoradiotherapy, but the overall QOL scores were similar, indicating that adjustment to loss of voice as well as other toxicities associated with chemoradiation may reduce the benefit of voice preservation on QOL. However, other studies have demonstrated better scores in terms of emotional and functional QOL measures in patients undergoing chemoradiation compared with surgery followed by radiation.[127] These studies demonstrate the complexity of QOL analysis following radical therapies for advanced head and neck cancer and highlight the need for prospective studies of QOL in these patients.

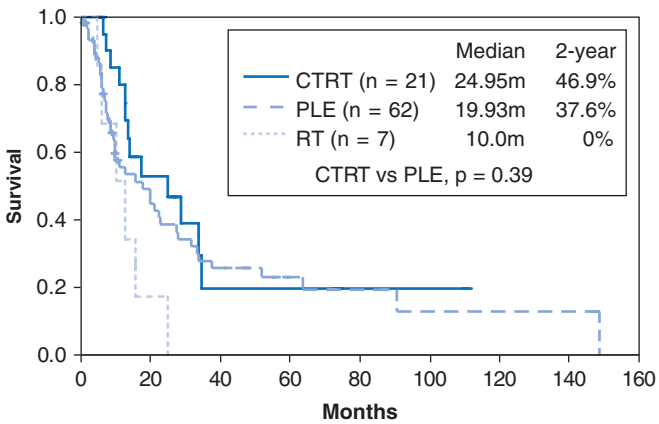



**FIGURE 19-16.** Survival of cervical esophageal cancer patients by treatment strategy. CTRT, chemoradiotherapy; PLE, pharyngolaryngoesophagectomy; RT, radiotherapy.

*Source:* Redrawn with permission from Tong DK, Law S, Kwong DL, et al. Current management of cervical esophageal cancer. *World J Surg.* 2011;35:600–607.

## Complications

***Surgical Management.*** Complications from surgery include anesthesia risk, bleeding, infection, and damage to structures in the surgical bed. When efforts are made to perform larynx-sparing procedures for hypopharyngeal cancers, significant dysphonia, aspiration, and refractory dysphagia requiring long-term gastrostomy feedings are not uncommon and may warrant completion laryngectomy. Laryngopharyngecomty is often accompanied by anastomotic leaks and fistulization. Graft necrosis can occur with free-tissue transfers. Stricture formation can occur late and may represent tumor recurrence.

The perioperative morbidity and mortality burden for cervical esophageal cancer is substantial with laryngopharyngoesophagectomy. One large population-based study recently reported a perioperative mortality rate of 4%.[128] A recent study reported a major complication rate of >40%[102] (Table 19.7). These can include pneumonitis, anastamotic leakage, pleural effusion, wound infection, and chylous fistula. Recurrent nerve palsy is common, as is stenosis requiring endoscopic dilation, both occurring in roughly 20% of patients.[100] Furthermore, significant dysphagia is common and problematic.

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**TABLE 19.7 Postoperative Complications in 208 Patients Undergoing Gastric Pull-up Reconstruction for Squamous Cell Carcinoma of the Hypopharynx and/or Cervical Esophagus at the Affiliated Provincial Hospital of Anhui Medical University in China from 1988 to 2007**

| Complications | Patients (n) |
|---|---|
| Pneumonitis | 23 (11.1%) |
| Anastomotic leakage | 19 (9.1%) |
| Pleural effusion | 15 (7.2%) |
| Wound infection | 8 (3.9%) |
| Chylous fistula | 4 (1.9%) |
| Heart failure | 4 (1.9%) |
| Hemothorax | 3 (1.4%) |
| Hemoperitoneum | 2 (1.0%) |
| Anastomosis stricture | 7 (3.4%) |
| Burst abdomen | 2 (1.0%) |
| Total | 87 (41.8%) |

*Source:* Reproduced from Shuangba H, Jingwu S, Yinfeng W, et al. Complication following gastric pull-up reconstruction for advanced hypopharyngeal or cervical esophageal carcinoma: a 20-year review in a Chinese institute. *Am J Otolaryngol.* 2011;32:275–278, with permission.

***Radiation Therapy.*** Acute effects of radiotherapy to the head and neck region are predictable, including mucositis, fatigue, dermatitis, xerostomia, and loss of taste acuity. Mucositis is the most problematic of these, limiting oral intake leading to malnutrition and dehydration commonly in patients without enteral feeding tubes. Mucositis typically develops during the third week of radiation and is exacerbated by concurrent chemotherapy and/or altered fractionation radiotherapy courses. Nonprescription analgesics may be utilized first, in combination with maalidoben (liquid maalox, lidocaine, and diphenhydramine) to aide in alimentation, but narcotic analgesics are commonly necessary. Nausea is commonly encountered and further complicates dehydration and malnutrition, frequently warranting use of antiemetics.

Late effects of radiation include permanent xerostomia, which can cause difficulty with speech and accelerated dental decay. Trismus can result, causing difficulty with mastication. Dysphagia is common as a late side effect and warrants speech and swallow rehabilitation in the posttreatment phase. Many patients struggle to maintain a satisfactory body weight. Permanent gastrostomy tube dependence is more common with tumors of the hypopharynx and cervical esophagus than in other head and neck tumor sites and can be seen in approximately 15% of surviving patients.[111] Stricture is commonly encountered, especially in cervical esophageal tumors, with approximately 10% to 15% of patients requiring repeated dilation.[118] Hypothyroidism is a common side effect of radiotherapy in this region, and surveillance with laboratory tests in surveillance is warranted every 6 to 12 months.

## Management of Recurrence

Given the disappointing results of upfront therapy, regardless of primary modality, locoregional and distant recurrence is common in both hypopharyngeal and cervical esophageal tumors. Therefore, close posttreatment surveillance is indicated. Changes on endoscopic examinations and/or surveillance imaging that are concerning for recurrence prompt biopsy for confirmation of recurrence. Before entertaining aggressive salvage treatment, complete restaging is warranted, as patients with locoregional recurrence have high rates of simultaneous distant metastases. Many patients with recurrent disease, even without distant metastases, may not be candidates for aggressive local salvage therapy and may be best served with systemic chemotherapy and/or hospice enrollment with best supportive care measures.

***Salvage after Initial Radiotherapy.*** Salvage surgery remains an option for patients with recurrent disease after upfront (chemo) radiation. In general, recurrent disease will require extensive surgery including sacrifice of the larynx. However, TLM has been used successfully in select patients with low-volume localized disease[129] and may be considered.

In patients with more advanced recurrent disease following initial radiotherapy, salvage laryngopharyngectomy (with or without esophagectomy) can be entertained. These resections are technically challenging for the surgeon and present healing challenges to the patient, but selected patients may benefit from this approach. One series demonstrated a 5-year overall survival of 31% for patients undergoing salvage pharyngectomy for recurrent hypopharyngeal cancer, with locoregional control rates of 70%,[117] although perioperative complications were high. Similarly, long-term survival can be achieved with salvage esophagectomy following definitive chemoradiation, but this operation is risky with high rates of anastomotic leakage and in-hospital mortality.[130]

Traditionally, patients initially treated with radiation have not been considered for reirradiation to the head and neck. However, with the development of advanced, highly conformal radiation delivery systems, selected patients may be good candidates for high-dose reirradiation. Two prospective RTOG trials have recently demonstrated this approach to be feasible.[131,132] Recent experiences with IMRT have demonstrated that long-term disease control may be achieved in appropriately selected patients with acceptable toxicity.[133,134]

***Salvage after Initial Surgery.*** When larynx-sparing initial surgery was performed, salvage pharyngolaryngectomy may be feasible, accompanied by either gastric pull-up or jejunal transfer. In rare occasions, further organ-sparing surgery may be considered, particularly in patients initially managed without adjuvant radiation. If patients are to undergo further larynx-sparing surgery and have not previously received radiation, adjuvant radiation can be utilized.

Alternatively, if recurrence after surgery occurs in patients without a history of receiving radiation, high-dose (chemo)radiotherapy can be considered. More commonly patients will have received adjuvant radiation as part of their initial treatment package, and reirradiation should be avoided in the majority of these cases (see above discussion).

***Palliative Chemotherapy.*** A large proportion (25%–40%) of patients with cancers of the hypopharynx or cervical esophagus will ultimately develop metastatic disease. When this occurs, long-term survival is rare and treatment intent is palliative in nature. Distant metastases are often accompanied by local recurrence, and palliative short-course radiation should be considered for local pain, bleeding, or significant dysphagia limiting QOL. Palliative surgery can also be considered to alleviate local symptoms, and narcotic pain medications are often valuable.

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Median overall survival for patients with metastatic head and neck cancer is 6 to 10 months.[135] In this situation, palliative chemotherapy can be considered in patients with good performance status, and single-agent cisplatin has been demonstrated to improve overall survival in head and neck cancer patients.[136] Historically, combinations of cytotoxic chemotherapies have not shown enhanced overall survival over cisplatin alone, and therefore they have not been commonly utilized.[137] Recently, however, randomized data have been published supporting the use of a triple-drug regimen in patients with recurrent or metastatic head and neck cancer, with (a) cisplatin or carboplatin (b) 5FU and (c) the anti–epidermal growth factor receptor monoclonal antibody cetuximab. In this setting, the addition of cetuximab to platinum and 5FU improved overall survival from 7.4 to 10.1 months,[138] and this regimen now has a category 1 recognition in the current NCCN guidelines.[75]

Chemotherapy options for recurrent esophageal cancer feature two-drug regimens. These regimens are commonly based on 5FU or capecitabine and platins (cisplatin or oxaliplatin). Randomized data supporting cetuximab use do not exist for tumors of esophageal origin to date, but biologic agents warrant continued investigation in these tumors given their dismal prognosis once metastatic.

## FUTURE DIRECTIONS

Cancers of the hypopharynx and the cervical esophagus present challenges to surgeons, radiation oncologists, and medical oncologists. As the majority of patients present with locally advanced disease, classical treatment approaches involve significant morbidity, and outcomes from an oncologic and functional standpoint remain disappointing in the majority of patients.

Advances in surgical techniques, such as the recent development of transoral laser techniques, may offer alternatives to the more aggressive traditional surgeries that involve laryngectomy and free-tissue reconstruction. In order to fully utilize these newer techniques, risk stratification for local recurrence following organ-preserving surgery must be more fully understood, in order to guide decisions regarding organ-preserving versus radical resection. Clinical experience, preferably in the form of prospective clinical trials, is also necessary to more uniformly guide the use of adjuvant (chemo)radiotherapy in patients treated using these more novel surgical techniques.

IMRT has significantly impacted the ability of the radiation oncologist to deliver high-dose treatment to the hypopharynx and the cervical esophagus while minimizing normal tissue toxicities. However, questions still remain regarding optimal target volumes, dose selection, and what chemotherapy should be delivered, especially for cervical esophageal tumors. Prospective clinical trials are difficult to perform in this setting, but are clearly indicated to address these issues.

Furthermore, there is increasing interest in the incorporation of biologic agents into the upfront and metastatic treatment paradigms for tumors of the hypopharynx and cervical esophagus. Ongoing preclinical and clinical work in these arenas will hopefully identify additional agents of value to patients afflicted with these aggressive malignancies.

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# PART B:
# Radiologic Imaging Concerns

Jeffrey A. Bennett

Imaging of the hypopharynx is typically performed in a patient with persistent, often unilateral sore throat, dysphagia, glomus sensation, or otalgia after a tumor has been found by endoscopy. The endoscopist is usually able to map out the mucosal extent of the tumor, but the relationship of the tumor to the esophageal verge, postcricoid area, or piriform sinus apex may be difficult to determine. The submucosal extent of disease also cannot be determined by endoscopy. Computed tomography (CT) with intravenous contrast is the usual first imaging study performed. There is no longer a role for fluoroscopy with oral contrast in primary diagnosis, but video fluoroscopy is still performed, mainly in posttreatment patients for analysis of swallowing and to look for the presence of aspiration or a fistula. Suggested CT and magnetic resonance imaging (MRI) protocols are given in Figures 19-17 through 19-19.

As in other areas of the head and neck, the purpose of imaging is to determine the full extent of the primary tumor and to look for perineural spread in this location along recurrent laryngeal nerve, or superior laryngeal neurovascular bundle, or lymphatic spread, typically not only to levels II through VI, but also to the retropharyngeal nodes (Fig. 19-20).[1,2] In addition, the possibility for acute airway obstruction should be assessed. The airway may be at risk in the posttreatment setting as well, if there is radionecrosis of the cricoid cartilage.

CT and MRI can both provide information on spread of tumor to the larynx, the oropharynx, the paraglottic space fat, or the preepiglottic fat. Figures 19-21 and 19-22 show piriform sinus primary tumors with spread into the larynx. Figure 19-23 shows a postcricoid tumor extending to the esophageal verge. Figures 19-24 and 19-25 show primary cervical esophageal tumors.

CT and MRI are both somewhat limited in the detection of early cartilage invasion, as there is variability in the ossification of the cartilage, but CT might be slightly better because of the ability to acquire very thin, $< 1$ mm thick slices. MRI of this region is often degraded by motion artifact. Where MRI provides an advantage is in its superior soft-tissue differentiation in determining whether tumor abuts or invades the esophagus or the trachea.

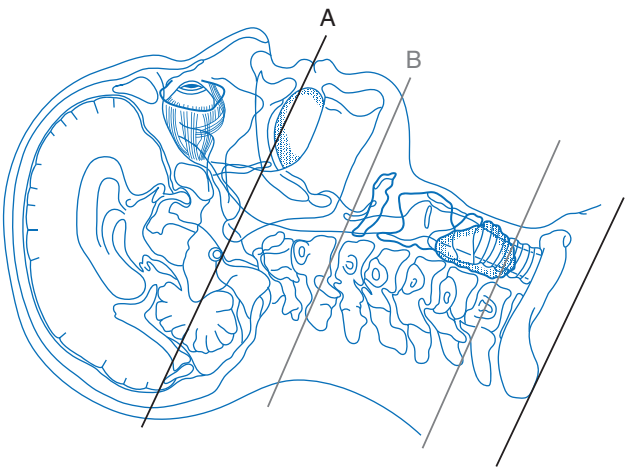
Since esophageal cancers can be synchronous with other head and neck squamous cell carcinomas, the radiologist should search for other mucosal-based tumors when an esophageal tumor is found. One study by Wang et al.[3] showed 69 of 315 patients (21.9%) had synchronous head and neck squamous cell cancer and esophageal neoplasia. Drinking alcohol was a significant risk factor. Another study[4] found the risk of synchronous esophageal and head and neck squamous cell cancers to be rare for the oral cavity, but were more common in the larynx, the hypopharynx, and the oropharynx.

FDG-PET has limited use in mapping the primary tumor, but does have a role in the detection of an additional primary tumor such as lung cancer and may help to identify positive lymph nodes. Some studies suggest that higher standard uptake values within the primary tumor may correlate with increased radioresistance and may be a negative predictive factor,[5,6] but as yet this information has not been used to alter treatment plans.

Posttreatment surveillance imaging is aimed at early detection of recurrence[7] or metastatic spread to lymph nodes (Fig. 19-26). CT, MRI, or PET-CT are all viable modalities to use for follow-up imaging, and all can direct biopsies when there is a suspicion for recurrence. It is useful to have a baseline posttreatment imaging study at 3 to 4 months after completion of treatment so that comparison can be made on future studies to best interpret areas that scar, or are growing, and thus suspicious for recurrence. This is important as total laryngopharyngectomy may offer a chance of cure for some patients who have had voice-sparing treatment initially.

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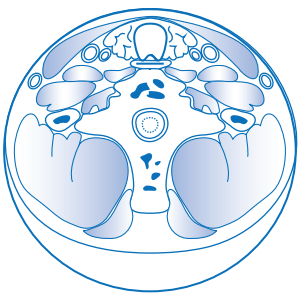
ACQUISITION




| | | |
|---|---|---|
| | Patient Position | Supine<br>Mandibular body perpendicular to tabletop |
| | Contrast | 100 mL total adult |
| | Injection Rate | 1 mL/sec |
| | Volume Acquisition Specs | Appropriate to achieve images as specified in following reconstruction tables.<br>Head FOV. |
| A | Contrast | 70 mL; 60 sec delay |
| | Respiration | Quiet, NO Swallowing |
| | Begin | Mid oral cavity |
| | End | Lung apices |
| B | Contrast | 30 mL; 30 sec delay |
| | Respiration | Breath-hold, NO swallowing |
| | Begin | Hyoid |
| | End | 1 cm below bottom of cricoid |

RECONSTRUCTION

A1



B1



| | | |
|---|---|---|
| A1 | Algorithm | Soft |
| | Thickness | 2.5 mm |
| | Spacing | 2.5 mm |
| | F.O.V. | Approx. 160–180 |

| | | |
|---|---|---|
| B1 | Algorithm | Soft |
| | Thickness | 1.5 mm |
| | Spacing | 1.5 mm |
| | F.O.V. | 100 |

**FIGURE 19-17.** Protocol for CT scan of the hypopharynx with intravenous contrast. CT, computed tomography.

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| Acquisition | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Plane | Sagittal | Axial | Axial | Axial |
| Sequence | T1 | T1 | T2-FSE | T1 |
| Contrast | None | None | None | Gd |
| SLT/SP | 3/0 mm | 3/0 mm | 3/0 mm | 3/0 mm |
| FOV | 16 cm | 16 cm | 16 cm | 16 cm |

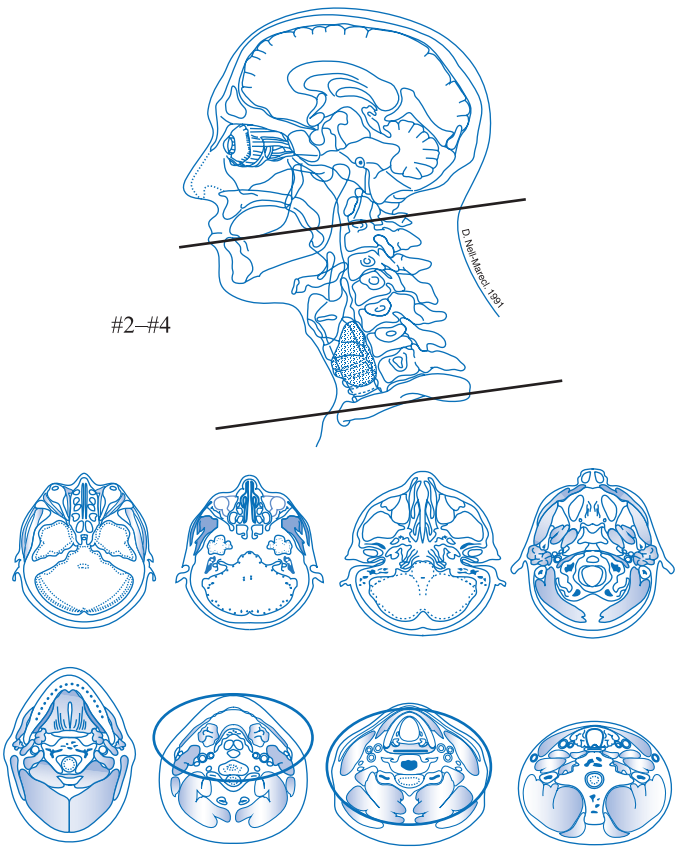



**FIGURE 19-18.** Protocol for MRI of the hypopharynx. MRI, magnetic resonance imaging.

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| Acquisition | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Plane | Sagittal | Axial | Axial | Axial | Coronal (angled) | Sagittal |
| Sequence | T1 | T1 | T2-FSE | T1 | T1 | T1 |
| Contrast | None | None | None | post-Gd | post-Gd | post-Gd |
| SLT/SP | 3/0 mm | 3/0 mm | 3/0 mm | 3/0 mm | 3/0 mm | 3/0 mm |
| FOV | 16 cm | 16 cm | 16 cm | 16 cm | 16 cm | 16 cm |

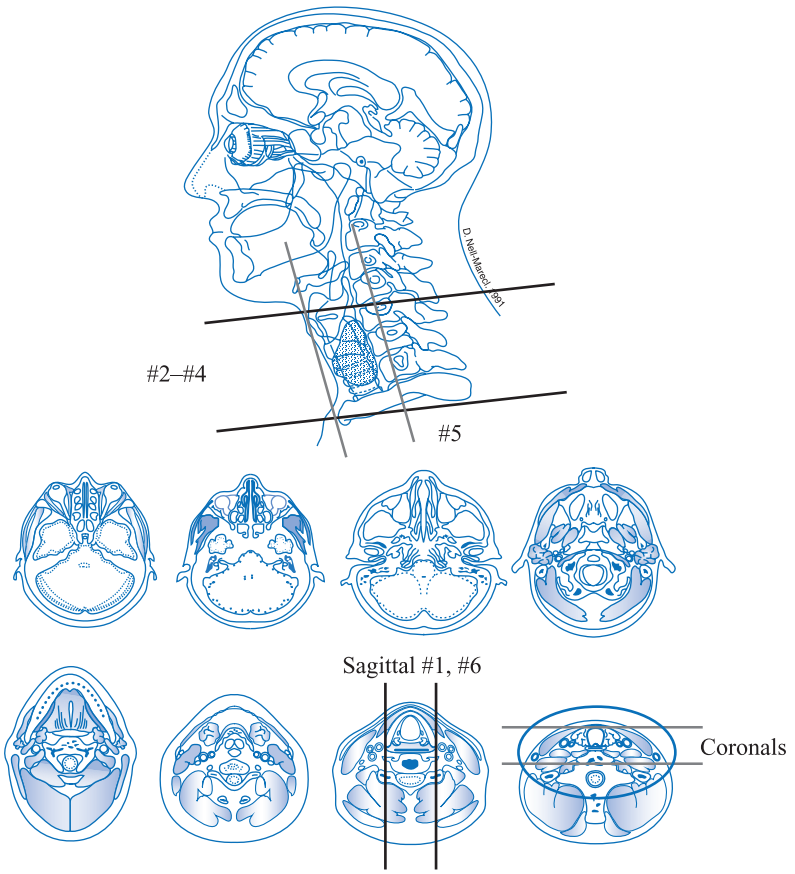



**FIGURE 19-19.** Protocol for MRI of the cervical esophagus. MRI, magnetic resonance imaging.

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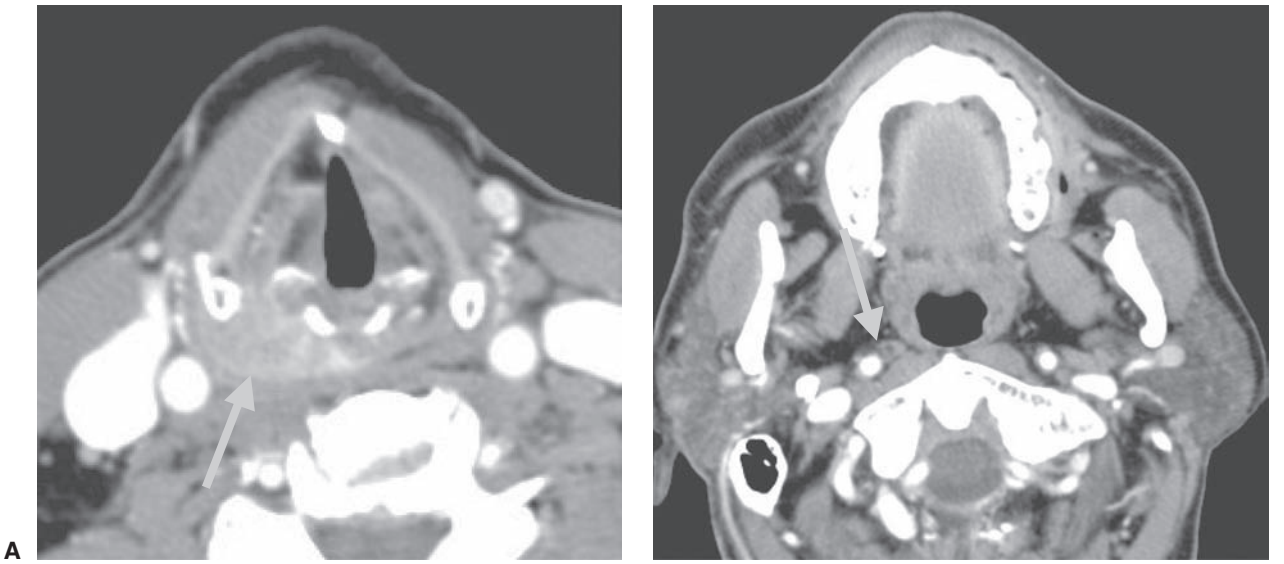


**FIGURE 19-20.** **A:** Axial contrast-enhanced CT shows a right pyriform sinus carcinoma (*arrow*). **B:** Axial image at the skull shows an asymmetrically enlarged ipsilateral retropharyngeal lymph node with central low attenuation (*arrow*). Retropharyngeal lymph is a primary echelon drainage pathway for the pyriform sinus. Because of this, this lymph was felt to be positive for metastatic disease. CT, computed tomography.

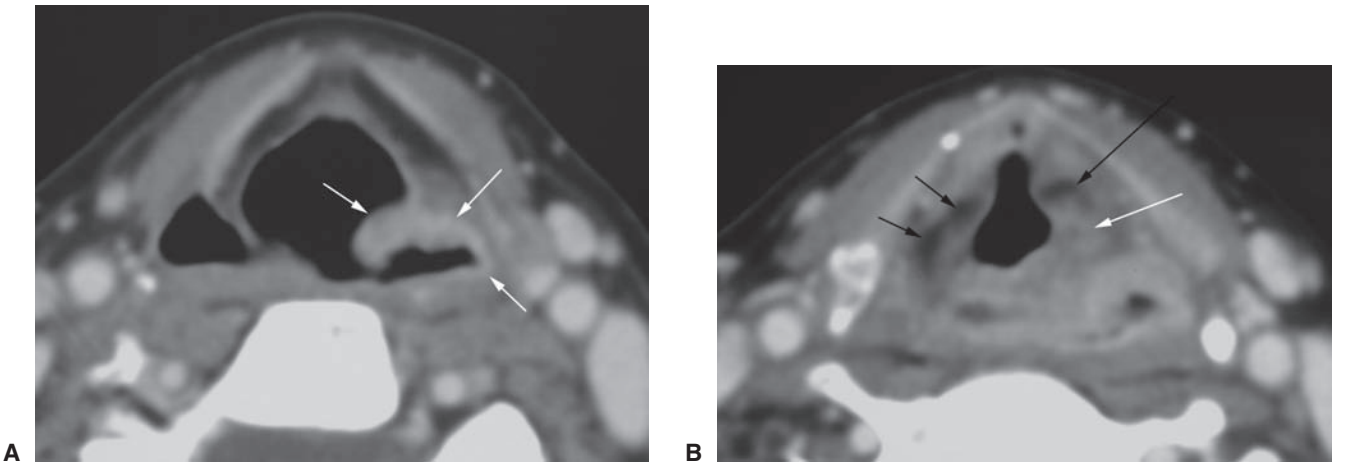


**FIGURE 19-21.** Axial contrast-enhanced CT scan of a patient with hypopharyngeal cancer with spread to the larynx. **A:** The primary tumor (*arrows*) is in the left piriform sinus and spreads along the aryepiglottic fold. **B:** Tumor infiltrates into the paraglottic space (*white arrow*) displacing the normal paraglottic fat (*long black arrow*). Normal paraglottic space fat on the opposite side (*short black arrows*) is shown for comparison. CT, computed tomography.

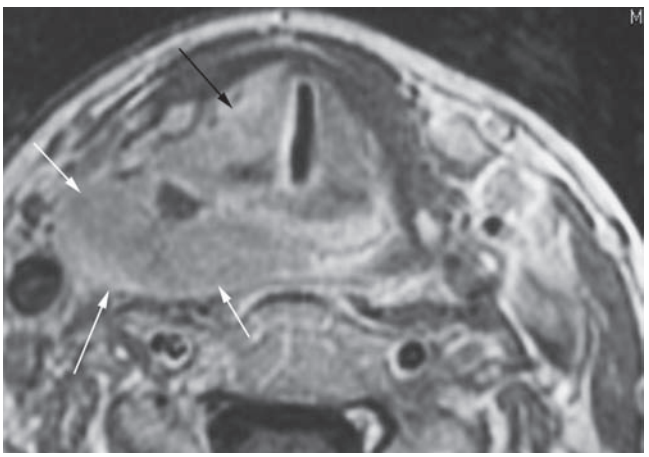
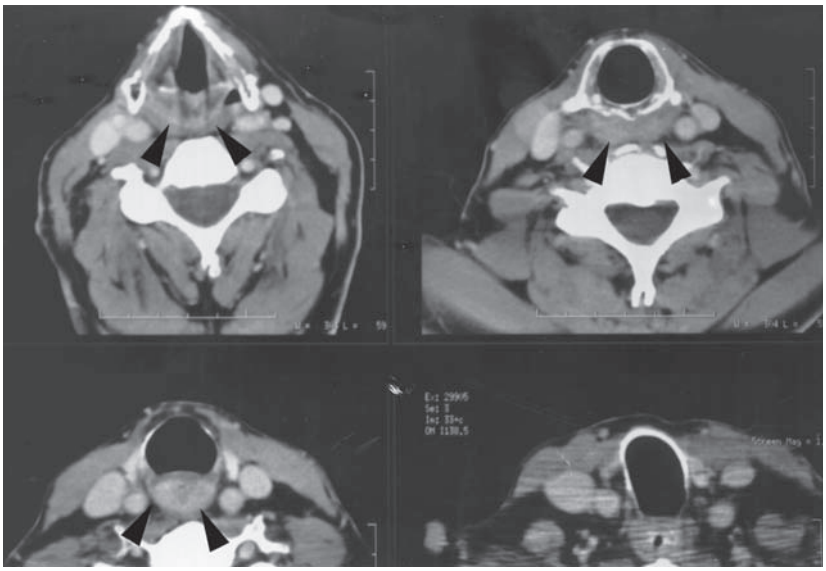


**FIGURE 19-22.** Axial postcontrast T1-weighted MRI shows a large right piriform sinus apex squamous cell cancer (*white arrows*) with direct invasion of the right true cord (*black arrow*). MRI, magnetic resonance imaging.



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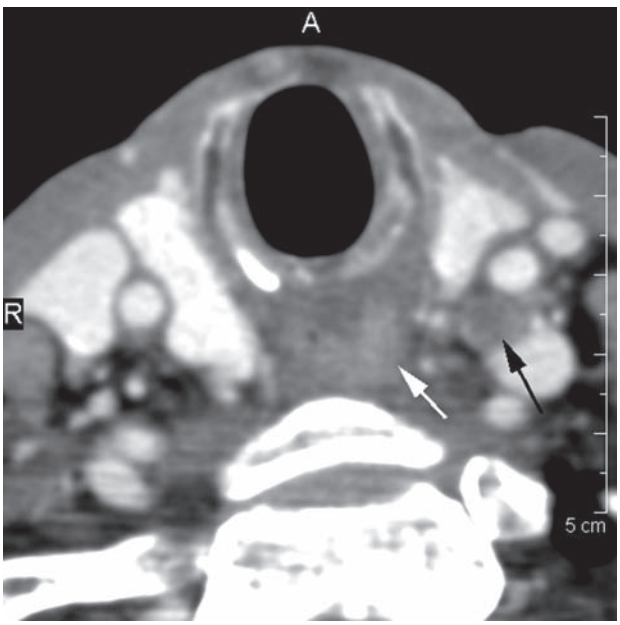
**FIGURE 19-23.** Hypopharyngeal carcinoma. Serial enhanced axial CT images show moderately thick lesion (*arrowheads*) of the low hypopharynx **(A)** involving the hypopharyngoesophageal junction **(B)**. CT, computed tomography.



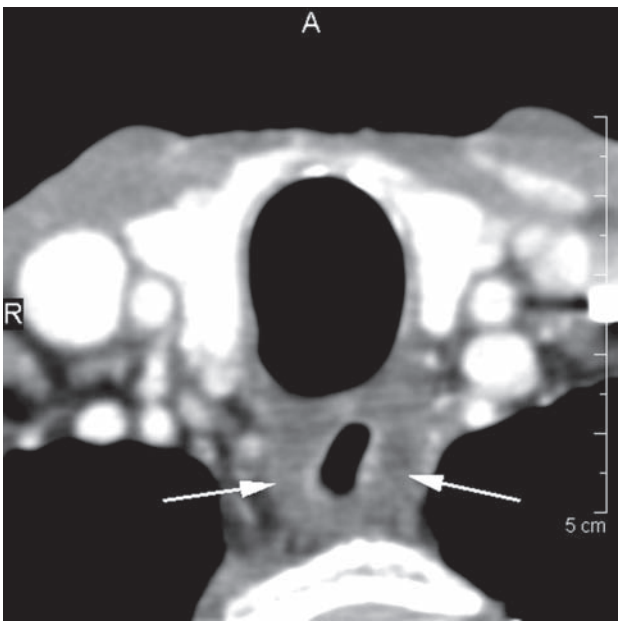
A




B




A

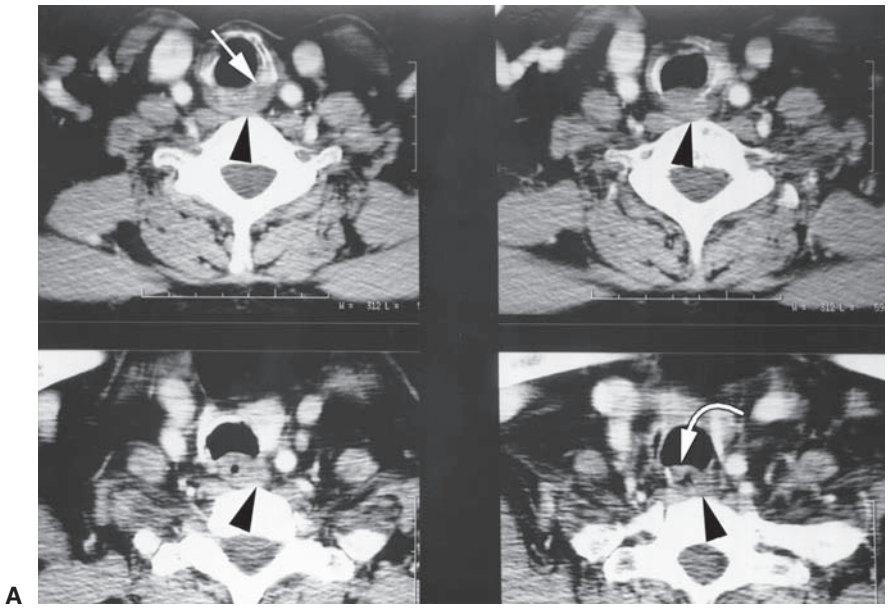



B

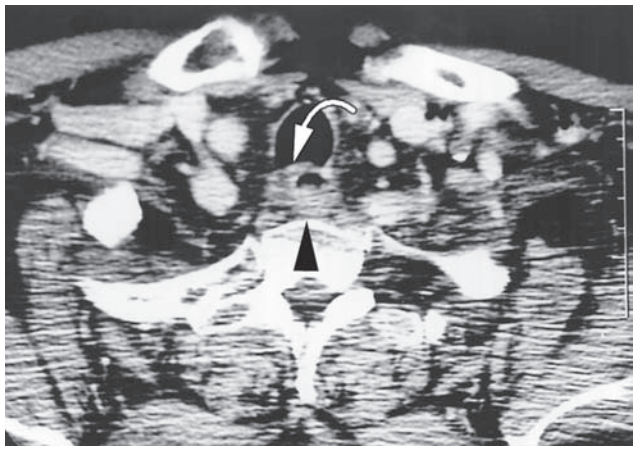
**FIGURE 19-24.** Axial contrast-enhanced CT scan of a patient with esophageal cancer. **A:** The enhancing tumor is seen at the esophageal verge (*white arrow*). A positive metastatic left level VI lymph node is present (*black arrow*). **B:** Thickening of the wall of the esophagus is seen (*arrows*). CT, computed tomography.



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A



B

**FIGURE 19-25.** Carcinoma of cervical esophagus. **A:** Serial enhanced axial computed tomographic views of low neck show thickening of the cervical esophagus (*arrowheads*) from junction with hypopharynx (**upper left**) to inlet (**lower right**). Note infiltration of base of cricoid (*arrow*) and **(B)** membranous portion of trachea (*curved arrow*). Note that the contrast bolus technique does not obscure inlet, allowing evaluation of the prevertebral plane.

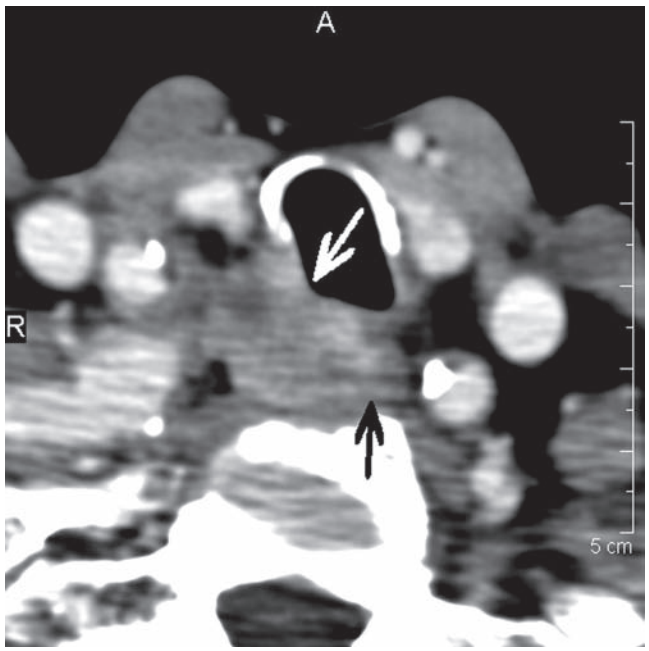



**FIGURE 19-26.** Axial contrast-enhanced CT scan shows failure of treatment of hypopharyngeal squamous cell carcinoma with the appearance of a positive level VI lymph node with extracapsular spread to invade the trachea (*white arrow*) and esophagus (*black arrow*). CT, computed tomography.

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# PART C:
# Radiation Therapy Technique

William M. Mendenhall

## PYRIFORM SINUS

Parallel-opposed portals are used to treat the primary cancer and both sides of the neck to include lymph nodes in levels II, III, IV, V, and the retropharyngeal nodes at the level of the C1–C2 vertebral bodies. It is difficult to detect subclinical disease at the pyriform sinus apex, which is located somewhere between the top and the bottom of the cricoid cartilage, even at direct laryngoscopy. Therefore, the inferior border of the initial portals is located 2 cm below the bottom of the cricoid cartilage. It may be difficult to obtain this margin if the patient has large shoulders and a low-lying larynx. If this is the case, the lateral portals are angled approximately 10 degrees inferiorly and the anterior portal used to treat the low neck is eliminated. The anterior field border may be placed just behind the skin of the anterior neck to avoid tangentially irradiating this area for patients with T1–T2 cancers and early-stage neck disease. The superior border is placed at, or just below, the jugular foramen, and the posterior border is placed just posterior to the spinous processes of the vertebral bodies (Fig. 19-27).[1] Reduction off the spinal cord is performed at approximately 45 Gy, and a second mucosal reduction occurs at 60 Gy. Electron beam is used to treat the posterior strips, if necessary, after reduction off the spinal cord.

Intensity-modulated radiation therapy (IMRT) may be employed to treat patients with a clinically negative neck or ipsilateral positive nodes to reduce the dose to the contralateral parotid to 26 Gy or less and to avoid a difficult match between the conventional lateral fields and the anterior low neck portal in the patient with a low-lying larynx and a short neck. Patients may be treated once daily or with an altered fractionation schedule.[2] The concomitant boost technique is employed at our institution and consists of 72 Gy in 42 fractions over 30 treatment days to gross disease (Fig. 19-28). Subclinical disease receives 49.5 to 54 Gy.[3] Alternatively, patients are treated to 74.4 Gy in 62 twice-daily fractions over 31 treatment days. Patients with a clinically negative neck receive elective RT to bilateral levels II, III, IV, V, and the retropharyngeal nodes.[4] Patients with ipsilateral positive nodes receive RT to ipsilateral levels IB, II, III, IV, V, VI, and the retropharyngeal nodes, as well as contralateral levels II, III, IV, VI, and the retropharyngeal nodes. Patients with stages III to IV cancers receive concomitant weekly cisplatin 30 mg/m$^2$. Those with positive nodes undergo a computed tomographic scan 1 month after RT to determine whether a neck dissection is indicated.[5]

The radiation therapy treatment technique after surgery that entails partial laryngectomy is as described above. The technique employed after a total laryngectomy is the same as that described in the "advanced larynx" chapter.

## PHARYNGEAL WALL

Because squamous cell carcinomas of the pharyngeal wall tend to spread submucosally, wide margins for the primary cancer are initially utilized. The portals are parallel opposed and usually weighted 1:1. The field margins for the initial fields usually extend to the bottom of the cricoid cartilage, 0.5 to 1.0 cm behind the skin of the anterior neck, the posterior processes of the vertebral bodies, and to (or just below) the jugular foramen. Because large tumors tend to extend posterolaterally around the vertebral bodies, the posterior border of the off-cord reductions is placed at the anterior edge of the spinal cord (Fig. 19-29).[6] The low neck is treated with an anterior field with a thin, tapered midline tracheal block. Electrons are used to treat the posterior strips after reduction off the spinal cord, if necessary.

As described in the pyriform sinus section, IMRT may be employed to reduce the dose to one or both parotids and/or avoid a difficult low neck match with conventional fields. The dose fractionation schedules are the same as those used for pyriform sinus malignancies. Patients with ipsilateral positive nodes receive elective RT to clinically uninvolved ipsilateral levels IB, II, III, IV, V, VI, and the retropharyngeal nodes, as well as contralateral levels II, III, IV, V, and the retropharyngeal nodes.[4] It may be difficult to treat patients with bilateral clinically positive nodes with IMRT and adequately spare the parotid(s).

## CERVICAL ESOPHAGUS

Anteroposterior opposed portals weighted anteriorly are used to treat the primary cancer of the upper mediastinum and the neck, if moderate-dose irradiation is planned prior to definitive surgery. The superior border is placed at mid mandible and splits the tragus; the neck is extended. The lateral borders include the supraclavicular fossae, and the inferior border is placed 5 cm below the inferior border of the primary cancer.

Treatment with high-dose irradiation alone or combined with adjuvant chemotherapy is more problematic because of

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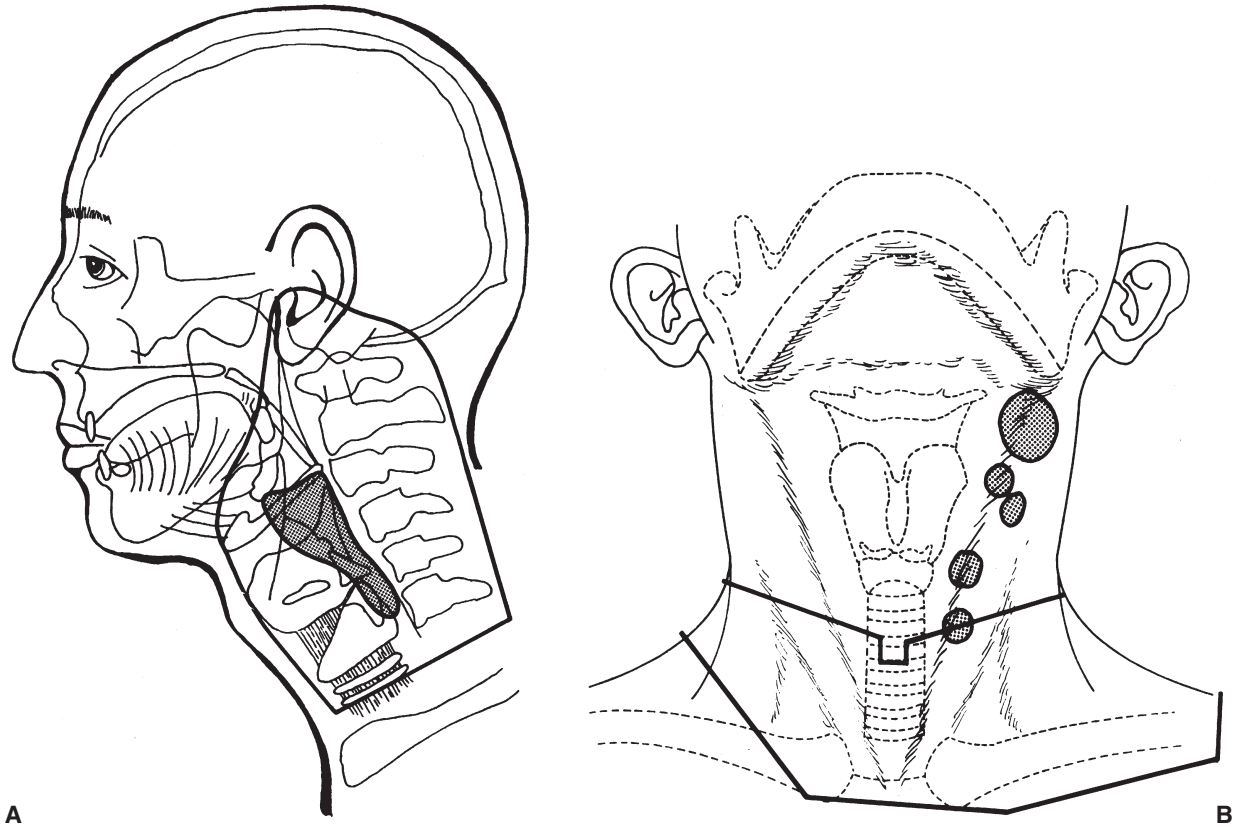


**FIGURE 19-27.** **A:** Portals used for the initial treatment volume in a patient with carcinoma (*stippled area*) of the pyriform sinus and a clinically negative neck. Superiorly, the portal covers the junctional and retropharyngeal lymph nodes. The submandibular nodes are not included, but the spinal accessory chain is included. Anteriorly, at least 1 cm of skin and subcutaneous tissues (as viewed from the lateral projection) is usually spared. The inferior border is 2 to 3 cm below the bottom of the cricoid cartilage and is slanted to facilitate matching with the low neck portal and to avoid irradiating the shoulders. The posterior field edge usually encompasses the spinous processes of the vertebral bodies. As treatment progresses, portal reductions are made to shield the spinal cord and to limit the volume of mucosa that receives high-dose irradiation. **B:** Anterior portal for treatment of low neck in patients with hypopharyngeal or laryngeal cancer. Low neck is irradiated bilaterally. Matchline is treated in primary portals, but excluded from low neck field. Usually, a $1 \times 1$ cm midline block is introduced at upper edge of field, except in postoperative patients in whom tracheal stoma is at risk. Each side of low neck portal is individualized according to risk and/or presence of lymph node metastases on that side.

*Source:* From Parsons JT, Palta JR, Mendenhall WM, et al. Head and neck cancer. In: Levitt SH, Khan FM, Potish RA, et al., eds. *Levitt and Tapley's Technological basis of Radiation Therapy: Clinical Applications*. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 1999:269–299, with permission (**A:** Fig. 16.3, p. 272; and **B:** Fig. 16.36, p. 297).

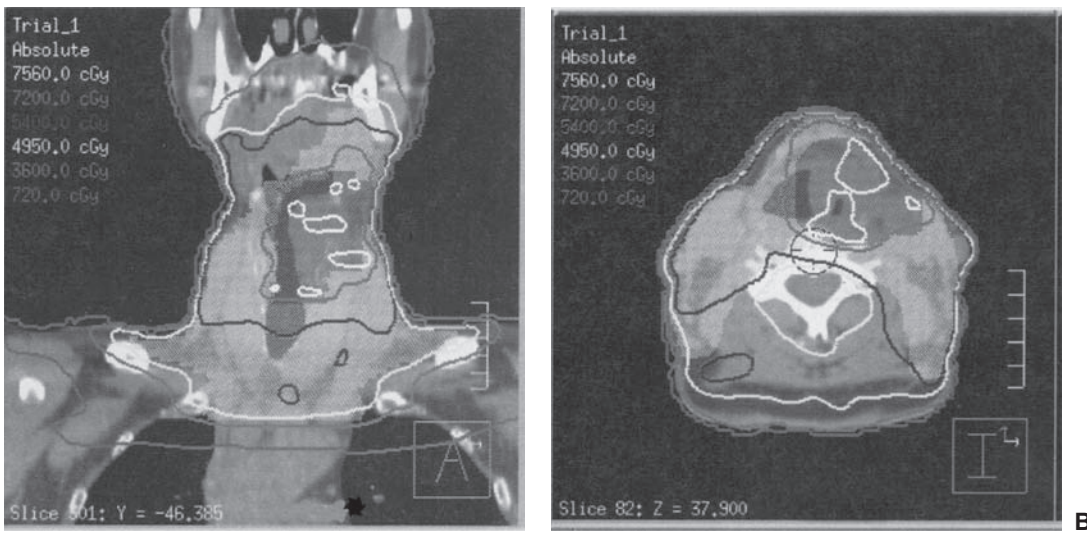



**FIGURE 19-28.** A seventy-nine-year-old man with a T3N2B squamous cell carcinoma of the left pyriform sinus. The gross tumor received 72.0 Gy in 42 fractions using the concomitant boost technique. The moderate risk volumes received 54.0 Gy. The patient received seven cycles of concomitant weekly cisplatin. The mean dose to the right parotid was 25.1 Gy. (See color insert.)

*Source:* From Mendenhall WM, Riggs CE, Amdur RJ, et al. Altered fractionation and/or adjuvant chemotherapy in definitive irradiation of squamous cell carcinoma of the head and neck. *Laryngoscope*. 2003;113:546–551, with permission.

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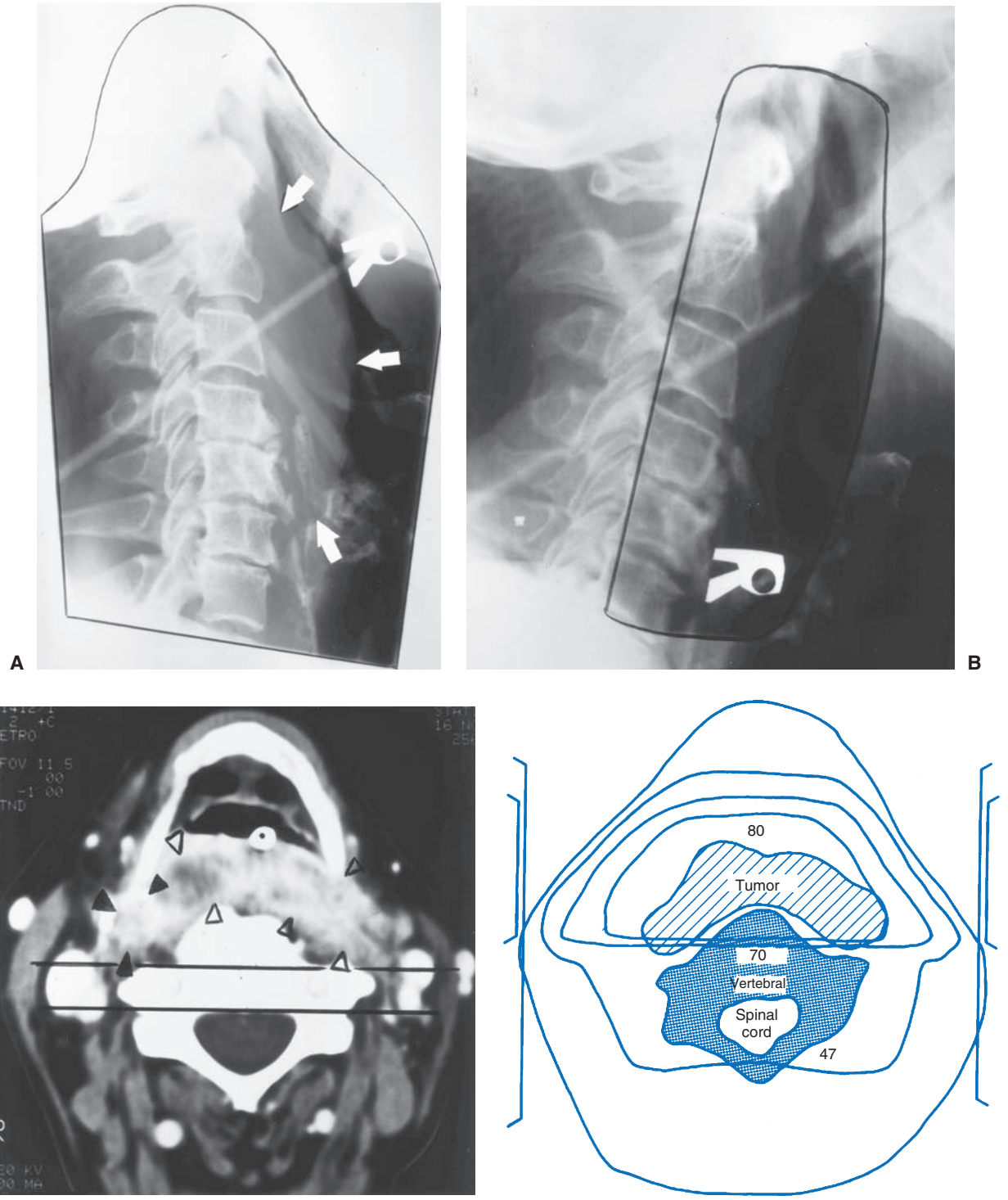
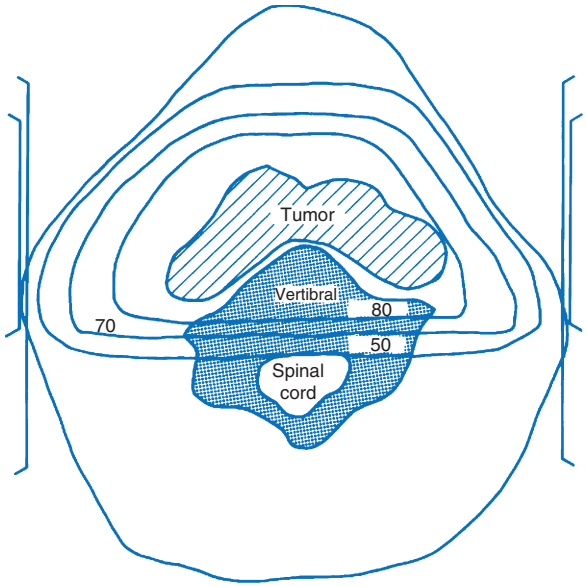



**FIGURE 19-29.** **A:** Initial treatment fields for a T3N2B squamous cell carcinoma of the posterior pharyngeal wall. *Arrows* indicate the superior and inferior margins of the tumor. The anterior border of the field does not flash the skin of the anterior aspect of the neck, thereby sparing the anterior portion of the larynx. **B:** Treatment field after reducing off the spinal cord. Note that the posterior edge of the field is at the posterior aspect of the vertebral bodies. **C:** Computed tomogram before treatment. The *open arrowheads* denote the primary tumor and the *closed arrowheads* indicate a retropharyngeal node. Note that there is tumor extending posterior to the anterior surface of the vertebral body. The anterior line indicates the posterior edge of the reduced field if it is designed to split the vertebral bodies. Note that tumor is on the edge of the field. The posterior line indicates the field margin if it is placed at the posterior edge of the vertebral bodies. These lines do not account for beam divergence and are drawn as if the central axis of the beam is placed at the posterior edge of the field. **D:** Computerized dosimetry for 45.6 Gy, 8 MV x-ray, weighted 1:1, followed by reduction off the spinal cord and 33.6 Gy, 17 MV x-ray, weighted 1:1 (specified total dose = 79.2 Gy). The posterior edge of the reduced field is placed at the anterior aspect of the spinal cord **(E)** as in **(D)** except that the posterior edge of the reduced field splits the vertebral bodies.

*Source:* From Mendenhall WM, Parsons JT, Mancuso AA, et al. Squamous cell carcinoma of the pharyngeal wall treated with irradiation. *Radiother Oncol.* 1988;11:205–212 (Fig. 3, pp. 210–211), with permission.

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E

**FIGURE 19-29.** *Continued*

the change in contour from the neck to the shoulders. Although several options exist, depending on the treatment planning and delivery system available, IMRT offers significant advantages compared with conventional techniques. The initial target volume includes the primary lesion with 5 cm distal and proximal esophageal and hypopharyngeal margins, respectively. The lymph nodes included are levels II, III, IV, VI, and the superior mediastinal lymph nodes. We currently use IMRT for all patients treated with definitive irradiation for cervical esophageal carcinoma. Subclinical disease is treated to approximately 45 to 50 Gy, and gross disease receives approximately 70 Gy. Patients may be treated once daily, or altered fractionation may be employed.

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# PART D:
# Surgical Technique

Ramon M. Esclamado and Liana Puscas

## INTRODUCTION

Contemporary reconstruction of ablative defects of hypopharyngeal carcinoma remains clinically challenging. Successful and appropriate reconstruction requires a thoughtful analysis of many factors that will ultimately impact the choice of the reconstructive technique employed. Careful consideration should be given to reconstructive goals, oncologic outcomes, patient related factors, and comorbidities, the extent of the surgical defect, as well as the expertise and preferences of the reconstructive surgeon. Ideally, the reconstructive team will have available the entire armamentarium of reconstructive options and will utilize the technique that is best suited for the patient, that optimizes function, while minimizing both short-term morbidity, long-term disability, and expense.

The reconstructive goals are straightforward but elusive: to restore continuity of the alimentary tract so that a patient is able to eat a normal diet, while preserving laryngeal voice or restoring alaryngeal speech. Oncologic factors are essential to consider. Although primary and salvage hypopharyngectomy have comparable locoregional control rates and survival, overall and disease-specific survival remains poor.[1] Therefore, reconstruction should be single stage, have a low rate of fistula and delayed wound healing, allow for early resumption of deglutition and voice restoration, and have a low rate of delayed strictures, particularly if postoperative radiation is required. Since surgical ablation nearly always includes unilateral or bilateral neck dissection, the choice of reconstructive technique will in part depend upon availability and location of recipient vessels for free tissue transfer and should consider minimizing shoulder disability, particularly if the spinal accessory nerve has been sacrificed.

Patient-related factors and comorbidities must be recognized and considered to optimize outcomes.[2] In this era of concurrent chemoradiation therapy (CRT), iatrogenic hypothyroidism occurs in 48% of patients as early as 4 weeks posttreatment.[3] These patients can also be nutritionally or metabolically debilitated from alcohol and tobacco abuse, tumor burden and odynophagia, or from CRT. When primary surgery and reconstruction is contemplated, nutrition should be optimized; in the salvage setting, a preoperative TSH should be obtained. Diabetics should be carefully selected and managed in the perioperative period. Preoperative radiation, malnutrition, diabetes, and unrecognized hypothyroidism are known to increase fistula rates and delay wound healing.[4,5] Many patients have COPD, and consideration should be given to choosing donor sites that are not intra-abdominal to minimize postoperative pulmonary complications.

The extent of the surgical defect is a primary determinant of the selected reconstructive option. Defect classifications have been proposed,[6] but not universally adopted. The first

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consideration is whether all or part of the larynx has been preserved. Reconstruction will require, thin, pliable tissue that can be contoured so as not to obstruct the airway and suspended with little downward traction to preserve laryngeal elevation. If total laryngectomy is performed, the second consideration is whether the pharyngectomy is total, requiring a completely tubed reconstruction, or partial, which would allow a "patch" graft. The superior extent of the defect must also be evaluated because there is a caliber mismatch between the base of tongue/oropharyngeal defect compared with the esophageal lumen that is magnified when resection includes portions of the tongue or oropharyngectomy. Finally, one must consider if the inferior anastomosis can be performed in the neck. Hypopharyngeal cancer can have significant submucosal spread, and historically total esophagectomy was regularly used to obtain a 4 cm or greater inferior margin, which precluded a cervical anastomosis. However, it has been shown that a 2-cm inferior esophageal margin is adequate and facilitates utilizing less morbid reconstructive techniques.[7,8]

The experience and preferences of the reconstructive surgeon or team, and the availability of facilities to appropriately care for these patients cannot be overlooked. The literature abounds with studies espousing the superiority of one reconstructive technique over another, and there are benefits of expertise gained in performing a specific reconstructive technique repetitively so that errors in technique or judgment are minimized. Ideally, the reconstructive decisions take into account all of the above-mentioned factors, so that the reconstructive method chosen is best suited for the particular patient.

## RECONSTRUCTIVE OPTIONS

A variety of reconstructive options are available. The pertinent surgical anatomy, blood supply, harvesting techniques, and donor site management and complications have been well described and are beyond the scope of this chapter. The myriad of the most commonly used flaps are listed in Table 19.8, and it is important to understand the broad principles as to their advantages and disadvantages.

Regional flaps are either fasciocutaneous or myocutaneous. They are readily harvested, do not require microvascular expertise, and are fairly reliable. The muscle pedicle of myocutaneous flaps can provide additional carotid protection. They can have limited reach and arc of rotation and can be bulky and not as pliable in a three-dimensional reconstruction. The bulk and weight of the flap and pedicle could cause undue wound tension and increase the risk of wound complications.[9] When the skin paddle is extended beyond the normal vascular territory, there can be a partial flap necrosis. Fasciocutaneous flaps usually require a two-stage reconstruction to close a pharyngectomy defect, but are very useful in creating a controlled fistula to exteriorize a persistent fistula in an infected neck.

Revascularized (free) flaps are generally excellent options, although microvascular expertise is required, and operative time can be prolonged, but minimized with a two-team approach. Adequate recipient vessels are essential, and flap survival rates exceed 95% to 98%. A postoperative fistula with infected saliva draining over the vascular pedicle can cause late thrombosis, which is rare in pedicled flaps. The lack of a fixed pedicle allows three-dimensional positioning to minimize tension on the suture lines, and wound tension from downward traction can be minimized. The variety of donor sites allows selection of texture, bulk, and flap size to optimally reconstruct the defect.

**TABLE 19.8 Reconstructive Options for Hypopharyngeal Reconstruction**

| | Regional Flaps | Revascularized Flaps |
|---|---|---|
| Fasciocutaneous | Deltopectoral<br>Superior trapezius | Radial forearm<br>Anterolateral thigh<br>Lateral arm |
| Myocutaneous | Pectoralis major<br>Latissimus<br>Lower island trapezius | Rectus<br>Latissimus |
| Enteric | Gastric pull-up | Jejunum<br>Ileocolic |

## DEFECT RECONSTRUCTION AND RESULTS

As previously mentioned, the extent of the surgical defect is the primary determinant of the selected reconstructive option. Therefore, we will approach reconstruction of hypopharyngeal defects primarily by analyzing the defect, defining reconstructive goals, and looking at the advantages and outcomes of the most commonly used reconstructive options.

### The Partial Pharyngectomy Defect with an Intact or Partially Resected Larynx

The more common defect is a partial pharyngectomy defect with an intact larynx. A limited lateral wall defect can be closed primarily or with a thin pectoralis myocutaneous (PMC) flap. Since most defects involve the posterior hypopharyngeal wall with or without the lateral wall of the piriform sinus(es), the surgical goal is to provide thin pliable tissue. When partially tubed, the reconstruction should not obstruct the airway nor impair laryngeal elevation. The radial forearm free flap (RFFF) is ideal in this setting, since it is thin, pliable, and very reliable.[10] The disadvantages are that the donor site generally requires skin grafting or alloderm to close, the skin is nonsecretory, the flap cannot be used in the absence of an intact palmar arch, and if the patient is unwilling to accept the donor-site cosmetic result. Alternatives include the lateral arm[11] or the anterolateral thigh (ALT) fasciocutaneous free flaps.[12,13] Both of these flaps allow primary closure of the donor site, but can be quite thick and bulky, so the donor site must be carefully evaluated prior to its use. The free jejunal patch graft is a viable alternative and is the preferred option in many centers. It has the theoretic advantage of being self-lubricating, and both fistula and stricture rates are reportedly low when compared with RFFF. It does require a laparotomy, and there is the potential risk of aspiration of jejunal secretion. In a recent series of 43 patients, the flap success rate was 95%, the fistula rate was 11%, which all healed with conservative treatment, and all patients were tracheotomy independent. There were no instances of pneumonia from aspiration of jejunal secretions, and 95% of patients were eating and G-tube independent, usually within 2 weeks postoperatively.[14]

A partial pharyngectomy defect with a partial laryngectomy defect is more challenging. Usually, the hemilarynx and lateral wall of the pyriform sinus are absent with an intact cricoid arch. The reconstructive goals require restoration of glottic closure, and sensation to optimize airway protection, create an adequate airway, and preserve swallowing. Instinctively, one would want to recreate structure and restore the "volume" of the hypopharynx. However, restoring the natural contour of the hypopharynx with an insensate, adynamic flap may not be a good functional restoration when the hemilarynx is also reconstructed. One should consider

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insetting enough soft tissue to restore continuity of the hypopharynx so that tension is minimized to facilitate wound healing. However, the reconstruction should "obliterate" the involved lateral piriform wall so that the food bolus will preferentially be diverted to the normal, sensate, and contractile pharyngeal wall. Swallowing can then be facilitated with a "chin tuck" to the involved side to further open the normal side. Kim et al.[15] recently reported a series of 31 patients reconstructed with a RFFF for a vertical hemipharyngolaryngectomy for hypopharyngeal carcinoma. The palmaris longus tendon was included to reconstruct the glottis, and in 23 patients, the flap underwent sensory reinnervation to the superior laryngeal nerve. Eighty-eight percent of patients were able to meet all their nutritional needs orally, 2 patients (6%) developed glottic stenosis, marginal flap necrosis was seen in 2 patients (6%) that resulted in fistulas, and 88% of patients were eventually decannulated. If these results can be duplicated, the opportunity will arise for more patients to undergo laryngeal preservation procedures in selected hypopharyngeal cancers because the laryngeal defect can be safely and functionally reconstructed.

## The Total Laryngectomy with Subtotal Pharyngectomy Defect

This defect is the most amenable to obtaining a good functional outcome encountered in the reconstruction of hypopharyngeal or laryngeal carcinoma. A preserved posterior strip of mucosa is helpful because it avoids a complete circumferential closure and cicatricial contracture (especially at the cervical esophageal anastomosis, which is the most common site of strictures) (Fig. 19-30). At first glance, the decision making seems straightforward: primary closure or closure with a pectoralis flap? However, in an era when chemoradiation therapy is commonly employed as definitive oncologic treatment in an effort to preserve the larynx, surgery is more often utilized for salvage. The surgeon is faced with heavily radiated tissues and patients with comorbid conditions that impair wound healing. The challenges faced in this situation were highlighted in a recent study of patients undergoing salvage surgery for laryngeal carcinoma after failed radiation or chemoradiation therapy.[16] Patients reconstructed with a soft-tissue free flap had lower fistula rate (18%) compared with the primary closure group (50%); a lower rate of stricture formations (18% vs. 25%), and feeding tube dependence (23% vs. 45%). Therefore, more extensive laryngopharygectomy defects, particularly in the salvage setting, require soft-tissue reconstruction that minimizes wound tension so that fistulas and late strictures are minimized. The ability to restore voice with tracheoesophageal speech should be considered, and some authors feel that the type of flap used impacts long-term voice rehabilitation.[17,18] However, it is the first author's personal experience that the type of flap used has more impact when one is not able to preserve a normal vibratory segment of the upper esophagus between the TEP site and the distal end of the flap-esophageal anastomosis.

The first option to consider is a partially tubed pectoralis myocutaneous flap. This can be performed quickly by a single team of surgeons and has acceptable donor-site morbidity, and the muscle pedicle provides some protection to the great vessels. It is useful in a debilitated patient who is thin or if recipient vessels are poor or unavailable. The reported fistula rate is about 14%,[19] and all patients were G-tube independent. The pedicled latissimus or lower island trapezius flaps are options in the above situation when the pectoralis flap is unavailable, but these tend to be less reliable and require repositioning of the patient. A thick, bulky flap is a relative contraindication because it can be difficult to tube, may place undue tension on the pharyngeal anastomosis, and potentially obstruct the tracheostoma. There is also some evidence to suggest that PMC reconstruction compared with free flaps results in higher complication rates and G-tube dependence, and hospitalization is prolonged.[9]

The radial forearm free flap is an excellent choice in this setting because it is thin, reliable, and adequate soft tissue is readily harvested. In addition, a monitoring segment can be included in the flap design and placed in an exterior location in the neck to aid in monitoring of the pharyngeal flap, which may otherwise be difficult to assess on clinical exam (Figs. 19-31 and 19-32).

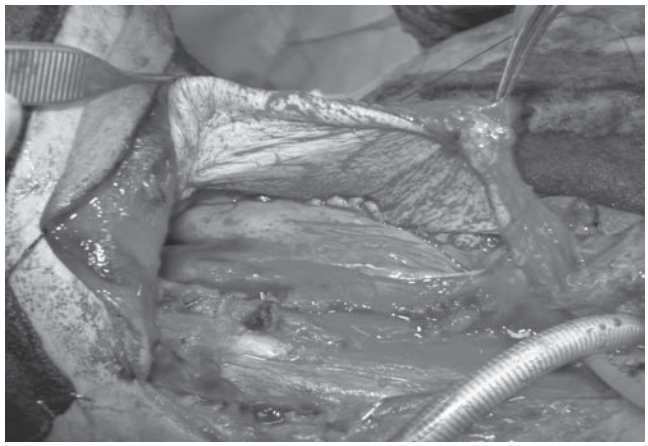


**FIGURE 19-30.** Pharyngeal reconstruction after total laryngectomy and partial pharyngectomy. (See color insert.)




A



B

**FIGURE 19-31.** Radial forearm free flap with monitoring segment.

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**FIGURE 19-32.** Monitoring segment incorporated into neck closure.



**FIGURE 19-33.** Total glossolaryngeal defect with near total pharyngectomy.

In a salvage situation, it is important to remember that when a strip of native hypopharynx is present, all of the flap will be sewn to irradiated tissue that has impaired wound healing. Gentle handling of native tissues and using the curvature of needle when sewing will minimize tearing of the native mucosa. The use of interrupted vertical mattress sutures everts the edges to eliminate a potential "trough" in the suture line where saliva can leak, and utilizing a long-lasting absorbable suture has reduced the incidence of late fistulas.[8] Distal structures can be minimized by vertically incising the proximal esophageal segment to create a V-shaped defect and designing a complementary V-shaped tip to the free flap that is then inset into this gap to avoid a circumferential suture line. The ALT or lateral arm fasciocutaneous flap are also reasonable options[20] and have the advantage of primary closure of the donor site. Care must be taken in choosing these sites because the upper arm and thigh can be quite thick with an abundance of subcutaneous fat.

If the resection also includes a subtotal or total glossectomy defect with an intact pharyngeal strip of mucosa, consideration should be given to using a flap with enough soft tissue and bulk to restore tongue volume, and it is partially tubed to reconstruct the neogullet (Fig. 19-33). Our preference is to use the rectus myocutaneous flap based on the deep inferior epigastric artery and vein. The rectus flap has an abundance of skin that can be harvested with primary closure of the donor site and is usually bulky with a substantial fat component that does not atrophy; the anterior rectus sheath can be suspended on the mandible to minimize down traction and tension on the closure and has a long vascular pedicle with muscle to provide carotid coverage. If the rectus donor site is not available, the latissimus free flap is a good second option. It may require repositioning of the patient and generally has less subcutaneous fat so that the initial bulk may not be maintained as the muscle atrophies. However, the latissimus muscle atrophy can be compensated by reinnervating the thoracodorsal nerve to the stump of a hypoglossal nerve, if available. One can also gain additional bulk by designing the skin paddle more proximally and near the posterior axillary line, then harvesting the entire muscle, and folding it under the skin paddle to gain additional bulk.

## The Total Laryngopharygectomy Defect

Reconstruction of the total laryngopharygectomy defect has a wide variety of options and, as a corollary, the most controversy. The surgical goals include a single-stage reconstruction that restores continuity of the oropharynx to the esophagus and a low fistula and stricture rate and tolerates radiation therapy. The circumferential size mismatch between the oropharynx and the esophagus must be adequately addressed (Fig. 19-34). The ideal functional results are resumption of a regular oral diet, voice rehabilitation with a tracheoesophageal voice prosthesis, and minimal donor site morbidity.

Recent modifications of the U-shaped pectoralis myocutaneous flap introduced by Fabian[21] have important clinical application. The PMC flap is shaped into a U, and the lateral edges are sewn directly to the prevertebral fascia, which is allowed to granulate over a salivary bypass tube. Reported fistula rates are 20% to 25%, which usually close spontaneously, and swallowing outcomes are acceptable.[19,22] In a long-term follow-up study of 52 patients reconstructed in this manner, the disease-free survival was 17.3%, leading the authors to advocate for this option in patients that are debilitated or have significant comorbidities.[23]

The ongoing controversy in the reconstruction of this defect is whether a tubed fasciocutaneous or jejunal free flap is superior. The jejunal free flap has been the workhorse for many decades and is preferred by many surgeons because it has >95% success rate, its caliber is similar to the esophagus, fistula rates are low, it is secretory, and it can tolerate radiation doses of up to 65 Gy. Modifications have been made to compensate for the size mismatch of the jejunum circumference to the oropharyngeal closure, and this is usually readily corrected by spatulating the jejunum at its antimesenteric border. The disadvantages include the need for an intra-abdominal procedure, but can be harvested laparoscopically to minimize complications and a "wet" TEP voice, which is unsatisfactory in some patients.[24,25] This flap is very sensitive to ischemia, and late stricture can occur due to necrosis and late scar contracture of the muscularis mucosa, even though the serosa and mucosa appear intact. We prefer to tack the flap into position and then revascularize the flap when it is covered in iced saline laparotomy sponges. Final flap trimming and insetting is performed once the flap is revascularized. In a direct comparison in a single institution of PMC, ALT, and jejunal flaps, the fistula rate was 23.9%, 12.5%, and 4.6%, respectively. The late stricture rate was 27.2%, 12.5%, and 2.3%, respectively, leading the authors to conclude that the jejunal free

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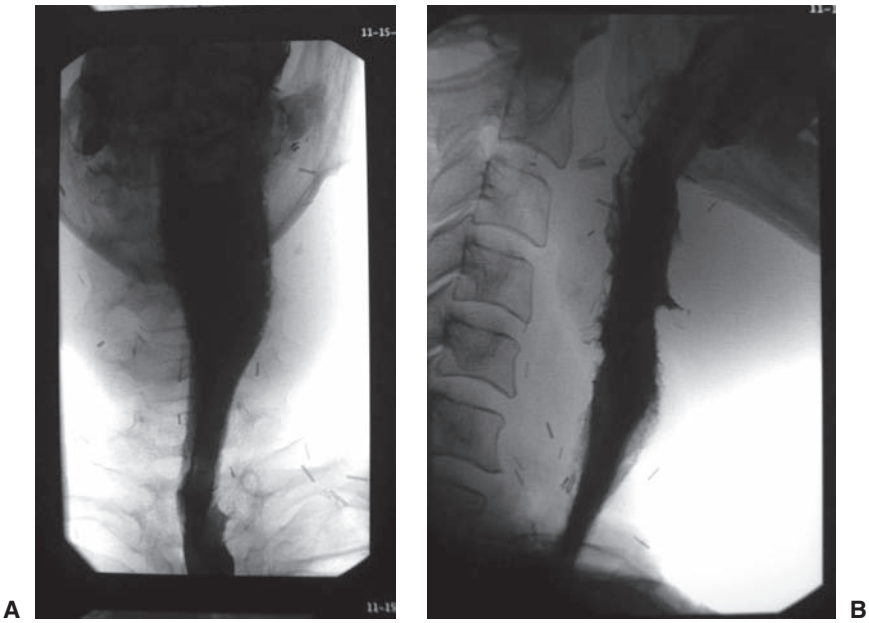


**FIGURE 19-34.** Postoperative swallow after reconstruction for total laryngopharyngectomy; anterior–posterior and lateral views.

flap provided the best functional outcome.[26] Early positive functional results are sustained with long-term follow-up. In a cohort of 19 patients who underwent total laryngopharygectomy, TEP and jejunal free flap reconstruction with a mean 4-year follow-up period, 18/19 were G-tube independent and 15/19 patients were using the TEP for communication. Poorer results with voice rehabilitation had been a shortcoming of the jejunal free flap, and the authors attributed the improvement in TEP voice to advances in prosthesis technology.[27]

Tubed fasciocutaneous free flaps are advocated by other centers because of less donor site morbidity, the availability of a larger volume of pliable tissue to reconstruct complex defects, and excellent functional outcomes. Fistula and stricture rates were initially worse, primarily because of three suture lines and the greater contraction of the skin–mucosa anastomosis versus a mucosa–mucosa anastomosis. After additional experience and modifications of technique, wound-healing complications and functional outcomes are at least equal to the jejunal free flap.[25] The tubed radial forearm free flap is an excellent option. In the authors' personal experience of 28 consecutive tubed RFFF for total laryngopharygectomy defects, flap survival was 100%; average length of stay was 8.0 days. There were two (8%) early fistulas and five (20%) late fistulas (>3 weeks). These late fistulas closed spontaneously within 1 to 2 weeks and were avoided in subsequent patients by changing the suture from vicryl to a slow absorbing suture. All patients resumed eating and were not using G-tubes, and 93% used TEP for communication.[28] Similar results were recently reported in a larger series of patients using the RFFF.[29] The disadvantage of the RFFF was the donor-site cosmetic defect from a large STSG, since often a large component of skin was harvested. The circumference mismatch was addressed by making the portion of the flap closer to the antecubital fossa wider than the distal part near the wrist, and the wider proximal part was used for the oropharyngeal defect. Alternatively, in some cases in this series, the flap could be "spiraled" to adjust for the circumference mismatch. Details of spiraling the flap is nicely outlined in a recent report using ALT free flaps.[20]

The ALT free flap is becoming a more popular option because it has the advantages of a fasciocutaneous flap, the donor site can often be closed primarily, and a large amount of tissue can be harvested to reconstruct complex defects of the pharynx and the external skin.[20] Each patient must be evaluated carefully because this flap can be quite thick and is difficult to tube in obese patients. In a single-institution comparison of ALT and jejunal free flaps, the ALT flap resulted in similar complication rates, shorter ICU and hospital stays, and better speech and swallowing compared with jejunal reconstruction.[17]

Reconstruction with the gastric pull-up continues to have its advocates because only one anastomosis is necessary, and the fistula rate may be better than the jejunal free flap or fasciocutaneous flaps. However, intra-abdominal complications can be significant, functional outcomes are worse, and vascular compromise of the stomach can be a devastating complication.[25,30] This should be reserved for when an esophagectomy is required for oncologic reasons.

## The Total Laryngopharyngoesophagectomy Defect

Fortunately, patients having to undergo this oncologic procedure are few, as survivorship is poor, and early mortality from a failed reconstruction is quite high. Patients with hypopharyngeal cancer that extends into the cervical esophagus require total esophageal resection when the inferior margin precludes a cervical anastomosis, regardless of the reconstructive method chosen. The gastric pull-up has been the reconstructive procedure of choice in this situation. When the anastomosis is high in the neck, care should be taken to ensure that the vascularity of the stomach is preserved and that the anastomosis is not under undue tension. If needed, a tubed free fasciocutaneous flap or jejunal flap can be interposed to bridge the oropharyngeal defect. Recently, a pedicled ileocolic flap has been described with reasonable functional success, although experience is limited with this procedure.[31]

## SUMMARY

In a disease with poor oncologic outcomes, it is essential to choose a reconstructive technique that will provide the patient with the fewest immediate complications so that hospital stay is minimized, long-term donor-site morbidity does not have a significant impact on quality of life, and functional outcomes

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maximize speech and swallowing. Advances in microvascular reconstruction have resulted in significant improvements in patient morbidity and functional outcomes. It is essential to use the reconstructive technique best suited for the individual patient to obtain the best result. Again, the reconstructive surgeon must carefully consider the reconstructive goals, oncologic outcomes, patient-related factors and comorbidities, and the extent of the surgical defect in recommending a procedure to a patient. The patient must have reasonable goals and expectations in understanding what can be accomplished with contemporary reconstruction so that the care of the patient is optimized.

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CHAPTER 20

Abtin Tabaee and Mark S. Persky

# Cancer of the Nasal Vestibule, Nasal Cavity, Paranasal Sinuses, Anterior Skull Base, and Orbit: Surgical Management

Neoplasms of the nasal cavity, the paranasal sinuses, the anterior skull base, and the orbit represent a heterogeneous group of disorders that are associated with multiple challenges and historically poor outcomes. Several factors have been implicated in the overall poor prognosis of these lesions including aggressive growth patterns, proximity to critical neurovascular structures, nonspecific clinical presentation, and initial presentation with locally advanced disease. A multidisciplinary approach is often invoked for these lesions with the goals of oncologic control and preservation of organ function. The relative rarity and heterogeneous variety of these lesions have to date precluded the ability to perform large, prospective, randomized studies. The current treatment algorithms are based largely on the collective experience of single-institutional experiences.

The past decade has witnessed an evolution in the management strategies and outcomes for sinonasal and anterior skull base malignancies. Distinction in the clinical behavior and treatment sensitivity of the various histopathologies has resulted in more tailored therapy. Additionally, the well-defined principles of open extirpative surgery, including extended skull base approaches and craniofacial surgery, have led to an increasing range of treatment options for advanced lesions. Finally, the increasing collective experience with the techniques and outcomes of endoscopic surgery is rapidly defining its role in the surgical treatment of select sinonasal and anterior skull base neoplasms.

## ANATOMY—NASAL CAVITY AND PARANASAL SINUSES

A thorough understanding of the anatomy of the sinonasal cavity, the anterior skull base, and the orbit is fundamental in the treatment of these lesions. An abridged review is presented below. The bony landmarks of the facial skeleton are presented in Figure 20-1. The nasal cavity and the paired paranasal sinuses are air-filled cavities, surrounded by a bony-cartilaginous framework and lined by pseudostratified, ciliated columnar (respiratory) epithelium interspersed with goblet cells and basal cells (Fig. 20-2). Individual ciliated cells have approximately 50 to 200 cilia per cell, beating approximately 700 to 800 beats/minute and achieving a mucociliary clearance rate of 1 cm/minute. This physiology is easily impaired by the events that occur during cancer treatment including surgery and radiation therapy. The physiologic function of the sinonasal cavities include respiratory conductance of air flow, humidification and warming of inspired air, voice resonance, particle filtration, decreased skull weight, mediation of olfaction, absorption of midface and forehead trauma, and immune response to respiratory antigens. With regard to sinonasal neoplasms, the presence of compartmentalized, air-filled spaces allows for a period of unabated, local tumor growth with minimal, nonspecific symptoms and no significant findings on examination. This is one of the primary factors that predispose these lesions to a delay in diagnosis and advanced stage at initial presentation. Additionally, the intimate relationship of the sinonasal cavity to critical neurovascular structures, including the orbit, the internal carotid artery, and the intracranial cavity has significant implications on overall prognosis and treatment efficacy. In certain areas, the bony walls separating the sinonasal cavity from the orbit (lamina papyracea) and the intracranial cavity (anterior skull base) are thin and easily eroded by tumor (Fig. 20-3). Additionally, the presence of multiple adjacent foramina and canals allow tumor spread along preformed perineural and perivascular channels (Fig. 20-4). An understanding of these potential pathways is critical to defining the pathophysiology of tumor spread and is highlighted in the following paragraphs.

### Nasal Cavity

The nose consists of paired nasal apertures and cavities supported by a bony and cartilaginous framework. It is divided by the midline nasal septum (Fig. 20-5). The anterior most portion of the nasal cavity, termed the nasal vestibule, is lined by squamous epithelium and numerous hair follicles or vibrissiae. The remainder of the nasal cavity is lined by respiratory epithelium. The nasal cavity extends from the nasal vestibule anteriorly to the choana posteriorly. It is bounded by the columella and nasal septum medially and the lower lateral cartilages laterally. The floor of the nasal cavity corresponds to the hard and soft palate orally, whereas the roof corresponds to the cribriform plate intracranially. The paired choana open to the nasopharynx directly and are bordered by the medial pterygoid plates on each side. Olfactory epithelium is interspersed with respiratory epithelium along the superior aspect of the nasal septum, roof of the nasal cavity, and the superior and the middle turbinates. Olfactory nerve bundles pass through multiple perforations in the cribriform plate, providing a potential pathway for perineural spread of tumor intracranially.

The paired inferior, middle, and superior turbinates are bony projections lined by respiratory mucosa arising from the lateral



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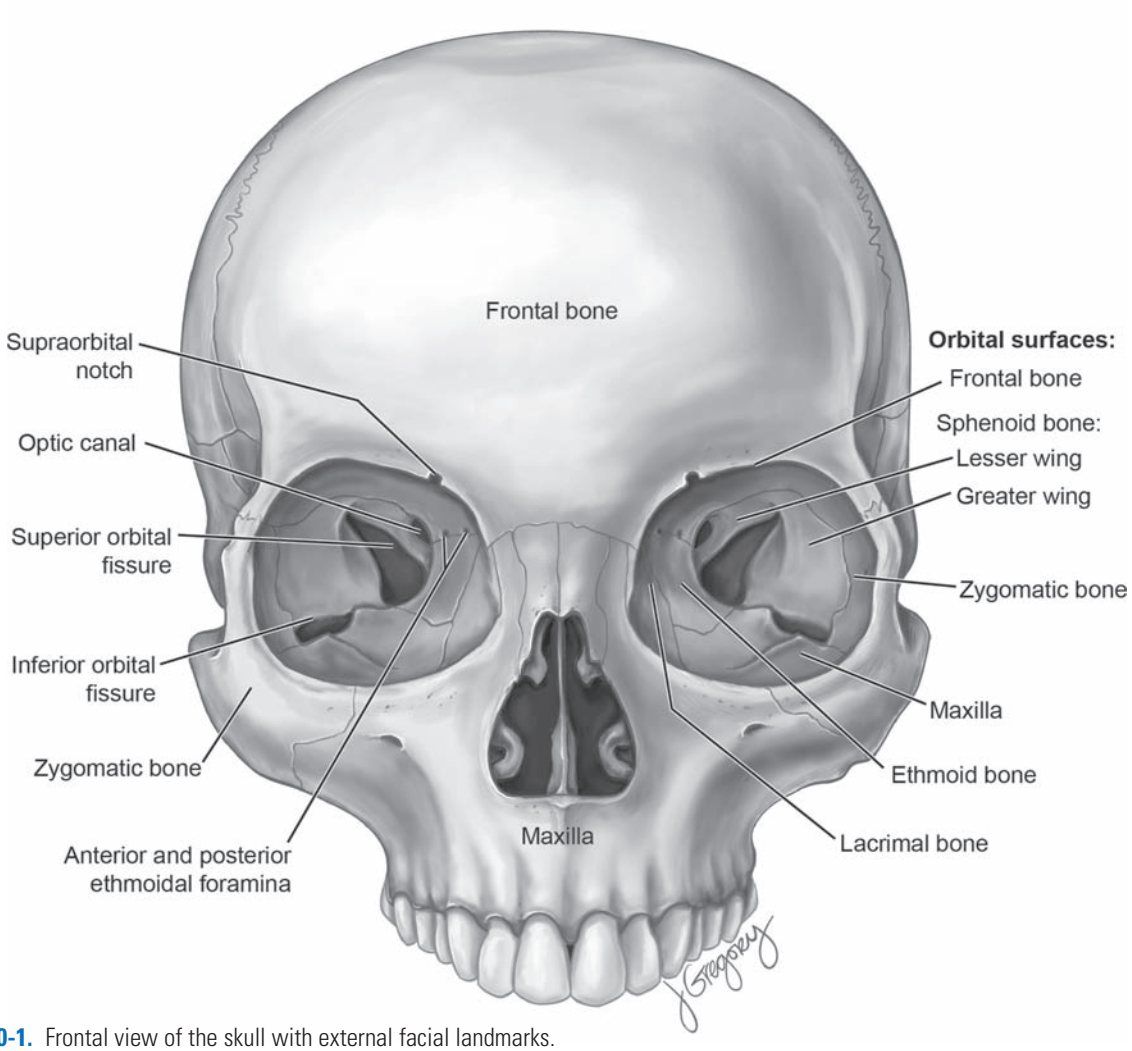



**FIGURE 20-1.** Frontal view of the skull with external facial landmarks.

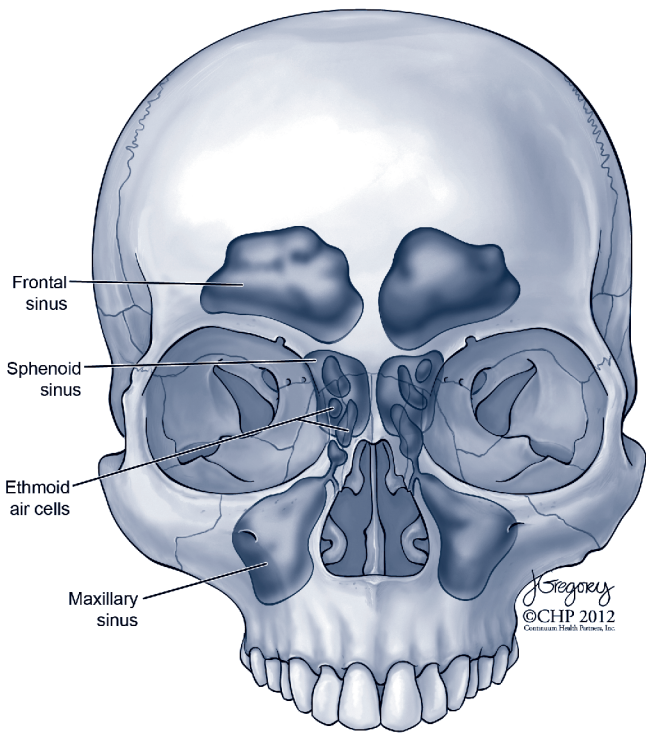
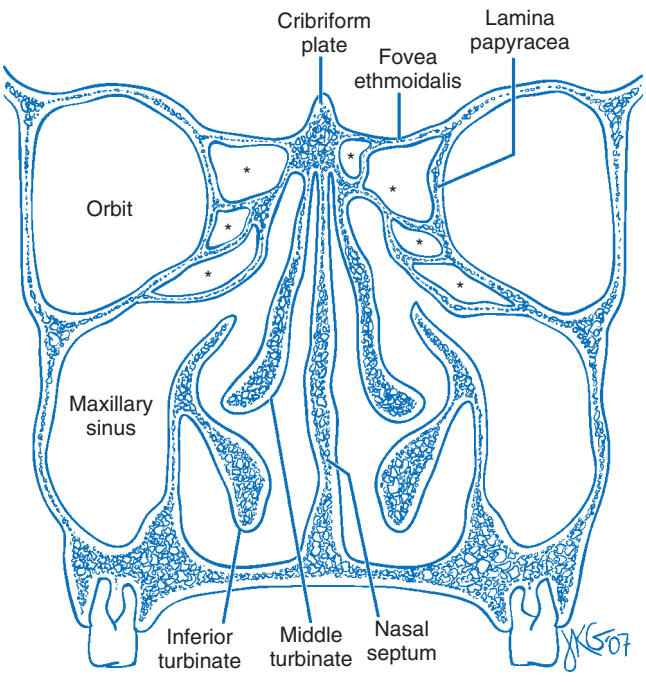



**FIGURE 20-2.** Schematic representation of the paranasal sinuses.




* Ethmoid sinuses

**FIGURE 20-3.** Coronal view of the maxillary and ethmoid sinuses and their relation to surrounding structures.



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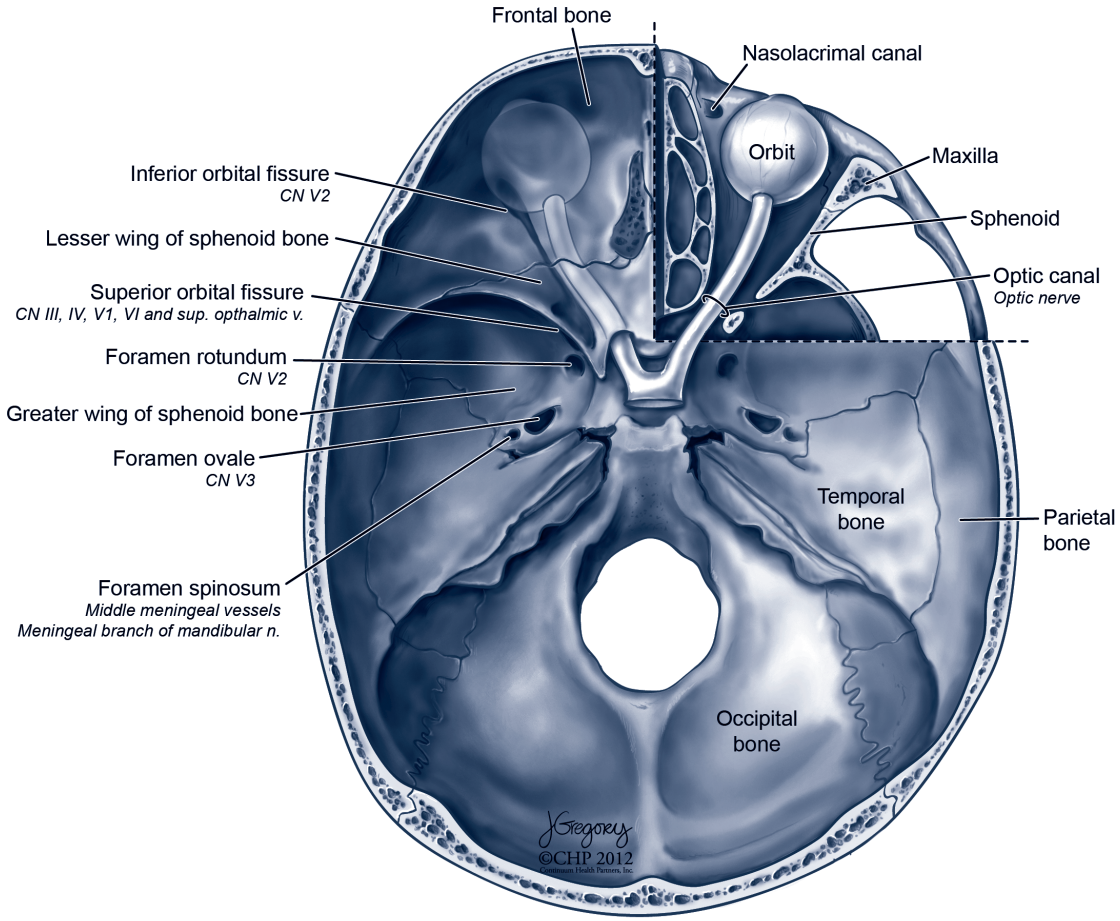
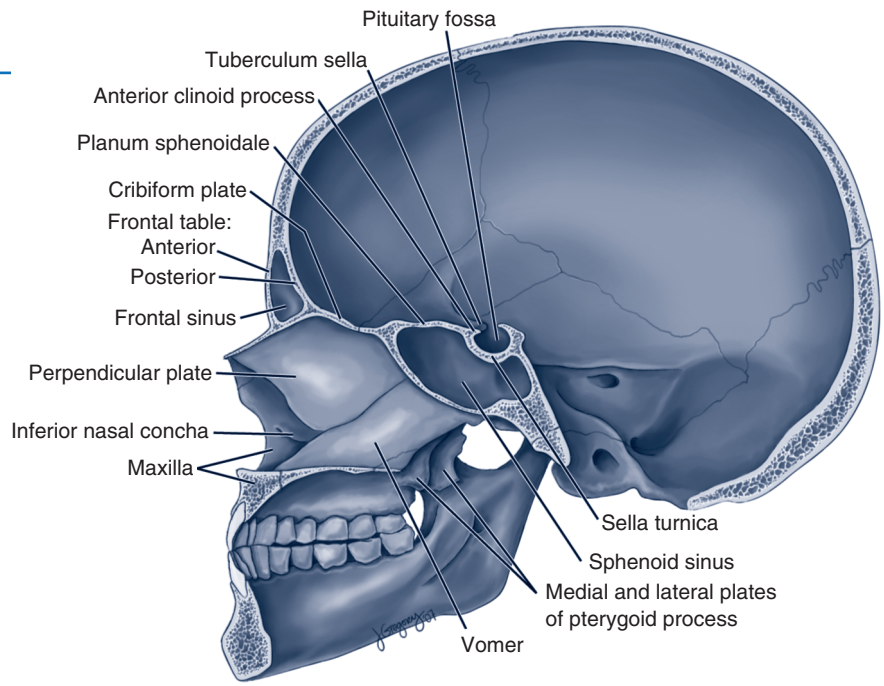



**FIGURE 20-4.** Axial view of the intracranial cavity.

**FIGURE 20-5.** Midsagittal view of the skull.




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nasal wall. The inferior turbinates are independent osseous structures whereas the middle and superior turbinates are portions of the ethmoid bone. The area underneath each turbinate, termed meati, has important physiologic relationships. The lacrimal duct arises from the lacrimal sac in the inferomedial portion of the orbit, runs inferiorly along the medial-posterior surface of the maxilla, and empties through Hasner valve into the inferior meatus. The anterior paranasal sinuses composed of the maxillary, the anterior ethmoid, and the frontal sinuses physiologically clear their contents into the middle meatus. Similarly, the posterior ethmoid cells and the sphenoid sinus clear their contents into the superior meatus. The sphenopalatine foramen is located on the lateral nasal wall, inferior-posterior to the horizontal attachment of the middle turbinate, and transmits the sphenopalatine artery and vein from the pterygomaxillary space in addition to the nasopalatine and the superior nasal branches of the maxillary division of the trigeminal nerve.

The nasal septum is composed of a bony-cartilaginous wall sandwiched between two layers of tightly adherent mucopericondrium. The anterior quadrangular cartilage sits on the bony maxillary crest and articulates with the bony vomer posteriorly and the perpendicular plate of the ethmoid superiorly. In addition to providing structural support and normal nasal physiology, the nasal septum may act as a barrier for tumor transgression. Multiple neural and vascular sources supply the nasal septum. Arterial branches arise from both the external (sphenopalatine and facial arteries) and the internal carotid arteries (anterior ethmoid artery). Sensation is transmitted through both the ophthalmic (nasociliary nerve) and the maxillary (nasopalatine nerve) divisions of the trigeminal nerve.

## Maxillary Sinus

The paired maxillary sinuses represent the largest of the paranasal sinuses and most common site of sinonasal malignancy. These inverted pyramidal structures have a total volume of approximately 15 mm. Dynamic mucociliary clearance transports sinus secretions toward the natural ostium in the superomedial aspect of the sinus into the middle meatus of the nasal cavity. Obstruction of the ostium results in stasis of secretions and potential bacterial superinfection. Accessory openings, termed fontanelles, may also exist in approximately 25% of the population. The maxillary sinuses are bordered medially by the lateral nasal wall and the nasal cavity (maxillary and palatine bones), superiorly by the orbital floor and the infraorbital canal, anteriorly by the anterior face of the maxilla, inferiorly by the alveolar process of the maxilla, posterolaterally by the infratemporal fossa, and posteromedially by the pterygopalatine fossa (PPF). The base of the pyramid is the nasal surface and the tip points toward the zygomatic process. The anatomic proximity of the maxillary sinus to these structures predicates the patterns of spread for advanced lesions and has significant treatment and prognostic implications. Anatomic variations of the maxillary sinus include the presence of septations and hypoplasia of the maxillary sinus. The floor of the maxillary sinus is intimately related to the upper gingiva and the hard palate and is typically 1 to 2 cm below the level of the nasal cavity floor in adults. Tumor extension inferiorly to the alveolus and medially to the lateral nasal wall is relatively more favorable and amenable to *en bloc* resection.

## Ethmoid Sinus

The ethmoid sinus consists of multiple individual compartments and has been aptly termed the ethmoid labyrinth. Significant variability in the number, size, and pneumatization pattern of the ethmoid sinus cells has been described. Examples of this include aberrant pneumatization of ethmoid sinus cells within the inferior orbital wall (Haller or infraorbital cell), the frontal recess and sinus (frontal cell), the sphenoid sinus (Onodi or sphenoethmoid cell), and the middle turbinate (concha bullosa). The ethmoid sinuses are bordered by the middle and the superior turbinates medially, anterior face of the sphenoid sinus posteriorly, the lamina papyracea laterally, and the anterior skull base (fovea ethmoidalis) superiorly. The latter two boundaries are thin walled and easily breached by both neoplasm and surgical injury. In the normal configuration, there is an approximately 15-degree anterior-to-posterior down-sloping of the fovea ethmoidalis although variability in its height and slope exist. The periorbital perichondrium and dura of the anterior cranial fossa are tightly apposed to the respective bony walls and represent a natural barrier to tumor extension. The bony optic canal houses the optic nerve and may traverse immediately adjacent to the lateral border of the posterior ethmoid cells to a variable extent. The ethmoid sinuses are divided both anatomically and functionally into an anterior and posterior set of cells as demarcated by the ground (basal) lamella, the horizontal lateral bony attachment of the middle turbinate to the lamina papyracea. The paired anterior and posterior ethmoidal arteries traverse the roof of the ethmoid sinus. These vessels arise from the ophthalmic branch of the internal carotid artery. The anterior ethmoidal artery courses over the medial rectus muscle, penetrates the lamina papyracea, and courses the roof of the ethmoid sinus, posterior to the frontal. The posterior ethmoidal artery enters the orbit approximately 3 to 5 mm anterior to the optic foramen, emerges from the orbit approximately 12 mm posterior to the anterior ethmoidal artery courses across the roof of the posterior ethmoid cavity and terminates with the dural, the ethmoidal, and the nasal septum branches.

## Sphenoid Sinus

The sphenoid sinus is the posterior most extension of the sinonasal cavity and develops as a pneumatization of the sphenoid bone (Fig. 20-6). It is bordered by the posterior ethmoid cells and the sphenoethmoid recess anteriorly, the sella and the clivus posteriorly, the internal carotid artery and the cavernous sinus laterally, and the planum sphenoidale superiorly. The natural ostium of the sphenoid sinus is located in the superior meatus, bounded by the superior turbinate laterally and posterior-most extension of the nasal septum medially. The ostium is located two-thirds up the vertical height of the sphenoid sinus cavity. The pneumatization of the sphenoid sinus is variable especially with regard to the sella medially and floor of the middle cranial fossa laterally. Variant numbers and insertions of the intersinus septation may also exist. The optic nerves run in the superolateral aspect of the sphenoid sinus, and the carotid artery canal is located at the junction of the lateral and posterior walls of the sinus. Dehiscences of the bony coverings of the optic nerve and the internal carotid artery within the sphenoid sinus may exist.

## Frontal Sinus

The frontal sinus is the most anterior and superior extension of the sinonasal cavity. The majority of humans have two asymmetric frontal sinus cells separated by a thin septation. Variability exists in the degree of frontal sinus development with approximately 10% of the population lacking pneumatization of the frontal bone. The frontal sinuses empty into the inferomedial aspect of the sinus through the frontal recess into the middle meatus. The thicker anterior frontal table separates the frontal sinus from the soft tissue of the forehead. The thinner posterior frontal table separates the frontal sinus from the anterior cranial fossa.

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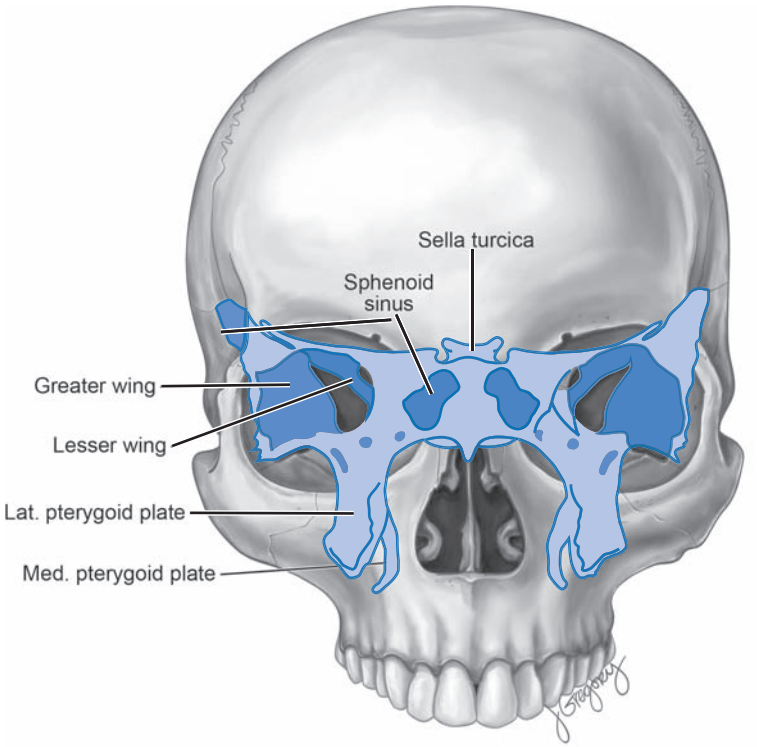



**FIGURE 20-6.** Schematic representation of the sphenoid sinus within the sphenoid bone.

## Sinonasal Lymphatics

The lymphatic drainage of sinonasal malignancies is based on the location of the primary site. In general, the lymphatics are profuse and two distinct patterns are described for the sinonasal cavity. The lymphatics originating from the anterior nasal mucosa and nasal vestibule pass through the first echelon facial, submandibular, and parotid lymph nodes and eventually continue to the jugulodigastric nodes. The majority of the nasal cavity and paranasal sinuses drain posteriorly to the retropharyngeal lymph nodes and eventually to the superior deep cervical chain.

# ANATOMY—ANTERIOR SKULL BASE

## Pterygopalatine Fossa

A description of the complex neurovascular relationships within the PPF is integral to an understanding of the pathophysiology and treatment concepts for tumors involving this area. Direct pathways between the PPF and the orbit, the middle cranial fossa, the infratemporal fossa, and the sinonasal cavities allow for contiguous spread. The fossa has the shape of an inverted pyramid. The anterior border is the posterior surface of the maxilla and the maxillary sinus cavity. The posterior border is composed of the base of the medial and lateral pterygoid plates and greater wing of the sphenoid (Fig. 20-7). The Vidian nerve enters the medial portion of the posterior PPF in the Vidian canal. The maxillary division of the trigeminal nerve exits the middle cranial fossa and enters the lateral portion of the posterior PPF through the foramen rotundum, courses through the PPF providing a branch to the pterygopalatine ganglion and reaches the inferior orbital fissure as the infraorbital nerve. The pterygoid plates and the pyramidal process of the palatine bones fuse to form the inferior aspect of the PPF. The greater wing of the sphenoid bone and the middle cranial fossa form the superior boundary of the PPF. The medial portion of the PPF is composed of contributions from the perpendicular plate of the palatine bone, the medial pterygoid plate, and the sphenoid bone. The sphenopalatine foramen within the medial wall of the PPF transmits the sphenopalatine nerve and sphenopalatine artery (branch of internal maxillary artery) into the nasal cavity. The PPF communicates laterally with the infratemporal fossa and the pterygomaxillary fissure. The contents of the PPF can be generally classified as an anterior vascular space housing the termination of the internal maxillary artery and its branches and a posterior neural space housing the maxillary division of the trigeminal and the pterygopalatine ganglion. The principal branches of the pterygopalatine ganglion are the Vidian nerve, maxillary nerve, and the lesser and the greater palatine nerves. The neurovascular structures of the PPF are embedded within fat.

## Anterior Sinocranial Junction

The anterior skull base separates the anterior cranial fossa from the sinonasal cavity. The complex anatomy of this area has critical physiologic and tumor-related implications. The osteology of this area encompasses contributions from the frontal, the ethmoid, and the sphenoid bones. The sagittal length of the anterior skull base spans the posterior table of the frontal sinus (anterior) to the planum sphenoidale and the anterior clinoid process (posterior) (Fig. 20-5). The frontal bones form the lateral bony boundaries including the superior orbital wall. This area houses the orbital portions of the frontal lobe. The central portion of the floor of the anterior cranial fossa is composed of portions of the ethmoid bone including the central crista galli dividing the paired cribriform plates. The falx cerebri separating the two cerebral hemispheres attaches to the crista galli. The depression of the cribriform plates represents the lowest and thinnest portion of the anterior cranial fossa and functions to transmit olfactory filia from the sinonasal cavity to the olfactory bulbs lying on the

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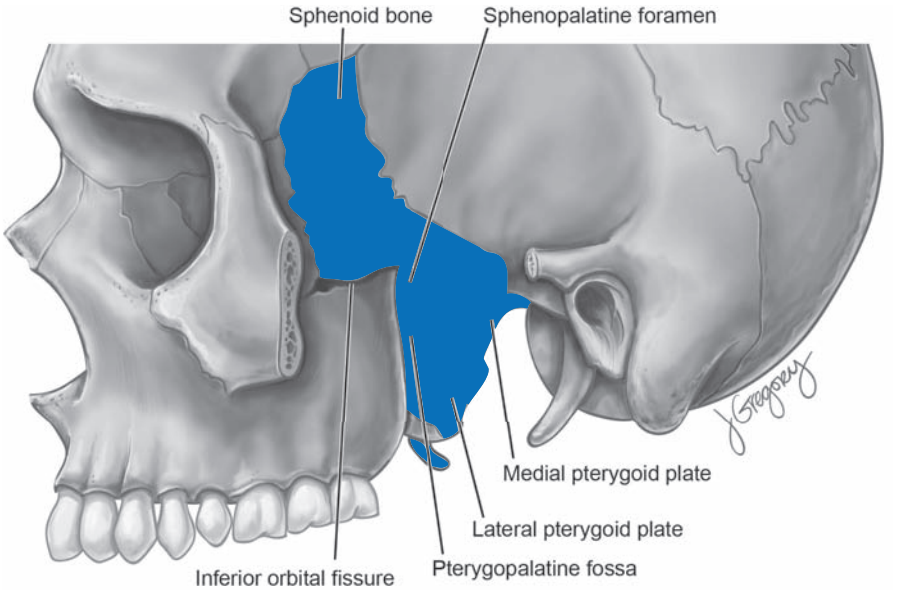



**FIGURE 20-7.** Bony relationships of the pterygopalatine fossa.

intracranial surface. The fovea ethmoidalis is immediately lateral to the cribriform plate. Variances in the difference in height between the cribriform plate and fovea ethmoidalis have been described, most notably in the Keros classification[1] (Fig. 20-8).

## ANATOMY—ORBIT

### Osteology

The bony orbit is pyramidal in shape with the anterior conjunctival surface (base) pointing to the posterior orbital apex (Fig. 20-1). Direct neurovascular communication and bony foramina have the potential to act as a route of transmission among the orbit, the paranasal sinuses, and the intracranial cavity (Fig. 20-9). The medial orbital wall extends from the anterior lacrimal crest to the orbital apex and separates the orbit from the ethmoid sinus. The thin-walled lamina papyracea comprises the anterior portion of the medial orbital wall, and the thicker sphenoid bone contributes to the posterior portion in the area of optic canal. The superior portion of the medial orbital wall transmits the anterior and posterior ethmoidal arteries through their respective foramina. The anterior ethmoidal artery pierces the medial orbital wall at the site of the frontoethmoid suture and then courses through the roof of the anterior ethmoid cells in the anterior ethmoidal sulcus, immediately posterior to the frontal recess. It enters the lateral lamella of the cribriform plate to supply the frontal sinus, the nasal septum, and the lateral nasal wall. A middle meningeal branch additionally enters the anterior cranial fossa. The floor of the orbit is composed of the orbital plate of the maxilla in addition to the zygoma and palatine bones and separates the orbit from the maxillary sinus. The infraorbital canal runs along the floor of the orbit and transmits the infraorbital artery and nerve to the cheek. The lateral wall of the orbit is formed by the zygoma anteriorly and the greater wing of the sphenoid posteriorly. The latter separates the orbit

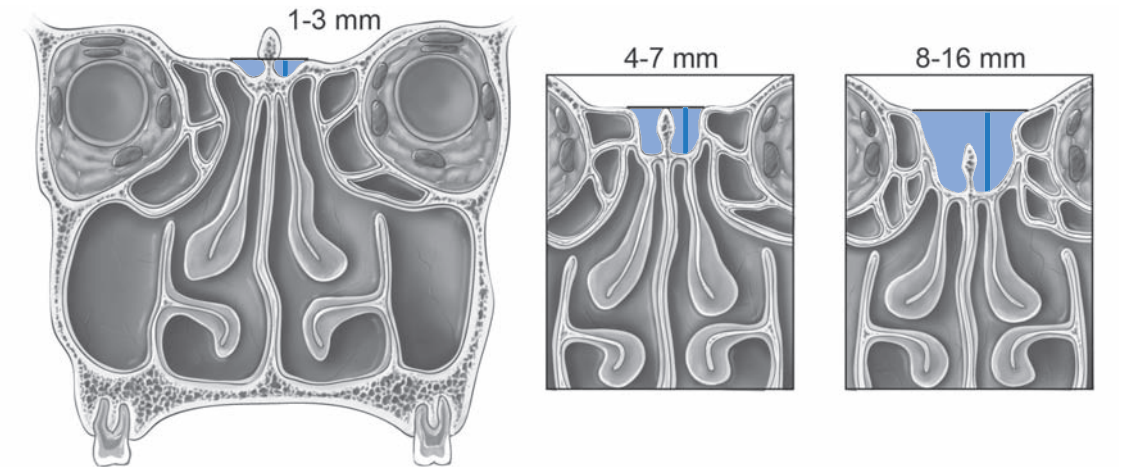



**FIGURE 20-8.** The Keros classification of the anterior skull base describing the relation between the depth of the cribriform plate and the fovea ethmoidalis.

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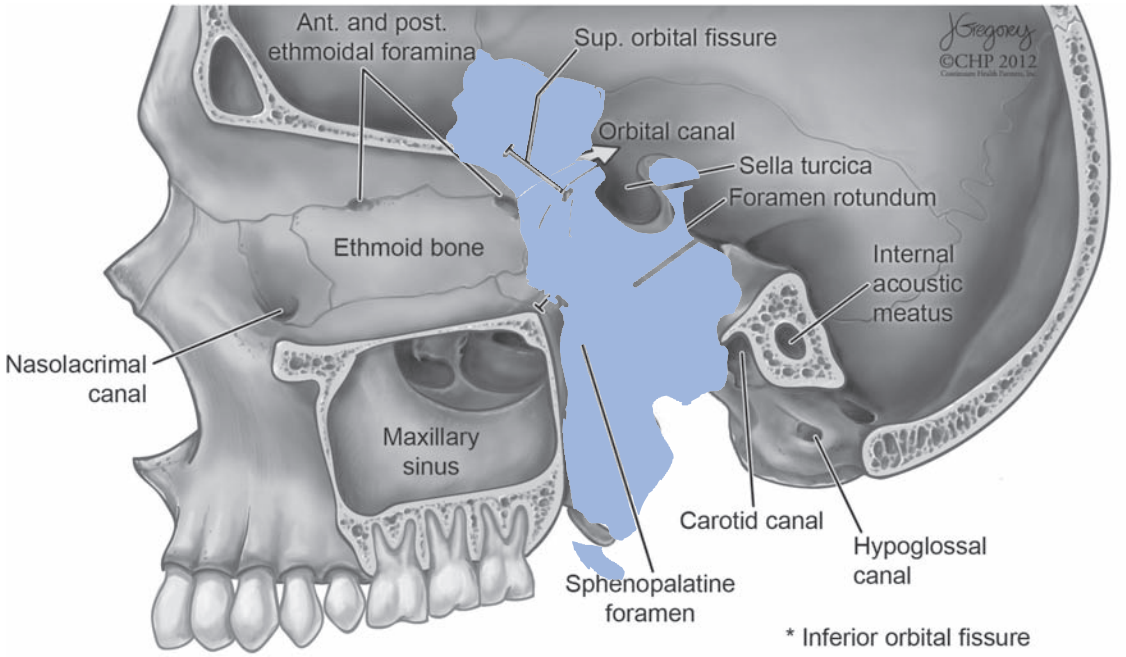



**FIGURE 20-9.** Schematic showing the multiple neurovascular channels connecting the orbit, the pterygopalatine fossa, and the skull base.

from the middle cranial fossa. The superior and inferior orbital fissures in addition to foramina transmitting the zygomaticofacial and zygomaticotemporal arteries exist on the lateral orbital wall. The lateral orbital tubercle acts as an attachment point for multiple tendons and ligaments and is located on the lateral aspect of the lateral orbital rim, approximately 1 cm inferior to the frontozygomatic suture line. The orbital roof is composed of the orbital plate of the frontal bone and has variable pneumatization by the ethmoid and frontal sinuses. The trochlea exists in the anteromedial aspect of the orbital roof approximately 4 mm posterior to the orbital rim. The supraorbital notch or foramen transmitting the supraorbital neurovasculature exists at the boundary of the medial third of the orbital roof. A periosteal layer, termed the periorbita, lines the inner surface of the orbit and has complex attachments with various areas of the surrounding bone, the fascia layers of the orbit, and the dura surrounding the optic nerve.

## Orbital Apex and Neurovascular Anatomy

The orbital apex provides direct intracranial communication and is marked by the posterior portion of the inferior orbital fissure, the superior orbital fissure, and the optic foramen. The optic foramen acts as an opening into the optic canal for the optic nerve and ophthalmic artery. The canal itself is housed within the lesser wing of the sphenoid bone, separating the canal contents from the posterior ethmoid cells and the sphenoid sinus medially. The superior orbital fissure lies between the greater and lesser wings of the sphenoid and transmits the oculomotor nerve (III), the trochlear nerve (IV), the lacrimal, the frontal, and the nasociliary branches of the ophthalmic nerve (V1), the abducens nerve (VI), branches of the ophthalmic vein and sympathetic fibers from the cavernous plexus. The oculomotor nerve divides into a superior and inferior branch within the cavernous sinus. The maxillary division of the trigeminal nerve from the PPF, the infraorbital branch of the maxillary artery, and the inferior ophthalmic vein pass through the inferior orbital fissure in the posterior-lateral portion of the orbital floor.

The optic nerve is approximately 5 cm in length and 4 mm in diameter. It consists of four anatomic segments in its length from the optic chiasm to the globe: intracranial, intracanalicular, intraorbital and intraocular. A dural layer surrounds the majority of the nerve course. The arterial supply to the optic nerve is primarily from the central retinal artery, a branch of the ophthalmic artery.

The ophthalmic division of the trigeminal nerve provides sensation to the orbit. It enters the orbit through the superior orbital fissure and divides into the frontal, the lacrimal, and the nasociliary nerves. The frontal branch divides into the supraorbital and supratrochlear nerves and supplies the upper eyelid and the forehead. The lacrimal nerve carries postganglionic parasympathetic fibers and somatic sensory innervation to the lacrimal gland. The nasociliary branch has multiple complex branches including the long and the short ciliary nerve (sympathetic and parasympathetic for pupil reactivity), anterior and posterior ethmoid nerves, the infratrochlear nerve (sensation to medial lower lid, conjunctiva, lacrimal sac, and side of the nose).

The primary vascular supply to the orbit is the ophthalmic artery (Fig. 20-10). The artery arises from the internal carotid artery as it exits the cavernous sinus and enters the orbit through the optic canal. Multiple branches arise from the ophthalmic artery within the orbit. Branches supplying ocular function include the central retinal artery, the ciliary artery, and the collateral branches to the optic nerve. Nonocular orbital branches include the lacrimal artery, the muscular arteries, and the periosteal branches. Nonocular extraorbital branches include the anterior and the posterior ethmoid arteries, the supraorbital artery, the medial palpebral artery, the supratrochlear artery, and the dorsal nasal artery. Anastomoses between the ophthalmic branches and branches of the external carotid artery system exist, namely, the superficial temporal artery and the angular arteries. Additional anastomoses exist between the cavernous portion of the internal carotid artery and the ophthalmic artery via the inferolateral trunk. Anastomoses additionally exist with the internal maxillary artery via the middle meningeal artery. The infraorbital artery is a branch of the internal maxillary artery and enters the orbit

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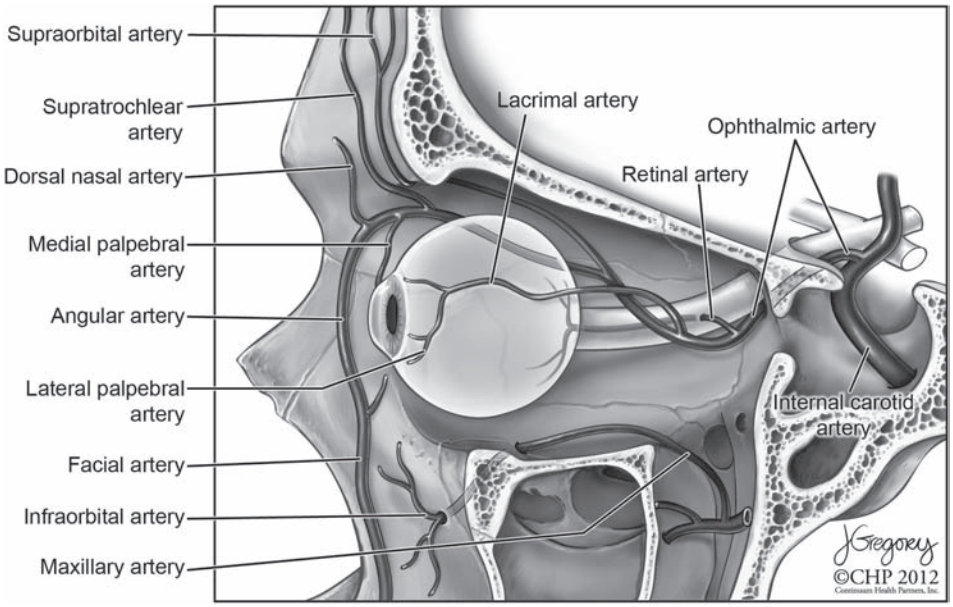



**FIGURE 20-10.** Lateral view of the primary arterial supply to the orbit.

through the inferior orbital fissure. It travels across the floor of the orbit and exits the skull at the infraorbital foramen. The venous supply to the orbit is represented in Figure 20-11.

## Extraocular Muscles

The annulus of Zinn is a ring of tight fibrous tissue at the orbital apex separating the superior orbital fissure into intra and extraconal spaces. The annulus acts as the origin site for the four rectus muscles (superior, medial, inferior, lateral) and the superior oblique muscle (Fig. 20-12). Innervation of the extraoccular muscles are conferred by the oculomotor nerve with the exceptions of the trochlear nerve (superior oblique muscle) and the abducens nerve (lateral rectus muscle). The innervation courses in the intraconal space and enters the muscles at approximately the posterior one-third junction. The medial and superior recti originate adjacent to the insertion of the annulus to the body of the sphenoid bone adjacent to the optic foramen. The medial rectus courses adjacent to the lamina papyracea before inserting on the globe, making it prone to surgical and traumatic involvement from injury to the lamina as well as contiguous spread from ethmoid sinus neoplasms. The superior rectus runs inferior to the levator palpebrae superioris before attaching to the globe. The latter forms an aponeurotic band in the region of Whitnall ligament and inserts onto the tarsal plate of the eyelid skin and the medial and lateral canthal tendons. The inferior rectus originates from a tendinous portion of the annulus that spans the body and greater wing of the sphenoid bone. The muscle runs close to the orbital floor, especially in its posterior course, intimating a relationship with maxillary sinus pathology. The lateral rectus

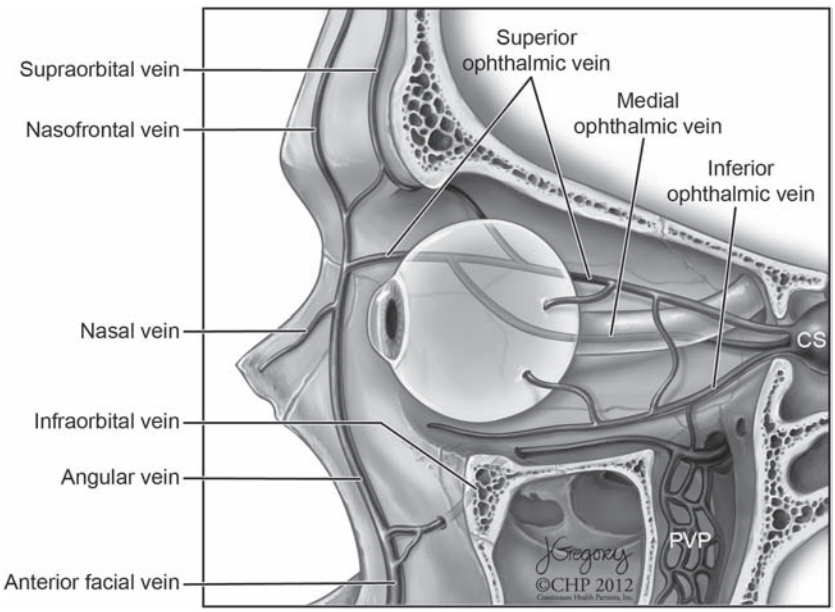



**FIGURE 20-11.** Lateral view of the primary venous supply to the orbit.

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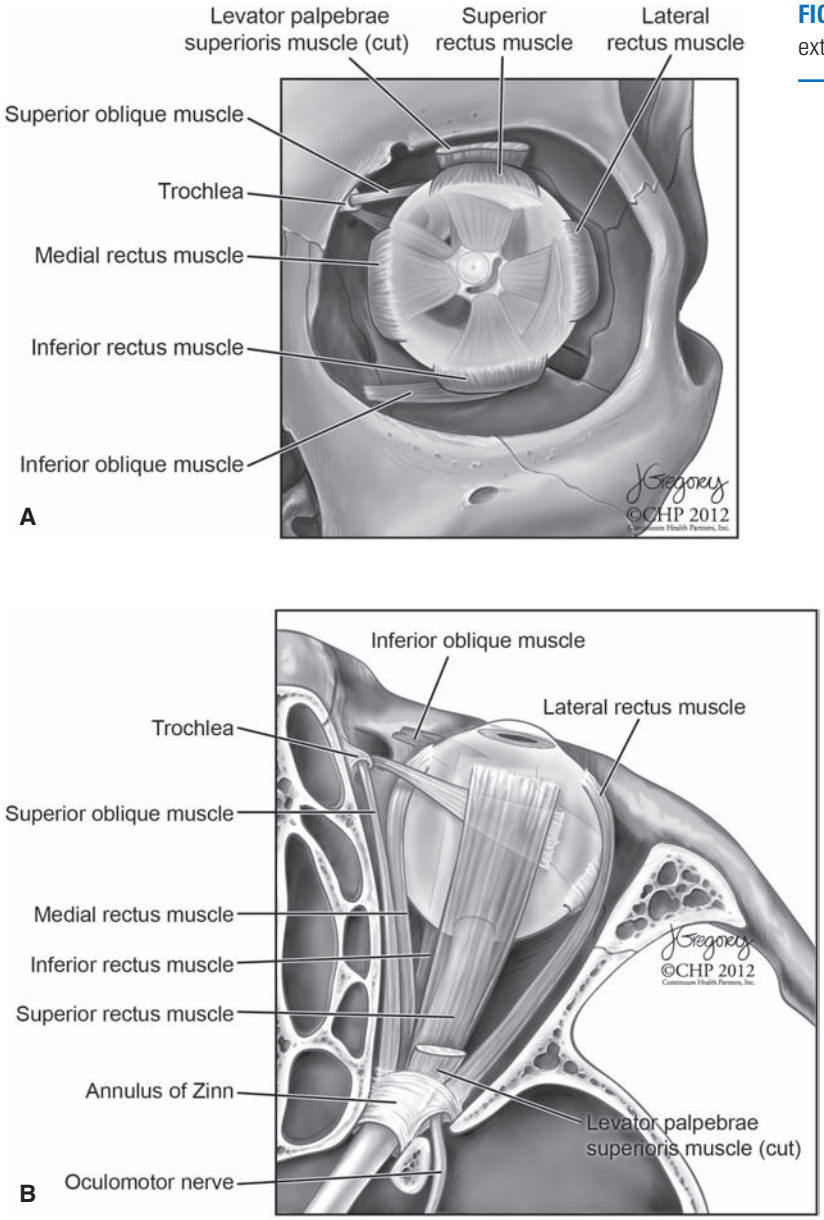



**FIGURE 20-12.** Frontal **(A)** and superior **(B)** views of the extraocular muscles.

originates from the body of the greater wing of the sphenoid near the lateral border of the superior orbital fissure and is separated from the optic nerve posteriorly by the ciliary ganglion. The insertion of the lateral rectus on the orbit is inferior to the lacrimal gland, the artery, and the nerve. The superior oblique muscle arises from the superomedial aspect of the annulus courses anteriorly through the trochlea before inserting in the posterolateral surface of the globe. The inferior oblique uniquely does not originate from the annulus of Zinn but rather arises from the periorbita of the inferomedial orbit lateral to the nasolacrimal duct. It courses lateral and posteriorly below the inferior rectus to insert on the inferolateral surface of the globe.

## Lacrimal Gland

The oval-shaped, bilobed lacrimal gland is located adjacent to the globe in the superior-lateral aspect of the orbit in a depression of the frontal bone termed the lacrimal gland fossa (Fig. 20-13). A pseudocapsule invests the gland. The orbital lobe of the lacrimal gland is approximately 2 to 3 times larger and is positioned posterior-superior to the smaller palpebral lobe. The two lobes are separated by the lateral horn of the levator aponeurosis, which along with Whitmall ligament and periostial fibers (Soemmering ligaments) provide support to the gland. Multiple excretory ducts exist for each lobe and ultimately pass through the palpebral lobe to reach the superior lateral conjunctival fornix, 5 mm above the superior tarsal margin. The boundaries of the lacrimal gland include the lateral rectus inferiorly, the orbital septum anteriorly, orbital fat posteriorly, and the globe medially. The serous function of the lacrimal gland is mediated by the columnar and myoepithelial cells that comprise the acini. The secretions formed in the acinar system drain into the intralobular space, followed by the interlobular space and ultimately into the main ducts. Arterial supply to the lacrimal gland is primarily from the lacrimal artery, a branch of the ophthalmic artery. Anastomoses between the lacrimal artery and the external

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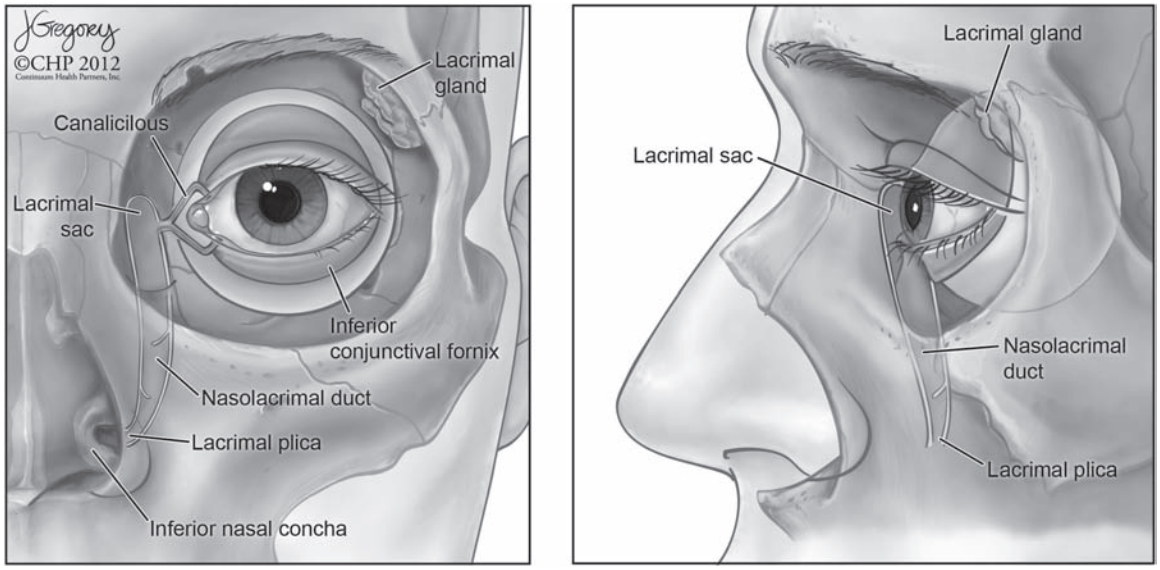



**FIGURE 20-13.** Schematic representation of the lacrimal system.

carotid artery system additionally exist including the middle meningeal artery, the anterior deep temporal artery, and, potentially, the infraorbital artery. Venous drainage is via the superior ophthalmic vein.

The complex pathway of the parasympathetic and the sympathetic innervations of the lacrimal gland initiates in the lacrimal nucleus in the pons and travels through the cerebellopontine angle as the nervus intermedius. The fibers course through the geniculate ganglion and exist as the greater superficial petrosal nerve. This merges with the deep petrosal nerve (sympathetic fibers from the internal carotid plexus) to form the Vidian nerve. Synapsing of the parasympathetic fibers occurs in the pterygopalatine ganglion. Postganglionic fibers travel via the zygomatic nerve and merge with the lacrimal nerve, a sensory branch of the ophthalmic division of the trigeminal nerve, prior to penetration of the lacrimal gland.

## Lacrimal Drainage System

Flow of tears away from the nasal bulbar conjunctival surface through the lacrimal system begins at the inferior and superior lacrimal puncta (Fig. 20-14). These openings into the lacrimal canaliculi face posteriorly toward the globe, are approximately 0.3 mm in diameter, and are separated by approximately 6 mm from the medical canthus. The puncta are positioned on an elevation termed the papilla lacrimalis. The paired upper and lower canaliculi traverse the distance from the puncta to the lacrimal sac. The canaliculi are lined by nonkeratinizing, stratified squamous epithelium surrounded by elastic tissue. The canaliculi have an initial vertical segment (2 mm) followed by an approximately 90-degree bend termed the ampulla and continue with the horizontal segment (8–10 mm). The common canaliculus is formed by the merger of the horizontal segments. The common

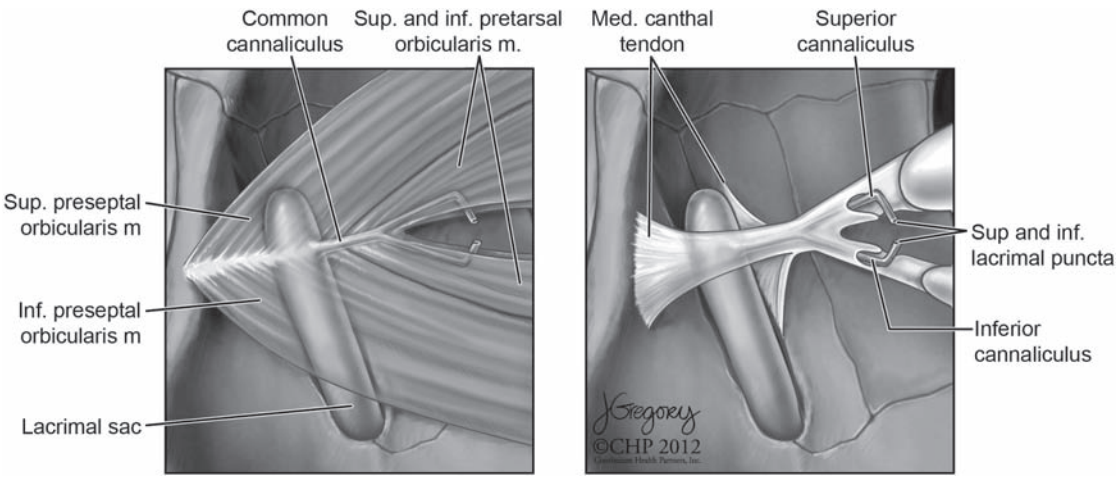



**FIGURE 20-14.** Schematic representation of the lacrimal drainage system.

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canaliculus pierces the lacrimal fascia to enter the lacrimal sac through the valve of Rosenmüller. The sinus of Maier is the dilation of the common canaliculus near the entrance to the lacrimal sac. The lacrimal fossa houses the lacrimal sac and is bounded by the anterior (frontal process of maxilla) and the posterior (lacrimal bone) lacrimal crests in the anterior-medial portion of the orbit. Visualization of the lacrimal sac through an intranasal approach, as is done in dacryocystorhinostomy, can be achieved by removal of the lacrimal bone in the superior aspect of the lateral nasal wall, anterior to the uncinate process. The lacrimal sac is divided into a superior portion termed the fundus and an inferior portion termed the body. The lacrimal fascia, an extension of the orbital periosteum, envelops the lacrimal sac and the nasolacrimal duct. Attaching fibers of the orbicularis oculi muscle are immediately deep to the fascia layer around the lacrimal sac. The nasolacrimal duct connects the lacrimal sac to the inferior meatus opening into the nasal cavity, termed Hasner valve. The nasolacrimal duct has a 12-mm superior intraosseous portion and a 5-mm inferior membranous portion and has a slight posterior-lateral trajectory as it enters the nose (Fig. 20-15). The approximate diameter of the duct is 1 mm. The lacrimal sac and the nasolacrimal duct are lined by stratified columnar epithelium with foci of ciliated cells and interspersed goblet cells.

## NASAL AND PARANASAL NEOPLASMS—NATURAL HISTORY, PATHOLOGY, PATHOGENESIS, AND PATTERNS OF SPREAD

### Natural History

Sinonasal malignancies are rare, comprising fewer than 3% of upper aerodigestive neoplasms. The most common malignancy, squamous cell carcinoma (SCC), has an estimated incidence of <1:100,000.[2,3] The rarity of these lesions limits epidemiologic data and formation of prospective, randomized treatment protocols. Hence, the literature on sinonasal malignancies is largely composed of single institutional, retrospective case series. The origin of these cancers is from the maxillary sinus in 60% to 70%, from the nasal cavity in 20% to 25%, and the ethmoid sinus in 10% to 15% of cases. Malignancies arising from the frontal and sphenoid sinuses are extraordinarily unusual, making up fewer than 5% of all cases. At presentation, the majority of lesions extend beyond the site of origin.[4,5] Sinonasal malignancy most commonly occurs in patients older than 40 years of age and has a slight male preponderance.[2–4]

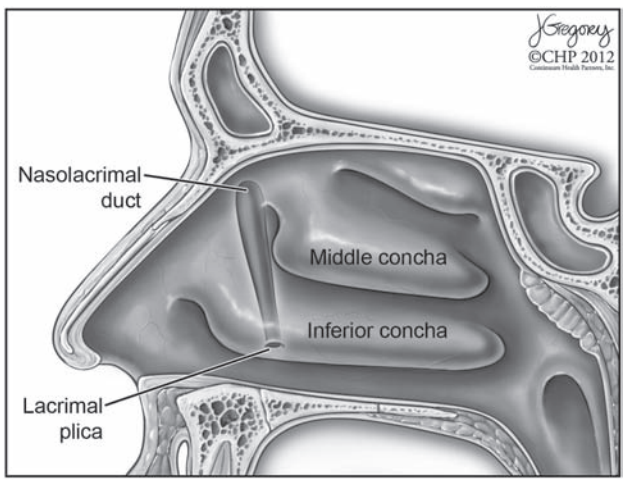



**FIGURE 20-15.** Sagittal orientation of the lacrimal duct.

The majority of treatment failures are related to local recurrence. Lymphatic metastasis at initial presentation for sinonasal malignancy is uncommon. At the time of initial diagnosis, a 10% to 20% rate of lymphatic involvement is noted in patients with carcinoma of the maxillary sinus. The incidence increases up to 35% during the course of the disease.[6–10] Lymphatic spread for lesions originating from the ethmoid sinus is less common and ranges from approximately 5% to 10%.[11–13] The propensity for lymphatic and distant spread of disease additionally varies based on the tumor histology and grade. The retropharyngeal location of the majority of lymphatics implies inaccessibility during routine examination and is evaluated by imaging studies. Additionally, the surgical treatment implications for this pattern of spread are significant as the first echelon nodes are not routinely accessible at the time of resection and are better addressed with radiation therapy. The unusual presentation of a sinonasal cancer with a cervical metastasis may portend a locally advanced lesion and/or aggressive histology.

### Benign Lesions

The differential diagnosis of sinonasal lesions is extensive and requires multimodality evaluation including endoscopic examination, radiography, and histopathology. Although this chapter primarily discusses malignancy, certain nonneoplastic processes can mimic the former and must be considered at the time of evaluation. One of the central challenges of successful detection of a sinonasal malignancy is differentiation from more common, inflammatory conditions including allergic rhinitis and sinusitis. Adding confusion to the issue is the frequent coexistence of sinusitis and neoplasm. Tumor growth may obstruct sinonasal outflow tracts and precipitate secondary infection. Older age at presentation, unilateral disease, symptoms, and examination findings consistent with aggressive behavior are more suggestive of malignancy and should increase clinical suspicion. These issues highlight the importance of close examination of preoperative imaging and collection of all sinus specimens for histology in patients undergoing surgery for presumed inflammatory sinusitis. An expanded discussion of two benign conditions, inverted papilloma and juvenile nasopharyngeal angiofibroma, is presented below given their clinical importance and the specific challenges associated with these lesions. The salient features of the other benign and inflammatory lesions that should be considered in the evaluation of a patient with a sinonasal lesion are presented in Table 20.1.

### Inverted Papilloma

Several different types of papilloma are identified in the sinonasal cavity. Squamous papilloma related to human papillomavirus (HPV) infection has a predilection for the nasal vestibule. Although local excision is considered curative, surveillance of the initial site and the remainder of the upper aerodigestive tract is required. Three different types of papilloma arising from the Schneiderian (respiratory) mucosa have been described. Although these lesions differ in their anatomic predilection and clinical behavior, the ultimate distinction requires histopathological analysis. Everted papilloma (fungiform) typically arise from the septum and are curable with local resection. Everted fronds of epithelium are noted on histology. Cylindric papillomas are rare and are similar in histology to everted papilloma. These latter two lesions are not felt to have significant malignant potential.

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**TABLE 20.1 Benign Sinonasal Lesions**

| Diagnosis | Salient Features |
|---|---|
| Acute invasive fungal sinusitis | Immuno-compromised host including neutropenia and poorly controlled diabetes; rapid tissue destruction; invasive fungal forms on histology; treated with wide local debridement, systemic antifungal therapy and reversal of immuno-compromised state if possible |
| Allergic fungal sinusitis | Atopic and immuno-competent host; polypoid changes with potential for bony erosion and expansion; characteristic radiographic features, allergic mucin and histology; treated with endoscopic sinus surgery, anti-inflammatory therapy |
| Fungal ball (mycetoma) | Immuno-competent host; single affected sinus with potential for bony expansion; characteristic radiographic features; treated with endoscopic opening of the affected sinus and removal of lesion |
| Granulomatous disease (Wegener granulomatosis, sarcoidosis, mycobacteria, syphilis) | Diffuse mucosal inflammation, granulation, and potential for tissue destruction especially the nasal septum; histology and systemic evaluation required; treated with systemic therapy |
| Osteoma | Most common benign sinonasal tumor, primary tumor of mature lamellar bone with characteristic radiographic findings; may be silent or cause local symptoms and/or sinus obstruction; surgical removal if symptomatic, enlarging, or obstructive |
| Fibrous dysplasia | Replacement of normal bone by fibroblasts and collagen; characteristic radiographic appearance; generally observed |
| Pyogenic granuloma (lobular capillary hemangioma) | More common in females especially around pregnancy, most commonly located on the anterior septum and the inferior turbinates, frequently associated with recurrent epistaxis, treated with wide local excision |
| Neurogenic tumors (schwannoma and neurofibroma) | Arise from peripheral nerves; potential for malignancy (neurofibroma); characteristic radiographic appearance; surgery considered for enlarging or symptomatic lesions |

Inverted papilloma most commonly arise from the lateral nasal wall of the nasal cavity but may occur anywhere in the sinonasal tract. The overall incidence is estimated to be between 0.5 and 1.5 cases per 100,000 per year.[14,15] The etiology of inverted papilloma remains unclear and theories suggesting inflammatory and viral (HPV) origin have been described.[16,17] The name arises from the characteristic histological finding of infolded projections of the epithelium into the underlying stroma. Recurrence after treatment may occur in up to 20% of lesions even with aggressive initial surgery. The potential for synchronous or metachronous transformation to squamous cell carcinoma has been described. A wide range of transformation rates has been described, with the majority of series reporting a rate of approximately 10%.[18] There is some uncertainty of the number, however, because carcinoma *in situ* changes occur on the surface of the papillomas. To condemn such lesions as malignant papilloma may be an overstatement, especially since the percentage of them that go on to full-blown malignancies is unknown.

Although medial maxillectomy through a transfacial, lateral rhinotomy approach has historically been considered the treatment of choice for inverted papilloma, application of endoscopic techniques for resection of these lesions has demonstrated favorable results. Avoidance of an external incision is an obvious advantage over the more traditional procedures.[19–21] Additionally, the endoscopic approach can be tailored to the specific site and extent of lesion, allowing for complete tumor removal and preservation of functional sinus physiology (Fig. 20-16). Although unsubstantiated by conclusive data, most experienced endoscopic surgeons believe the critical factor associated with successful surgical management of inverted papilloma lesions is identification of the site of origin and drilling of the underlying bone. This is greatly facilitated with the panoramic visualization

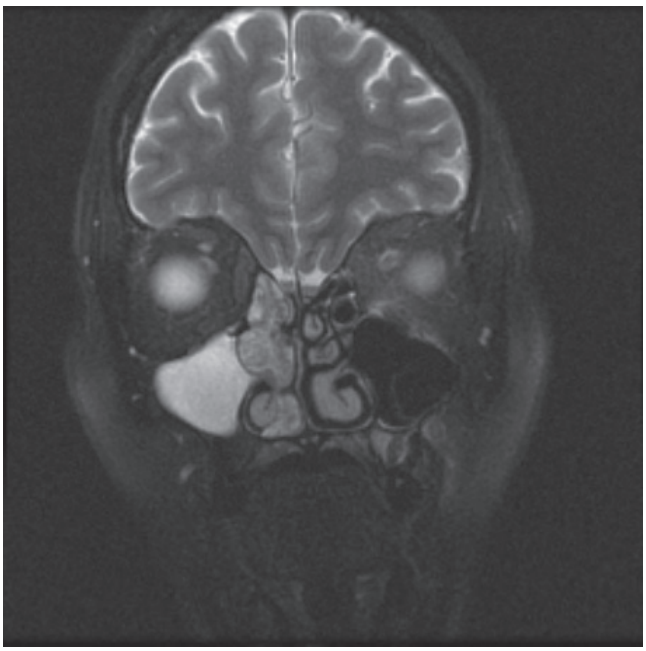


**FIGURE 20-16.** Postcontrast, coronal T-2 weighted MRI of a sinonasal inverted papilloma with involvement of the right nasal cavity, the middle turbinate, the infundibulum, and the ethmoid sinus. Postobstructive pattern without tumor involvement noted in the right maxillary sinus. This lesion is potentially amenable to endoscopic resection.

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provided by endoscopy. In a large meta-analysis of surgical treatment for inverted papilloma, Hwang et al. reported a lower rate of recurrence (12% vs. 20%) in patients treated endoscopically versus conventional surgical means.[22]

## Juvenile Nasopharyngeal Angiofibroma

Juvenile nasopharyngeal angiofibroma (JNA) accounts for approximately 0.05% of all head and neck tumors and has an estimated incidence of 1:150,000.[23,24] These lesions occur exclusively in males and are most common in the second decade of life, likely secondary to androgen hormone responsiveness. The most common site of origin is the area around the sphenopalatine foramen and multiple potential patterns of local spread may exist. Medial spread occurs into the sinonasal cavity and nasopharynx with limited resistance. Lateral extension occurs into the pterygopalatine and infratemporal fossa. Posterior-superior growth may involve the sphenoid sinus and cavernous sinus. Erosion of the sphenoid bone may result in intraorbital and intracranial extension (middle cranial fossa). The most common presenting symptoms include nasal obstruction, epistaxis, facial pain, headache, and facial swelling. Symptoms related to orbital, sinonasal, and Eustachian tube mass effect may also occur. Endoscopic examination reveals a hypervascular appearing soft tissue mass.[23]

A combination of CT and contrast-enhanced MRI are used to characterize JNA lesions including the soft tissue extension, bony erosion, anterior bowing of the posterior maxillary wall (Holman-Miller sign), and vascularity (Fig. 20-17). The characteristic imaging studies combined with patient demographics is typically adequate for pretreatment diagnosis. Office-based biopsy is associated with the potential for extraordinary hemorrhage and should not be performed for suspected JNA. Histopathology from surgical specimens demonstrates a complex and heterogeneous proliferation of blood vessels with absent or thin elastic laminae and variably thick vascular walls. A background collagen matrix with spindle-shaped cells is noted around the blood vessels.[25] Extensive vascular arcades may be identified on angiography with the predominant vascular supply arising from the internal maxillary artery and a minor contribution possibly arising from the ascending pharyngeal artery, the internal carotid artery, and the contralateral external carotid artery system. Several staging systems have been proposed as described by Sessions, Chandler, and Fisch.[26–28] Staging is essential for reporting of treatment outcomes and possibly for predicting the prognosis for recurrence. For clinical purposes, the critical aspects of "advanced" disease that impact surgical planning include extension to the infratemporal fossa, the orbit, the cavernous sinus, and the middle cranial fossa.

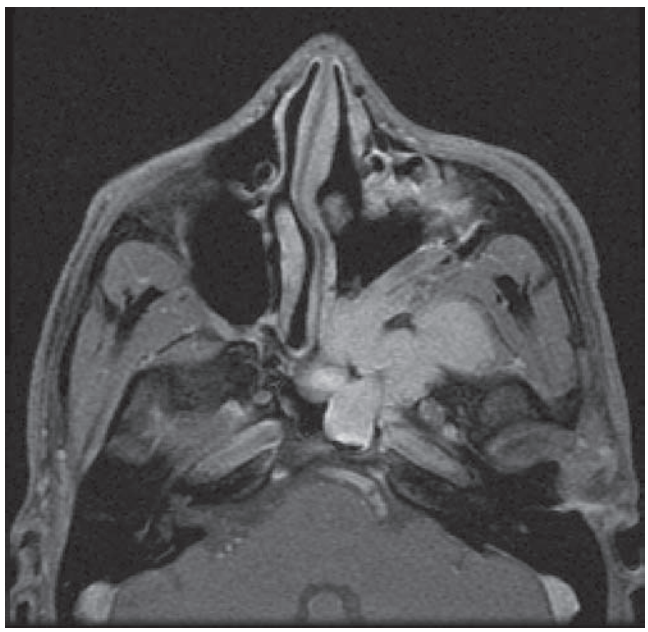


**FIGURE 20-17.** Axial postcontrast, fat-suppressed T-1 weighted image demonstrating a large, recurrent juvenile nasopharyngeal angiofibroma with multicompartmental involvement including the sphenoid sinus, the pterygopalatine fossa, and the infratemporal fossa.

Surgery represents the primary treatment modality for JNA. Although local control has been associated with radiation therapy, the potential long-term adverse effects in this young population (secondary malignancy, oribital and intracranial dysfunction) limit its use to unresectable and enlarging lesions.[29–31] Not surprising, given the complex anatomic location of JNA lesions, multiple surgical approaches have been described. The hypervascularity of these lesions is counteracted by presurgical angiography and emobilization. Choice of the available surgical approaches is based on the location and extent of the lesion. Open skull base approaches include midface degloving, facial translocation, lateral rhinotomy, transpalatal, craniofacial, and subcranial approaches. The application of expanded endoscopic techniques has rapidly emerged as a meaningful primary treatment modality for the majority of JNA lesions. Excellent tumor control rates have been reported from multiple centers with an overall favorable perioperative morbidity profile including decreased blood loss, shorter hospital stay, and avoidance of facial incisions. Lateral access to the infratemporal fossa and masticator space can be achieved with limited additional morbidity by the inclusion of a sublabial incision and a limited bony opening through the maxillary antrum.[32–36]

Regardless of the approach, a significant risk of recurrence is associated with JNA with reported rates ranging from 15% to 45%. The likelihood of recurrence correlates with the stage and location of the primary lesion especially if there is bony skull base involvement, prior history of recurrence, and an incomplete resection of both the soft tissue and bony components. Routine surveillance imaging with MRI scan is advocated to identify early recurrence of lesions.[37–39]

# MALIGNANT LESIONS

The World Health Organization has described a histological classification of primary sinonasal malignancies with categories based on the tissue type: epithelial, soft tissue, bone and cartilage, hematolymphoid, and neuroectodermal. More than 25 types are listed. The more common lesions are briefly discussed.[40]

## Squamous Cell Carcinoma

Squamous cell carcinoma is the most common sinonasal malignancy accounting for 70% to 80% of malignant tumors. The most common site of origin for sinonasal SCC is the maxillary sinus cavity, followed by the nasal cavity and the ethmoid sinus.[41–43] A possible association between tobacco inhalation and sinonasal SCC has been described,[44,45] although this is unclear. The potential malignant transformation of inverted papilloma, especially when recurrent, has also been well described[46–48] (Fig. 20-18). The majority of patients with sinonasal SCC present with advanced local disease (T3/T4). Although nodal disease is present at presentation in only 10% to 20% of cases, the incidence increases to 20% to 35% for recurrent lesions.[3,5,42,43]

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**FIGURE 20-18.** Coronal noncontrast CT scan of a patient with sinonasal squamous cell carcinoma with orbital involvement in the setting of inverted papilloma.

A higher incidence of nodal metastasis is associated with SCC of the maxillary sinus cavity compared with other sinonasal sites.[49] The presence of nodal disease is a poor prognostic sign.

## Adenocarcinoma

Adenocarcinoma represents the second most common primary malignancy of the paranasal sinuses, accounting for up to 20% of lesions. These lesions are more commonly localized to the superior aspects of the nasal vault and ethmoid sinuses and have been associated with a history of industrial inhalant exposures, especially wood dust and leather.[50–53] The possibility of the combined carcinogenic effects of industrial chemicals and wood dust has been described by Wolf et al. in a study of dysplastic changes occurring in a cohort of factory workers.[54] Adenocarcinoma accounts for >50% of malignant lesions of the ethmoid sinus and has a propensity for intracranial spread.[55,56]

## Minor Salivary Gland Malignancies

Mucoepidermoid and adenoid cystic carcinomas originate in the minor salivary glands and can involve the paranasal sinuses. Together they make up fewer than 15% of all cases of salivary gland tumors.[57] As in other sites of the head and neck, adenoid cystic carcinoma of the sinonasal cavity has a propensity for perineural spread and delayed recurrence.[58] Despite aggressive surgery, positive histologic margins and skip lesions may occur.

## Neuroendocrine Tumors

Neuoendocrine lesions are theorized to arise from the neuroectoderm of the nasal cavity and include esthesioneuroblastoma, sinonasal undifferentiated carcinoma, small cell carcinoma, and neuroendocrine carcinoma. The prognosis for this group of disorders correlates strongly with histology[59]; esthesioneuroblastoma have the best prognosis and small cell carcinoma the worst. Histopathological differentiation of these lesions is challenging and is significantly aided by immunohistochemistry.

Esthesioneuroblastoma (olfactory neuroblastoma) arises from the neural crest cells in the olfactory epithelium of the superior nasal and sinus cavity. A bimodal age distribution is identified at 10 to 20 and 50 to 60 years of age. The gross morphology varies and may be either polypoid or sessile. A propensity for intracranial spread through the olfactory nerve bundles and the cribriform plate is noted. Cervical lymph node and distant metastasis (lung, bone) occur in 10% to 15% during the course of the disease and may be delayed.[60–66] Histopathology reveals rosettes of neuroblastoma cells with varying degrees of differentiation. Immunohistochemical staining with neural markers is positive for neurospecific enolase, S-100 protein, and neurofilament protein.

The Kadish staging system divides lesions into stage A (confined to the nasal cavity), stage B (involving the paranasal sinuses), stage C (extending beyond the sinonasal cavity), and stage D (regional or distant spread).[67] A large review in 1997 identified 945 cases of esthesioneuroblastoma published in the literature.[60] This and other reports have noted improved survival and disease control rates with combination radiation therapy and surgery. However, a significant incidence of local (50%–75%) and regional (20%–30%) recurrences is expected.[60] The correlation of overall outcomes to the histopathological tumor grade as described by Hyams et al.[64] has been reported in several independent series. Five-year disease-free survival rates are noted to be significantly improved in patients with low-grade (65%–80%) versus high-grade (12%–25%) tumors.[61–66] The greatest experience to date in the surgical management of these lesions is the craniofacial approach which addresses both the sinonasal and intracranial aspects of the tumor through *en bloc* resection. The collective experience of endoscopic resection of these lesions has suggested comparable early outcomes for select lesions.[68–78]

Sinonasal undifferentiated carcinoma (SNUC) is a unique tumor that is characterized by extremely malignant behavior with a propensity for local recurrence, distant metastasis, and poor overall survival. The diagnosis can be difficult given the rarity of these lesions and their histopathologic similarity to other poorly differentiated neuroendocrine tumors, such as high-grade esthesioneuroblastoma. Histopathology reveals poorly differentiated or undifferentiated small and medium-sized polygonal cells with vascular and perineural invasion, high mitotic rates, high nuclear to cytoplasmic ratios, and tissue necrosis. Positive immunohistochemical staining with epithelial membrane antigen and cytokeratin is noted. Although the ideal treatment for these lesions remains controversial, multimodality therapy including neoadjuvant chemoradiation followed by surgery in resectable cases may result in improved overall outcomes. Despite their overall poor prognosis, dramatic response to chemoradiation has been described.[79–82]

## Mucosal Melanoma

Mucosal melanoma constitutes approximately 3% of all sinonasal malignancies and 1% to 2% of all malignant melanoma. A significantly worse prognosis compared with cutaneous lesions is noted.[83,84] The most common sites are the nasal septum, the maxillary sinus, and the ethmoid sinus, respectively. Examination reveals a soft tissue lesion with variability in pigmentation. Melanin is identified in approximately two-thirds of lesions. Positive immunohistochemical staining for vimentin, HMB-45, and S-100 protein is confirmatory. Therapy typically involves a combination of wide surgical resection and radiation therapy. Long-term survival is poor with 5-year survival rates ranging from 10% to 47%. Negative prognostic factors include older age

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at presentation, poorly or undifferentiated histology, recurrent lesions, and occurrence of regional or distant spread.[83,85–87]

## Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is the most common sinonasal malignancy in children and is felt to arise from mesenchymal progenitor cells of skeletal muscle. The orbit is the single most common site of head and neck RMS with the nasal cavity and paranasal sinuses representing 14% and 10%, respectively, of head and neck sites of occurrence. The histological subtypes include embryonal, alveolar, and pleomorphic. Localization to the primary site and embryonal subtype appear to be favorable factors. The treatment for these lesions has evolved significantly over the past 40 years, largely due to the work of the Intergroup Rhabdomyosarcoma Study Group (IRSG).[88,89] Multimodality therapy including surgery, radiation, and chemotherapy is typically indicated.[88–91] The role of surgery may be limited to tissue diagnosis in patients with small, metastatic or unresectable lesions. In patients with localized and resectable disease, a wide local excision with preservation of function and cosmesis is generally advocated prior to chemoradiotherapy. The staging and outcomes following treatment for rhabdomyosarcoma are directly correlated to the adequacy of the surgical resection.[88–90] In patients with RMS of the sinonasal cavity, a high incidence of parameningeal involvement is noted. This is noted by the presence of cranial nerve palsy, skull base erosion, and intracranial extension of the tumor. The morbidity and overall poor outcomes of surgery in this area has prompted protocols based on chemoradiation without surgery as defined by the IRSG with 5-year survival rates of 74%.[91]

## Hemangiopericytoma

Hemangiopericytoma are rare vascular lesions arising from the pericytes of Zimmerman, found on the outside of capillaries. These lesions are felt to be low-grade malignancies. Although metastases from these lesions are rare, the propensity for aggressive local behavior and recurrence after inadequate resection has been described. The majority present with some degree of epistaxis and a soft, pale, rubbery lesion on endoscopy.[92,93] The majority of lesions are treated with aggressive local surgery with radiation reserved for unresectable disease.[94]

## Lymphoma

Lymphoma may primarily involve the sinonasal cavity and is more commonly of the non-Hodgkin variety. The symptom complex may correlate with the histological grade with low-grade lesions presenting as a nasal mass with obstruction and epistaxis and high-grade lesions presenting with local tissue destruction, cranial nerve paresis, and facial swelling. Destruction of the nasal septum by what was previously referred to as "midline lethal granuloma" likely represents T-cell lymphoma. The origin of these lesions from natural killer cells is suggested by their positive staining for CD56.[95–98] The role of surgery in sinonasal lymphoma is largely limited to tissue diagnosis and treatment relies on a combination of chemotherapy and radiation. The majority of patients present with only local, extranodal disease although both local and distant spread are possible. The overall prognosis is dependent on stage and grade with 5-year overall survival rates ranging from 25% to 65%.[99–101]

## Etiology and Pathogenesis

The pathogenesis in the majority of cases of sinonasal malignancy is unknown. Multiple inhalant exposures have been linked to an increased risk of sinonasal adenocarcinoma especially of the ethmoid sinus including wood dust, aflatoxin, heavy metals, industrial chemicals, and leather tanning.[54,102–104] The reported interval between exposure and occurrence of disease ranges from one to five decades. Although heavy tobacco and alcohol have not historically been implicated as risk factors for paranasal sinus malignancy, an association of tobacco exposure and sinonasal SCC may exist.[44,45] Additionally, the occurrence of synchronous and metachronous SCC in the setting of inverted papilloma has been well documented and may occur in up to 10% of cases.

## Patterns of Spread

The presence of advanced local disease at the time of initial presentation in the majority of patients with sinonasal malignancy is due in part to the readily accessible pathways for spread. The pattern of tumor extension to adjacent structures is based on multiple factors including the location of the original lesion, presence of preformed channels, and histopathology. Lesions originating from the nasal vestibule and the nasal cavity may spread to the nasal soft tissue, the lateral nasal wall, the nasal septum, or floor of the nasal cavity into the premaxilla. The propensity for perineural spread is noted in patients with minor salivary gland lesions, especially adenoid cystic carcinoma.

The pattern of spread from primary lesions of the maxillary sinus is variable and may involve any of the surrounding structures. The relatively thin anterior maxillary wall that separates the sinus from the soft tissues of the face may be eroded directly. Inferior spread will result in oral and dental symptoms and may occur either through direct bony destruction or the dental roots. Spread superiorly into the orbit may similarly occur through the infraorbital canal or destruction of the orbital floor itself. The area around the natural maxillary sinus ostium allows somewhat unimpeded spread of tumor into the nasal and the ethmoid cavity. From there, further spread intracranially may occur as in primary ethmoid lesions. Finally, lateral and posterior extension into the infratemporal and the pterygomaxillary fossa, respectively, may occur through direct bone erosion.

Involvement of surrounding structures is noted at the time of initial diagnosis in the overwhelming majority of patients with malignancies of the ethmoid sinus. Inferior spread into the nasal cavity and the maxillary sinus occurs with minimal impedance. Spread to the frontal and the sphenoid sinuses may similarly occur through the natural recesses. Intracranial extension involves either direct bony destruction or passage of tumor through preformed neurovascular channels. Areas of naturally thin bony separation, including the fovea ethmoidalis and the lamina papyracea, allow intracranial and intraorbital spread of ethmoid lesions. The cribriform plate can also allow intracranial spread through its multiple perforations that provide nasal entry for olfactory nerve projections. Lesions involving the ethmoid sinus can spread along the anterior and the posterior ethmoidal neurovascular bundles to the intracranial cavity. Extension to the middle cranial fossa from paranasal sinus lesions may occur through the orbital apex or the lateral sphenoid wall. Involvement of the orbital apex is particularly ominous given the intimate relationship of the optic canal and the superior orbital fissure to the intracranial cavity.

The frontal and the sphenoid sinuses are infrequently the initial site of sinonasal malignancy and are more commonly involved secondarily by spread from adjacent locations. The potential directions of spread from the frontal sinus may include the superior orbit, the anterior cranial fossa, and the facial soft tissue. The bony confines of the frontal sinus serve as barriers to this spread, but microscopic communications do exist including valveless emissary veins between the posterior frontal sinus and the anterior cranial fossa (Behcet plexus). The sphenoid sinus has numerous potential pathways of spread including anteriorly into the ethmoid sinuses and the nasal cavities, inferiorly into

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the nasopharynx, laterally into the cavernous sinus, posteriorly into the clivus and the brain stem, and superiorly into the sella and anterior and middle cranial fossas. The morbidity of this pattern of spread and associated treatment challenges highlight the poor prognosis of advanced disease in this area.

## NASAL AND PARANASAL MALIGNANCY—CLINICAL PRESENTATION, EVALUATION, AND STAGING

### Clinical Presentation

The nonspecific symptoms and rarity of sinonasal neoplasms present a diagnostic challenge. Distinguishing early symptoms from inflammatory sinusitis requires a high index of suspicion and a delay in diagnosis is not uncommonly seen. Evaluation of patients with suspected sinonasal neoplasms incorporates clinical history, physical examination, radiography, and histology. Concerning clinical features include new onset of sinonasal symptoms at an older age, unilateral nasal polyps and masses, and symptoms atypical of sinusitis including facial hypesthesia, epiphora, diplopia, and orbital proptosis. The clinical manifestations of a given lesion are dependent on its size, invasiveness, and location. Common early symptoms associated with nasal cavity lesions include unilateral nasal obstruction, nasal pain, rhinorrhea, and epistaxis. Symptoms representing extension beyond the paranasal sinus cavity suggest advanced disease. Orbital signs and symptoms include proptosis, epiphora, diplopia, and decreased visual acuity. Soft tissue involvement of the face may result in facial swelling, cheek pain, and infraorbital hypesthesia. Symptoms localized to the oral cavity include trismus, pain, and dental hypesthesia and may result from direct erosion into the oral cavity or extension into the infratemporal and PPFs. Loosening of teeth, malocclusion, or expansion of the premaxilla resulting in ill-fitting dentures may also occur. Additional findings include a neck mass indicative of nodal spread and serous otitis media for tumors extending to the nasopharynx with involvement or obstruction of the Eustachian tube.

### Evaluation

The algorithm for evaluation and diagnosis and sinonasal malignancies is presented in Figure 20-19. Following a detailed history, the initial evaluation involves examination of the nose, the sinus

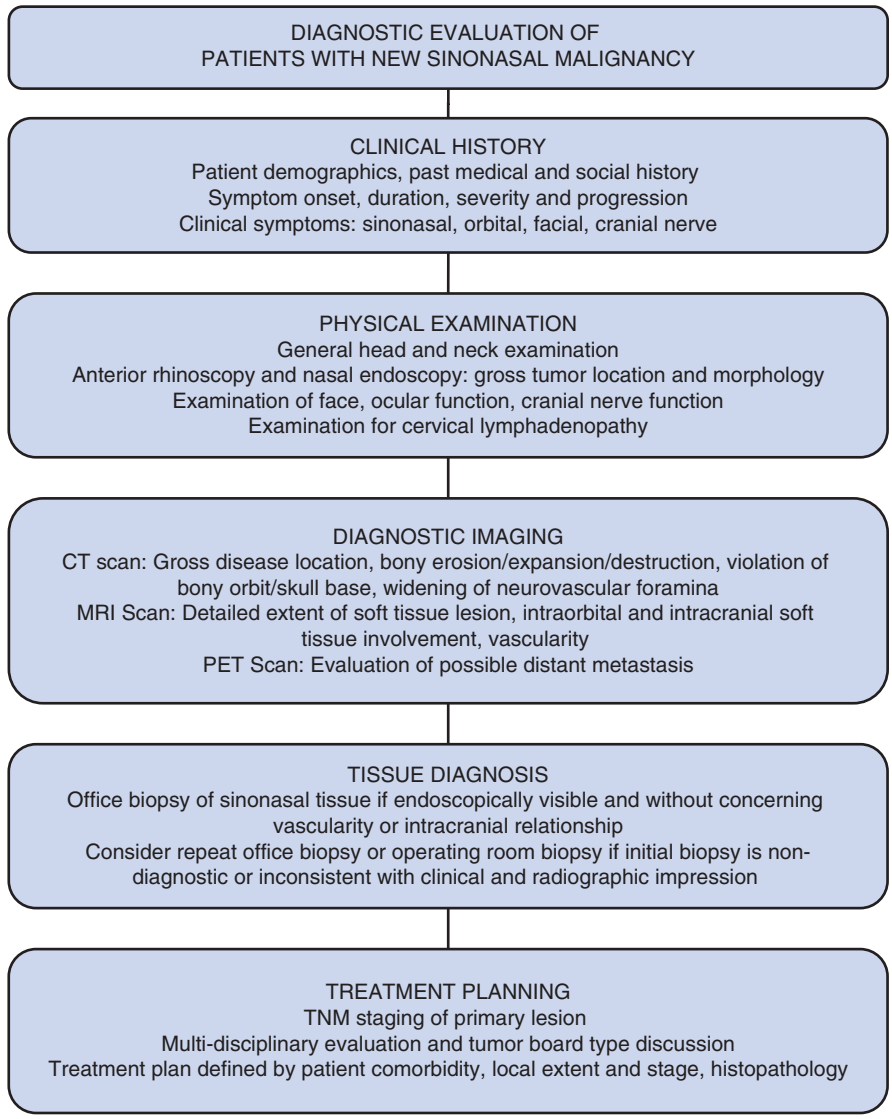



**FIGURE 20-19.** Algorithm for evaluation and diagnosis of sinonasal malignancies.

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cavity, the orbit, the face, the oral cavity, the cranial nerves, and the lymph nodes. Suspicious findings on endoscopy include unilateral, friable, and irregular changes of the mucosa. Unilateral nasal "polyps" should also raise suspicion for the possibility of malignancy. Lesions within the paranasal sinuses, however, are not directly visible unless they have extended beyond the sinus confines. Worrisome symptoms in the setting of a normal examination should prompt radiographic studies. Computed tomography (CT) and magnetic resonance imaging (MRI) provide complementary information in the evaluation of these lesions. Critical bony areas, including the walls of the paranasal sinuses, the skull base, the orbit, and the neurovascular foramina are best visualized by CT. Malignancy is suggested by erosion and destruction of bone in distinction to benign lesions which may result in bony expansion and displacement. Defining the soft tissue extent and distinguishing among neoplasm, mucosal edema, and retained secretions is, however, challenging with CT and is best achieved with gadolinium-enhanced MRI. Additionally, MRI is superior in identifying periorbital invasion and perineural spread for neurotropic tumors. Dural enhancement and intraparenchymal tumor extension are also better defined by MRI. The role of positron emitted tomography (PET) is still incompletely defined but may be useful in defining the extent of suspected metastases.

Histologic analysis of a suspected sinonasal lesion is critical in determination of ideal treatment modality and should be routinely performed prior to any intervention. Obtaining diagnostic tissue from a sinonasal lesion is associated with several challenges including the cavitary location, potential vascularity, and proximity to critical neurovascular structures. Office-based endoscopic-guided biopsies under local anesthesia may be performed after review of appropriate imaging studies for possible vascularity and intracranial extension of the tumor. Although the procedure has been shown to be overall safe, limitations in sensitivity and specificity do exist, likely related to sampling error. In patients with a suspicious lesion, extensive surgical biopsies may be appropriate in the setting of a negative office biopsy.[105,106]

## Staging

The 2009 American Joint Committee on Cancer (AJCC) staging of sinonasal malignancies incorporates a TNM classification scheme and is presented in Table 20.2.[107] Separate staging criteria for the primary tumor are described for maxillary versus nasal-ethmoid lesions. Specific staging of carcinomas arising from the frontal or sphenoid sinus is not addressed. The majority of patients present with advanced disease and the critical issue of resectability is suggested by the staging system as the distinction between stage T4a versus T4b. Although stage T4a is considered moderately advanced, lesions involving the orbit, soft tissue of the face, the pterygoid plates, the infratemporal fossa, the cribriform plate, the sphenoid sinus, and the frontal sinus are still often surgically resectable. In contrast, involvement of the orbital apex,

**TABLE 20.2 2009 American Joint Committee on Cancer Staging System for Sinonasal Malignancy**

**Primary Tumor (T)**

**Maxillary sinus**

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma *in situ*
- T1: Tumor limited to the maxillary sinus mucosa with no erosion or destruction of bone
- T2: Tumor causing bone erosion or destruction including extension into the hard palate and/or the middle of the nasal meatus, except extension to the posterior wall of the maxillary sinus and the pterygoid plates
- T3: Tumor invades any of the following: bone of the posterior wall of the maxillary sinus, the subcutaneous tissues, floor or medial wall of the orbit, the pterygoid fossa, or the ethmoid sinuses
- T4a: Tumor invades the anterior orbital contents, the skin of cheek, the pterygoid plates, the infratemporal fossa, the cribriform plate, the sphenoid, or the frontal sinuses
- T4b: Tumor invades any of the following: the orbital apex, the dura, the brain, the middle cranial fossa, the cranial nerves other than maxillary division of the trigeminal nerve ($V_2$), the nasopharynx, or the clivus

**Nasal cavity and ethmoid sinus**

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma *in situ*
- T1: Tumor restricted to any one subsite, with or without bony invasion
- T2: Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
- T3: Tumor extends to invade the medial wall or floor of the orbit, the maxillary sinus, the palate, or the cribriform plate
- T4a: Tumor invades any of the following: the anterior orbital contents, the skin of nose or cheek, minimal extension to the anterior cranial fossa, the pterygoid plates, or the sphenoid or frontal sinuses
- T4b: Tumor invades any of the following: the orbital apex, the dura, the brain, the middle cranial fossa, the cranial nerves other than $V_2$, nasopharynx, or clivus

*(continued)*

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**TABLE 20.2 2009 American Joint Committee on Cancer Staging System for Sinonasal Malignancy (Continued)**

**Regional lymph nodes (N)**

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension
- N2: Metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, ≤6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, ≤6 cm in greatest dimension
  - N2a: Metastasis in a single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension
  - N2b: Metastasis in multiple ipsilateral lymph nodes, ≤6 cm in greatest dimension
  - N2c: Metastasis in bilateral or contralateral lymph nodes, ≤6 cm in greatest dimension
- N3: Metastasis in a lymph node >6 cm in greatest dimension

**Distant metastasis (M)**

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

**AJCC staging**

**Stage 0**

- Tis, N0, M0

**Stage I**

- T1, N0, M0

**Stage II**

- T4a, N1, M0
- T4b, any N, M0
- Any T, N3, M0

**Stage IVC**

- T2, N0, M0

**Stage III**

- T3, N0, M0
- T1, N1, M0
- T2, N1, M0
- T3, N1, M0

**Stage IVA**

- T4a, N0, M0
- T1, N2, M0
- T2, N2, M0
- T3, N2, M0
- T4a, N2, M0

**Stage IVB**

- Any T, any N, M1

*Source:* American Joint Committee on Cancer. Nasal cavity and paranasal sinuses. In: Edge SB, Bryd DR, Compton CC, et al., eds. AJCC Cancer Staging Manual, 7th ed. New York: Springer, 2009:93–101.

extensive aspects of the intracranial cavity, the nasopharynx, or the clivus usually represent very advanced, and often unresectable, lesions. As with any staging system, there are a number of limitations of the current classification scheme including its uniform application to different histolopathologies with widely disparate behavior. Additionally, there may be a correlation between histolopathologic tumor differentiation and prognosis that is not addressed by the AJCC classification.

Lesions of the nasal vestibule are staged according to the 2009 AJCC system for primary cutaneous carcinomas excluding carcinoma of the eyelid: T1, tumor 2 cm or smaller in greatest dimension with fewer than 2 high-risk features; T2, tumor >2 cm

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or any size tumor with 2 or greater high-risk features; T3, tumor with invasion of the maxilla, the mandible, the orbit, or the temporal bone; T4, tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base. High-risk features applicable to the nasal vestibule skin refer to depth of invasion, perineural invasion, or poorly/undifferentiated histology.[108]

Several prior classification schemes have been described in the past.[109–112] Ohngren highlighted the negative prognostic significance of posterosuperior extension of maxillary sinus lesions. This was defined in a practical way by a line, termed "Ohngren's line," drawn from the medial canthus to the angle of the mandible.[109] Lesions extending posterosuperior to this line are more likely to be associated with locally advanced disease including extension into the orbit and the pterygomaxillary fossa. Surgical respectability is additionally more challenging for lesions above "Ohngren's line." His classification scheme additionally incorporated histologic grading and the presence of metastasis.

# ORBITAL TUMORS

## Tumors of the Orbit

Primary tumors of the orbital cavity are relatively rare. A variety of benign and malignant histopathologies have been described (Table 20.3). A detailed description of the diverse array of lesions that may occur is beyond the scope of this chapter. Any of the different tissue types found in the orbit may represent the origin of a neoplastic lesion. Additionally, the origin of the primary lesion may be outside of the orbit itself, as is the case with sinonasal lesions extending to the orbit and with metastatic lesions. The variety and rarity of these lesions represent a clinical challenge in diagnosis and treatment. This is further compounded by the need to differentiate a neoplastic process from more common disorders including Graves' disease, inflammatory lesions (i.e., orbital "pseudotumor"), and infection. Stratification of the differential diagnosis is based on age onset, time frame of symptom progression, clinical characteristics, and imaging findings. The spectrum of possible symptoms reflects the location, invasiveness, and growth pattern of the lesion. Potential symptoms include proptosis and swelling, pain, epiphora, change in visual acuity, diplopia, and drooping of the eyelid. The physical examination of a patient with a suspected neoplasm encompasses evaluation of visual acuity, visual fields, globe position (proptosis), extraocular muscle movement, pupil response, and examination for any visible lesions. Proptosis is the most common finding and is identified when the globe protrudes >18 to 20 mm beyond the orbital rim or if there is a >2 mm asymmetry between the two globes. Imaging studies including a combination of CT and MRI are useful for defining the anatomic relationships of the lesion and providing possible diagnostic characteristics including vascularity and surrounding bony changes. The role of pretreatment biopsy for primary orbital lesions is patient specific. Although FNA or open biopsy is indicated for most lesions, two important exceptions exist. Patients with radiographic evidence of vascular lesions should not undergo FNA given the risk of hemorrhage. Additionally, open biopsy is contraindicated in patients with suspected pleomorphic adenoma of the lacrimal gland given the risk of tumor seeding of the surgical field.

**TABLE 20.3 Common Benign and Malignant Orbital Lesions in Children and Adults**

| Benign and malignant orbital tumors | |
|---|---|
| Benign tumors in children | Dermoid or epidermoid cyst |
| | Neurofibroma |
| | Capillary hemangioma |
| | Lymphangioma |
| | Orbital glioma |
| | Arteriovenous malformations |
| Malignant tumors in children | Rhabdomyosarcoma |
| | Retinoblastoma |
| | Metastatic disease (neuroblastoma, Wilms tumor) |
| | Lymphoma/leukemia |
| Benign tumors in adults | Cavernous hemangioma |
| | Benign mesenchymal tumors (fibrous histiocytoma, solitary fibrous tumor, fibrous dysplasi, osteoma) |
| | Langerhans cell histiocytosis |
| | Hemangiopericytoma |
| | Meningioma |
| | Schwannoma |
| Malignant tumors in adults | Lymphoma |
| | Sinonasal/lacrimal gland lesions |
| | Metastatic lesions (breast, lung, prostate, renal cell |
| | Malignant melanoma |
| | Malignant nerve sheath tumors |
| | Osteosarcoma, chondrosarcoma, Ewing sarcoma, fibrosarcoma |
| | Cutaneous malignancy (squamous cell, basal cell) |
| | Fibrous histiocytoma |

## Tumors of the Lacrimal Gland

Primary tumors of the lacrimal gland account for approximately 5% to 25% of all orbital neoplasms. Twenty percent of these are related to epithelial lesions, and the remaining 80% are represented by inflammatory and lymphatic lesions. Of the primary epithelial neoplasms, approximately half are benign and half are malignant.[113–115] Several classification schemes have been described including those of the 1980 World Health Organization and those related to salivary gland disorders.[116,117] The most common benign neoplasm is pleomorphic adenoma and, as in their counterparts within the salivary glands, malignant transformation may occur. Up to 90% of lesions involve the orbital lobe. Primary resection through a lateral orbitotomy approach is indicated for the majority of these lesions.[118,119] Other benign tumors of the lacrimal gland include oncocytoma, myoepithelioma, hemangioma, dacryops, and dermoid cyst. The most common malignant neoplasm of the lacrimal gland is adenoid cystic carcinoma. Rarer lesions include malignant mixed tumor, adenocarcinoma, mucoepidermoid carcinoma, adenoid cystic carcinoma, squamous cell carcinoma, and lymphoma. Adenoid cystic carcinoma is associated with a poor overall prognosis with the most common cause of death secondary to intracranial disease.[120–122]

Clinical presentation of lacrimal gland tumors includes presence of a visible mass, proptosis, pain, and restriction in ocular movement with diplopia. Decreased visual acuity, optic disc

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swelling, and loss of trigeminal sensation are less common and may be associated with more advanced or more aggressive histopathology. CT imaging of suspected lacrimal gland neoplasms may help to differentiate a benign from a malignant process. Findings concerning for malignancy include irregular bone invasion and destruction, invasion of adjacent soft tissue structures, irregular surface, and calcification within the primary lesion.

## Tumors of the Lacrimal Drainage System

A variety of neoplasms may affect the lacrimal drainage system, with approximately 70% malignant in nature. The different histopathologies can be classified based on the tissue of origin: epithelial (70% of cases), mesenchymal (12% of cases), lyphoid (11% of cases), malignant melanoma (4% of cases), and other histopathologies (1% of cases).[123] Secondary lacrimal tumors may originate from other orbital structures, surrounding skin, sinonasal cavities, and rarely metastatic sites. Inflammatory lesions may additionally present with mass effect and may be confused for neoplasm. The most common epithelial neoplasms of the lacrimal system include papillomas, oncocytomas, benign mixed tumors, and fibrous histiocytoma.[124,125] The majority of benign neoplasms of the lacrimal drainage system can be managed by wide local excision.

Malignant neoplasms involving the lacrimal system may similarly arise from primary or secondary tissues of origin. Primary epithelial lesions include squamous cell carcinoma, transitional cell carcinoma, mucoepidermoid carcinoma, adenoid cystic carcinoma, and adenocarcinoma. Nonepithelial lesions include lymphoma and malignant melanoma. Management of primary malignancies is complex and individualized. Local resection of the lacrimal apparatus through a lateral rhinotomy approach may be indicated for localized lesions and when adequate clearance of margins can be achieved. Extensive resection including exenteration and inclusion of adjuvant therapy is indicated for more advanced disease.[124,125]

# TREATMENT OF NASAL AND PARANASAL SINUS MALIGNANCY

## General Considerations

The multidisciplinary team approach to the treatment of sinonasal neoplasms includes head and neck surgery, neurosurgery, radiation oncology, medical oncology, neuroradiology, ophthalmology, plastic surgery, and prosthodentics. Given the complexity of these lesions, the strategy is most effectively developed in a multidisciplinary tumor board. Treatment is based on the location, stage, and histology of the lesion (Fig. 20-20). Additionally, the presence of patient comorbidities may alter treatment planning given the physiologic stress associated with surgery, radiation therapy, and the increasing use of chemotherapy. In patients with histologically confirmed benign lesions, complete gross tumor removal with minimization of morbidity is typically indicated. Radiation therapy may be considered in select cases including unresectable lesions or unacceptable surgical morbidity. Surgery for malignancy is challenging given the need for complete tumor removal, the proximity of critical neurovascular structures, and need for functional and cosmetic restoration.

The contraindications to surgery remain controversial and may potentially include extensive involvement of the nasopharynx and the clivus precluding complete resection, especially when associated with internal carotid involvement. Bilateral orbital cavity or optic nerve involvement additionally represents a contraindication to surgery given the poor prognosis and the morbidity involved with surgery of this area. Involvement of the internal carotid artery represents a relative contraindication to surgery. Tumor involvement of either the brain or the cavernous sinus represents a poor prognostic sign and denotes an aggressive lesion. Although extension to these structures has traditionally been considered unresectable, surgical treatment has been described.[126] In contrast to primary brain malignancies, brain involvement from a sinonasal origin may spread in a continuous

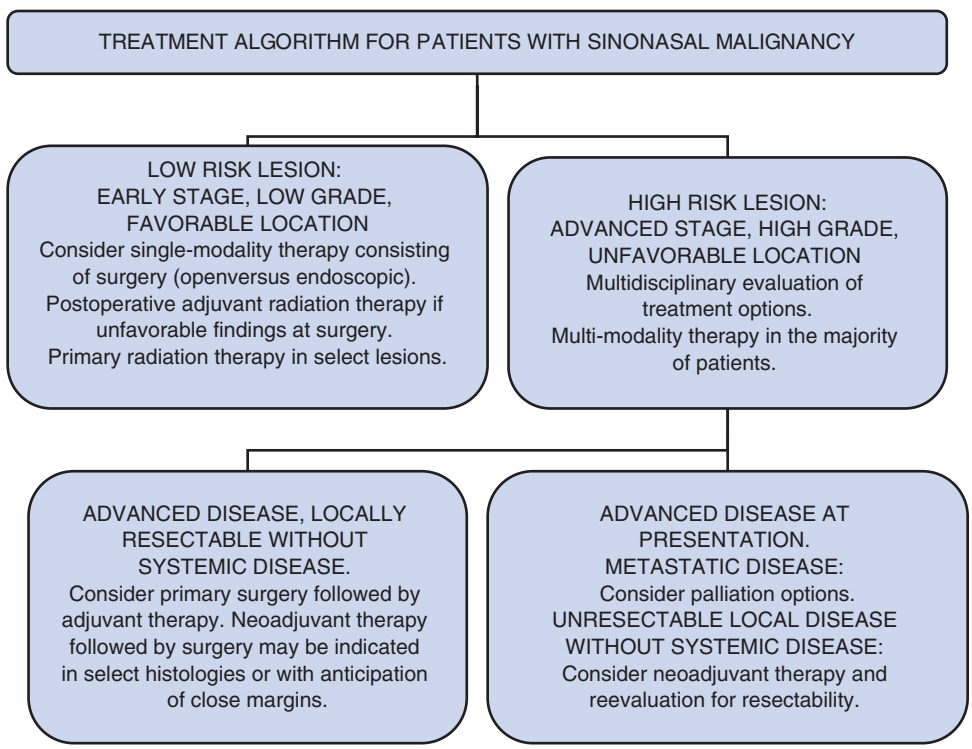



**FIGURE 20-20.** Treatment algorithm for patients with a new diagnosis of sinonasal malignancy.

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manner, reinforcing the possibility of local resectability. Multifocal leptomeningeal disease, however, may also occur and would be considered unresectable. Additionally, resection of a portion of the gyrus rectus of the frontal lobe may result in minimal functional deficits. In contrast, surgical resection of the cavernous sinus is extremely challenging given the presence of extensive venous network, the internal carotid artery, and multiple cranial nerves. Given the high morbidity and overall poor outcome of lesions involving the cavernous sinus, only selective lesions should be considered surgical candidates. The limits and indications for brain or cavernous sinus resection, however, are not clear, remain controversial, and are dependent on the specific clinical situation and the experience of the surgical team.

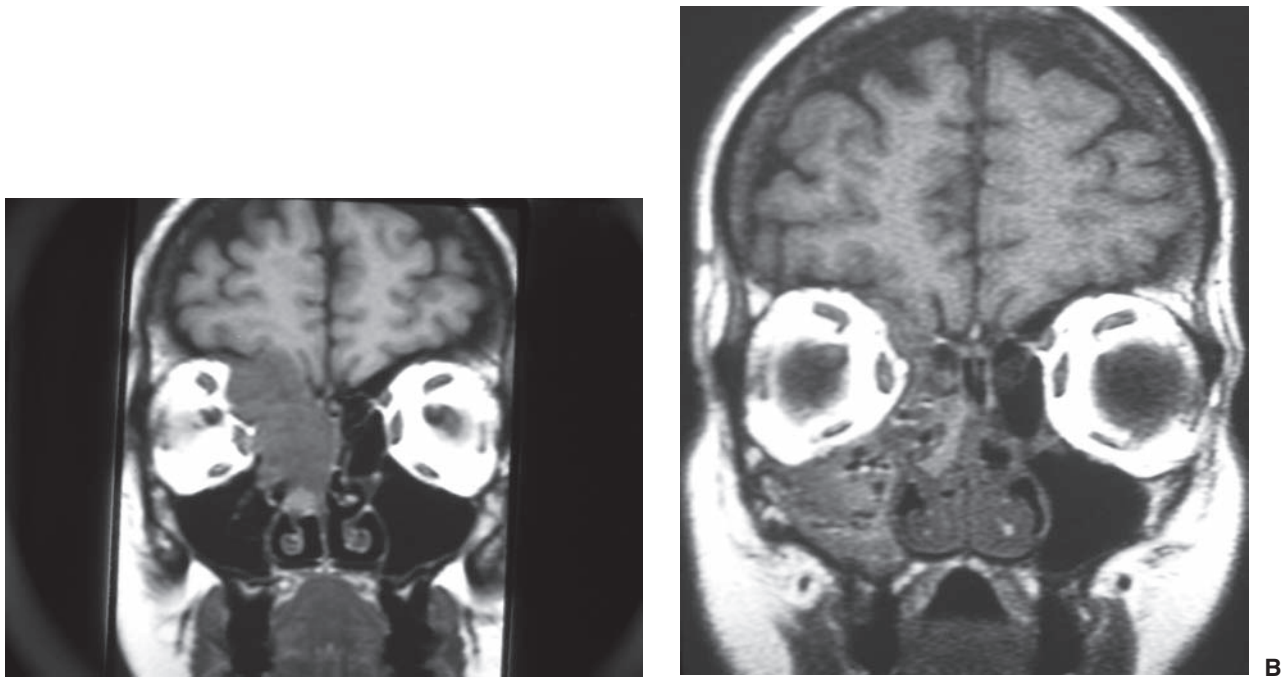
Regardless of the approach, tumor-free margins are essential in surgery for these malignancies. Given the overall poor prognosis, potential for aggressive behavior and limitations of therapy for recurrent disease, an optimum result requires an aggressive initial surgical treatment. The goal of negative margins typically requires multiple frozen section specimens at the time of surgery and extension of the resection to include positive areas. This is especially challenging in surgery for sinonasal malignancy. The majority of lesions are locally advanced at the time of initial presentation and have complex three-dimensional patterns of spread. Additionally, the neurotropism of certain lesions with the occurrence of skip lesions is responsible for residual disease potential despite negative histologic margins. Finally, the greatest obstacle to performing a wide local excision is the proximity of a given tumor to multiple critical neurovascular structures.

Early lesions (T1, T2), especially of the anterior nasal cavity and maxillary sinus, that are amenable to wide local excision may be treated with surgery alone. Multiple factors must be considered if surgery without radiation is planned for a small lesion including the anatomic confines of the tumor, the robustness of the resection, and the histolopathologic findings at the time of surgery including neurovascular extension. In patients who are poor surgical candidates secondary to medical comorbidities, such lesions may alternatively be treated with radiation therapy alone. The majority of patients, however, present with locally advanced disease and benefit from multimodality therapy including surgery, radiation therapy, and, possibly, chemotherapy. Patients with advanced, but resectable, disease are treated with surgery followed by radiation. In patients with unresectable disease, combined chemotherapy and radiotherapy are indicated with consideration of subsequent surgery when there is a positive response to treatment (Fig. 20-21). The role of chemotherapy in patients with resectable disease, however, is not clear and is largely dependent on histopathology. For example, chemotherapy is incorporated in the initial treatment protocol in the majority of patients with sinonasal undifferentiated carcinoma and rhabdomyosarcoma.

Given the overall low incidence of nodal involvement (<20% at presentation) in patients with sinonasal carcinoma, treatment of the neck is indicated only with clinically or radiographically positive disease. The management of the neck in patients with locally advanced disease without evidence of neck disease is not clear. A 20% overall incidence of nodal involvement during the course of treatment has been described and suggests the possible need for additional management of the neck. Possible strategies include observation alone, staging neck dissection at the time of initial surgery or elective radiation therapy to the neck. The latter approach is supported by the significantly lower incidence of both lymph node failure and distant metastasis in patients who received elective radiation therapy to the neck.[7,8,13]

## Surgical Therapy

If resectability is suggested by preoperative assessment, the surgical planning involves determination of the tumor boundaries and reconstructive requirements. The surgical procedure



A B

**FIGURE 20-21.** Squamous cell carcinoma of the ethmoid sinus with intracranial and intraorbital extension **(A)**. Significant reduction of the tumor volume noted following induction chemo-radiation **(B)**.

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for sinonasal malignancies can be classified based on the approach and the anatomic boundaries of the resection. The transfacial approach may incorporate variations of several different facial incisions. The lateral rhinotomy incision begins adjacent to the medial eyebrow, extends halfway between the nasal dorsum and the medial canthus running inferiorly along the lateral aspect of the nose at the boundary of the aesthetic subunits and terminates around the nasal ala. The lateral rhinotomy incision allows for adequate exposure of the nasal septum, the medial maxilla, the ethmoid sinus, the sphenoid sinus, and the medial orbital wall. Extension of the lateral rhinotomy to incorporate incisions of the upper lip and lower eyelid is termed the Weber-Ferguson incision and additionally allows for exposure of the inferior and the lateral maxilla, the nasal floor, the lateral orbit, and the infratemporal fossa (Fig. 20-22).

The midfacial degloving allows for exposure of the entire bony midface without external facial incisions. A sublabial incision allows for subperiosteal elevation of the soft tissues over the anterior maxilla. Exposure of the nasal cavity involves a combination of a complete transfixion and intercartilagenous and pyriform aperture incisions with dissection of the nasal soft tissue. Transcranial approaches may incorporate a bifrontal craniotomy or subcranial approach. The versatility of the midfacial degloving allows for exposure of the nasal cavity, the nasopharynx, and the maxillary sinus. With additionally bony removal, the exposure can be extended to the pterygomaxillary space and the infratemporal fossa.

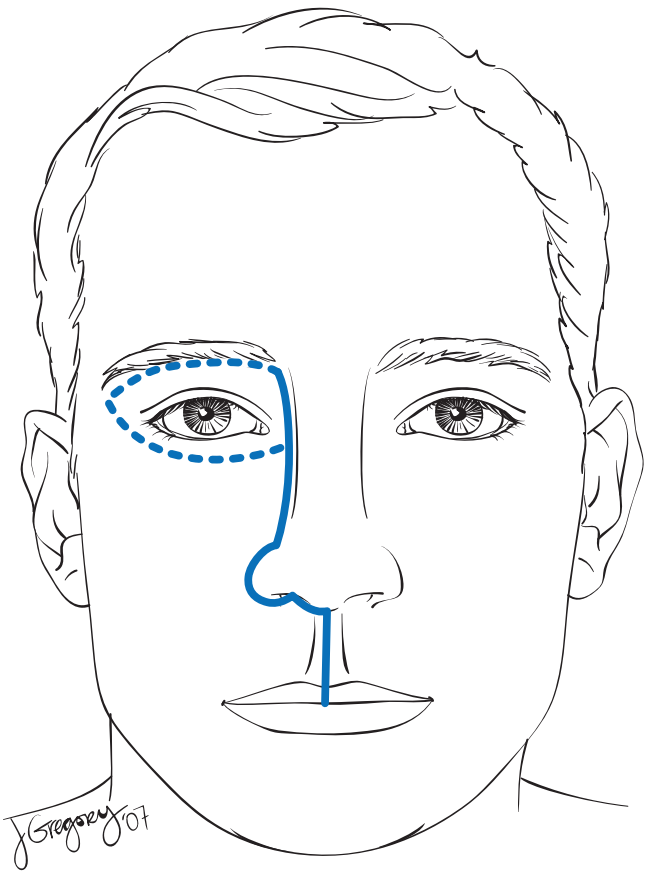



**FIGURE 20-22.** The lateral rhinotomy incision (*solid line*) can be extended to encompass the orbit (*dashed line*) as indicated.

## Medial Maxillectomy

Medial maxillectomy allows for *en bloc* resection of the lateral nasal wall including the inferior turbinate and the ethmoid sinus, and the medial orbital wall if necessary (Fig. 20-23). Following either a lateral rhinotomy or a Weber-Ferguson incision, a facial flap is elevated off the anterior maxilla. The angular vessels are identified medial to the medial canthus and ligated. The periosteum over the anterior face of the maxillary sinus is elevated with identification and preservation of the infraorbital nerve. The medial canthal ligament is mobilized in a subperiosteal fashion and reapproximated at the end of the case to the area of the nasofrontal suture line with a nonabsorbable suture. The bony lateral rhinotomy cuts can be made either with an osteotome or powered drill and extends from the pyriform aperture to the frontal process of the maxilla. In patients where preservation of the orbit is anticipated, the medial orbital perichondrium is elevated off the lamina papyracea. The anterior and posterior ethmoidal arteries are controlled by surgical clips or bipolar. The lacrimal fossa may either be spared or is usually incorporated to the resection. The orbital contents are then retracted laterally while the medial orbital wall and the ethmoid sinuses are opened. Orbital retraction is maximized by transecting the proximal nasolarcrimal duct adjacent to the lacrimal sac. An inferior bony cut is made along the nasal floor from the pyriform aperture to the posterior maxillary wall. The posterior dissection is performed last as the exposure of this area is limited. Curved scissors may be used to separate the surgical specimen from the posterior maxillary wall. The surgical area is packed with packing material. Depending on the origin and extent of the lesion, this may be modified to incorporate less tissue. For example, the lateral nasal wall and the inferior turbinate alone may be resected for limited disease.[127,128] The management of the lacrimal duct during this surgery is variable. Transection of the duct without a formal reconstruction results in recannulation and normal tear drainage in the majority of patients. If ductal obstruction is a concern, a stent may be passed through the lacrimal system and left in place for 4 to 6 weeks as is done following dacrocystorhinostomy. Adequate exposure of small lesions localized to the nasal septum can be achieved either through a lateral rhinotomy, alarotomy, or midface degloving approach. These lesions may additionally be amenable to endoscopic resection.

## Infrastructure Maxillectomy

Infrastructure maxillectomy is indicated for lesions confined to the floor of the maxillary sinus, the hard palate, and the premaxilla, traditionally described as tumors below Ohngren line. The area of resection encompasses the maxillary floor, the gingival arch, the hard palate, and the lower lateral nasal wall (Fig. 20-24). These lesions more commonly arise from the oral cavity with secondary involvement of the maxillary sinus. In locally advanced lesions, the tumor may extend to involve the nasal cavity and the facial soft tissues. If the preoperative imaging suggests no significant involvement superior to the maxillary floor, a sublabial incision alone may be adequate. The osteotomy cuts are tailored to the extent of the lesion and may encompass the entire length of the premaxilla. Multiple reconstructive options are possible including free tissue transfer with an osteocutaneous free flap or placement of an obturator. Preservation of the soft palate promotes improved speech and swallowing function. A temporary prosthesis may be placed at the time of surgery and promotes rapid return to function.

## Radical Maxillectomy

Radical maxillectomy is indicated for locally advanced carcinoma of the maxilla with major involvement of the maxilla, the pterygomaxillary fossa, the orbit, and the ethmoid sinus.

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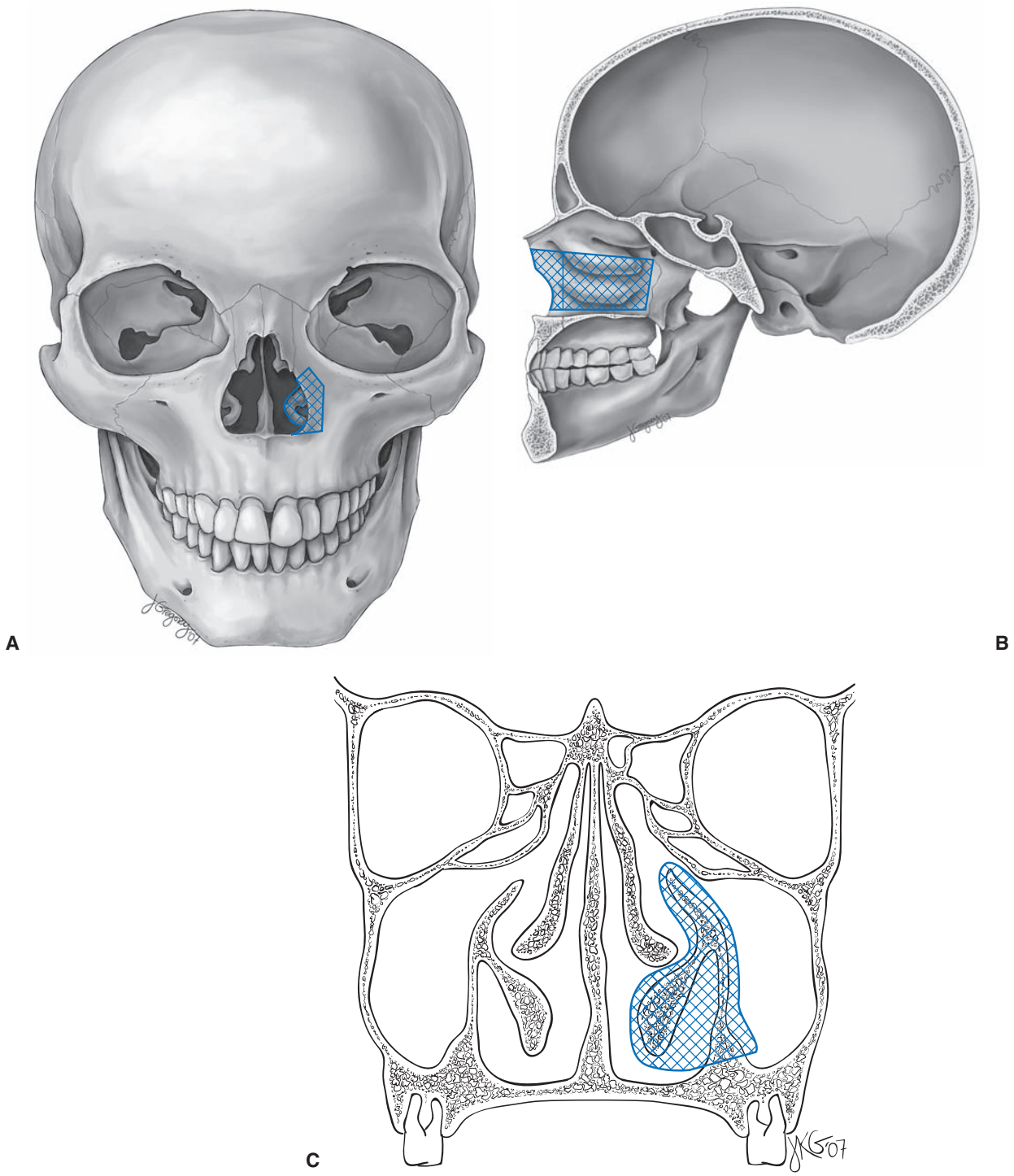



**FIGURE 20-23.** Frontal **(A)**, sagittal **(B)**, and coronal **(C)** views of the medial maxillectomy margins including the lateral nasal wall, the nasal floor, and the inferior turbinate. The margins of the resection can be extended to include portions of the lamina papyracea, the inferior orbital wall, the ethmoid sinus, the nasal septum, and the posterior maxillary wall as indicated.

A Weber-Ferguson incision is used for exposure of the anterior maxilla, the nasal bones, and the ethmoid sinus and may be extended to encompass the orbit. In patients where an orbital-sparing procedure is proposed based on preoperative imaging, the medial and inferior orbital walls are inspected during the time of surgery to confirm lack of involvement. Following the elevation of a facial flap, multiple bony cuts are made to mobilize the maxilla at the malar bone, the zygomatic arch, the hard palate, and the nasal process of the maxilla (Fig. 20-25). If possible, preservation of a portion of the premaxilla facilitates fitting of a prosthesis. The superior bone cuts are performed to encompass the ethmoid sinus at the frontoethmoid suture and necessary portions of the bony

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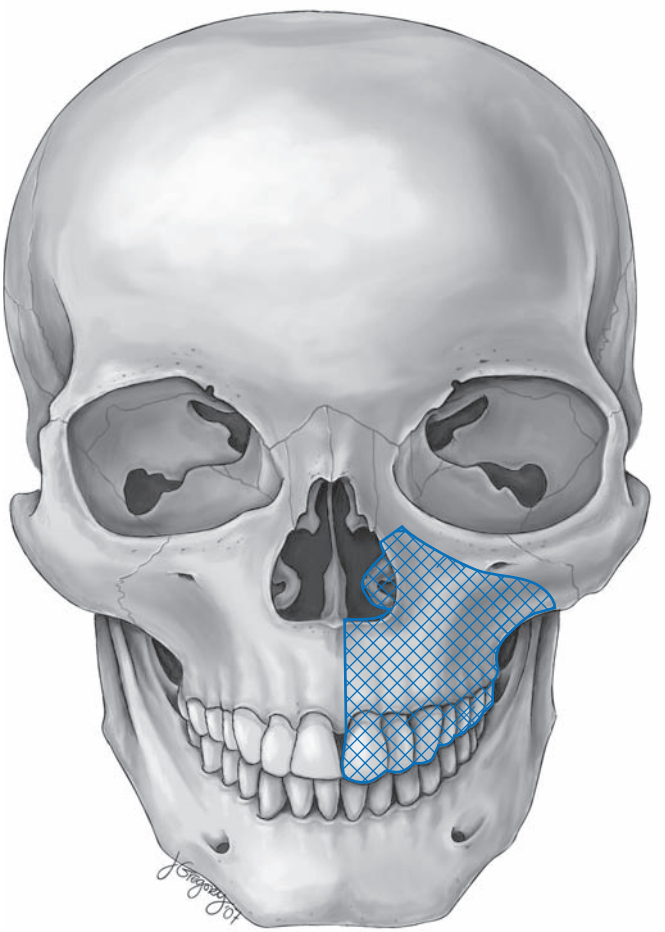


**FIGURE 20-24.** The surgical margins of the infrastructure maxillectomy include the upper gingiva and the dentition, the hard palate, the soft palate, the floor of the maxillary sinus, and the lateral nasal wall. Tumors amenable to this approach are often of oral cavity origin with extension superiorly.

orbit. The posterior cuts are based on the extent of tumor and can encompass either the posterior wall of the maxillary sinus alone or include the pterygoid plates. Anterior tumor extension may result in a partial or total defect of the nose. This may be addressed with a complex reconstruction or a prosthesis. Free flap reconstruction of the defect may also be performed depending on the reconstructive issues. The wound is packed and a temporary prosthesis should be placed. This approach may also include the ethmoid roof, the orbital contents, and the pterygomaxillary fossa as indicated by the location of the tumor.

## External Ethmoidectomy

External ethmoidectomy may be performed through a Lynch or lateral rhinotomy incision. This approach may be used for open excision of ethmoid sinus lesions and the medial orbital wall (Fig. 20-26). The exposure is limited notably in the area of the skull base and is indicated only in small, well-delineated lesions. The indications for this approach may also have become more limited with the increasing role of endoscopic surgery for small lesions. Surgical injury to the frontal recess predisposes to stenosis and chronic frontal sinusitis. Long-term stenting may help prevent this complication. Management of the lacrimal duct as

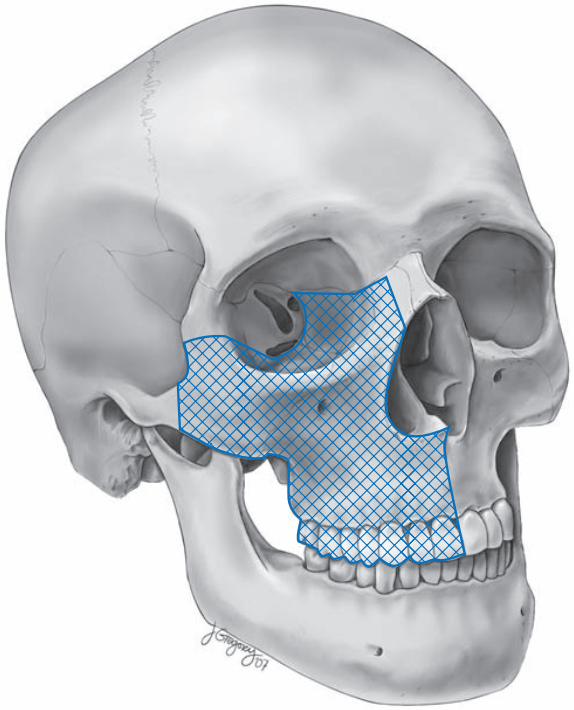


**FIGURE 20-25.** A radical maxillectomy is indicated for locally advanced carcinoma of the maxillary sinus and encompasses the anterior maxilla, the lateral nasal wall, the lamina papyracea, the inferior orbital wall, and the ethmoid sinus. Orbital exenteration may be performed through this approach as indicated.

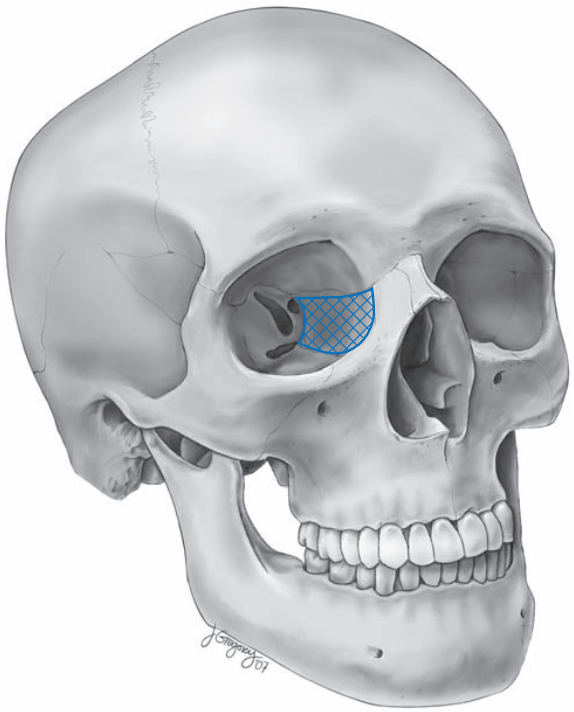


**Figure 20-26.** The indications for the external ethmoidectomy are limited to well-defined lesions confined to the ethmoid sinus and the lamina papyracea.

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discussed previously may be required to prevent postoperative stenosis and epiphora.

## Craniofacial Resection

Craniofacial resection represents a major advancement in the surgical treatment of tumors involving the anterior skull base. It is indicated for tumors of the nasal cavity and the ethmoid and the frontal sinuses involving the skull base. This requires a dedicated team approach with head and neck surgery and neurosurgery. Through a combination of a facial and craniotomy approach, an *en bloc* resection of the anterior skull base including the fovea ethmoidalis, the cribriform plate, the planum sphenoidale, the ethmoid and the frontal sinuses, and the superior aspect of the nasal septum is performed. Inclusion of the orbit and the dura is also possible if necessary (Fig. 20-27). Contraindications

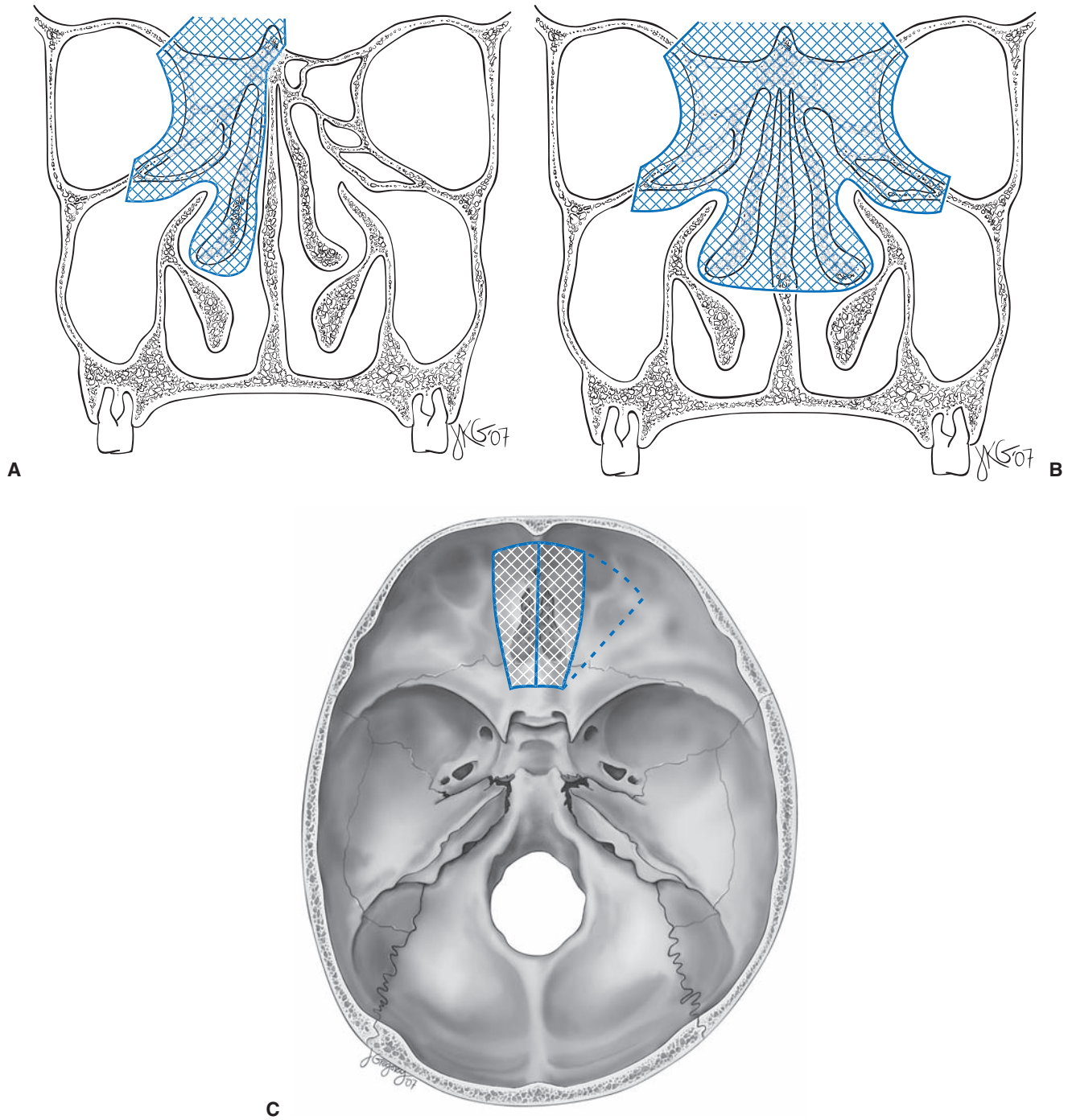



**Figure 20-27.** The external bony margins of the craniofacial approach are shown in Frontal 3. The coronal views of the unilateral **(A)** and the bilateral **(B)** approach demonstrate the areas encompassed with the resection including the anterior skull base, the ethmoid complex, the nasal septum, the middle turbinates, and the lamina papyracea. The intracranial component **(C)** traditionally encompasses the cribriform plate and the fovea ethmoidalis but can be extended laterally (striped margins) to incorporate the superior orbital wall and posteriorly toward the sella.

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may vary according to the histopathology and experience of the surgical team. Major involvement of the clivus, the cavernous sinus, or the brain parenchyma are typically considered contraindications to surgery.

The sinonasal portion of the procedure is performed initially to delineate the tumor margins from below and to minimize the duration of an open intracranial cavity and frontal lobe retraction. The sinonasal component can be approached in a variety of ways including through a lateral rhinotomy, midfacial degloving, or possibly endoscopic approach. The lateral margins are defined with exploration of the orbit, usually toward its apex. Appropriate extracranial osteotomies are performed according to the extent of the necessary resection.

The intracranial component is approached through a bicoronal incision, preferably behind the hairline. Elevation is performed in the subgaleal plane with preservation of the superficial temporal (anterior branches), supraorbital, and supratrochlear neurovascular bundles. A separate inferiorly based pericranial flap is developed and preserved for reconstruction. A frontal bone plate is removed for exposure of the intracranial cavity (Fig. 20-28).

Retraction of the frontal lobe allows for wide exposure of the anterior cranial floor. Complete anosmia results from the bilateral transection of olfactory fibers, which is often necessary for exposure. Retraction trauma of the frontal lobe should be minimized. The intracranial components of the tumor margins are delineated and drilling of the floor of the anterior cranial fossa proceeds according to the extent of skull base involvement. The tumor may be removed *en bloc* by working above and below the skull base during mobilization. The posterior limits of the resection through this approach are the anterior clinoids and the internal carotid artery.

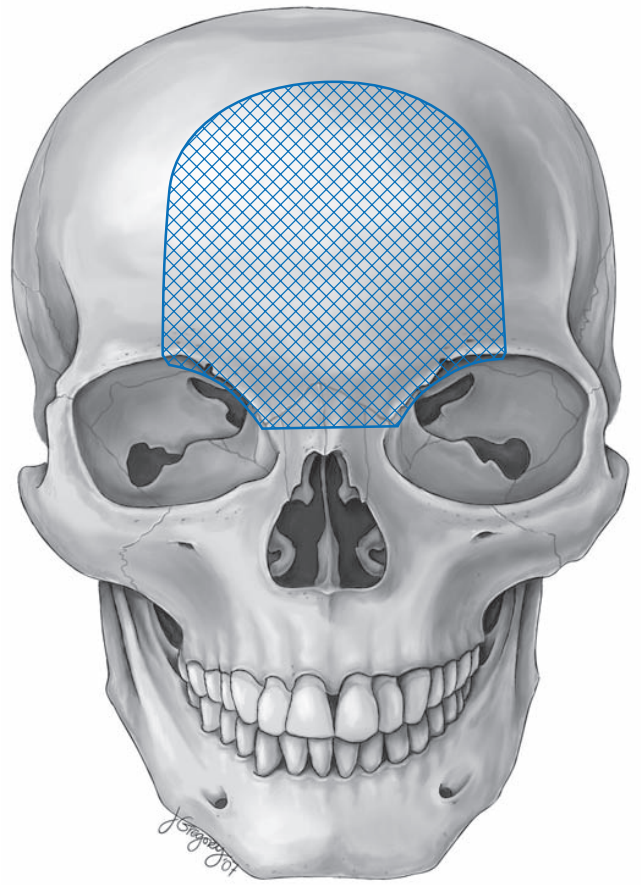


**Figure 20-28.** Craniotomy for intracranial portion of the craniofacial approach.

The major challenge associated with reconstruction following craniofacial resection is the need for a watertight separation between the intracranial and sinonasal cavities. Inadequate reconstruction may result in significant morbidity including cerebrospinal fluid (CSF) leak, pneumocephalus, meningitis, brain abscess, and death. The exposure afforded by this approach, however, offers versatile reconstructive options. Typically, the defect closure is accomplished with the previously mobilized vascularized pericranial flap. Free allografts of dermis have also been quite successful. In patients with an extensive defect, a soft tissue–based free tissue flap (e.g., rectus abdominus free flap) may be inset for reconstruction. Bone grafts are usually not necessary. The reconstructed floor of the anterior cranial fossa is temporarily supported from below with nasal packing. Spinal drainage is also used to decompress the CSF during the postoperative period.

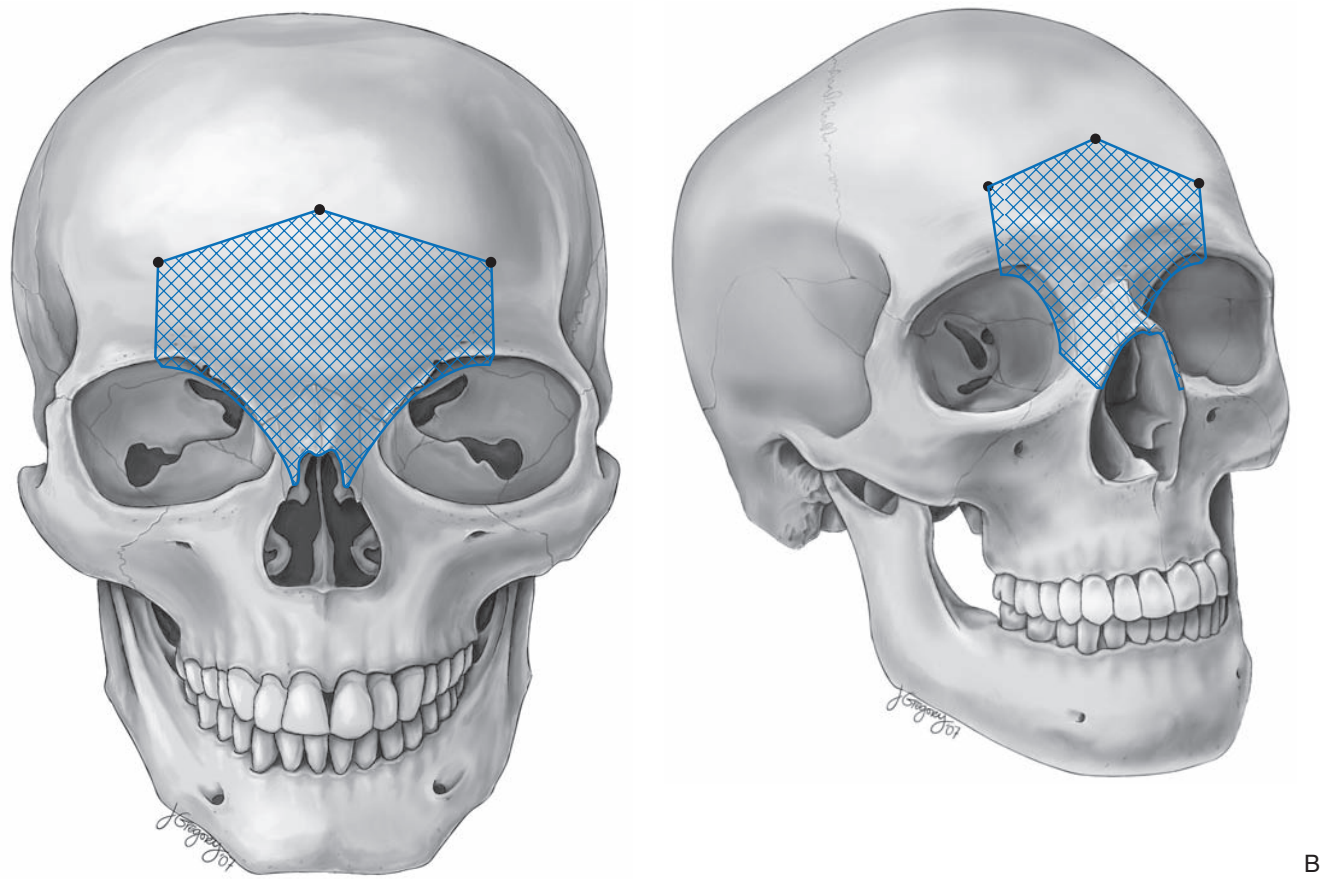
## Anterior Subcranial Approach

The subcranial approach addresses the anterior skull base from an anteroinferior approach. Frontoethmoid and orbital osteotomies provide exposure to the anterior skull base with the advantage of minimal retraction of the frontal lobes. The more inferior angle of approach provides excellent exposure of the fovea ethmoidalis, the cribriform plate, and the orbital roofs (Fig. 20-29).

The technique involves a bicoronal incision, elevation of a subgaleal flap to the level of the frontozygomatic suture lines laterally, and the pyriform aperture and rhinion in the midline. The periorbital plane is developed along the superior and lateral aspects of the orbit, thereby exposing the bony superior orbital rims and frontonasal area. The placement of the osteotomy sites is based on the location and extent of the lesion. The initial anterior cuts for the bone flap are placed along the frontal bone, the medial orbital wall, and the nasomaxillary grooves. The posterior, vertical aspect of the bone flap is based on the location of the tumor. In patients in whom the posterior table of the frontal sinus is to be incorporated into the resection, the posterior osteotomy is made anterior to the table. In patients in whom this area is not involved with tumor, the entire frontonasal segment including the posterior table is removed as a single bone flap. During the elevation of the bone flap, care is taken to protect the dura and the frontal lobe.

Following removal of the bone flap, the olfactory filaments and the dura are separated from the skull base. The subsequent tumor resection involves circumferential definition of the desired margins in an anterior to posterior direction. The resection is tailored to incorporate the fovea ethmoidalis, the cribriform plate, and the medial and the superior orbital walls. Posterior extension of the resection may be extended to include the sphenoid sinus and the clivus as indicated. Adequate reconstruction following the subcranial approach is critical given the potential for postoperative CSF leak. In patients with small- to medium-sized dural defects, a tissue graft consisting of autologous fascia, synthetic dura, or a dermal allograft with tissue sealant may be adequate. Extensive defects may require an inferiorly based pericranial flap. Well-designed reconstruction of the bony framework is required for maximal cosmetic and functional outcome. Reconstruction of the medial orbital walls may be performed with free cartilage or bone grafts in cases in which an extensive portion of the orbital wall and the periorbita are resected. Replacement of the nasofrontal bone flap is optimized by predrilling the micro and miniplate screws at the time of initial flap design. The medial canthal ligaments are repositioned with a nonabsorbable suture anchored to the bone flap.[129–131]

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A B

**Figure 20-29.** Frontal **(A)** and oblique **(B)** views of the anterior subcranial approach. The inferior trajectory of the approach allows for decreased retraction of the frontal lobes.

## Surgery and Management of the Orbit

The extent of orbital resection indicated for sinonasal lesions has undergone evolution over the past several decades and remains a source of discussion. In a series published in 1985, Ketcham and Van Buren reported a significant improvement in overall survival when the orbit was resected at the time of the initial surgery.[132] Improvements in radiation therapy coupled with the significant morbidity associated with orbital exenteration for a questionable improvement in outcomes has resulted in a trend toward orbital preservation. The decisions regarding management of the orbit in patients with primary sinonasal and skull base neoplasm are highly complex and individualized. The factors that impact treatment decisions include the histology, extent, and location of the lesion, patient comorbidities, and overall prognosis (Fig. 20-30). For low-grade lesions abutting the lamina papyracea without radiographic or intraoperative evidence of periorbital invasion, the orbit may be spared. High-grade lesions or a greater degree of invasion including involvement the orbital apex, the extraocular muscles, the orbital fat, and a significant portion of the eyelid represent indications for orbital exenteration.[133,134] Preoperative treatment with radiation and possibly chemotherapy may result in tumor retraction from previously involved orbital contents. This may then allow an orbit-sparing procedure. An algorithmic approach is presented in Figure 20-30. In addition to the histology of the lesion and imaging findings, the decisions regarding orbital management may necessitate intraoperative biopsy of the periorbita to define the presence or absence of tumor.

The various surgical approaches for orbital neoplasms that preserve ocular function can be classified based on the trajectory of the approach. In orbit-sparing procedures, the various approaches can be extended and combined to allow for more complete exposure and mobilization of the orbital contents. The exposure associated with a number of these approaches is limited and may be most appropriately applied to purely orbital benign and small malignant neoplasms and for biopsy purposes.

The lateral approach begins with a lateral canthotomy incision, mobilization of the temporalis muscle, and exposure of the lateral orbital wall. The lateral canthal tendon is divided and the periorbita is elevated allowing for osteotomies to mobilize the lateral orbital rim. The posterior extent of bone exposure is flexible and can be extended to the superior orbital fissure and the skull base. Incision of the lateral periorbita allows for exposure of extraconal lesions of the lateral compartment. Laterally based intraconal lesions require either retraction or detachment of the lateral rectus.

Several incisions allow for access to the medial orbit. A vertical incision (Lynch) can be made 6 to 7 mm medial to the medial canthal tendon to allow for elevation of the medial orbital periostium. Retraction of the orbital contents allows for visualization of the medial-most aspect of the orbit. The addition of an external ethmoidectomy allows for increased exposure. Retraction or displacement of the medial rectus is required for intraconal lesions. A transcaruncular, conjunctival incision and dissection posterior to the lacrimal sac is an alternative option for entrance to the medial orbital compartment. Finally, the endoscopic transethmoid approach

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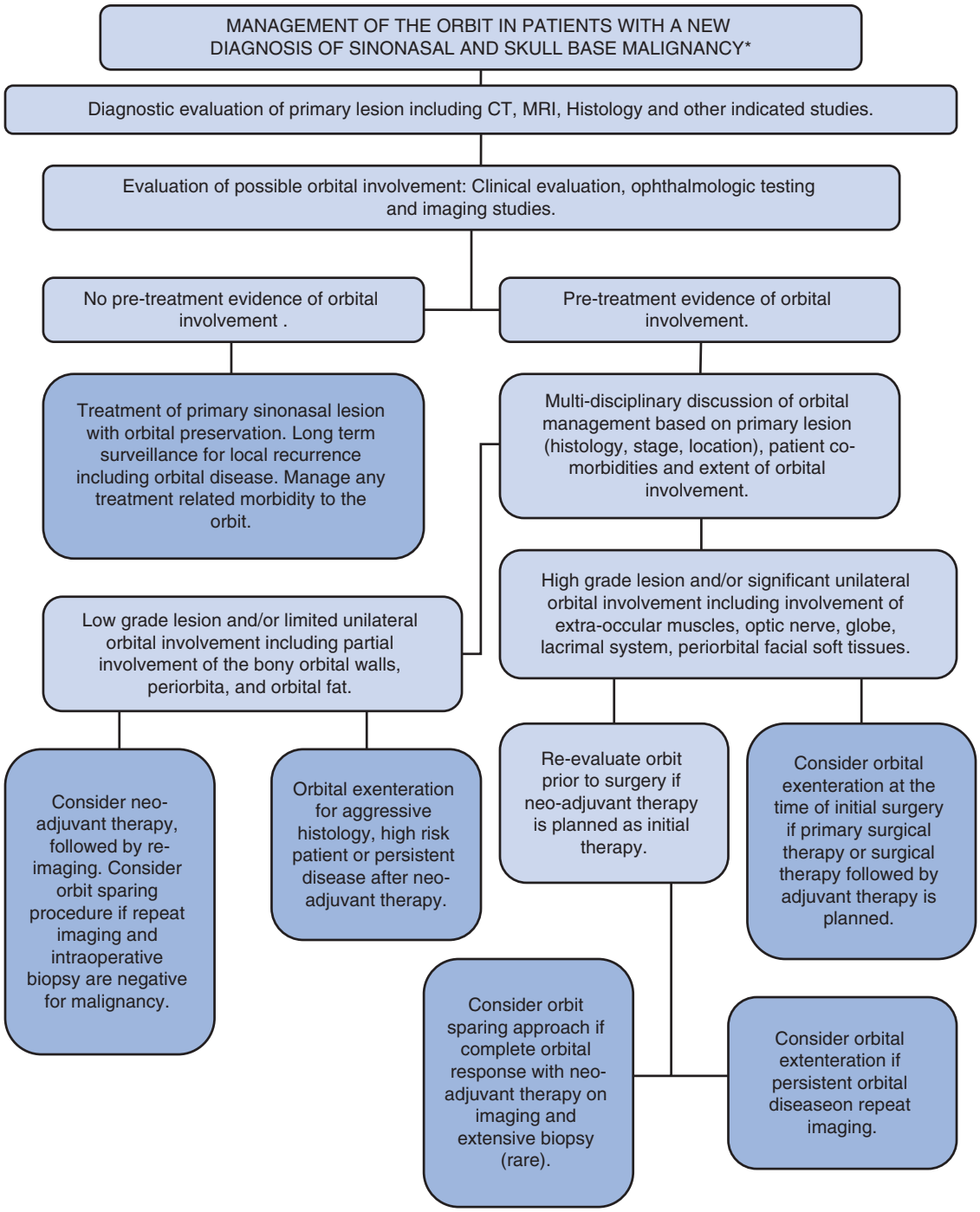



**Figure 20-30.** Algorithm for management of the orbit in patients with primary sinonasal and anterior skull base malignancy.

to the medial orbit allows for avoidance of facial incision and retraction of orbital structures. This technique has been successfully described for orbital decompression and resection of benign lesions.

Open access to the inferior orbit is planned according to the anterior-posterior location of the lesion and the extent of planned resection. For anterior lesions, a transconjunctival approach affords visualization of limited lesions in the inferior orbit and the orbital floor. For posterior and more extensive lesions, removal of the orbital floor through the maxillary antrum may be performed. This allows for visualization along the entire length of the inferior orbit. Intraconal access requires retraction or disinsertion of the inferior rectus muscle.

A purely superior approach can be accessed through either an eyelid fold or infra-brow incision. A periosteal dissection allows for visualization of peripheral and bony lesions. The transseptal approach involves incision of the skin, orbicularis muscle, and orbital septum to access the superior extraconal space including the area of the lacrimal gland. Greater visualization of the superior-medial orbital contents can be gained by mobilization of the lacrimal sac, ligation of the anterior and the posterior ethmoid arteries,

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and retraction of the orbital contents. A frontal craniotomy allows for wide exposure of the superior orbit for more extensive lesions.

Enucleation is primarily indicated for intraocular malignancies that involve the globe but allow for preservation of the orbital suprastructure. The procedure involves circumferential incision of the conjunctiva around the corneal limbus followed by transaction of the insertions of the extraocular muscles. Rotation of the globe at this point allows for visualization and transection of the optic nerve approximately 3 to 4 mm away from the globe. The Tenon capsule and conjunctival layers are closed. An orbital prosthesis may be implanted if single-stage reconstruction is planned.

Orbital exenteration is performed for lesions that are not amenable to orbit-sparing therapies. The standard exenteration procedure involves resection of all of the orbital soft tissue structures and the eyelid skin. Variations including preservation of the eyelids and various soft tissue components can be tailored based on the extent of the lesion. The procedure commences with a circumferential incision around the orbit, either around the eyelid skin or at the eyelash margin. A plane superficial to the orbicularis oculi muscle is elevated to the orbital rims. The medial and lateral canthal tendons are detached. The periosteum is incised and circumferentially dissected. The lacrimal apparatus is mobilized and divided from its nasal component. The orbital contents are now fully mobilized and are transected posteriorly at the orbital apex. Minimal traction and early ligation of the optic nerve and the ophthalmic artery decrease the risk of vagal response and hemorrhage, respectively. Additional removal of the orbital walls and combination with transcranial and transfacial approaches can be used for more extensive lesions. Reconstructive options of the orbital cavity include delayed healing with granulation tissue, placement of a skin graft, and placement of either a pedicled or free soft tissue flap.

## Principles of Reconstruction

The goals of reconstruction include a rapid return-to-normal function and adequate cosmetic appearance with minimal morbidity. The complex physiology, extensive nature of the surgical defect, stresses created by mastication and normal sinonasal function, and presence of contaminated and irradiated field create specific challenges. Fabrication of an oral prosthesis for the maxillary defect allows for rapid rehabilitation and direct inspection of the tumor site. This may be combined with relining of the sinus with a skin graft or temporoparietal rotation flap. Alternatively, free flap reconstruction results in closure of the defect with vascularized bone and soft tissue that may be contoured and allows for osseointegrated dental implants. Options for this include fibula, scapula, or iliac crest. In patients undergoing orbit-sparing procedures, reconstruction of orbital wall defects is critical. Functional and cosmetic optimization of the orbit requires symmetric positioning of the globe, restoration of normal intraorbital volume, and preservation of extraocular muscle function. Multiple reconstructive options are available including free tissue transfer, rotational flaps, bone grafts, and placement of synthetic graft material. If orbital exenteration is necessary, the resultant cavity can be filled with temporalis muscle flaps, temporoparietal fascia flaps, or free flaps. Placement of osseo-integrated implants allows for better postoperative prosthesis rehabilitation.

## Endoscopic Surgery

The past 15 years has witnessed the rapid development of advanced endonasal, endoscopic approaches for a variety of sinonasal lesions. The foundations of these techniques are based on endoscopic surgery for inflammatory sinus disease. With technological improvements in instrumentation and visualization including angled endoscopes, image guidance, and powered instruments, more complex procedures such as CSF leak closure, orbital decompression, and approaches for benign intracranial lesions (i.e., pituitary adenoma) are now routinely performed endoscopically. The theoretical advantages of endoscopic surgery, in general, include its minimally invasive nature, avoidance of facial incisions, and improved panoramic visualization of the entire surgical field including surgical margins and critical neurovascular structures. To date, the paradigm for a number of different sinonasal lesions has shifted such that endoscopic surgery is the mainstay in surgical therapy. This includes endoscopic surgery for benign sinonasal neoplasms such as inverted papilloma[22,135–138] and juvenile nasopharyngeal angiofibroma[36,38,39] as well as repair of CSF leak.[139–142] The lower perioperative morbidity for these lesions coupled with outstanding short- and long-term surgical outcomes support the role of endoscopic surgery. Endoscopic surgery also appears to have a well-defined role in certain aspects of sinonasal malignancies including biopsy of suspicious lesions,[105,106] palliation of unresectable disease[143] and excision of small, well-demarcated tumors.

Extension of endoscopic surgery for management of sinonasal malignancy has been the subject of a great deal of interest and debate. The benefits outlined above for benign and inflammatory pathology also theoretically apply for endoscopic surgery for malignancy. The focus of debate centers on the oncologic outcomes associated with endoscopic surgery. Although an equivalent rate of gross tumor removal with frozen section confirmation of margins can be achieved endoscopically in selective cases, the main theoretical distinction between endoscopic and open surgery for malignancy is the inability to perform an *en bloc* excision for locally advanced disease. The oncologic implications of piecemeal versus *en bloc* tumor resection for malignancy require systematic examination as it represents a significant deviation from the traditional principles of surgical oncology. The potential for tumor seeding and inadequate margins of resection are potentially increased with piecemeal resection. This is further compounded by the fact that the majority of treatment failures for sinonasal malignancy are local in nature, emphasizing the need for adequate initial resection. However, *en bloc* resection may not be possible even with open approaches in patients with advanced lesions, including intracranial extension.

The primary advantages of endoscopic surgery include the potential for decreased perioperative morbidity, improved visualization of cavitary areas, and decreased manipulation of critical neurovascular structures. The avoidance of facial incisions, elevation of facial flaps, and open transfacial approaches implies improved cosmesis and faster postoperative recovery. In patients with limited intracranial involvement, the bony skull base and dura may be addressed entirely with the endoscopic technique, thereby avoiding the need for craniotomy and frontal lobe retraction. Additionally, visualization with straight and angled endoscopes allows for panoramic visualization of the tumor and surrounding neurovascular structures throughout the procedure. This contrasts with open surgery where visualization of certain aspects of the tumor, notably the superior and posterior margins is limited until the end of the procedure and is often deeply recessed in the surgical field.

Oncologic resections extend the techniques used in endoscopic surgery for benign sinonasal and intracranial pathology. The surgery can be conceptually divided into the stages of treatment planning, tumor exposure, resection, and skull base reconstruction. Treatment planning, as in all sinonasal malignancies, is complex and requires a multidisciplinary consideration of the role of the various surgical and adjuvant therapy options. If surgical resection is indicated, the critical question of whether endoscopic surgery is appropriate is based on both the tumor characteristics and the expertise of the surgical center. Given the complexity of the surgical challenges encountered during approaches for malignancy combined with the potential for neurovascular

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complications and negative impact on outcomes of an incomplete resection, these surgeries should be performed in centers with the appropriate expertise. Careful consideration of contraindications to endoscopic surgery should be considered preoperatively including involvement of the facial soft tissue, extensive orbital cavity requiring exenteration, extensive maxillary involvement necessitating maxillectomy, anterior and far lateral involvement of the frontal and the maxillary sinuses, extensive intracranial involvement, and far lateral extension into the pterygomaxillary and the infratemporal fossa. Intracranial extension, however, does not necessarily represent a contraindication as the lesion may be managed entirely through an endoscopic procedure or a combined endoscopic-transcranial approach. Endoscope-assisted surgery which combines the exposure of open surgery with the visualization of endoscopic surgery is also possible.

The technical challenges associated with endoscopic resection of sinonasal malignancies are best addressed by a team approach with expertise in advanced sinonasal and intracranial pathology. General principles include wide endoscopic exposure, two- or four-handed surgical dissection, and incorporation of multiple surgical tools including powered instrumentation and image guidance. The resection progresses through stages including demarcation of gross tumor involvement, central debulking, mobilization of critical neurovascular structures, and clearance of the tumor margins. Serial frozen section confirmation of the margins is critical. The various endoscopic procedures available can be divided based on the target of the resection and the approach necessary to reach this location. Several descriptions of a compartmentalized approach to the various lesions have been described.[144–146] The approaches describe the different sinonasal cavities that are traversed including transnasal, transsphenoidal, transmaxillary, and transethmoidal approaches. Following opening of the various sinonasal passages, the approach is further expanded to encompass the necessary aspects of the intracranial and the skull base cavities. The transnasal corridor does not traverse any of the paranasal sinuses and can be used to target the medial aspects of the nasal cavity (nasal turbinates, nasal septum, chaona), the midline of the anterior skull base (cribriform fossa), and the nasopharynx. Extension posteriorly into the transsphenoidal corridor allows for exposure of the sella, the suprasella, and the sphenoidal clivus. Transmaxillary approaches allow for access to the inferior orbit, the PPF, the infratemporal fossa, and the middle cranial fossa. Transethmoid approaches allow for exposure of the lateral aspects of the skull base including the fovea ethmoidalis, the anterior cranial fossa, and the medial orbital wall. These approaches are often combined for sinonasal lesions to allow for a complete circumferential exposure and clearance of margins. Advanced endoscopic techniques and instrumentation are available for tumor removal.

Following tumor resection, skull base reconstruction is performed. This aspect of the surgery has critical importance in order to prevent postoperative CSF leak and associated sequelae, promote healing of the surgical cavity, restore sinonasal physiology, and allow for tumor surveillance. This is additionally associated with a number of technical challenges if a purely endoscopic approach has been used, including the cavitary, three-dimensional nature of the dissection, the presence of a large surgical defects with high-volume intraoperative CSF leak, the limited ability to directly instrument the reconstruction site as can be done with open surgery, and the stresses applied to the repair site from intracranial pressure, gravity, and normal sinonasal function. The primary goal of reconstruction is the re-creation of a separation between the sinonasal and the intracranial cavities. A number of options exist including various combinations of free tissue/synthetic grafts and vascularized pedicled grafts including the nasal septal flap. Expertise in applying the various techniques for skull base reconstruction is a requisite aspect of endoscopic skull base surgery to achieve a high rate of successful repair at the time of initial surgery. Overall, a low incidence of postoperative CSF leak has been reported in multiple independent series.[147–150]

## Complications

The major complications following surgery for sinonasal malignancy can be divided into systemic, local, and neurovascular. The combination of extensive surgery and older age is associated with an increased risk of perioperative medical morbidity including cardiovascular events, pneumonia, and deep-vein thrombosis. These issues may be minimized with dedicated nursing protocols. Postoperative epistaxis may be brisk and may arise from several named neurovascular bundles including the internal maxillary artery, the sphenopalatine artery, and the ethmoidal arteries. The wound is typically packed at the conclusion of the case for prevention, but the bleeding event may be delayed until the time of pack removal. Treatment options for persistent epistaxis include replacement of the packing, surgical exploration, or interventional radiographic embolization in refractory cases. Facial and sinonasal wound infections are uncommon, likely secondary to the extensive vascular supply to this area. Optic nerve injury resulting in blindness may occur secondary to direct surgical trauma, ischemia from devascularization, or increased intraorbital pressure. CSF leak occurs from persistent communication between the sinonasal and intracranial cavities and may secondarily result in meningitis. This is compounded in patients with a large defect where a one-way flow of air may result in tension pneumocephalus and rapid neurologic deterioration. Urgent treatment is required and may involve placement of a burr hole followed by surgical exploration of the reconstruction site. In patients with a low-volume CSF leak, a trial of lumbar drainage, bed rest, and head of bed elevation may be initially employed. Surgical exploration and repair of the defect site is indicated if the leak persists. Local infections may be minor if confined to the sinonasal cavity or severe if intracranial. The latter may result in meningitis, epidural, or subdural abscess. Broad-spectrum antibiotics and abscess drainage, if present, are indicated. Carotid artery injury and intracranial bleeding are rare, but potentially catastrophic events. Frontal lobe edema and contusion occurs in patients with transcranial surgery and extensive brain retraction. This may result in altered neurocognitive function and seizures. Cranial nerve injury is dependent on the extent of the surgery and may be greatest in patients undergoing surgery of the cavernous sinus.

# OUTCOMES

A definition of the outcomes following treatment for sinonasal malignancies is challenging given the overall low incidence of these lesions, heterogeneous histopathologies, and nonuniform treatment protocols. Adequately powered, case-controlled or prospective, randomized studies are challenging given these issues and would best be addressed with multi-institutional treatment protocols. The current understanding of the efficacy of various treatment options is instead largely pooled from the various single-institutional experiences. The majority of these reports are retrospective in nature which introduces significant issues in the interpretation of the available literature. For example, although higher rates of local disease control and survival have been suggested for surgery alone or surgery with radiotherapy compared with radiation alone, a significant selection bias likely exists. Patients receiving radiation alone likely had more advanced disease and may have been considered palliative.

Although single-modality therapy may be indicated in early lesions (T1),[41] the majority of patients present with advanced local disease. Multimodality therapy incorporating at a minimum

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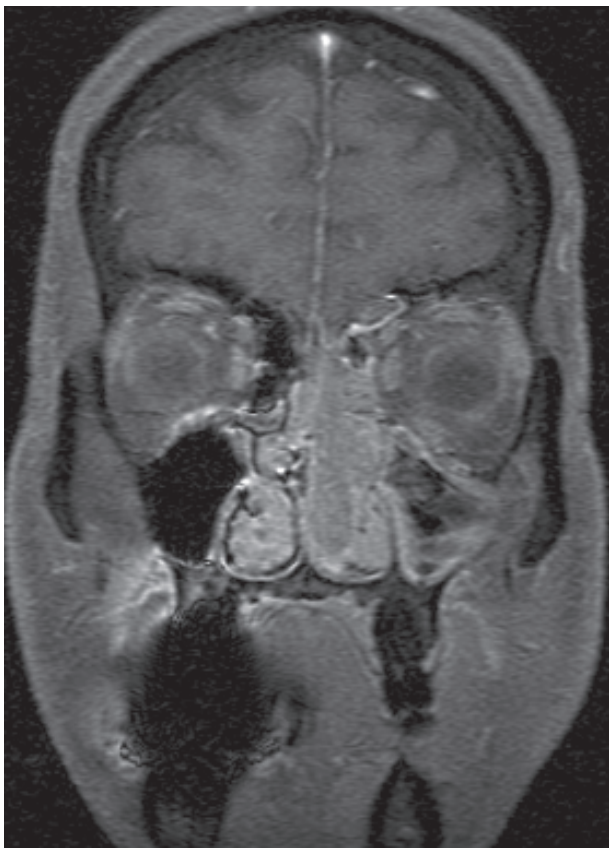
radical surgery combined with external beam radiation is advocated for the majority lesions. There have, however, been isolated reports of favorable outcomes following radical surgery alone. Terz et al. described a 72% 3-year and 50% 5-year survival in a case series of 28 patients with T3 and T4 paranasal sinus malignancy treated with radical craniofacial surgery including resection of the anterior and the middle cranial fossa, the orbit, and the soft tissues of the face. Three deaths were attributed to the surgery.[151] Similar outcomes with surgery alone, however, have not been reproduced and most centers routinely use postoperative radiation therapy.

The improved outcomes of radiation therapy combined with surgery versus either modality alone have been reported in multiple independent series.[152–155] The timing of radiation therapy with respect to surgery remains controversial. Radiation therapy with or without chemotherapy prior to surgery may result in shrinkage of the tumor and improve resectability for advanced lesions.[156,157] The possibility of improved ability to spare structures such as the orbit has also been discussed for this approach[158,159] but remains controversial. The surgical extent should be based on pretreatment imaging as the results of less aggressive resection do not seem favorable.[160,161] The local control and survival outcomes are significantly improved if no viable tumor is identified at the time of surgery.[162] Conversely, radiation therapy following radical surgery may improve eradication of microscopically positive margins. Additionally, since the concern for tissue healing is less pronounced with radiation therapy following surgery, a higher total dose may be considered. The impact of recent advances in radiation therapy, including conformal radiotherapy and intensity-modulated radiation therapy (IMRT) offer the hope of more directed therapy and preservation of critical structures[163] including orbital function.

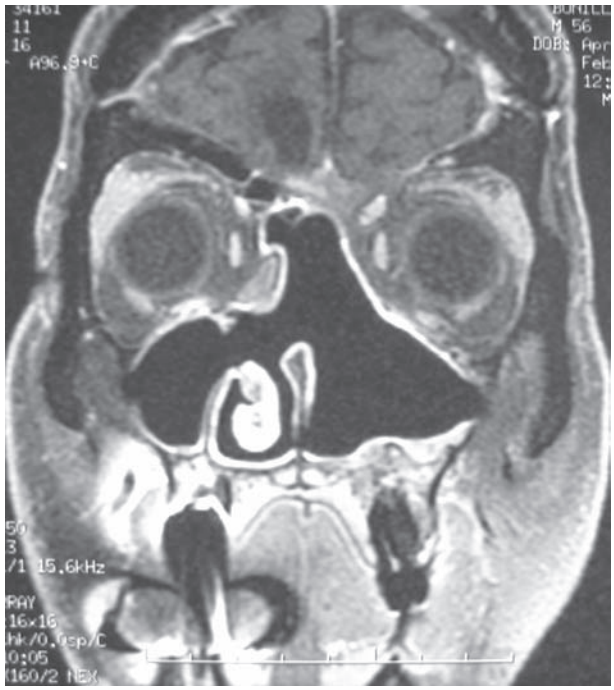
The outcomes of craniofacial resection for paranasal sinus malignancies involving the anterior skull base reflect the challenges associated with these lesions. The majority of ethmoid sinus lesions present with skull base involvement at initial presentation. Multimodality therapy with surgery and radiation is indicated in the majority of the lesions. Inclusion of chemotherapy may also be indicated in advanced esthesioneuroblastoma.[164,165]

In a multi-institutional review of 334 patients with paranasal sinus malignancies excluding esthesioneuroblastoma, Ganly et al. reported 5-year overall, disease-specific, and recurrence-free survival rates of 48.3%, 53.3% and 45.8%, respectively. Rates of perioperative mortality of 4.5% and complications of 32.9% were noted. The complications associated with this cohort included local wound, central nervous system, systemic, and orbital complications. The presence of medical comorbidities, prior radiation therapy, positive surgical margins, various histologic subtypes, and intracranial tumor involvement were identified as independent risk factors.[166] Similar outcomes have been reported in other, smaller series.[56,167,168] Suarez et al. identified histology, recurrent lesions and involvement of the brain, orbital soft tissue, and sphenoid sinus as negative prognostic factors.[169]

The treatment paradigm for esthesioneuroblastoma varies depending on the size of the lesion and the institutional philosophy. For localized lesions (Kadish A and B), multiple case series have reported favorable long-term results with surgical resection followed by radiation therapy[61–66] (Fig. 20-31). The overall prognosis is poor in patients with local-regional recurrence or distant



A



B

**Figure 20-31.** Pretherapy **(A)** and 10-year follow-up **(B)** coronal MRI of an esthesioneuroblastoma treated with craniofacial resection followed by radiation therapy.

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spread. A standardized protocol for advanced lesions has been described by the University of Virginia and involves presurgical radiation therapy (50 Gy) for patients with Kadish stage A–C disease. Chemotherapy (cyclofosphamide and vincristine) is additionally given for patients with Kadish C disease prior to radiation therapy to minimize tumor burden. Craniofacial surgery is performed following chemoradiation. Five- and 10-year survival rates of 81% and 54%, respectively, have been reported following this protocol.[170] As mentioned earlier in this chapter, the olfactory apparatus, intracranial extension, and paranasal sinus components of the tumor should be resected in continuity.

The outcomes following therapy for sinonasal melanoma remain poor overall. Several single-institutional case series over the past two decades have reported 5-year survival rates ranging from 10% to 47%. The majority of these patients were treated with aggressive surgery followed by radiation therapy.[83,85,86,171,172] Ganly et al. used the same multi-institutional database described above to report outcomes following craniofacial for surgery for melanoma with 3-year overall, disease-specific, and recurrence-free survival rates of 28.2%, 29.7% and 25.5%, respectively.[173]

The role of chemotherapy in sinonasal malignancy has been limited to date, but may develop an increasing role in the future. The utility of chemotherapy is strongly related to the histology of the lesion and with a clear role in sinonasal lesions that are both drug sensitive and have a propensity for regional and distant spread. Appropriate lesions may include sinonasal undifferentiated carcinoma, lymphoma, and rhabdomyosarcoma.[79,99–101] The efficacy of chemotherapy for the common sinonasal malignancies including squamous cell carcinoma remains unclear. To date, there have been few reports addressing this issue. Lee et al. reported a series of 19 patients with advanced paranasal sinus carcinoma treated with a combination of surgery and chemoradiation with 16 patients additionally receiving induction chemotherapy with cisplatin and 5-fluorouracil. The 10-year disease-free survival and local control rates were 66.6% and 76.1%, respectively.[162] Samant et al. reported a 53% 5-year survival rate in 19 patients with advanced paranasal sinus malignancies treated with neoadjuvant radiochemotherapy consisting of 50 Gy and 3 to 4 doses of intra-arterial cisplatin followed by surgery.[174]

The outcomes following endoscopic surgery for sinonasal malignancy is an active area of clinical investigation and has important implications in defining its indications and limitations. Several centers have described favorable early results with endoscopic management of selected sinonasal malignancies.[68–78,175–177] The greatest experience to date is with esthesioneuroblastoma, and favorable early results in selected lesions have been reported.[68,69–73] The majority of these patient series involved early-stage (Kadish A and B) lesions. The past 5 years has witnessed a growing body of literature describing favorable outcomes following endoscopic surgery for other malignant histologies. Goffart et al. reported 2- and 5-year survival rates of 73.1% and 52.3%, respectively, in 78 patients undergoing endoscopic surgery for sinonasal malignancy including adenocarcinoma, SCC, and esthesioneuroblastoma.[178] Lund et al. reported an 88% rate of survival at last follow-up in 49 patients undergoing endoscopic surgery for sinonasal malignancy including adenocarcinoma, malignant melanoma, and esthesioneuroblastoma.[179] Favorable tumor control and improved perioperative morbidity were described by Nicolai et al. in a single-institutional experience in the management of ethmoid sinus adenocarcinomas. The 25-year duration of this case series reflects the authors' evolution from craniofacial to endoscopic resection for these tumors.[76] In a case series of 120 patients with multiple histologies treated over a 15-year period at MD Anderson, Hanna described overall favorable outcomes for patients undergoing purely endoscopic and cranioendoscopic surgery. An 85% rate of local disease control was noted with a mean follow-up period of 37 months.

The overall positive outcomes associated with endoscopic surgery for sinonasal malignancy must be tempered by the relatively limited collective experience and duration of follow-up. In general terms, the application of endoscopic surgery for sinonasal malignancies requires ongoing critical analysis. These procedures should be done on a selective basis and by experienced practitioners after careful consideration of potential contraindications.

## FUTURE DIRECTIONS

Neoplasms of the nasal cavity and paranasal sinuses represent a challenging group of disorders. The rarity of these lesions, advanced stage at presentation, critical neurovasculature of the involved anatomy, and aggressiveness of the various histopathologies have traditionally resulted in poor overall outcomes. However, an evolving understanding of the clinical behavior and treatment response of the various lesions has resulted in more sophisticated treatment options and the promise of improved outcomes. Given the rarity of these lesions, continued scientific reporting is imperative to further the collective body of knowledge, likely in the form of pooling of data from individual centers that would allow for sophisticated statistical analysis of the epidemiology and treatment outcomes of these rare lesions. Ideally, the implementation of prospective, multi-institutional protocols may allow for a critical examination of treatment efficacy, as has been done for rhabdomyosarcoma. The roles of diagnostic and treatment advances include PET, IMRT, and proton beam therapy are still inadequately defined and need further study. In the future, biomolecular markers may allow for more directed, "customized" therapy. However, given the diverse spectrum of histopathologies, future studies with adequate patient sample size would be necessary to justify dramatic changes in the treatment protocols. Finally, the application of endoscopic surgery for sinonasal malignancy is an area of active debate. Multiple advances in the technique are the subject of active exploration including application of various forms of powered instrumentation, three-dimensional endoscopy, and robotic surgery. However, the most critical questions that have only been partially answered to date involve the indications, limitations, and outcomes of endoscopic surgery for sinonasal malignancy.

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CHAPTER 21

# Cancer of the Nasal Cavity and Paranasal Sinus: Radiation Therapy and Chemotherapy Management

## PART A:
## General Principles and Management

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Carcinomas arising from the nasal cavity and the paranasal sinuses are rare tumors of the head and neck accounting for approximately 3% to 5% of all upper respiratory tract malignancies and <1% of all new cancers.[1] They are twice as common in males as in females and typically occur after 40 years of age.[2,3] Owing to their inconspicuous locations along the anterior skull base, these tumors generally present at advanced stages unless the cancer impinges on vital organs or extends from the maxillary sinus to the nasal cavity producing subsequent symptoms of epistaxis or obstruction. Because these tumors frequently involve multiple adjacent sites, determination of the exact site of origin may be difficult. Similarly, treatment decisions have historically been complicated by the close proximity of these cancers to critical normal tissue structures such as the optic pathways and the brainstem.

Owing to the rarity of paranasal sinus or nasal cavity tumors, published clinical outcomes are largely limited to retrospective reviews of single institutional experiences. Additionally, the heterogeneity of these study populations with respect to both clinical presentation and treatment strategy often makes drawing definitive conclusions challenging. For instance, primary sites and different histological subtypes are often grouped together, which lead to some confusion in comparing treatment results across series. Moreover, the proportion of patients treated by a nonsurgical approach in these studies can vary greatly. In general, early-stage cancer is often successfully managed with surgery alone, whereas more advanced disease requires the addition of postoperative radiotherapy.[4–9] In select situations, chemotherapy has been added to postoperative radiotherapy as adjuvant treatment. The use of primary radiotherapy has been reported in older series but with apparently higher treatment-related complications, perhaps due to the inability to give adequate dose to the gross disease without having to compromise the surrounding normal tissues. Because these tumors are often surrounded by multiple critical normal tissues, such as the optic structures and the brainstem, delivery of a high therapeutic dose to gross disease is often difficult and maximal tumor resection should be attempted whenever possible before radiation therapy. However, for patients who are medically or surgically inoperable, definitive radiotherapy with or without chemotherapy is a feasible alternative approach, although reported outcomes have been less favorable.[10]

Intensity-modulated radiation therapy (IMRT) offers the potential to reduce dose to critical structures while maintaining desired doses to the targeted tumor volume through inverse planning and the use of optimized nonuniform beams.[11] As a result, a higher tumoricidal dose of radiation can be administered while minimizing the dose delivered to the surrounding normal tissues.[12] Although numerous treatment-planning studies have demonstrated through dosimetric comparisons that IMRT can offer a superior dose distribution for the treatment of tumors of the nasal cavity and paranasal sinuses in comparison to three-dimensional (3D) conformal and conventional methods,[13,14] several recently published articles suggest that the theoretic advantages associated with this technique do indeed translate into tangible benefits for patients treated in the clinical setting[5,15–17] directly compares 3DCRT to IMRT patients in paransal patients. Although most of these single-institutional series are limited by relatively short follow-up, the preliminary data with respect to both efficacy and toxicity are encouraging. In this chapter, the authors will discuss the management of cancer of the nasal cavity and paranasal sinuses using radiation therapy with or without chemotherapy.

## CLINICAL PRESENTATION

The diagnosis of cancer of the nasal cavity and paranasal sinuses is often delayed for considerable periods of time due to the lack of specific symptoms.[4,18] Early symptoms are vague and can mimic sinusitis. Unilateral nasal obstruction, chronic unilateral nasal discharge, and intermittent epistaxis can result from nasal cavity tumors. Other less common symptoms include headache, epiphora, and localized pain. Diagnosis can often be delayed



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further because these patients have a history of nasal polyps, which produce similar symptoms. Tumors of the maxillary antrum also tend to remain silent until they extend outside the sinus. As a result of tumor extension to the premaxillary region, patients can complain of facial pain, numbness, localized swelling, nasal obstruction, and epistaxis. Nasal obstruction from tumor extension to the nasal cavity and tumor extension into the orbit causing ocular problems such as epiphora, proptosis, diplopia, eye pain, and inner canthal mass are the most common symptoms of ethmoid sinus tumors. Sixth nerve palsy, severe morning headaches, and diplopia are common symptoms for primary sphenoidal tumors. Lastly, frontal sinus tumors can present with bilateral swelling of the glabella and the supraorbital ridge and with frontal pain.

Cervical lymph node metastases on initial clinical presentation are uncommon with an incidence of approximately 10% to 15%. Depending on the histological subtype and extent of the primary tumor, the incidence ranges from 20% to 44%.[19–21] Distant metastasis at the time of diagnosis is rare.

## PATHOLOGY

Squamous cell carcinoma (SCC) or one of its variants is the most common histological subtype, making up 80% to 85% of all neoplasms of the nasal cavity and paranasal sinuses. Minor salivary gland tumors such as adenoid cystic carcinoma and adenocarcinoma comprise approximately 10% to 15% of all neoplasms in this region. Mucoepidermoid carcinomas are extremely rare. Adenocarcinoma can also represent a metastasis, most often from the kidney, the breast, or the lung. Although malignant melanoma accounts for approximately 10% to 15% of nasal cavity cancers, it is rare in the paranasal sinuses. Other less common histological subtypes include undifferentiated carcinoma, plasmacytoma, lymphoma, esthesioneuroblastoma, sarcoma, and inverted papilloma. Undifferentiated carcinomas have an extremely poor prognosis with up to 90% of patients dying within the first year from either extensive local or metastatic disease. Although histologically benign appearing, inverted papilloma often has a very aggressive clinical course even in the absence of malignancy. It is associated with SCC in 10% to 15% of cases.[18,22]

## STAGING

Nasal cavity and paranasal sinus tumors are staged according to the current seventh edition of the American Joint Committee on Cancer (AJCC) TNM (tumor, node, metastasis) staging system. Within the paranasal sinuses, frontal and sphenoid sinuses are rare and not formally staged according to the AJCC TNM staging system. Magnetic resonance imaging (MRI) in addition to computed tomography (CT) is very useful as part of the staging workup as it can potentially differentiate between tumor and sinusitis. Table 21.1 contains the details of the staging system.

## RADIATION TECHNIQUES

Over the last several decades, a remarkable evolution of radiotherapy techniques for the treatment of nasal cavity and paranasal sinus cancer has been witnessed. Reported techniques have included conventional radiotherapy using two-dimensional (2D) imaging to three-dimensional conformal radiotherapy (3D-CRT) using CT simulation, to more recently, IMRT with dose painting. Proton beam has also been utilized for the treatment of these tumors but its use is limited to few centers.

**TABLE 21.1 Seventh Edition of AJCC Staging for Nasal Cavity and Paranasal Sinus Cancer**

| | |
|---|---|
| **Primary Tumor (T)** | |
| **Maxillary sinus** | |
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Tis | Carcinoma *in situ* |
| T1 | Tumor limited to the maxillary sinus mucosa with no erosion or destruction of bone |
| T2 | Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates |
| T3 | Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses |
| T4a | Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses |
| T4b | Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve V2, nasopharynx, or clivus |
| **Nasal cavity and ethmoid sinus** | |
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Tis | Carcinoma *in situ* |
| T1 | Tumor restricted to any one subsite, with or without bony invasion |
| T2 | Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion |
| T3 | Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate |
| T4a | Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid, or frontal sinuses |
| T4b | Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx, or clivus |
| **Regional nodes (N)** | |
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastases |
| N1 | Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension |

*(continued)*

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**TABLE 21.1 Seventh Edition of AJCC Staging for Nasal Cavity and Paranasal Sinus Cancer (Continued)**

| | |
|---|---|
| **Primary Tumor (T)** | |
| N2 | Metastasis in a single ipsilateral lymph node, >3 cm but not >6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension, or bilateral or contralateral lymph nodes, none >6 cm in greatest dimension |
| N2a | Metastasis in a single ipsilateral lymph node >3 cm but not >6 cm in greatest dimension |
| N2b | Metastasis in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension |
| N2c | Metastasis in a lymph node >6 cm in greatest dimension |
| N3 | Metastasis in a lymph node >6 cm in greatest dimension |
| **Distant metastasis (M)** | |
| MX | Distant metastasis cannot be assessed |
| M0 | No distant metastasis |
| M1 | Distant metastasis |

**Stage grouping**

| | | | |
|---|---|---|---|
| 0 | Tis | N0 | M0 |
| I | T1 | N0 | M0 |
| II | T2 | N0 | M0 |
| III | T3 | N0 | M0 |
| | T1 | N1 | M0 |
| | T2 | N1 | M0 |
| | T3 | N1 | M0 |
| IVA | T4 | N0 | M0 |
| | T4 | N1 | M0 |
| IV B | Any T | N2 | M0 |
| | Any T | N3 | M0 |
| IVC | Any T | Any N | M1 |

*Source: AJCC Cancer Staging Manual.* 7th ed. New York, NY: Springer; 2010, with permission.

Conventional 2D radiotherapy techniques typically incorporate the use of a three-field technique with two lateral wedged fields and an anterior field. Because the dose required for treatment ranges from 66 to 70 Gy, significant toxicity can result from the excess radiation delivered to adjacent structures, especially optic structures, in which threshold doses for toxicity are below 60 Gy.[8,23] Notably, with the introduction of 3D-CRT, the dose inadvertently given to the surrounding normal tissues can be significantly reduced without compromising delivery of high doses to the target volume. However, this technique relies significantly on the expertise of the radiation oncology and physics team, and careful manipulations with dose distributions are needed to optimize delivery of a high dose to the target while minimizing dose to critical structures.[5,24,25] More recently, advances in radiation technology have resulted in additional refinement of 3D-CRT with the development of IMRT.[16] IMRT utilizes a computer dose distribution optimization process to deliver the radiation dose to the tumor while minimizing the dose delivered to the surrounding normal structures. The delivery of IMRT is based on the use of multileaf collimators (MLCs) and allows for painting or sculpting of dose distribution with superb precision resulting in a rapid dose fall-off near normal tissue. Although several different treatment planning systems are available, the basic principles underlying this technology are similar.[11] The technical aspects of IMRT are discussed further in Chapter 5.

Tumors of the skull base, including those involving the nasal cavity and the paranasal sinuses, appear to be especially well suited to the use of IMRT, given the irregular contours of these cancers and the presence of vital structures in this region such as the brainstem, the optic nerves, the optic chiasm, and the spinal cord. Multiple dosimetric studies have eloquently shown that improved dose distributions with increased dose delivery to the tumor target while minimizing the dose delivered to the surrounding normal tissues can be achieved with IMRT when compared with conventional radiotherapy[13,26] (Fig. 21-1). From a practical standpoint, the dose delivered to the optic pathways can be reduced selectively by IMRT, which has the potential to save binocular vision particularly for patients who have extensive and large-volume disease in the paranasal sinuses. Preliminary clinical data from several centers have demonstrated minimal toxicity from IMRT when compared with the historical series where the toxicity rates can be as high as 35%.[15,27,28] In a longitudinal analysis of 127 patients treated with radiation therapy from 1960 to 2005 at the University of California, San Francisco (UCSF), the incidence of grade 3 and 4 late ocular toxicity among patients treated with CRT, 3D-CRT, and IMRT was 20%, 9%, and 0%, respectively.[15] In another series from Memorial Sloan-Kettering Cancer Center, none of the 85 patients who underwent postoperative radiotherapy treated with CT simulation developed grade 3 to 4 late complication of the eye with a median follow-up of 60 months among surviving patients.[5,29] Other series have shown similar results in terms of the reduction of late complications due to radiotherapy. As more centers publish their experience with IMRT in the treatment of paranasal sinus cancer, it is hopeful that the late complication rates continue to decrease. In addition to its ability to spare the organs at risk, IMRT can potentially increase disease control as a result of improvement in tumor coverage and by allowing the delivery of higher radiation doses than with conventional technique.[13]

## ANATOMY AND PATTERNS OF SPREAD

### The Nasal Cavity

The anterior, the superior, the inferior, and the posterior borders of the nasal cavity are located at the limen nasi, the base of skull (the frontal sinuses, the cribriform plate, and the ethmoid air cells), the hard palate, and the choanae, respectively (Fig. 21-2). The limen nasi is the line of transition from the skin to the mucous membrane. The septum divides the nasal cavity into right and left halves and attaches to the perpendicular plate of the ethmoid bone posteriorly (Fig. 21-3). The medial walls of the maxillary sinuses define the lateral borders of the nasal cavity. The nasopharynx is located directly behind the nasal cavity. There are three turbinates or conchae (superior, middle, and inferior), which protrude downward and medially from the lateral wall into the nasal cavity, forming the superior, middle, and inferior meatus. Superiorly, the cribriform plate contains the branches of

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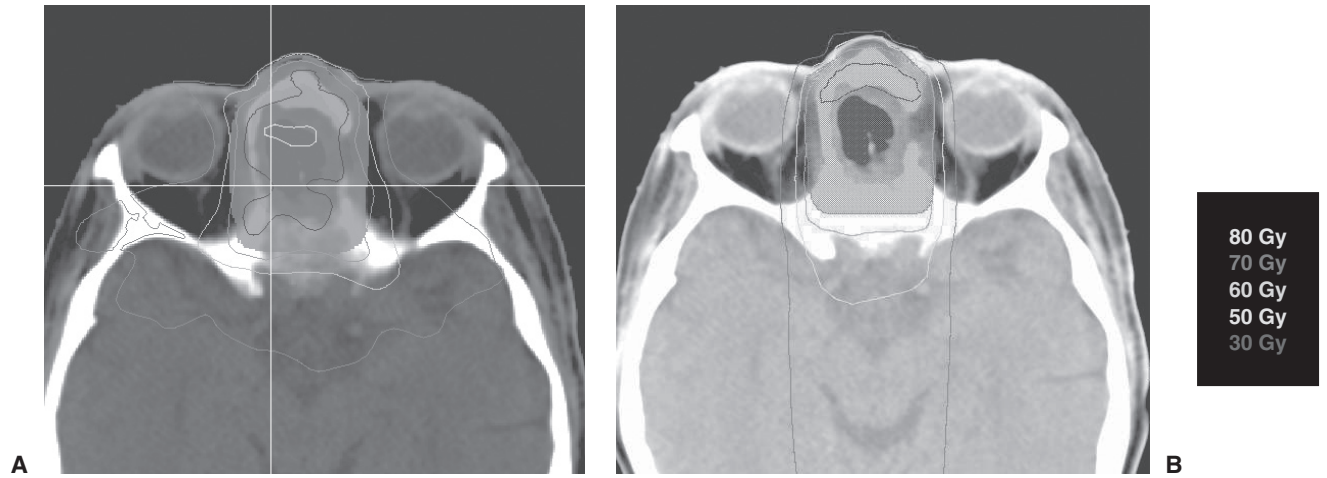



**FIGURE 21-1.** An example of an ethmoid sinus tumor being planned using **(A)** IMRT and **(B)** 3D-CRT. Notice that the 70-Gy isodose line (dark blue) coverage is superior in the IMRT versus the 3D-CRT plan. In addition, there is superior sparing of the optic chiasm when compared with the 3D-CRT plan. IMRT, intensity modulated radiation therapy; 3D-CRT, three-dimensional conformal radiotherapy. (See color insert.)

the olfactory nerve, which innervates the superior nasal concha and upper third of the septum.

Nasal cavity tumors tend to spread by local extension into adjacent bones and sinuses because the bony partitions between the nasal cavity, the sinuses, the orbits, and the cranial vault are quite thin and offer little resistance to cancer infiltration. Nasal cavity tumors can also destroy the septum and invade through the nasal bone to the skin. Lateral wall tumors can spread to destroy the medial maxillary sinus wall and invade into the maxillary antrum, whereas tumors arising in the middle meatus invade first the ethmoid sinus and then the orbit. The sphenoid sinus and the nasopharynx are also sites of tumor extension particularly in more advanced cases. The cribriform plate serves as an avenue for cancer spread to the anterior cranial fossa. Minor salivary gland tumors, particularly adenoid cystic carcinoma, have a higher chance of perineural spread. Commonly involved nerves for perineural spread include olfactory nerves, infraorbital nerve, and the nerves within the superior orbital fissure.

Regional lymph node metastasis occurs in <5% at presentation and approximately 10% of patients have distant metastases. Lymphatic drainage is to the retropharyngeal lymph nodes and the cervical chain. One series from MD Anderson Cancer Center (MDACC) of 51 patients showed a 6% nodal relapse in the subdigastric region in patients who did not receive elective nodal irradiation.[30]

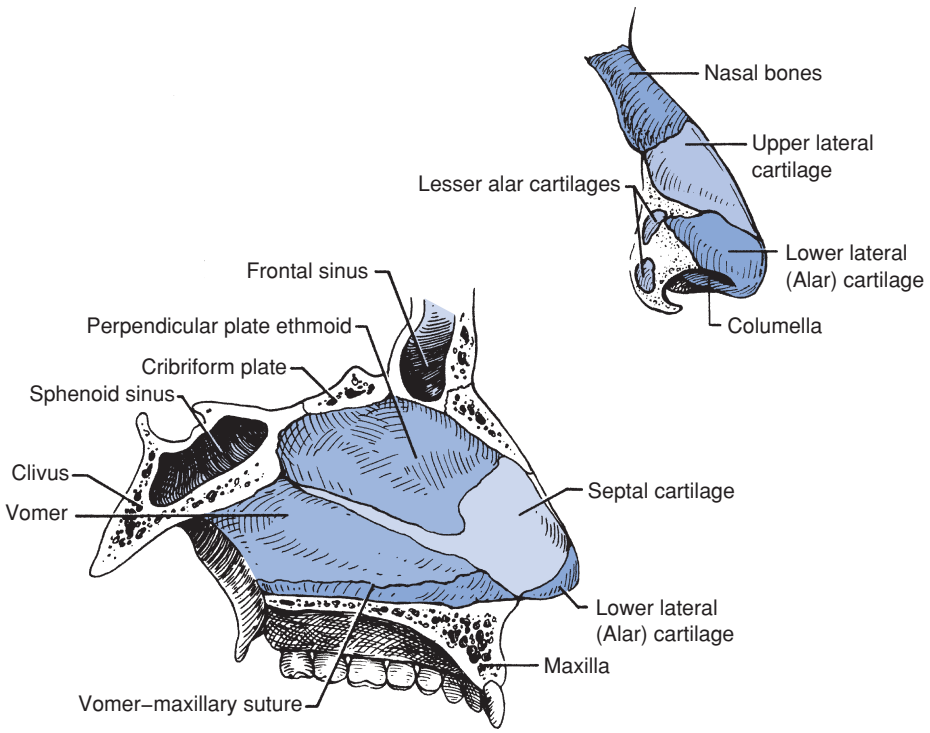



**FIGURE 21-2.** Relationship of bones and cartilages of the nose.

*Source:* From Milton RR, Cassisi NJ, Wittes RE. Cancer in the head and neck. In: Devita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology.* 2nd ed. Philadelphia, PA: JB Lippincott Co; 1985: 407–506, with permission.

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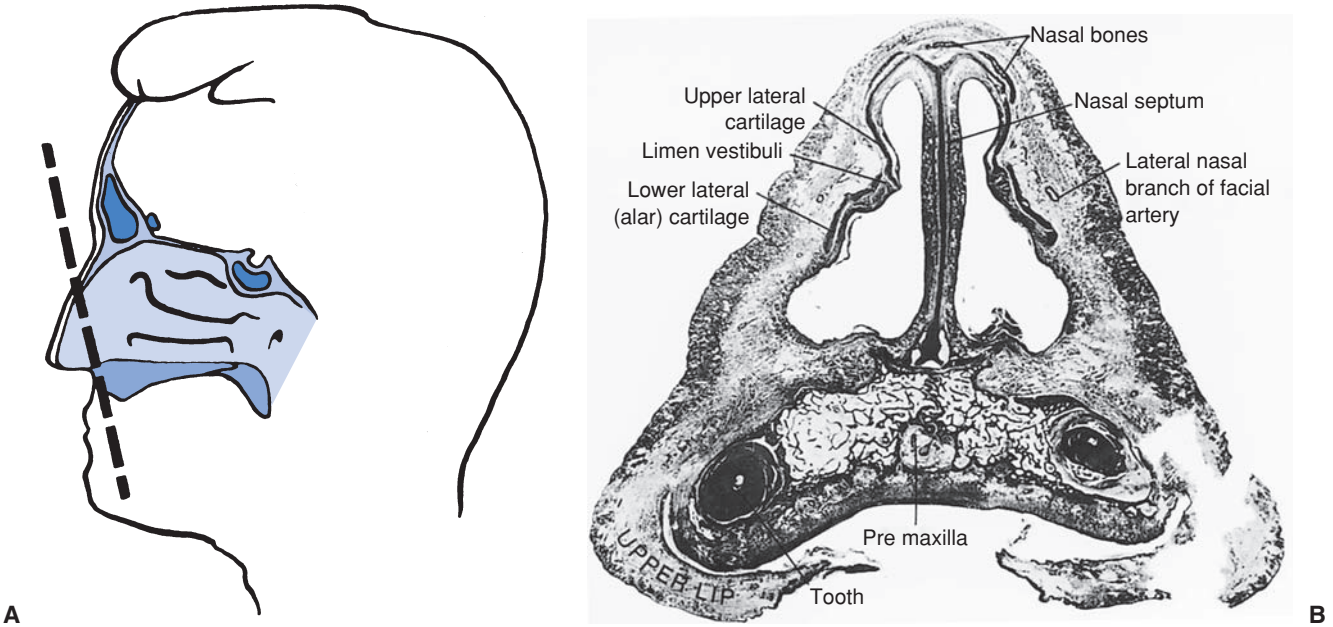



**FIGURE 21-3.** **A:** Coronal whole-organ section through the vestibule. **B:** The upper lateral alar cartilages fuse with the cartilaginous septum. The nasal bones overlap the upper and lower cartilages. The limen vestibule is the junction of the upper and lower lateral cartilage.

*Source:* From Bridger MWM, van Nostrand AWP. The nose and paranasal sinuses—applied surgical anatomy: a histologic study of whole organ sections in three planes. *J Otolaryngol.* 1978;7(suppl 6):1–30, with permission.

## Esthesioneuroblastoma

Esthesioneuroblastoma, also commonly known as *olfactory neuroblastoma*, was initially described in the early 1900s and remains a relatively rare disease accounting for approximately 1% to 6% of all nasal cancers.[31–33] Arising from the olfactory mucosa, it frequently invades the paranasal sinuses, the orbits, and the skull base. Compared with other tumors located in this site, esthesioneuroblastoma is more likely to spread intracranially through the cribriform plate. Nasal obstruction, epistaxis, nasal discharge, pain, visual changes, facial numbness, or a neck mass are symptoms on presentation. Cervical nodal metastases have been reported to range from approximately 17% to 27% of the patients on presentation although distant metastases have been in the order of 10% to 40%.[31] Although different staging systems have been proposed, the Kadish staging system is the most commonly used[34] (Table 21.2). Because esthesioneuroblastoma typically expresses a variety of neuroendocrine markers such as neuron-specific enolase, chromogranin, and synaptophysin, immunohistochemistry can facilitate its diagnosis.

## The Ethmoid Sinus

The ethmoid sinus contains several small cavities, namely, the ethmoid air cells located between the medial wall of the orbit and the lateral wall of the nasal cavity (Figs. 21-4 and 21-5). The ethmoidal sinuses are divided into anterior, middle, and posterior groups of air cells, where the middle group opens directly into the middle meatus. These groups are distinguished from each other on the basis of their sites of communication with the nasal cavity. The lamina papyracea, a porous bone, separates the ethmoid sinus from the orbital cavity and is a source of tumor spread.

Tumors confined to the ethmoid sinus without any involvement of the surrounding structures and sinuses are extremely rare. Tumor extension to the ipsilateral nasal cavity, the maxillary sinus, the orbit, the sphenoid, the anterior cranial fossa, the frontal sinus, and the nasopharynx are common. Contralateral spread to the opposite ethmoid sinus is infrequent and reported to be approximately 10%.[22] Tumors can extend to the orbit through the lamina papyracea and superiorly into the anterior cranial fossa through the cribriform plate, particularly esthesioneuroblastoma. If the dura is compressed but not involved with tumor, it does not portend the poor prognosis when compared with tumor extension with histologic involvement of the dura.

Lymphatic spread is reported to be 3% to 7%.[22] Approximately 10% of the patients subsequently present with nodal failure when the lymph nodes are not electively radiated.

**TABLE 21.2 Kadish Staging of Esthesioneuroblastoma**

| | |
|---|---|
| **Kadish A** | Disease confined to the nasal cavity |
| **Kadish B** | Disease confined to the nasal cavity and involving one or more of the paranasal sinuses |
| **Kadish C** | Disease extends beyond the nasal cavity and the paranasal sinuses to involve either the orbit, base of the skull, cervical lymph nodes, distant metastasis, or with intracranial extension |

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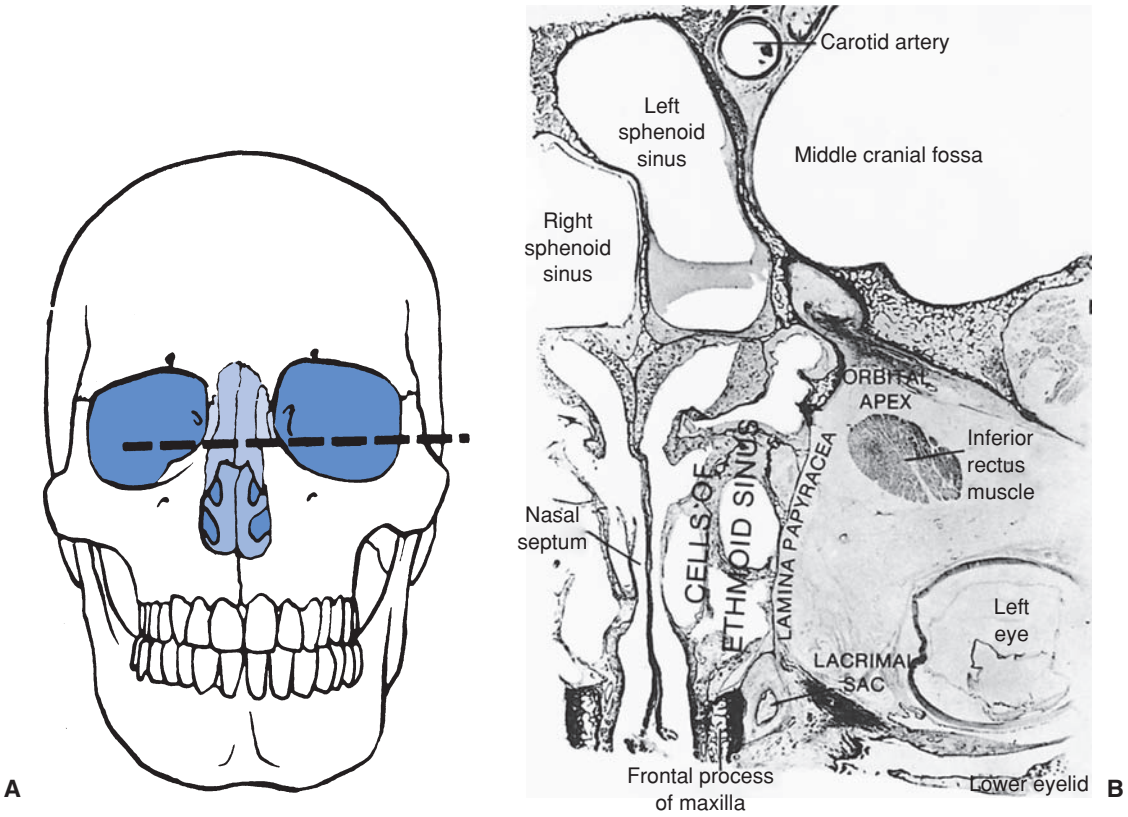



**FIGURE 21-4.** **A:** Horizontal section through the lacrimal sac, the orbit, and the ethmoid and the sphenoid sinuses. **B:** The posterior ethmoid cells extend farther laterally than the anterior cells. The sphenoid sinus is in close relationship to the optic nerve and the orbital apex. Note the short distance between the anterior ethmoid sinuses and the inner canthus.

*Source:* From Bridger MWM, van Nostrand AWP. The nose and paranasal sinuses—applied surgical anatomy: a histologic study of whole organ sections in three planes. *J Otolaryngol.* 1978;7(suppl 6):1–30, with permission.

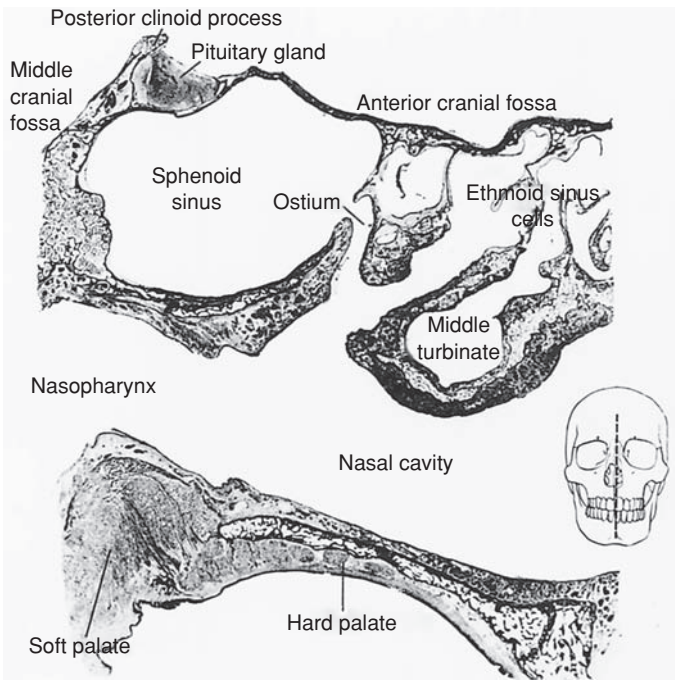



**FIGURE 21-5.** Sagittal section through the nasopharynx and the sphenoid sinus, just left of midline. Note relationship of the sphenoid sinus ostium to the nasopharynx and the posterior nasal cavity. The anterior wall of the sphenoid sinus and the floor of the sella are thin bone.

*Source:* From Bridger MWM, van Nostrand AWP. The nose and paranasal sinuses—applied surgical anatomy: a histologic study of whole organ sections in three planes. *J Otolaryngol.* 1978;7(suppl 6):1–30, with permission.

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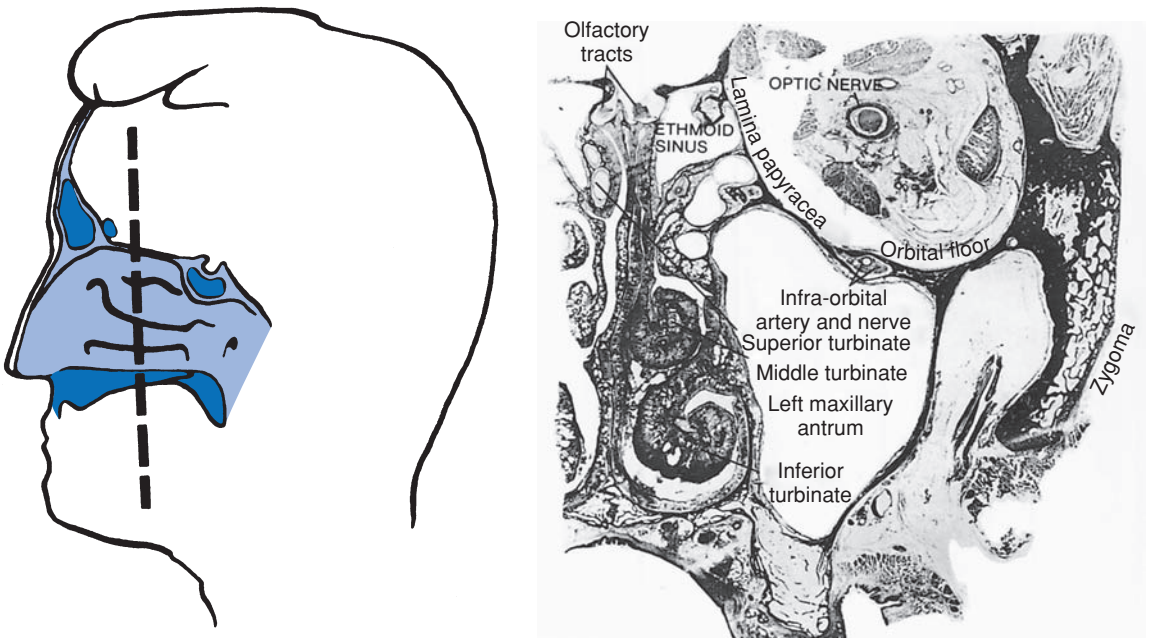



**FIGURE 21-6.** **A:** Coronal section through the maxillary antrum. **B:** Note the thinness of all walls except the hard palate. Lateral to the antrum is the buccinators muscle and fat pad.

*Source:* Modified from Bridger MWM, van Nostrand AWP. The nose and paranasal sinuses—applied surgical anatomy: a histologic study of whole organ sections in three planes. *J Otolaryngol.* 1978;7(suppl 6):1–30, with permission.

## The Maxillary Sinus

The maxillary sinus is shaped like a pyramid where the base separates the maxillary sinus from the nasal cavity (Figs. 21-6 and 21-7). The floor of the maxillary sinus is composed of the alveolar process, and it resides inferior to the floor of the nasal cavity, particularly for the edentulous patients. Superiorly, the floor of the orbit forms the roof of the maxillary antrum, which contains the infraorbital canal. The apex extends to the zygomatic bone. The facial wall is the anterior boundary of the maxillary sinus. Posteriorly, the infratemporal wall borders the infratemporal and the pterygopalatine fossae. Tumors gain access to the base of the skull when they spread posteriorly into these structures.

The Ohngren line, a theoretic plane joining the medial canthus of the eye with the angle of the mandible, divides maxillary sinuses into a suprastructure and an infrastructure.

Tumors can invade the nasal cavity through the medial wall, can involve the maxillary gingiva, may spread to the infratemporal fossa or the pterygopalatine fossa, or invade the orbit by direct superior extension through the ethmoids. In some sense, the pattern of spread of maxillary sinus cancer can vary depending on the site of origin within the antrum. Tumors in the suprastructure can extend to involve the nasal cavity, the ethmoid cells, the orbit, the pterygopalatine fossa, the infratemporal fossa, and the base of the skull. The routes of spread for infrastructure lesions include the hard palate, the alveolar process, the gingivobuccal sulcus, the soft tissue of the cheek, the nasal cavity, and the pterygoid fossa.

Lymphatic drainage ranges between 10% and 20%[20] The incidence can be as high as 30% for poorly differentiated histology. Approximately 10% to 15% will develop nodal relapse if elective lymph node irradiation is not done. When patients relapse in the lymph node region, they are rarely cured and also have high rates of distant metastases. The rate of distant metastasis is approximately 15% to 25%.[19]

## The Sphenoid Sinus

The sphenoid sinus is a midline air cavity within the body of the sphenoid bone. It is located anterior to the clivus, posterior to the superior meatus of the nasal cavity, and medial to the cavernous sinuses (Figs. 21-2 to 21-5). The sphenoid sinus is divided by a septum into the right and left sphenoid sinuses. The septum is often incomplete or very thin and is rarely in the anatomic midline. The pituitary fossa and the optic chiasm lie above and the nasopharynx lies inferior to the sphenoid sinus. Tumors can spread to the cavernous sinus and intracranially to the anterior or the middle cranial fossae. There can be involvement of the adjacent ethmoid sinuses, the clivus, the sella turcica, the nasal cavity, the nasopharynx, and the orbit.

## The Frontal Sinus

The frontal sinuses lie between the outer and inner tables of the frontal bone representing an extension of anterior ethmoidal cell (Figs. 21-2 and 21-8). The two frontal sinuses are irregularly shaped and asymmetric and are separated by a thin bony septum. The sinuses lie above the orbits and drains into the maxillary sinus through the frontal nasal duct.

# TARGET DETERMINATION AND DELINEATION

Understanding the patterns of failure for nasal cavity and paranasal sinus cancers is essential for adequate target determination and delineation. Before delineation of the target, determination

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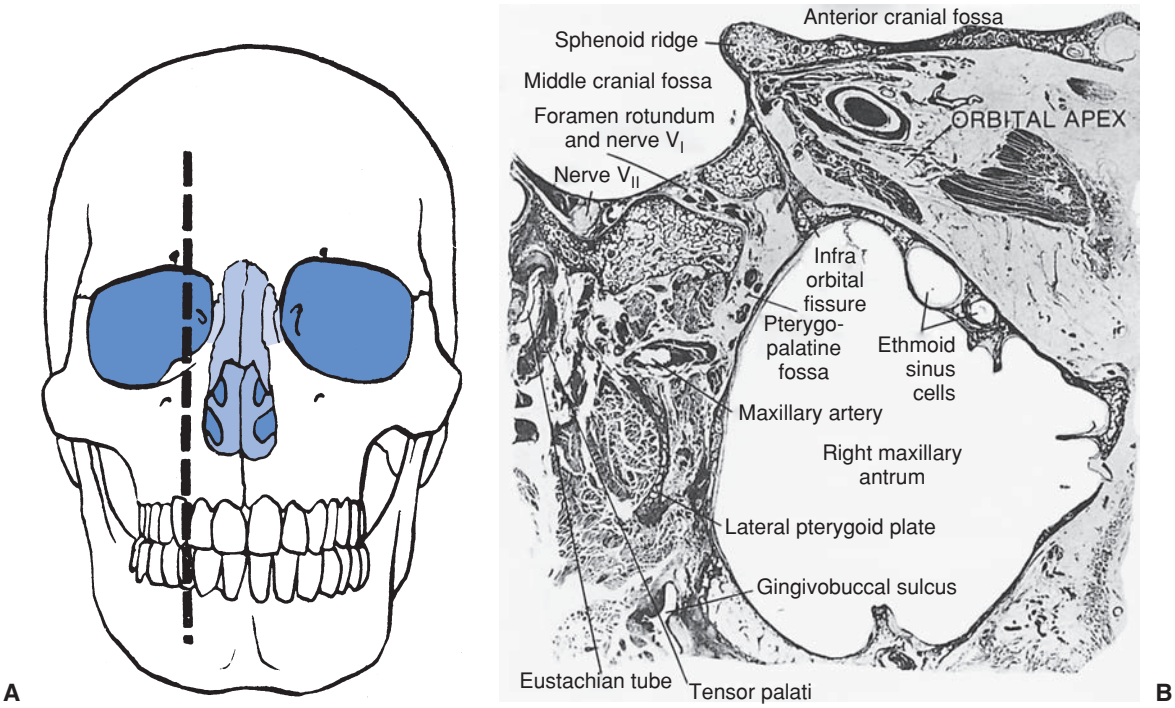



**FIGURE 21-7.** **A:** Sagittal section through the antrum and the apex of the orbit. **B:** The orbital apex communicates with the pterygopalatine fossa by way of the infraorbital fissure. Extension of antral tumor through the posterior wall provides access to the middle cranial fossa along the cranial nerves and the vascular foramina.

*Source:* From Bridger MWM, van Nostrand AWP. The nose and paranasal sinuses—applied surgical anatomy: a histologic study of whole organ sections in three planes. *J Otolaryngol.* 1978;7(suppl 6):1–30, with permission.

of proper sites to be irradiated must be considered. For example, for patients with tumors at risk for perineural spread such as adenoid cystic carcinomas, the planned target volume should include the neural pathways up to the cranial nerve ganglion at the base of skull.

For definitive treatment, the gross tumor volume (GTV) is outlined by using all available imaging, that is, MRI and/or positron emission tomography (PET). MRI fusion with treatment planning CT scan can further aid in the delineation of the GTV. Unless contraindicated, every patient should undergo MRI due to the complex anatomy of this region as MRI is superior in differentiating between mucous versus tumor as well as visualizing more clearly the different nerve pathways. One study from Hokkaido University School of Medicine compared clinical outcomes among 82 patients who underwent CT-assisted planning to those of 88 patients who had no such treatment planning.[35] The investigators found that the combined use of CT and the shell for immobilizations in treatment planning allowed greater accuracy in tumor coverage. Multivariate analysis for predicting significant prognostic factors confirmed the critical role of CT in terms of overall survival and primary tumor control. Notably, the actuarial 5-year survival rate was improved by 10% in patients who underwent CT-assisted treatment planning with a particular improvement observed among patients whose tumors were located adjacent to critical organs at risk such as the brain and eye. The clinical tumor volume (CTV) is defined as the GTV plus microscopic spread of the tumor. Typically, this involves one or more adjacent sinuses. The planning target volume (PTV) typically includes a margin ranging from 3 to 5 mm surrounding the CTV. Each institution should have its own set of guidelines on the margin needed to account for patient motion and daily setup errors. For postoperative lesions, the CTV is defined as the postoperative bed which should include previous sites of gross disease as depicted from preoperative imaging, as well as the entire postoperative bed (Fig. 21-9). Areas with positive margins and/or gross residual disease should receive a higher dose, although every attempt to achieve gross total resection is needed to maximize local control.[36] Due to the possibility of surgical seeding, postoperative CTV should also include all tissue planes surgically violated.[37,38]

## REGIONAL LYMPH NODE IRRADIATION

For patients treated with radiation therapy for carcinomas of the nasal cavity and the paranasal sinuses, uncertainty exists regarding the optimal treatment volume, particularly with respect to irradiation of the neck for patients without clinical evidence of nodal involvement. This issue is especially pertinent because the proportion of patients with clinical evidence of lymph node metastasis at presentation is relatively low, ranging from 3% to 25%, depending primarily on the histological subtype and location of the primary tumor.[19,39,40] Presently, elective neck irradiation (ENI) is controversial and indications for its use differ both within and between institutions.

Over the last couple of decades, studies attempting to identify groups of patients who may benefit from ENI have been published. Although several small historic series had suggested that

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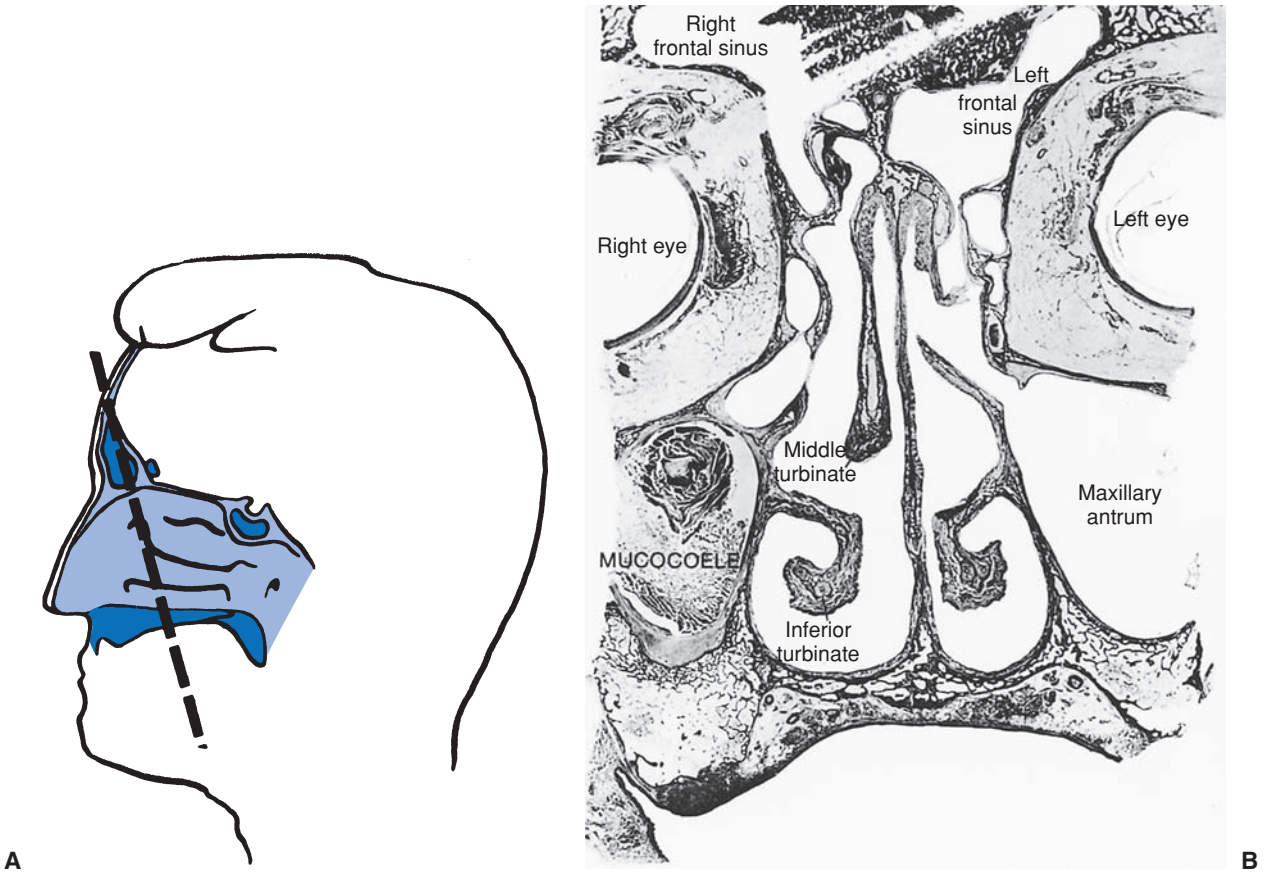



**FIGURE 21-8.** **A:** Coronal section through the frontal sinuses, the midnose, and the anterior ethmoids. **B:** Note left frontonasal duct and ostium of the left maxillary antrum, which open into the middle meatus. The middle turbinate appears to arise from the roof of the nasal cavity near the septum, which is the appearance during physical examination.

*Source:* From Bridger MWM, van Nostrand AWP. The nose and paranasal sinuses—applied surgical anatomy: a histologic study of whole organ sections in three planes. *J Otolaryngol.* 1978;7(suppl 6):1–30, with permission.

ENI was not necessary due to the low incidence of nodal relapse among patients with carcinomas of the nasal cavity and the paranasal sinuses, investigators from MDACC reported a nodal relapse rate of 38% among 73 patients treated for maxillary sinus carcinomas with squamous cell and undifferentiated carcinomas.[39] A subsequent analysis from Loyola University demonstrated a 29% rate of nodal recurrence among 42 patients and recommended routine ENI for those with SCC of the maxillary sinus.[19]

More recently, investigators from Stanford University and UCSF demonstrated a 5-year actuarial nodal relapse rate of 12% among 97 patients treated for maxillary sinus carcinoma.[19,20] On the basis of observation that all patients who failed in the neck had T3 or T4 cancers, the authors recommended ENI for these subsets of patients. University of Florida concurred with Stanford on their series of SCC of the maxillary sinus. The authors recommended that at least ipsilateral ENI be done for T3 or T4 N0 disease and

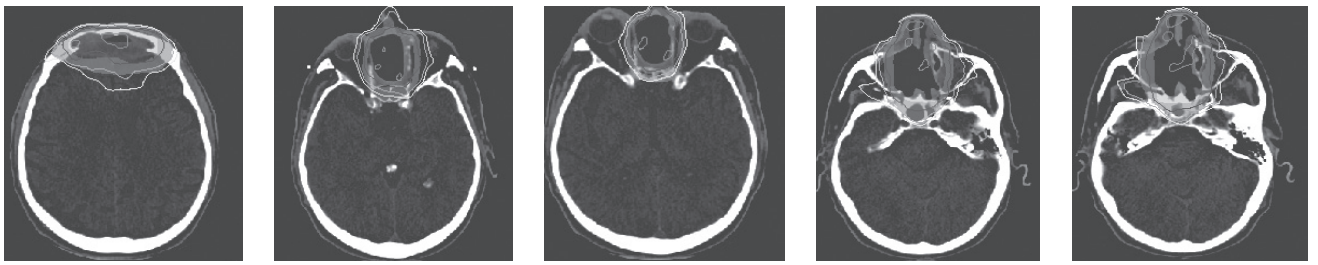


**FIGURE 21-9.** An example of different axial slices showing contours of a patient with ethmoid sinus tumor who underwent craniofacial resection. Red is the clinical target volume, which encompassed the preoperative GTV plus postoperative bed, whereas magenta is the PTV. Light blue is the 60-Gy prescription isodose line. (See color insert.) GTV, gross tumor volume; PTV, planning target volume.

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that bilateral ENI should be offered to patients with very large or recurrent primaries that cross the midline. The authors further noted a neck failure in a patient with T2 N0 disease and recommended that ENI should also be considered for early-staged T1–2 N0 patients.[41] Due to the relative rarity of patients with nonmaxillary sinus and nonsquamous cell cancers, the data reporting on ENI in this setting are extremely limited. However, a recent report from the University of Florida showed that the rate of nodal relapse was 27% among patients with esthesioneuroblastoma, thereby suggesting that ENI may be of benefit.[21] However, others have challenged the need of ENI for patients who presents with N0 esthesioneuroblastoma as effective salvage can be done at a later time when patients do recur in the neck.[42] Unlike SCC, SNUC, or esthesioneuroblastoma, ENI is not recommended for adenocarcinoma with N0 disease. In one study reporting on 47 patients with adenocarcinoma of the ethmoid sinuses, no patients experienced nodal relapse.[43] Similarly, a series from France showed neck irradiation is not needed for N0 disease in their experience with 95 patients with ethmoid adenocarcinoma.[44]

## RADIATION THERAPY TECHNIQUE—DOSE SPECIFICATIONS

IMRT has been shown to improve coverage while limiting the dose to the surrounding normal tissues by several institutions when compared with conventional radiotherapy techniques. Compared with historical controls, the authors reported more encouraging local control rates when paranasal sinus tumors are treated with IMRT.[5,13,16,17]

Different institutions have different guidelines regarding dose specifications. For definitive cases, treatment plans are generally designed to provide a dose of 70 Gy in 2 Gy to 2.12 Gy fractions to 95% or more of the gross disease. This is known as the $PTV_{GTV}$. A dose of 59.4 to 63 Gy is prescribed to 95% or more of the high-risk CTV, namely, $PTV_{CTV\ high\ risk}$. A low-risk CTV can also be prescribed, as determined by the treating physician, where 95% or more receives 54 to 56 Gy. This is known as the $PTV_{CTV\ low\ risk}$. For postoperative cases, the dose delivered to the high-risk CTV can range from 60 to 66 Gy, whereas the low-risk CTV receives typically 54 Gy. Examples of sample treatment plan can be found in Figures 21-9 and 21-10. For critical normal structures, dose constraints are designed to limit the maximum dose to 54 Gy for the brain stem and the optic nerves, 54 Gy to the optic chiasm, 45 Gy for the spinal cord, and 60 Gy for the temporal lobes. Table 21.3 lists dose specifications and normal tissue dose volume constraints.

## TREATMENT RESULTS

### The Nasal Cavity

The preferred treatment approach for cancer of the nasal cavity is surgery with or without radiotherapy, except for small lesions where radiotherapy and surgery are equally effective.[4] The choice of one modality over another is contingent upon the size, location, and the potential cosmetic outcome of treatment. Posteriorly located lesions are treated best by surgery, whereas anteriorly located lesions are best served with brachytherapy. Of note, although definitive radiotherapy yields a high cure rate for small nasal cavity SCCs, complications as a result of high doses of radiotherapy such as optic nerve injury can occur. One series from MDACC treated 45 patients with curative intent.[30] Eighteen patients were treated with radiotherapy alone of which brachytherapy was used in five. Postoperative radiotherapy was given to the remaining 27 patients. Thirty-one patients had lesions located in the lateral wall or floor of the nasal cavity, and 14 lesions were located in the nasal septum. SCC comprised 67% of the cohort. The 5- and 10-year disease-specific survival and overall survival rates were 83% and 69% versus 80% and 58%, respectively.

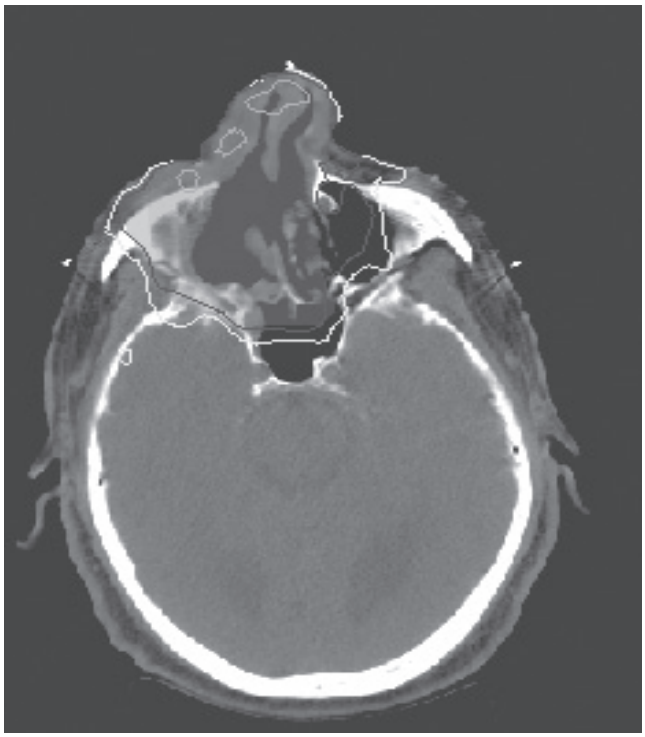


**FIGURE 21-10.** An example of a patient with maxillary sinus tumor who underwent craniofacial resection. Red is the clinical target volume which encompassed the preoperative GTV plus postoperative bed, whereas magenta is the PTV. Dark blue is the 60-Gy isodose line, whereas yellow is the 54-Gy isodose line. (See color insert.) GTV, gross tumor volume; PTV, planning target volume.

**TABLE 21.3 Dose Specification and Normal Tissue Constraint for Cancer of the Paranasal Sinus**

| Structure | Dose Specifications | Dose Constraint (Maximum) |
|---|---|---|
| GTV (unresectable) | 70 Gy | — |
| CTV (high-risk postoperative) | 60–66 Gy | — |
| CTV (low-risk postoperative) | 50–54 Gy | — |
| Brain stem | — | 54 Gy |
| Spinal cord | — | 45 Gy |
| Optic nerves | — | 54 Gy |
| Chiasm | — | 54 Gy |
| Retinae | — | 50 Gy |

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**TABLE 21.4 Overall Survival Rate with Radiation to the Nasal Cavity**

| Center | 5-yr Survival (%) |
|---|---|
| MDACC[30] | 75 (actuarial) |
| Roswell Park[32] | 67 (actuarial) |
| University of Puerto Rico[46] | 56 (overall) |
| Mallinckrodt[75] | 52 (actuarial) |

Several others also published their outcomes with survival rates up to 75%[30,45–47] (Table 21.4). Patient population varies among these series but, in general, small lesions involving the nasal septum are best cured with radiotherapy, particularly brachytherapy.

## Esthesioneuroblastoma

Due to the rarity of this disease, no prospective studies are available to determine the optimal treatment. In one series, combined modality treatment consisting of surgery and postoperative radiotherapy has demonstrated greater benefits when compared with single-modality therapy where the recurrence-free survival is 92% in those who underwent surgery followed by adjuvant radiation versus 14% surgery alone versus 40% radiation alone.[48] The 5- and 10-year overall survival rates were 74% and 60%, respectively. The traditional postoperative radiotherapy dose ranges from 50 to 66 Gy. An analysis of the Surveillance, Epidemiology, and End Results (SEER) database showed that for the 511 olfactory neuroblasoma cases, 5-year overall survival stratified by treatment modality was 73% for surgery with radiation, 68% for surgery alone, 35% for radiation alone, and 26% for neither surgery nor radiation. There was a significant overall survival difference between the four treatment groups with a $p < 0.001$.[49] In general, most series favor surgery followed by postoperative radiotherapy for Kadish A lesions where the disease is limited to the nasal fossa and Kadish B lesions where the disease extends to the paranasal sinuses. For the patients with disease extension beyond the paranasal sinuses, chemotherapy (i.e., cisplatin, etoposide, doxorubicine, vincristin cyclophasphamide) is often added to surgery and radiation.[50] Cisplatin and etoposide chemotherapy has been used successfully in conjunction with proton beam radiotherapy (equivalent to 68 Gy of photon irradiation) in a small series of nine patients with success. Eight out of nine patients have been controlled with a median follow-up of 20.5 months. Longer follow-up will be required to determine the long-term success rate.[32]

Whereas most centers advocated surgery followed by postoperative radiotherapy in the treatment of esthesioneuroblastoma, some centers prefer preoperative radiotherapy plus chemotherapy as a complement to radical craniofacial resection, attempting to reduce the tumor burden before surgery. Polin et al.[51] reported 34 consecutive patients with biopsy-proven esthesioneuroblastoma who underwent preoperative radiation therapy with or without chemotherapy followed by surgical resection. Patients received 50 Gy along with either single-agent cyclophosphamide, vincristine, or in combination with Adriamycin. The overall 5- and 10-year survival rates were 81% and 54.5%, respectively. The results are impressive as 23 patients had Kadish C disease. In light of all these promising results, a recent meta-analysis of results from different centers showed that the 5-year overall and disease-free survival averaged 45% and 41%, respectively.[33] In terms of the surgical approach, a recent meta-analysis has shown that endoscopic sinus surgery achieved comparable survival to open surgery and the authors suggest that it is a valid treatment method. However, prospective studies should be done to validate this finding.[52]

Several prognostic factors are noted for esthesioblastoma. Female patients and patients older than 50 years of age have a worse prognosis.[53] Overall survival is worse with those who present with node-positive disease versus those with node-negative disease (29% vs. 64% at 5 years). Patients who present with a high Hyams grade (defined by examining the histologic features such as having a lobular architecture, neurofibrillary background, rosettes, nuclear pleomorphism, mitosis, necrosis, and calcification of the tumor) did significantly worse in one series when compared with low Hyams grade, 36% versus 81% 5-year overall survival.[54] The failure rates are in the range of 24% to 75% with the 5-year overall survival rates ranging from 60% to 78% (Table 21.5). A multicenter retrospective review showed T1–3, N0, R0/R1 resection, and at least 54 Gy of postoperative radiation therapy in multivariate analysis, were independent factors predicting the outcome in olfactory neuroblastoma.[55]

**TABLE 21.5 Overall Survival and Locoregional Recurrence Rates with Radiation for Esthesioneuroblastoma**

| | | Overall Survival | | | Disease-free Survival (%) | | |
|---|---|---|---|---|---|---|---|
| Center | Follow-up Year | 5 yr | 10 yr | 15 yr | 5 yr | 10 yr | LR (%) |
| University of Virginia[45] | 10.8 | 78% | 71% | 65% | — | — | 38 |
| UCLA[33] | 7.2 | 74% | 60% | | — | — | 33 |
| Mayo Clinic[91] | 6.0 | 61% | | | 55 | — | 34 |
| University of Iowa[74] | 6.3 | 61% | 24% | | 56 | 42 | 31 |
| Northwest[71] | 4.3 | 60% | | | 33 | — | 75 |
| Mallinckrodt[75] | 8.0 | 66% | | 56 | — | 27 | |
| Germany[63] | 7.2 | 7.8 yr (median survival) | | | 60 | — | 24 |
| Rare Cancer Network | 6 | 64% | | | 57% | | |

LR, local recurrence; UCLA, University of California, Los Angeles.

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## The Paranasal Sinus

Local disease progression and recurrence constitute the predominant patterns of failure for patients treated for carcinomas of the nasal cavity and the paranasal sinuses. The fact that most patients with uncontrolled tumor growth at the primary site will ultimately die of their disease is a testament to the paramount importance of local control. With the reported rates of 5-year overall survival ranging from 27% to 54%, it is clear that treatment results remain suboptimal and that considerable room exists to improve outcomes.[7,39,56]

Owing to their rarity, the literature to date reporting on patient outcomes after treatment for carcinomas of the paranasal sinuses and the nasal cavity are largely limited to retrospective single-institutional reports. Although some generalizations regarding treatment can be made based on these data, comparisons between series are complicated by the tremendous amount of heterogeneity with respect to such factors as therapeutic strategy, stage, histology, and disease site. Furthermore, it is unknown how potential imbalances in seemingly important prognostic variables such as intracranial invasion, orbital infiltration, and cranial nerve involvement influence treatment results.

The most consistently identified factor predicting for improved survival among those treated for carcinomas of the nasal cavity and the paranasal sinuses is gross total tumor resection. Among 127 patients treated at UCSF, the 5-year local control was 65% for those treated with postoperative radiation therapy after gross total resection compared with 44% among those who underwent postoperative radiation therapy in the presence of macroscopic disease.[15] In another study from the Netherlands, the addition of debulking surgery before radiation therapy dramatically improved 5-year overall survival from 9% to 60%.[57] The other variable which has been consistently demonstrated to correlate with outcome is tumor extent, with most studies confirming that patients with T1–2 tumors having superior rates of local control and overall survival compared with those with T3–4 tumors.[58–60] Because the vast majority of patients present with locally advanced cancers, additional data analyzing prognostic factors such as intracranial invasion, cranial nerve involvement, dural attachment, and orbital infiltration—all of which would currently categorize a tumor as T4 in the current AJCC staging system—is urgently needed. Although the AJCC staging system published in 2002 attempted to address this by dividing cases into T4a (resectable) and T4b (unresectable), it is still unclear how this distinction may influence prognosis. Mendenhall et al. reported their experience from the University of Florida and found that the probability of local control and cause-specific survival is better after surgery and radiation compared with definitive radiation.[61] However, there is still a need to improve the efficacy of treatment for this disease despite surgery being the preferred treatment and providing the best results, even accounting for the inherent bias in patient selection as discussed above.[62]

Despite the biases discussed earlier, several large series reporting treatment results are particularly instructive. Investigators from Memorial Sloan-Kettering Cancer Center recently analyzed 85 patients with carcinomas of the nasal cavity and the paranasal sinuses uniformly treated by gross total resection followed by postoperative radiation therapy and reported a 5-year local control of 62%.[5] On multivariate analysis, squamous cell histology and involvement of the cribriform plate predicted for an increased likelihood of local recurrence. In another series from Washington University, the 5-year local control was 58% among 106 patients treated by radiation therapy alone or combined with surgery for paranasal sinus cancer.[7] Likewise, investigators from UCSF reported a 5-year local control rate of 62% among 127 patients treated by radiation therapy with or without surgery from 1960 to 2005.[15] Although most of the patients included in the above-mentioned series had maxillary sinus cancers and squamous cell histology, the respective proportions nevertheless ranged from 43% to 76% and 53% to 82%, respectively. These differences are potentially significant because other studies have suggested that patients with maxillary sinus tumors have better outcomes than those whose primary tumors arise from the ethmoid, the frontal, and the sphenoid sinuses. The infrequency of the latter as well as the difficulty in determining the exact site of origin make drawing definitive conclusions problematic.[8,43,63] Similarly, others have shown that patients with nonsquamous cell histologies have improved outcomes compared with those with SCC of the nasal cavity and paranasal sinuses. Although a study from the University of Florida reported a very encouraging 5-year local control rate of 70% among 78 patients treated with radiation therapy, this study was notable for its large proportion of patients with adenocarcinoma.[8]

More recently, studies have attempted to evaluate the significance of radiotherapy technique on patient outcome, particularly with the widespread acceptance of 3D-CRT and IMRT. Using 3D conformal techniques, investigators from the University of Michigan reported a 5-year local control rate of 65% among 24 patients treated through surgery and postoperative radiation therapy.[64] Although this finding suggested that 3D radiation therapy improved local control compared with historic controls, a study from France showed that 14 of 25 patients experienced local recurrence after 3D-CRT with or without surgery for carcinomas of the paranasal sinuses.[65] However, it must be noted again that attempts to draw comparisons between respective series are complicated by the wide variability in surgical and radiation techniques employed across institutions. Tables 21.6 and 21.7 are selected treatments results from different institutions focusing on maxillary sinus and ethmoid sinus tumors.

Regarding IMRT for the nasal cavity and the paranasal sinuses, investigators at UCSF reported on 36 patients, 32 of whom were referred after gross total resection, treated between 1998 and 2004.[16] With a median follow-up of 39 months, the 2- and 5-year estimates of local control were 62% and 58%, respectively. The authors concluded that IMRT did not appear to improve disease control, but the low incidence of complications was encouraging. An important finding from this study was that all failures occurred within the high-dose region and that no geographic misses or marginal failures were observed. Investigators from Belgium similarly reported a 4-year local control of 68% among 39 patients treated with IMRT in the postoperative

**TABLE 21.6 Overall Survival Rates with Radiation to the Maxillary Sinus**

| Author | 5-yr Overall Survival (%) |
|---|---|
| Sakata et al. (1993)[69] | 46 |
| Zaharia et al. (1989)[6] | 42 |
| Robertson et al. (1992)[96] | 61 |
| Shibuya et al. (1994)[97] | 65 |
| Paulino et al. (1998)[98] | 47 |
| Tiwari et al. (2000)[99] | 64 |
| Ozsaran et al. (2003)[100] | 53 |
| Nishino et al. (2000)[101] | 76 |
| Ogawa et al. (2001)[102] | 48 |
| Hinerman et al. (2011)[41] | 30 |

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**TABLE 21.7 Overall Survival Rates with Radiation to the Ethmoid Sinus**

| Author | 5-Year Overall Survival (%) |
|---|---|
| Lin et al. (2004)[103] | 49.4 (3 yr) |
| Claus et al. (2002)[104] | 60 |
| Magrini et al. (2004)[105] | 48.6 |
| Cantu et al. (1999)[106] | 47 |
| Jiang et al. (1998)[107] | 55 |
| Knegt et al. (2001)[108] | 79 |
| Tiwari et al. (1999)[109] | 63 |
| Moreau et al. (1997)[110] | 48 |
| De Gabory et al. (2010)[44] | 78 (DSS) |

DSS, disease-specific survival.

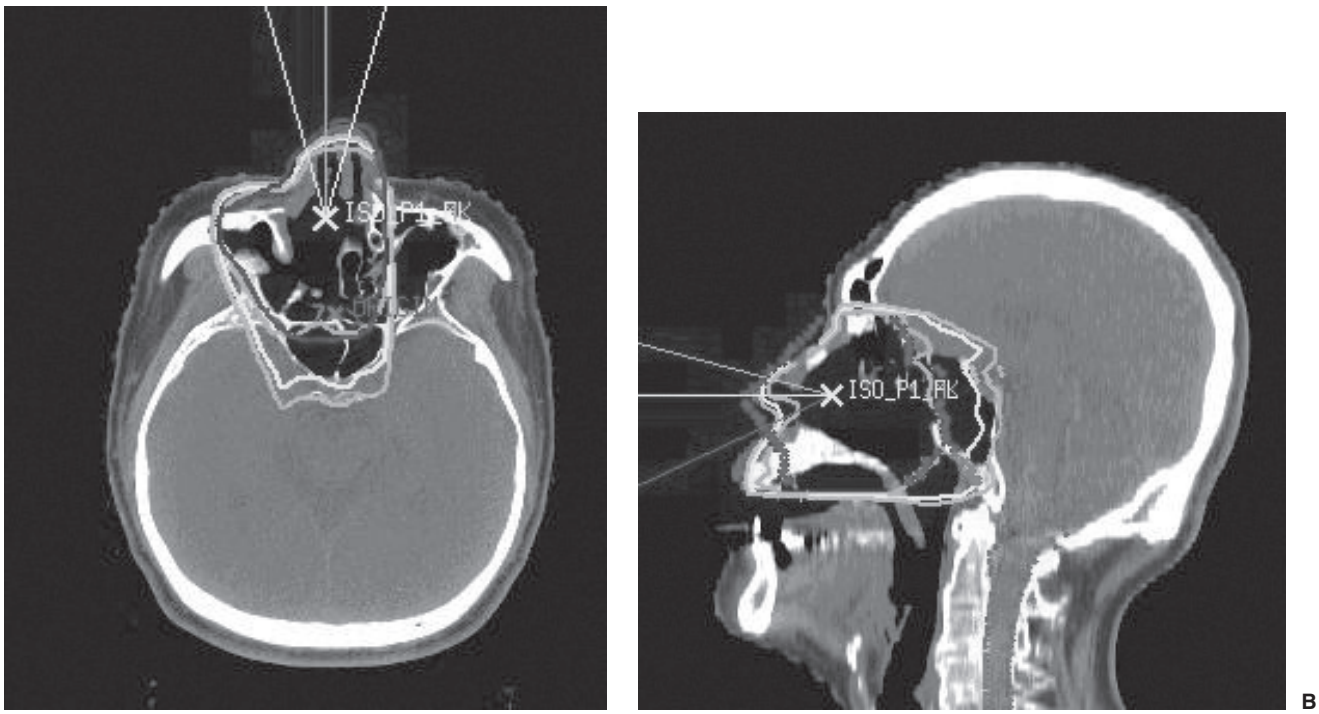
setting.[66] A study from Stanford of 52 patients treated with IMRT demonstrated a 25% rate of local failures, with 12 of 13 failures being in-field.[37] There were six regional failures, of which four were out-of-field regional failures; however, all four of these patients had received bilateral nodal irradiation and all four were extranodal recurrences. An example of a patient with nasal cavity and maxillary sinus tumor who underwent postoperative IMRT is shown in Figure 21-11.

Although some have shown that the addition of chemotherapy to radiation therapy has the potential to improve local control and/or overall survival for patients with carcinomas of the nasal cavity and paranasal sinuses, the published data are limited to small, single-arm studies on highly selected patients.[67–69] Similarly, although strategies such as altered fractionation, brachytherapy, and particle beam therapy have been proposed as a means of improving the therapeutic ratio, their use is largely considered investigational.

Lastly, the question of whether advances in surgical and radiation therapy technique have contributed to improvements in clinical outcome remains somewhat controversial. A recent meta-analysis of 154 publications demonstrating survival rates of 28%, 36%, 43%, and 51% among patients treated in the 1960s, 1970s, 1980s, and 1990s, respectively, suggested that outcomes have improved over time.[70] However, a review of the UCSF experience did not corroborate this finding and instead suggested that the lack of improvement was due to underlying selection bias with the observation that cases referred for definitive therapy have become more complex with innovations in skull base surgery and radiation therapy delivery methods.[15]

## Sinonasal Undifferentiated Carcinoma

Primary sinonasal neuroendocrine tumors can be divided into four major histologic phenotypes: esthesioneuroblastoma (discussed in preceding text), sinonasal undifferentiated carcinomas (SNUC), neuroendocrine carcinoma, and small cell undifferentiated carcinoma.[71] SNUC portend a poor prognosis owing to its high rates of locoregional failures as well as distant metastases. Early reports on patients with SNUC were dismal.[72–74] An international collaborative study reporting on the results of craniofacial resection for malignant paranasal sinus tumors reported a 5-year overall survival rates of 0% for the undifferentiated




A B

**FIGURE 21-11.** An example of a patient with squamous cell carcinoma and the nasal septum and the right maxillary sinus. The patient underwent surgery with a close margin. Notice the nice conformality of the 60-Gy isodose line encompassing the nasal cavity and the right maxillary sinus while keeping the optic structures and the brainstem below tolerance. **A:** Axial view. **B:** Sagittal view. Four noncoplanar beams were used in this IMRT plan. (See color insert.) IMRT, intensity modulated radiation therapy.

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tumors.[56] Investigators have suggested that the poor outcomes in these series could have been attributed to the lack of chemotherapy or the inclusion of small cell histologies, as recent data are more promising.[71] Rischin et al.[75] have reported promising results with chemoradiation for SNUC patients. In their series, 10 patients of whom 9 had T4 disease underwent three cycles of induction platinum and 5-flurouracil followed by concurrent chemoradiation using cisplatin. With a median follow-up of 43 months (range, 8–101 months), the 2-year progression-free and overall survival rates were 43% and 64%, respectively. Rosenthal et al.[71] also reported a 5-year overall survival rate of 64.2% for patients with SNUC histology in their cohort of sinonasal neuroendocrine tumors. Some investigators also have used superselective high-dose cisplatin infusion with concomitant radiotherapy and achieved promising results where a majority of the patients with advanced cancer of the nasal cavity and the paranasal sinuses are cured while their organs are preserved. None of these patients underwent surgery. In this series, almost 20% had undifferentiated tumors.[76] The authors from University of Michigan showed that in their 13-year experience of 19 SNUC patients, local control was best among those treated nonsurgically, although statistically nonsignificant. The survival remains dismal at 22% at 5 years. The authors concluded that although it is possible that upfront radiation or chemoradiation will lead to better local control rates, surgery remains a mainstay of treatment.[77] Chen et al. has shown in their series that gross total resection should be the goal of all treatment whenever possible. With a median follow-up of 58 months among living patients, the 5-year local control rate was 74% for those who had gross tumor resection compared with 24% with subtotal tumor resection.[36] An example of treatment planning for a patient with T4 SNUC is shown in Figure 21-12.

## COMPLICATIONS OF TREATMENT

For patients treated with radiation therapy for malignancies of the nasal cavity and the paranasal sinuses, the high doses required to achieve local control coupled with the proximity of disease sites to sensitive normal tissue have historically been associated with a high incidence of treatment-induced morbidity. In particular, the location of these tumors in relation to the optic pathways, central nervous system, and bony structures has raised concerns regarding the potential development of such complications as blindness, brain injury, and osteoradionecrosis. In analyzing the frequency and severity of clinical complications reported across the literature for patients treated with radiation therapy for tumors of the paranasal sinuses and the nasal cavity, it is important to recognize that most publications have focused on those treated using conventional techniques.

Investigators from Keio Hospital in Japan reported a 25% incidence of radiation retinopathy and a 7% incidence of neovascular glaucoma among 25 patients treated for malignancies of the nasal cavity and the paranasal cavity.[78] Another study from Hokkaido University Hospital in Japan observed a 28% incidence of ocular complications among 115 patients who survived >2 years after radiation therapy with or without surgery for carcinoma of the maxillary sinus.[79] Investigators from the Netherlands noted that 19 of 73 patients (26%) developed visual complications including 3 patients who required enucleation due to infectious causes and 15 patients who developed blindness.[57] A study from Florida detected a 27% and 6% incidence of unilateral and bilateral blindness, respectively, among 78 patients treated by conventional radiation therapy techniques for carcinomas of the paranasal sinuses and the nasal cavity. In this same study, the authors reported that osteoradionecrosis developed in 6 of 78 patients.[8]

The data on neurocognitive functioning after radiation therapy for malignancies of the nasal cavity and the paranasal sinuses is more limited. Investigators from the MDACC analyzed 19 patients and found that memory impairment developed in 80% of patients during the follow-up period, with one-third of patients having difficulty with motor functioning and coordination.[80]

Although several studies have suggested that newer techniques such as IMRT have the potential to reduce complications, careful attention to targeting and dose constraints are essential to minimized radiation-induced complications.[81–83] In the UCSF series reporting on 36 patients treated using IMRT, reported acute complications included mucositis, conjunctivitis, keratitis, cellulitis, dacrocystitis, and parotiditis—all of which resolved with conservative management.[16] In the late setting, no patients experienced a complete loss of vision as a result of treatment with reported side effects including chronic xerophthalmia, chronic lacrimal stenosis, cataract formation, Eustachian tube dysfunction, and radiation necrosis of the gyrus rectus muscle resulting in gaze limitation. A longitudinal analysis of the UCSF experience showed that the incidence of grade 3 or higher late complications differed significantly among patients treated with conventional radiation therapy compared with those treated by 3D-radiation therapy and IMRT. For instance, 13% of patients treated with IMRT developed any grade 3 or higher late complication compared with 22% and 54%, respectively, of patients treated using 3D-radiaiton therapy and conventional radiation therapy, respectively.[15] Investigators from Belgium found that there is a high rate of radiation-induced hypopitutitarism after high-dose radiotherapy and therefore recommend endocrinologic surveillance for these patients. Thirteen of the 21 patients evaluated at the late morbidity clinic had hormonal disturbances of whom 24% had definitive evidence of hypopituitarism with multiple homonal definciencies.[84]

Further studies focusing on time-dose factors, particularly with respect to ocular and central nervous system toxicity, are needed to better delineate the optimal treatment parameters for patients undergoing radiation therapy for carcinomas of the nasal cavity and paranasal sinuses. It is likely that with increased understanding of the tolerance levels of normal tissue combined with continued improvements in image-based radiation therapy, treatment-related complications will continue to decline. Among long-term survivors, studies evaluating the incidence of pituitary dysfunction should be performed given the intricate relationship between the hypophysis and the base of skull. Formal ophthalmologic and auditory testing should also be considered in the prospective setting for patients treated for carcinomas of the nasal cavity and the paranasal sinuses.

## CHEMOTHERAPY

Chemotherapy has been used as a single agent for recurrent disease or as a radiosensitizer for unresectable SCC of the nasal cavity or the paranasal sinuses. Cisplatin-based chemotherapy is the most commonly used regimen and preliminary results have been promising.[85,86] Harrison et al. reported a series of 20 patients with T4 malignant skull base tumors, in which case high-dose cisplatin at 100 mg/m$^2$ was given on days 1 and 22 of radiation therapy using a delayed accelerated fractionation to a total dose of 70 Gy. With a median follow-up of 11 months, the 2-year local progression–free, distant metastases–free, and overall survival rates were 94%, 57%, and 80%, respectively.[10] The authors subsequently published a prospective phase II trial using the same treatment regimen for T4 unresectable tumors of the head and neck. With a minimum follow-up of 3 years and a mean follow-up of 45 months, the 3-year overall local control was 58% and 78%, respectively, for tumors of the paranasal

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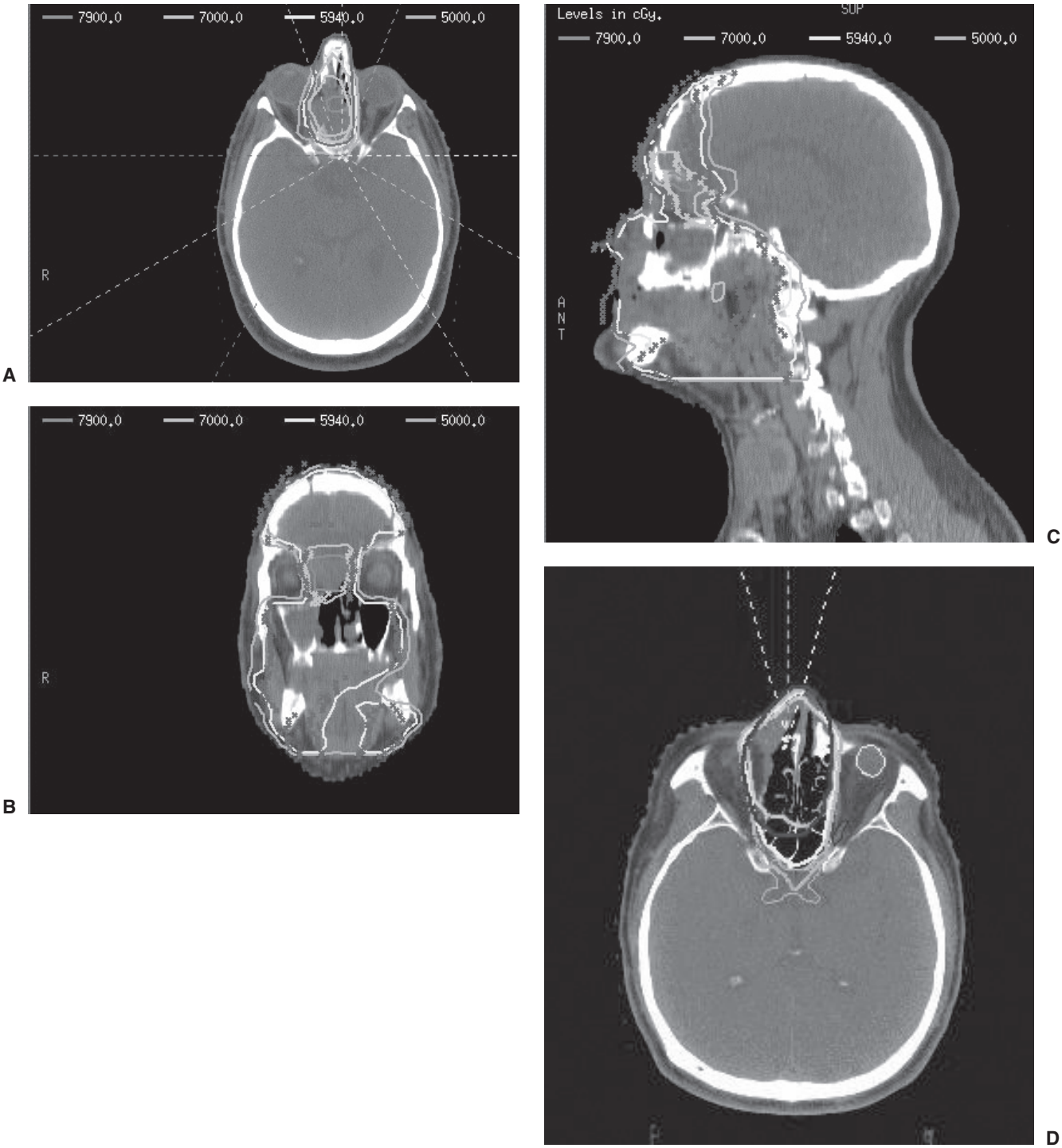



**FIGURE 21-12.** An example of a patient with sinonasal undifferentiated carcinoma where the tumor extended through the cribriform plate into the anterior cranial fossa. Despite two attempts at surgery, there was still gross residual disease. **A:** Notice the conformal dose distribution surrounding the gross tumor while sparing the optic structures. **B:** Axial view. **C:** Coronal view. **D:** Sagittal view. (See color insert.)

sinus. For all patients, the distant metastases–free rate was 56%.[87] Intra-arterial 5-fluorouracil chemotherapy as a radiosensitizer in an attempt to reduce the extent of surgery has been reported by Japanese.[88] Other investigators have also reported high tumor response using highly selective intra-arterial infusion of cisplatin-based chemotherapy.[89] Madison et al.[90] reported 11 cases of advanced sinonasal carcinomas of which the majority are T4 disease. Patients were treated with selective intra-arterial cisplatin with concurrent radiation therapy followed by conservative craniofacial resection. The mean follow-up was 57.2 months (range: 12–95 months). The overall 5-year survival was 81% with a 67% progression-free survival. In light of the

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above-mentioned available data along with the ability to target more precisely with IMRT, a new concept worthy of investigation is to use chemotherapy and definitive dose IMRT for advanced tumors involving the skull base where the alternative is extensive surgery requiring orbital exenteration. This concept of organ preservation is not new, and with the advent of highly conformal techniques such as IMRT, it is anticipated that the complication rates will decrease without compromise in locoregional control.[15] Lastly, chemotherapy has also been used as a palliative modality with modest efficacy in patients with present with esthesioneuroblastoma with intracranial metastases. However, median survival is poor at 10.5 months.[91]

## Proton Beam Radiotherapy

Proton beam radiotherapy has been used to treat tumors at the Massachusettes General Hospital (MGH) for >50 years. The rationale for using protons for skull base tumors is to deliver high doses of radiation with minimal doses delivered to the surrounding normal tissues. Proton radiation with its superior physical properties known as the Bragg peak can minimize the exit dose to the normal tissue beyond the target while achieving excellent coverage of the target.[92] Truong et al. reported the MGH experience of 20 patients with primary sphenoid sinus cancer that underwent proton beam to a median dose of 76 Gy equivalent. With a median follow-up of 27 months, the 2-year local, regional, and freedom from distant metastasis rates were 86%, 86%, and 50%, respectively. The disease-free and overall survival rates were 31% and 53% at 2 years, respectively. Brain invasion and involvement of the oropharynx and the anterior cranial fossa are important prognostic factors and portended worse outcomes.[93] From the same institution, protons resulted in a 5-year disease-free and overall survival rates of 90% and 85.7%, respectively, for esthesioneuroblastoma. No patients from their series suffered any severe radiation toxicity. The authors concluded that esthesioneuroblastoma can be safely and effectively be treated with craniofacial resection followed by proton beam irradiation.[94]

High-dose conformal proton beam results in a very encouraging local control for patients with adenoid cystic carcinoma of the skull base with a 5-year local control of 93%. In this series, approximately 50% of the patients had biopsy only. Overall, proton beam seems promising; however, complete surgical resection is still predictive of improved disease-free survival and decreased rate of distant failures among 102 patients with locally advanced sinonasal cancers treated with proton beam with or without surgery.[95] Now with more centers having the capabilities of delivering proton radiotherapy, prospective cooperative trials should be conducted to measure the true efficacy of protons versus IMRT.

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# PART B:
# Radiologic Imaging Concerns

Jeffrey A. Bennett

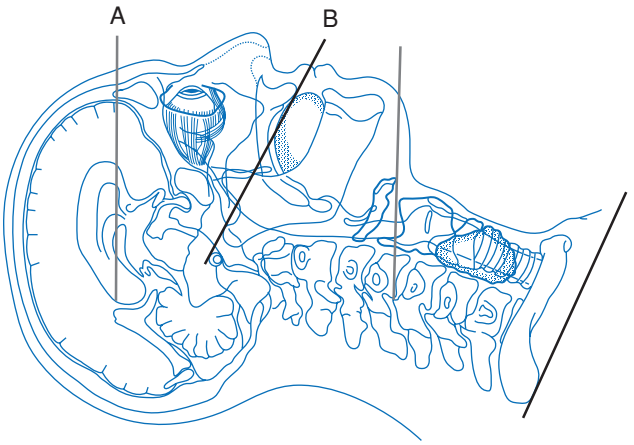
Imaging is critical in cases of cancer of the nasal cavity and paranasal sinuses, and computed tomography (CT) and magnetic resonance imaging (MRI) are complementary in evaluating lesions extending to the skull base and the orbit.[1,2] Both modalities are good at differentiating benign mucosal disease from more aggressive disease.[3] CT is typically performed first because of its speed and superior ability to show bony detail and destruction. CT must be performed with very thin sections, down to 0.5 mm, and reconstructed in bone and soft tissue algorithms. It is no longer necessary to acquire direct coronal CT images because the speed of imaging limits motion artifact, and very good quality coronal and sagittal reformations can be obtained from the very thin axial data. Both CT and MRI should be performed with contrast when a mass is suspected or known.[4] A combination of CT to evaluate bone and MRI to evaluate tumor versus obstructed mucosal disease has been shown to be essential.[5,6] Suggested protocols are given in Figures 21-13 and 21-14. The value of FDG PET-CT in the initial workup of sinonasal tumors is still being debated. These studies have a high negative predictive value, which is very useful for evaluation of tumor recurrence. However, the high rate of false-positive studies require the results to be viewed with caution.[7]

The approach to interpreting the images, as in other regions of the head and neck, is to determine the full extent of the primary tumor and to determine the presence of perineural and lymphatic spread.

In the nasal cavity and paranasal sinuses, a description of the local extent of a tumor includes a discussion of the amount of bone destruction present in the nasal cavity, facial bones, and sinuses and whether some of the abnormalities seen are a result of obstructed mucosal drainage, such as mucocele formation (Fig. 21-15) rather than tumor. Occasionally, imaging features will suggest a certain histology, such as lymphoma when the tumor is low signal on T2-weighted images and restricts on diffusion-weighted sequences, but usually determination of histology is reserved for the biopsy results. Both MRI and contrast-enhanced CT can demonstrate features of hypervascular tumors, showing large flow voids on MR and large vascular pedicles on

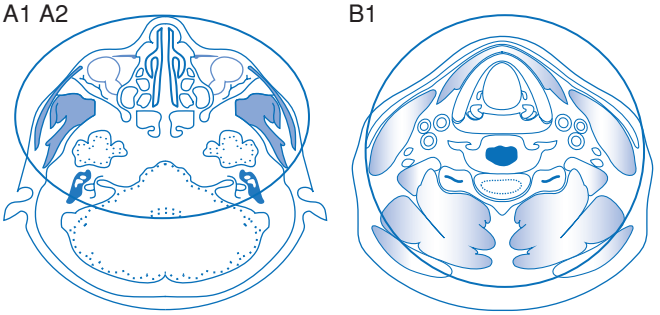
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ACQUISITION




| | | |
|---|---|---|
| | Patient position | Supine<br>IOML perpendicular to tabletop |
| | Contrast | 100 mL adult |
| | Injection rate | 1 mL/sec; 60 sec delay |
| | Respiration | Quiet, NO swallowing |
| | Volume acquisition specs | Appropriate to achieve images as specified in following reconstruction tables.<br>Head FOV. |
| A | Begin | Above frontal sinus |
| | End | Through mandible |
| B | Begin | Mid oral cavity |
| | End | Apices |

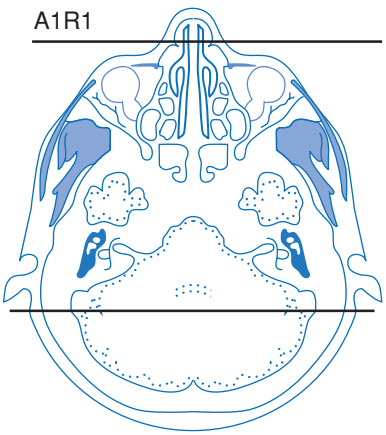
RECONSTRUCTION




| | | |
|---|---|---|
| A1 | Algorithm | Soft tissue |
| | Thickness | 1.0 mm |
| | Spacing | 0.8 mm |
| | F.O.V. | Approx. 170–190 |

| | | |
|---|---|---|
| A2 | Algorithm | Bone |
| | Thickness | 1.0 mm |
| | Spacing | 0.8 mm |
| | F.O.V. | Approx. 170–190 |
| B1 | Algorithm | Soft tissue |
| | Thickness | 2.5 mm |
| | Spacing | 2.5 mm |
| | F.O.V. | Approx. 160–180 |

REFORMATION




| | | |
|---|---|---|
| A1R1 | Algorithm | Soft tissue |
| | Thickness | 1.0 mm |
| | Spacing | 1.0 mm |
| | F.O.V. | Approx. 180 |
| | Plane | Coronal |
| | Begin | Frontal sinus |
| | End | Through IAC |

**FIGURE 21-13.** Protocol for CT of the maxillofacial region and neck with intravenous contrast.

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| Acquisition | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| Plane | Sagittal | Coronal | Coronal | Coronal | Axial | Axial | Axial |
| Sequence | T1 | T1 | T1 | T2-FSE | T1 | T2-FSE | T1 |
| Contrast | None | None | Gd | Gd | Gd | Gd | Gd |
| SLT/SP | 4/0 mm | 3/0 mm | 3/0 mm | 3/0 mm | 3/0 mm | 3/0 mm | 4/1 mm |
| FOV | 16 cm | 16 cm | 16 cm | 16 cm | 16 cm | 16 cm | 20 cm |

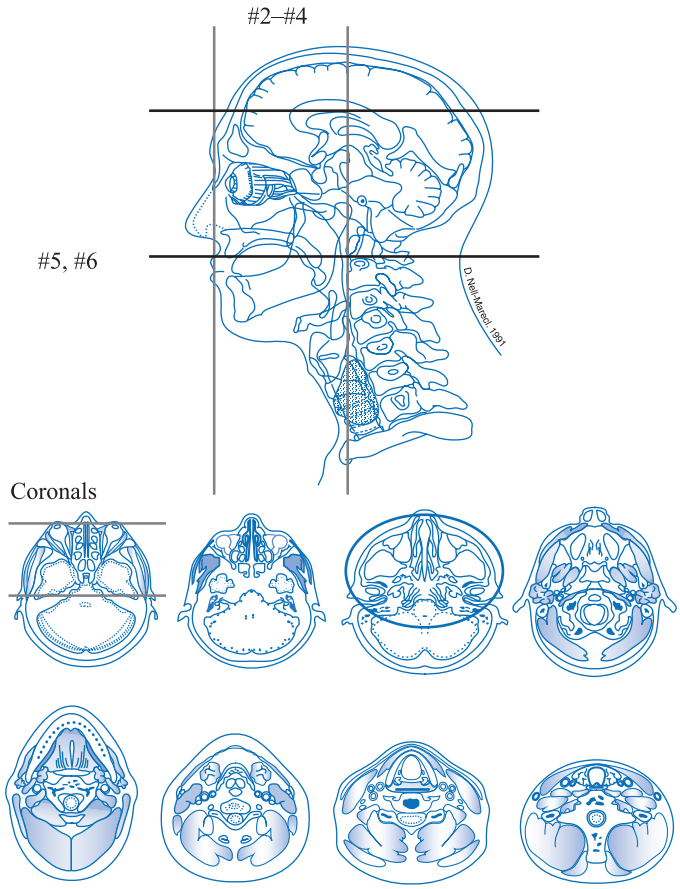



**FIGURE 21-14.** Protocol for MRI of the sinonasal region with intravenous contrast.

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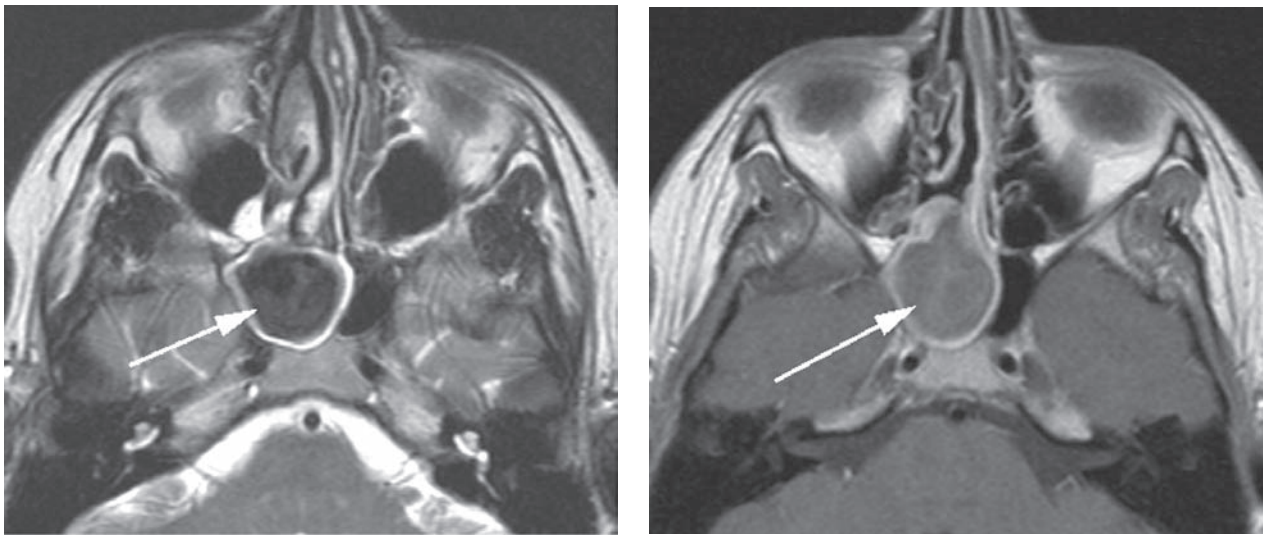



**FIGURE 21-15.** Axial T2-weighted (T2W) MRI **(A)** and axial postcontrast T1W MRI **(B)** show expansion of the right portion of the sphenoid sinus (*arrows*) consistent with a mucocele which is filled with very dark inspissated secretions on T2W image.

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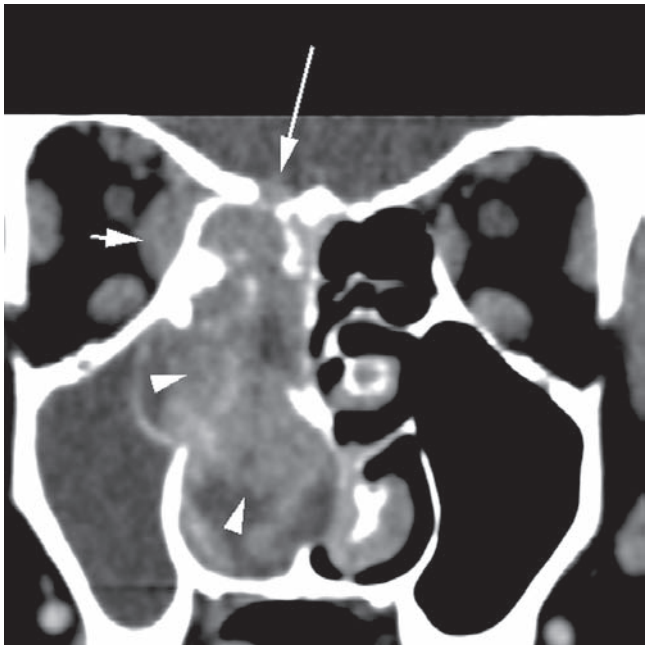


**FIGURE 21-16.** Coronal reformation of a postcontrast CT scan shows an aggressive poorly differentiated carcinoma (*arrowheads*) which invades the orbit (*short arrow*) and spreads through the fovea ethmoidalis to reach the intracranial, likely extradural space (*long arrow*).

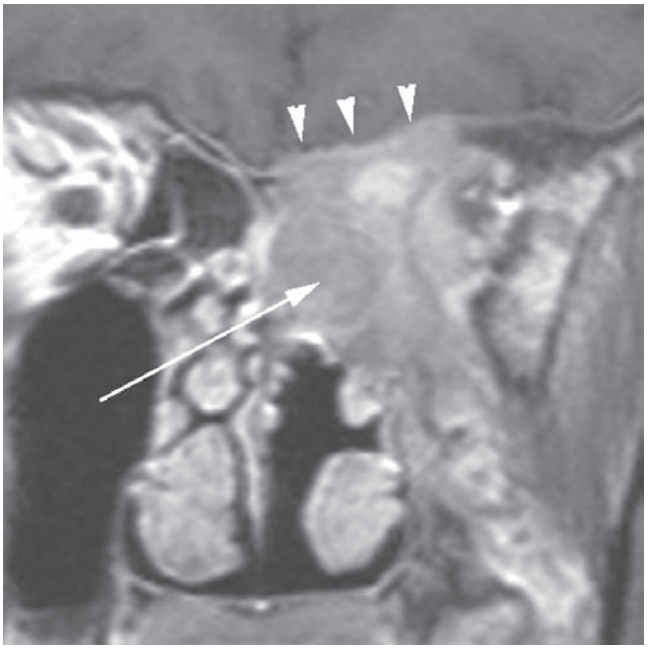
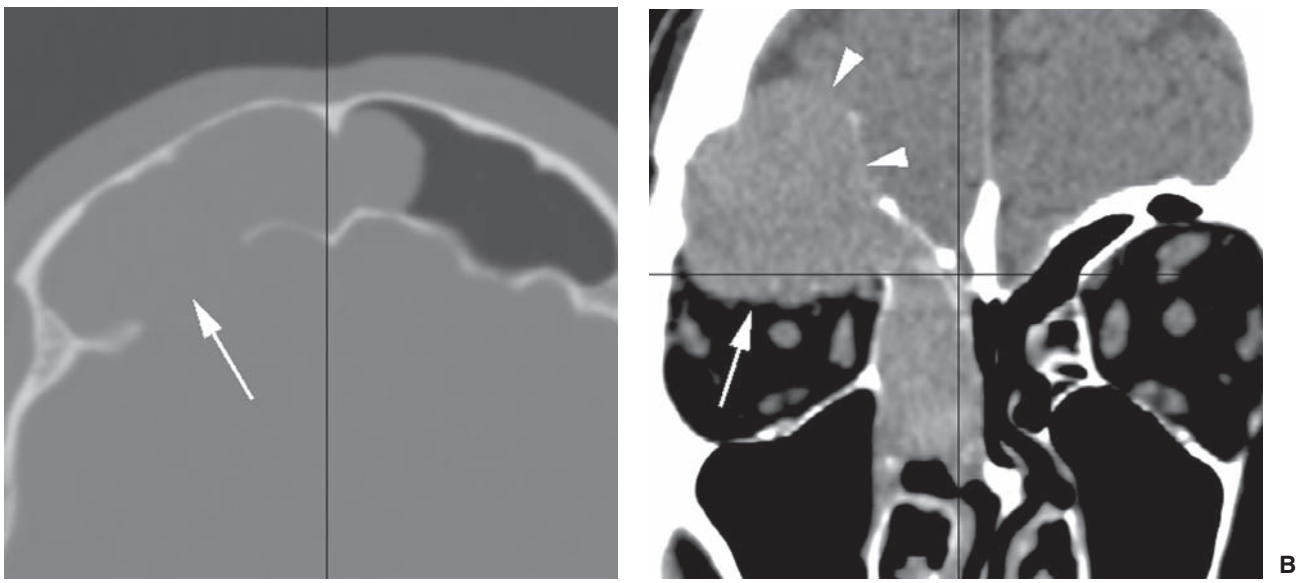


**FIGURE 21-17.** Coronal postcontrast T1-weighted MRI shows an aggressive ethmoid sinus malignancy (*arrow*) with direct intracranial extension. Tumor has invaded the dura (*arrowheads*) but has not yet invaded the brain.

CT angiography. These findings can warn the surgeon to expect bleeding during biopsy or resection.

The amount of spread of tumor beyond the nasal cavity and sinuses is critical to the surgical approach and for determining whether postoperative radiation therapy is necessary. Tumor can cross the cribriform plate or paranasal sinuses to involve the intracranial compartment. In these cases, MRI should be performed to determine whether intracranial disease is confined to the extradural space, involves the dura, has spread through the dura to involve the arachnoid and the pial membranes, or invades the brain (Figs. 21-16 through 21-19).

The extent of orbital involvement determines whether the eye can be spared. CT is better at determining the extent of orbital bony destruction or erosion, and MRI is usually superior to determine



**A** **B**

**FIGURE 21-18.** **A:** Axial CT scan at bone window shows opacity of the right frontal sinus with dehiscence (*arrow*) of the inner table of the frontal sinus. **B:** Coronal reformation of the noncontrast CT shows a hyperdense mass involving the right nasal cavity and right ethmoid and frontal sinuses found on pathology to be a plasmacytoma. The mass invades the orbit (*arrow*) and extends intracranially (*arrowheads*).

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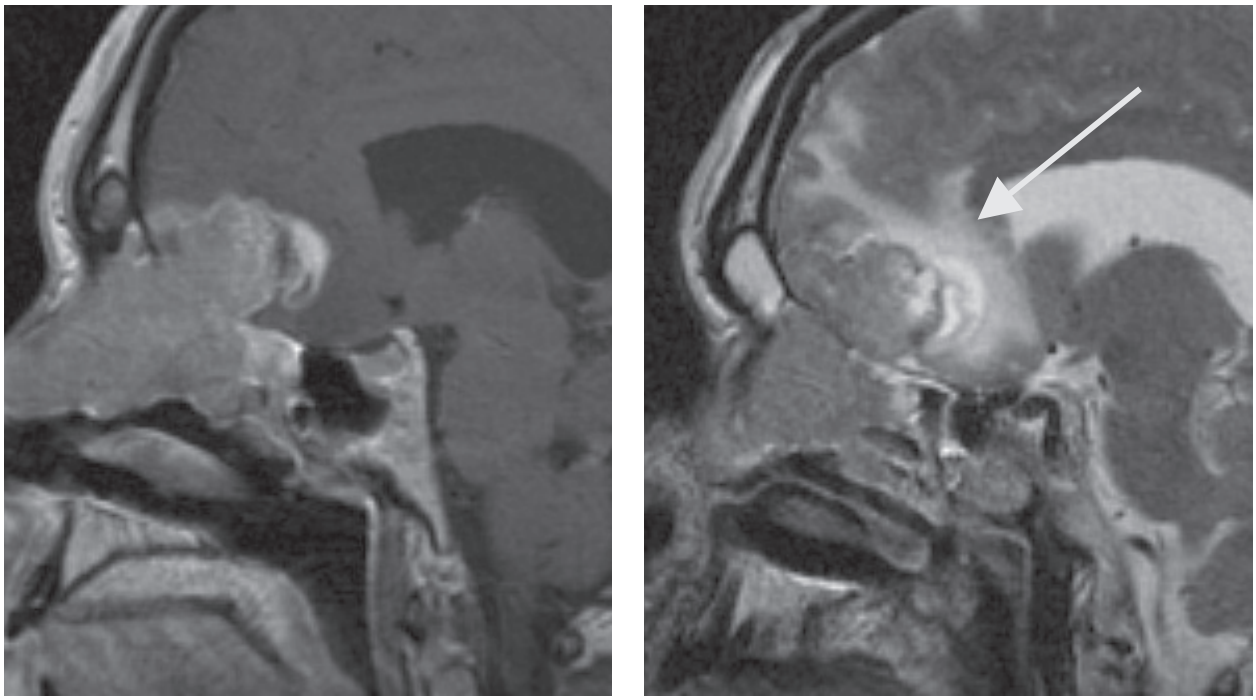


**FIGURE 21-19.** Intracranial involvement with brain invasion. **A:** Sagittal contrast-enhanced T1-weighted (T1W) image shows intracranial extension of a large sinonasal carcinoma. **B:** Sagittal T2W image demonstrates brain edema (*arrow*) indicative of invasion of the pial covering of the brain.

whether tumor has invaded the extraconal fat, the extraocular muscles, and the intraconal fat (Fig. 21-20). Fat suppression is essential when evaluating the orbit with MRI. Preseptal soft tissue tumor spread can affect the eyelid. Involvement of the lacrimal gland and nasolacrimal duct should be described when present.

Tumor can spread posteriorly to involve the nasopharynx and can also spread to the premaxillary fat, the retroantral fat, the infratemporal fossa, and the masticator space. Perineural spread can occur from any of these sites. Perineural spread of tumor can be seen with both CT and MRI, but MRI is preferred.

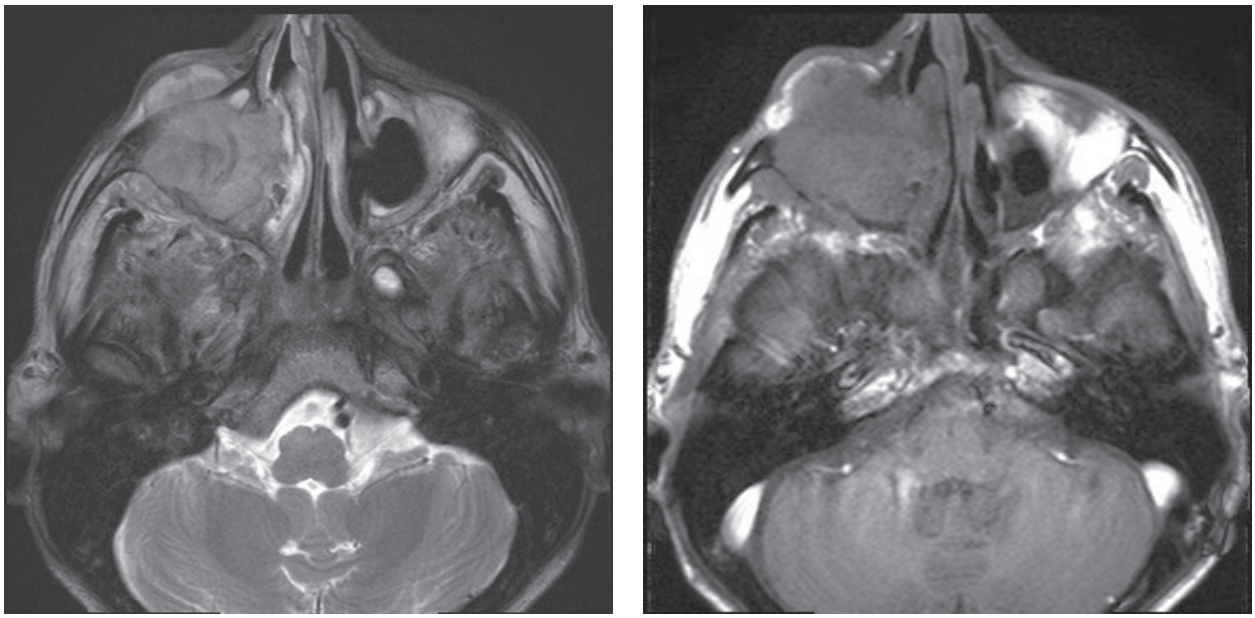
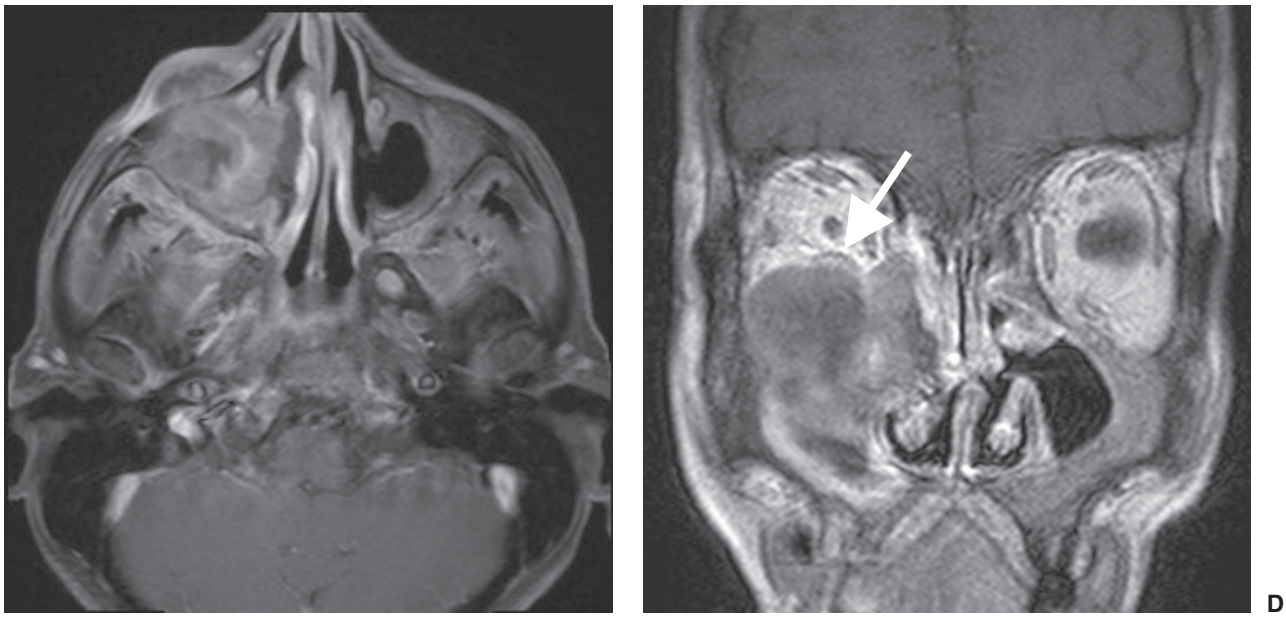


**FIGURE 21-20.** Squamous cell carcinoma (SCC) of the maxillary sinus. **A:** The tumor is intermediate to slightly high signal on T2-weighted (T2W) sequences. **B:** The tumor is intermediate signal on noncontrast T1W sequences. **C:** The fat-suppressed T1W images show that the tumor heterogeneously enhances. **D:** The coronal images demonstrate that the tumor erodes through the floor of the orbit and is indistinct from the inferior rectus muscle (*arrow*).

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C D

**FIGURE 21-20.** *Continued*

When maxillary sinus tumors spread to the cheek, perineural spread along the superficial musculoaponeurotic system should be sought. In nasal cavity tumors, spread can occur along the olfactory nerve through the cribriform plate. Spread along the branches of the trigeminal nerve must be described. Perineural spread can often be seen in the pterygopalatine fossa, and from there tumor can spread through foramen rotundum to Meckel cave and the cavernous sinus, through the vidian canal, or inferiorly along the greater and lesser palatine neurovascular bundles (Figs. 21-21 through 21-23).

Lymphadenopathy should be looked for in the facial, the parotid, the retropharyngeal, and the cervical lymph nodes.

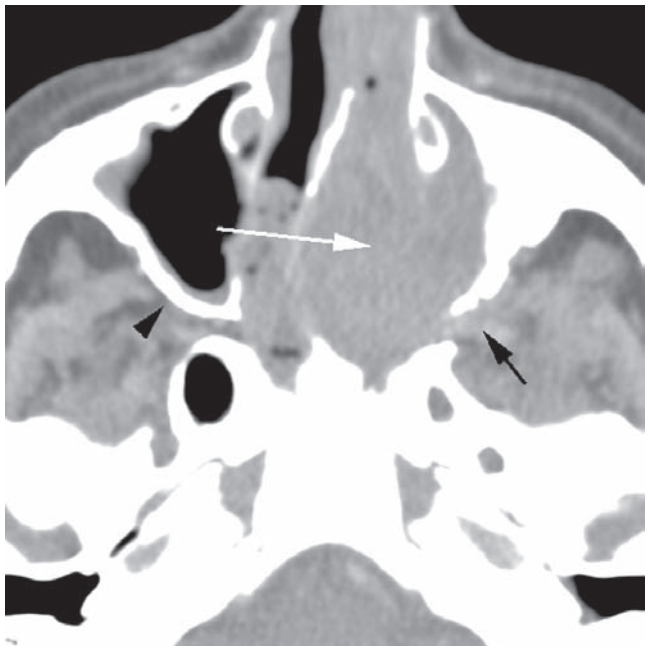


**FIGURE 21-21.** Axial contrast-enhanced CT scan shows a large nasal cavity carcinoma (*white arrow*) extending through the sphenopalatine forman into the pterygopalatine fossa (*black arrow*). Compare the normal retroantral fat pad on the right (*black arrowhead*).

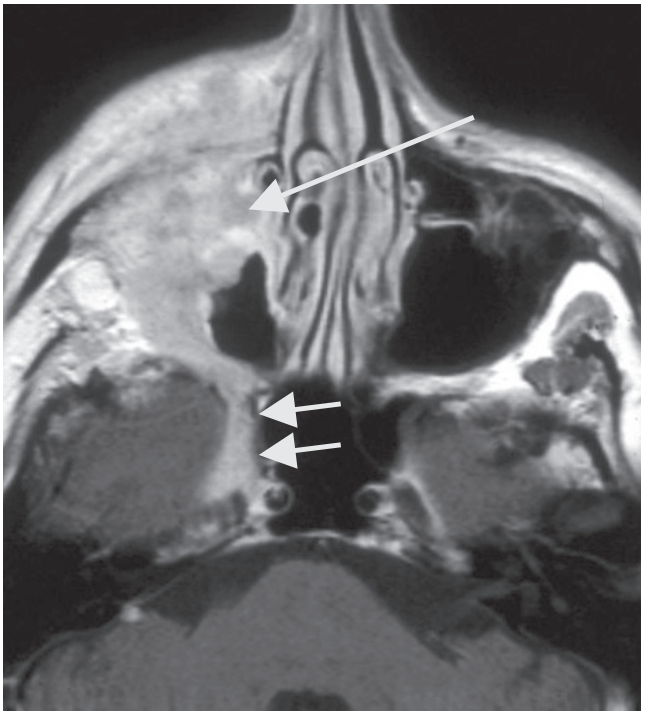


**FIGURE 21-22.** Perineural tumor spread. Axial contrast-enhanced T1-weighted (T1W) image shows an aggressive maxillary sinus carcinoma (*long arrow*). The tumor is extending retrograde along V2 into the cavernous sinus (*short arrows*). The deep extension of this tumor is clinically occult and imaging is necessary to determine that there is extension into the cavernous sinus, thereby staging this tumor as T4.

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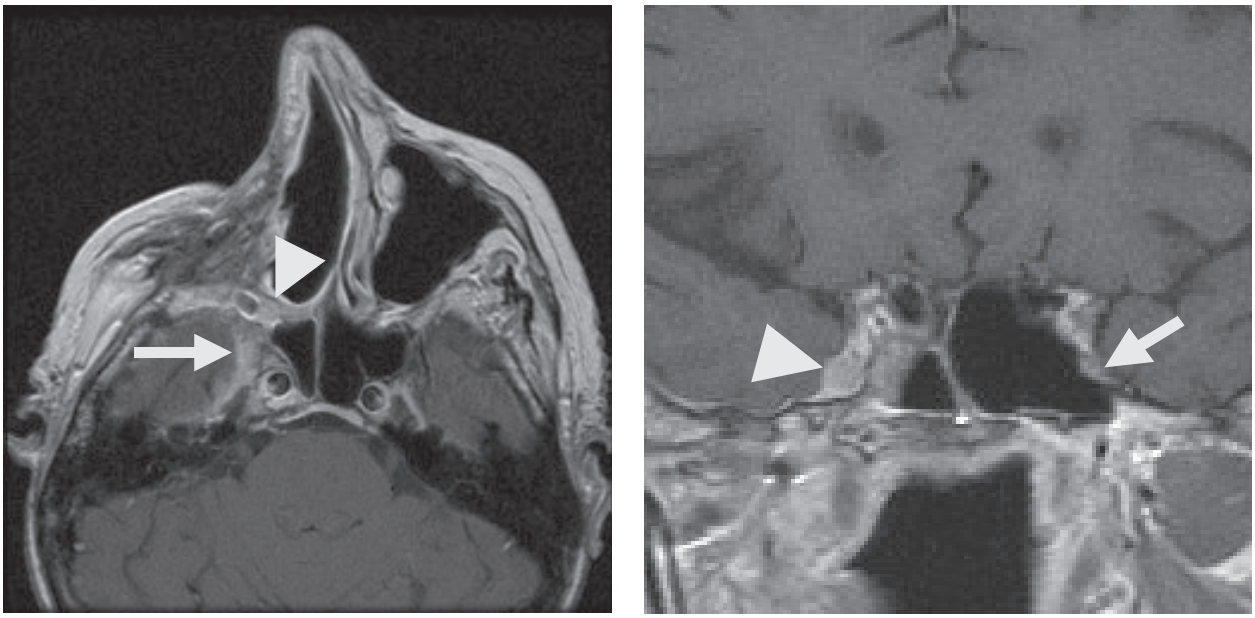


**FIGURE 21-23. A:** Axial contrast-enhanced T1-weighted (T1W) image through the orbit demonstrates a patient who has undergone orbital exenteration as part of a resection of a maxillary sinus carcinoma. This study was performed for routine surveillance. There is a subtle enhancing lesion present in the adjacent pterygopalatine fossa (*arrowhead*) and asymmetric linear enhancement just lateral to the sphenoid sinus (*arrow*) suggestive of retrograde perineural spread along V2. Note the normal appearance of these areas on the opposite side. **B:** Coronal postcontrast T1W image confirms the presence of retrograde perineural extension along V2. Note the enlargement and increased enhancement of the left V2 (*arrowhead*) compared with the normal appearance on the opposite side (*arrow*).

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# PART C:
# Radiation Therapy Technique

Louis B. Harrison, James E. Dolan, Rudolph Woode, and Kenneth S. Hu

Intensity-modulated radiation therapy has become the standard of care for the delivery of radiation therapy for cancers of the nasal cavity and the paranasal sinus complex. The close proximity of vital structures such as the orbital contents; ocular structures such as the retina, the optic nerve, and the lens; the brain stem; and the optic chiasm, all represent challenges.

Like any other anatomic area, it is important to assess the gross tumor volume (GTV) and the clinical tumor volume (CTV). However, the authors do not use a routine volume expansion to determine the planning target volume (PTV). The PTV design must be individualized for each patient, as the closeness of key structures factor into this determination. The opportunity to use image-guided radiation therapy (IGRT) has added to the radiation oncologist's ability to design highly restricted PTVs and use daily imaging to verify position and fields and be tighter with margins. There is no general formula beyond observing the daily setup accuracy with IGRT, making the necessary shifts, and diligence to the interfaces between normal tissue and tissue at risk.

Basic technical issues are addressed in the body of the chapter in the section "Target Determination and Delineation" as well as "Radiation Therapy Technique—Dose Specification." In this section, we will show several specific patient examples, along with the figures that show the anatomical distribution of tumor, the PTV, and the isodose display (Figs. 21-24 and 21-25). We will also show the dose–volume histogram display, so the doses to both target and vital normal organs can be reviewed.

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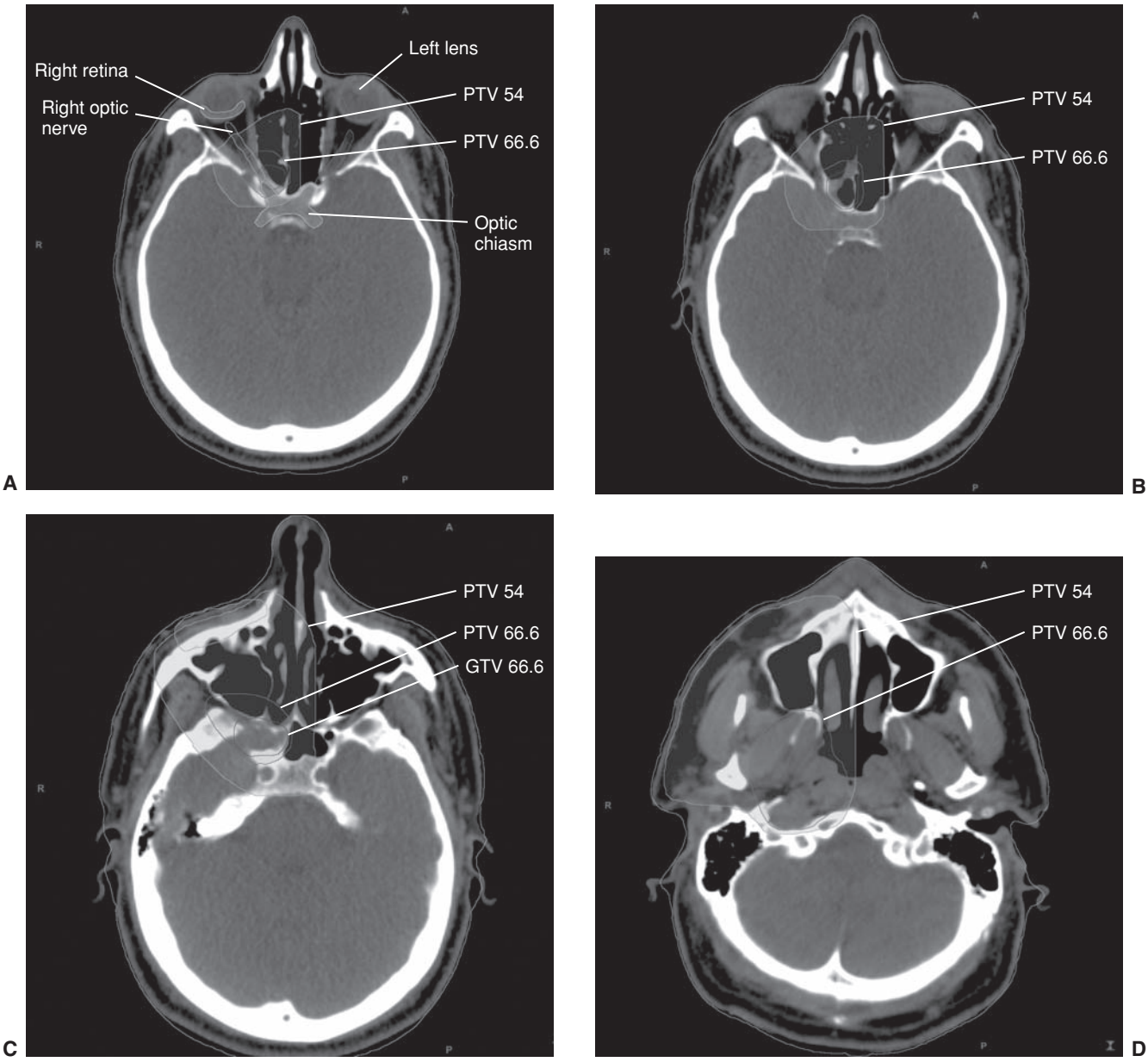
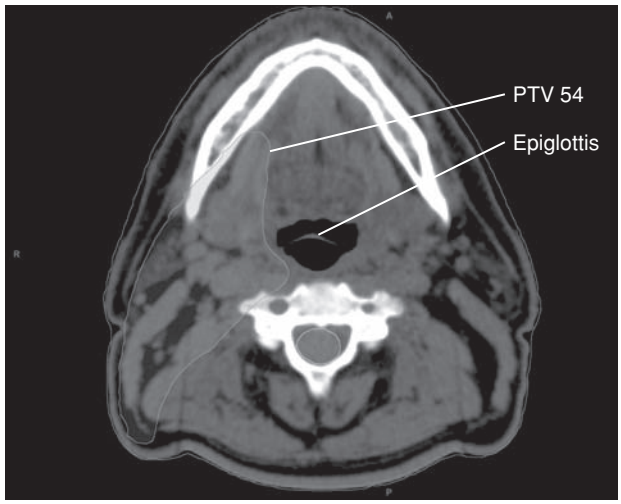


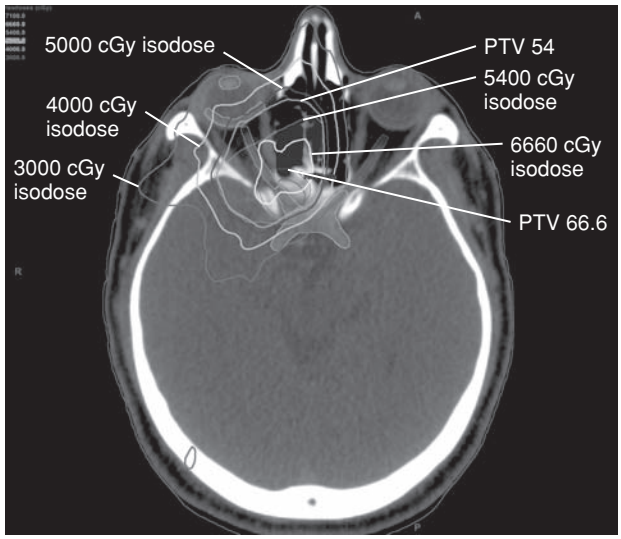

**FIGURE 21-24.** A 60-year-old male with a poorly differentiated carcinoma arising from the right side of the skull base. The tumor involves the sphenoid sinus, the ethmoid sinus, and the posterior aspect of the maxillary sinus and invades the posterior aspect of the right orbit. Tumor is very close to the right optic nerve as it enters the optic chiasm. The tumor did extend to the posterior nasal cavity. The stage was T4N0M0 AJCC stage IV. **A:** CT planning slice showing the optic chiasm, the right optic nerve, the retina, PTV 66.6, and PTV 54. The total dose used was 66.6 Gy at 1.8 Gy/fraction to the primary tumor volume plus margin (PTV 66.6). PTV 54 is an expansion of PTV 66.6. Care is taken to respect the anatomy as there is also a risk of total blindness due to the location of tumor near the optic chiasm. **B:** CT cut through the orbit showing PTV 66.6 and PTV 54. **C:** CT cut through the infraorbital area showing PTV 66.6, GTV 66.6, and PTV 54. Due to disease extent, PTV 54 is generous at this level, to include the entire right maxillary sinus and the nasal cavity with anterior expansion to the skin. **D:** CT cut through the midface showing PTV 66.6 involving the right pterygoid muscles, the pterygoid plates, and the most posterior nasal cavity. Again, PTV 54 represents a generous expansion to cover the entire right maxillary sinus, the anterior cheek/face, the skull base, the nasal cavity, and the preauricular area. This expansion covers routes of local disease progression and surrounding lymphatics. **E:** CT cut through the neck which shows PTV 54 including the neck nodes. Due to the advanced nature of the primary site, we delivered elective neck irradiation of 54 Gy at 1.8 Gy/fraction to the right-sided retropharyngeal nodes, as well as right levels 2, 3, and 4. **F:** Isodose distribution similar to Figure 1A above, showing coverage of PTV 66.6 with the 6,660 cGy isodose curve and coverage of PTV 54 with the 5,400 cGy isodose curve. The tightness of the coverage is noted due to the critical anatomy. The 5,000, 4,000, and 3,000 isodose lines are shown, which help protect the optic chiasm. **G:** Sagittal isodose display showing good coverage of PTV 66.6, PTV 54, protection of the spinal cord, the oral cavity, and the brain. **H:** Coronal dose distribution showing isodose display covering PTV 66.6 at the skull base; PTV 54 is well covered including the upper neck and the retropharyngeal nodes. **I:** Dose–volume histogram showing strong target coverage of PTV 66.6 and PTV 54, and respected tolerances of vital structures like the brain stem, the spinal cord, the optic chiasm, and the retina. A portion of the right optic nerve and the optic chiasm get higher doses because they are within PTV 66.6, as tumor is in these locations.



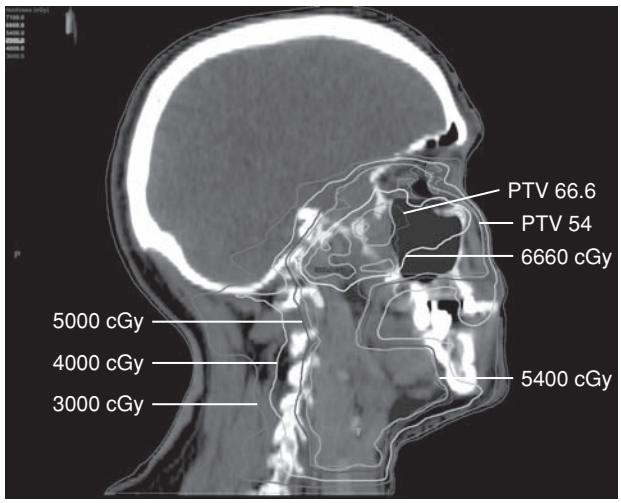
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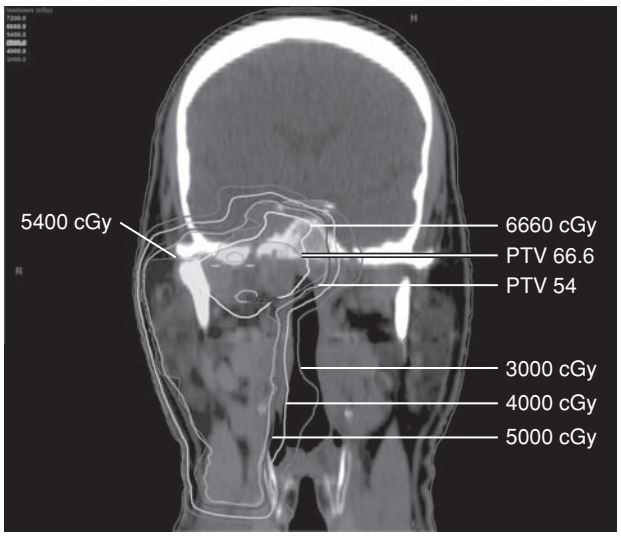

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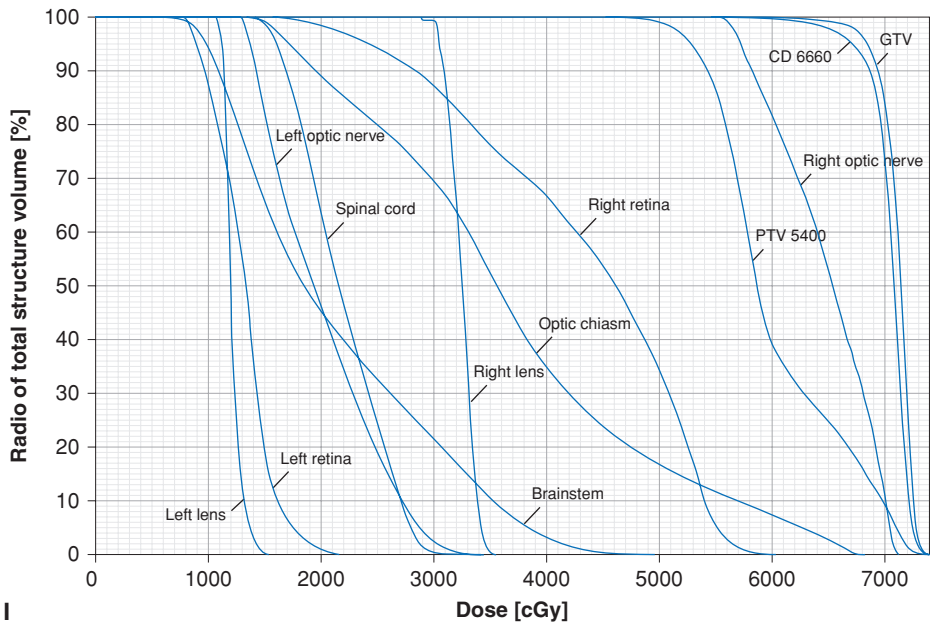

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**FIGURE 21-24.** *Continued*

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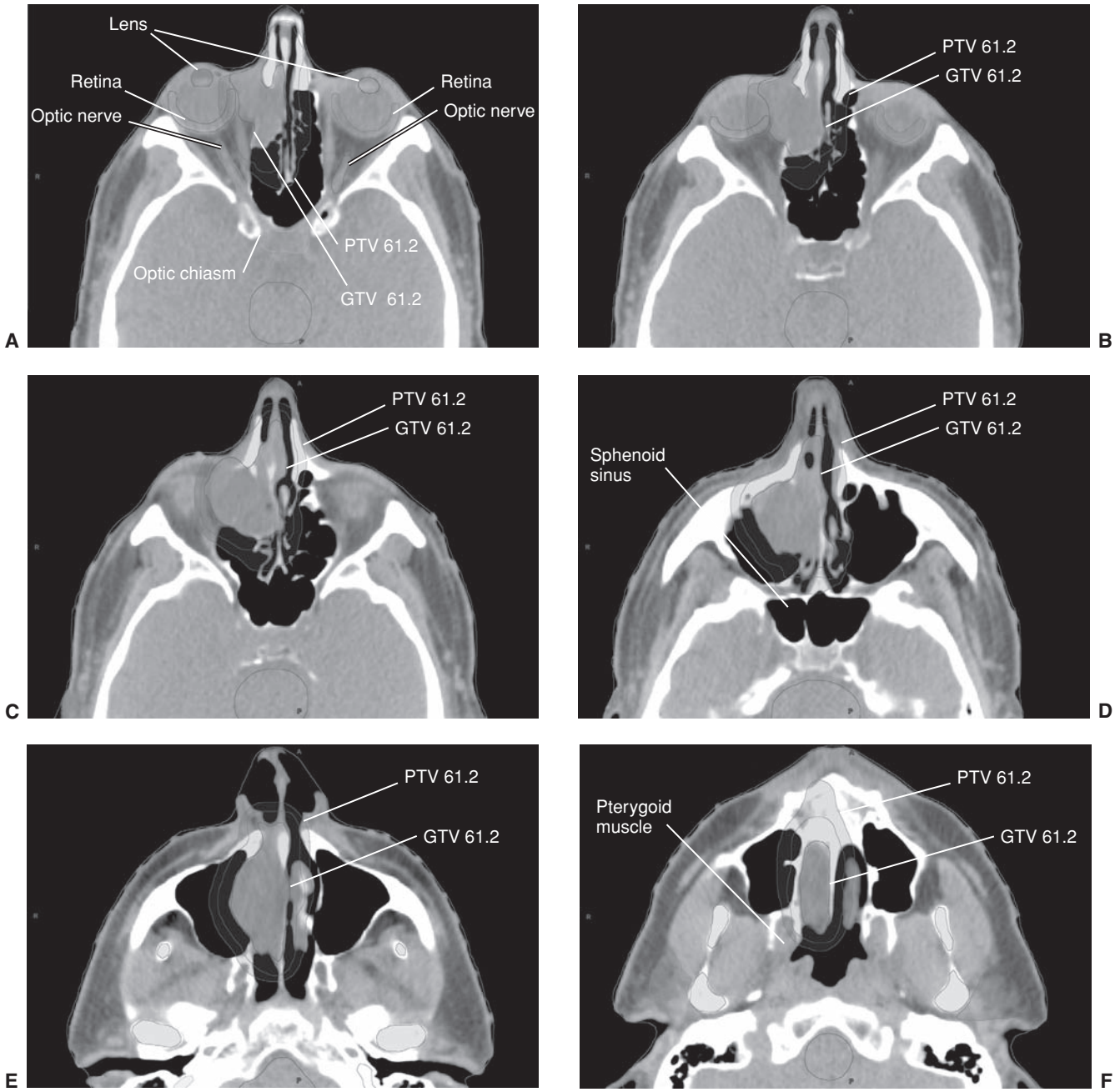
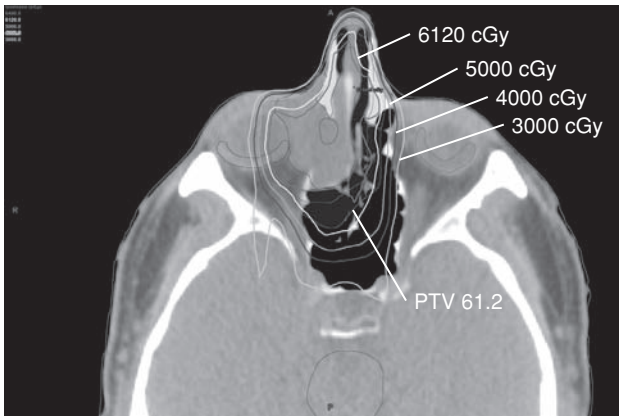


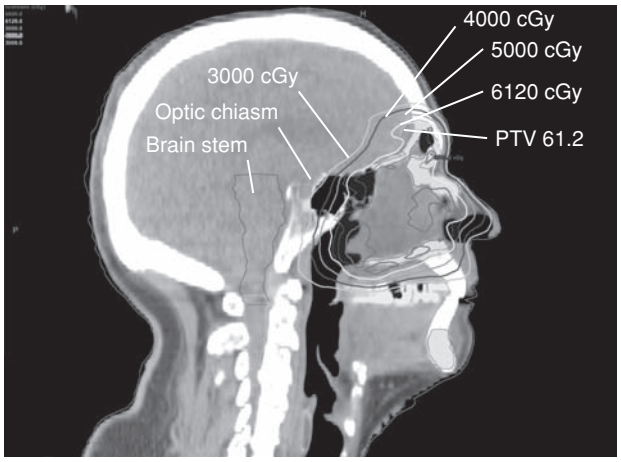

**FIGURE 21-25.** A 67-year-old male with a sinonasal undifferentiated carcinoma (SNUC) involving the right nasal cavity, the maxillary sinus, and the ethmoid sinus with disease beginning to encroach on the medial aspect of the right orbit. Our approach to SNUC involves initial concomitant chemotherapy and IMRT, followed by a planned resection which spares the orbital contents. Here, the primary tumor is represented by PTV 61.2. The planned, preoperative dose is 6,120 cGy at 180 cGy/fraction. **A:** CT planning slice showing the optic chiasm, the optic nerves, the retinas and the lenses, as well as PTV 61.2. The planned total dose is 6,120 cGy at 180 cGy/fraction. Note the care in the PTV expansion to try to respect the adjacent right optic nerve and the contralateral left optic nerve. **B:** CT cut through the orbit showing PTV 61.2 and GTV 61.2. Note that PTV 61.2 extends to skin surface at the medial aspect of the orbit. **C:** CT cut through the inferior orbit showing PTV 61.2 and GTV 61.2 with tight medial margin to respect the orbit. **D:** CT cut through midface showing PTV 61.2 and GTV 61.2 involving the right nasal cavity and the adjacent maxillary sinus. Note the entire nasal cavity is included in PTV 61.2, but the sphenoid sinus is not involved and not included. **E:** CT cut through the nasal cavity showing PTV 61.2 and GTV 61.2, which are becoming smaller as we move inferiorly. **F:** CT cut at the inferior nasal cavity showing PTV 61.2 and GTV 61.2 as they continue to get smaller. Note the PTV expansion respects the adjacent right pterygoid muscles, which are not involved. Avoiding high dose to these muscles helps to avoid trismus. **G:** Isodose distribution similar to Figure 2B above, showing coverage of PTV 61.2 with the 6,120 cGy isodose line. Note the steep dose gradient and the adjacent 5,000 cGy isodose line. This tight dose distribution is essential to optimizing both oncologic and functional outcome. **H:** Sagittal isodose display showing good coverage of PTV 61.2 with the 6,120 cGy isodose line. With dose fall off, note the protection of the optic chiasm and the brain stem. **I:** Dose–volume histogram showing strong target coverage of PTV 61.2 and respected tolerances of vital structures like the brain stem, the optic chiasm, the optic nerve, and the retina.



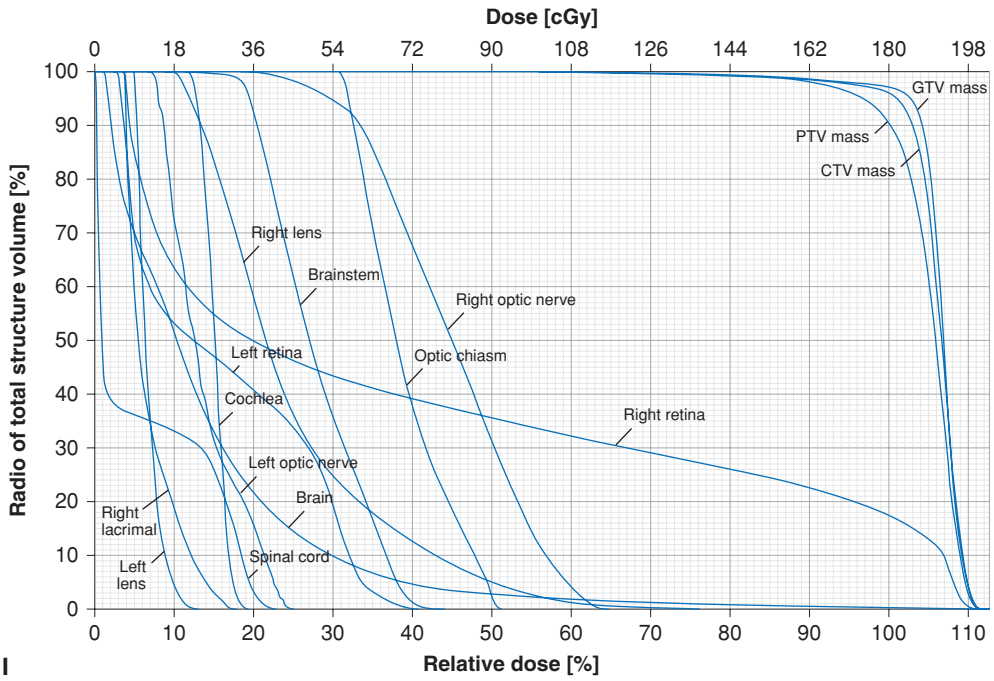
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**FIGURE 21-25.** *Continued*

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CHAPTER 22

# Cancer of the Nasopharynx

## PART A:
## General Principles and Management

Kenneth Hu, Anthony T.C. Chan, Peter Costantino, and Louis B. Harrison

### EPIDEMIOLOGY

The global incidence of nasopharyngeal carcinoma (NPC) is 84,400 new cases annually with 51,600 deaths.[1] It is an endemic disease in Southern China, with incidence rates of 15 to 50 per 100,000 persons, making it the third most common cancer in men.[2–5] However in the West, where it is associated with risk factors that are common to other cancers of the head and neck, NPC is a rare disease.[5,6] There is an intermediate incidence in populations in Alaskan Eskimos and in the Mediterranean basin.[4] The incidence rate rises after age 20 years and decreases after age 60 years, with a male–female ratio of 3:1. The median age of presentation is 40 to 50 years, which is significantly younger than that of other head and neck cancers.[2,4] Young adults and children comprise up to 1% of all patients. However, in non-Asian areas (e.g., Northern/Central Africa), younger patients between 10 and 20 years comprise up to 15% of cases. In the United States, there is four- to sevenfold increased risk of NPC among southern Black children compared with the Caucasian population.[7–10]

### ETIOLOGY

Unlike squamous cell carcinomas at other sites in the head and neck, the etiology of nasopharynx carcinomas is not usually related to tobacco and alcohol use, but is multifactorial with viral, genetic, and environmental factors.[3,11,12] Genetic, behavioral, and environmental cofactors are implicated as suggested from decreasing rates of cancer among successive generations of Chinese migrants to the United States and increased risk of NPC among people usually considered low risk who are born and raised in an endemic area.[13–15] Carcinogens related to diet (salted fish high in nitrosamine), poor hygiene, poor ventilation, smoking, and use of nasal balms have been implicated.[4,16] Genetic risk factors involving the HLA-A2, B-17, B246, and BW58 have been associated with increased genetic susceptibility whereas the A11, B13, and B22 loci have been associated with a decreased risk.[4,16] There has been a 40% drop incidence of new cases in Hong Kong from 33.1/100,000 in 1976 to 1990 to 19.5/100,000 during 1996 to 2000, pointing to the importance of environmental etiologic factors.[3] For nonendemic cases, traditional risk factors such as smoking and alcohol have been identified.[17,18]

Viral etiology has clearly been implicated in the majority of nasopharynx cancers. For endemic undifferentiated NPC, there is a strong association with Epstein-Barr virus (EBV), a human B-lymphotropic herpesvirus that is implicated in a variety of tumors,[19] and it is proposed that EBV plays a key role in NPC pathogenesis as EBV is consistently detected even in the earliest NPC lesions (severe dysplasia and CIS) with clonal viral genomes and latent-membrane-protein (LMP 1 oncoprotein) expression,[20] whereas EBV infection is not detected in normal nasopharyngeal epithelium.[21]

EBV is more commonly associated with WHO type II/III, where as a smaller proportion of type I is EBV associated. Conversely, there is a growing recognition that type I has a greater association with HPV compared with type II/III.[22] HPV-associated nasopharynx carcinoma were found to involve tumors that extended to the oropharynx and postulated to represent primary oropharynx tumors. In this study, p16 was positive in all HPV ($n = 3$) positive NPCs but none of the EBV-associated nasopharynx cancers ($n = 34$) and felt to be an important molecular tool to differentiate between an HPV- versus EBV-driven tumor.[23]

As early detection of NPC may be crucial to achieve better outcome of patients, serological markers have been developed taking advantage of the presence of EBV in the tumor. Tumor markers may be useful for early detection, diagnosis, prognostication and monitoring of treatment response. All serological markers of NPC have been based on the detection of antibodies to EBV[24] or on the detection of EBV genetic materials.[25,26] These markers may not be applicable to the patients with WHO type I well-differentiated squamous cell carcinoma. Immunoglobulin A (IgA) antibody titres to the viral capsid antigen of EBV has been widely used as a marker with a sensitivity of 80% to 90%.[24,27,28]



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The detection of plasma tumor-associated EBV DNA using polymerase chain reaction assays has opened up new possibilities in the detection and management of nasopharynx cancer. Lo was the first to quantitate plasma levels of EBV DNA using a PCR technique and detected EBV DNA in the plasma of 96% (55/57) with nasopharynx cancer versus 7% of control patients (3/43).[25] Plasma EBV DNA correlates with tumor staging, survival, and recurrence.[25,29,30] It has a diagnostic sensitivity of 96% and specificity of 93%.[25,31] A recent publication demonstrated that the combined interpretation of EBV DNA with UICC staging improved risk discrimination in early-stage disease.[32]

Pretreatment levels are associated with tumor volume[33] with prognostic implications beyond anatomic staging[32] and elevated posttreatment EBV DNA levels associated with higher risk for recurrence, distant metastasis, and poorer disease-free and overall survival whereas clearance of EBV DNA to undetectable or low posttreatment levels are associated with clinical remission.[29,32,33,34,35] Several groups have shown that patients can be stratified by pre- and posttreatment EBV levels into distinct survival groups with posttreatment EBV plasma levels as the major factor impacting on survival. For patients with undetectable posttreatment plasma EBV, a high pretreatment level prognosed a worse overall (87% vs. 71%) and relapse-free survival (86% vs. 76%) compared with low pretreatment levels.[36]

Harmonization of the plasma EBV DNA assay is crucial before it is accepted for routine clinical use as there are varying sensitivities of the assay depending on the part of the EBV viral genome that is detected. Most commonly the BamH1-W assay yields the highest concentrations due to multiple copies of this in different EBV genomes compared with single copy of other genes that have been tested including EBNA01, polymerase-1, or latent membrane protein-2. Even with the same target and assay conditions, the concentration can vary significantly and there is also a high degradation rate that depends on the age of the blood specimen.[36] The RTOG is attempting to standardize the assay prior to proceeding to use it as a stratification factor for adjuvant treatment.

# GROSS AND MICROSCOPIC ANATOMY

## Gross Anatomy

The nasopharynx is a cuboidal cavity located behind the choanae of the nasal cavity (Fig. 22-1). It is composed of two lateral walls with a roof which slopes downward toward the posterior pharyngeal wall down to the level of the uvula. The soft palate forms the floor. Behind the roof and posterior pharyngeal wall are the clivus composed of the basisphenoid, basiocciput, and anterior arch of the atlas. In the lower part of the lateral wall, the superior constrictor muscle sends its fibers posteriorly to attach to the basisphenoid. Between the upper border of the superior constrictor muscle and the skull base is the pharyngobasilar fascia with the Eustachian tube lodged between the medial pterygoid plate and the superior constrictor muscle. The posterior lip of the opening of the Eustachian tube is the torus tubarius behind which is a mucosal fold called the fossa of Rosenmüller. The cartilaginous part of the Eustachian tube enters the lateral pharyngeal wall through a muscle opening called the sinus of Morgagni. This serves as an easy source of entry/exit for nasopharynx cancer.

The nasopharyngeal lymphoid tissue or adenoid is concentrated in the nasopharyngeal roof and other lymphoid aggregates exist about the tubal openings. Adenoidal tissue in the pharyngeal bursa along the roof can result in inflammation or Thornwald cyst formation. The sensory nerve supply to the postnasal space is provided by the glossopharyngeal and the maxillary nerves. Multiple foramina are adjacent to the nasopharynx including the foramen lacerum at the roof with fibrocartilage that is a minimal barrier of entry into the middle cranial fossa for cancer, the foramens juglare, the ovale and the spinosum as well as the carotid and the hypoglossal canals.

## Microscopic

The epithelial lining of the nasopharynx is composed of three basic cell types with a pseudostratified columnar epithelium predominant at birth, a squamous cell type present in adulthood as well as an intermediate pseudostratified cuboidal type which exists in the transition zones between the first two. In the adult, the squamous cell type comprises 60% of the lining of the anterior wall and 80% to 90% of the posterior wall whereas the respiratory type comprises one-third of the anterior wall, 15% to 20% of the posterior wall and about half the area of the lateral walls.[4] The intermediate epithelium is most susceptible to oncogenesis as the areas of the nasopharynx where cancers originate correspond to the same areas that have the greatest amount of the intermediate type. The most common sites of origin are the lateral walls including the fossa of Rosenmüller, the posterior wall, and the anterior walls in descending order.[4]

# PATHOLOGY

## Classification and Histology of NPC

***Diagnosis.*** Tumors arise from the nasopharyngeal epithelium and may present as frank tumor with ulceration or as occult submucosal lesions. Diagnosis is made by pathologic confirmation usually by biopsy. Biopsy may show solid sheets, irregular islands, dyscohesive sheet, and trabeculae of tumor with interspersed lymphocytes and plasmas cells.[5] Undifferentiated subtype is characterized by syncitial appearing large tumor cells with scant cytoplasm and indistinct borders, round to oval vesicular nuclei, and large central nucleoli. Differentiated subtype shows cellular stratification and pavementing with plexiform growth similar to transitional cell carcinomas with less prominent nucleoli.

Immuhohistochemistry shows virtually all tumor cells staining strongly for pan-cytokeratin (AE1/AE3) and high-molecular-weight cytokeratins.[5] Nearly all nonkeratinizing tumors, including differentiated and undifferentiated subtypes, will show EBV viral infection, best detected by *in situ* hybridization for EBV encoded early RNA localized in the nuclei of tumor cells.

Fine-needle aspiration (FNA) of a neck node showing clusters of cohesive tumor cells with vesicular nuclei and prominent nucleoli that is cytokeratin positive and leukocyte common antigen (LCA) negative can detect an occult nasopharyngeal primary or residual/recurrent disease.[37] Fine-needle aspiration has a diagnostic sensitivity of 70% to 90%.[5] Cytologic examination of nodes shows a background of lymphocytes and plasma cells with irregular clusters of large cells with overlapping vesicular nuclei and large nucleoli. The diagnosis is confirmed by *in situ* hybridization for EBV and immunostaining for cytokeratins, which rules out a diagnosis of lymphoma.

***Classification.*** According to the World Health Organization (WHO) classification of head and neck carcinomas, NPCs encompass (keratinizing) squamous cell carcinoma, nonkeratinizing carcinomas, and basaloid squamous cell carcinoma.[38] Prior designations for these tumor types are no longer used and included WHO I for squamous cell carcinomas, WHO II for nonkeratinizing carcinoma (also previously referred to as transitional cell carcinoma), and WHO III for undifferentiated carcinoma; the latter also previously referred to as lymphoepithelioma, Schminke-type lymphoepithelioma, and Regaud-type lymphoepithelioma.[38]

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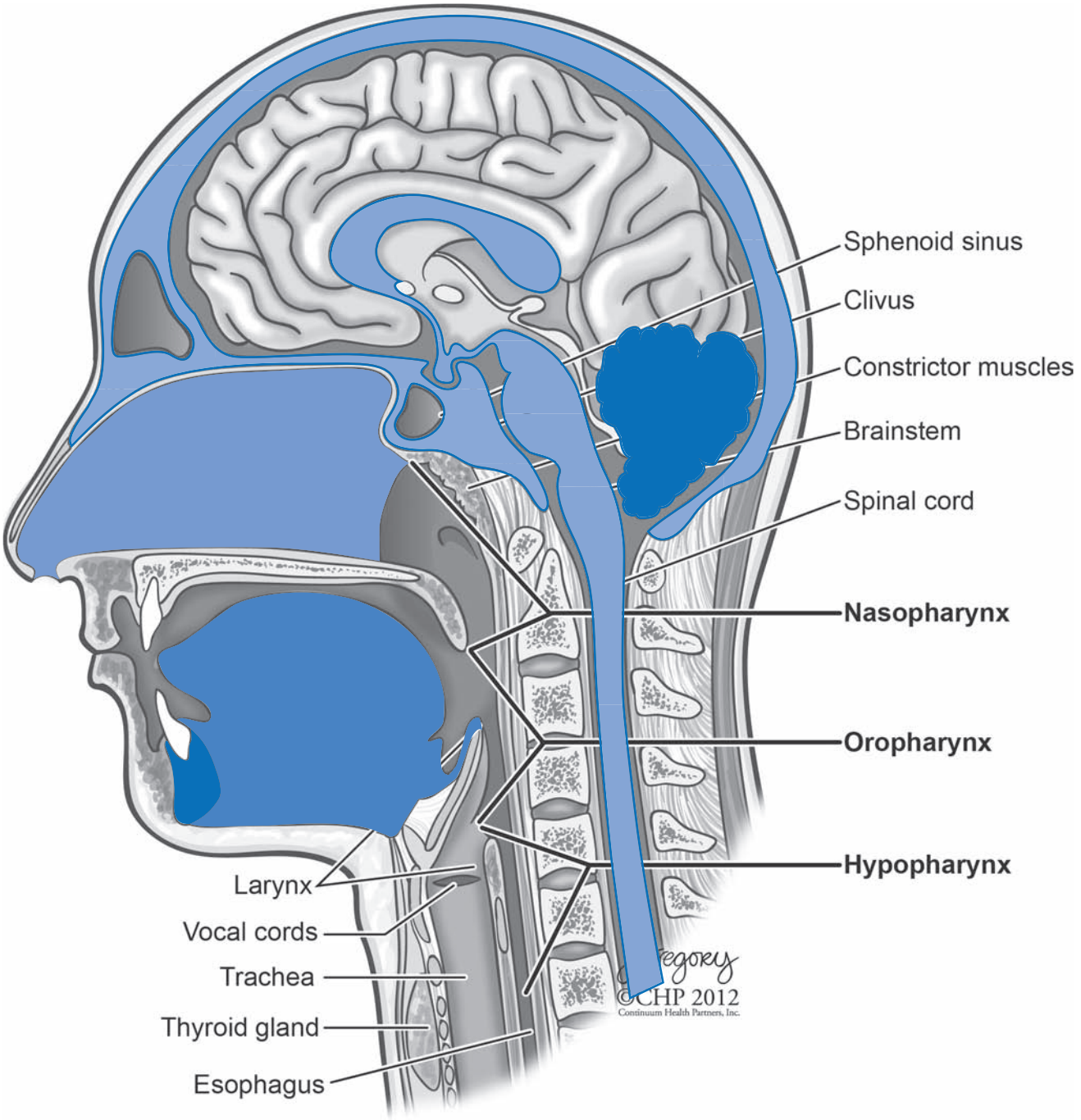



**FIGURE 22-1.** Anatomy of head and neck region and location of the nasopharynx.

The squamous cell carcinomas include well-, moderately and poorly differentiated carcinomas. Keratinizing carcinomas comprises <0.3% in southern China and about 3% in Hong Kong[2,3] but about 25% of all NPC in North America and has a conventional keratinization pattern with intercellular bridges, squamous pearls and graded as well, moderately, or poorly differentiated. It is associated with a desmoplastic response due to invasive growth.[5] It rarely occurs in patient younger than 40 years. These carcinomas are not associated with EBV.[38]

The category of nonkeratinizing carcinomas is subdivided into differentiated and undifferentiated types. The nonkeratinizing carcinoma, differentiated type shows little to absent keratinization and typically lacks a desmoplastic response. It represents about 12% of all NPCs both in Hong Kong and in North America[5,39] and has a growth pattern similar to transitional carcinoma of the bladder with stratified cells well-delineated from the surrounding stroma. Growth may be papillary or plexiform. This tumor type may show prominent cystic degeneration with associated necrosis, and such lesions may metastasize to the cervical neck as cystic metastatic carcinoma. The nonkeratinizing carcinoma, differentiated type, is associated with EBV.[38]

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The nonkeratinizing carcinoma, undifferentiated type represents 60% of all NPC in adults and is the most frequent type in the pediatric population. The cells of undifferentiated carcinoma have prominent eosinophilic nucleoli with dispersed to vesicular-appearing nuclear chromatin and a round nucleus often with prominent eospinophilic nucleoli.[5] In contrast to the other NPC types, the cell margins of this carcinoma are often indistinct creating a syncitial growth pattern. A prominent benign lymphoid component is usually present, and despite invasive growth there is often an absence of a desmoplatic response. As such, in the face of a prominent lymphoid cell proliferation that may overrun the neoplastic cells and the absence of a desmoplastic response, it may be difficult by histologic evaluation to identify the presence of invasive carcinoma. In this setting, the use of cytokeratin staining will greatly facilitate the identification of the malignant cells. Furthermore, the cytomorphologic features of the neoplastic cells as well as the tendency to grow in a dyscohesive manner may result in diagnostic confusion with a non-Hodgkin's malignant lymphoma. Since the neoplastic cells are of epithelial origin, they will be immunoreactive for epithelial markers (e.g., cytokeratins) and negative for lymphoid markers (e.g., leucocyte common antigen, others). The nonkeratinizing carcinoma, undifferentiated type can have a syncitial growth with cohesive cells (Regaud type) or a diffuse cellular infiltrate with independent, dyscohesive cells (Schmincke type). The growth characteristics of a given neoplasm has no bearing on the diagnosis, therapy, or prognosis of these neoplasms, and these two have no distinctly different clinical behavior compared with each other.[5] The nonkeratinizing carcinoma, undifferentiated type is highly associated with EBV.[38]

All three histologic types stain positive for cytokeratin and negative for leukocyte common antigen. Also, these three types may overlap with each other in up to 26% of cases[40] but the tumor will be classified according to the dominant component.

The categories have distinct clinical implications.[40] Undifferentiated NPC has a predilection for dissemination to regional nodes and distant sites and are radioresponsive. The keratinizing squamous cell carcinomas behave like those in other head and neck sites, typically occurring in patients 40 years or older and associated with a smoking/drinking history.[6] Nasopharyngeal squamous cell carcinomas tend to present with more locally advanced primary tumors with fewer involved nodes and metastases than the nasopharyngeal nonkeratinizing carcinomas but with increased radioresistance compared with the other two.[40–44] Overall survival is lower for patients with nasopharyngeal squamous cell carcinomas compared with those with nasopharyngeal nonkeratinizing carcinoma, undifferentiated type.[40,45–47] Five-year disease-free survival is reported to be 15% to 42% lower with squamous cell carcinoma versus nonkeratinizing carcinoma, undifferentiated type.[41,43,48] The nonkeratinizing carcinoma, differentiated type is clinically more similar to nonkeratinizing carcinoma, undifferentiated type than to squamous cell carcinoma and are associated with elevated EBV serology.[49]

Basaloid squamous cell carcinoma, a high-grade variant of squamous cell carcinoma, can rarely occur as primary tumor of the nasopharynx. It is morphologically identical to the same tumor more commonly occurring in other head and neck sites, such as the hypopharynx (pyriform sinus) and larynx. Histologically, the tumor is infiltrative composed of lobules, festoons, trabeculae, and solid foci of pleomorphic, mitotically active basaloid cells with pale-staining nuclei, interspersed with variable amounts of mucoid matrix or hyaline material. Comedo necrosis is common. Neurotropism is often identified. An identifiable squamous cell carcinoma, either in the form of invasive carcinoma or *in situ*, is often identified but may be absent. When present, it usually is limited in extent and represents a minor component in this carcinoma. Immunohistochemical staining is consistently reactive for epithelial markers including cytokeratins (AE1/AE3, CAM5.2, CK903, others) and epithelial membrane antigen. Neuroendocrine markers, including chromogranin and synaptophysin, are typically absent but in rare case may be positive. Melanocytic markers are negative.

Carcinomas histologically similar to nasopharyngeal nonkeratinizing carcinomas, differentiated and undifferentiated types, have been found in other head and neck sites including the oropharynx, the Waldeyer ring,[50] the larynx,[51] the thymus,[52] and the major salivary glands.[53] These "lymphoepithelial carcinomas" are infrequent (e.g., <5% of base of tongue and tonsil carcinomas), but their biologic behavior and response to treatment qualifies them further as carcinomas of nasopharyngeal type. The role of EBV in some of these carcinomas is strongly suggested by serologic profiles, presence of EBV-associated nuclear antigen in the carcinoma cells, and by high levels of viral genomes in the DNA.

## Signs and Symptoms

***Patterns of Spread and Clinical Presentation.*** NPC, especially of the WHO types II and III, usually arises in the region of the fossa of Rosenmüller.[4] The primary tumor may extend anteriorly into the nasal cavity, superiorly into the floor of the sphenoid sinus, anterosuperiorly into the posterior ethmoid air cells and the orbits, laterally into the parapharyngeal space and the pterygoid muscles, superiorly into the foramen lacerum and the sphenopalatine fossa, and inferiorly into the oropharynx (Fig. 22-2).[38] Tumor extension through the fibrocartilage of the foramen lacerum enables direct entry into the cavernous sinus and the middle cranial fossa, resulting in cranial neuropathy including diplopia due to involvement of cranial nerve VI as well as facial pain and paresthesias due to infiltration of the branches of cranial nerve V. Involvement of cranial nerves III and IV indicates more advanced disease along the cavernous sinus (Fig. 22-3). Tumor extension into the parapharyngeal space and involve cranial nerves IX, X, and XI, thus producing a jugular foramen syndrome.

First echelon lymphatic spread most commonly involves the superior jugular, the retropharyngeal, and the posterior cervical chain nodes.[38] Ninety percent of patients will have clinical evidence of unilateral nodal involvement whereas 50% will have bilateral lymphadenopathy. Involvement of the upper jugular and the posterior chain nodes are usually painless unless very large. However, retropharyngeal lymph node metastasis, when extensive, produces a characteristic syndrome of pain referred to the ipsilateral neck, ear, head, forehead, and the orbit. It may be associated with a stiff neck or pain upon neck flexion.

Patients most commonly present with a painless neck mass in more than one-third, whereas other common manifestations including hearing loss or ear drainage in about one-quarter and nasal bleeding or obstruction. Nasal symptoms including breathing obstruction, epistaxis, and discharge can occur. A small proportion of patients may present with cranial nerve deficit, most commonly involving the cranial nerves VI and V (V2 most commonly). Patients may also present with facial pain, headaches, or neck discomfort. Proptosis will occur when cancer invades through the posterior portion of the orbit. Trismus is an indication of the pterygoid muscle invasion.

Physical examination includes inspection of the nasopharynx, either indirectly with a mirror or preferably by direct visualization through a fiberoptic endoscope. The tumor usually appears as an asymmetric mass with telangiectasia on its friable surface and is centered in the fossa of Rosenmüller. Depending on the size of the primary tumor, distortion of the soft palate can occur. Straw-colored serous otitis media is usually unilateral. The earliest signs of cranial nerve involvement are usually extraocular muscle dysfunction, especially lateral rectus palsy, and signs of trigeminal nerve involvement such as hyperesthesia and atrophy of masticatory muscles.

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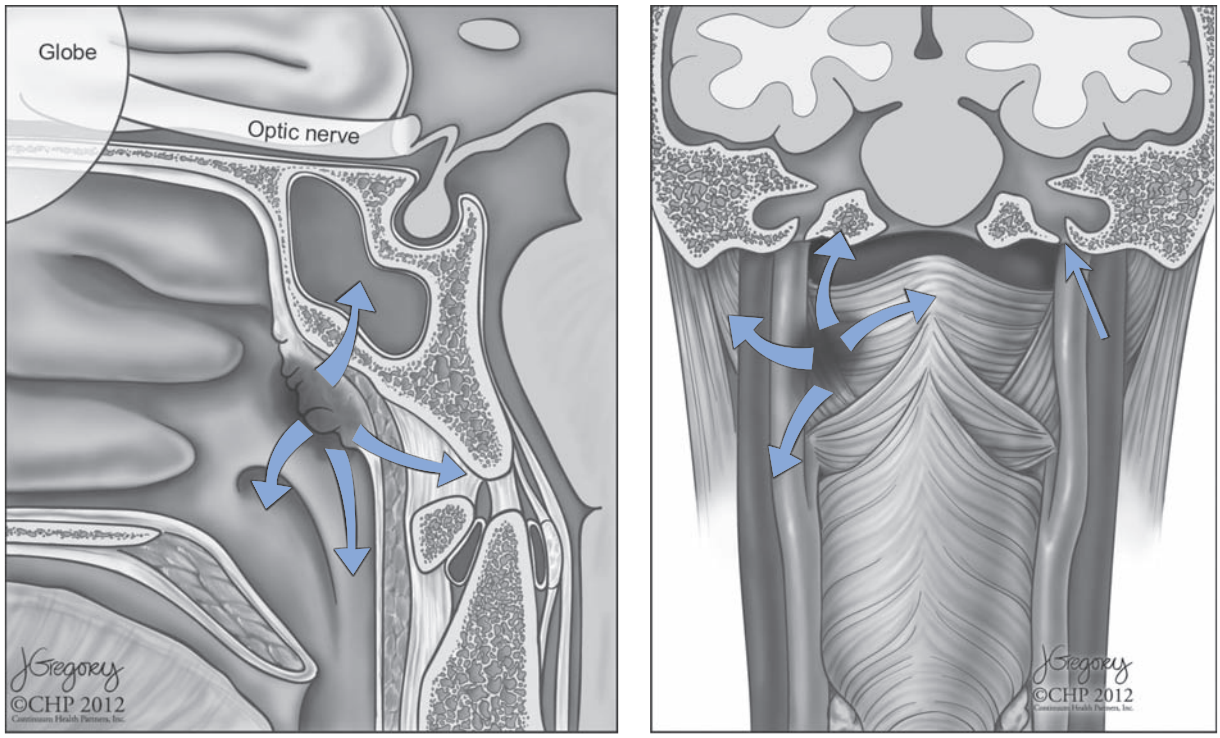



**FIGURE 22-2.** Patterns of spread in sagittal and coronal views. Potential areas of spread include superiorly into the sphenoid sinus/clivus, anteriorly into the nasal cavity/maxillary sinus, posteriorly into the prevertebral muscles and prepontine cistern as well inferiorly into the oropharynx. Note proximity of the brain stem, the spinal cord, and the visual pathways as well as the superior and the middle constrictor muscles. Lymphatic spread to the jugular and the retropharyngeal nodes is common.

For patients in whom the tumor in the nasopharynx is clinically obvious, biopsy can usually be done under the topical anesthetic by topical anesthetic applications through the nasal cavity. Sometimes, however, no primary lesion is evident in the nasopharynx but NPC is suspected on the basis of the presence and location of the cervical lymph nodes. In such cases, fine-needle aspiration cytology will usually establish whether the cell type is consistent with NPC.[37] Usually, clusters of cohesive tumor cells with vesicular nuclei and prominent nucleoli that stain for cytokeratin are present. If it is, radiologic assessment of the nasopharynx may indicate a target lesion for biopsy at examination under anesthesia. If not, a core biopsy of an involved node will provide tissue for fluorescent *in situ* hybridization (FISH) analysis to detect EBV viral genome constituents in the neoplastic cells, which is sufficient to establish the diagnosis of NPC.

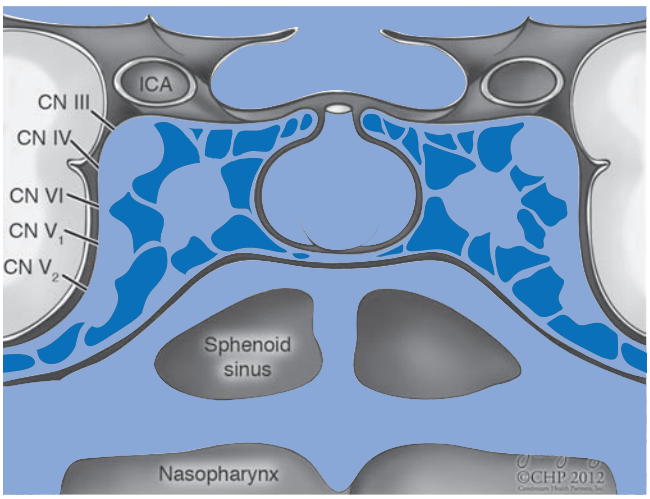



**FIGURE 22-3.** Anatomy of the cavernous sinus showing position of the cranial nerves in relationship to the nasopharynx. Cranial nerve V2 and V1 are in closest proximity to the skull base, while involvement of cranial nerve III and IV indicate advanced involvement of the cavernous sinus.

## CLINICAL EVALUATION AND STAGING

Clinical staging begins with examination by indirect mirror exam and direct endoscopy of the nasopharynx, particularly the fossa of Rosenmüller, and the roof as well as areas of potential spread including the nasal cavity and the oropharynx (Fig. 22-4). Inspection of the posterior pharyngeal wall may reveal bulging suggestive of bulky retropharyngeal nodes. Palpation of the neck nodes is essential especially of the posterior cervical and the upper jugular nodes. Neurologic examination of all cranial nerves is required.

Radiologic examination of the nasopharynx, its surrounding soft tissue, cavities, osseous structures, and lymphatics requires computed tomography (CT) evaluation of the face, the paranasal sinuses, the skull base, and the neck. CT provides excellent evaluation of the draining nodal basins as well as detection of bone invasion of the floor of the sphenoid sinus, the adjacent middle cranial fossa, the clivus, and the pterygoid plates. It provides good soft tissue delineation of tumor

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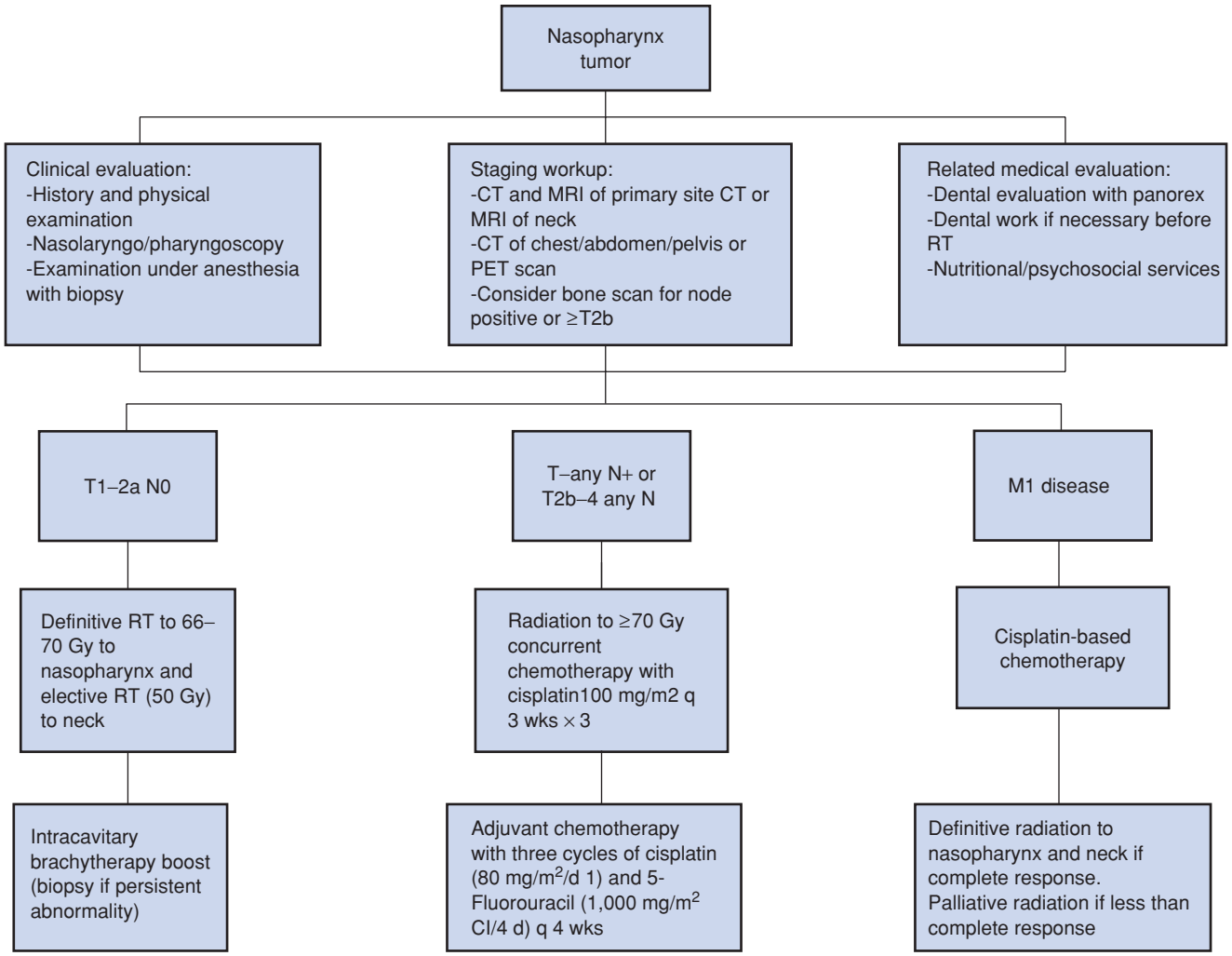



**FIGURE 22-4.** Algorithm for the workup and management of nasopharynx cancer.

extension through the foramen lacerum into the middle cranial fossa, laterally into the parapharyngeal space, anteriorly into the nasal cavity and the maxillary sinuses, inferiorly into the oropharynx, and anterolaterally into the ethmoids and the orbit. Magnetic resonance imaging (MRI) allows superior soft tissue delineation of tumor involvement into the sinuses where it can discriminate between mucus secretions and tumor, as well as evaluate intracranial extension of the prepontine area, the cavernous sinus, and the Meckel cave. MRI can also detect infiltration of the clivus more accurately than CT.[54] It is also useful in the tracking of perineural spread to the skull base foramina and the pterygopalatine fossa area. Moreover, MRI offers superior multiplanar imaging in identifying the course of spread. Evaluation of the jugular chain, the posterior cervical, and the retropharyngeal nodes is crucial given the propensity of early nodal involvement. CT of the neck with contrast is usually the primary imaging modality that is important; however, PET imaging is complementary.

The majority of patients with NPC present with locoregionally advanced disease, and at least one-fifth will have occult distant metastases (DM).[55,56] Sites of predilection for metastatic spread most commonly include in order of greatest frequency: bone, the lung, and the liver.

## Staging

The current staging system is the seventh edition of the American Joint Committee on Cancer[57] and represents the outcome of an evolution of 20 different systems and an international consensus of different staging systems used by the International Union Against Cancer (UICC) system and the AJCC and that used in Southeast Asia according to Ho as well as prognostic factors culled from clinical data from the Asian databases, primarily from Hong Kong.[58] The seventh edition has led to modifications from the sixth edition in both T and N staging. Most importantly, for early-stage tumors, those involving the oropharynx or the nasal cavity have been down staged from T2a to T1. Regarding nodal staging, the presence of unilateral or bilateral retropharyngeal nodes <6 cm are classified as N1. Thus, stage T2aN0 (IIa) patients from the sixth edition are now stage I whereas T2bN0-1 (AJCC stage IIB) are now stage II (T2N0-1). The sixth edition and fifth editions are identical with regard to nasopharynx staging. A comparison of the fourth (1992) versus sixth (2002) edition of the American Joint Committee on Cancer staging is shown below[59] (Table 22.1). It incorporates the importance of parapharyngeal extension especially in the T2 group as well as a nodal staging system that is distinct from that of other head and neck tumor

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## TABLE 22.1 Comparison of the 6th and 7th American Joint Committee on Cancer (AJCC) Staging Systems

T Stage

| AJCC 7th edition (2010) | AJCC 6th edition (2002) |
|---|---|
| T1: Tumor involving nasopharynx with or without extension into oropharynx or nasal cavity | Tumor confined to nasopharynx |
| T2: Tumor involving soft tissue with parapharyngeal extension | T2a: Tumor involving oropharynx or nasal cavity<br>T2b: Tumor involving parapharyngeal space |
| T3: Tumor involves bony structures and/or paranasal sinuses. | Same |
| T4: Tumor with intracranial extension or involvement of the cranial nerves, infratemporal fossa, hypopharynx, orbit or masticator space. | Same |

Parapharyngeal involvement is defined as the posterolateral spread of tumor beyond pharyngobasilar fascia. This corresponds to the line drawn from the medial pterygoid plate to the lateral aspect of the carotid artery. Tumor spread beyond the anterior surface of the lateral pterygoid muscle, lateral extension beyond the posterolateral wall of the maxillary antrum or involvement of the pterygopalatine fissure defines masticator space invasion.

7th Edition Nodal:

Regional Nodal staging is unique for nasopharynx cancers compared to other head and neck squamous cell cancers:

N1: Unilateral nodes up to 6 cm or less in greatest dimension without supraclavicular fossa involvement. Unilateral or bilateral retropharyngeal nodes up to 6 cm.

N2: Bilateral nodes up to 6 cm or less in greatest dimension without supraclavicular fossa involvement.

N3: Nodes >6 cm or involvement of the supraclavicular fossa.

N3a: >6 cm

N3b: Extension to the supraclavicular fossa.

The supraclavicular fossa is a 3-point area outlined as Ho's triangle: 1) superior margin of the sternal end of the clavicle, 2) superior margin of the lateral end of the clavicle and 3) point where neck meets shoulder.

6th Edition Nodal Staging is the same as 7th edition except retropharyngeal nodes not specified.

7th Edition Staging:

| | | | |
|---|---|---|---|
| 0 | Tis | N0 | M0 |
| I | T1 | N0 | M0 |
| II | T1 | N1 | M0 |
| | T2 | N0–1 | M0 |
| III | T1 | N2 | M0 |
| | T2 | N2 | M0 |
| | T3 | N0–2 | M0 |
| IVa | T4 | N0–2 | M0 |
| IVb | | Any N3 | M0 |
| IVc | | | Any M1 |

6th Edition Staging:

| | | | |
|---|---|---|---|
| 0 | Tis | N0 | M0 |
| I | T1 | N0 | M0 |
| IIA | T2a | N0 | M0 |
| IIB | T1 | N1 | M0 |
| | T2a | N1 | M0 |
| | T2b | N0–1 | M0 |
| III | T1 | N2 | M0 |
| | T2a/b | N2 | M0 |
| | T3 | N1–2 | M0 |
| IVa | T4 | N0–2 | M0 |
| IVb | | Any N3 | M0 |
| IVc | | | Any M1 |

*Source:* From American Joint Committee on Cancer (AJCC). *Cancer Stastaging Manual.* 6th ed. New York, NY: Springer-Verlag; 2002; 7th ed., 2010, with permission.

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sites. Also of importance is that the sixth edition downstages N1 patients from stage III in the fourth edition to stage IIb, which is relevant in evaluating the Intergroup 0099 study which enrolled AJCC fourth edition stage III/IV patients.[60]

Teo reported that parapharyngeal extension is the strongest independent prognosticator for distant metastasis and survival in 903 NPC patients in patients without cervical nodal disease or skull base/cranial nerve palsy.[61] Chua further detailed that the extent of parapharyngeal extension impacted both on local control (LC) and distant metastasis in 364 patients.[62] The incidence of parapharyngeal extension was 73% and degree of extension subgrouped into grade 1 (poststyloid), grade 2 (prestyloid), and grade 3 (masticator space) (Fig. 22-5). Patients with no or grade 1 extension had better 5-year LC (87% vs. 72%, $p < 0.0001$) and lower 5-year distant metastasis (13% vs. 32%, $p = 0.0002$) compared with those with grade 2/3 extension, respectively. The increased risk for local failure with advanced parapharyngeal extension was seen in T2 but not in T3 patients. The increased risk for distant metastasis with advanced parapharyngeal involvement was independent of nodal status and was independently prognostic in N2 and N3 patients.

## Clinical Prognostic Factors

Early stage, female gender, nonkeratinizing histology, and younger age predict a more favorable outcome.[16,40] Patients with haplotype Aw33-C3-B58/DR3 have a poorer prognosis compared with those with A2-Cw-11Bw46/DR9.[4,16] Staging with MRI predicts a better outcome given the improved tumor delineation.[63] Tumor volume based on CT showed an independent prognostic factor of treatment outcome beyond the Ho staging system, but a small study showed the tumor volume derived from MRI was not.[64,65] Serum LDH was predicted for DM in two studies.[54,66] Serum EBV markers are clearly an important predictive and prognostic factors that are to be explored to tailor management in upcoming trials (see "Etiology").

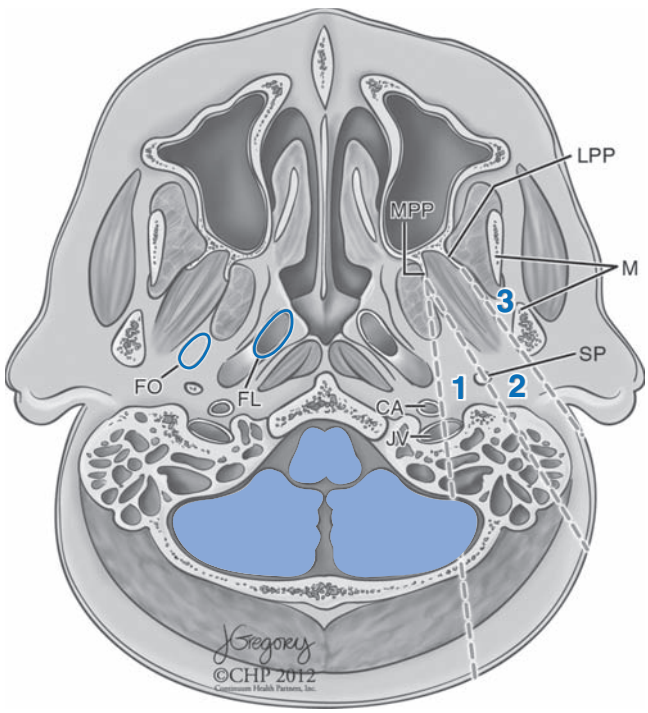



**FIGURE 22-5.** Schematic diagram outline the grading of parapharyngeal extension by nasopharyngeal carcinoma. Grade 1: extension into the retrostyloid space as it invades past the line between the medial pterygoid plate (MPP) to the internal jugular vein (JV), Grade 2: extension in to the prestyloid space at it extends past the line between the medial pterygoid plate and the styloid process (SP) and Grade 3: extension into the masticator space as delineated by extension beyond the line between the lateral pterygoid plate (LPP) and the posteromedial margin of the ascending ramus of the mandible (M).

# MANAGEMENT STRATEGIES

NPC is a highly radiosensitive head and neck cancer that can be treated effectively with radiation therapy (Fig. 22-4). Radiation therapy has been the mainstay treatment as it is able to cover the large areas of potential locoregional spread in a comprehensive manner. Nasopharynx cancers are located in a highly enriched lymphatic drainage area that favors early regional spread to the retropharyngeal and cervical nodes both unilaterally and bilaterally. The primary tumor exists in an occult location with a strong inclination to invade the skull base, surrounding sinuses, nerves, and soft tissue spaces before presenting clinically. Advances in radiation delivery, imaging, integration of chemotherapy, standardization of an internationally agreed upon staging system, improvement of multidisciplinary care as well as increased scientific exchange have led to significant advances in tumor control and quality of life (QOL).

In general, patients with early-stage tumors are amenable to treatment with radiation therapy alone with high rates of locoregional control, whereas those with T3/T4 lesions or significant nodal disease require more intensive treatment as outcomes with radiation therapy alone lead to higher rates of locoregional failure and DM. For the latter group, multiple large trials testing the addition of chemotherapy either sequentially concurrently or both with radiation therapy have been evaluated. Dose escalation and improved conformality of radiation therapy using a wide variety of techniques appear to improve outcomes. Altered fractionation has been explored as well as new biologic agents. For patients with recurrence after standard radiation, the role of surgical salvage and reirradiation have been explored.

## Patterns of Failure

Patterns of spread include invasion into adjacent soft tissues, paranasal sinuses, skull base as well as spreading intracranially (Fig. 22-2).[38] Potential areas of microscopic spread include the sphenoid sinus, the foramen ovale and the petrous tip, the posterior third of the nasal cavity/the maxillary sinus, the clivus, and the parapharyngeal space/the pterygoid fossa. Critical normal structures which are adjacent to the target volume and with tolerance doses that must be respected include the brain stem, the spinal cord, the optic nerve, the chiasm, the lens, the temporomandibular joints (TMJs), the cochlea, the vestibulocochlear nerves, the oral mucosa, and the external auditory canal. Most common sites of primary tumor spread based on MRI imaging of 308 patients have been reported (Table 22.2).[38]

## Radiation Technique

Radiation treatment of nasopharynx cancer is technically challenging due to the proximity of tumors to critical structures including the spinal cord, the brain stem, the temporal lobes, the optic pathways as well as structures important for QOL and function such as the masticatory/the constrictor muscles, the temporomandibular joint, the salivary glands, and the auditory nerves. These tumors often wrap around the brain stem in a

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**TABLE 22.2 Percentage Incidence of Involvement of 308 Nasopharynx Patients on MRI Imaging**

| Adjacent Soft Tissues | % | Bony Erosion/Paranasal Sinus | % | Intracranial/ Orbital Extension | % |
|---|---|---|---|---|---|
| Nasal Cavity | 87% | Clivus | 41% | Cavernous sinus | 16% |
| Parapharyngeal space | 68% | Sphenoid sinus, foramina lacerum, ovale, rotundum | 38% | Cerebrum, meninges | 4% |
| Pterygoid muscle | 48% | Pterygoid plate, pterygomaxillary fissure, pterygo-palatine fossa | 27% | Orbit, orbital fissure | 4% |
| Oropharynx | 21% | Petrous bone | 19% | Pituitary fossa | 3% |
| Prevertebral muscle | 19% | Ethmoid sinus | 6% | | |
| Infratemporal fossa | 9% | Maxillary antrum | 4% | | |
| Nasal septum | 3% | Jugular foramen, hypoglossal canal | 4% | | |

*Source:* Chan JKC, Bray F, McCarron P. World Health Organization of tumours. Nasopharyngeal carcinoma. In: Eveson JE, Barnes L, Reichart P, et al., eds. *Pathology and Genetics of Head and Neck Tumors.* Lyon, France: IARC Press; 2005:87–99, with permission.

concave manner as they spread into the parapharyngeal space, as well as intracranially through the skull base, the foramina, and along the nerves. As such, they may extend too close to critical adjacent structures for an adequate tumoricidal dose to be delivered depending on the treatment technique.

Radiation therapy treatment has improved vastly from the initial use of orthovoltage/radium sources, block-shaped beams, and plain film–based imaging with large setup uncertainty, to high-energy linear accelerator with dynamic leaf collimation and more sophisticated CT-based treatment planning with precise setup and immobilization.[67] The evolution in treatment planning has provided for better targeted radiation delivery and dose escalation from 50–60 to 80 Gy.[68–70]

For many years, two-dimensional (2D) technique had been the mainstay of treatment and continues to remain so for many centers with good LC for early-stage cancers.[67,71] Traditional 2D treatment planning involves parallel opposed lateral fields and a low anterior neck field. After an initial phase in which the brain stem and the cord are in the treatment field, shielding of these structures is required to maintain the dose within tolerance, potentially compromising dose to areas of tumor that extend to the skull base, the parapharyngeal area, or intracranially. Simultaneously, normal structures such as the parotids and the constrictor muscles are unavoidably treated with high doses.[72,73] In addition, 2D technique does not account for tissue inhomogeneities that exist in the paranasopharyngeal area including the air cavities, multiple bony interfaces and variation in contour, and head and neck separation.[74]

Incorporation of volumetric imaging for treatment planning is crucial for improved dosimetry. Jian reported that the use of CT for 2D treatment planning was critically important to define an adequate clival margin, which was one of the most important factors for locoregional control in patients treated with radiation.[75] Since the 1990s, technologic advances in treatment planning systems incorporating CT have led to the development of conformal therapies such as three-dimensional conformal therapy (3D CRT)[74] and intensity-modulated radiation therapy (IMRT), which have enhanced dose conformality, improved dose homogeneity, permit dose escalation while simultaneously decreasing dose to normal tissue to lessen chronic toxicities.[76–78]

3D-CRT exploits the spatial relationship between tumor and normal tissue by manual selection of beam angle with a beam eye's view and through an iterative process of beam weighting with correction of tissue inhomogeneities to achieve optimization. It has been estimated that 3D-CRT can increase the mean tumor dose by >10% and potentially increasing tumor control probability by 15% without added normal tissue complications.[74]

IMRT represents a major advance beyond 3D-CRT, adding an extra degree of freedom to treatment planning by modulating the dose intensity within each beam to generate virtually any shape of dose distribution. Instead of manually changing beam weighting and angles as with 3D-CRT, the IMRT planner sets the dose to the target volumes, assigns normal tissue penalties/constraints, and selects the number of beams/beam angles at the outset for delineated structures, before an inverse treatment planning system attempts to satisfy these criteria through a least-squares, cost-function optimization process.[78–80] Adjustments of the number of beams/constraints/penalties refine the plan further. Dose gradients of 5% per millimeter can be achieved with a dose uniformity of 10% or less within the PTV.[79]

A crucial component toward achieving the maximal therapeutic benefit from conformal therapy is accurate delineation of the tumor volumes and adjacent critical structures. The appropriate dose and treatment margin to cure the tumor must be weighed against the potential to cause permanent toxicity. It requires not only precise visualization of gross tumor based on clinical and radiologic evaluation, but also a comprehensive understanding of potential areas of spread locally and regionally. If too precise, the probability of a geographic miss of occult disease increase which may be further magnified if small errors in reproducing patient setup occur. Thus, high-resolution imaging becomes a prerequisite toward achieving that goal. The latter should include both transverse and coronal CT cuts. Fusion with MRI or PET/CT as well as viewing in coronal and axial planes to accurately follow tumor spread three dimensionally is crucial.

## Dose Prescription

The standard radiation dose prescribed to the primary site in nasopharyngeal cancer in most centers is an equivalent of 70 Gy over 7 weeks. Doses of 66 to 70 Gy are given to involved nodes, and clinically uninvolved nodes typically receive 50 Gy in 5 weeks whereas intermediate risk areas for subclinical disease receive 60 Gy. With IMRT, dose painting is possible in which differential doses to various target volumes are delivered simultaneously. Typically, higher doses per fraction (212–220 cGy/fraction) are delivered to areas of gross disease are delivered while lower dose (180 cGy/fraction) are delivered for areas at risk for occult disease.[76,81,82]

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Kam demonstrated that superiority of IMRT-based plans compared with 3D-CRT and 2D technique of Ho in three different but common clinical stages: early stage (T1N0), a tumor with parapharyngeal extension and significant nodal disease (T2bN2), and a tumor with intracranial extension T4N2.[81] All patients were treated to a final prescription dose of 66 Gy with standard dose constraints to the normal tissue. CTV included potential sites of microscopic disease as described above and GTV with at least 1-cm margin except a 5-mm posterior margin. A 3-mm margin was added to the CTV for the PTV. A total of 66 Gy in 33 fractions was prescribed to the gross volume whereas 60 Gy in 33 fractions was prescribed to cover areas at high risk for microscopic disease. In the Ho technique, the initial phase to 40 Gy is composed of opposed laterals with a low anterior neck, followed by a cone down to the primary with the addition of an anterior field to the opposed laterals with blocking of the pituitary, the optic nerve, and the tongue. The 3D technique comprised initial opposed laterals to 40 Gy, followed by six to eight coplanar beams as a 3D cone down. The IMRT plan consisted of seven coplanar beams. In the dosimetric comparison of the three techniques for the early-stage (T1N0) scenario, IMRT did not improve target coverage or dose, but better spared dose to the parotid (dose to 50% [D50] was 31 Gy [IMRT] vs. 50 Gy [3D-CRT] vs. 57 Gy [2D]) and the TMJs (D50 was 31 Gy [IMRT] vs. 64 Gy [3D-CRT] vs. 59 Gy [Ho-2D]). In the case of the tumor with parapharyngeal extension, the IMRT plan showed improved tumor coverage (D95 of PTV was 68 Gy [IMRT] vs. 64.8 Gy [3D-CRT] vs. 57.5 Gy [2D]). In the third scenario of intracranial extension of tumor, IMRT improved both PTV coverage (D95 of PTV was 67.5 Gy [IMRT] vs. 62 Gy [3D-CRT] vs. 55 Gy [2D]) and normal tissue sparing of the brain stem (maximum dose was 48 Gy [IMRT] vs. 65 Gy [3D-CRT] vs. 64 Gy [2D]) and temporal lobes (maximum dose was 46 Gy [IMRT] vs. 57.5 Gy [3D-CRT] vs. 66.5 Gy [2D]). Furthermore, in the IMRT-treated patients with T2b or T4 disease, an additional 3D boost of 14 Gy increased the probability of normal tissue complications primarily to the parotid gland by 20% but <1% to the brain stem, the spinal cord, and the TMJ. The latter data demonstrate the potential of IMRT to permit safe dose escalation to 80 Gy.

## Radiation Therapy Only

Outcomes after radiation therapy alone using conventional fractionation and 2D technique have shown generally good locoregional control rates for early-stage tumors but suboptimal outcomes for locoregionally advanced tumors. After conventional radiation, local failure occurs in 5% to 25% for T1–2 and 20% to 56% for T3–4 tumors (Table 22.3).[43,63,68,83–87] Improvements in outcomes using 2D technique have resulted from better staging, comprehensive radiation coverage, improved imaging, use of a simulator, mobilization, a high-output linear accelerator, customized blocks, accurate dose calculation, verification films, training of radiation technical staff, addition of boost techniques, and integration of chemotherapy for locoregionally advanced cases.[67,68,88–90]

One of the largest North American series of nonendemic patients was reported by the MD Anderson Cancer center on the outcomes of 378 patients treated from 1954 to1992 with primary radiation therapy.[68] Three-quarters were of Caucasian origin and 51% with WHO I histology whereas 41% were lymphoepitheliomas. The median age of patients was 52 years with 74% male and three-quarters presented with stage IV disease (AJCC, 1992). Patients were treated to doses ranging from 60 to 72 Gy depending on T stage with dose escalation for all T stages in the more modern eras (61 Gy [1954–1971] → 67 Gy [1972–1982] → 70 Gy [1983–1992]) as well as a transition from multifield 2D technique at the primary site in nearly two-thirds at the beginning of the study period to opposed laterals for nearly all patients during the latest period. At a median follow-up of 10 years, the 5-/10-year actuarial rates of local, regional control, and overall survival were 71%/66%, 84%/83%, and 48%/34%, respectively. LC was increased over 20% for tumors with lymphepithioloma versus squamous cell histology ($p < 0.0001$) with a trend toward improved control with higher doses ($p = 0.09$). The 5-/10-year actuarial rates of grade 3 to 5 late complications were 16%/19%. The incidence of treatment-related mortality was 3% (primarily spinal cord and cranial nerves) with virtually all cases occurring before 1971. There was a strong influence of treatment technique with incidence of grade ≥3 late complications highest in the three-field technique (AP/lats) versus 25% with opposed laterals ($p < 0.0001$).

The largest series of endemic patients treated with conventional fractionation and 2D technique was reported by Lee on the outcomes of 2,687 consecutive patients treated at multiple institutions in Hong Kong from 1996 to 2000.[91] The breakdown of patients were as follows: stage I: 7%; stage II: 41%; stage III: 25%; and stage IV: 28%. Patients were treated to a median total dose of 66 Gy and 90% were treated with the 2D technique of Ho. About 55% had additional boost treatment with external beam or brachytherapy. About one-fourth received chemotherapy (14% concurrent, 9% sequential). At a median follow-up of 3.4 years, 5-year local, nodal, and distant failure-free survival rates were 85%, 94%, and 81%, respectively. Five-year progression-free, overall, and cancer-specific survival were 63%, 75%, and 80%, respectively. Five-year LC by T stage were as follows: T1: 91%;

**TABLE 22.3 Local Control by Tumor Stage after Conventional Radiation Therapy**

| | T1 (No. of Patients) | T2 (No. of Patients) | T3 (No. of Patients) | T4 (No. of Patients) |
|---|---|---|---|---|
| Hoppe et al. (1976)[88] | 87% (38) | 94 (16) | 68 (19) | 44 (9) |
| Chu et al. (1984)[98] | 76% (25) | 79 (14) | 37 (19) | 55 (22) |
| Vikram et al. (1984)[140] | 65% (47) | | 100 (3) | 48 (57) |
| Wang et al. (1971)[85] | 76% (17) | 54 (23) | 34 (11) | 42 (10) |
| BID | 67 (14) | 84 (30) | 78 (12) | 52 (12) |
| Sanguineti et al. (1997)[68] | 93% (55) | 79% (138) | 68% (67) | 53% (118) |
| Perez et al. (1992)[96] | 85% (21) | 75% (33) | 67% (26) | 45%(63) |
| Lee et al. (1993)[89] | 91% | 87% | 80% | 77% |

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T2: 87%; T3: 80%; and T4: 77%. Five-year regional control by N stage were as follows: N1: 95%; N2: 92%; and N3: 83%. Among stages I to II patients, 5-year distant metastasis–free survival (DMFS) was 90% versus 81%, for those with locoregional control versus those with locoregional failure. For stage III to IV, the corresponding 5-year DMFS was 75% versus 65%, respectively. The results of this period (1996–2000) were compared with 5,037 patients treated from 1976 to 1985 and showed significantly better LC (85% vs. 66%, nodal control 94% vs. 67%, distant-free survival 81% vs. 62%, and overall survival 80% vs. 52%). Better imaging (CT/MR vs. plain radiography/tomography) and radiation delivery technology (linear accelerator) and use of conventional fractionation are identified as the most important factors for the improvement. The one-third of patients staged by MRI (860/2,687 = 32%) achieved better overall survival regardless of stage compared with those staged only by CT (stages I–II 93% vs. 83%, $p = 0.001$ and stages III–IV 72% vs. 63%, $p = 0.001$). MRI-staged patients had better LC (T1–2: 91% vs. 87% and T3–4: 83% vs. 76%).

## NECK CONTROL

In contrast to carcinomas at other head and neck sites, neck disease is managed with primary radiation regardless of N stage. Regional control with primary radiation therapy is excellent regardless of N and T stage. Regional control rates of 80% to 90% for N1–2 are the rule after definitive radiation without chemotherapy and 70% to 80% for N3.[68,85,91,92] In the MD Anderson series reported by Sanguinetti, regional control for 378 patients treated from 1954 to 1992 was 83% at 5 years for the entire group and by N stage (AJCC, 1992). Five-year actuarial rates were as follows: 95% (N0), 94% (N1), 91% (N2a), 80% (N2b), 77% (N2c), and 71% (N3).[68] The series from Washington University reports regional control of 98% for N0–1, 71% for N2, and 64% for N3.[92] Patients with recurrent disease to the neck after definitive radiation are treated with salvage neck dissection.

## CRANIAL NERVE IMPROVEMENT AFTER RT

Due to the proximity of the nasopharynx to the skull base and the cavernous sinus, a small but significant group of patients can present with cranial neuropathy from 11% to 29% in some series.[93,94] In a study of 93 patients who presented with CN palsy, 70% of patients showed improvement after definitive radiation therapy.[95] The most common cranial nerve palsies involved CN V (38%), CN VI (26%), CN XII (11%), and CN III (9%). Upon completion of RT, the complete recovery rate was 51% and partial recovery rate was 19%. At 6 months, the rate improved slightly to 58% complete recovery and 17% partial recovery. Patients with parasympathetic nerve, CN II, IX, and XI palsies showed complete recovery rates of 100% (3/3), 100% (2/2), 87% (7/8), and 100% (1/1), respectively, whereas the rate of complete recovery was worst for CN VII and XII (40% [2/5] and 40% [8/20], respectively). For the most common palsies, the complete recovery rate of CN V and CN VI were 44% (29/66) and 50% (23/46), respectively. Pretreatment duration of >3 months was associated with worse recovery of CN function (62% vs. 88%, $p = 0.002$) than those with a shorter period of cranial nerve palsy.

### Dose-response Effect of RT

The preponderance of retrospective data reports that dose escalation above 66 Gy improves LC.[43,70,71,83,88,89,92,96–99] However, some have shown no relationship.[90,100,101] The lack of consistency is likely related to confounding factors including small patient numbers, historic bias in which patient outcomes are compared over long periods of time, different staging systems, improved conformality of treatments with 3D planning, brachytherapy and stereotactic radiation, better target identification with improved imaging such as MRI, use of altered fractionation regimens, and integration of chemotherapy.[63,68,90]

Vikram reported on 107 nasopharynx patients treated with definitive radiation alone using consistent staging and treatment techniques.[83] More than half had T4 lesions and 87% with stage IV disease. Radiation was delivered with a 3-field technique to doses ranging from 40 to 77 Gy to the primary site with conventional fractionation. Minimum follow-up of at least 2 years was achieved in 98 of the 107 patients. Fifty-five patients relapsed, of whom 60% relapsed at the primary site. Patients receiving 57 to 67 Gy were at increased risk for local failure compared with those treated to 67 to 77 Gy (local failure: 43% [26/60] vs. 28% [12/43], $p = 0.08$, respectively). The dose response was especially pronounced for T4 lesion (local failure 46% [11/24] vs. 7% [1/14]). Patients having treatment breaks of >3 weeks had increased local failure (67% vs. 34%, $p < 0.05$) compared with those treated without such breaks and higher dose did not appear to compensate for the treatment break. Patients receiving the higher doses without treatment break had LC of 84%.

In a large multicenter pooled analysis of 2,426 patients treated in five Hong Kong regional centers, the benefit of escalation of dose beyond 66 Gy is evident.[102] All centers used the same 2D technique according to Ho. All patients received 66 Gy with external beam radiation and about two-thirds ($n = 1,572/2,426$) received a boost dose. Boosts doses and technique depended on the tumor stage. For T1/T2a tumors, intracavitary boost was favored ($n = 146$, 10 Gy/2 fractions or 18–24 Gy/3 fractions) although some were boosted with 2D EBRT ($n = 61$, 15 Gy/3 fractions). All T2b–4 tumors were boosted with EBRT as follows: ipsilateral 3D posterior oblique boost ($n = 211$, 20 Gy/10 fractions and $n = 634$, 10 Gy/5 fractions) for T2b tumors and 2D boost ($n = 487$, median dose 10 Gy/fractions) for T3/T4 tumors. The boost was planned for most T2b/T3/T4 tumors and given to T1–T2a if biopsy residual disease remained after initial treatment. About 20% ($n = 511$) received chemotherapy with 12% receiving concurrent chemotherapy. Median follow-up was 4.2 years. Both early-stage T1–T2 and advanced tumors (T3–T4) treated with radiation alone benefited from an RT boost above 66 Gy, but not patients treated with chemotherapy regardless of T stage. For T2b patients, a 20-Gy boost was superior to 10 Gy in decreasing local failure. Although the impact of boost on long-term morbidity was not reported, no excess mortality were attributable to RT complications.

A steep dose–response relationship for LC was demonstrated in the range from 65 to 85 Gy of physical dose delivered and for biologic equivalent dose (BED) 10 Gy from 80 to 125 Gy.[103] The data suggest a 15% decrease in local failure for every additional increase in 10 Gy BED 10 corrected for treatment time. However, dose escalation beyond 72 Gy using 2D technique is associated with significantly higher incidence of chronic toxicity such as hearing impairment, trismus, and temporal lobe necrosis based on a retrospective analysis of 849 consecutively treated patients in a single institution.[104]

An attempt to dose escalate using a 3D boost after initial 2D treatment was reported.[69] Sixty-eight patients were treated with initial 2D technique up to 50.4 Gy followed by a 3D boost to 7,020 to 7,560 cGy (median dose 70 Gy). Lateral fields were prescribed to midplane whereas the boost was prescribed to an isodose curve. The mean dose to the PTV was on average 13% higher with the 3D portion compared with the 2D technique. About half of patients received concurrent cisplatin chemotherapy. At a median follow-up of 42 months, the 5-year LC was 77%, regional control was 97%, and progression-free survival

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was 56%. These did not appear to have dramatically improved compared with a historic group of 33 patients treated with 2D technique at the same institution. However, the dose escalation was modest, the patient cohorts were small, and it is unclear how similarly imaged and staged was the historic control compared to the reported group.

## Brachytherapy

Dose escalation using adjuvant brachytherapy have primarily been confined to early-stage tumors which can be encompassed adequately by the dosimetry. The combinations of external beam and brachytherapy approach have included (a) external beam doses of 60 to 70 Gy with HDR brachytherapy of 12 to 18 Gy in 3Gy BID fractions,[105] (b) 60 to 62.5 Gy EBRT combined with brachytherapy boost of 18 to 24 Gy/8 Gy × 2 to 3 weekly fractions,[61] (c) 64.8 to 68.4 Gy of EBRT followed by brachytherapy boost of 5 to 16.5 Gy in 1 to 3 fractions,[106] and (d) 64 Gy → 7 to 10 Gy intracavitary boost (Table 22.4).[97]

The literature supports the benefit of brachytherapy in decreasing local failure by 50% for T1–2 patients treated with radiation alone with modestly improved disease-free survival.[102] The largest series is reported by Teo in a retrospective analysis of 743 patients with T1–2 cancers all treated with the Ho 2D technique.[102] One-hundred eighty-eight received brachytherapy (18–24 Gy in 3 fractions over 2 weeks) plus EBRT whereas 555 received EBRT alone. EBRT was delivered to a dose of 60 Gy in 4 weeks in the majority of patients. Neoadjuvant chemotherapy was delivered in 13% of patients. Brachytherapy was delivered within 4 to 6 weeks after EBRT for persistent disease in 126 patients (24 Gy) and as adjuvant (18 Gy) to complete responders in 62 patients. Median follow-up was 79 and 88 months in the brachytherapy arm and EBRT-alone arms, respectively. At 5 years, the brachytherapy group had fewer local failures (5.8% vs. 11.7%, $p = 0.013$) and lower disease-specific mortality (12.2% vs. 15.2%, $p = 0.08$) compared with the EBRT-alone group. No difference in regional failure (8% in each arm) or DM (13% in each arm) are reported. Multivariate analysis showed the independent benefit of brachytherapy in decreasing local failure. The two groups showed comparable chronic radiation complications. However, patients receiving brachytherapy had an increased incidence of nasopharyngeal ulceration and necrosis occurring in 6% versus 0.2% in the EBRT-alone arm.

Levandag reported on 42 patients treated from 1991 to 1995 with EBRT and high-dose rate brachytherapy.[105] The patient population consisted of 12 T1–2 and 30 T3–4 AJCC (1992) tumors, of whom 32 were N2 or greater. Patients with T1–3 tumors were treated with 60 Gy EBRT followed by 18 Gy brachytherapy given in 3Gy BID fractions, whereas T4 patients were treated with 70 Gy followed by 12 Gy brachytherapy in 3 Gy BID fractions. One of 42 received induction chemotherapy. The brachytherapy group was compared with a historic cohort of 109 patients treated from 1965 to 1991 with EBRT alone ($n = 69$) or chemotherapy with EBRT ($n = 40$). T1–2 tumor comprised 59% (64/109) of the historic group whereas 58% (63/109) were N2 or greater. The median dose of EBRT in the EBRT-alone group was 70 Gy and in the chemotherapy group was 64 Gy. Overall, the addition of brachytherapy was well tolerated except for the development of late grade 3 mucosal toxicity consisting of synechiae of the nasal cavity requiring surgical correction. At a median follow-up of 2.6 years, 3-year LC was 86% in the brachytherapy group and 3-year DFS was 71%. These outcomes were significantly superior to the corresponding outcomes in the nonbrachytherapy group (3-year LC 60% [$p = 0.004$] and 3-year DFS 52% [$p = 0.005$], respectively). Patients receiving induction chemotherapy had the worse LC (3-year 54%) versus the EBRT-alone group (3-year 64%). The American Brachytherapy Society recommends the applicator developed by this group.[107] The applicator can be positioned against the roof of the nasopharynx closer to where tumor originates, unlike pediatric endotracheal tubes which may sit on the soft palate away from the recurrent tumor.

## Stereotactic Radiosurgery and Radiation Therapy

Brachytherapy offers an excellent approach to escalate dose for early-stage lesions. However, for more advanced lesions where coverage with brachytherapy is suboptimal, alternative methods using stereotactic approaches have been used to provide highly conformal radiation with sharp fall off of dose to surrounding normal tissues.

The role of SRS boost after EBRT was reported for 23 patients.[108] EBRT doses of 66 Gy/33 fractions were delivered (64.8–70 Gy) in 23 patients. Fifteen received cisplatin-based chemotherapy. Twelve patients were T4. An SRS boost using frame-based linear accelerator technique to deliver an additional median dose of 12 Gy (range 7–15 Gy). At a mean follow-up

**TABLE 22.4 Local Control after Combined External Beam Radiation and Brachytherapy**

| Author | No. of Patients (% T1/2) | Median F/U (mo) | EBRT Dose | BT Dose | LC | Toxicity from BT |
|---|---|---|---|---|---|---|
| Thiagarajan et al. (2006)[264] | 33 (100%) | 67 mo | 66 Gy | 10 Gy/ fraction (HDR) | 94% (5 yr) | None reported |
| Teo et al. (2000)[102] | 188 | 88 mo | 60 Gy | 18–24 Gy/ 3 fraction | 94% | 6% necrosis/ulceration of nasopharynx |
| Levendag et al. (2002)[105] | 42 (29%) | 2.6 yr | 60–70 Gy | 12–18 Gy/ 4–6 fraction | 86% (3 yr) | Nasal cavity synechiae |
| Wang (1991)[97] | 64 (84%) | NS | 60–64 Gy BID | 10–15 Gy | 90% (T1–2)100% (T3) | |
| Chang et al. (1996)[106] | 133 (100%) | | 65–68 Gy | 5–16.5 Gy/ 1–3 fraction | 94% (5 yr) | Necrosis/perforation of sphenoid sinus |
| Lee et al. (2002)[265] | 43 (91%) | 36 mo | 66 Gy (median) | 5–7 Gy (HDR) 10–54 Gy (LDR) | 89% | |

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of 21 months LC was 100% whereas two patients developed a regional recurrence and seven had distant metastasis. No complications caused by SRS were reported.

An update was reported by Le on 45 patients treated with a stereotactic radiosurgery (SRS) boost after EBRT to a dose of 66 Gy.[109] Of the 45 patients, 22 had T3–4 tumors and 23 had N2 disease or greater. EBRT was delivered with 2D technique in 38 patients and IMRT in 7. Thirty-six patients received concurrent chemotherapy per the Intergroup 0099. SRS was delivered to a median dose of 12 Gy with Linac-based technique in 33 and cyberknife in 12 patients. At a median follow-up of 35 months, LC was 100% at 3 years whereas the incidence of metastasis was 31%. Regional failure occurred in three patients, one of whom was salvaged with neck dissection. No acute toxicity was reported from the SRS although long-term toxicity included cranial nerve palsy in four patients, temporal lobe necrosis in three patients, and retinopathy in a patient with cranial neuropathy.

## Stereotactic Radiation Therapy Boost

Sixty-four patients were treated with conventionally fractionated radiotherapy to 64.8 to 68.4 Gy with chemotherapy given in 81% as induction (22%) or concurrent (59%) followed by stereotactic radiation therapy (SRT) (12–15 Gy boost in 3 fractions).[110] At a median follow-up of 31 months, the LC was 93%, regional control was 91%, freedom from distant metastasis was 90%, and overall survival was 85%. No grade 4 acute or chronic radiation-related complications were reported.

***Toxicity.*** The primary acute complications during external beam radiation include mucositis, odynophagia, lymphedema, alteration of taste, xerostomia, fatigue, loss of appetite, dermatitis, alopecia, serous otitis media, and thrush.[90,111,112]

Long-term toxicities include xerostomia, lymphedema, fibrosis, osteoradionecrosis, soft tissue necrosis, cranial neuropathy, carotid artery stenosis, temporal lobe necrosis, pharyngeal stricture, dysphagia, feeding tube dependence, trismus, otitis media, tympanic membrane perforation, deafness, hypopituitarism, hypothyroidism, and dental caries.[90,111–114]

Analysis of 849 consecutively treated nasopharynx patients at a single institution treated with 2D radiation therapy without chemotherapy showed that EBRT doses >72 Gy resulted in a higher incidence of hearing impairment, trismus, and temporal lobe necrosis.[104] Patients were treated with EBRT combined with brachytherapy boost to total doses of 68.4 to 79.8 Gy. At 5 years, 90% had xerostomia, 54% had hearing impairment, 52% had tinnitus, 32% had otorrhea, 25% had neck fibrosis, 21% had Lhermitte sign, 12% had trismus, and 6% had temporal lobe necrosis (including 6% of cases associated with severe symptoms—seizure, debilitation, and change of consciousness). Hypopituitarism is detected in up to 25% of patients with most having hypogonadism or hyperprolactinemia without the need for hormonal replacement.[81] Hypothyroidism is also possible after neck irradiation.[81] Doses >72 Gy was associated with incontinence. Other chronic complications include dysphagia, lymphedema, carotid artery stenosis (8%–16%),[115] osteoradionecrosis of the mandible (up to 2%), cranial nerve palsy in 2% to 6%, and pharyngeal stricture in 2%.[90,111,112]

Patients with temporal lobe necrosis can demonstrate impairment of cognitive function including verbal ability, visual memory, language, abstract thinking, and motor ability based on a comprehensive battery of neuropsychologic testing of 53 patients performed at least 1 year after radiotherapy.[116–118] Lee reports that patients at risk for temporal lobe necrosis were those undergoing dose-escalation with an external beam parapharyngeal boost of 5 Gy (5-year incidence 8.3%) and in those undergoing accelerated radiotherapy in the setting of concurrent chemotherapy (5-year incidence 2.7%).[119] Patients treated to mean temporal lobe dose >22 Gy had higher rates of TLE compared with those with below (2.2% vs. 0%). Neurocognitive dysfunction including short-term memory loss and language abilities was increased if the mean dose to the temporal lobe was >36 Gy.[120]

With regard to deafness, patients who received a dose of >50 Gy had a higher risk whether treated by conventional radiotherapy alone (18% vs. 7%) or in the setting of concurrent chemoradiation (22% vs. 14%).[121] The incidence of cranial neuropathy was 1.7%, that of soft tissue ulceration was 1.2%, and that of hypopituitarism was 9.7% (6.7% hypothyroidism) with no statistical difference between those receiving radiotherapy alone versus concurrent chemoradiation.

***IMRT and Xerostomia.*** One of the primary benefits of IMRT radiation has been the amelioration of chronic xerostomia, the most common QOL complaint after head and neck irradiation affecting the sense of comfort, taste, dental hygiene, and swallowing. Both objective and subjective data have been established. Liu reported the time frame for parotid salivary flow recovery using sialoscinitigraphy in 45 NPC patients treated with IMRT with a component of the dose delivered with 3D (9–20 Gy) technique or high-dose rate brachytherapy (7 Gy/2 fractions).[122,123] The dose to 50% of the parotid volume was constrained at 35 Gy. Objective flow was analyzed by serial scialoscintigraphy pre-RT, and 1, 6, 12, and 18 months post radiation. The LENT/SOMA scale assessed subjective salivary function. At a median follow-up of 37.5 months, objective salivary flow remained decreased during the first year compared with the baseline, but after 1 year, flow recovered such that there was no significant difference from the baseline at 12 and 18 months. Mean parotid doses >38 Gy impacted on the preservation of parotid function. There was significant correlation ($p = 0.024$) between subjective and objective salivary function at 12 months. At 1 year, 47% reported grade 2 or greater xerostomia based on the LENT scale (grade 2 partial but persistent dryness, grade 3 complete dryness but not-debilitating). These results are comparable with those reported with the UCSF experience. Lee reported a grade 2 xerostomia rate of 2% at 2 years using RTOG scale after IMRT and that a the mean dose to 50% of the parotid volume was 34 Gy.[82]

Two randomized trials for early-stage nasopharynx cancer treated with radiotherapy alone showed a benefit of IMRT over conventional techniques to preserve salivary function. Kam showed the incidence of observer-rated xerostomia to be decreased from 82% to 39.4% ($p = 0.010$). However, patient-reported xerostomia was not statistically improved. Pow showed improved parotid sparing and QOL in patients treated with IMRT compared with conventional technique.[124]

***IMRT and Hearing.*** Although the adverse impact of radiation on salivary gland function is well appreciated, the impact of radiation on auditory function is not broadly recognized. In covering the skull base and the posterior cervical nodes, the auditory structures are at risk. These include the cochlea and the eighth cranial nerve, especially as cisplatin, an ototoxic chemotherapy agent, is given with radiation therapy. To that end, the mean dose tolerance for sensorineural hearing loss has been shown to be 48 Gy.[125] Bakst reported that 1 of 25 patients had grade 3 hearing loss at a median audiogram follow-up of 14 months with a mean cochlear dose of 43 Gy.[126]

***IMRT and QOL.*** The ability of IMRT to optimize tumor control and decrease toxicity enables endpoints to optimize patient QOL to be measured such as a patient's physical functioning as well as emotional and psychosocial well-being. A QOL analysis of 237 patients treated from 1996 to 2003 who were cancer free from their NPC for minimum of 2 years was performed.[127] Eighty-five patients

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received conformal therapy consisting of 52 patients treated with IMRT and 33 with 3D-CRT. One Hundred and fifty two patients received conventional treatment (2D only or 2D with 3D boost). The two groups had no statistically significant differences noted in distribution of clinical stages or sociodemographic characteristics. The EORTC core (QLQ-C30) and head and neck module (QLQ-H&N35) QOL questionnaires were performed as a longitudinal cross-sectional analysis. Patient receiving conformal RT had significant improvement in global QOL, all functional scales and six core symptom scales (fatigue, nausea, pain, dyspnea, insomnia, and appetite loss) as well as 12 head and neck symptom scales (pain, swallowing, sense, speech, social eating, social contact, teeth, mouth opening, xerostomia, sticky saliva, coughing, and feeling ill). Patients in the conformal group experienced a clinically significant improvement (mean score >10 points) in global QOL, pain, speech, xerostomia, appetite, social eating, feeling ill, and dental QOL. No significant differences were noted between 3D versus IMRT nor did 3D boost to an initial 2D plan improve QOL. Those who received conformal RT had a 2.70-fold lower probability of reporting high levels of xerostomia (relative risk 0.37 [0.20–0.66]). On logistic regression analysis accounting for education level, income, employment, and comorbidity, radiation technique retained a significant association with global QOL.

***Altered Fractionated Radiation.*** The role of altered fractionated radiation in NPC has been investigated. As demonstrated in RTOG 90-03 and DAHANCA trials, altered fractionated radiation using accelerated radiation by concomitant boost (AFX-CB), DAHANCA regimen (six conventional treatments/week), or hyperfractionation improves locoregional control and disease-free survival compared with conventionally fractionated radiation therapy (CFRT).[128,129] Similar to treatment of nonnasopharyngeal head and neck cancers where CFRT with concurrent chemotherapy has now been established as standard of care,[130,131] the role of altered fractionated radiation remains to be defined.[132–134]

Early experience reported the benefit of altered fractionated radiation therapy compared with conventional treatment. Wang reported a benefit using split-course accelerated radiation for T3 and T4 nasopharynx cancers treated at Massachusetts General Hospital with improved 5-year LC compared with historic controls treated with conventional therapy (77% vs. 45%).[135] For all patients, the twice-daily fractionation had improved 5-year LC (69% vs. 60%, $p = 0.008$) and 5-year disease-free survival (69% vs. 49%, $p = 0.0001$) compared with a historic control treated with conventional fractionated radiation.

Jen reported a single-institution experience exploring the efficacy of hyperfractionated BID radiation in 88 patients with nasopharynx carcinoma.[136] All patients were treated with using primarily 2D technique with cobalt or 6 to 10 MV photons. Eighty-eight patients with stage III/IV nasopharynx cancer received hyperfractionation ($n = 76$) to 1.2 Gy BID or split-course accelerated radiation ($n = 12$) with 1.6 Gy BID. A median dose of 78 Gy (64–82 Gy) was delivered. These patients were compared with 134 patient treated with conventional fractionation to a dose of 70 Gy in 8 weeks. Chemotherapy was integrated into treatment in 2 of 88 BID patients and 60 of 134 CFRT patients, the latter group receiving primarily adjuvant chemotherapy (90%, 54/60). Groups were well balanced with regard to age, gender, T, N, and overall stage. At a median follow-up of >70 months, there was a trend toward better locoregional control in patients receiving altered fractionated radiation compared with conventional treatment (83% vs. 67%, $p = 0.055$) with improvement in disease-specific survival (70% vs. 60%, respectively) but no difference in overall survival (62% vs. 58%, $p = 0.41$). Acute grade 3/4 mucositis was increased 59% versus 21%, $p < 0.0001$ and moist desquamation (21% vs. 14%, $p = 0.04$) in patients receiving BID radiation, respectively. The primary increased long-term toxicity experienced by BID patients over the CFRT group was temporal lobe necrosis (3% vs. 0%, $p = 0.06$) and was confined primarily to the split-course accelerated BID patients. For T4 patients, LC was only 35% to 45% regardless of fractionation whereas it was excellent for T1–3 patients (82%–97%). The authors conclude that given the small patient numbers and the confounding effect of differences in chemotherapy, a benefit of hyperfractionated radiation may be born out in a larger trial.

Lee reported on the efficacy of a DAHANCA-type accelerated radiation regimen using 6 fractions per week on 158 consecutive patients treated to 66 Gy/33–37 fractions and compared them with a cohort of 167 consecutive patients treated to the same dose with conventional fractionation of 5 fractions/week prior to the change in treatment policy. All were treated with the Ho 2D technique.[137] Parapharyngeal boost (10 Gy) was given in 101 patients in the accelerated versus 80 patients in the conventional arm. Cisplatin-based chemotherapy was given to 41 patients in the AF arm and 13 patients in the CFRT arm. Patients in the AF group had higher progression-free rate (74% vs. 63% at 3 years, $p = 0.02$) and a 25% improvement in LC for T3–4 patients (87% vs. 62%, $p < 0.01$) but not for all patients (83% vs. 77%, $p = 0.07$). No difference in disease-specific survival (86% vs. 80%, $p = 0.39$) or overall survival could be detected (81% vs. 78%, $p = 0.9$). Although acute grade 3+ complications were increased in the accelerated arm (primarily mucositis 71% vs. 13%, $p < 0.001$), no significant increase in late complication was observed (20% vs. 15% at 3 years, $p = 0.19$). The promising outcomes for T3–4 patients from this treatment regimen led to its study in a four-arm randomized trial evaluating the role of DAHANCA versus conventional fractionation and role of concurrent chemotherapy versus radiation alone in a $2 \times 2$ format.[138]

***Randomized Studies of Altered Fractionated Radiation Therapy.*** A two-arm study of 159 patients with nodal disease up to N1 with maximal nodal size ≤4 cm in size were randomized to receive conventionally fractionated radiation (60 Gy/4 weeks) alone or split-course accelerated treatment (20 Gy/8 fractions/2.5 weeks QD → 22.4/1.6 Gy BID/9 days → 28.8 Gy/18 fractions/11 days). Total dose was 71.2 Gy in the altered fractionation arm.[139] Both arms could receive an additional parapharyngeal boost of 14 Gy in 4 fractions. Both arms used the 2D technique of Ho. At a median follow-up of 59 months, no significant difference was noted in LC (85% vs. 89%, respectively), distant metastasis (overall survival [87% vs. 85%] and relapse-free survival [77% vs. 85%, $p = 0.141$]) in arm I versus II, respectively. The accelerated arm did significantly increase total iatrogenic CNS complication affecting the temporal lobe, cranial nerves, and brain stem/cord (49% vs. 23%) and more often caused neck fibrosis, trismus, and hypopituitarism. The trial was terminated early because of the increased temporal lobe necrosis (29% vs. 16%) in the altered fractionation arm.

# CHEMOTHERAPY MANAGEMENT STRATEGIES

## Chemotherapy for Locoregionally Advanced Disease

Although excellent outcomes are obtained for treatment of early-stage disease with radiotherapy alone,[68,85,88,89,96,98,140] 20% to 60% of patients with advanced-stage disease experience locoregional failure after radiotherapy alone[68,85,88,89,96,98,140,141] and high rates of DM (50%–70%)[63,142–144] with 5-year overall survival of 28% to 56%.[89,98,145–147]

For advanced-stage NPC, the specific aims of integrating systemic chemotherapy with chemotherapy are twofold: improving LC of the primary tumor and prevention of subsequent DM. With

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the continued improvement in radiation therapy techniques and hence better LC, DM has increasingly become the predominant cause of treatment failure in NPC.[148] Systemic therapy has been integrated with radiation in various combinations of induction, concurrent, and adjuvant regimens. There has been continued debates based on theoretical grounds that concurrent chemoradiotherapy improves LC by radiosensitization whereas neodjuvant and adjuvant chemotherapy improves DM by eradicating micrometastases. However, based on clinical trial results, this has not been a consistent finding, with neoadjuvant treatments being beneficial in improving LC, whereas concurrent treatments resulted in improvement of DM in several of the studies. Hence, chemotherapy can clearly play a dual role of radiosensitization as well as eradication of occult micrometastases, and the optimal strategy is likely to be one that enables delivery of maximal drug-dose intensity without a significant negative impact on radiation therapy delivery and related toxicities.

Cisplatin-based regimens have been found to be the most effective, and over the past two decades, multiple phase III trials have been reported for both endemic and nonendemic nasopharynx cancer populations.[60,143,147] However, the optimal timing, dosing duration, and regimens of chemotherapy drugs to be combined with radiation therapy remain to be defined.

## Concurrent Chemotherapy

In North America, the standard of care was established by the landmark Intergroup Study 0099.[60] One hundred forty-seven patients with stage III/IV (AJCC, 1992, 5th ed.) tumors were randomized to conventional fractionated radiation therapy (CFRT) to 70 Gy alone versus CFRT concurrent with 3 cycles of CDDP (100 mg/m$^2$ q3 weeks) followed by adjuvant CDDP/5-Fluorouracil (5FU) (80 mg/m$^2$ and 1,000 mg/m$^2$ × 4 days, respectively) for 3 cycles in a phase III randomized study.[29] Results at a median follow-up of 32 months showed improved locoregional control (crude locoregional failure 14% vs. 41%) and fewer DM (crude distant metastasis 13% vs. 35%) which translated into an approximate 30% to 40% increase in 3-year progression-free (69% vs. 24%, $p < 0.001$) and overall survival (76% vs. 46%, $p < 0.001$). The worse grade 3/4 acute toxicity was increased in the chemoradiation arm (76% vs. 50%) with a higher incidence of grade 3/4 leukopenia and vomiting. Compliance to the planned regimen was suboptimal as only 63% were able to complete all 3 cycles of concurrent cisplatin with an additional 23% able to complete 2 concurrent cycles whereas 27% were unable to complete the chemoradiation program. Only 60% of patients received two to three planned cycles of adjuvant chemotherapy. Importantly, 33% did not receive any adjuvant chemotherapy. The accrual goal was 270 patients. However, the trial was stopped early after interim analysis showed an increased risk of death in the radiation alone arm with a hazard ratio of 3.28. A follow-up analysis with 185 patients including those excluded initially due to missing documentation confirmed the 3-year overall and progression-free survival benefit of the chemoradiation arm (76% vs. 46%, $p < 0.001$ and 66% vs. 26%, $p < 0.001$, respectively).

The trial has been criticized for having small patient numbers and apparently poorer outcomes in the CFRT-alone arm compared with historic results as well as the concern that its results based on one-fourth of patients who were WHO type I histology may not be extrapolated to endemic patients where there is a distinct predisposition for WHO type II, and III carcinomas.[149]

Several pivotal trials conducted in Asia have confirmed the benefit of concurrent chemoradiation or concurrent chemoradiation followed by adjuvant chemotherapy. Wee reported on a randomized trial of 221 patients all treated with conventional radiation to 70 Gy in 7 weeks half randomized to radiation alone and the other half to concurrent cisplatin (25 mg/m$^2$ on days 1–4 on weeks 1, 4, and 7) followed by adjuvant cisplatin 20 mg/m$^2$ days 1 to 4 and 5FU (1,000 mg/m$^2$ day 1–4) for 3 cycles.[150] At a median follow-up of 3.2 years, the concurrent arm versus radiation-alone arm showed superior 3-year overall survival (80% vs. 65%, $p = 0.0061$) and decreased distant metastasis (2-year 13% vs. 30%, $p = 0.0029$), respectively. Unlike the Al-Sarraf trial, no difference in locoregional control was shown.

Chan reported on a phase III trial involving two major institutions in Hong Kong randomizing 350 locoregionally advanced patients to 6 weekly doses of cisplatin (40 mg/m$^2$) during radiation compared with radiation therapy alone.[151,152] The 5-year overall survival was improved from 58.6% to 70.3% and after adjusting for significant prognostic factors, the difference in overall survival was significantly in favor of concurrent cisplatin-radiation ($p = 0.049$). This outpatient regimen was well tolerated with only 5.1% of the patients requiring nasogastric tube-feeding. In endemic areas of NPC where supportive therapy is not as readily available and where acceptance of enteral feeding is lower, this regimen has been widely accepted as standard practice.

Lin reported on a phase III trial of 284 stage III/IV endemic patients randomized to 2 cycles of chemotherapy (CDDP 20 mg/m$^2$ days 1–4 and 5FU 400 mg/mg$^2$ × 4 days, continuous infusion, weeks 1 and 5) concurrent with conventional radiation and compared with patients receiving the same radiation treatment alone.[153] No adjuvant chemotherapy was given. At a median follow-up of 65 months, the concurrent arm showed increased 5-year overall survival (72% vs. 54%, $p = 0.0022$) and 5-year LC (89% vs. 73%, $p = 0.0009$) with a trend toward decreased distant metastasis (21% vs. 30%, $p = 0.0577$) compared with radiation alone. Compliance to chemotherapy was 94%. Patients receiving chemotherapy had increased leukopenia and emesis. No treatment associated mortality was reported on either arm.

A subsequent analysis of the aforementioned trial according to risk stratification was reported.[154] Patients were categorized as high risk ($n = 165$) if they satisfied one of the following criteria: (a) nodal size >6 cm, supraclavicular node involvement, T4N2 (AJCC 5th ed.) or multiple neck nodes with one node >4 cm or low risk ($n = 119$) if they satisfied none. Concurrent chemoradiation improved outcomes for low-risk patients with no obvious benefit for the high risk. Among the low-risk patients, the concurrent chemoradiation arm improved LC (95% vs. 77%, $p = 0.0012$), distant metastasis–free survival (90% vs. 78%, $p = 0.0282$), progression-free survival (87% vs. 62%, $p = 0.0003$), and overall survival (75% vs. 68%, $p = 0.0003$) over radiation alone. For the high-risk patients, there was no significant difference in LC (75% vs. 68%, $p = 0.25$), distant metastasis–free survival (60% vs. 60%, $p = 0.55$), progression-free survival (44% vs. 43%, $p = 0.39$), and overall survival (56% vs. 46%, $p = 0.18$) in patients receiving concurrent chemoradiation versus radiation alone. The authors conclude that the addition of neoadjuvant or adjuvant chemotherapy should be considered for high-risk patients.

Lee reported the preliminary results of a two-arm NPC-9901 Trial by the Hong Kong Nasopharyngeal cancer study group randomizing 348 T1–4N2–3 patients to the Intergroup 0099 regimen versus radiation alone.[155] One hundred seventy-six received conventional fractionated radiation therapy alone versus 172 patients undergoing the Intergroup 0099 regimen of concurrent chemoradiation followed by 3 cycles of adjuvant chemotherapy. At a median follow-up of 2.3 years, the chemoradiation arm achieved improved locoregional control (92% vs. 82%, $p = 0.005$), failure-free survival (72% vs. 62%, $p = 0.027$) but no improvement in distant metastasis–free survival (76% vs. 73%) or overall survival (78% vs. 78%). Acute and late toxicities were increased in the chemoradiation arm (84% vs. 53%, $p < 0.001$) and (28% vs. 13%, $p = 0.024$), respectively.

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A 5-year update of the NPC 99-01 trial was reported by Lee. At a median follow-up of 5.9 years, in patients receiving chemotherapy, there was a 12% improvement in 5-year freedom from relapse (67% vs. 55%, $p = 0.014$), 9% increase in 5-year progression-free survival (62% vs. 53%, $p = 0.035$), and a 10% improvement in 5-year locoregional control 88% versus 78%, $p = 0.005$. However, there was no difference in incidence of distant metastasis at 5 years (26% vs. 32%, $p = 0.32$) or overall survival (68% vs. 64%, $p = 0.22$). The lack of statistically significant improvement in overall survival despite improved disease-free survival was due to an increase in nonnasopharyngeal cancer–related deaths (infection, secondary malignancy, and suicide) (8.1% vs. 3.4% $p = 0.015$) and treatment-related mortality (1.7% vs. 0% $p = 0.015$) in patients receiving chemotherapy. Chemotherapy increased acute toxicity (83% vs. 53%, $p < 0.001$, primarily hematologic and nausea) but not chronic toxicity (30% vs. 24%, $p = 0.30$). Subset analysis suggested that stage III patients benefited the most from chemotherapy with respect to better survival (hazard ratio = 0.64, $p = 0.09$) whereas stage IVA/B patients had a locoregional control benefit. Similar to the Intergroup 0099 study, only 60% were able to complete all 3 cycles of cisplatin (compared with 63% in Intergroup 0099); however,76% were able to complete all adjuvant cycles compared with 55% in the Intergroup 0099.

Lee reported on a $2 \times 2$ phase III (NPC 99-02) study of 189 patients with T3–4N0–1 patients determining the benefit of concurrent with adjuvant chemotherapy versus radiation alone and the role of accelerated radiation given in 6 weeks versus conventional fractionation in 7 weeks (*Radiother and Oncol*. 2011;98:15–22).[155a] The chemotherapy tested was the Intergroup 0099 regimen and the accelerated regimen consisted of six treatments per week similar to the scheduled pioneered by the Danish cooperative group (DAHANCA). At a median follow-up of 6.3 years, patients receiving accelerated radiotherapy and chemotherapy had the highest 5-year failure-free survival (88%) compared with those treated with conventional radiotherapy and chemotherapy (65%, $p = 0.027$) and compared with the accelerated radiotherapy–alone group (56%, $p = 0.001$). Improvement of overall survival was increased 85% versus 66% with a trend toward significance ($p = 0.058$). Both locoregional control and distant metastasis–free survival was highest in this arm (90% and 5%, respectively). There was a non–statistically significant increase in chronic toxicity (36% vs. 20%, $p = 0.25$) especially grade 3 neck fibrosis (16/44 vs. 0/51 in the conventional fraction with chemotherapy) and death due to non-cancer-related causes (9% vs. 2%, $p = 0.62$).

A pooled analysis of NPC 99-01 and NPC 99-02 comprising 441 patients evaluated the benefit of chemoradiotherapy using the intergroup regimen versus radiation alone. The median follow-up was 6.1 years. By intent-to-treat analysis, the chemoradiotherapy arm had improved failure-free, locoregional control, and disease-specific survival without improvement in overall survival. By actual treatment, three patients in the chemoradiation arm did not receive chemotherapy whereas three patients in the radiation only received chemotherapy. Despite the adjustment, the two groups remained well balanced for patient characteristics. If analyzed by actual treatment received, those undergoing chemoradiotherapy had improved survival compared with those treated with radiotherapy alone (5-year overall survival 72% vs. 63%, $p = 0.037$). Multivariate analysis showed that those patients receiving 2 or 3 cycles of cisplatin during radiotherapy had improved locoregional control and overall survival compared with those receiving 0 to 1 cycles whereas those receiving 2 to 3 cycles of adjuvant chemotherapy had improved distant metastasis–free survival. Subset analysis revealed that the survival benefit was significant for stage III patients (12% increase in 5-year overall survival, $p = 0.047$) but not stage IV (7% increase in 5 years, $p > 0.19$), suggesting that the intergroup regimen is best for intermediate-stage patients and that more intensive treatment may be needed in those with the most advanced disease.

## Benefit of Concurrent Chemoradiation for Stage II Cancer

Moreover, the benefit of concurrent chemoradiation over radiation alone for stage II patients has been confirmed in a randomized trial conducted at the Sun-Yat Sen University in Guangzhou, China.[156] Two hundred thirty endemic patients with WHO II/III were randomized to receive radiation therapy to a dose of 66 to 68 Gy with or without weekly cisplatin (30 mg/m$^2$). Patients were treated without CT-based planning but with diagnostic MRI for determination of pretreatment tumor location as well as post-treatment surveillance. Stage II was based on a Chinese staging system, and when restaged according to AJCC, approximately 13% (31/230) were reclassified as III. Based on the restaging, there was an imbalance biased against group receiving chemoradiation with a greater percentage of stage III or N2 (16% vs. 10%) and a lower percentage of node-negative patients (10% vs. 15%) compared with radiation alone. At a median follow-up of 60 months, the addition of concurrent chemotherapy increased 5-year overall survival (86%–95%), progression-free survival (from 79% to 88%,), and distant metastasis–free survival (84% to 95%) but no difference in locoregional control (91% vs. 93%). Acute toxicity was increased primarily grades 3 to 4 mucositis (from 32.5 to 45.6%, $p = 0.04$), grade 3/4 nausea/vomiting (0% to 8.6%, $p = 0.001$) and grade 3/4 leucopenia/neutropenia (0% to 12.9%, $p < 0.001$). No patients experience treatment-related mortality. Compliance to at least six doses of CDDP was 78% with 26% completing seven doses. No statistically significant differences in chronic morbidity was reported especially with regard to grade 3/4 deafness (9.5% vs. 7%) or skin fibrosis (2.6% vs. 1.8%). The benefit of weekly cisplatin in this trial suggest a subset of patients who have a low-volume of occult distant metastatic volume who may not need adjuvant chemotherapy and challenges the uniform recommendation of the Intergroup 0099 regimen for stage II patients. Also the authors suggest that the lower dose of weekly cisplatin (30 mg/m$^2$) may be better tolerated than the 40 mg/m$^2$ dosing used in the Chan trial in which 44% were able to tolerate six doses.

Alternative concurrent platinum regimens have been explored in phase II studies including the use of weekly oxaliplatin (70 mg/m$^2$) in a small randomized study found to be safe with improved survival compared with radiation alone[157] and another trial of weekly carboplatin compared with weekly cisplatin study showing no difference in overall or disease-free survival at 2 years.[158]

## Altered Fractionated Radiation Therapy and Concurrent Chemotherapy

Given the results of the randomized NPC 99-02 trial showing that integrating accelerated radiation therapy (six treatments per week) with concurrent chemotherapy followed by adjuvant chemotherapy yielded the best locoregional control and lowest incidence of distant metastasis in patients with T3–4N0–1, the role of altered fractionation in the treatment of nasopharynx cancer with chemotherapy remains to be defined as the NPC 99-02 did not complete accrual. Several groups have evaluated other altered fractionation radiation such as accelerated radiation with delayed concomitant boost and hyperfractionation.

Delayed concomitant boost radiation with concurrent cisplatin followed by adjuvant chemotherapy according to Intergroup 0099 was reported in a phase II study.[159] Forty-five patients with newly diagnosed stage IIa to IV NPC (66% T3/4 and 55% N2/3) were treated with AFX-CB to 70 Gy/6 weeks (BID RT last 2 weeks

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with a 3D-conformal plan, 6-hour interfraction interval) with 2 to 3 cycles of concurrent CDDP (100 mg/m$^2$) on days 1, 22, and 43 of radiation followed by adjuvant 5FU/CDDP for 3 cycles. All patients completed the prescribed chemoradiation regimen, and 84% completed 2 to 3 cycles of adjuvant chemotherapy. At a median follow-up of 27 months (3–78 months), the 3-year actuarial LC, regional control, locoregional control, freedom from distant metastasis, disease-free survival, and overall survival were 95%, 98%, 93%, 94%, 86% and 87%, respectively. Among 29 T3/T4 patients, LC was 93%. Major grade 3 acute toxicities include mucositis (59%), dysphagia (41%), vomiting (20%), and anemia (4.5%). Ninety percent of patients received erythropoietin support and near 20% required blood transfusion. Late toxicities included grade 3 tinnitus in 1, grade 2 serous otitis in 1, osteoradionecrosis in 1, brain necrosis in 2, and grade 2 xerostomia in 80%.

Wolden et al. reported the MSKCC experience using the same chemoradiation regimen in the treatment of locally advanced nasopharynx cancer (54% T3/4 and 54% N2–3) and compared the results with a historic control treated with CFRT (31% T3–4 and 22% N2–3).[160] With a median follow-up of 42 months, their 3-year actuarial LC was 84%, progression-free survival was 66%, and overall survival was 84% for patients treated with AFX-CB. Comparison with patients treated with CFRT showed superior 3-year LC (89% vs. 74%, $p < 0.01$), disease-free survival (66% vs. 54%, $p = 0.01$), and overall survival (84% vs. 71%, $p = 0.04$) in the AFX-CB cohort. This was despite a selection bias against the altered fractionation group, which had a greater proportion patient with T3/T4 (54% vs. 32%), N2/N3 (44% vs. 22%), and stage III/IV (78% vs. 51%) disease compared with CFRT group. Acute grade 3 mucositis was increased in the accelerated arm compared with the CFRT (84% vs. 43%, $p < 0.001$) as well as need for gastric tube (46% vs. 20%, $p < 0.01$).

Hyperfractionated radiation concurrent with CDDP-based chemotherapy was used to treat locally advanced nasopharynx cancers.[161] Forty-eight patients with T3 or T4 (1997 AJCC) were treated with 1.2 Gy BID (74.4 Gy total; 1-week break after 3.5 weeks of radiation) with concomitant CDDP (100 mg/m$^2$) alone ($n = 28$) or CDDP (60 mg/m$^2$)/5FU (600 mg/m$^2$ × 5 days) ($n = 16$) on weeks 1 and 6 of radiotherapy followed by adjuvant CDDP/5FU for 2 to 3 cycles. Three-dimensional treatment planning was used after an initial standard three-field technique. Eighty-eight percent of patients were able to complete their treatment within 8 weeks. At a median follow-up of 57 months, the 3-year locoregional control was 93%, disease-free survival was 71%, and overall survival was 72%. For T4 patients, the 3-year corresponding LRC, DFS, and overall survival were 91%, 62%, and 63%, respectively. Comparison at the same institution of T4 NPC patients treated with conventional fractionation and concurrent chemotherapy demonstrated improvement in 3-year locoregional control (89% vs. 72%, $p = 0.2$) and disease-free survival (66% vs. 35%, $p = 0.14$) favoring those treated with hyperfractionation.

In summary, the role of altered fractionated radiation with concurrent chemotherapy appears to improve outcome but if given with conventional radiation delivery technique, the toxicity may be prohibitive. However, with newer conformal techniques such regimens may be delivered with acceptable toxicity. The patient population which best benefits from such treatments remains to be defined.

## IMRT and Concurrent Chemoradiation

IMRT allows even more conformal dose distributions to be obtained than is possible with 3D technique.[79] IMRT may be particularly relevant to patients with T3/T4 with intracranial or skull base invasion due to proximity of critical structures such as the optic nerves/the chiasm, the brain stem, and the spinal cord.

## Single-institutional Experience with IMRT

Multiple centers report significant series of nasopharynx patients treated with IMRT (Table 22.5). The IMRT experience from University of California, San Francisco (UCSF) for nasopharynx cancer has been discussed in multiple reports. Sultanem et al.[76] reported their initial experience on 35 patients treated between April 1995 and March 1998. A later report on 67 stage I to IV nasopharynx cancers showed a favorable experience.[82] Gross tumor and positive lymph nodes were treated to a dose of 65 to 70 Gy at 2.12 to 2.25 Gy per fraction over 6.5 weeks whereas high-risk or electively treated nodes were simultaneously treated using l.8 to 2.0 Gy to a dose of 60 and 50 Gy, respectively, using a standard fractionation scheme. Thirty-nine percent (26/67) received a brachytherapy boost to a dose of 5 to 7 Gy whereas 75% (50/67) received cisplatin-based chemotherapy. At a median follow-up of 31 months, the 4-year estimates of LC, local-regional control, metastatic disease–free survival, and overall survival were 97%, 98%, 66%, and 88%, respectively. Grade 3/4 acute toxicities were seen in 24% and grade 3/4 late toxicities in 12%. At 24 months, only one of the 41 (2.4%) evaluable patients had grade 2 or higher xerostomia, demonstrating significant sparing of the salivary glands. The crude incidence of the worst acute grade 3/4 toxicity was 24% with mucositis, the most common side effect, and worst grade 3/4 late toxicity was 12%, primarily xerostomia. With a mean dose of 34 Gy delivered to the parotid

**TABLE 22.5 Intensity Modulated Radiation Therapy (IMRT) Treatment of Nasopharynx Cancer**

| | No. of Patients | Median F/U (mo) | Local (%) | Regional (%) | Overall Survival (%) |
|---|---|---|---|---|---|
| Lee et al. (2002)[82] | 67 | 31 | 97% | 98% | 73% |
| Kwong et al. (2006)[266] | 50 | 25 | 96% (locoregional) | | 92% |
| Kam et al. (2004)[81] | 64 | 29 | 92% | 98% | 90% |
| Wolden et al. (2006)[163] | 74 | 35 | 91% | 93% | 83% |
| Bakst et al. (2011)[126] | 25 | 33 | 91 | 91 | 89 |

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glands, the incidence of grade 2 xerostomia at 2 years was 2%. A later report of 118 patients treated between 1995 and 2003.[162] At a median follow-up of 30 months, the 4-year actuarial LC, regional control, and distant metastasis–free survival were 96%, 98%, and 72%, respectively, whereas overall survival was 74%.

Wolden reported the MSKCC experience using IMRT for 74 nasopharynx patients who were treated with accelerated radiation by delayed concomitant boost ($n$ = 59) or dose painting with once-daily fractionation ($n$ = 15).[163] All patients were treated to a total dose of 70 Gy. Patients in the accelerated radiation by delayed concomitant boost (AFX-DCB) were treated at 180 cGy once a day during the first 4 weeks then twice a day during the last 2 weeks with 180 cGy in the A.M. and 160 cGy in the P.M. fractions. Patients in the dose painting were treated with 2.34 Gy to the GTV for 30 fractions. Sixty-nine patients received concurrent and adjuvant platinum-based chemotherapy similar to that in the Intergroup 0099 trial. Patient characteristics were as follows: 72% males, 35% Caucasian, 32% Asian, WHO II/III 95%, T3/4 51%, II/IV 77%. At a median follow-up of 35 months, the 3-year actuarial LC was 91%, regional control was 93%, distant metastasis–free survival was 78%, progression-free survival was 67%, and overall survival was 83%. Six patients recurred locally and all of them had T3–4 disease. The local failure rate for patients with T3/4 disease was 16% (6/38) whereas none with T1–2 disease failed. Five of the 6 patients failed in field whereas the other patient was a T4 patient who failed both within and beyond the high-dose volume adjacent to the brain. The mean number of adjuvant chemotherapy cycles received was 2.5.

A follow-up report of 25 patients treated with IMRT using the dose-painting technique confirmed excellent 3-year LC (91%), freedom from distant metastasis (91%) and overall survival (91%). However, 12% of patients developed temporal lobe necrosis at a median follow-up of 33 months and this dose-painting regimen was not recommended.[126]

Kam reported on the efficacy of IMRT in 63 newly diagnosed NPC patients treated with IMRT.[81] Patient characteristics were as follows: 51% T3/4, 57% stage III/IV, 76% males. Patients were treated to a dose of 66 Gy to the GTV, 60 Gy to the PTV, and 54–60 Gy to the clinically negative neck. Brachytherapy boost (12 Gy/4 fractions/2 weeks) was given to all 20 T1–T2a patients whereas additional external beam boost (8 Gy/4 fractions) was given to 15/42 T2b–T4. Thirty percent (19/63) received induction ($n$ = 3) or concurrent chemotherapy (weekly cisplatin). At a median follow-up of 29 months, the 3-year LC, regional control, distant metastasis–free survival was 92%, 98%, and 79%, respectively. Three-year overall survival was 90%. All four patients who failed had T3–4 disease and had not received boost therapy. On multivariate analysis, dose escalation above 66 Gy was associated with improved progression-free and distant metastasis–free survival. Acute side effects included grade 3 mucositis in 41% with a need for tube feeding in 8%. Chronic grade 2 to 3 xerostomia at 3 months was 57% and at 2 years was 23%. Long-term grade 3 hearing impairment occurred in 13%.

Xiao reported on 68 patient treated with an alternative IMRT prescription dose regimen of 68 Gy in 30 fractions with dose-painting elective areas of 54 Gy in 30 fractions using a simultaneous boost technique. Two cycles of cisplatin (80 mg/m$^2$) were given on week 1 and 4 of radiotherapy. At a median follow-up of 54 months, the 5-year LC was 95% with 5-year disease-free and overall survival of 77% and 75%, respectively. Acute toxicity was not reported. Patients were followed for a minimum of 48 months to assess longer toxicity. Twelve patients developed temporal lobe injury ($n$ = 11) or brainstem injury ($n$ = 1). The authors note that such patients had advanced disease extending intracranially or to the skull base. Thus, for such patients, such a fractionation regimen may not be optimal for patients with advanced tumors.

## RTOG Multi-institutional Phase II Study

A phase II trial to assess the feasibility of IMRT treatment in a multi-institutional setting was investigated in RTOG 0225. Patient were treated with the Intergroup 0099 regimen if advanced stage. Sixty-eight patients with stage I to IVB were enrolled with 94% WHO types II and III. The target delineation as prescribed in the protocol was delivered in 84%. The 2-year locoregional control, distant metastasis–free survival, and overall survival were 89%, 85%, and 80%, respectively. Acute grade 4 toxicity occurred in 12% primarily leucopenia ($n$ = 4), mucositis ($n$ = 3), anorexia ($n$ = 3), hyponatremia ($n$ = 2), and neutropenia ($n$ = 2). Treatment-related morality occurred in 4% due to febrile neutropenia ($n$ = 1), pneumonitis ($n$ = 1), and esophagitis ($n$ = 1). Incidence of xerostomia at 1 year was as follows: grade 2: 14%; grade 3: 3%; and grade 4: 0%. Currently, even patients with stage III/IV typically attain LC rates of 90% or greater, regional control rates of 95%, whereas distant metastasis remains the dominant pattern of failure occurring in up to 25%.

## Adjuvant Chemotherapy

Adjuvant chemotherapy is often poor tolerated by patients deconditioned after radiation therapy with or without chemotherapy. Although seven published randomized trials have included the use of adjuvant chemotherapy, two studies addressed solely the use of adjuvant chemotherapy after radiation alone. Both studies were negative and are discussed below.

The role of adjuvant therapy after radiation therapy was evaluated in a randomized phase III study.[164] One hundred fifty-seven patients with stage IV cancers all were treated with standard radiotherapy to 70 to 72 Gy and then randomized to no further treatment or 9 weekly cycles of 5FU/leucovorin/CDDP after radiation therapy. At a median follow-up of 49.5 months, there was no statistical difference in 5-year overall survival (60.5% vs. 54.5, $p$ = 0.5) or relapse-free survival (49.5% vs. 54.4%, $p$ = 0.38) in the no adjuvant vs. adjuvant chemotherapy arms, respectively. Patients received adjuvant chemotherapy did have a lower rate of distant metastasis (36% vs. 20%, $p$ = 0.03 respectively). The treatment was relatively well tolerated with a 2% incidence of grade ≥3 leukopenia. However, 34% refused adjuvant chemotherapy.

Rossi et al. randomized two hundred twenty-nine patients to 6 cycles of adjuvant vincristine, doxorubicin, and cyclophosphamide compared with no adjuvant therapy for patients who have achieved a complete response to radiation therapy. At a median follow-up of 32 months, there was no difference in overall survival or relapse-free survival. A major limitation of this study was the choice of a non-cisplatin-containing regimen.[143]

## Benefit of Adjuvant Chemotherapy after Concurrent Chemoradiation

Chen reported on a phase III randomized trial testing the benefit of adjuvant chemotherapy in patients treated with concurrent chemoradiation.[165] Two hundred fifty-one stage III/IV nasopharynx patients were all treated with weekly CDDP (40 mg/m$^2$) with conventional radiation to a total dose of 66 Gy. More than two-thirds of patients were N2/3 and >70% were T3/4. Adjuvant chemotherapy comprised CDDP (80 mg/m$^2$) and 5FU (800 mg/m$^2$) given every 4 weeks for 3 cycles. Forty percent to 45% were able to complete the prescribed concurrent chemotherapy with median total dose delivered of 240 mg/m$^2$ in both arms whereas in the adjuvant arm, 63% were able to complete all 3 cycles while 18% received no chemotherapy. The most common grade 3/4 acute toxicity during adjuvant therapy was

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stomatitis 21%, nausea 11%, vomiting 10%, and neutropenia 10%. At a median follow-up of 38 months, the 2-year failure-free survival rate was no different in those receiving adjuvant chemotherapy (86% vs. 84%, $p = 0.13$). Likewise, the incidence of distant metastasis at 2 years was not statistically different (13% vs. 18%, $p = 0.12$). The trial has been criticized as being underpowered to show equivalence.

The use of adjuvant chemotherapy after radiation is not recommended and its benefit after concurrent chemoradiation is undergoing reevaluation. Future studies are underway to integrate serum EBV DNA levels to select a high-risk subpopulation which may benefit from standard or intensified systemic treatment.

## Induction Chemotherapy

The advantages of induction chemotherapy include (a) better tolerance and compliance to chemotherapy in patients who are treatment-naïve, (b) a higher chance of eradication of micrometastases, and (c) *in vivo* testing of chemosensitivity by evaluating clinical response. The theoretical disadvantages include (a) delay in initiation of definitive radiation therapy and (b) accelerated tumor repopulation and hence increased radioresistance.

Three large randomized studies of induction chemotherapy before radiation alone conducted by the International Nasopharynx Cancer Study Group,[166] the Asian-Oceanian Clinical Oncology Association,[167] and the Sun Yat-sen University of Medical Sciences in Guangzhou[168] reported improved relapse-free survival but no overall survival benefit after 2 to 3 cycles of induction consisting of (a) epirubicin, CDDP, and bleomycin;[166] (b) epirubicin and CDDP;[167] or (c) CDDP, 5FU, and bleomycin[168] in advanced-stage NPC patients. Induction chemotherapy improved LC compared with radiation alone. In the International NPC Study Group study, there were 9% treatment-related deaths in the induction arm which suggest that any possible survival benefit may be offset by the increased treatment-related mortality.

## Induction and Concurrent Chemoradiation

Numerous phase II studies have been reported testing the benefit or feasibility of induction chemotherapy prior to concurrent chemoradiation.

In a pilot study reported by Rischin,[169] 35 patients with locoregionally advanced NPC cancer were treated with 3 cycles of induction chemotherapy consisting of epirubicin (50 mg/m$^2$), CDDP (75 mg/m$^2$), and continuous infusion 5FU (200 mg/m$^2$) for 3 cycles/weeks. This was followed by conventionally fractionated radiation to a reduced dose of 60-Gy 2 Gy/fractions with CDDP 20 mg/m$^2$/days × 5 days on weeks 1 and 6 of radiation. Seventeen patients were treated with conventional technique whereas 18 were treated with conventional technique to 36 Gy followed by arc technique for the final 24 Gy. Forty percent were stage IV by UICC 5th Edition criteria and 74% had WHO type III histology. At a median follow-up of 43 months, only 6% (2/35) failed locoregionally (l local, 1 regional), 6% failed distantly whereas the actuarial 4-year progression-free survival and overall survival were 81% and 90%, respectively. All patients completed induction chemotherapy and 97% completed chemoradiation. Acute toxicities during induction chemotherapy included grade 3/4 neutropenia in 31%, grade 3/4 stomatitis in 11%, and grade 3 vomiting in 26% with no febrile neutropenic episodes. During concurrent chemoradiation, acute toxicities included grade 3 mucositis (31%), grade 3 dermatitis in 23%, grade 3/4 vomiting in 23%, and febrile neutropenia in 6%. Anemia occurred in 63% with grade 2/3 in 9%. Common late toxicities included grade 2 to 3 xerostomia in 100%, hearing loss in 50% (primarily WHO type II 32%), and peripheral neuropathy in 24%. These single-institution results appeared to be about 10% better than the Intergroup trial with respect to progression-free survival (4-year 81% vs. 3-year 69%) and overall survival (4-year 90% vs. 3-year 78%).

Four other phase II studies demonstrated similarly encouraging results.[170–173] Chan et al. reported 2-year overall and progression-free survival rates of 91.8% and 78.5% using 2 cycles of induction weekly paclitaxel and 3 weekly carboplatin followed by concurrent weekly cisplatin-radiation therapy.[173] The same group recently demonstrated in a phase II study that patients randomized to receive induction taxotere and cisplatin followed by concurrent weekly cisplatin and radiation had improved overall survival at 3 years (94% vs. 68%, $p = 0.012$) and 3-year progression-free survival (88% vs. 60%, $p = 0.12$) compared with those treated with concurrent chemoradiation only (Chan, *JCO.* 2002; 20:2038–2044). Hui reported on a phase II randomized study of 65 patients treated concurrent weekly cisplatin and radiation with or without 2 cycles of induction taxotere and cisplatin.[174] The endpoint was toxicity. The study concluded that induction chemotherapy was feasible without compromise of concurrent chemotherapy. Three-year overall survival was increased from 68% to 94% ($p = 0.012$).

In contrast, Fountzilas reported on a Hellenic Cooperative Oncology Group phase II randomized study comparing induction chemotherapy with CDDP, epirubicin, and taxol for 3 cycles followed by concurrent weekly CDDP with radiation compared with concurrent chemoradiation alone. One hundred forty-one stages IIB to IVB patients were enrolled with 86% in the induction arm completing the neoadjuvant chemotherapy. At a median follow-up of 55 months, no difference in 3-year progression-free (64.5% vs. 63.5%, $p = 0.708$) and overall survival (67% vs. 72%, $p = 0.652$) was noted. Grade 3/4 toxicity from induction chemotherapy were infrequent. Huang reported a Chinese trial of 408 patients who all underwent induction carboplatin/floxuridine and then randomized to radiation alone or radiation with carboplatin. The addition of carboplatin yielded no survival or locoregional control benefit.[175] Xu reported on a randomized trial showing no difference in survival for patients treated with neoadjuvant chemotherapy followed by radiotherapy versus concurrent chemoradiation.[176]

Multiple other induction regimens prior to concurrent chemoradiation have been studied as nonrandomized phase II or phase I studies using taxol/carboplatin,[177] nedaplatin/5FU,[178] taxol/cisplatin,[179] TPF,[180,181,182] and taxotere/platinum/xeloda[183] have been evaluated.

## Phase III Trials

Currently, five phase III studies testing the benefit of induction chemotherapy followed by concurrent chemoradiation versus concurrent chemoradiation alone are underway (Table 22.6).[184] One of the five compares the Intergroup 0099 regimen directly to an induction regimen followed by concurrent chemoradiation using the same chemotherapy but reversing the sequencing. The study conducted by the Hong Kong group (HKNPCSG 0501) is a three-arm trial which also investigates the benefit of capecitabine over 5FU as well as accelerated radiation (DAHANCA type) compared with conventional fractions. Four of the trials have concurrent chemoradiation alone as the standard arm without adjuvant chemotherapy. Of these four, three are designed using weekly cisplatin during the radiation whereas one is every 3-week cisplatin. Two trials explore the benefit of induction TPF which have been shown to improve survival in nonnasopharyngeal head and neck cancer.[185,186]

## Meta-analysis

Meta-analysis of eight randomized trials with 1,753 patents comparing chemotherapy and radiation to radiation therapy alone reported a hazard ratio of 0.82 ($p = 0.006$) favoring chemotherapy

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**TABLE 22.6 Phase III Randomized Trials Testing the Benefit of Induction Chemotherapy versus Concurrent Chemoradiation alone or Followed by Adjuvant Chemotherapy**

| | Accrual Goal | Treatment Arms | End Point |
|---|---|---|---|
| HKNPCSG 0501 | 798 III/IV | CCRT (CF or AF) → PF × 3 (Int 0099) | PFS and OS |
| | | PF×3 → CCRT | |
| | | PX×3 → CCRT | |
| GORTEC | 260 T2b-4N1–3 | TPF×3 →CCRT | EFS |
| | | CCRT | |
| China | 216 III/IV | TPF×3 → CCRT | FFS |
| | | CCRT | |
| Singapore | 216 III/IV | GCaTI → CCRT | OS |
| | | CCRT | |
| Taiwan | 480 IV | MEPFL → CCRT | DFS |
| | | CCRT | |

T = taxotere; P=cisplatin; F = 5-Fluorouracial; M = Mitomycin C; E = epirubicin; L = leucovorin; G = gemcitabine; Ca = carboplatin; Tl = taxol; X = capecitabine; 3 = q 3 week cisplatin 1 = weekly cisplatin.

and corresponding to a 6% absolute 5-year survival benefit.[132] Concurrent chemotherapy provided an absolute event-free survival benefit of 10% at 5 years. Induction chemotherapy improved event-free survival (HR = 0.82 [CI 0.67–0.97]) but not overall survival (HR = 0.99 [CI 0.8–1.21]). The survival benefit of chemotherapy was most pronounced for WHO type I tumors (HR = 0.30 [CI 0.15–0.59]) but also for WHO types II and III (HR 0.85 [CI 0.73–0.98]).

Meta-analysis of seven randomized trials of 1,608 endemic patients showed a survival benefit of concurrent chemoradiation over radiation alone (hazard ratio at 3- and 5-year of 0.61 and 0.74, respectively).[187] Concurrent chemoradiation also decreased locoregional failure (3-year HR = 0.67 [CI 0.49–0.91]) and distant metastasis (HR = 0.71 [CI 0.58–0.88]). Five of the seven trials also incorporated CDDP/5FU adjuvant chemotherapy after concurrent chemoradiation. Distant metastasis was also decreased in those trials incorporating concurrent and adjuvant chemotherapy compared with radiation alone to a similar degree (HR = 0.71 [CI 0.54–0.92]). The benefit of adjuvant chemotherapy beyond concurrent chemotherapy was not reported in this population-based meta-analysis.

## Follow-up

Standard follow-up as recommended by NCCN guidelines include history and physical every 1 to 3 months the first year after treatment, 2 to 6 months the second year, and 4 to 8 months years 3 to 5 with imaging every 6 months, as well as regular thyroid function testing every 6 to 12 months in addition to speech and swallowing evaluation.

The potential of surveillance with posttreatment plasma EBV DNA in endemic patients has been reported in a single-institution study at Taichung Veterans Hospital in Taiwan. A prospective study of 245 nasopharynx carcinoma patients who achieved clinical remission were followed with serial plasma EBV DNA levels every 3 to 6 months as well as annual anatomic imaging of the head and neck area (MRI or CT), bone scan, and chest radiography. A total of 36 patients were found to have elevated plasma EBV DNA levels (>0 copy/mL) and underwent PET/CT. An additional five were felt to have clinical signs concerning for recurrence but whose plasma DNA EBV were negative. All 36 patients with elevated EBV DNA had recurrence subsequently detected on PET/CT whereas none of those with negative EBV DNA recurred. Patients with distant metastasis had higher median levels compared with those with locoregional failure only (median 1531 vs. 625 copy/mL, $p = 0.08$). The cost of a EBV DNA level reduced cost of surveillance 77% to 88% compared with one in which serial PET/CT were to be used for surveillance. The value of surveillance plasma EBV DNA remains to be validated.

## Secondary Primary Tumors

In contrast to other head and neck sites with incidence of secondary malignancies of 5% to 7%/year,[188] the incidence is markedly lower after treatment for NPC. The incidence of secondary malignancies was examined in 326 consecutively treated patients with definitive radiation therapy.[189] At a median follow-up of 5.6 years, the annual rate was 1.0% and the 5-year cumulative incidence was 5.8%. Two-thirds of secondary malignancies were aerodigestive tract tumors (lung in 44% and head and neck in 44%). All tumors were histologically distinct from the index nasopharyngeal cancer. Advanced age (age > 50 years) appeared to be associated with SPT development 11% versus 3% at 5 years for those aged >50 versus <50, respectively. The actuarial incidence of in-field SPT was 1.2% at 5 years with an annual rate of 0.35%.

## Salvage Therapy

***Salvage of Persistent Disease after External Beam Radiation Therapy.*** About 7% to 13% of patients may have persistent disease after EBRT alone[63,190,191] with failure rates of about 39% to 60% in such patients.[63] Leung reported on the use of salvage brachytherapy for locally persistent NPC in 87 patients treated with HDR-brachytherapy from 1990 to 1998.[191] Persistent disease was documented by biopsy 3 to 6 weeks after EBRT (median time 6 weeks). The EBRT dose was 65 to 66 Gy delivered with the Ho 2D technique with parapharyngeal boost (10 Gy/4 fractions) in patients with parapharyngeal involvement. No patients received concurrent chemotherapy. Initial T stage was as follows: T1: 19 patients; T2: 48 patients; and T3: 20 patients. Patients received 22.5 to 24 Gy in 3 fractions spaced 1 week apart using cobalt or iridium sources. The 5-year LC was 85% and disease-specific survival was 77%. Outcomes were compared with 383 patients treated with radiation alone. Brachytherapy improved LC in T1 and T2 patients but not T3 with 5-year LFFS as follows for brachytherapy patients: T1, T2, and T3 were 97%, 88%, and 67%, respectively, compared with 84%, 80%, and 63%, respectively, in the EBRT-alone patients. The iridium-treated patients showed better LC than the cobalt-treated patients, especially in the T1–2 (95% vs. 77%, $p = 0.03$, respectively). Complications attributed to brachytherapy included soft tissue necrosis in two patients within 6 months of treatment, both of whom healed, and perforation of the nasal septum with bilateral optic nerve atrophy in one patient.

Yan reported on a randomized study of 78 patients with T1–3 NPC tumors treated to 70 Gy to the nasopharynx and then biopsied within 2 weeks after EBRT.[192] Of the 30 positive patients, 16 were randomized to receive an external beam boost 20 Gy in five fractions versus the 14 who were randomized to observation. Local recurrence was 6% versus 36% in patients receiving

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additional EBRT versus those observed. Thus, boost with either EBRT or brachytherapy can salvage a significant percentage of those with persistent disease.

***Salvage of Recurrent Disease.*** Locoregionally recurrent disease after previous radiation therapy presents a challenging situation which requires multidisciplinary evaluation. Multiple surgical and radiation approaches are feasible salvage options particularly for the early-stage recurrences. With more advanced disease, options are usually limited to external beam radiation techniques with integration of chemotherapy. Neck dissection is routinely incorporated in patients with resectable nodal recurrence.

When local failure occurs, the chance for LC with subsequent treatment varies widely with reported 5-year control rates of 15% to 60%.[193–199] Prognostic factors important for LC and survival that are consistently reported from single institutional series include the stage of the recurrent tumor (T1–2 have more favorable outcomes), interval from previous radiation treatment (>2 year interval from previous radiation), and whether the chronology suggest persistent versus recurrent disease.[193–199] In general, for patients undergoing reirradiation, doses of >60 Gy are required for effective chance of salvage.[193–198] Patients with persistent disease do better than those with recurrent. The series are too limited and fraught with selection bias to make definitive conclusions as to which treatment should be recommended. The best salvage treatment must be individually tailored.

***Salvage Reirradiation.*** Dose escalation in patients undergoing reirradiation is important. A prospective, randomized study of dose escalation using 2D technique followed by boost delivery with 3D radiotherapy for patients with locally recurrent NPC showed a LC benefit for higher dose.[200] Thirty-six patients with >6 month interval from previous radiation (68–72 Gy) with local recurrence without nodal or distant metastasis were all treated with 2D EBRT to 54 Gy and then randomized to receive 3D-CRT boost doses of 16 Gy, 20 Gy, and 24 Gy in 4 Gy fractions/3× week. The median time to recurrence was approximately 3 years, and 56% had tumor confined to the nasopharynx. The dose allowed to the spinal cord and the brain stem was 15 to 20 Gy after previous treatment to 40 Gy. At a median follow-up of 27 months, 3-year local recurrence-free survival were 37%, 28%, and 72%, respectively, with the higher dose showing a statistically significant increase in LC ($p = 0.047$). No difference in 3-year overall survival was noted, 72%, 59%, and 82%, respectively, nor was any incidence in distant metastasis. The 3-year overall survival and incidence of distant metastasis for the entire three cohorts were 65% and 10%, respectively. One patient in the highest dose group had a fatal bleed, but there appeared to be no increase in grade 3/4 acute toxicities in the highest dose group. Late toxicities for the entire group included a 67% with trismus, 31% with posterior cranial nerve damage, 61% with tooth decay, and 8% with temporal lobe necrosis.

The addition of brachytherapy as a component of reirradiation appears to be important (Table 22.7). The role of brachytherapy was examined in 91 patients with recurrent nasopharynx cancer who were treated with reirradiation.[197] Eight patients were treated with brachytherapy alone (24–45 Gy in 3–10 fractions), 42 with EBRT (median dose 50 Gy) + brachytherapy (14.8 Gy in fractions), and 41 with EBRT alone (median dose 57.3 Gy). The breakdown of recurrent T stage were as follows: rT1: 37; rT2: 14; and rT3: 40. Fifty-eight percent of local recurrences were within 2 years of completion of initial radiation therapy. Neoadjuvant chemotherapy was given in 19%. Patients receiving EBRT+ brachytherapy had better LC compared with EBRT-only patients (57% vs. 34%, $p = 0.003$); however, there was a greater proportion of T3 patients in the EBRT arm. If only rT1–2 patients were analyzed, the EBRT+ brachytherapy showed a trend toward improved LC compared with EBRT alone (72% vs. 54%, $p = 0.13$). Fifty percent of patients treated with brachytherapy alone achieved LC. For all patients, the local failure-free survival for rT1, rT2, and rT3 were 64%, 62%, and 18%, respectively. Total dose >60 Gy and low rT stage were found on multivariate analysis to predict for tumor control.

One of the earliest reports advocating reirradiation as a salvage option was reported from the Massachusetts General Hospital (MGH). Wang reported the outcomes after reirradiation of 51 recurrent nasopharynx patients treated from 1950 to 1981.[193] The mean time from previous treatment to recurrence was 18 months. Patients were treated with 40 Gy EBRT followed by two brachytherapy boost of 10 Gy using $^{137}$ Cesium. EBRT alone to 66 Gy was used for T3/4 lesions. The 38 (33 T1–2, 5 T3–4) patients who received ≥60 Gy had a better 5-year survival than the 13 receiving <60 Gy (45% vs. 0%, $p = 0.0001$, respectively). Among patients receiving >60 Gy, the 5-year overall survival for T1–2 was 38% and 15% for T3/4 lesions. Patients who developed recurrence >24 months after initial treatment had better 5-year survival compared with those with a shorter time of relapse (66% vs. 13%, $p = 0.005$, respectively). The incidence of

**TABLE 22.7 Outcomes after Salvage Reirradiation with Brachytherapy**

| | No. of Patients | % T1–2 | LC | OS | Complications |
|---|---|---|---|---|---|
| EBRT → BT | | | | | |
| Wang et al. (1987)[193] | 51 | 76% | | 33% | 8% severe |
| Pryzant et al. (1992)[194] | 53 | | 35% | 21% | 15% |
| Lee et al. (2007)[195] | 706 | | 32% | 14% | 24% |
| Lee et al. (1993)[196] | 12 | 91% | 61% | 91% | |
| Leung et al. (2000)[197] | 42 | | 57% | | |
| Teo et al. (1998)[198] | 176 | | 15% | 8% | 61% severe |
| BT alone (interstitial implant) | | | | | |
| Syed et al. (2000)[199] | 34 | 46% | 59% | 30% | |

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long-term toxicities were reported to be 8% and included cranial neuropathies, osteoradionecrosis of the skull base, mucosal necrosis, trismus, and soft palate fibrosis.

Others have reported similar findings. Pryzant reported a 5-year LC of 35% and overall survival of 21% in 53 patients with best LC in those undergoing EBRT followed by brachytherapy.[194] Hwang showed a 5-year survival of 37% in 74 patients after reirradiation.[201] Lee reported a small series from UCSF of 12 recurrent cases treated with external beam 30 to 42 Gy with 5 to 7 Gy boost with HDR intracavitary brachytherapy or 10 to 54 Gy LDR.[195] The majority of patients were ethnic Chinese and all patients had WHO II or III histology. At a median follow-up of 50 months, the 5-year LC was 64% and overall survival was 91%. Three patients developed complication including osteoradionecrosis, stricture, and trismus.

The largest series of reirradiated patients was reported by Lee on a series of 706 patients with locally recurrence treated with EBRT with or without brachytherapy from 1976 to 1985.[196] Recurrent T1 comprised 40% of patients whereas 21% were T2. The 5-year overall survival for rT1 and rT2 were 27% and 17%, respectively, whereas survival was only 4% in rT3 or rT4. Late toxicity was 24% with a treatment mortality of 1.8%.

***Toxicity from Reirradiation and Brachytherapy.*** The incidence of severe complications is related to the total cumulative doseof external beam radiation. Patients receiving cumulative doses of external beam radiation >100 Gy had a higher incidence of severe complications (39% vs. 4%, $p = 0.066$) compared with those receiving <100 Gy. Such toxicities included cranial nerve damage, trismus, lymphedema, otoxicity, and temporal lobe necrosis.[194] The authors recommend limiting reirradiation doses of 20 to 30 Gy with EBRT followed by brachytherapy boost of 40 to 50 Gy. A 61% incidence of severe complications is reported by Teo, who attempted salvage therapy of 54 to 60 Gy followed by brachytherapy boost of 10 to 24 Gy in patients who previous received 60 to 62.5 Gy/24 to 29 fractions with possible additional treatment with parapharyngeal boost 20 Gy/10 fractions and/or brachytherapy 24 Gy/3 fractions.[198] Toxicities include soft tissue and bony necrosis, fistula formation, and cranial nerve damage. Complication rates reported by Leung were severe as nearly three-quarter of patients had a major complication with 50% having central nervous system complication at 5 years.[197] Temporal lobe necrosis occurred in 28% of EBRT-treated patients. Trismus was noted in 30% and deafness in 20%.

***IMRT for Recurrent Tumor.*** Lu reported the use of IMRT for reirradiation of recurrent nasopharynx cancer. Forty-nine patients with recurrent cancers were treated with IMRT to doses of 68 to 70 Gy at the primary site and 60 Gy to involved nodes. Mean doses to the brain stem, the spinal cord, the optic pathways, and the temporal lobes ranged from 20 to 28 Gy. T1–2 tumors comprised 13 of the patients while N0–1 comprised 46 patients. No comment is made about previous radiation doses or interval since initial treatment. Three patients with involved nodes were treated with chemotherapy after IMRT. The median time to recurrence after initial treatment for the study group was 19.5 months. At a median follow-up of 9 months, locoregional control was 100%, and 3 patients developed metastatic disease. Acute grade ≥3 toxicity was 4%, and tumor necrosis was noted in 29% without associated mucosal ulceration or bleeding.

Chua reported the results of reirradiation using IMRT for 31 patients with locally recurrent nasopharynx cancer.[202] rT3 or T4 comprised 74% (23/31) of the patients. Median time from the first course of treatment was 51 months. Median prescribed dose was 54 Gy (50–60 Gy) with induction chemotherapy in two-thirds and SRS boost (8.6–12.5 Gy) in one-third. At a median follow-up of 11 months, 1-year LC was 56% and overall survival was 63%. Local progression-free survival was 100% in 17 patients with rT1–3 tumors versus 35% in rT4. The 1-year actuarial rate of grade 3 or greater late toxicity was 25% (cranial neuropathy, otoxicity, and brain necrosis). Grade 3 to 4 toxicity occurred in 25% and included cranial neuropathy, neuropathy, otoxicity, and brain necrosis. Ototoxicity was most common and occurred in 42%. These results are preliminary and need longer follow-up before any assessment of efficacy and toxicity can be concluded.

## NASOPHARYNGECTOMY

With modern imaging, surgical technique, and supportive care, salvage nasopharyngectomy represents a good alternative to consider. Retrospective series reported LC in the 40% to 67% with best outcomes for early-stage patients.[203–205] Multiple surgical approaches are considered depending on tumor location. Subtotal nasopharyngectomy can be undertaken via a transpalatal approach with centrally located small tumors, with a maxillary swing approach for more extensive tumors and anterolateral approach with facial translocation for advanced tumors. An anterior and/or middle fossa resection is indicated when the tumor extends superiorly to involve the infratemporal fossa or the cavernous sinus.

Fee reported on 37 patients treated with nasopharyngectomy with or without RT.[204] Twenty-two patients with rT1 and 5 patients with rT2 were included. Mean time to recurrence after radiation was 29 months, and a median dose of 68 Gy was delivered. Patients underwent transpalatal, transmaxillary, or transcervical resection with or without neck dissection. Eight were treated with additional radiation for positive margins. At a median follow-up of 5.2 years, 5-year LC was 67%, 5-year disease-free survival was 52%, and overall survival was 60%. Five-year overall survival was 73% for rT1, 40% for rT2, 14% for rT3, and 0% for rT4. Corresponding 5-year LC was 77%, 40%, 57%, and 0%, respectively. Fifty-four percent had surgical complications with one perioperative death from carotid artery injury and one patient with pharyngeal plexus paralysis with resultant dysphagia. Transitory complications included osteoradionecrosis/osteomyelitis, palatal fistulas, thyroid storm, and pneumonia.

King reported on 31 patients (94% rT1 or rT2) undergoing nasopharyngectomy with 70% receiving postoperative radiation.[203] Five-year overall survival was 47% and LC was 43%. Complications included palatal defect in 55%, trismus in 48%, otitis media in 65%, dysphagia in 39%, and nasal regurgitation in 26%. Wei reported a 43% tumor control at 2.5 years in 45 patients with recurrent NPC undergoing nasopharyngectomy.[205]

Teo reported on 123 patients with locally recurrent NPC treated with reirradiation ($n = 103$) or nasopharyngectomy ($n = 20$).[198] rT1 and T2 comprised 44% of EBRT treated patients and 75% of surgery patients of whom 70% received postoperative radiation. At a median follow-up of 20 months, 5-year overall for all patients was 8% and 5-year LC was 15%. Survival was 26% for rT1, 8% for rT2, and 3% for rT3. Survival appeared to better in patients receiving nasopharyngectomy and post-op RT versus RT alone. At 2 years, freedom from further relapse was 40% of the 20 resected patients versus 20% for reirradiated patients. Among rT1–2 patients, nasopharyngectomy appeared to be superior to radiation. Temporal lobe necrosis occurred in 24%, trismus 70%, and hearing loss in 56%.

Chua showed no difference in survival in surgically treated patients ($n = 12$) compared with those treated with RT ($n = 94$) despite a selection bias in favor of surgery.[206] Five-year overall survival for T1/T2 was 57%. Thirty-four percent had neurologic complication with 30% incidence of trismus.

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## Stereotactic Radiosurgery

SRS represents another option for salvage. Forty-eight patients with local failures were treated with SRS between 1996 and 2005 using a linac-based system with single or multiple isocenters.[207] A median dose of 12.5 Gy was delivered. At a median follow-up of 54 months, the LC was 47%, and 5-year overall survival 47%. Neuroendocine complication occurred in 27% without treatment-related deaths. Time interval from initial treatment, recurrent T stage, prior treatment failures, and tumor volume were significant predictive factors of LC and survival.

Cmelak reported the outcomes of 8 patients with recurrent nasopharyngeal cancers who had recurred 6 to 96 months after previous EBRT (58.2–79.2 Gy) and treated with SRS for 12 lesions (one patient had three separate lesions).[208] Patients were treated to a median SRS dose of 18 Gy (15–20 Gy). At a median follow-up of 17 months, about 7 of 12 lesions remain controlled locally. One patient experienced a facial nerve palsy 1 month after treatment.

## Fractionated SRT

Ahn reported the outcomes of 12 recurrent disease patients treated with fractionated SRT alone delivering a median total dose of 54 Gy in 2.5 to 3.0 Gy fractions.[209] Three patients received chemotherapy and one underwent debulking surgery. At a median follow-up of 13 months, the LC and survival at 2 years was 92% and 60%, respectively. One patient died of radiation myelopathy and six developed DM.

## SRS and Intracavitary Brachytherapy

Thirty-six patients with locally recurrent rT1 ($n$ = 19) or rT2 ($n$ = 17) were treated with SRS and intracavitary high-dose rate brachytherapy.[210] Eighty-six percent had locally recurrent disease (disease recurrence >4 months after previous EBRT). Median target volume was 36.3 cc (10.3–856.2 cc). Patients received 18 Gy of linac-based SRS to the 90% isodose followed by two intracavitary boosts of 6 Gy given a week apart. At a median follow-up of 4.2 years, the 5-year actuarial LC was 65% (rT1: 82%; rT2: 49%). Five-year overall and disease-free survival was 57% (rT1: 78%; rT2: 39%) and 62% (rT1: 80%; rT2: 48%), respectively. Complication-free survival rate was 31% at 5 years and consisted primarily of trismus (20%), cranial nerve palsy (20%), palatal fibrosis (17%), and osteoradionecrosis (17%) and temporal lobe necrosis (8%). No treatment-related mortality was reported.

## Interstitial Implant

Interstitial implant may offer higher and better accuracy of dose delivery to the recurrent tumor. Several interstitial series report excellent control that appears higher than intracavitary brachytherapy alone. However, this may be due to patient selection of more favorable lesions. The interstitial implants may be permanent or temporary and may be placed with exposure of the nasopharynx by soft palate retraction or via a transpalatal approach.

Gold-grain implants have been reported to offer favorable outcomes.[211,212] Fifty-three patients with recurrent or persistent tumors underwent gold-grain implant with a split palate direct visualization approach.[211] The 5-year LC was 63% and overall survival 56% in patients with rT1. The 5-year overall survival was 72% in those with persistent versus 54% in recurrent disease. Late complications comprised primarily headache in 28%, palatal fistula in 19%, mucosal necrosis in 16%, and neurologic complications in 12%.

Syed reported on 41 patients treated with interstitial implants and intracavitary brachytherapy alone for either recurrent ($n$ = 34) or new primary nasopharynx cancers ($n$ = 7) having received previous external beam radiation to the head and neck.[199] A mean dose of 50 to 58 Gy was delivered without external beam radiation using a temporary afterloading interstitial [192] Ir implant and an intracavitary applicator. Hyperthermia was used in about half of patients (21/41) with 8 patients receiving chemotherapy prior to implant and 17 patients received concurrent chemotherapy with 5FU and/or cisplatin. At a median follow-up of 7 years, the LC at 5/10 years was 59%/49%, overall survival 30%/20% and disease-free survival of 41%/34%. There were four perioperative deaths related to myocardial infarction, pneumonia, stroke, and cardiopulmonary failure. One patient died of massive epistaxis 9 months after treatment. About 45% experienced late complications including soft tissue necrosis (14%), dysphagia (11%), soft palate atrophy (11%), and nasal crusting (11%).

## Chemotherapy for Recurrent and Metastatic Disease

NPC is highly chemosensitive, and there has been multiple phase II trials demonstrating response rates of 50% to 90% to first-line combination chemotherapy, all of which containing platinum.[213–220,151,213–223] There has not been any phase III trial to compare between these multiple regimens, and hence the choice of chemotherapy regimen is currently based more on toxicity profile and reported response rates from phase II trials. Phase II studies using >2 drug combinations have generally been associated with a higher complication rate[224–228] although a recent study from Singapore using paclitaxel, carboplatin, and gemcitabine appears to be well tolerated.[229] Short of randomized phase III data, current options of first-line chemotherapy will be cisplatin in combination with infusional 5FU, paclitaxel, or gemcitabine. Newer chemotherapeutic agents demonstrating activity for NPC include irinotecan, capecitabine, docetaxel, vinorelbine, and oxaliplatin.[230–234] Combination first-line studies are ongoing.

## Long-term Survivors after Chemotherapy for Metastatic Disease

Several retrospective series have reported long-term survivors after systemic chemotherapy in metastatic NPC. The Institute Gustav-Russy series reported 20 survivors of >36 months after achieving complete response to chemotherapy.[235] The Hong Kong NPC Study Group series reported that patients with lung metastases only had a more favorable survival outcome after systemic chemotherapy compared with patients with other sites of failure.[148] Hence an aggressive approach to manage metastatic NPC patients with a good performance status is recommended, especially if the metastasis is confined to the intrathoracic site.

# FUTURE DIRECTIONS

## Targeted Therapy

***Epidermal Growth Factor Receptor (EGFR).*** EGFR is highly expressed in NPC and two recent reports demonstrated that EGFR expression is an independent predictor of poorer clinical outcome in NPC.[236,237] The activity of the monoclonal antibody against EGFR, cetuximab, has been investigated in a multicenter phase II study in combination with carboplatin in patients with recurrent or metastatic NPC who progressed within 6 months of platinum-based chemotherapy.[238] Thirty percent of the patient population had received >2 lines of prior chemotherapy. There were seven partial responses (11.7%) and 29 stable disease (48.3%) giving a combined clinical benefit of 60%. The toxicities were mild, and

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hence anti-EGFR therapy has significant activity in heavily pretreated metastatic NPC. Cetuximab is now being investigated in locally advanced NPC in combination with cisplatin-RT.

The EGFR tyrosine-kinase inhibitors gefitinib and erlotinib are both being tested in phase II trials in metastatic NPC. The preliminary result of a phase II study of gefitinib in patients who progressed after 1 to 2 lines of chemotherapy (at least one line containing platinum) for metastatic or locoregionally recurrent NPC has been reported.[239] Gefitinib was well tolerated and achieved stable disease for >6 months in 2 out of 11 evaluable patients, with no partial responders. Single-agent anti-EGFR therapy appears to be insufficient to achieve clinical response and ongoing studies combining these agents with chemotherapy in a sequential manner is ongoing. EGFR and Co × 2 are frequently overexpressed in NPC and there may be synergism between Co × 2 and EGFR inhibitors.[240] Investigators from Singapore are testing the combination anti-EGFR and Co × 2 inhibitor approach using celecoxib and gefitinib.

***Vascular Endothelial Growth Factor (VEGF).*** Overexpression of VEGF and its receptor VEGFR-1 and VEGFR-2 occurred in 60% to 90% of NPC biopsies and have been reported to be associated with regional and DM and poor survival outcome.[241–244]

Preclinical studies demonstrated promising activity targeting angiogenesis in NPC cell lines and xenograft.[245–247] Evidence of coexpression of c-kit and stem cell factor in NPC biopsies provide further support for the use of multitargeted tyrosine kinase inhibitors in NPC.[248] In a phase I study of the multitargeted receptor tyrosine kinase inhibitor sunitinib, one NPC patient demonstrated significant tumor shrinkage and necrosis.[249] A phase II study evaluating sunitinib is ongoing.

With the demonstrated survival benefit of bevacizumab (monoclonal antibody against VEGF) in multiple solid tumors including colon, lung, and breast cancer and the knowledge that NPC patients with elevated VEGF have a higher likelihood of DM and poorer survival. The RTOG conducted a phase II trial to determine the feasibility of the addition of bevacizumab during the concurrent and adjuvant phase of the Intergroup 0099 regimen in 44 patients. The dose limiting toxicity evaluated with grade 3 hemorrhage. No grade 3 hemorrhage was reported although 20% experienced a grade 1/2 hemorrhage while 9 patients had grade 4 hematologic toxicity. Seventy percent of patients received all 3 cycles of adjuvant chemotherapy. At a median follow-up of 2.5 years, the 2-year locoregional control was 84% and 2-year DM was 9% with a 2-year overall survival of 91% (Lee, *Lancet Oncol.* 2012;13:172–180).

## Epigenetic Therapy

CpG promoter methylation and histone deacetylation play crucial roles in the transcriptional regulation of gene expression in the EBV genome.[250] Silencing of the immunodominant EBV nuclear antigen (EBNAs-2, 3A, 3B, 3C) expression through methylation may serve as a target for epigenetic therapy using DNA methyltransferace (DNMT) inhibitors. In patients with EBV-positive malignancies who have failed conventional treatment, a clinical trial of the DNMT inhibitor Azacitidine was conducted aiming at the demethylation of EBV promoters and also upregulating expression of the silenced viral antigens.[251] In the 5 patients with adequate pre- and posttreatment biopsies, demethylation to varying degrees of all the latent and early lytic EBV promoters was demonstrated. Viral gene reexpression was observed in one antigen by immunohistochemistry. This pioneering study demonstrated for the first time that demethylation of tumor DNA in patients can be achieved using azacitidine. A follow-up study combining the histone deacetylase inhibitor SAHA with azacitidine is ongoing.

## Immunotherapy

EBV is ubiquitous in undifferentiated NPC, and hence the viral antigens expressed by the tumor provide potential targets for immunotherapy.[252–255] Adoptive therapy using cytotoxic T cells (CTLs) have been highly successful in treatment of EBV-associated, posttransplant lymphoproliferative disease (PTLD), which express the immunodominant EBV nuclear antigens EBNA 3A, 3B, and 3C. In contrast, NPC express a restricted set of less immunogenic viral antigens EBNA1, LMP1, and LMP2.

## Adoptive Therapy

The first pilot study to treat NPC using adoptive T-cell therapy was reported by Chua et al.,[256] where autologous EBV-transformed B-lymphoblastoid cell line (LCL) reactivated T cells were generated *in vitro* and used to treat four advanced cases of NPC. No adverse events occurred and infusion of CTL was associated with reduction of plasma EBV load. However, there was no evidence of tumor regression.

The use of autologous EBV specific CTL for NPC has since been evaluated in two clinical trials with 10 patients treated in each study.[257,258] Both studies demonstrated that EBV targeted autologous CTL is safe, induces LMP2-specific immune response, and is associated with objective response and control of disease in advanced NPC. Interestingly, Comoli et al. also reported the adoptive transfer of an allogeneic EBV specific CTL in one patient with relapsed NPC resulted in temporary stabilization of disease. Local tumor biopsy showed increase in tumor infiltrating CD8 T cells.[259] Taken altogether, the result of these studies showed that it is feasible to boost EBV-specific immune response in NPC patients and provide further rationale to explore EBV as a target for immunotherapy.

## Vaccination

A vaccine consisting of dendritic cells pulsed with peptides derived from LMP2 has been evaluated in 16 patients with local recurrence or distant metastasis after conventional treatment.[260] Peptide-specific T-cell response were elicited or boosted in nine patients and partial tumor reduction was observed in two patients. A vaccination trial is ongoing using a modified vaccinia virus expressing an EBNA1-LMP2 fusion protein to elicit CD4+ and CD8+ T cell against two EBV proteins expressed in NPC patients.[261] Alternatively, an LMP-based polyepitopte vaccine has also been developed for EBV-associated Hodgkin disease and NPC.[262,263]

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# PART B:
# Radiologic Imaging Concerns

Jeffrey A. Bennett

Cancer of the nasopharynx is staged differently than other pharyngeal primaries in that more emphasis is placed on tumor extension to other spaces than on size. Therefore, it is critical that imaging clearly shows the full extent of the primary lesion. As with other mucosal tumors, endoscopy can show the mucosal extent of the tumor very well, but deep tumor invasion requires imaging. Extension to the nasal cavity or oropharynx as well as parapharyngeal invasion classifies the tumor as T2 (Fig. 22-6). A T3 lesion involves bony structures and/or the paranasal sinuses. The tumor is upstaged to T4 if there is intracranial extension, involvement of the cranial nerves, the infratemporal fossa, the hypopharynx, the orbit, or the masticator space (Fig. 22-7). Because of the importance of detecting soft tissue invasion, intracranial extension, and perineural spread, magnetic resonance imaging (MRI) is preferred to computed tomography (CT) for imaging of nasopharyngeal cancers.[1–4] However, care must be taken with fat suppression as this often produces artifacts at air-bone interfaces at the skull base. CT is not without benefit as it is very good at showing cortical bone erosion.

Usually, the diagnosis of nasopharyngeal cancer is known at the time of imaging, but occasionally it is found incidentally when imaging patients with unilateral serous otitis media and Eustachian tube dysfunction, otalgia, sore throat, or cranial neuropathies. When a tumor is discovered, it is essential to describe its pattern of spread and full extent so that the patient can be correctly staged and treated appropriately. Often both CT and MRI are obtained and these certainly give complementary information. Usually, the neck is scanned with CT to evaluate lymphadenopathy as the addition of a neck MR adds significant time and expense to the MR study. Suggested protocols are given in Figures 22-8 and 22-9.

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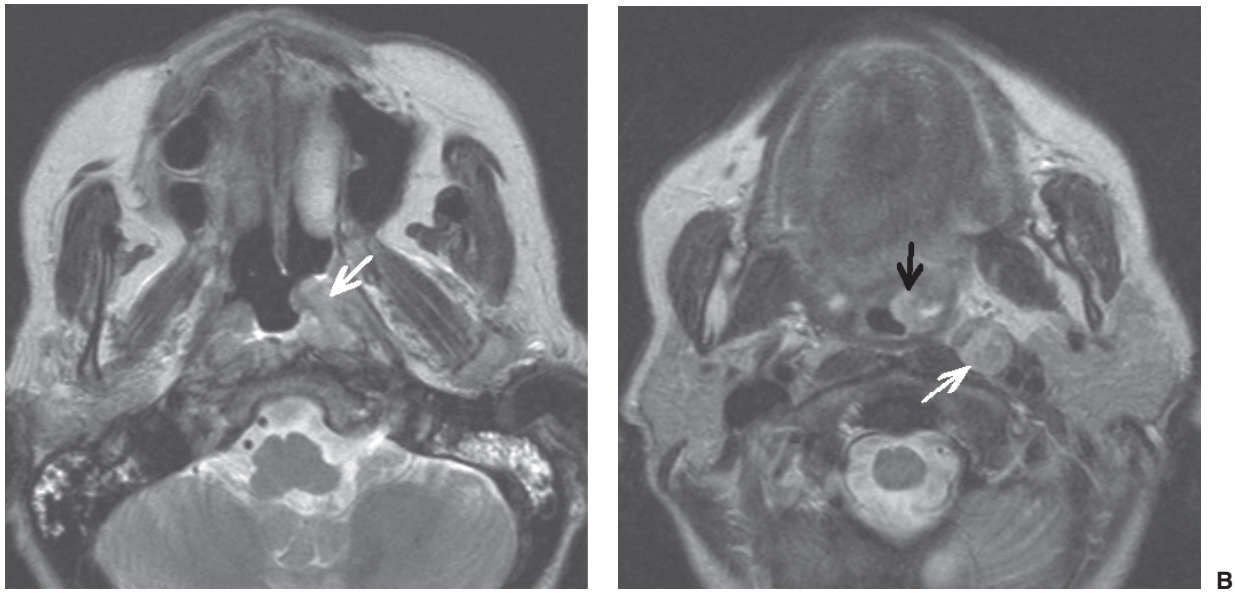
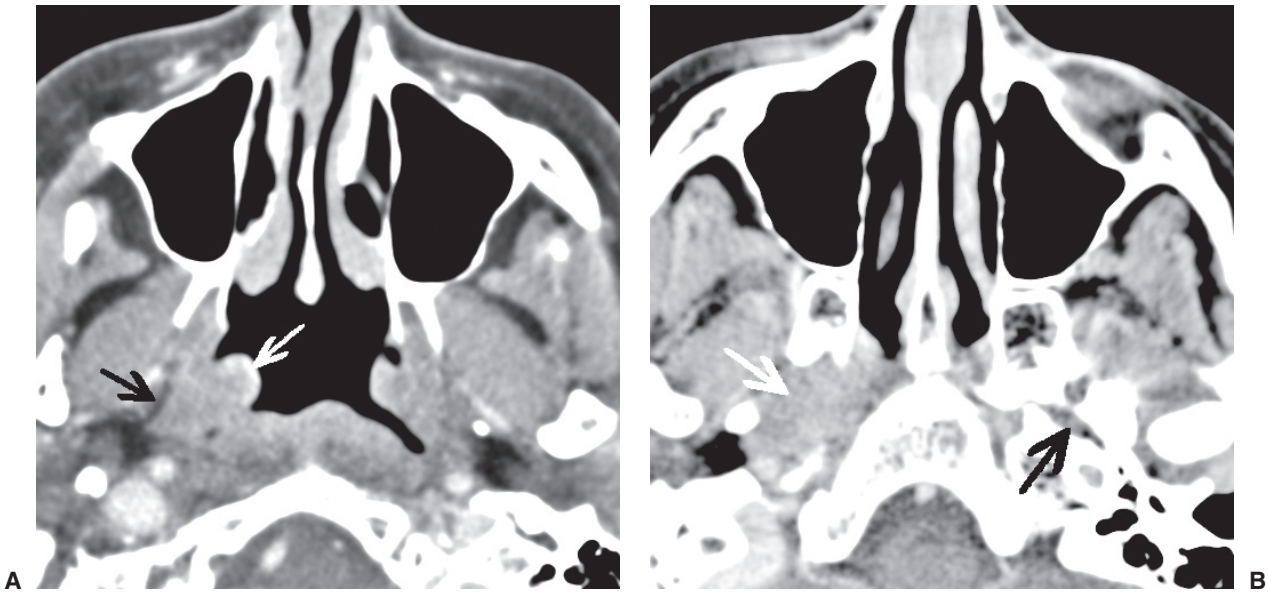



**FIGURE 22-6.** **A:** Axial T2-weighted MR image shows an infiltrating mass (*arrow*) in the left nasopharynx which has expanded the torus tubarius and obstructed the Eustachian tube orifice. No extension is seen into the parapharyngeal space fat. **B:** Axial T2-weighted MR image inferior to shows extension of tumor along the lateral pharyngeal wall into the oropharynx (*black arrow*). This stages the tumor as T2a. A positive left lateral retropharyngeal lymph node is well demonstrated (*white arrow*).



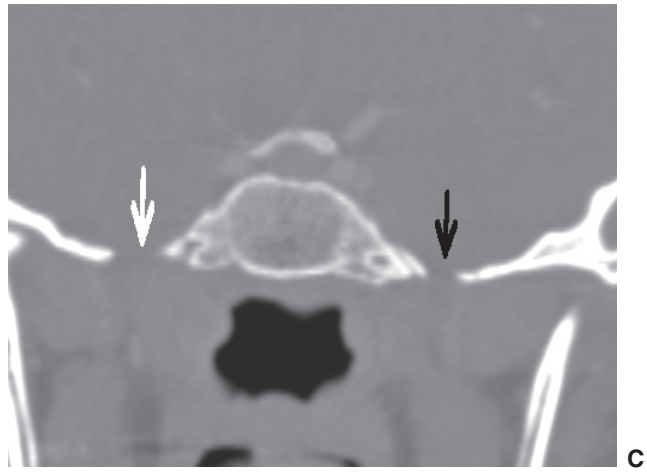
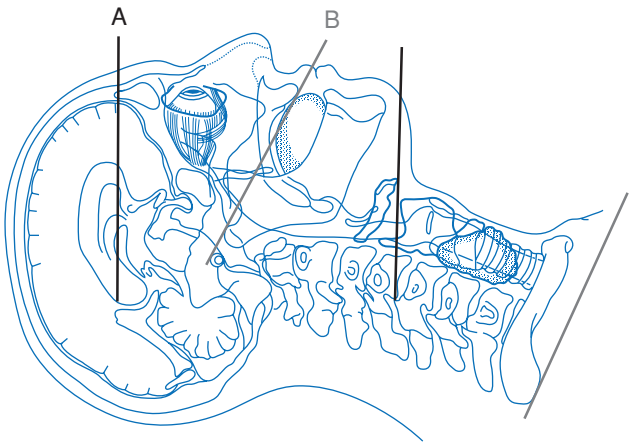




**FIGURE 22-7.** **A:** Axial postcontrast CT scan shows a right nasopharyngeal mass (*white arrow*). Note the preservation of fat in the parapharyngeal space deep to the pharyngobasilar fascia (*black arrow*). **B:** Axial postcontrast CT at the level of the temporomandibular joints shows that the tumor has spread superiorly (*white arrow*) and has destroyed bone at the petrous apex in the region of the foramen lacerum. Note the normal foramen lacerum on the opposite side (*black arrow*). **C:** Coronal reformat of the CT scan with bone windows shows enlargement of the right foramen ovale (*white arrow*) compared with the normal left foramen ovale (*black arrow*). At this point, an MRI would be warranted to look for more proximal spread of tumor along V3 to the trigeminal ganglion.



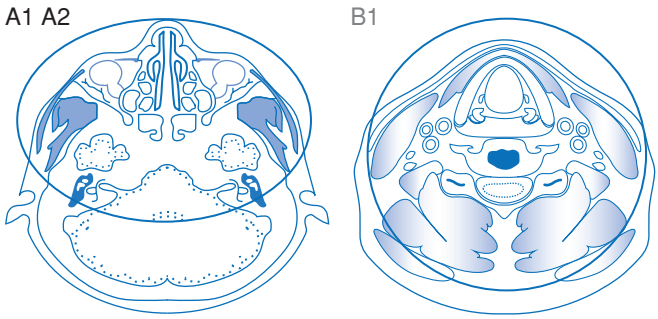
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ACQUISITION




| | | |
|---|---|---|
| | Patient position | Supine<br>IOML perpendicular to the tabletop |
| | Contrast | 100 mL adult |
| | Injection rate | 1 mL/sec; 60 sec delay |
| | Respiration | Quiet, NO Swallowing |
| | Volume acquisition specs | Appropriate to achieve images as specified in following reconstruction tables.<br>Head FOV. |
| A | Begin | Above frontal sinus |
| | End | Through mandible |
| B | Begin | Mid oral cavity |
| | End | Apices |

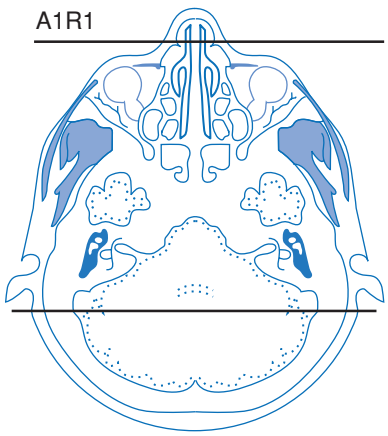
RECONSTRUCTION




| | | |
|---|---|---|
| A1 | Algorithm | Soft tissue |
| | Thickness | 1.0 mm |
| | Spacing | 0.8 mm |
| | F.O.V. | Approx. 170–190 |

| | | |
|---|---|---|
| A2 | Algorithm | Bone |
| | Thickness | 1.0 mm |
| | Spacing | 0.8 mm |
| | F.O.V. | Approx. 170–190 |
| B1 | Algorithm | Soft tissue |
| | Thickness | 2.5 mm |
| | Spacing | 2.5 mm |
| | F.O.V. | Approx. 160–180 |

REFORMATION




| | | |
|---|---|---|
| A1R1 | Algorithm | Soft tissue |
| | Thickness | 1.0 mm |
| | Spacing | 1.0 mm |
| | F.O.V. | Approx. 180 |
| | Plane | Coronal |
| | Begin | Frontal sinus |
| | End | Through IAC |

**FIGURE 22-8.** Protocol for CT maxillofacial detail and neck with intravenous contrast.

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| Acquisition | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Plane | Sagittal | Axial | Axial | Axial | Coronal | Coronal |
| Sequence | T1 | T1 | T1 | T2-FSE | T1 | T2-FSE |
| Contrast | None | None | Gd | Gd | Gd | Gd |
| SLT/SP | 5/0 mm | 3/0 mm | 3/0 mm | 3/0 mm | 3/0 mm | 3/0 mm |
| FOV | 16 cm | 16 cm | 16 cm | 16–18 cm | 16 cm | 16 cm |

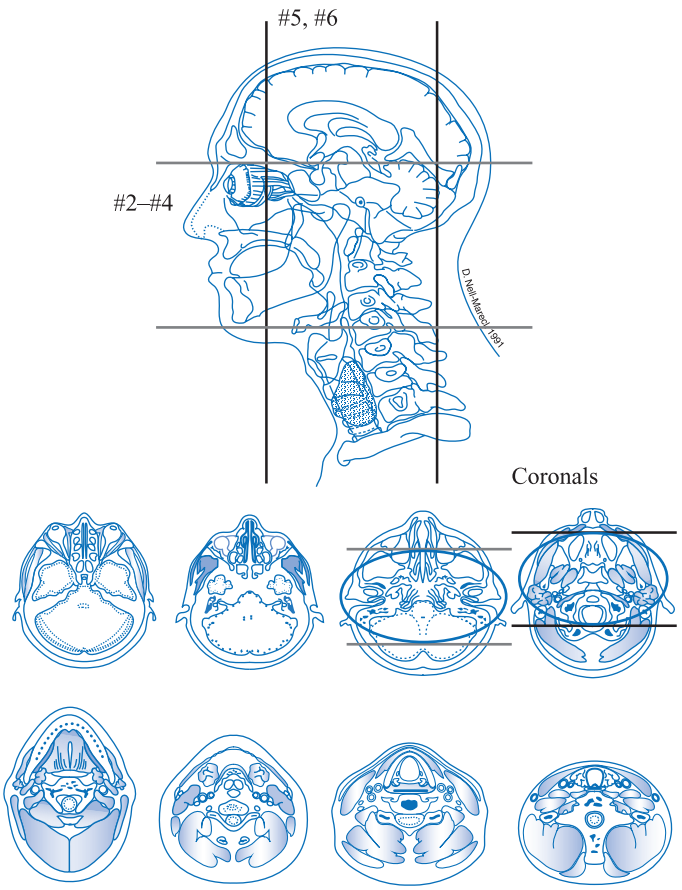



**FIGURE 22-9.** Protocol for MRI of the nasopharynx with intravenous contrast.

*Source:* Reprinted from Mancuso AA, Hanafee WN. *Head and Neck Radiology.* Philadelphia, PA: Lippincott Williams & Wilkins; 2011:2232, with permission.

Nasopharyngeal carcinoma can arise from any of its mucosal walls and occasionally will arise deep within the crypts of the adenoids where it may hide from the endoscopist leading to the diagnosis of unknown primary. However, when found, the unknown primary is more often discovered in the oropharynx or piriform sinuses.

Tumor can spread in all directions from the nasopharynx. Inferior extension is common into the lateral oropharyngeal wall or the palatine tonsil. This spread may be submucosal. Apparent bulky inferolateral spread may in fact be due to large lateral retropharyngeal nodes which are commonly involved (Fig. 22-10). Anterior spread through the posterior choana into the nasal cavity is usually seen in large tumors and is often detected clinically (Fig. 22-11).

Lateral spread to the parapharyngeal space is usually through the gap in the pharyngobasilar fascia called the sinus of Morgagni. Once in the parapharyngeal space, tumor can grow laterally into the infratemporal fossa and the masticator space (Fig. 22-12), or superiorly to the skull base (Figs. 22-13 and 22-14). In addition, from the parapharyngeal space, the tumor can extend along the trigeminal nerve to the skull base (Fig. 22-15).

Direct invasion of the skull base is primarily at the central and posterior skull base (Fig. 22-16). Invasion into the sphenoid

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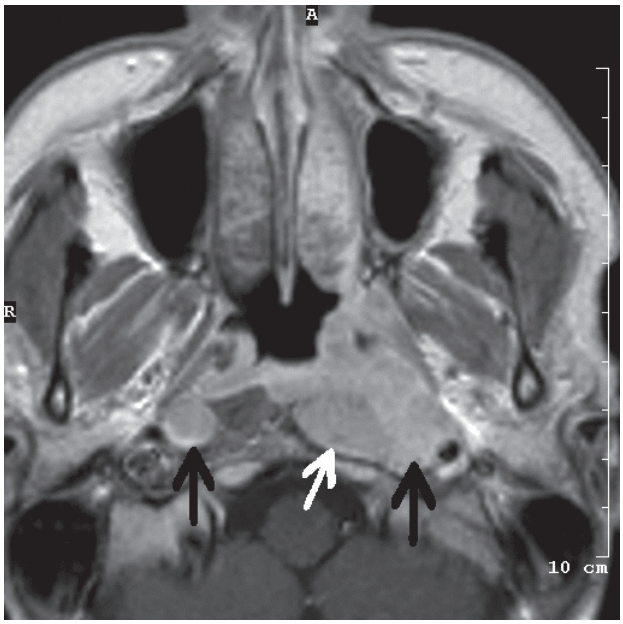



**FIGURE 22-10.** Axial T1-weighted postcontrast MRI shows a large left nasopharyngeal squamous cell carcinoma. There is apparent posterolateral extension into the retrostyloid parapharyngeal space. However, this is actually a positive lateral retropharyngeal lymph nodes with extracapsular spread and a positive right retropharyngeal node is also present (*black arrows*). Tumor has grown posteriorly to invade the prevertebral space with involvement of the flexor muscles of the neck (*white arrow*).

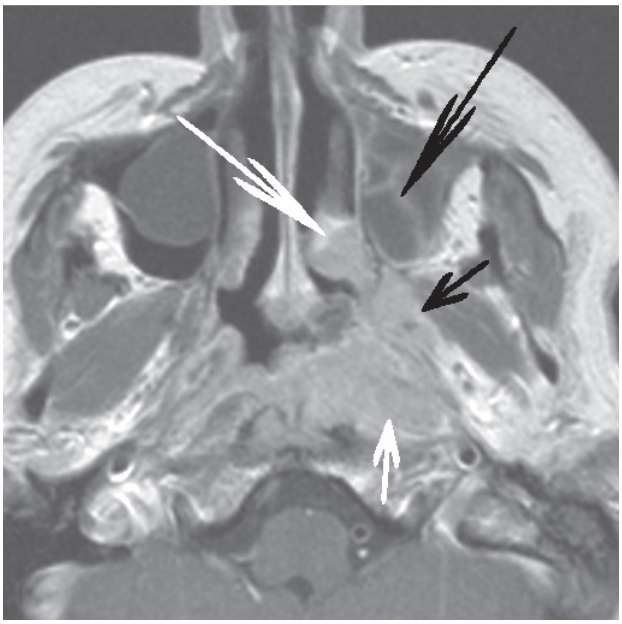


**FIGURE 22-11.** Axial T1-weighted contrast-enhanced MRI shows an infiltrating mass in the left nasopharynx (*short white arrow*) that has spread anteriorly through the posterior choana to invade the nasal cavity. The left superior turbinate is involved with tumor (*long white arrow*). Tumor has spread laterally into the parapharyngeal space (*short black arrow*). Notice the different signal of mucosal disease in the maxillary sinuses where there is reactive mucosal enhancement (*long black arrow*).

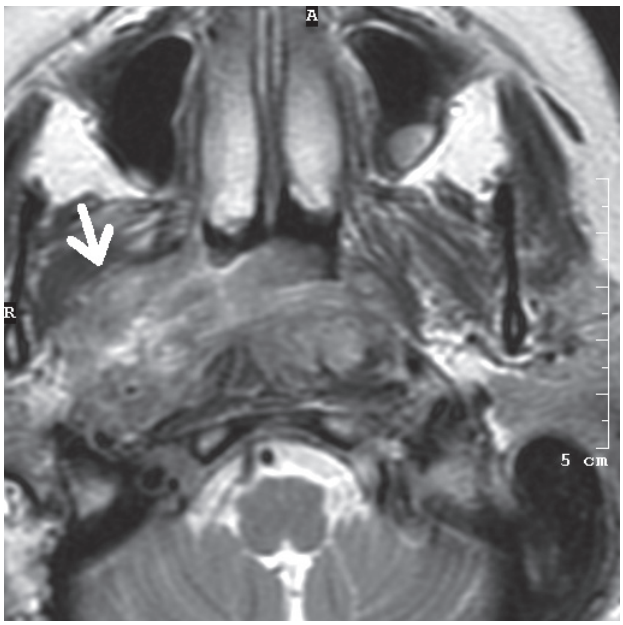



**FIGURE 22-12.** Axial T2-weighted MRI shows lateral spread of a nasopharyngeal mass into the masticator space where the pterygoid muscles have been invaded (*arrow*) resulting in trismus.

sinus is common. Direct extension to the petroclival fissure and region of the foramen lacerum is also common. Tumor can also spread along the tensor veli palatini muscle and the levator veli palatini muscles to encroach on the skull base.

The lymphatic plexus in the nasopharynx is very extensive which is why even small nasopharyngeal tumors often present with extensive lymphadenopathy. The spread pattern is to the lateral retropharyngeal nodes and then inferiorly to level 2 through 5. Bilateral positive lymph nodes are not uncommon.

A recent positron emission tomography (PET)/CT study investigated a measure of the heterogeneity of fluorodeoxyglucose (FDG) uptake in nasopharyngeal cancers and found a correlation with maximum SUV, tumor volume, and T category.[5] The tumors with greater FDG uptake heterogeneity were more aggressive. This may be another quantitative factor along with maximum SUV uptake that might help determine tumor aggressiveness and may help predict patient survival.

Posttreatment follow-up scanning is typically performed with CT or MRI and may require a baseline posttreatment scan performed 3 to 4 months following completion of therapy and subsequent surveillance scans to look for nodular growth suggestive of tumor recurrence. FDG-PET has not had established accuracy in the assessment of recurrence of the primary lesion. This may be because of the normal high FDG uptake in the adjacent brain and poor spatial resolution. A negative PET scan 3 to 4 month after treatment is still very encouraging. FDG-PET is still excellent for the detection of lymphadenopathy (Fig. 22-17) and distant disease.

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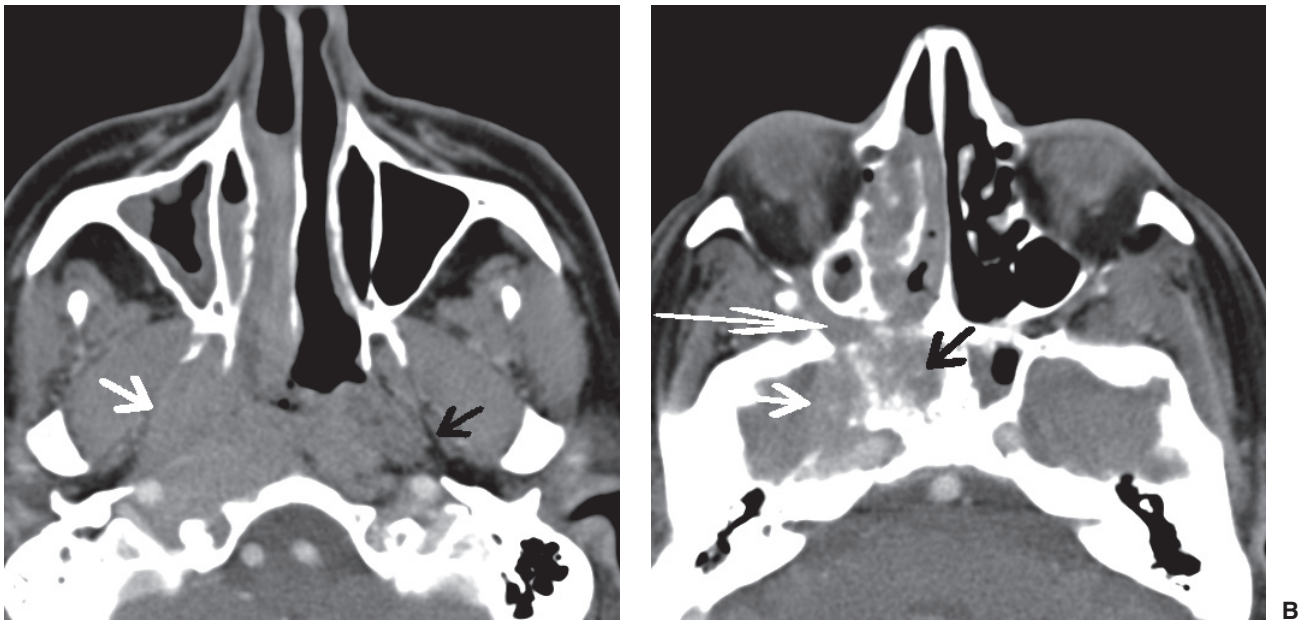


**FIGURE 22-13.** **A:** Axial contrast-enhanced CT scan shows an infiltrating nasopharyngeal mass which has extended into the parapharyngeal space on the right (*white arrow*). The normal fat-filled parapharyngeal space (*black arrow*) is shown for comparison. **B:** Section from the same patient at a more superior level shows direct invasion of the sphenoid sinus (*black arrow*) and middle cranial fossa (*short white arrow*). The mass also extends into the right pterygopalatine fossa (*long white arrow*) and through the superior orbital fissure.

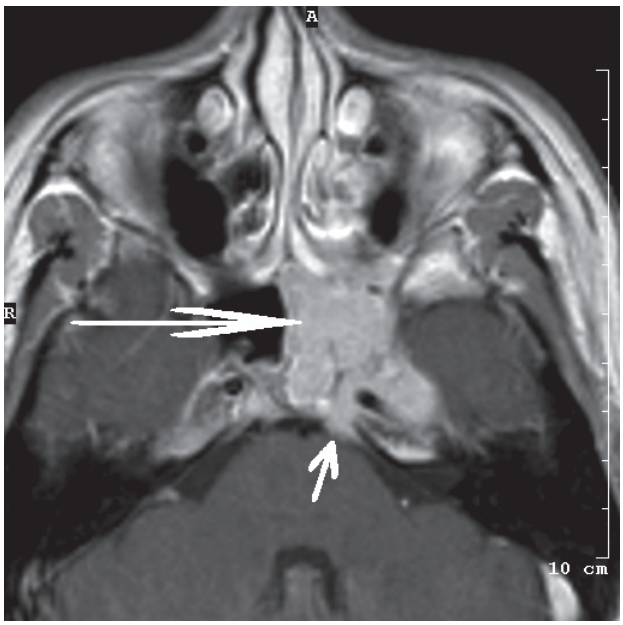



**FIGURE 22-14.** Axial postcontrast T1-weighted MRI shows a left nasopharyngeal squamous cell carcinoma which has invaded the sphenoid sinus (*long white arrow*) and also eroded through the clivus to enter the posterior fossa (*short white arrow*).

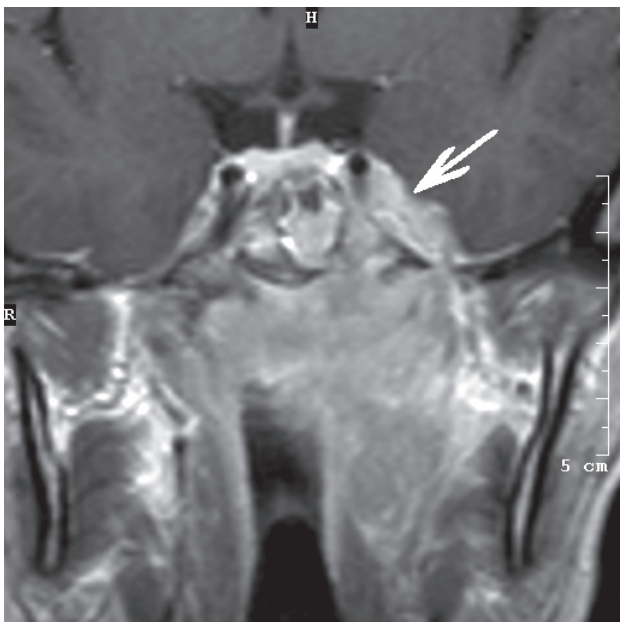
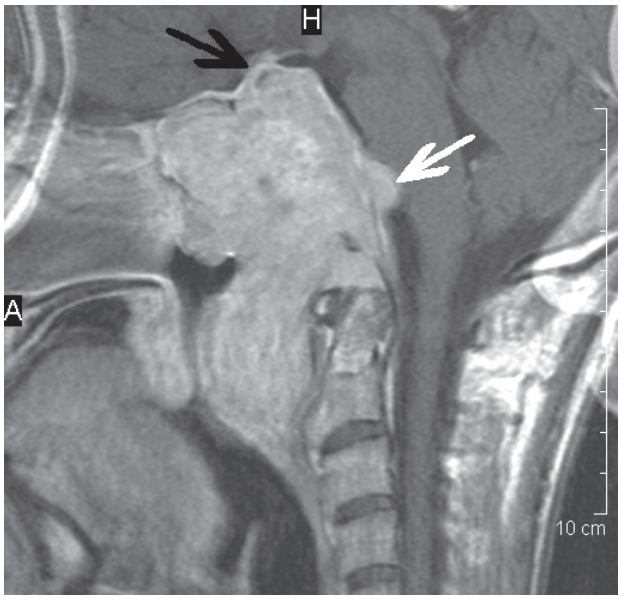



**FIGURE 22-15.** Coronal postcontrast T1-weighted MRI shows an advanced nasopharyngeal cancer that demonstrates perineural spread along V3 to enter the cavernous sinus (*white arrow*).

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**FIGURE 22-16.** Sagittal postcontrast T1-weighted MRI shows a very advanced nasopharyngeal cancer which has completely replaced the clivus to enter the posterior fossa (*white arrow*) and completely replaced the sphenoid sinus to invade the sella and push the pituitary gland superiorly (*black arrow*).



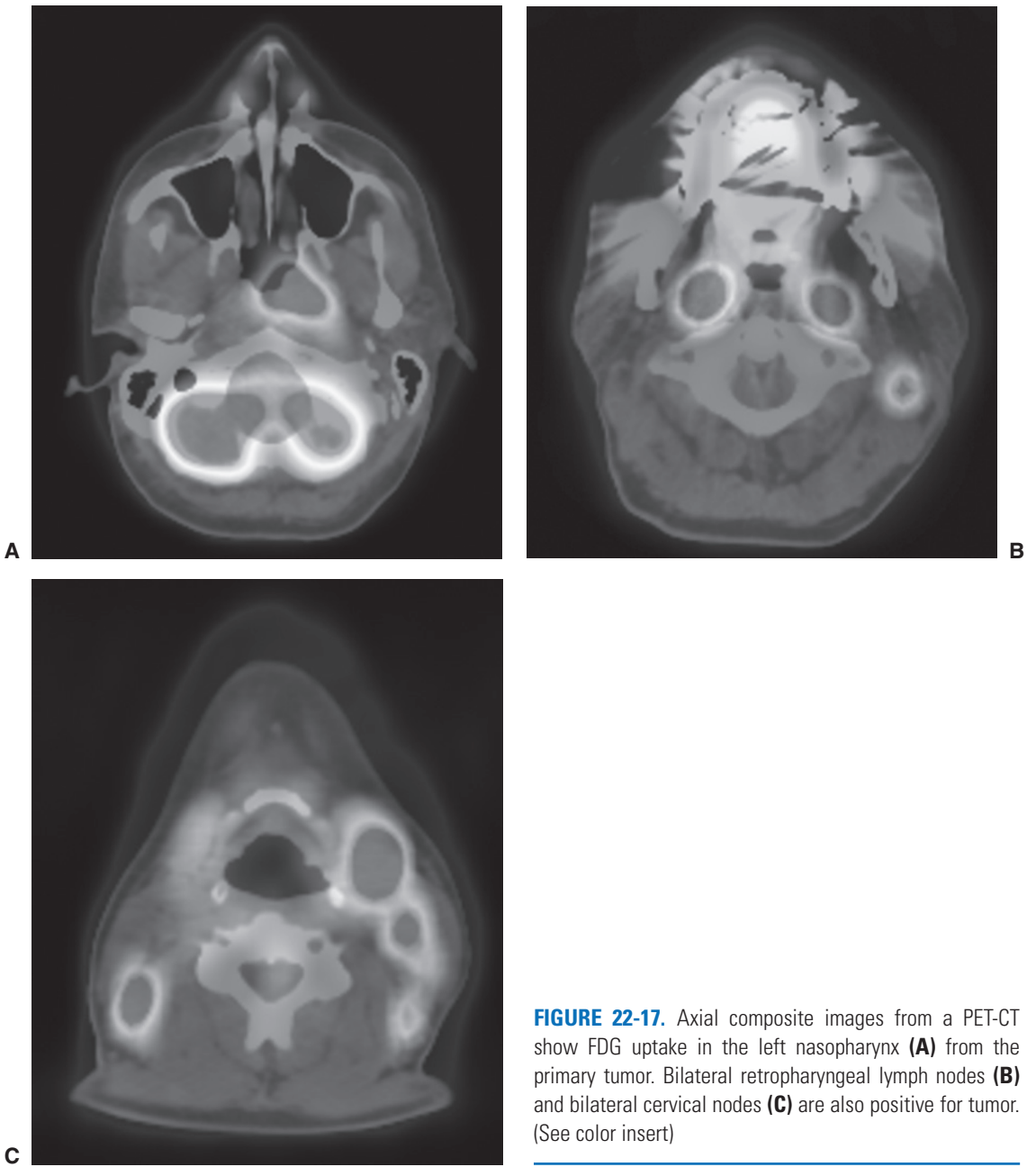




**FIGURE 22-17.** Axial composite images from a PET-CT show FDG uptake in the left nasopharynx **(A)** from the primary tumor. Bilateral retropharyngeal lymph nodes **(B)** and bilateral cervical nodes **(C)** are also positive for tumor. (See color insert)

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# PART C:
# Radiation Therapy Technique

Kenneth S. Hu, Louis B. Harrison, James E. Dolan, and Rudolph Woode

As discussed in the body of Chapter 22, intensity-modulated radiation therapy (IMRT) has been shown to produce extremely high rates of local and regional control. Indeed, in the IMRT era, local failure for nasopharyngeal carcinoma (NPC) has become increasingly uncommon. No doubt, the ability of the radiation oncologist to encompass the entire disease extent, while maintaining protection of the adjacent vital structures, is core to the success achieved with IMRT.

IMRT also allows the opportunity for some dose reduction to the parotid glands. Care must be taken while contouring the neck nodes and the parotids because there can be nodes near the glands. In the authors' experience, although some parotid sparing is usually feasible, it is not as complete as it is for other sites. This may reflect the authors' conservatism in our contouring and treatment delivery. IMRT is very much physician dependent, and the authors recognize that variations in contouring and delivery will occur from one radiation oncologist to another, and from one center to another.

Figure 22-18 shows a clinical example of a patient with NPC treated with IMRT. The authors' technique generally involves seven fields for the primary site and upper neck, matched to a low neck field. Careful contouring of the primary site (including extension to the parapharyngeal space, the skull base, and any intracranial extension), the regional lymphatics (including the retropharyngeal nodes), and nearby vital organs (the optic chiasm, the spinal cord, the brain stem, the parotid glands, and any other organ dictated by the extent of disease) are crucial.

Figures 22-19 through 22-25 show a second patient and some added technical details. This patient is a 34-year-old Asian female who presented with rhinorrhea, epistasix, bussing in the right ear, and headache. Figure 22-19 shows the Positron emission tomography (PET)-computed tomography (CT) with the PET component beside the CT component, for ease in visual display. Disease extends into the oropharynx and involves bilateral retropharyngeal nodes. This patient was treated with IMRT. Figure 22-20 shows isodose display through the superior nasal cavity, at the inferior orbital level. Figure 22-21 shows a CT cut and isodose display at the level of the maxillary sinuses. The skull base, the superior nasal cavity, the maxillary sinus, and the pterygopalatine fossa were included in the intermediate risk CTV and treated to 5,400 cGy in 6 weeks. The temporal lobes and the brain stem are contoured in Figure 22-20 and the right cochlea is seen in Figure 22-21.

Figure 22-22 shows the isodose display through the nasopharynx. The gross tumor volume (GTV) is shown as the inner contour. The planning target volume (PTV) margin was 3 mm expansion on the GTV. An intermediate risk CTV was added to an additional minimum 5-mm margin which included the entire right parapharyngeal space and part of the left parapharyngeal space. Figures 22-23 and 22-24 show isodose displays through the oropharynx and neck. The GTV covers the primary disease extension as well as the involved lymph nodes. The oral cavity is contoured in Figure 22-23B in an effort to spare the minor salivary gland tissue.

Figure 22-24 shows the isodose display through the neck at the level of the larynx. The relative sparing of the larynx and the constrictor muscles is demonstrated, which is a key ingredient to a successful IMRT plan. The GTV is also shown correlating with an involved level 3 node. The brachial plexus is also protected.

Figure 22-25 shows the dose–volume histogram. There is good target coverage and good protection of all appropriate normal structures.

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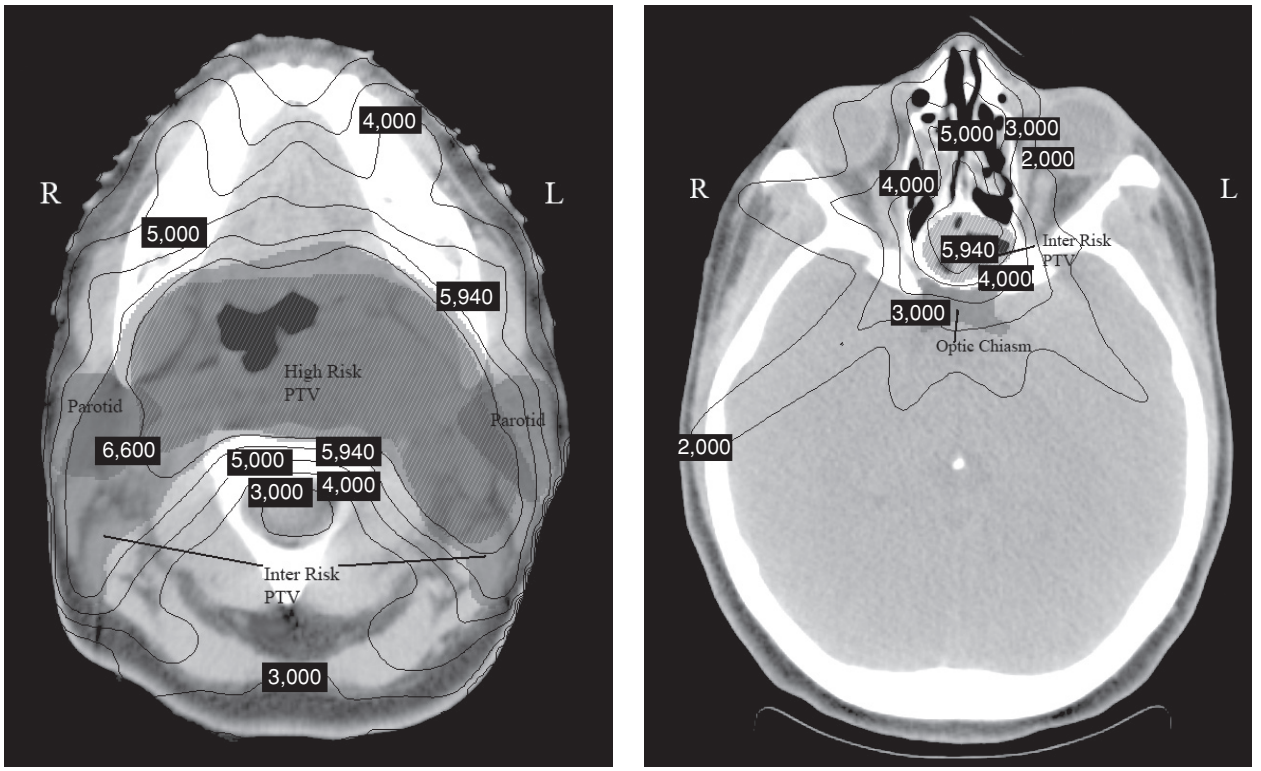
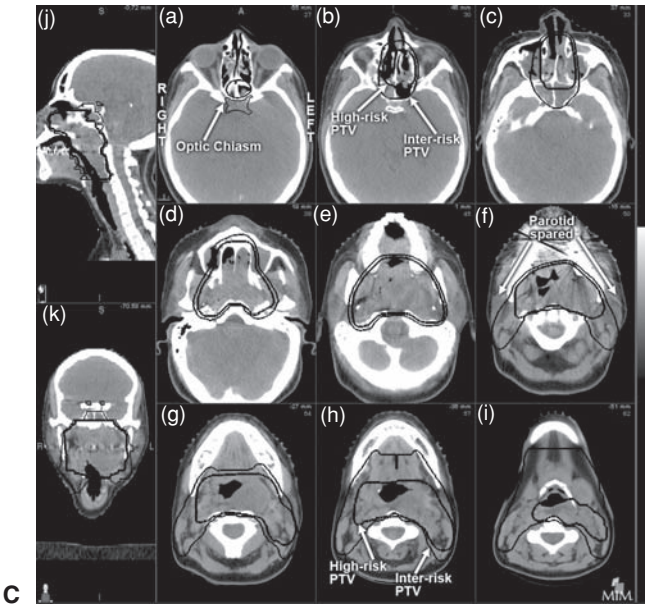


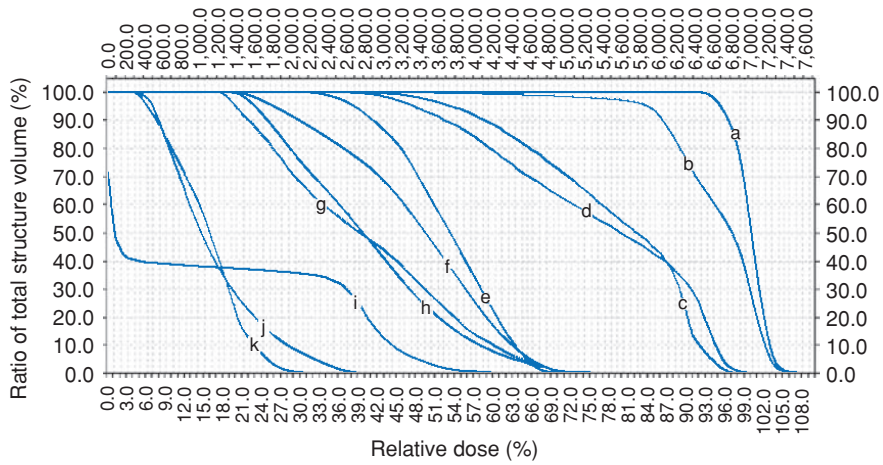

**FIGURE 22-18.** This patient had a T3-N2-M0 American Joint Commission for Cancer (AJCC) stage III squamous cell cancer of the nasopharynx. Positron emission tomography (PET)-computed tomography (CT) revealed the primary tumor mass occupying the nasopharynx with bone erosion through the floor of the sphenoid sinus and with extension into the oropharynx. There was left-sided retropharyngeal adenopathy and bilateral cervical adenopathy at level II. There was no evidence of distant metastases. The treatment plan utilized intensity-modulated radiation therapy (IMRT) with concomitant and adjuvant chemotherapy. The prescription dose to the high-risk PTV (primary site and all known nodal disease) was 6,600 cGy, and the intermediate risk PTV (safety margin around gross disease and adjacent, uninvolved nodal stations) received a minimum of 6,000 cGy. Care to protect the optic chiasm, the brain stem, the spinal cord, the bilateral retinas, and the parotid glands (spared to a lesser extent due to nodal involvement) are demonstrated in the dose–volume histogram. **A:** Isodose distribution displayed on an axial CT used for treatment planning. This shows the high-risk PTV, the interrisk PTV, both parotid glands, and the spinal cord. The high-risk PTV is well covered by the 6,600 cGy isodose, and the interrisk PTV is well covered by the 5,940 cGy isodose. A dose-painting technique was used which delivered 200 cGy/fraction to the high-risk PTV and 180 cGy/fraction was used for the interrisk PTV. Sometimes, the authors do increase the daily dose to the high-risk PTV beyond 200 cGy, but elected not to do so in this case. The patient was 19 years old and the volume was fairly large. **B:** Isodose distribution at a superior aspect of the axial CT used for treatment planning. It shows the sparing of the optic chiasm, which was of great importance to this patient. She made it explicitly clear that she would rather lose her life than her vision. There were secretions in the sphenoid sinus that represent the upper borders of the interrisk PTV. This area was not hypermetabolic on PET-CT. Most of it was encompassed by the 5,940 cGy isodose, although extra caution was taken due to her concerns about vision. **C:** This figure was produced using the Mim-Vista system. It shows representative serial radiation therapy (RT) planning slices as well as representative contours. (a) Contours show the upper limit of the interrisk PTV (extra safety margin around high-risk PTV including nonhypermetabolic secretions in the sphenoid sinus) as well as the optic chiasm. (b) Contours show the interrisk PTV and the superior limit of high-risk PTV. (c) Contours show high-risk and interrisk PTV. The authors' practice is to add additional safety margin around the high-risk PTV and include that in the interrisk PTV. Note that the entire sphenoid sinus is included in the interrisk PTV in this cut. (d) High-risk and interrisk PTV. (e) Same as (d). (f) Same as (c). The uninvolved regional neck nodes are part of the interrisk PTV. There is relative parotid sparing. (g) Same as (f). The involved regional neck nodes are part of the high-risk PTV. The uninvolved nodes are part of the interrisk PTV. (h) Same as (g). (i) Same as (g). This is the inferior cut, at level of the hyoid bone. The low neck is treated with an anteroposterior (AP) low neck field. (j) Midsagittal contour showing high-risk and interrisk PTV. (k) Coronal reconstruction showing high-risk and interrisk PTVs and extreme lateral aspects of the optic chiasm. **D:** Dose–volume histogram.

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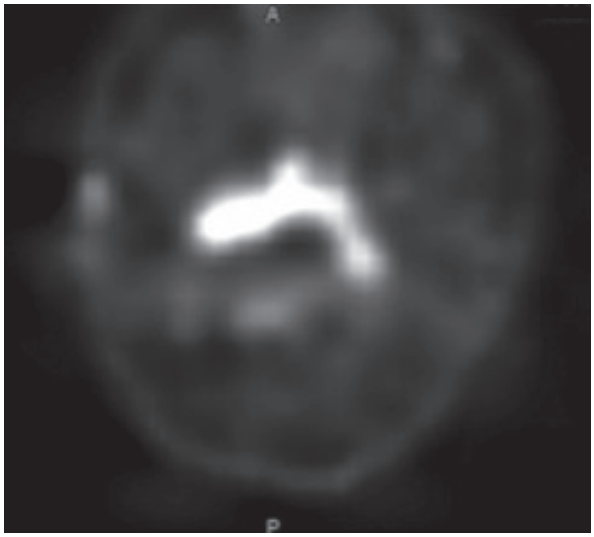
**FIGURE 22-18.** *Continued*



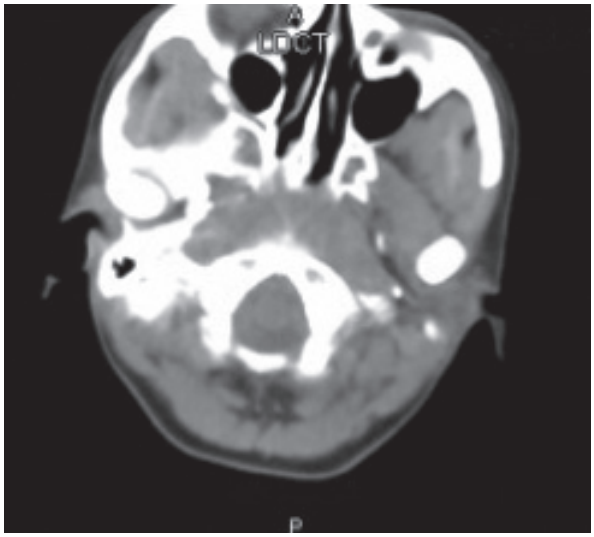

C




D a = High risk PTV; b = Inter risk PTV; c = Right parotid; d = Left parotid; e = Optic chiasm; f = Right optic nerve; g = Brainstem; h = Left optic nerve; i = Spinal cord; j = Right retina; k = Left retina




A

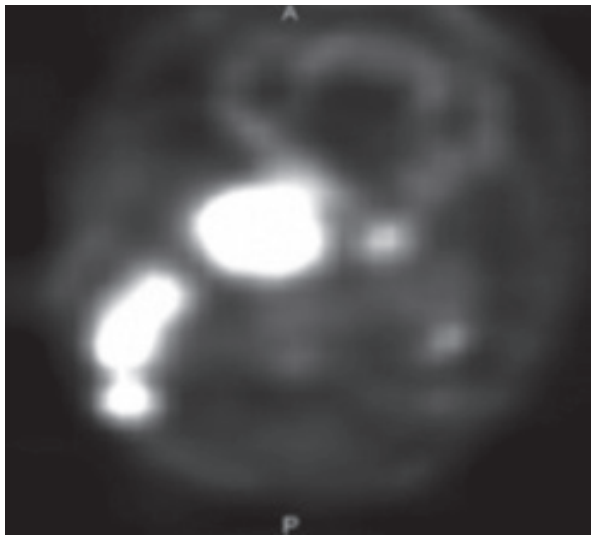



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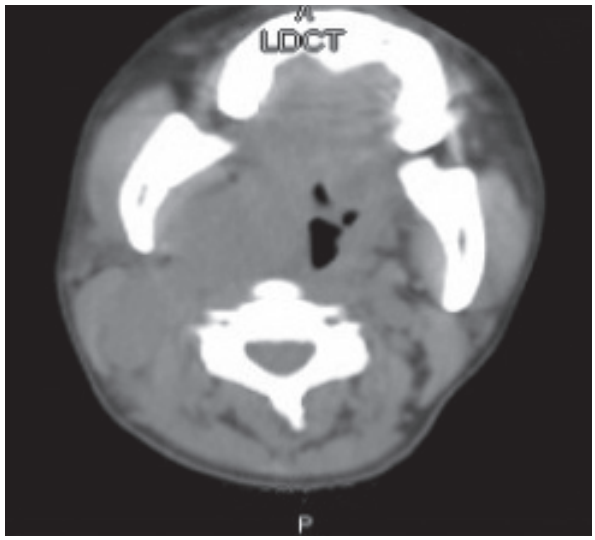
**FIGURE 22-19.** Positron emission tomography (PET)-computed tomography (CT) revealed a hypermetabolic 4.4 cm right nasopharyngeal mass (max SUV 13.8) extending into the oropharynx with bilateral retropharyngeal and level I–III nodes (max SUV 8.6). **A:** PET axial image through nasopharynx. **B:** CT image corresponding to **A**. **C:** PET axial image through lower nasopharynx/oropharynx. **D:** CT image corresponding to **A**.



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C




D

**FIGURE 22-19.** *Continued*

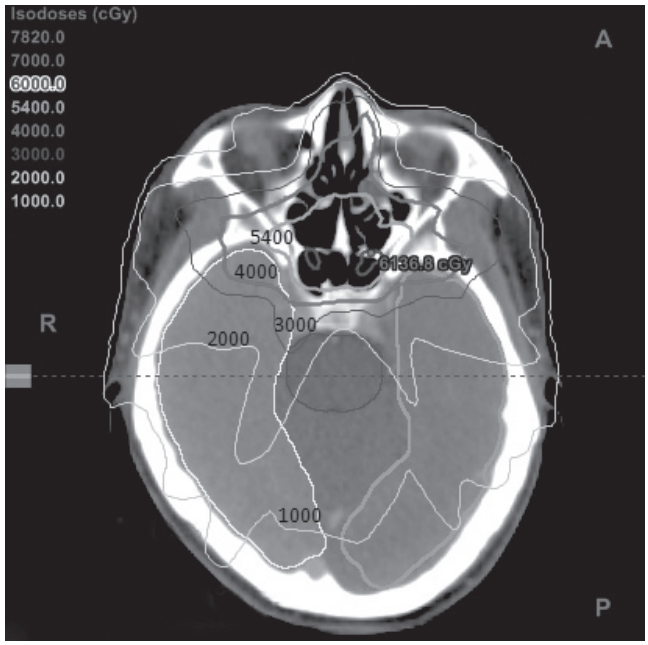



**FIGURE 22-20.** Isodose display through computed tomography slice at level of the superior nasal cavity and the inferior orbit. The temporal lobes, the optic tracts, and the brain stem are contoured. Isodose levels, from inside out, are 5,400, 4,000, 3,000, 2,000, and 1,000 cGy.

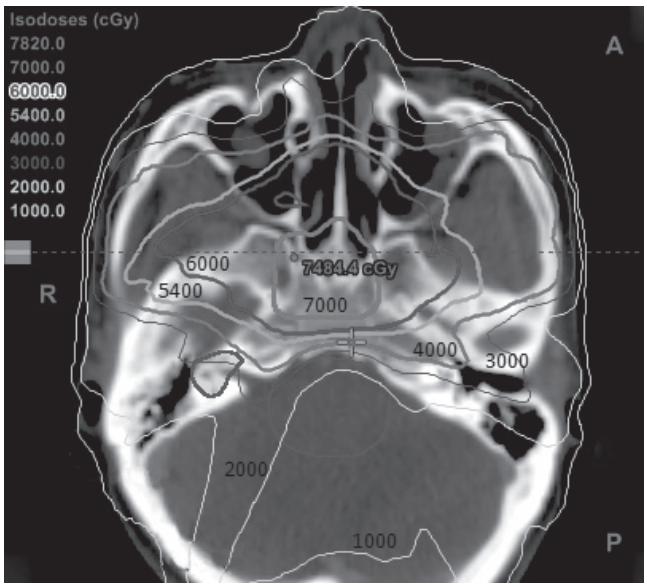
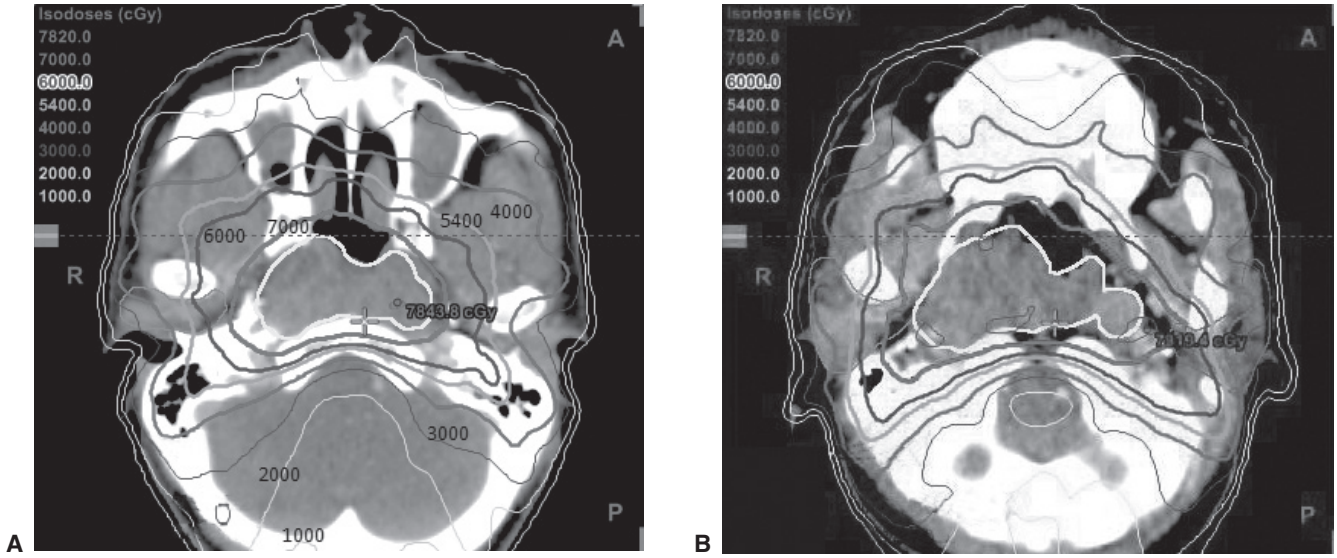


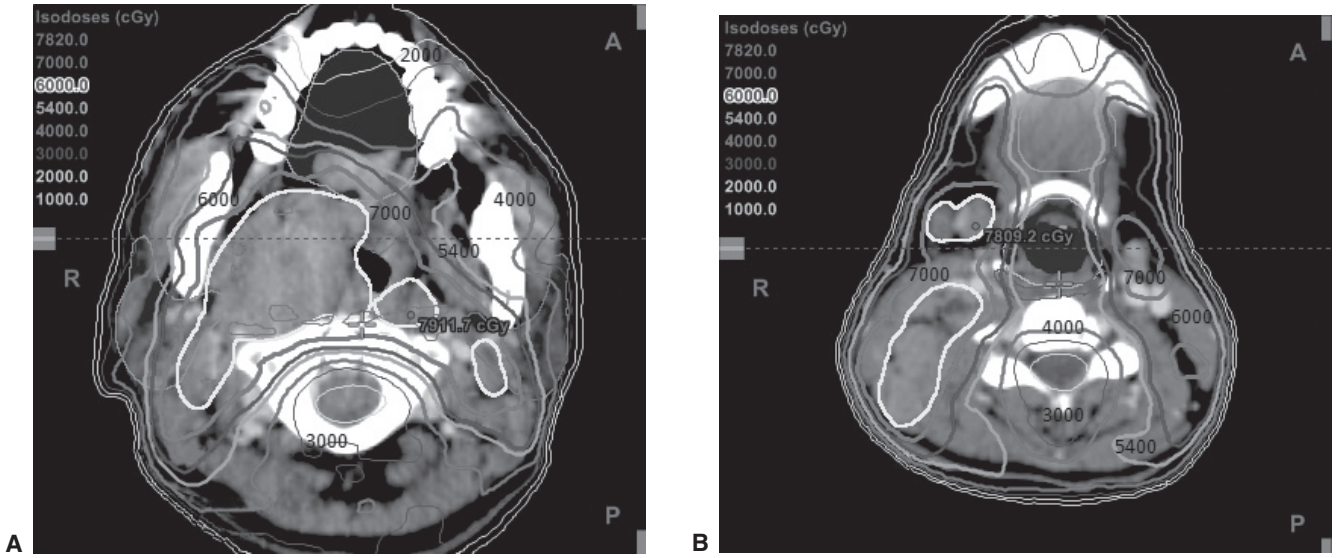

**FIGURE 22-21.** Isodose display through computed tomography slice at level of the maxillary sinus. The right cochlea is contoured. Isodose levels, from inside out, are 7,000, 6,000, 5,400, 4,000, 3,000, 2,000, and 1,000 cGy.

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**A** **B**

**FIGURE 22-22.** Isodose display through the nasopharynx **(A)** and through the superior aspect of the oropharynx **(B)**. The inner contour is the gross tumor volume covering the primary tumor and adjacent retropharyngeal nodes. The next contours, from inside out, are isodose levels 7,000, 6,000, 5,400, 4,000, 3,000, 2,000, and 1,000 cGy. (See color insert)




**A** **B**

**FIGURE 22-23.** Isodose display through oropharynx **(A)** and neck **(B)**. The gross tumor volume covers the primary tumor extension and the involved lymph nodes. The isodose contours, from inside out, are 7,000, 6,000, 5,400, 4,000, 3,000, 2,000, and 1,000 cGy. The oral cavity is outlined on **(B)** so it can be relatively spared, in an effort to protect the minor salivary glands. (See color insert)

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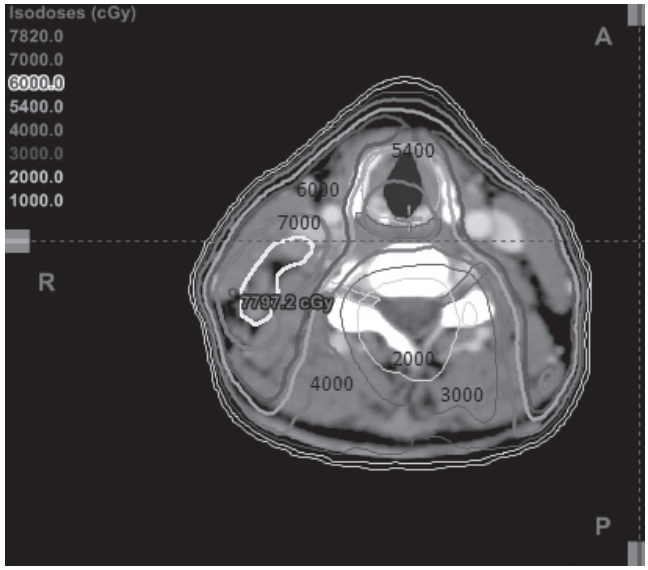



**FIGURE 22-24.** The larynx, the constrictor muscles, and the brachial plexus were outlined given the level III nodal involvement. The gross tumor volume (GTV) corresponds to a right level III node. The isodose display demonstrates good GTV coverage while respecting the brachial plexus, the larynx, and the constrictor muscles.

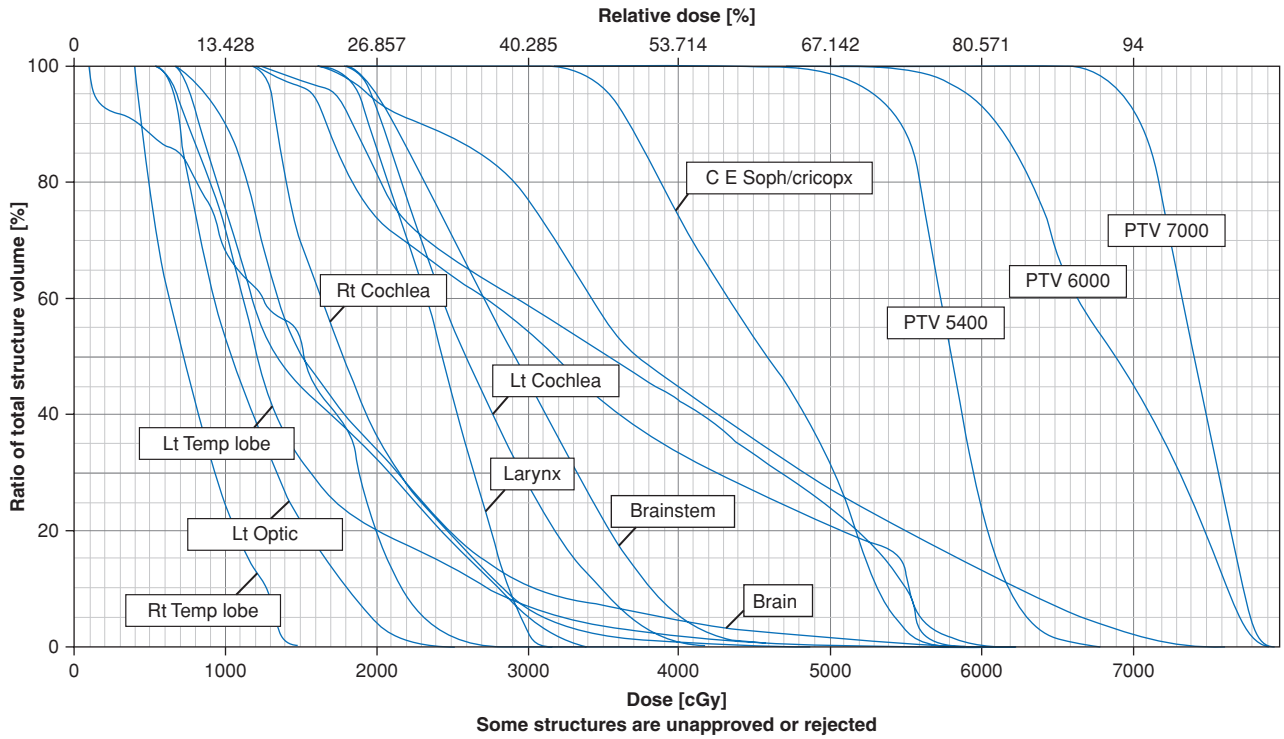



**FIGURE 22-25.** Dose–volume histogram showing the planning target volumes and organ at risk. The dose constraints to the optic tracts, the cochlea, the brain stem, the spinal cord, the oral cavity, the brachial plexus, and the inferior constrictor/cervical esophagus were achieved. The mean dose to the larynx of 44 Gy was accepted with a dose objective of 40 Gy. The objectives to the mean dose of the parotids were not achieved given the bulk of nodal disease.

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# PART D:
# Surgical Technique

William Ignace Wei and Jimmy Yue Wai Chan

## INTRODUCTION

The primary treatment modality for cancer of the nasopharynx is radiotherapy for early-stage diseases and concomitant chemotherapy and radiation for advanced-stage diseases. Surgical resection of cancer of the nasopharynx is only applicable when the cancer persists or recurs after the initial treatment.[1] For a group of 246 patients who underwent salvage nasopharyngectomy with a median follow-up of 38 months, the 5-year actuarial control of disease was 74% and the 5-year disease-free survival was 56%. Tumor size of <1.5 cm and negative resection margins were the two independent factors that affected the local tumor control and survival.[1]

The nasopharynx is located at the central skull base that anatomically is in the centre of the head and it is >10 cm from the skin surface from all directions. It is difficult to expose this region adequately for surgical resection of the tumor comfortably; this is particularly so when the lesion is malignant and has potential to infiltrate nearby structures.

Currently, there are two surgical techniques commonly employed for the resection of cancer of the nasopharynx.

1. Maxillary swing approach to expose the nasopharynx and the central skull base so that the malignant tumor in the region can be resected with adequate margin.[2]
2. The palate was split to expose the cancer in the nasopharynx and the tumor resection was carried out with the Da Vinci Robot.[3]

The maxillary swing approach originated from the observation that during maxillectomy for carcinoma of the maxillary antrum, the nasopharynx was widely exposed when the maxilla bone was removed. The anterolateral approach to the nasopharynx was thus developed; the maxillary antrum including the lateral walls and the floor attached to the anterior cheek flap could be swung laterally as an osteocutaneous flap to expose the pathology in the nasopharynx. After removal of the pathology, the maxillary antrum was returned to its original position and fixed to the rest of the facial skeleton (Fig. 22-26).

The surgical approach involves a Weber Ferguson facial incision as in maxillectomy, incision on the palate, osteotomies of the anterior wall, medial wall of the maxillary antrum, and lower portion of the zygomatic arch. The pterygoid plates are also separated from the maxillary tuberosity. This anterolateral approach exposed the nasopharynx and its vicinity from the side of the swing. With the removal of the posterior part of the nasal septum, the contralateral nasopharynx can be exposed. Persistent or recurrent cancer of the nasopharynx after chemoradiation can be removed adequately, and if there are paranasopharyngeal lymph nodes, these can be resected under direct vision. With the wide exposure of the nasopharynx and its vicinity following the maxillary swing approach, the internal carotid artery lying in the paranasopharyngeal space could be identified with palpation and vision, thus avoiding its injury during tumor extirpation; this is particularly important during the dissection of the paranasopharyngeal lymph node.[4] A microvascular free flap could also be employed to cover the exposed vessel and the raw area following removal of tumor in the nasopharynx. With this additional new vascular supply, further adjuvant therapy could then be considered.[5]

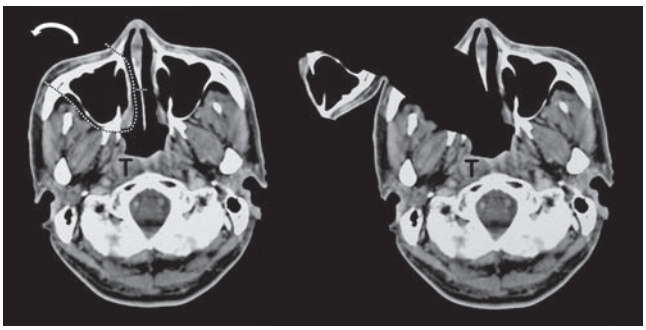



**FIGURE 22-26.** Schematic computed tomography. **Left:** Dotted line marks the osteotomy, the posterior part of the nasopharynx is removed to increase the exposure of the contralateral nasopharynx. **Right:** The maxillary antrum attached to the anterior cheek flap is swung laterally as one osteocutaneous complex, exposing the nasopharynx and a small tumor (T).

The morbidity associated with the operation was acceptable. The facial scar usually heals well and becomes less obvious with time. The development of significant trismus in patients who had previous radiation could be managed with passive mechanical stretching and this frequently improves the trismus. With the resection of the Eustachian tube, the patient develops serous otitis media on the side of the swing and this results in deterioration of hearing acuity.

The Da Vinci Robot have been reported for the resection of recurrent nasopharyngeal carcinoma. With the splitting of the palate, the tumor in the nasopharynx is exposed. It is, however, difficult to employ the ordinary instruments to resect the tumor en bloc with a good resection margin. With the versatility of the endowrist of the Da Vinci Robot and the 3D camera, adequate resection is possible with splitting of the palate. The location and the size of the tumor are determinants for a successful resection. Those tumor of around 1 cm diameter, not deeply infiltrative and located in posterior wall, not extending laterally beyond the floor of pharyngeal recess, have a better chance of being resected completely with the robot. The morbidities associated with this split palate approach are limited, patient might develop palatal fistula as the patient had previous radiation with or without chemotherapy. Exposure of the raw area in the nasopharynx following resection might lead to the development of osteoradionecrosis of the skull base bone.

## PREOPERATIVE PREPARATION AND ANAESTHESIA

For patients undergoing the resection of persistent or recurrent cancer in the nasopharynx, full cardiopulmonary assessment is essential to evaluate whether he or she can stand the procedure

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as the blood loss might occasionally be significant, especially with the maxillary swing procedure. The interalveolar distance should be at least 3 cm wide as otherwise it is difficult to raise the palatal flap transorally and to insert the curved osteotome to separate the pterygoid plates from maxillary tuberosity. A significant degree of trismus will also prevent the insertion of the robotic arm transorally for tumor resection. The interalveolar distance also prompts the anaesthetist to consider the appropriate route to insert the endotracheal tube. An upper alveolar dental plate is fabricated for each patient before the maxillary swing procedure; this is used to clip onto the teeth on the upper jaw upon return of the swung maxilla, ensuring correct repositioning and precise dental alignment.

Preoperative evaluation of the extent of persistent or recurrent cancer of the nasopharynx is mandatory before surgical resection. In addition to a full clinical examination, an endoscopic examination of the nasal cavities, the nasopharynx, and the oropharynx together with a cross-sectional imaging study such as computed tomography or magnetic resonance imaging is required to determine the extent of the cancer in the nasopharynx. Magnetic resonance imaging with contrast evaluates the proximity of the tumor to the internal carotid artery and possible involvement of soft tissue in the regions, such as the paranasopharyngeal lymph nodes. Computed tomography with bone window should be carried out to see whether the clivus or skull base bone is affected. For more extensive tumor in the nasopharynx or patients with both recurrent tumor in the nasopharynx and cervical lymph nodes, a positron emission tomography is indicated to rule out distant metastasis.

## SURGICAL TECHNIQUE

### Maxillary Swing Procedure

The operation is carried out under general anesthesia with the patient in supine position. The head is placed on a soft head ring to allow mobility and there is no need for any support behind the shoulders to extend the neck, unless a neck dissection or neck exploration is also planned. Endotracheal intubation is carried out through the mouth if possible as this avoids disturbance of pathologies in the nasopharynx. A temporary tracheostomy is then carried out and the endotracheal tube is withdrawn. The tracheostomy is optional as the procedure can be carried out with the transoral endotracheal tube in position. The presence of the tube, however, interferes to a certain extent the raising of the palatal flap and the osteotomy of the hard palate.

At the completion of the operation, the nose and the nasopharynx is usually packed with ribbon gauz and the discharge from the raw surface and the oropharynx might lead to partial airway obstruction. A temporary tracheostomy aids to maintain the airway. If this is not done following the endotracheal intubation at the start of the operation, it is usually carried out at the completion of the procedure. Endoscopic examination to confirm extent of the persistent or recurrent tumor in the nasopharynx was carried out before starting the operation.

Protective eye ointment is used in the contralateral eye, which is drafted off the operative field. The oral cavity and the nasal cavities are irrigated with copious amount of antiseptic solution such as chlorohexidine. Preoperative intravenous antibiotics are given, which usually include a metronidazole for anaerobic bacteria and a cephalosporin for aerobic bacteria.

The Weber Ferguson facial incision is used as, for maxillectomy, the horizontal limb of the incision is placed at about 5 mm below and parallel to the lower eyelid margin. The incision over the lip is designed to be zigzag to prevent postoperative contracture (Fig. 22-27) and the horizontal limb curves down laterally along the skin crease to stop at about 0.5 cm above the lower edge of the zygomatic arch. Tarsorraphy is done for the eye on the side of the swing to avoid inadvertent trauma to the cornea.



**FIGURE 22-27.** The facial incision is marked, with the incision over the lip in zigzag form.

The lip incision on the lingual surface continues to extend posteriorly to stop between the two central incisors. The palatal wound is a curved incision placed at a distance of 0.5 mm from the teeth margin, and it is continued posteriorly until the last molar tooth and then continued laterally behind it to stop just before reaching the buccal mucosa (Fig. 22-28). This allows the elevation of soft tissue and mucoperiosteum over the hard palate as a palatal flap with blood supply from the opposite mucosperiosteum of the hard palate and the soft palate.[6]

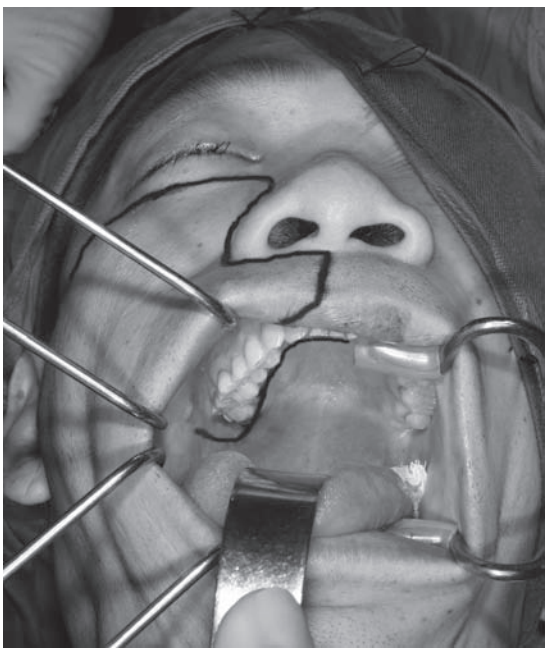


**FIGURE 22-28.** The palatal incision is marked, goes along the lingual aspect of the upper alveolar margin, and curves laterally behind the last molar tooth.

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The skin incision over the face goes through the skin, the subcutaneous tissue, and also the orbicularis oris muscle. The thin muscle is lifted together with the facial skin until the orbital rim is reached. The orbital septum should not be cut, or else the periorbial fat will be herniated into the wound. Although it is not harmful to the patient, it could be a nuisance during the elevation of the facial flap. The skin incision over the lip is continued and the orbicularis orris muscle is divided in the line of skin incision.

The horizontal limb of the facial incision goes down to the anterior wall of the maxilla, and limited amount of soft tissue over the anterior wall of the maxilla is elevated to expose a strip of bone for osteotomy. This osteotomy site is 0.5 cm below the orbital rim and frequently goes through the infraorbital foramen. The infraorbital nerve and the vessels are identified and divided. This reduces blood loss when the oscillating saw cuts through the infraorbital foramen. This osteotomy divides only the lower half of the zygoma (Fig. 22-29).

In preparation of the midline osteotomy, soft tissue and mucoperiosteum over the hard plate have to be lifted off the bony hard palate. The palatal incision goes down to hard palate bone, and the soft tissue together with the mucoperiosteum is lifted with a sharp periosteal elevator. The greater palatine vessels coming through the palatine foramen are seen. These should be divided and the palatal flap can then be raised further medially across the midline and posterior to the posterior edge of the hard palate. The attachment of the soft palate on the hard palate is divided with diathermy and the nasal cavity is entered.

A cured osteotome is inserted into the groove between the maxillary tuberosity and the pterygoid plates. The groove lies behind the hamulus which is lying posteromedial to the molar tooth. The osteotome has to be curved so that when it is placed in the groove and driven by the mallet, hitting on its head, it goes vertically upward separating the posterior wall of the maxillary antrum from the pterygoid plates (Fig. 22-30).

Before the start of the osteotomy, a four-hole titanium plate is placed across the osteotomy line on the anterior wall of the maxilla. Holes are drilled and screws are inserted and then removed. These preosteotomy-drilled holes will ensure accurate position of the maxilla bone when it is returned to its original site after tumor resection and fixed with the plate and the screws. The osteotomy over the anterior wall is carried out by an oscillating saw with a thin, long blade. The anterior wall of the maxilla is cut and this osteotomy extends laterally horizontally until the middle portion of the zygomatic arch and then turned downward. Only the lower part of the zygomatic arch is divided and thus, after completion of the osteotomy, the inferior orbital rim remains attached to the zygoma.

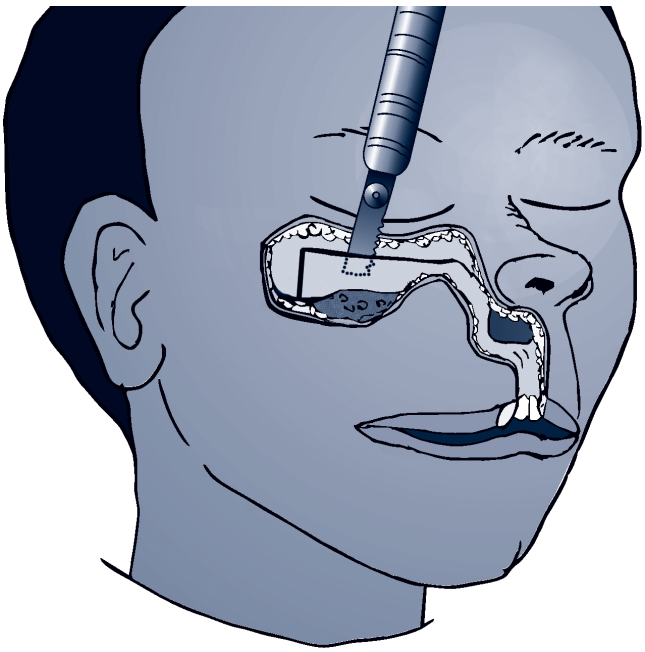


**FIGURE 22-29.** The horizontal osteotomy is shown to go through the anterior wall of the maxilla.

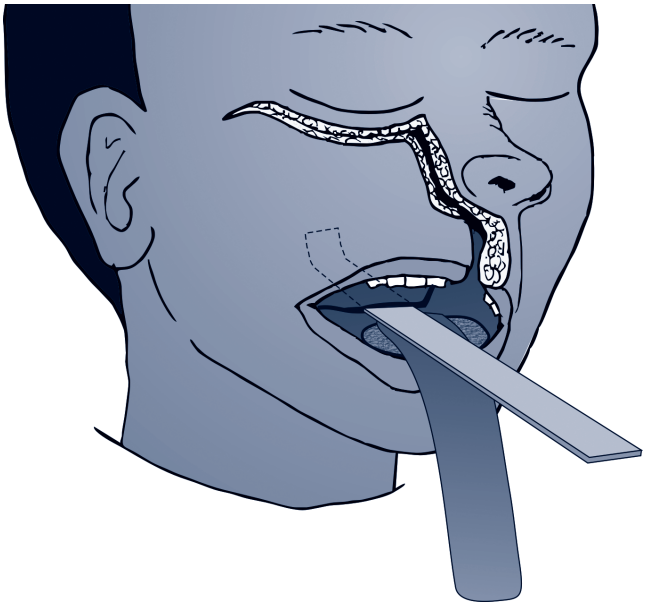


**FIGURE 22-30.** A curvedosteotome is inserted behind the maxillary tuberosity to separate it from the posterior wall of the maxillary antrum from the pterygoid plates.

The soft tissue over the midline is elevated to expose the underlying bone, in preparation for a midline osteotomy. Sometimes, the patient may have a high nasal spine, and this can be removed with a burr or a rongeur creating a flat bone surface where the titanium plate is placed. Holes are drilled and screws are inserted and removed similar to the procedure applied on the anterior wall of the maxilla.

An oscillating saw divides the hard palate from anterior to posterior in a straight line. The lifted palatal flap is retracted from the path of the osteotomy and protected. This osteotomy cuts through the entire length of the hard palate and lower part of the nasal septum if there is septal deviation. The blood loss is minimal with this osteotomy, and so it is carried out as the first osteotomy. Then the osteotomy of the anterior wall of the maxilla is carried out with the long, thin blade. The blade goes through the antrum and divides the lateral wall on its way until it reaches and cuts the posterior wall. The last osteotomy goes through the medial wall of the antrum. This is placed above the inferior turbinate and below the middle turbinate.

After the completion of the osteotomies, the maxilla bone drops down, but remain attached to the anterior cheek flap (Fig. 22-31). The whole osteocutaneous complex is retracted laterally to expose the nasopharynx and the paranasopharyngeal space (Fig. 22-32). With this exposure, persistent or recurrent cancer in the nasopharynx and the paranasopharyngeal lymph nodes can be removed together with the Eustachian tube under direct vision.

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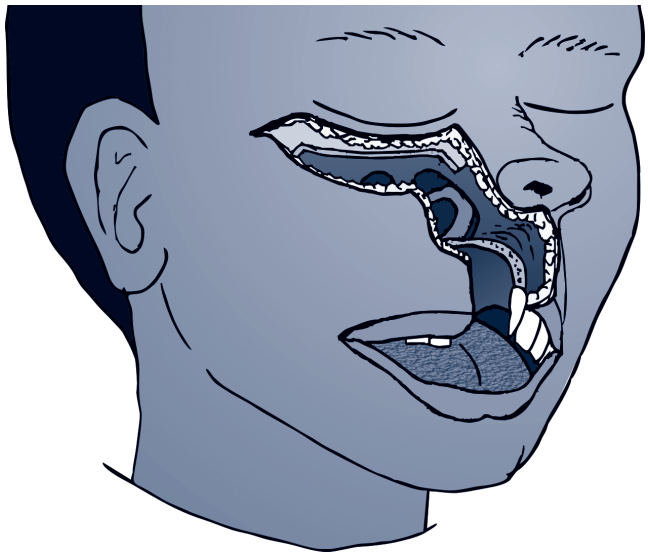


**FIGURE 22-31.** After completion of the osteotomies, the maxilla drops down but remains attached to the anterior cheek flap.

With the osteocutaneous complex including the maxilla swung laterally, the tumor in the nasopharynx with its surrounding tissue is adequately exposed and can be removed with conventional surgical instruments such as scissors, diathermy, and the like. The pterygoid plates together with the pterygoid muscle can be removed to improve exposure of the paranasopharyngeal space on the side of the swing, and any pathologic lymph nodes if present in the region can be removed under direct vision. The internal carotid artery lying outside the pharyngobasilar fascia is situated posteriorly or posterolaterally to the paranasopharyngeal lymph node. Sometimes, it could be adherent to the lymph node following radiotherapy. With this wide exposure, the carotid artery can be located with palpation of its pulsation and thus safeguarded during resection of the paranasopharyngeal lymph node.

When the pharyngobasilar fascia has to be resected with the tumor or the paranasopharyngeal lymph node, the petrosal part of the internal carotid artery will be exposed. This can be covered with a microvascular free muscle flap to prevent subsequent carotid artery rupture.

The frequently employed free muscle transfer are the rectus abdominis or the vastus lateralis muscle of the anterolateral thigh. The pedicle is delivered through a tunnel made above the oropharynx to the upper neck. The artery of the flap is joined to the facial or the superior thyroid artery and the venous return is anastomosed to a tributary of the internal jugular vein. The transferred muscle is covered by mucous membrane within a short period, and this avoids the crusting when skin is used to cover the wound in the nasopharynx.

Increased exposure of the contralateral nasopharynx is achieved following the removal of the posterior part of the nasal septum. Lesion that has extended across the midline can be resected up to the medial edge of the Eustachian tube of the opposite side. Following this wide exposure, en bloc resection of the nasopharyngeal carcinoma can be carried out and the resection includes the Eustachian tube crura. The inferior turbinate on the side of the swing is removed and the mucosa covering it is taken off. This mucosal sheet is laid onto the raw area in the nasopharynx as a free mucosal graft. This graft frequently survives and this facilitates healing; even if it does not survive, it acts as a temporary dressing for the wound in the nasopharynx.

After tumor extirpation and covering the raw area over the nasopharynx, the maxilla is returned to its original position. A few holes are drilled on the posterior edge of the hard palate, and sutures passing through these holes attach the soft palate to the hard palate. A hole is drilled on the base of the nasal bone, and a corresponding hole is drilled on the superomedial part of the anterior wall of the maxilla. A size 26 wire is passed through these holes. The intraoral placement of the prefabricated dental plate ensures accurate repositioning of the maxilla.

While the maxilla is maintained in position with the hand, the two titanium plates are placed over the zygoma and the midline where screw holes was predrilled, and the screws are inserted (Fig. 22-33). The wire on the superomedial angle of the anterior wall of the maxilla is also tightened to give additional support.

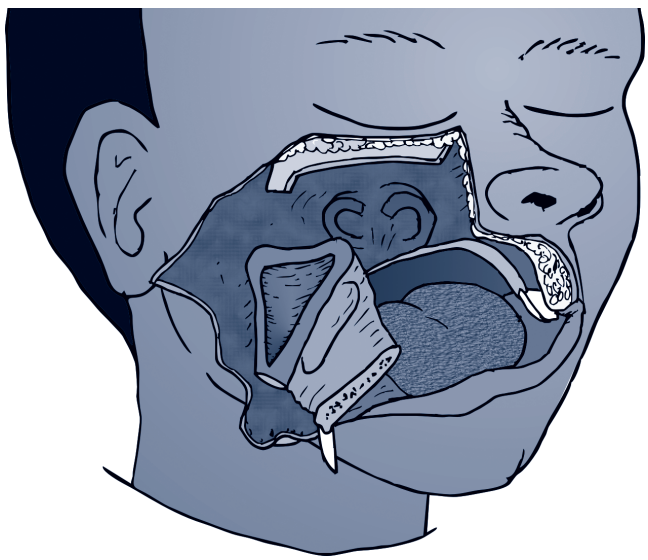


**FIGURE 22-32.** The osteocutaneous complex is swung laterally to expose the nasopharynx and its vicinity.

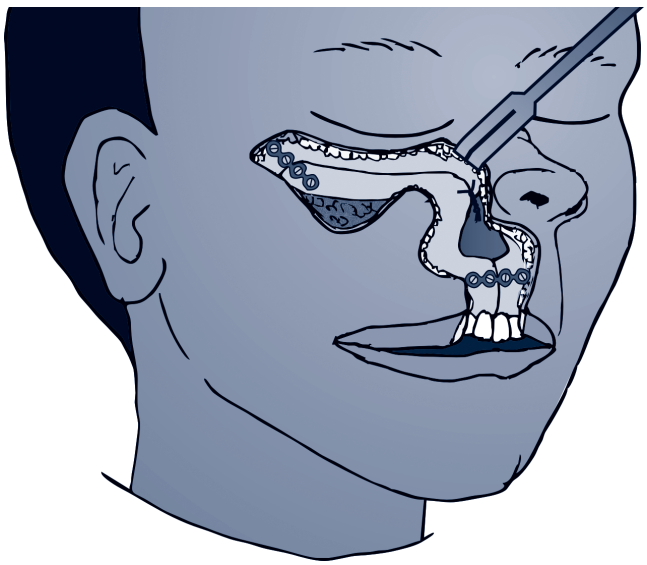


**FIGURE 22-33.** The maxilla is returned to its original position and fixed to the facial skeleton with two titanium plates.

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The dental plate is then removed and the palatal flap is returned. Two to three sutures are used to fix the posterior part of the flap to the alveolar margin, and the dental plate is reinserted to keep the palatal flap in position. This dental plate is normally removed on the third day after operation. Nasal cavity is packed with antiseptic ribbon gauz, and the facial wound is closed in layers.

## Nasopharyngectomy with the Da Vinci Robot

When robotics is used for transoral resection of pathologies in the oropharynx, the robot is docked from the caudal aspect of the patient. When employed for resection of tumor in the nasopharynx, the robot is docked from the cephalic direction.

The operation is carried out under general anesthesia with the patient in supine position, and ventilation is maintained with a nonkinking endotracheal tube, which is preferably placed over the central lower lip. A Dingman mouth gag is inserted and maintained in position with a pneumatic holding device (Aesculap AG, Tuttlingen, Germany). The soft palate is split in the midline with the incision placed at the base of the uvula. The incision extends onto the mucoperiosteum over the hard palate. The split soft palate and the mucoperiosteum of the hard palate are retracted with stay sutures to expose the nasopharynx with the lesion. The Da Vinci surgical robot, model S (Intuitive Surgical Inc., Sunnyvale, California) is docked from the cephalic aspect of the operating table and the 12-mm dual-channel endoscope is introduced transorally. This allowed good visualization of the lesion in the nasopharynx including both fossae of Rosenmüller.

The Maryland forceps, 5 mm in diameter, is mounted to the left robotic arm and a spatula dissector of scissors with monopolar diathermy is mounted to the right robotic arm. The incision around the tumor is performed with the diathermy, and this incision goes through mucosa and prevertebral muscle. The crura of the Eustachian tube cushion should be included in the resection together with the tumor. The tumor and its surrounding tissue are then lifted with the Maryland forceps while the diathermy cuts and cauterizes the tissue deep to the undersurface of the tumor. The pathology with a margin of soft tissue is removed en bloc. The internal carotid artery is not exposed or seen during dissection.

When the sphenoid sinus has to be entered to increase the resection margin, this can be done with power instruments under endoscopic guidance before docking the robot.[7]

Following resection of the tumor, the defect in the nasopharynx becomes a slanting trough; the deepest part is bone followed by the prevertebral muscle, the submucosa, and then the mucosa of the nasopharynx. A free mucosal graft is taken from the posterior oropharyngeal wall to be placed over raw area in the nasopharynx as a free graft. This is secured with the balloon of a urinary catheter as posterior nasal packing. The palatal wound is closed in layers, and a nasogastric tube is inserted for feeding.

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CHAPTER 23

# Basal and Squamous Cell Skin Cancers

## PART A: General Principles and Management

Louis B. Harrison, Par S. Mehta, Matthew Halpern, and Desiree Ratner

Nonmelanoma skin cancers (NMSCs) are the most frequently occurring cancers in the United States, with basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs) being the most common histologies. More than 1 million cases are expected annually in the United States, and the incidence has been rising rapidly over the last decade.[1] The head and neck are the most common sites of presentation, accounting for >80% of all basal and SCCs.[2] These lesions are typically slow growing and infrequently metastasize. If neglected, they can cause significant local destruction and invade critical structures. These lesions can cause significant morbidity, especially cosmetic deformity. Metastasis can occur and can be life threatening. Treatment of these cancers is important, and multidisciplinary considerations are essential.

## EPIDEMIOLOGY

### Basal Cell Carcinoma

BCCs are thought to originate from pluripotent cells in the basal layer of the epidermis. Although formal statistics are not maintained for the incidence of BCCs of the skin, the American Cancer Society estimates 800,000 to 900,000 BCCs in the United States per year,[1] equating to 300 to 350 per 100,000 patient years. The incidence is significantly higher with increased age and is much greater in Whites than in African Americans. Men are also more likely to develop BCCs than are women. The incidence of BCC has also increased approximately 100% in the last decade, but still account for <1% of cancer deaths.[3] Whites in the United States have a 30% lifetime risk of developing a BCC, and those previously diagnosed with a BCC have a 35% to 50% chance of developing a second tumor over a 5-year period. BCCs are typically present over sun-exposed areas of the skin, accounting for the increased incidence in the head and neck. Geographic location also plays a significant role, with the highest incidence worldwide in Australia.

### Squamous Cell Carcinoma

Cutaneous SCC is a malignant tumor of epithelial keratinocytes and represents the second most common form of skin cancer. This neoplasm was first described in the literature in 1775 by Sir Percival Pott, who noted the relationship between scrotal carcinoma and exposure to chimney soot. Although most of the cases are easily treated with a high cure rate, a subset of tumors will behave more aggressively and recur or metastasize, resulting in most NMSC mortalities in the United States.[4]

The precise incidence of SCC is difficult to ascertain because the National Cancer Institute only collects data on tumors of the genitalia. Epidemiologic studies suggest, however, that in the United States, the rate approaches 100 to 150 cases per 100,000 persons per year. The age-specific incidence among persons older than 75 years is increased by a factor of 10.[4–8] In addition, it appears that this rate has increased by 50% to 200% over the last 10 to 30 years.[4–6,8–10] Geographic variations in sun exposure also contribute to differences in regional incidence data, with rates in Arizona of approximately three to six times those reported in more northern areas.[11] Similarly, in Australia, incidence rates are significantly elevated relative to the United States, with 1% to 2% reported most recently.[12]

## RISK FACTORS

### Basal Cell Carcinoma

Exposure to ultraviolet radiation is recognized as the major etiology of BCC, with ultraviolet B (UVB) more implicated than ultraviolet A (UVA). Ultraviolet radiation induces covalent bonds in DNA between adjacent pyrimidines, resulting in mutagenic lesions if not repaired. Both cumulative exposure and less frequent but intense exposure to direct sunlight are implicated in the pathogenesis of BCC. The amount of ultraviolet radiation exposure is especially important for patients with Fitzpatrick skin types I–II.



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Exposure to ionizing radiation is also a risk factor for developing BCC. This increase is limited to the surface area exposed to radiation therapy. Lichter et al. showed in a population-based case-control study that the relative increase in incidence of BCC was 3.3 in skin previously irradiated for acne treatment, with lower increase in patients receiving radiation therapy for malignancies, at 2.0.[13] Lower-dose exposure to ionizing radiation is associated with more mutagenesis and may account for this discrepancy, and this study showed that there was no increase in the incidence of NMSC in adjacent areas of nonirradiated skin.

Other risk factors include chemical carcinogen exposure with arsenic or coal tar, and immunosuppression. Smoking and human papillomavirus (HPV) infection are also risk factors for development of BCC,[14] with smoking likely functioning as a carcinogen.

Each of the aforementioned risk factors is thought to contribute to genetic mutations responsible for BCC. Several pathways have been implicated, most commonly mutations in tumor suppressor genes. The *p53* mutations are the most common genetic aberrations involved in NMSC, although more common in SCC than in BCC. *p53* plays an important role in apoptosis, and effects of involvement of ataxia-telangiectasia mutated gene (ATM gene), *p38*, and mitogen-activated protein (MAP) kinases in the phosphorylation of *p53* serine residues are seen in response to ultraviolet radiation.[15] Exposure to ultraviolet radiation can result in the loss of Fas ligand interaction, with resulting accumulation of *p53* mutations in the skin.

Mutations in the patched tumor suppressor gene also play a role in the development of BCC.[16] Located on chromosome 9, the *PTCH1* gene is a component of the sonic hedgehog (SHH) signaling pathway and encodes for a transmembrane protein which, along with another transmembrane protein, smoothened, inhibits transcription factors regulating genes involved in tissue morphogenesis. This pathway is implicated in the increased incidence of BCC seen in genetic syndromes, including Gorlin syndrome and xeroderma pigmentosum, as well as sporadic BCC.[17]

Gorlin syndrome (basal cell nevus syndrome) is a rare autosomal dominant disorder, with a prevalence of approximately 1 in 100,000 found mostly in whites.[18,19] Patients with this disorder have a variety of clinical abnormalities, including early development of multiple BCCs, palmar and plantar pitting, craniofacial abnormalities, and bifid ribs. These patients are also at increased risk of medulloblastoma with a 3% to 5% incidence.[20]

Xeroderma pigmentosum is characterized by a deficit in nucleotide excision repair. This results in accumulation of defects induced by exposure to ultraviolet radiation and an increase in BCC. Xeroderma pigmentosum clinically presents with excessive skin reaction to sunlight, photosensitivity, multiple solar keratoses, and skin cancers.

## Squamous Cell Carcinoma

Table 23.1 lists known risk factors for the development of SCC. UVA (320–400 nm) and UVB (290–320 nm) result in thymidine dimer DNA mutations in the *p53* tumor suppressor gene and is the most common cause of SCC.[21–23] The highest risk exists among people with light skin, hazel or blue eyes, and blonde or red hair, and in those with chronic accumulated lifetime sun exposure.[24,25] Not surprisingly, the use of oral methoxsalen in combination with ultraviolet A radiation (PUVA) for the treatment of psoriasis and other conditions has been definitively associated with an elevated risk of SCC.[26,27] Ionizing radiation including x-rays, gamma rays, and grenz rays used either therapeutically or as occupational exposures also contribute to the risk of SCC.[28] This risk is directly related to the cumulative dose of radiation.[28] There are several genodermatoses that predispose individuals to SCC. In oculocutaneous albinism, patients have absent or decreased production of protective melanin resulting in increased SCC in sun-exposed areas.[29] Patients with xeroderma pigmentosum are deficient in the enzymes responsible for repairing ultraviolet-induced DNA damage and develop skin cancers beginning from an early age. Other inherited conditions associated with SCC include Ferguson-Smith syndrome and dystrophic epidermolysis bullosa.[30] HPV is associated with SCC development, especially with the periungual and genital regions. This is particularly evident in patients with epidermodysplasia verruciformis and in patients with HIV who develop the verrucous carcinoma subtype of SCC.[31,32] Multiple chemical exposures are associated with SCC development, including arsenic and polycyclic aromatic hydrocarbons.[21] Patients who are immunosuppressed are also at an increased risk of developing SCC. In particular, solid organ transplant recipients have a 40 to 250 times increased incidence of SCC compared with the general population.[33] In fact, the ratio of SCC to BCC is reversed in organ transplant recipients.[21] Patients with AIDS have a slightly increased risk of SCC, with a particular increase in anal lesions that are notable for a more aggressive clinical course.[30] SCCs are also known to occur more commonly in areas of skin affected by chronic inflammation, including ulcers (so-called Marjolin ulcers), osteomyelitis, radiation dermatitis, and vaccination scars, and a variety of inflammatory conditions such as discoid lupus erythematosus, lichen sclerosis, lichen planus, and cutaneous tuberculosis.[21] Infection with HPV has also been definitively linked to the development of nongenital SCC. In particular, HPV types 5, 16, and 18 have been shown to have increased oncogenicity relative to other subtypes.[34] Although the specific pathway by which HPV induces carcinogenesis has not been determined, it is known that HPV infection results in synthesis of the viral proteins encoded by the *E6* and *E7* genes that bind and inactivate the *p53*, *pRB*, and *Bak* tumor suppressor genes.[35] In addition, it appears that infection with HPV alone is insufficient to produce SCCs and that cocarcinogens such as ionizing radiation or ultraviolet radiation are required to produce malignant transformation.[36] It also appears that HPV infection in the setting of immunosuppression leads to carcinogenesis as evidenced by the increased risk of SCC and cutaneous warts in organ transplant recipients.[37]

**TABLE 23.1 Risk Factors for Development of Squamous Cell Carcinoma**

| |
|---|
| Exposure to ultraviolet radiation (UVA/UVB) |
| Therapy with methoxsalen and ultraviolet radiation (PUVA) |
| Ionizing radiation |
| Genodermatoses (Albinism, XP) |
| HPV (types 5, 6, 11, 16, 18) |
| Chemical carcinogens (arsenic, polycyclic hydrocarbons) |
| Immunosuppression/immunosuppressive medications |
| Chronic inflammation (ulcers, osteomyelitis, dystrophic epidermolysis bullosa) |
| Radiation dermatitis |
| Actinic keratosis |
| Arsenical keratosis |

XP, xeroderma pigmentosum.

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## PREVENTION

Duration and intensity of sun exposure has been associated with both BCC and SCC.[38] BCC is more associated with recreational exposure, whereas SCC is more often associated with occupational exposure.[39] Prevention of both types of NMSC can be achieved by limiting overall exposure, as well as using protective clothing to minimize exposed areas. Regular use of sunscreen is a cost-effective approach to skin cancer prevention in subtropical settings.[40] The efficacy of sunscreens in reducing photocarcinogenesis and photaging is widely documented.[41] In August 2007, the FDA proposed an amendment to update sunscreen-labeling regulations, whose major points included limiting SPF labeling to 50+ for products with SPF values of 60 and higher, addition of a 4-star UVA protection rating system, approval of new combinations of sunscreen ingredients, and improved usage directions placed on approved products.[42]

## CLINICAL PRESENTATION AND HISTOLOGY

### Basal Cell Carcinoma

Unlike SCC of the skin, there are no precursor lesions associated with BCC. Patients typically present with a slow-growing, nonhealing papule, most commonly of the head and neck, although multiple clinical variants exist. Locally advanced tumors can show symptoms of disease progression into adjacent structures, including numbness, pain, and weakness.

There are several histologic subtypes of BCC, with nodular, superficial, and micronodular being the most common (Fig. 23-1).[43] Other less common variants include infiltrative, basosquamous, morpheaform, and clear cell.[44]

Nodular-type BCC resembles a translucent papule with telangiectatic-rolled borders, often with a central ulcer (Fig. 23-2). When these tumors are neglected, they may become large and exophytic (Fig. 23-3). Histologically, these lesions have islands of tumor cells encased in a mucin-rich stroma. When pigmented, these tumors can often be confused clinically with melanoma. However, the melanocytes have a benign histologic appearance. Nodular BCC tends to be slow growing and is rarely associated with aggressive disease.

Superficial-type BCC presents as red, scaly lesions, often on the trunk or extremities, which may be confused clinically with eczema or psoriasis. They are also less aggressive clinically, but may become large when neglected, forming crusted, scaling erythematous patches. These lesions are also associated with younger women. Unlike nodular subtype, which increases in incidence with advancing age, the superficial subtype tends to peak and then steadily decrease into the late 70s.[2]

The morpheaform BCC, also described as sclerosing type, presents as flat, indurated, whitish, ill-defined plaques. As they enlarge, they often become depressed and resemble a scar and, because of this subtle clinical appearance, may not be diagnosed until they are relatively large. The morpheaform histology is associated with small islands of tumor cells with dense fibrosis. At the periphery, there is often microscopic extension into the surrounding dermis. This histologic subtype is among the more aggressive BCCs.

Tumors with mixed histologies should be treated as tumors of the more aggressive subtypes. This includes patients with basosquamous carcinomas, which behave more like SCC. Infiltrative BCCs are also more aggressive than the more common nodular and superficial subtypes.

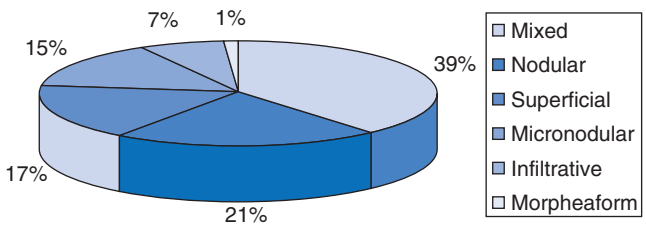



**FIGURE 23-1.** Incidence of specific basal cell carcinoma histologies.

*Source:* From Sexton M, Jones DB, Maloney ME. Histologic pattern analysis of basal cell carcinoma. Study of a series of 1039 consecutive neoplasms. *J Am Acad Dermatol.* 1990;23(6 Pt 1):1118–1126, with permission.

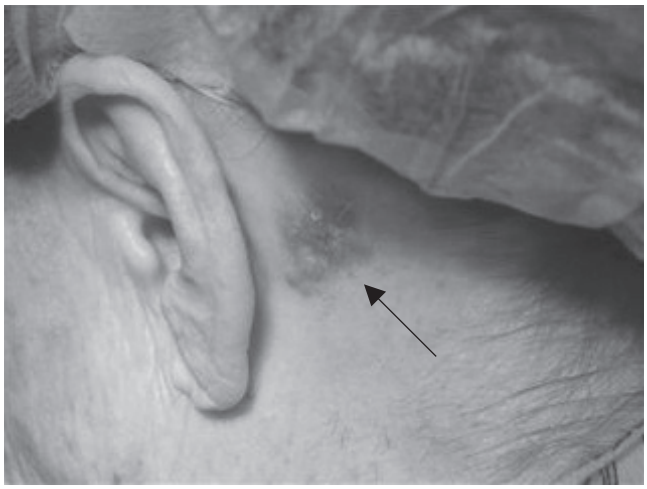


**FIGURE 23-2.** Retroauricular basal cell carcinoma presenting as a pearly plaque with numerous telangiectasias.

*Source:* Photo courtesy of Dr. Ratner.

### Squamous Cell Carcinoma

SCCs are believed to arise primarily from precursor lesions known as *actinic keratoses* (Fig. 23-4). These scaly 1- to 3-mm, pink, skin-colored, or brown papules have a characteristic rough



**FIGURE 23-3.** Basal cell carcinoma of the antihelix. Central erosion of the lesion is characteristic and referred to as a *rodent ulcer*.

*Source:* Photo courtesy of Dr. Ratner.

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**FIGURE 23-4.** Numerous actinic keratoses on the temple of a man with extensive photo damage.

*Source:* Photo courtesy of Dr. Ratner.

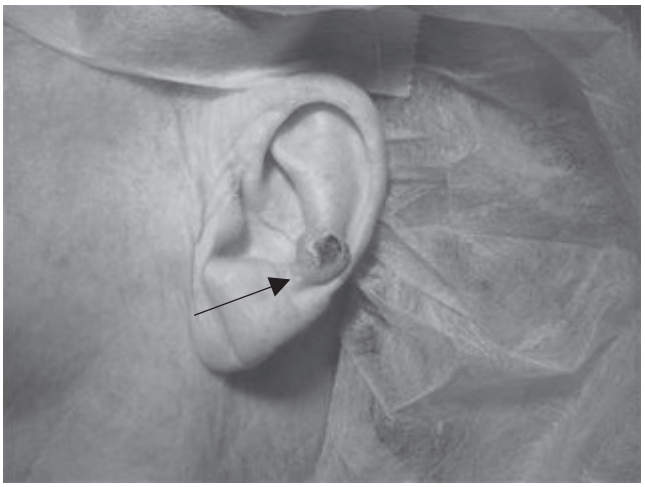


**FIGURE 23-5.** Rapidly growing keratoacanthoma of the left ear with characteristic central keratin core.

*Source:* Photo courtesy of Dr. Ratner.

texture and are oftentimes more easily palpated than visualized. These lesions commonly occur in a typical sun-exposed distribution, including the face, scalp, and dorsal hands. Histologically, actinic keratoses consist of atypical keratinocytes confined to the basilar layers of the epidermis with overlying parakeratosis. Estimates of the rate of progression to SCC vary from 0.025% to 20% per year.[45,46]

SCC *in situ* (Bowen disease) presents as solitary, well-demarcated, pink, brown, or erythematous scaly plaques. Most commonly, these lesions occur in sun-exposed areas. Erythroplasia of Queyrat is SCC *in situ* occurring as smooth red plaques on the glans penis of uncircumcised men. Histologically, SCC *in situ* is characterized by keratinocyte atypical that involves the full thickness of the epidermis, but does not penetrate the basement membrane. SCC *in situ* may progress to invasive disease if not treated completely.[28]

Invasive SCCs are commonly scaly, pink- or skin-colored papules, or plaques that occur on the head, neck, trunk, and other sun-exposed areas. Patients may complain of pruritus, pain, or bleeding, with mild trauma to affected areas. Biopsy reveals keratinocyte atypia that traverses the basement membrane and involves the dermis and underlying structures. Tumors may be well differentiated, with minimal cytologic atypia, obvious keratinization, or they may be poorly differentiated with significant atypia and mitotic figures seen, with immunohistochemistry required for diagnostic confirmation.

Verrucous carcinoma is an uncommon variant of SCC that is characterized by a slow growth rate and exophytic, wart-like clinical appearance. This tumor occurs most commonly in the oral cavity (oral florid papillomatosis), anogenital region (giant condyloma of Buschke-Lowenstein), and the plantar surfaces of hands and feet (carcinoma cuniculatum).[28] It is associated with multiple HPV subtypes, including HPV 6, 11, 16, and 18.[47] Unlike other SCCs, irradiation is specifically contraindicated for verrucous carcinoma because it can result in increased tumor aggressiveness.[48]

Keratoacanthoma (Fig. 23-5) is a more common variant of SCC that presents as a rapidly growing solitary papule or nodule with a central keratin plug. These lesions are believed to regress without treatment in 6 to 9 months and most closely resemble well-differentiated SCC on histology.[49] Ultimately, however, the diagnosis of keratoacanthoma requires clinicopathologic correlation, and indeterminate lesions should be regarded as SCC for treatment purposes because metastasis has been reported in rare cases.[50]

## NATURAL HISTORY

### Basal Cell Carcinoma

Most BCCs are localized at presentation. Growth of these tumors is slow, estimated at 5 mm or less per year for the vast majority of tumors, but neglected tumors can become quite large. With adequate treatment, the recurrence rate is <10%, but more advanced lesions are associated with lower cure rates. The histology of the tumor may also predict the natural history. Sexton et al. examined 1,039 patients with BCC and noted that negative margins were achieved in >93% of patients with nodular or superficial tumors, compared with 81.4% for micronodular, 73.5% for infiltrative, and 66.7% for morpheaform histologies.[43] Location of the primary tumor is also important for prognosis. Tumors along the H-zone (Fig. 23-6) include the nose, nasolabial regions, upper lip, columella, periauricular skin, and frontozygomatic areas. These locations are associated with deeper invasion and higher recurrence rates.[51] This zone is also a cosmetically

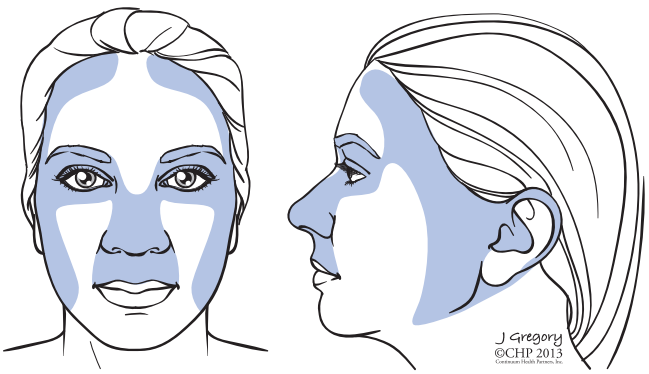



**FIGURE 23-6.** Anatomic depiction of the "H-zone" including areas associated with higher recurrence rates.

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**TABLE 23.2 Risk Factors for Basal Cell Carcinoma (BCC) Recurrence**

| |
|---|
| T stage > T1 |
| Histology: Infiltrative/morpheaform/basosquamous |
| Margin status <4 mm |
| Location—"H-zone" |
| Perineural invasion |
| Site of prior radiation therapy |
| Poorly defined borders |
| Recurrent |

prominent region where cosmetic results of treatment are particularly important. Local extension is through pathway of least resistance, including fascial planes, periosteum, perichondrium, and nerve sheaths. High-risk features of BCC are shown in Table 23.2. The primary tumor stage may be the most significant factor in determining the progression of disease. BCCs rarely metastasize to lymph nodes or distantly, and most cases are associated with T3 or T4 tumors. In addition, locally advanced tumors are more likely to have perineural invasion, which can result in cranial nerve palsies. Periorbital lesions have potential for invasion into the ethmoid sinuses and subsequently to the base of skull. The incidence of nodal metastases from BCC is exceedingly rare, between 0.01% and 0.5%, and associated with high-risk tumor features.[44,52] However, the prognosis is poor after spread of disease, with median survivals between 8 months to 3 years. Distant spread of disease is to the lymph nodes, followed by bone, the lung, and the liver.

## Squamous Cell Carcinoma

Most patients with cutaneous SCC have an excellent prognosis. Invasive SCC does, however, have the potential to recur and metastasize. Although estimates vary, the approximate 5-year recurrence rates for primary cutaneous lesions is reported to be 8%, whereas the 5-year metastasis rate is 1.4% to 6%.[53–55] In 1992, Rowe, Carroll, and Day reviewed all relevant studies on recurrence and metastasis rates of SCC from 1940 to 1992 (Table 23.3). Large lesions (>2 cm) have been reported to metastasize at a rate of 30%.[53] Rapidly growing lesions on the eyelid or ear are also thought to be more aggressive and may metastasize in up to one-third of cases.[56] Similarly, rates of metastasis are relatively high for lesions on the ear (11%) and the lip (13.7%), with associated 5-year survival rates that range from 25% to 40%.[28,57–59] It should be noted that with improved abilities to diagnose and treat SCC, current rates of recurrence and metastasis may be lower than previously reported, but more recent prospective studies have not been performed.

Several histologic features may portend a worse prognosis. Depth >4 mm, extension into the reticular dermis or subcutaneous fat, and involvement of underlying fascia, muscle, bone, or cartilage are all associated with a greater risk of metastasis.[60] Lesions that are poorly differentiated behave more aggressively and metastasize three times as often as well-differentiated tumors.[53] Perineural invasion, in which tumor cells invade and travel along nerve fibers, occurs in 5% of SCCs.[28,58] Discontinuous skip lesions are characteristic of perineural invasion, and the risk of metastasis approaches 50% despite aggressive surgical excision.[28,58,61]

**TABLE 23.3 Factors Predisposing to Recurrence and Metastasis of Cutaneous Squamous Cell Carcinoma (SCC)**

| Risk Factor | RR of Recurrence | RR of Metastasis |
|---|---|---|
| Rapid growth | — | — |
| Size >2 cm | 2 | 3 |
| Site: lip | 2 | 3 |
| Site: ear | 2 | 3 |
| Immunosuppression | 2 | — |
| Radiation | — | — |
| Previous recurrence | 3 | 4 |
| Depth >4 mm or Clark IV/V | 2 | 5 |
| Poor differentiation | 2 | 3 |
| Perineural invasion | 5 | 5 |
| Infiltrative margins | — | — |
| Spindle cell histology | — | — |
| Acantholytic histology | — | — |

Relative risk (RR) for small primary squamous cell carcinoma (SCC) is defined as 1.

For patients with metastatic disease, the long-term prognosis is poor. In patients with regional lymph node involvement, 10-year survival rates are <20%. In patients with distant metastases from SCC, 10-year survival rates are <10%. Eighty-five percent of cases with metastasis involve regional lymph nodes, whereas the remaining 15% of cases involve the lungs, the liver, the brain, and bone.[28,57,62–64] Primary SCC of the head and neck also metastasizes to the parotid gland and the neck, not uncommonly. In this subset of high-risk patients, approximately 50% develop local recurrence within 1 year of surgical excision. Not surprisingly, positive surgical margins at the time of excision were associated with a greater risk of recurrence. Postoperative radiotherapy was not associated with improved outcomes or prolonged survival.[65]

# STAGING

Staging for primary nonmelanoma cutaneous malignancies is outlined in Table 23.4. Size and invasion of extradermal structures determines T stage, whereas presence of nodal metastasis results in a stage III classification and presence of distant metastases results in stage IV classification. Eyelid tumors are staged differently, and that system is provided in Table 23.5. Note that no stage groupings are currently recommended for eyelid tumors.[66]

# DIAGNOSTIC IMAGING

Most NMSCs are localized to the site of presentation and do not require any type of diagnostic imaging. However, locally advanced tumors as well as tumors located in the medial canthus or fixed to bone should be imaged to determine the extent of disease and to evaluate for invasion. Most commonly, computed

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**TABLE 23.4 American Joint Cancer Committee (AJCC) 6th Edition Staging for Nonmelanoma Skin Cancer (NMSC)**

**Primary tumor (T)**

| | |
|---|---|
| Tx | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Tis | Carcinoma *in situ* |
| T1 | Tumor 2 cm or less in greatest dimension |
| T2 | Tumor >2 cm, but not >5 cm, in greatest dimension[a] |
| T3 | Tumor >5 cm in greatest dimension |
| T4 | Tumor invades deep extradermal structures |

**Regional lymph nodes (N)**

| | |
|---|---|
| Nx | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Regional lymph node metastasis |

**Distant metastasis (M)**

| | |
|---|---|
| Mx | Distant metastasis cannot be assessed |
| M0 | No distant metastasis |
| M1 | Distant metastasis |

**Stage grouping**

| | | | |
|---|---|---|---|
| 0 | Tis | N0 | M0 |
| I | T1 | N0 | M0 |
| II | T2/T3 | N0 | M0 |
| III | T4 | N0 | M0 |
| IV | Any T | Any N | M1 |

[a]For multiple tumors, the tumor with highest T category will be classified and the number of separate tumors will be indicated in parentheses.

*Source:* From American Joint Committee on Cancer (AJCC). *Cancer Staging Manual.* 7th ed. New York, NY: Springer, 2010, with permission.

**TABLE 23.5 American Joint Cancer Committee (AJCC) 6th Edition Staging for Eyelid Tumors**

**Primary tumor (T)**

| | |
|---|---|
| Tx | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Tis | Carcinoma *in situ* |
| T1 | Tumor of any size, not invading the tarsal plate or, at the eyelid margin, 5 mm or less in greatest dimension |
| T2 | Tumor invades tarsal plate or, at the eyelid margin, >5 mm but not >10 mm in greatest dimension |
| T3 | Tumor involves full eyelid thickness or, at the eyelid margin, >10 mm in greatest dimension |
| T4 | Tumor invades adjacent structures, which include bulbar conjunctiva, sclera and globe, soft tissues of the orbit, nasal cavity and paranasal sinuses, and central nervous system |

**Regional lymph nodes (N)**

| | |
|---|---|
| Nx | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Regional lymph node metastasis |

**Distant metastasis (MM)**

| | |
|---|---|
| Mx | Distant metastasis cannot be assessed |
| M0 | No distant metastasis |
| M1 | Distant metastasis |

*Source:* From American Joint Committee on Cancer (AJCC). *Cancer Staging Manual.* 7th ed. New York, NY: Springer, 2010, with permission.

tomography (CT) and magnetic resonance imaging (MRI) are used to evaluate these tumors. For SCC, CT with contrast should be done to evaluate the primary echelon of nodes to determine if the disease has spread regionally. Positron emission tomographic (PET) scan may also play a role for patients with high-risk SCC. Cho et al. showed PET correlation with both local and distant disease extent for all nine patients with high-risk features.[67] Another modality is the use of high-frequency ultrasonography to determine the depth of the lesion. A study by Lassau et al. examined 32 patients with BCC and was able to identify each as hypoechoic on ultrasonography.[68] Perhaps of more importance, 29% of BCC lesions were found to be larger than that predicted by clinical examination. This may represent an important tool in the pretreatment setting.

## TREATMENT

The rationale for treatment of NMSC is twofold. First, local control is important to limit the extent of immediate tumor destruction and preserve vital functional and cosmetic structures (particularly on the face). Second, complete eradication (either surgical or radiotherapeutic) is crucial for eliminating the risk of metastatic spread. Because the risk of locoregional recurrence and metastasis increases with increasing tumor size, there is particular incentive to treat tumors when they are small.[60]

## PATIENT EVALUATION AND RISK STRATIFICATION

Work-up of a patient with possible NMSC begins with thorough history-taking, physical examination, and possible skin biopsy. The history should focus on the duration, growth rate, and previous therapy for a suspected lesion. In addition, history of previous radiation or ultraviolet light therapy and personal or family history of previous skin cancers should be elicited. Standard medical history, including current medical problems, medications, and allergies should be reviewed, with particular attention to possible sources of immunosuppression, such as organ transplantation, HIV, immunosuppressive medications, and hematologic malignancy.

Physical examination of the lesion in question should be performed. It should first be assessed for location, size, whether the borders are well defined or poorly defined, and the presence of associated scars to indicate previous therapy. The site should be palpated to evaluate the depth of the lesion, as well

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as connections to underlying structures. Regional lymph node evaluation is indicated for all SCCs, and thorough full-body skin examination is essential to identify any additional primary skin cancers.

Lesions suspicious for cutaneous malignancy should be biopsied. Shave biopsy is sufficient in instances where a more superficial process is clinically evident such as superficial BCC or SCC *in situ*. When a deeper tumor is suspected, punch biopsy is the preferred method to obtain a diagnosis. If the biopsy is consistent with NMSC, the report should identify the subtype of BCC or SCC. In addition, the presence of any high-risk histologic features should be noted, including the degree of differentiation for SCCs and the presence of vascular or perineural invasion.

On the basis of this assessment, it should be possible to assign tumors to either high-risk or low-risk categories for recurrence and metastasis (Tables 23.2 and 23.3). This designation is essential in selecting the appropriate treatment regimen for an individual patient.

# TREATMENT MODALITIES

There are numerous proven treatment options for NMSC including cryosurgery, electrodessication and curettage, standard excision, Mohs micrographic surgery, and radiation therapy. In addition, there are several novel therapies, including laser surgery, photodynamic therapy, topical chemotherapy, and the biological response modifiers. These individual approaches, as well as an overall algorithm for the management of NMSC, are now discussed.

## Curettage and Electrodesiccation

Curettage and electrodesiccation is a simple and cost-effective treatment for low-risk NMSCs.[69] In this technique, a sharp curette is used to scrape away tumor that provides less resistance than normal healthy tissue. Gentle, deliberate pressure is utilized such that the relatively soft tissue of the tumor is removed without disturbing adjacent uninvolved skin. Following curettage, the area is treated with electrodesiccation to achieve hemostasis, as well as to delineate the borders of the tumor. By convention, this cycle of curettage and electrodesiccation is repeated for a total of three treatment cycles. One disadvantage of this procedure is that no pathologic specimen is sent for margin evaluation. This technique is not indicated in hair-bearing skin because of the risk that tumor extending down the hair follicles will not be adequately treated.[70] In addition, curettage and electrodesiccation is not appropriate when there is tumor extension into the subcutaneous layer, because it is more difficult to distinguish friable tumor from the surrounding fat.[70] When employed for the treatment of small, primary tumors, with nonaggressive growth patterns in low-risk areas, 5-year cure rates for NMSCs as high as 96% are reported.[53,71–74] Cure rates for tumors with high-risk features are much lower; however, controlled studies have not been performed,[75] and this technique is not recommended for aggressive NMSCs.

## Superficial Therapies

There are multiple superficial therapies that are available for treatment of NMSCs, including vigorous cryotherapy, photodynamic therapy, topical 5-fluorouracil (5FU), and topical imiquimod. Although they are minimally invasive and well tolerated, these therapies are associated with lower cure rates and should be reserved for patients in whom surgery or radiation are contraindicated or impractical.[76,77]

## Cryosurgery

Modern cryosurgery involves the use of liquid nitrogen in a closed system that enables continuous and rapid extraction of heat from tissue. The most commonly employed techniques include the hand-held canister with a spray-tip accessory and the cotton-tipped applicator. Freezing tissue results in vascular stasis, disruption of cell membranes, intracellular pH changes, loss of homeostasis, ice crystal formation, and thermal shock. Rapid cooling with slow thawing and repeated freeze–thaw cycles are ideal for producing maximal tumor destruction. Extensive tissue necrosis is required for eradication of malignant lesions. BCC cells have been demonstrated to be histologically absent at 3 days following treatment with cryosurgery. Specifically, temperatures of −50 to −60°C are required to produce sufficient tissue freezing for treatment of basal cell and SCCs.[78,79]

Cryosurgery is considered to be an effective therapy for the treatment of premalignant lesions and *in situ* malignancies, including actinic keratoses, actinic cheilitis, lentigo maligna, Bowen disease, and erythroplasia of Queyrat. Cryosurgery may be used to treat NMSCs, but is usually appropriate only for select circumstances. Tumors that may be considered include those with less aggressive histologic growth patterns, such as nodular and superficial BCC, and well-differentiated lesions for SCC, lesions with well-defined borders, small primary lesions (<1 cm), and those on low-risk locations.[80] Multiple authors have reported a >97% 5-year cure rates for treatment of these selected low-risk tumors.[78,81–84] NMSCs with aggressive growth patterns such as morpheaform and infiltrative BCC, and moderately/poorly differentiated SCC, those with ill-defined borders, recurrent tumors, or deeply penetrating lesions are not good candidates for cryosurgery. Although it is not considered first-line therapy for these more aggressive tumors, cryosurgery can be considered as an alternative treatment option for patients who are poor operative candidates or as palliative therapy to relieve pain and debulk large tumors.[80]

## Topical Medications

5FU is a pyrimidine analog that inhibits RNA processing and thymidylate synthesis and is used topically for treatment of actinic keratoses and actinic cheilitis. Topical 5FU is available in 0.5%, 2%, and 5% preparations, and treatment involves once-daily or twice-daily applications to affected areas for 2 to 4 weeks. Significant erythema and discomfort at the site of application is common, and residual erythema following treatment may persist for several months. Diclofenac sodium gel is an alternative topical therapy approved for the treatment of actinic keratoses. Twice-daily application for 60 to 90 days is the recommended treatment regimen. Although these topical therapies are not considered effective treatment for SCCs, they may be used to clear the field in severely actinically damaged patients so that new or transforming lesions may be detected earlier.

Imiquimod cream is a topical immune response modifier. Although the imiquimod strength used is generally 5%, a 3.75% formulation was recently approved to treat actinic keratoses on the face and balding scalp. Although the precise mechanism of action is unknown, imiquimod binds to toll-like receptor 7 to stimulate both innate and adaptive immune functions through the production of local cytokines, including interferon-α (IFN-α), interleukin-6, and tumor necrosis factor-α.[85] For actinic keratoses, imiquimod 5% was shown to have an 87.5% clearance rate following three times weekly treatment for 2 weeks, followed by twice-weekly treatment for 12 weeks in a randomized, double-blind, vehicle-controlled study.[86] For Bowen disease, once-daily application of imiquimod 5% for 16 weeks resulted in >93% clearance rates; however, only 66% of patients were able to

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complete the treatment protocol secondary to local skin reactions.[87] For superficial BCC, once-daily application of imiquimod 5% cream for 6 weeks has been shown to produce 77% to 93% histologic clearance at 12 weeks. Interim data from an open-label study to assess the 5-year recurrence rates among patients treated with imiquimod 5% for superficial BCC demonstrated that 79% of patients who were clinically free of disease at 12 weeks remained clear at 24 months.[88–90] The histologic clearance rate for nodular BCC appears to be significantly lower and ranges from 42% to 76%.[91,92] Imiquimod is not recommended for treatment of invasive SCC or BCC that are recurrent, occur in high-risk locations, or have a morpheaform, infiltrative, or nodular growth pattern.

## Photodynamic Therapy

Photodynamic therapy is a treatment modality that involves the delivery of a photosensitizing agent, which localizes to the site of a tumor and induces selective destruction upon activation with visible light.[93] The wavelength of light utilized for treatment determines the maximum therapeutic depth. Topical, oral, intralesional, and intravenous routes have all been explored for administration of photosensitizing agents such as 5-(δ)-aminolevulinic acid (ALA) and methyl-esterified ALA that are precursors of protoporphyrin IX in the porphyrin pathway.[94] These low-molecular-weight hydrophilic molecules are translocated to individual cells in both the targeted tumor and normal surrounding tissue, where they are converted to protoporphyrin IX, a potent photosensitizer. Exposure to a visible light source in the presence of oxygen results in the generation of highly reactive oxygen intermediates and free radial molecules and ultimately causes cellular death. Maximal selective necrosis of tumor versus surrounding normal tissue is achieved by delaying the timing of light delivery because the relative absence of lymphatic channels results in photosensitizer accumulation in malignant tissues.[94] Topical photosensitizers are advantageous in that they are easy to apply and photosensitivity is confined to the site, but they may be limited by the depth of tumor perfusion that can be obtained.

Photodynamic therapy has been demonstrated to be an effective treatment for actinic keratoses.[95,96] Numerous trials have been conducted that suggest a response rate of 71% to 100% for actinic keratoses on the face after a single treatment session.[97–100] Nonfacial and hyperkeratotic actinic keratoses respond less favorably, and studies demonstrate more modest cure rates of approximately 45%.[101] Response rates of ALA photodynamic therapy for treatment of actinic keratoses appear to be comparable to those obtained using topical 5FU and cryotherapy.[93,102] Case reports also suggest the effectiveness of topical photodynamic therapy for the treatment of actinic cheilitis, including one that demonstrated 100% clearance in three patients with excellent cosmetic results noted at 12-month follow-up.[103]

Bowen disease has also been shown to have excellent responses to photodynamic therapy. Studies of systemically administered photosensitizers demonstrate 89% to 100% clearance rates, even with larger tumors (>2.0 cm) and multiple tumors requiring increased numbers of treatment sessions.[104–106] In a comparison of cryotherapy versus 20% ALA photodynamic therapy for SCC *in situ*, Morton et al. demonstrated that photodynamic therapy had a higher clearance rate (75%) than cryosurgery (50%) after a single treatment session, although all lesions eventually cleared with multiple treatments.[102] Topical photodynamic therapy may be used for Bowen disease, but it should be coupled with more deeply penetrating red light to obtain adequate depth of treatment. Photodynamic treatment of invasive SCC has been attempted with unreliable results, and it is not a recommended modality at this time.[97,107,108]

Numerous investigations have been conducted to evaluate the efficacy of photodynamic therapy for treatment of BCC. Systemic photodynamic therapy provides cure rates of 51% to 95% depending on the intensity of the light source used.[109–112] Lesions on the nose and those with infiltrative growth patterns are most likely to recur. Topical photodynamic therapy with ALA is an effective treatment for superficial BCC with complete response rates ranging from 79% to 100%.[113] Methylation enhances the lipophilic properties of the ALA and results in increased tissue penetration.[94] Topical photodynamic therapy with methyl ALA has been shown to produce 89% complete tumor clearance for BCC of mixed histology and 91% for nodular BCC, but was ineffective in treating morpheaform lesions.[114,115] A more recent study of 194 BCCs treated with MAL-PDT found a better response for superficial BCC (82% tumor clearance) than nodular BCC (33% tumor clearance), with truncal lesions showing the best response to treatment.[116] In general, the use of photodynamic therapy for BCC is limited by unreliable cure rates, and treatment should be reserved for low-risk lesions with superficial histology.

## Excision with Postoperative Margin Assessment

Standard excision with postoperative margin assessment is a commonly utilized treatment modality for low-risk NMSCs. In contrast to curettage and electrodesiccation, surgical excision offers the advantages of histologic margin confirmation, rapid healing, and potentially improved cosmesis, although the 5-year cure rates do not differ significantly between the two techniques.[21] Zitelli et al. have demonstrated that for NMSCs that are well-circumscribed and <2 cm in diameter, excision with 4 mm of normal adjacent tissue results in tumor clearance with 95% confidence.[59,116] The authors note that for SCC, peripheral erythema must be included in the clinical margin of the tumor. For SCC, recurrence rates after excision for low-risk tumors range from 5% to 8%.[53] Tumors with high-risk features are associated with higher recurrence rates following excision, with lesions >2 cm recurring at a rate of 15.7% and poorly differentiated lesion recurring at a rate of 25%.[53] Accordingly, 6-mm margins are recommended for these high-risk lesions.[59] For BCC, surgical excision of primary lesions occurring on the neck, the trunk, arms, and legs is associated with a 99% 5-year cure rate.[69] Surgical excision of BCC occurring on the head demonstrate decreasing cure rates with increasing tumor size, with 97% cure rates for lesions <6 mm and 92% cure rates for lesions >6 mm.[69] According to the 2007 National Comprehensive Cancer Network (NCCN) guidelines, 4- to 6-mm margins are recommended for treatment of SCC because of concerns about achieving complete tumor removal. In addition, standard excision is reliably utilized for treatment of NMSCs occurring in low-risk locations that are considered to be high risk, either because of positive margins on initial excision or size >2 cm. For these lesions, however, the NCCN recommends that 1-cm margins be taken.[70] The NCCN guidelines also state that following excision of the tumor, wound closure utilizing side-to-side closure, skin grafting, or secondary intention healing are all appropriate. Closure involving tissue rearrangement (i.e., cutaneous flaps) that might alter the location of residual tumor must be avoided unless intraoperative margin evaluation is performed.[70]

## Mohs Micrographic Surgery

Mohs surgery is a highly specialized excisional technique used for the treatment of high-risk cutaneous neoplasms that permits examination of the complete peripheral and deep margins of the specimen. This procedure is named after Dr. Frederick Mohs, a general surgeon at the University of Wisconsin, who first described the technique in the 1930s.[117] Mohs surgery is performed under local anesthesia and involves removal of a narrow margin

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of clinically normal skin around a given tumor. The orientation of this specimen relative to the patient is carefully mapped using a series of tissue hatches before removing the specimen. Once the tissue is excised, it is further marked using colored inks, and a map is drawn such that a given color corresponds to a specific area of the patient's defect. The specimen is then processed using fresh frozen sections in such a way that the surgeon is able to visualize 100% of the peripheral and deep margin in a single section. In contrast, the traditional "bread-loafing" style that is commonly used for standard pathological specimens allows visualization of <1% of the complete margin of the surgical specimen, and residual tumor may unknowingly exist in between examined sections.[118] If residual tumor is seen at one of the margins of a Mohs layer, its location is mapped, and an additional layer is excised from the area of the patient's defect, which was positive. This process is repeated until a Mohs layer is obtained with no residual tumor, and the excision is then complete.

Mohs surgery offers two main advantages over traditional excision for NMSC. The first is that by processing specimens to examine 100% of the surgical margin, Mohs surgery offers the highest cure rates for all NMSC. For primary BCCs, the 5-year cure rate is 99% with Mohs surgery versus 90% to 93% using standard techniques.[119] For recurrent BCCs, the 5-year cure rate was 94.4% with Mohs versus 80.1% for standard treatments.[120] For SCCs, Mohs surgery for primary tumors offers a 5-year cure rate of 96.9% versus 89.1% for non-Mohs treatments. Mohs surgery for recurrent SCCs results in a 90% cure rate versus 76.7% for non-Mohs treatments.[53] The second advantage is that by obtaining a series of narrow excisional margins for a given tumor as opposed to one standardized margin, the Mohs technique removes the smallest amount of normal tissue possible to achieve histologic clearance. These advantages are particularly important for high-risk tumors such as those occurring on the face, where standardized margins might unnecessarily compromise functionally or cosmetically critical structures. The most significant disadvantages of Mohs surgery are that it is more time-consuming and expensive than standard excision, and therefore it is commonly reserved for high-risk tumors.

Once histologic clearance has been obtained, the Mohs surgeon must determine the optimal method for repair of the surgical defect. Whenever possible, wounds are closed primarily. Layered closures, flaps, and grafts are often utilized when sufficient tissue reservoirs exist immediately adjacent to the wound. In certain specific locations, wounds may be left to heal by secondary intention with excellent results. Commensurate with the degree of difficulty of the closure and the level of reconstructive training of the Mohs surgeon, referral to other surgical specialties such a plastic surgery, otolaryngology, and oculoplastic surgery may be indicated (Figs. 23-7 to 23-10).




**FIGURE 23-7.** **A:** Basal cell carcinoma of the right malar cheek. **B:** Defect following two stages of Mohs micrographic surgery extending to the subcutaneous fat. **C:** Linear closure oriented along the nasofacial sulcus. **D:** Wound appearance at suture removal after 1 week.

*Source:* Photos courtesy of Dr. Ratner.

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**FIGURE 23-8.** **A:** Squamous cell carcinoma (SCC) of the left alar crease. **B:** Defect following one stage of Mohs micrographic surgery extending to deep dermis. **C:** Repair using a laterally based rhombic flap. **D:** Follow-up at 1-week suture removal.

*Source:* Photos courtesy of Dr. Ratner.

## Radiation Therapy

Radiation therapy has been used successfully in the management of NMSC, with cure rates similar to those with surgical techniques. Radiation therapy is used for both definitive treatment and in the adjuvant setting. Although the goal of radiation therapy is to maintain or exceed cure rates achieved with other modalities, an emphasis on maintaining form and function is also critical.

There are several advantages to using radiation therapy in the treatment of NMSC. Primarily, radiation therapy is noninvasive and therefore requires no anesthesia, which is important in this patient population where median age is in the 70s. In addition, there is no removal of normal tissue. This is especially important for cosmetically sensitive areas and for larger tumors adjacent to critical structures. There may also be an advantage for patients receiving anticoagulants, which would have to be discontinued for surgery. The major disadvantage to the use of radiation therapy is the inability to histologically determine margins. This allows for the potential of "geographic miss," where the entire extent of tumor is not adequately included in the treatment field. However, the noninvasive nature of radiation allows for generous margins to be used without significant toxicity. Also, patients are typically given multiple radiation treatments, spread over 2 to 6 weeks, which may be difficult for patients who do not have adequate means of transportation or who do not live in close proximity to a radiation center. The treatment-related effects of radiation therapy are limited to the area treated. With proper technique, <3% of patients should have significant toxicity.

Most patients with head and neck NMSC are candidates for treatment with radiation therapy. Absolute contraindications include patients with Gorlin syndrome and other genodermatoses because ionizing radiation may result in significant adverse effects, as well as induce more skin cancers. An exception to this is xeroderma pigmentosum, where the defect is in nucleotide excision repair, and there does not seem to be an enhanced reaction to ionizing radiation. In addition, patients with active autoimmune disease such as scleroderma and systemic lupus erythromatosus may have increased morbidity from radiation therapy.

There are several techniques used to deliver radiation therapy in the management of NMSC. Brachytherapy involves the direct placement of radioactive sources into the tumor to treat the cancer with surrounding margin. This technique is less often used currently for skin cancers because it requires an invasive procedure and hospitalization to minimize radiation exposure to others. Superficial x-rays have long been used in the management of cutaneous malignancies because of the dose distribution peaking at the surface and rapidly decreasing with depth.

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**FIGURE 23-9.** **A:** Squamous cell carcinoma of the left medial canthus. **B:** Surgical defect extending to muscularis after one stage of Mohs micrographic surgery. **C:** Repair of the defect using a laterally based advancement flap. **D:** Surgical site appearance 2 months postoperatively.

*Source:* Photos courtesy of Dr. Ratner.

This spares deep tissues and maximizes dose to the surface of the tumor. Superficial x-rays are still used, although the application of these machines is limited to treatment of superficial tumors. Therefore, many centers no longer have these machines. Also, superficial x-rays are limited in the depth of tumor that can be treated. To treat tumors of >5 mm depth, there is a substantial dose gradient between the surface and the deepest extent of the tumor. Electrons have been used more in recent years. Electrons are produced from the same linear accelerators used to treat most other patients with external beam radiation therapy. In addition, electrons are available in different energies so that differences in tumor depth can be taken into account. The major drawback of using electrons is the wider penumbra (the distance between the area receiving 80% of the prescribed dose and the area receiving 50% of the prescribed dose), and the uncertainty in dose distributions when very small field sizes are used. As a result, margins should be 1.5 to 2 cm for treatment with electrons compared with 1 cm for superficial x-rays. Recurrence rates with superficial x-rays or electrons are similar. Initial reports of electron use showed higher recurrence rates. Lovett et al. reported on 339 patients and showed a local control rate of 98% for superficial x-rays and 88% with electrons.[52] However, a report by Locke et al. from the same institution showed that with more recently treated patients, there was no longer a difference between superficial x-rays and electron treatments.[121] The initial difference may have been secondary to treatment technique and margins. Griep et al. looked at 389 patients with BCCs and SCCs and noted a 2.2% local recurrence rate with both superficial x-ray treatment and electrons. In addition, the cosmetic outcome was better for patients treated with electrons.[122]

The optimal time, dose, and fractionation scheme for treatment of cutaneous SCC and BCC have not been determined. Several studies have shown that a higher biologically effective dose is required for adequate tumor control.[123,124] This can be achieved in several ways: by increasing the dose per treatment (fraction size) or increasing the total number of treatments delivered (total dose). Fraction size can be increased, and several regimens have been used with excellent local control rates, including 2,600 cGy in 2 fractions, 3,500 cGy in 5 fractions, 4,500 in 10 to 12 fractions, and 5,100 cGy in 17 fractions. The latter is commonly used by the authors. Although effective, several studies have shown increased morbidity and worse cosmesis with fraction size >5 Gy.[122–124] Large fraction size is only suggested for small tumors <2 cm, where critical structures will not be in the treatment field and for patients unable to come for a more protracted sequence. Schedules using 3 Gy × 17 fractions (5,100 cGy) or 2.5 Gy × 20 fractions (5,000 cGy) are associated with similar recurrence rates and better toxicity and cosmetic

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**FIGURE 23-10.** **A:** Basal cell carcinoma of the right nasal supratip. **B:** Defect following one stage of Mohs micrographic surgery extending to the alar cartilage. **C:** Repair using a bilobed transposition flap. **D:** Follow-up at 1-week suture removal demonstrates early thickening of the flap, which resolved with intralesional cortisone injections.

*Source:* Photos courtesy of Dr. Ratner.

profiles. For very large tumors, or when bone or cartilage are in the treatment field, 2-Gy fractions are recommended to a total dose of 6,500 cGy to 7,500 cGy.[125] Fraction size of <2 Gy is associated with increased local recurrence and should not be used.[121]

Treatment of BCC should include the primary lesion with an adequate margin taking into account beam profile and microscopic extension of tumor. The incidence of nodal involvement is <0.5%, and routine treatment of the primary echelon of nodes is not indicated. Treatment of SCC should also be directed to the primary tumor site. However, for tumors with high-risk features (Table 23.3), treatment should be extended to include the first echelon of nodes, typically the periparotid nodes with or without upper cervical nodes.

Results with radiation therapy in the management of BCCs and SCCs of the skin are excellent. Factors associated with recurrence after radiation therapy include, larger tumor size, recurrent tumors, invasion of adjacent structures, inadequate dose, and squamous cell histology. Table 23.6 shows outcomes with several large trials of radiation therapy. Petrovich et al. showed the influence of tumor size. Out of 646 patients, the local recurrence rate was significantly higher for tumors 2 to 5 cm and >5 cm compared with those <2 cm.[125] Lim et al. showed the importance of adequate effective dose to achieve cure of these tumors.[123]

The decision to use radiation therapy in the management of these patients is often due to the location of the primary tumor. Although flat surfaces of the forehead and neck are often treated surgically, the pinna, the nasal skin, and the periorbital regions are often treated with radiation therapy, as well as lip cancers, which are discussed with oral cavity tumors. As mentioned previously, H-Zone lesions are well suited to radiation therapy due to cosmetic outcomes. Surgical resection in these areas can result in tissue defects that may require significant reconstruction or result in functional impairment. Each of these sites has significant cosmetic importance and, in the case of periorbital tumors, significant functional importance. Radiation therapy has been used successfully in all the three sites.

***Pinna.*** Radiation therapy can be used to treat the pinna with either brachytherapy or external beam radiation therapy. Mazeron reported on 70 patients treated with low-dose rate iridium-192 ($^{192}$Ir) and had a 99% local control rate. These procedures were completed under local anesthetic using $^{192}$Ir wires with the most common dose 60 Gy delivered at 0.3 to 0.9 Gy/hour. Thirty-nine of these patients had SCC, whereas 31 had BCC. For patients with tumors <4 cm, 78% had good cosmesis. However, cosmesis was good in only 1 of 9 patients with tumor size >4 cm.

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**TABLE 23.6 Local Recurrence Rates for Basal Cell Carcinoma (BCC) and Squamous Cell Carcinoma (SCC) of the Head and Neck with Radiation Therapy**

| Author | Follow-up (yr) | No. of Primary Tumors | Local Control (%) | Cosmesis (Good/ Excellent) (%) |
|---|---|---|---|---|
| **BCC** | | | | |
| Rowe et al. (1989)[120a] | 5.0 | 4,695 | 91.3 | — |
| Griep et al. (1995)[126] | 2.0 | 295 | 95.9 | 93 |
| Locke et al. (2001)[121] | 5.8 | 285 | 95.0 | 92 |
| Petrovich et al. (1987)[125] | 5.0 | 464 | 99.0 | — |
| Avril et al. (1997)[128] | 4.0 | 173 | 92.5 | 69 |
| **SCC** | | | | |
| Petrovich et al. (1987)[125] | 5.0 | 115 | 94.0 | — |
| Griep et al. (1995)[126] | 2.0 | 94 | 92.5 | 93 |
| Locke et al. (1989)[121] | 5.8 | 79 | 89.0 | 92 |

[a]Meta-analysis.

Ten percent of the patients with SCC developed regional nodal metastases in this population.[127] Silva et al. reported experience with 334 skin cancers of the pinna treated with superficial x-rays or electrons and noted local control rates of 86.6% at 2 years and 79.2% at 5 years. Grade IV toxicity was reported in 7.3% of patients, each of whom received fraction size >4 Gy. Of the failures, all but two patients underwent successful salvage therapy.[124]

***Nasal Skin.*** Radiation therapy has often been used for skin cancers of the nasal skin because this area is in a critical location for cosmesis and function (Figs. 23-11 to 23-13). Several studies have shown low recurrence rates with radiation therapy of approximately 5% (Table 23.7).[124,128,129] The largest study was a European multicenter retrospective review by Mazeron et al. with 1,676 patients with cancers of the nasal skin or nasal vestibule. Local control rates were 93% at 2 years and the necrosis rate was 2%. Patients with tumors <2 cm had a 96% control rate, and tumors of the external nasal skin fared better than those with vestibule tumors (94% vs. 75%).[130] Caccialanza[131] reported a large retrospective series of 671 patients with basal and squamous cell cancers of the nasal skin, treated with kilovoltage radiotherapy between 1972 and 2007. For the entire group, with mean follow-up of 38 months (range 1–351 months) local control was 88% with good cosmetic outcomes in 97%. No major complications were observed.

***Periocular Tumors.*** Treatment of periocular skin cancers results in higher recurrence rates than other sites. This is likely due to hesitancy in treating larger margins with critical adjacent structures. Radiation therapy is very effective for these lesions resulting in excellent form and function, unless the tumor has already destroyed much of the adjacent tissue (Fig. 23-14).

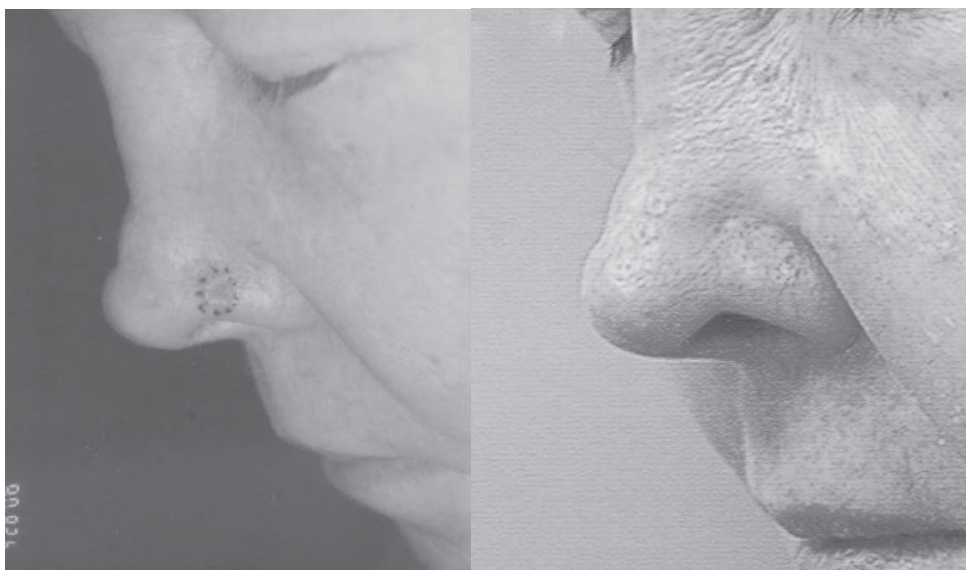


**FIGURE 23-11.** Small basal cell carcinoma of the nose before and after external radiation therapy.

*Source:* Photos courtesy of Dr. Harrison.

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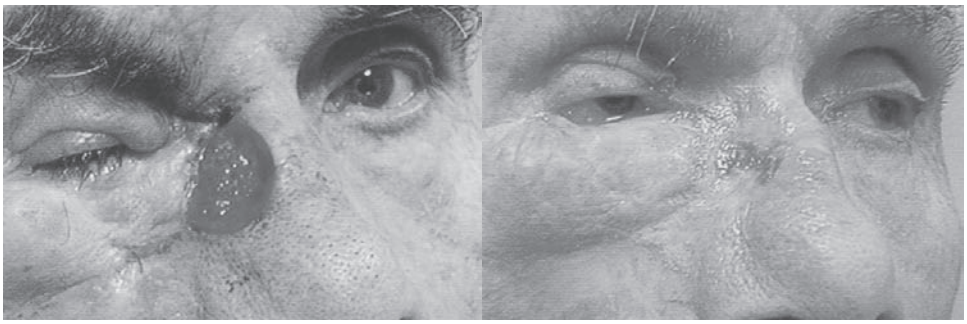


**FIGURE 23-12.** Tumor involving the nose and medial canthus before and after external radiation therapy.

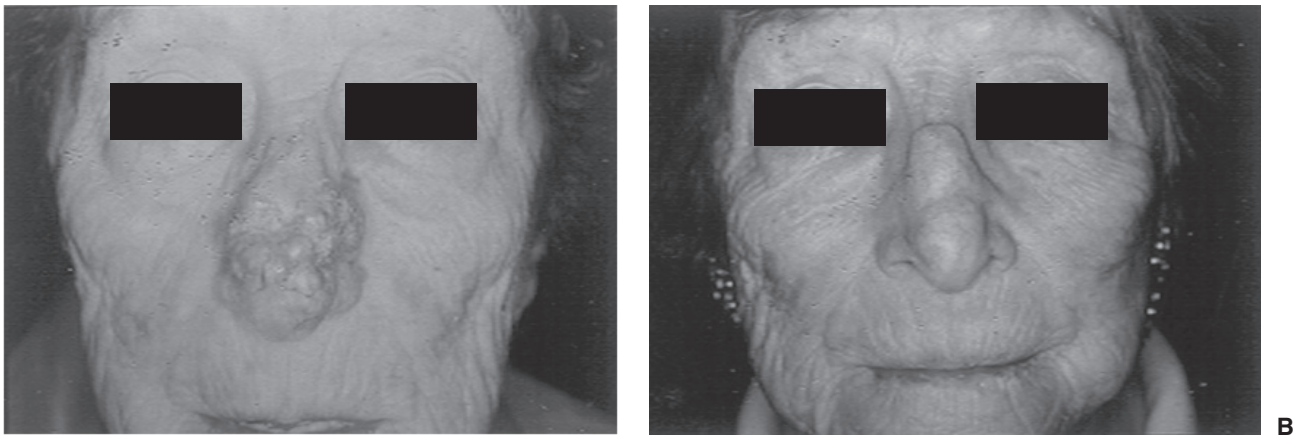
*Source:* Photos courtesy of Dr. Harrison.

Fitzpatrick[132] reviewed 1,062 patients with BCC or SCC of the eyelids and found local control rates of 95% and 93%, respectively (Table 23.8). Technique must take into account the lens that is typically shielded, as well as the lacrimal gland to avoid dry eye after treatment. Most tumors arise in the lower lid or medial canthus.[133] Tumors are treated with 1 to 1.5 cm margins using fraction size of 3 Gy or less.

## TREATMENT ALGORITHM

### T1 and Small T2 Tumors

Most patients with T1 and small T2 basal or SCCs of the skin can be treated with any of the aforementioned treatments and expect recurrence rates of <10%, usually with good or excellent cosmetic and functional outcome. High-risk tumor factors should be taken into account and should be treated with Mohs surgery or radiation therapy (Tables 23.2 and 23.3). In addition, crucial to the decision regarding treatment modality is the anatomic area of the lesion and the specific treatment-related morbidity with respect to the individual patient. Few studies have compared different treatment modalities in a randomized prospective manner. A pivotal trial from the Institut Gustave-Roussy compared surgery and radiation therapy.[126] Because this study used techniques which are not used today, the results are of questionable value in the current era. This trial prospectively enrolled 347 patients with <4 cm BCC of the face and randomized them to surgery versus radiation therapy. The primary endpoint was the failure rate (persistent or recurrent disease) after 4 years of follow-up. The secondary endpoint was the cosmetic result assessed by the patient, the dermatologist, and three persons not involved in the trial. Of the 174 patients in the surgery group, 71% had local anesthesia and 91% frozen section examination. Of the 173 patients in the radiotherapy group, 55% were treated with interstitial brachytherapy, 33% with contact therapy, and 12% with conventional radiotherapy. The 4-year actuarial failure rate (95% confidence interval [CI]) was 0.7% (0.1%–3.9%) in the surgery group compared with 7.5% (4.2%–13.1%) in the radiotherapy group (log-rank $p = 0.003$). The cosmetic results assessed by four of the five judges were significantly better after surgery than after radiotherapy. Eighty-seven percent of the surgery-treated patients and 69% of the radiation-treated patients considered the cosmetic result as good ($p < 0.01$). A follow-up study compared the cosmetic outcomes of these patients as noted by five different evaluators, as well as photographic evaluation. This also showed a better cosmetic outcome for the patients treated with surgery. Proponents of radiation therapy note that patients treated with radiation in this trial were treated with suboptimal techniques compared with what is typically done currently. One of the key advantages to radiation therapy for NMSC is the noninvasive aspect of the therapy. Fifty-five percent of patients in the radiation arm of this trial were treated with brachytherapy, an invasive form of delivering radiation therapy yielding poorer cosmesis. In addition, many patients were treated with large fraction size. As discussed previously, large fraction size is associated with greater late morbidity and suboptimal cosmetic outcomes. Although the



**A** **B**

**FIGURE 23-13. A, B:** Multifocal basal cell carcinoma of the nasal skin, before **A** and after **B** RT. Patient treated with 6,000 cGy in 6 weeks with 6 MeV electrons and custom bolus.

*Source:* Photos courtesy of Dr. Harrison.

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**TABLE 23.7 Radiation Therapy Outcomes for Basal Cell Carcinoma (BCC) and Squamous Cell Carcinoma (SCC) of Nasal Skin**

| Author | Histology | Follow-up (Years) | No. of Patients | Local Control (%) | Cosmesis (Good/ Excellent) (%) | Grade 4 Toxicity (%) |
|---|---|---|---|---|---|---|
| Tsao et al. (1997)[128] | SCC | 5.0 | 100 | 85 | — | 0 |
| Petrovich et al. (1987)[125] | BCC and SCC | 5.0 | 350 | 95 | — | — |
| Childers et al. (1986)[129] | BCC | 9.3 | 26 | 96 | 81 | 0 |

recurrence rate with radiation therapy was higher than surgery in this trial, salvage rates for patients who have recurrences after radiation therapy are excellent with more radical surgical approaches. This trial showed that outcomes with either surgery or radiation provide excellent outcomes, and the practitioner must therefore individualize the optimal treatment strategy for each patient. Surgical techniques involve removal of tissue, and when in critical areas of function and cosmesis, reconstruction must be done to achieve adequate outcomes. Radiation therapy results in destruction of the tumor, but functional and cosmetic result is limited by the amount of destruction already done by the primary tumor. The tissue deficit after destruction of the tumor may be unacceptable. Therefore, the best approach is often a multidisciplinary one including medical, surgical, and radiation techniques. For most small lesions of the head and neck, either surgery or radiation provides excellent outcomes, cosmesis, and function. Surgery has the advantage of limited office visits and should be considered for most patients. Patients who undergo resection with positive margins should undergo additional resection or adjuvant radiation therapy. Again, the advantage of Mohs surgery is that residual tumor is identified and further excision can be completed on the same day. Pathology showing extensive perineural involvement or large nerve involvement should also be treated with adjuvant radiation therapy. Elderly patients, especially those who are unable to undergo resection and reconstruction, or who are at risk for poor wound healing, may benefit from radiation therapy. In addition, larger lesions involving the tip of the nose, the eyelids, and the pinna may sometimes be treated preferentially with radiation therapy because reconstruction in these areas may be less likely to provide adequate cosmetic and functional outcome. When surgical techniques are concerned, Mohs micrographic surgery allows control of margins and results in minimal tissue removal. The goal with standard surgical resection is to achieve margins of 4 mm or more with BCC and 1 cm with SCC, but it is important to note that normal tissue may be significant when taking margins, resulting in a large deficit. This may be required for complete removal. When radiation therapy is used, treatment with fraction size <4 Gy results in optimal cosmesis. In cases where bone or cartilage is likely to be included in the treatment field, one should consider fraction sizes of <3 Gy. Regardless of chosen modality, the recurrence rate should be <10% and 90% of patients should have good or excellent cosmetic outcomes with minimal morbidity. A treatment algorithm based on NCCN recommendations is provided for low-risk BCC and SCC in Figure 23-15 and for high-risk BCC and SCC in Figure 23-16.

## Recurrent Tumors

Recurrent tumors should be treated similar to primary lesions, although recurrence rates are generally 5% to 10% higher. Before initiating treatment, the tumor should be thoroughly reevaluated, particularly for extent of invasion. Treatment with a margin evaluating modality (Mohs) or wide-margin treatment (radiation therapy) results in lower recurrence rates. Rowe et al. reviewed outcomes for patients with recurrent BCC.[120] The 5-year recurrence rate was 5.6% for Mohs micrographic surgery and 9.8% for radiation therapy. Recurrence rates with other modalities were >17%, with the highest recurrence rate for curettage and electrodesiccation at 40%. Figures 23-17 and 23-18 show two clinical examples of recurrent disease.

## Locally Advanced and Metastatic Disease

Large T2 and T3 tumors can also be treated with either surgical resection or radiation therapy. Mohs micrographic surgery is the preferable surgical technique for these tumors to achieve negative margins. Radiation therapy allows for normal tissue sparing, and local control rates of >80% can be achieved when including those salvaged with surgery.[134] While most BCCs are adequately controlled with these interventions, patients with inoperable tumors or innumerable BCCs not amenable to surgery have had fewer treatment options. As a result, the development of targeted molecular therapy for BCC has been met with considerable excitement.[135] Targeted molecular therapy for BCC has focused mainly on the Hedgehog signaling pathway. Patched (PTCH) and



**FIGURE 23-14.** Eyelid nonmelanoma skin cancers (NMSCs) before and after external radiation therapy.
*Source:* Photos courtesy of Dr. Harrison.

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**TABLE 23.8 Outcomes with Radiation Therapy for Periorbital Nonmelanoma Skin Cancer (NMSC)**

| No. of Patients | F/U | Recurrent | Primary | BCC | SCC | Local Control BCC | Local Control SCC |
|---|---|---|---|---|---|---|---|
| 1,062 | 5 yr | 25% | 75% | 90% | 10% | 95% | 93% |

F/U, follow-up; BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

*Source:* From Fitzpatrick PJ, Harwood AA. Acute epithelioma—an aggressive squamous cell carcinoma of the skin. *Am J Clin Oncol*. 1985;8:46–71, with permission.

smoothened (SMO) are two key genes involved. PTCH, a member of the patched gene family, is a receptor important for its inhibition of SMO, a protein that results in downstream target gene transcription. Mutations in PTCH that result in continuous SMO activation are the most common genetic alterations found in BCC. GDC-0449 or vismodegib (Genentech, San Francisco, CA) is a small molecule inhibitor of the SMO protein. In a recently reported phase I study, 18 of 33 patients with BCCs that could not be treated with surgery, radiation, or other systemic therapy had an objective response to the drug on a basis of imaging, physical examination, or both. There were two complete responders and 16 partial responders, defined as a 50% reduction in visible or palpable tumor.[136] In another open-label, multicenter two cohort phase II study, 43% of patients with locally advanced BCC and 30% of patients with metastatic BCC showed improvement from baseline. Side effects included muscle spasms, hair loss, altered taste sensation, weight loss, fatigue, nausea, decreased appetite, and diarrhea.[137]

The presence of perineural invasion has been shown to be a significant factor in determining outcome. A clear distinction has been made between perineural invasion that is clinically obvious (cPNI) versus perineural invasion which is not clinically apparent, but is pathologically evident (pPNI). Postoperative RT has been used in both of these situations, with the general consensus that it improves the outcome. Jackson[138] reviewed 118 patients with PNI (97 with pPNI and 21 with cPNI) who received RT. With medial follow-up of 84 months (range 4–201), local control was 90% and 57% ($p < 0.001$) for pPNI and cPNI, respectively. This translated into worse relapse-free survival, disease-specific survival, and overall survival (76% vs. 46%, $p = 0.003$; 90% vs. 76%, $p = 0.002$; 69% vs. 57%, $p = 0.03$, respectively). Basal cell cancers with pPNI had better local control than squamous cell cancers with pPNI (97% vs. 84%, $p = 0.02$).

For patients presenting with nodal disease, neck dissection, radiation therapy, or a combination is effective, although there are limited data in the literature. Combination therapy for regional disease is associated with a 5-year cure rate of 30% to 40%.[53] NCCN recommends consideration of adjuvant radiation therapy for patients with multiple nodes positive, extracapsular extension, and nodes >3 cm after neck dissection.[70] Radical neck dissection and modified neck dissections may be helpful for debulking metastatic cervical disease.[139] Taylor et al. reviewed 60 patients with NMSC metastatic to regional nodes. Fifty-seven of these patients had SCC. At a follow-up of 2 years, local control was 63% with surgery alone, 46% with radiation alone, and 89% with a combination. Of the 60 patients, 30 (60%) underwent combined modality therapy.[140] Moore[141] reported 193 patients with squamous cell skin cancer of the head and neck. Twenty-one percent had nodal metastases. Interestingly, the nodal disease was not clinically apparent in 42% of cases. Recurrent cancers, lymphovascular invasion, perineural invasion, and inflammatory changes were factors predisposing patients to nodal disease. Regional control with surgery and postoperative RT was 95%.

Treatment of metastatic SCC may include systemic chemotherapy or treatment with biologic response modifiers, but the efficacy of these therapies has not been well established.[142–144] Epidermal growth factor receptor (EGFR) inhibitors are a new class of medicines which are proving effective in the treatment of locally advanced and metastatic cutaneous SCC.[145] A recent study of 8 patients with unresectable or metastatic cutaneous SCC showed that treatment with cetuximab alone or with concomitant radiotherapy can be effective, with 6/8 responses, including three complete responses, and a median overall survival of 22.5 months.[146]

Metastatic BCC is a rare occurrence with an estimated incidence of 0.03%.[147] Until recently, with the exception of isolated

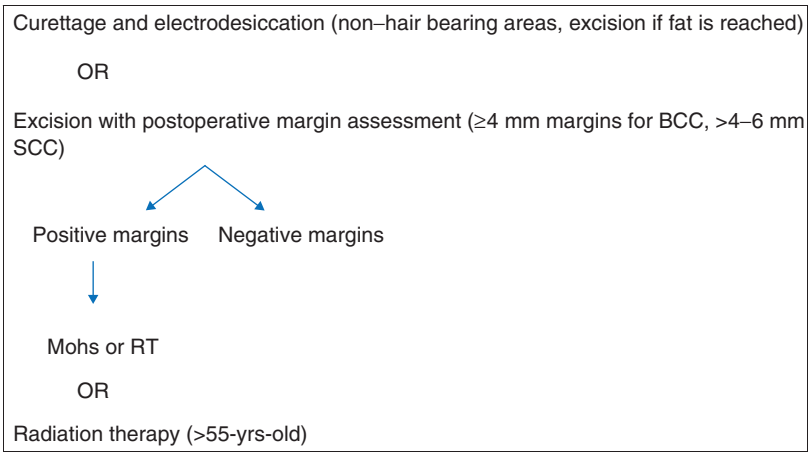



**FIGURE 23-15.** National Comprehensive Cancer Network (NCCN) treatment algorithm: local low-risk basal and squamous cell skin cancer of the head and neck.

*Source:* National Cancer Comprehensive Network. *National Cancer Comprehensive Network Guidelines*. http://nccn.org, 2007, with permission.

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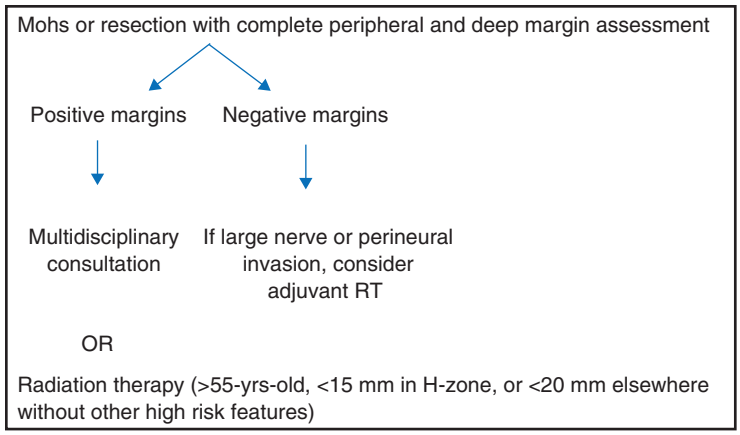



**FIGURE 23-16.** National Comprehensive Cancer Network (NCCN) treatment algorithm: local high-risk basal and squamous cell skin cancer of the head and neck.

*Source:* National Cancer Comprehensive Network. National Cancer Comprehensive Network Guidelines. http://nccn.org, 2007, with permission.

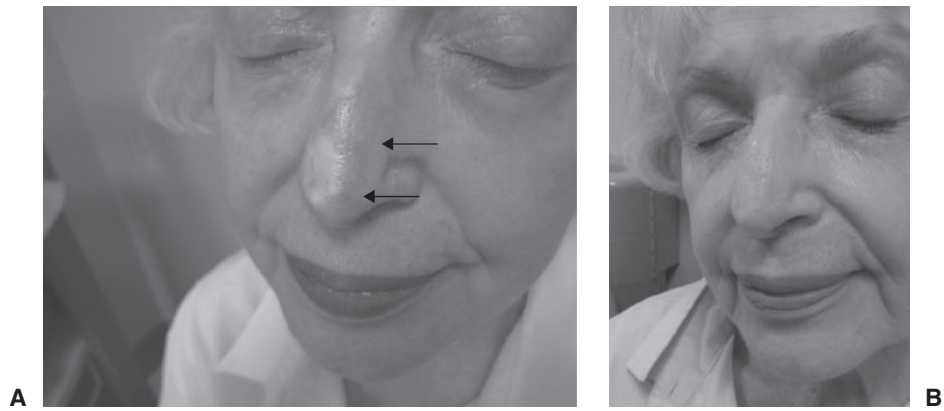



**FIGURE 23-17.** **A**: Patient had Mohs surgery and developed local recurrence in two separate locations along the margin of resection. This is a basal cell carcinoma. **B:** Patient was treated with radiation therapy using 6 MeV electrons and custom bolus. The dose was 6,000 cGy in 6 weeks. She remains free of disease.

*Source:* Photos courtesy of Dr. Harrison.

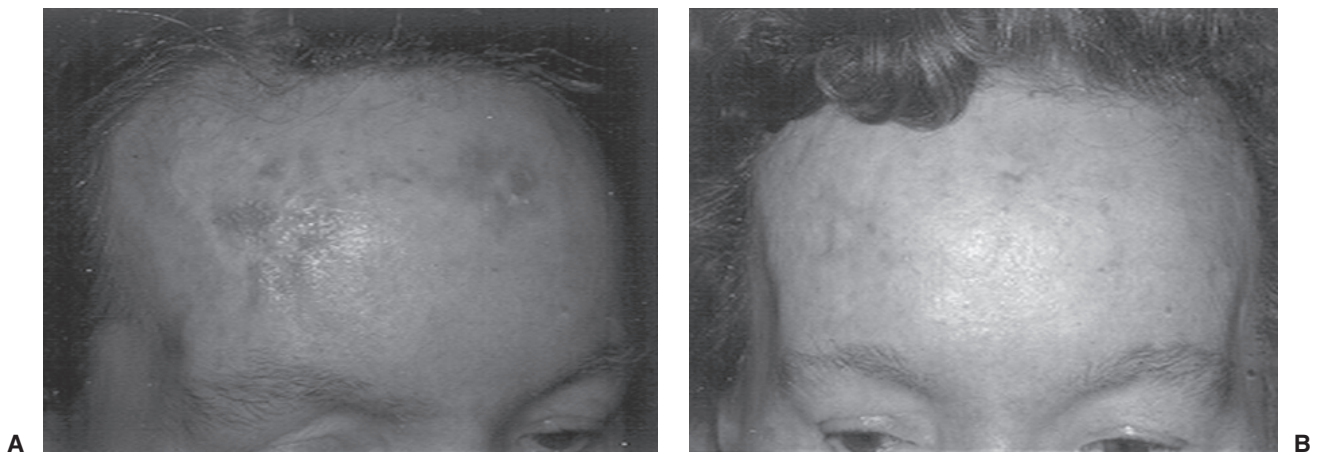



**FIGURE 23-18.** Multifocal recurrence of squamous cell cancer of the skin of the forehead, before **(A)** and after **(B)** RT. Patient treated with 6,000 cGy in 6 weeks with 6 MeV electrons and 1 cm bolus.

*Source:* Photos courtesy of Dr. Harrison.

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case reports, radiation, surgery, and chemotherapy for metastatic BCC yielded only disappointing results.[148,149] However, the advent of targeted molecular inhibitors has given new hope to this small subset of BCC patients. Further studies will provide a better understanding of the full potential of vismodegib, cetuximab, and other targeted molecular therapies in the treatment of advanced NMSC.

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# PART B:
# Radiologic Imaging Concerns

Jeffrey A. Bennett

The role of imaging for the patient with skin cancer, similar to any other head and neck cancer, is to determine the full extent of the primary tumor, with special attention to bone invasion, perineural spread, and lymphatic spread. Initial inspection of the primary site involves evaluation of the subcutaneous fat, and deep to that, the superficial musculoaponeurotic system (SMAS) (Fig. 23-19). Evaluation of the SMAS and the fat plane deep to it is critical as this is where branches of the facial nerve and trigeminal nerve innervate the muscles of facial expression. Once the SMAS is involved by tumor, the more proximal course of the facial and trigeminal nerves need to be examined to look for more extensive perineural spread (Fig. 23-20).

Imaging helps to determine the extent of cosmetic reconstruction that may be required. It is critical to evaluate bone invasion in this regard. CT is more sensitive than MRI for the detection of cortical bone invasion (Fig. 23-21), but MRI may be better for showing bone marrow extension. Critical areas for cosmesis include the orbits and also the eyelids where basal cell cancer is common[1] (Figs. 23-22 and 23-23). When skin cancer invades the calvarium, MRI should be obtained to evaluate the extent of dural or brain involvement (Fig. 23-24).

Perineural spread of skin cancer can occur with squamous cell cancer and basal cell cancer.[2] Central perineural spread is more common in basal cell or basaloid squamous lesions,[3] and skip lesions are possible. Therefore, the more proximal cranial nerves 5 and 7 should be evaluated with imaging. CT can show perineural spread, but MRI is definitely preferred (Figs. 23-25 and 23-26).[4–6] A recent study was performed to

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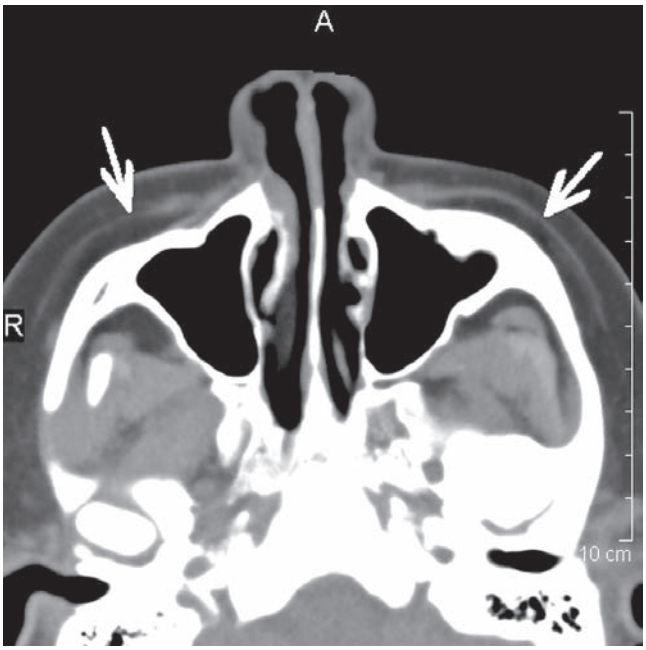



**FIGURE 23-19.** Axial CT scan shows the normal thin line of soft tissue (*arrows*) deep to the subcutaneous fat, which is the superficial muscoloaponeurotic system (SMAS) consisting of the muscles of facial expression and small branches of the facial and trigeminal nerves.

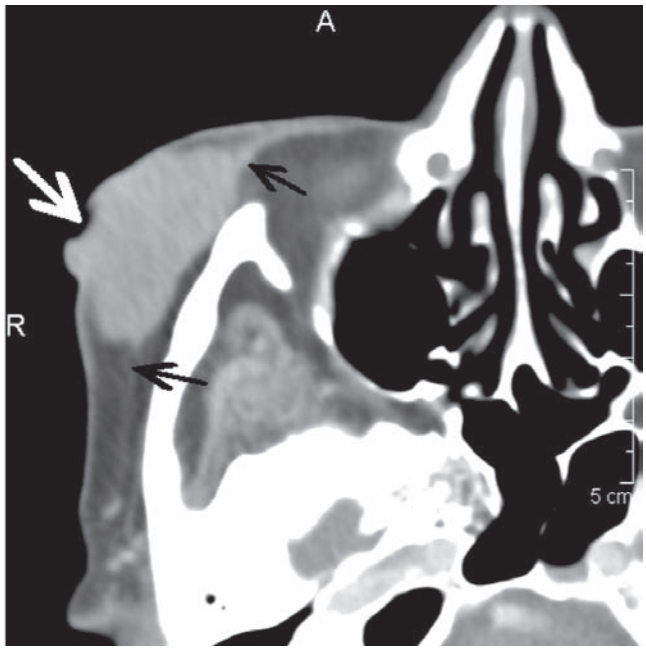
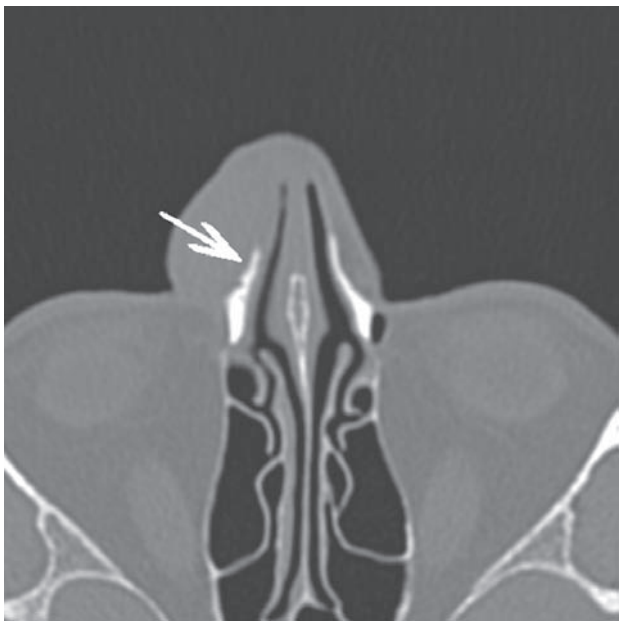



**FIGURE 23-20.** Axial contrast-enhanced CT scan showing an ulcerated Merkel cell cancer of the skin (*white arrow*), which has invaded and engulfed the superficial musculoaponeurotic system (*black arrows*).



A



B

**FIGURE 23-21.** **A:** Axial CT scan with bone windowing shows a right-sided squamous cell cancer of the nose, which has invaded and eroded the nasal bone (*arrow*). Notice the irregular contour of the outer surface of the bone. **B:** Axial noncontrast T1-weighted MR image of the same patient shows the low signal tumor invading the medial orbital septum (*arrow*).

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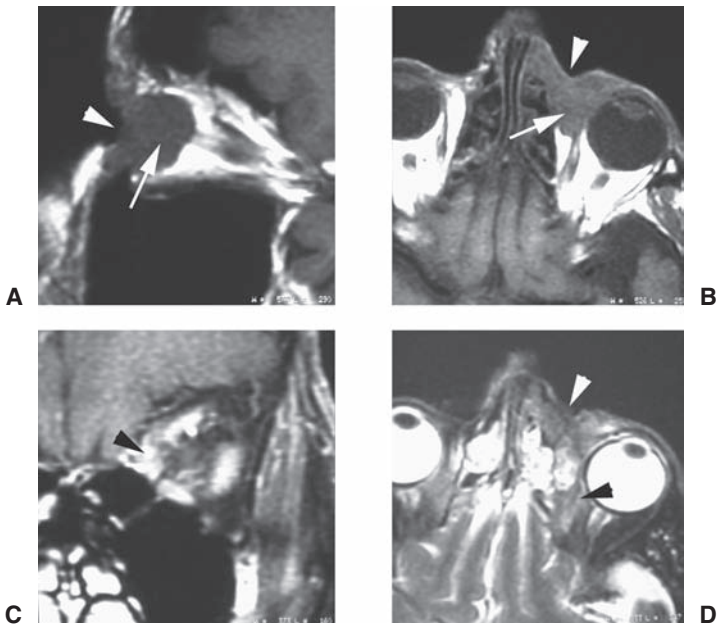



**FIGURE 23-22.** Recurrent skin cancer (clockwise from top left). **A:** Sagittal T1, **B:** axial T1, **C:** axial T2, and **D:** contrast coronal T1 images show an ulcerated squamous cancer recurrent at the medial canthus of the eye (*white arrowheads*) with deep postseptal extension (*arrows*) and invasion of the extraocular muscles (*black arrowheads*).

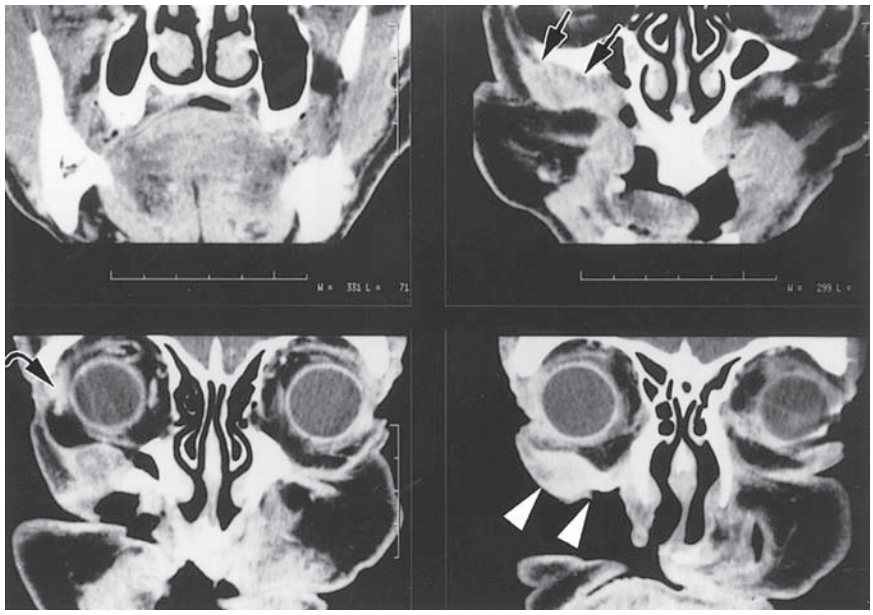
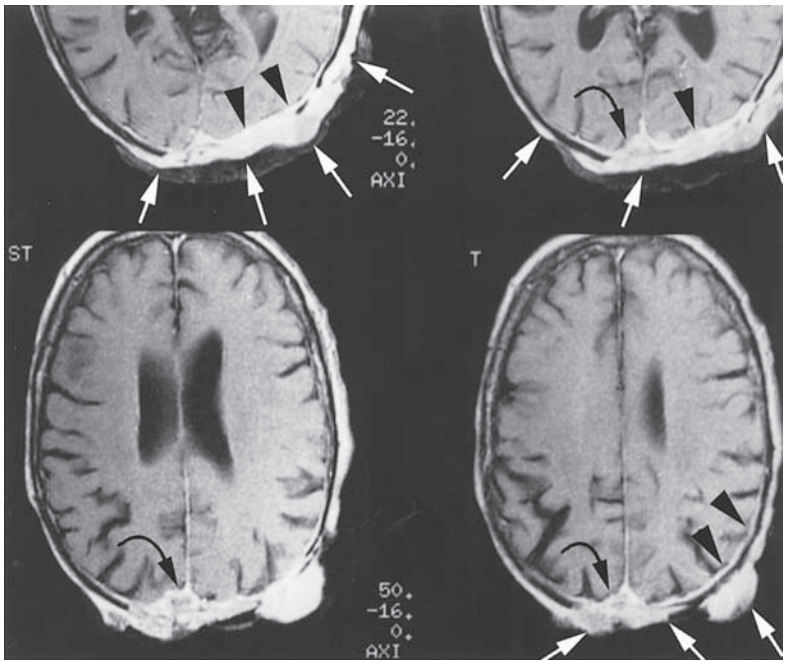
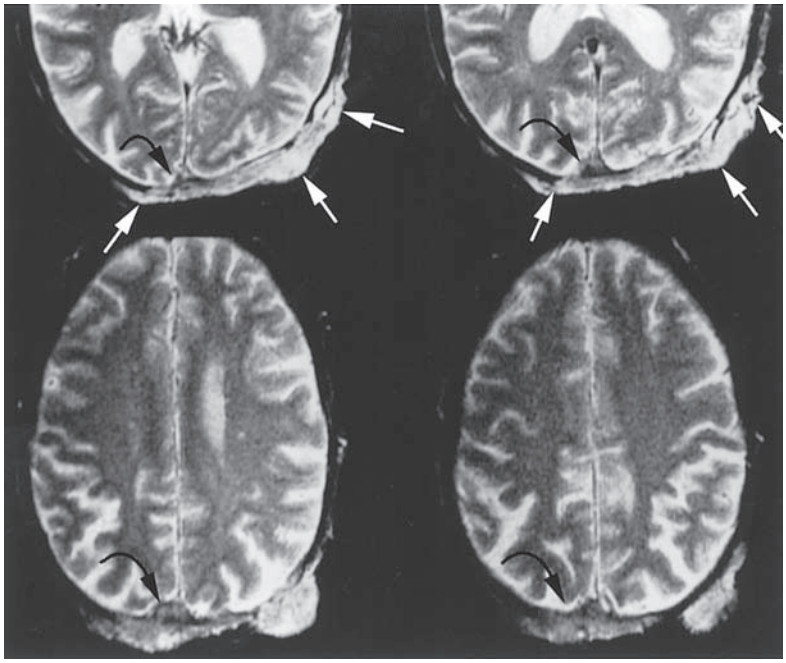


**FIGURE 23-23.** Limited orbital involvement. Enhanced direct coronal views through the face show ulcerating skin lesion (*arrowheads*) poorly marginated with the orbital rim (*arrows*), with early invasion of the extraconal compartment of the orbit. Normal lacrimal gland (*curved arrow*).

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A



B

**FIGURE 23-24.** Extensive scalp cancer. **A:** Serial-enhanced axial T1 magnetic resonance imaging. **B:** T2 magnetic resonance imaging shows extensive scalp lesion (*arrows*) with an intracranial extradural component (*arrowheads*) and direct invasion of the superior sagittal sinus (*curved arrow*). No cortical abnormality to indicate pial involvement.

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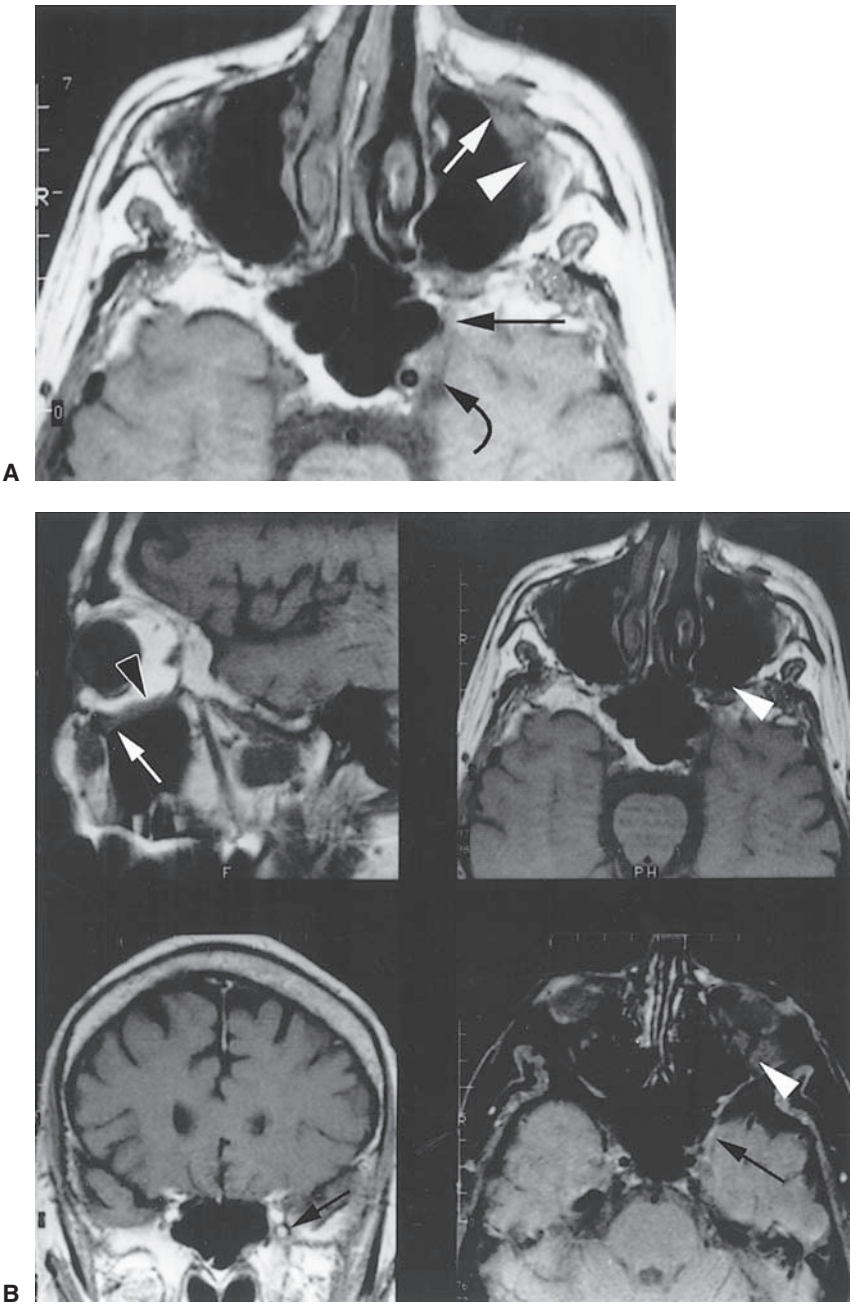


**FIGURE 23-25.** Neurotropic basal squamous cancer. Axial T1 magnetic resonance imaging **(A)** and fat-suppressed contrast axial T1 **(B)** views showing proximal neurotropic involvement entering the infraorbital foramen (*arrow*), extending along the inferior orbital groove (*arrowheads*), through the expanded foramen rotundum (*long arrow*), and into the cavernous sinus (*curved arrow*), producing anesthesia of the second division of the fifth nerve, despite healed primary nasolabial site.

determine the accuracy of well-protocoled MRI for the detection of perineural spread of malignancy.[7] This study not only found a 100% detection rate, but also showed that MRI underestimates microscopic spread proximal to the Gasserian ganglion.

Lymphatic spread is usually a late finding. Common sites of spread are to intraparotid nodes, as well as occipital and level 5 nodes (Fig. 23-27). Facial nodes are also at risk (Fig. 23-28).

Recurrent skin cancer should be imaged as spread may be deeper than appreciated on physical exam, and perineural extension is quite common. Image-guided biopsies are usually an option when disease recurrence is suspected in deep locations such as the pterygopalatine fossa or in lymph nodes. FDG-PET may be useful for recurrent squamous cell cancer or Merkel cell cancer. Distant metastasis from basal cell cancer is rare. Suggested protocols are given in Figures 23-29 to 23-31.

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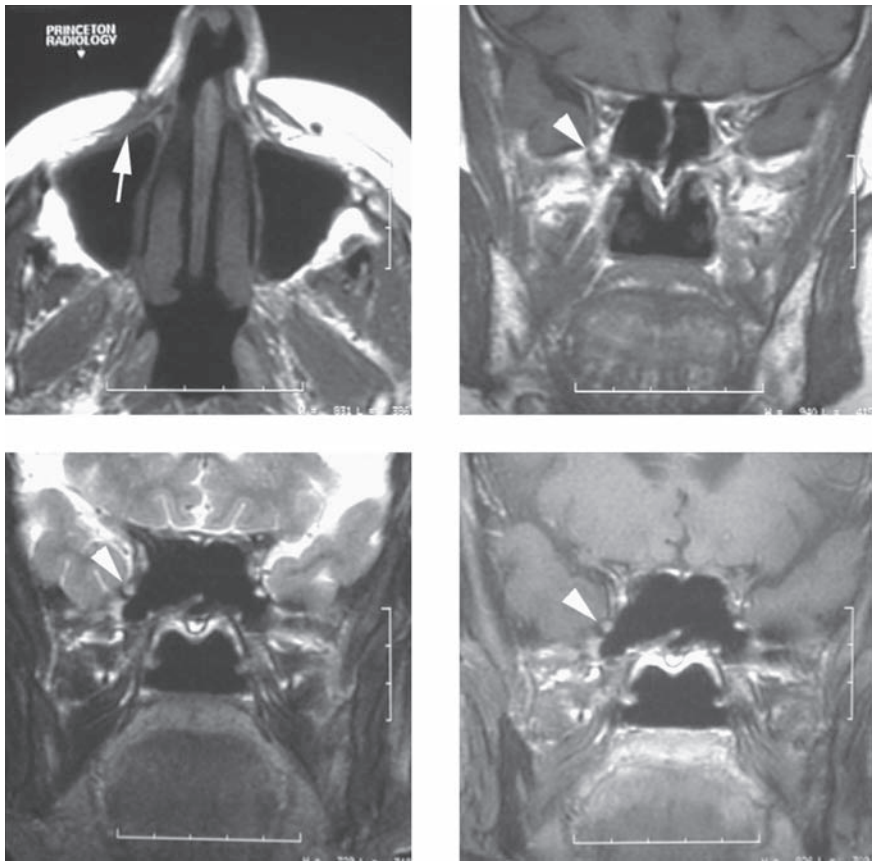



**FIGURE 23-26.** Neurotropic extension. Abnormal enhancing signal at right foramen rotundum (*arrowheads*) remote from recurrent right nasolabial lesion (*arrow*) related to perineural extension along the maxillary nerve.

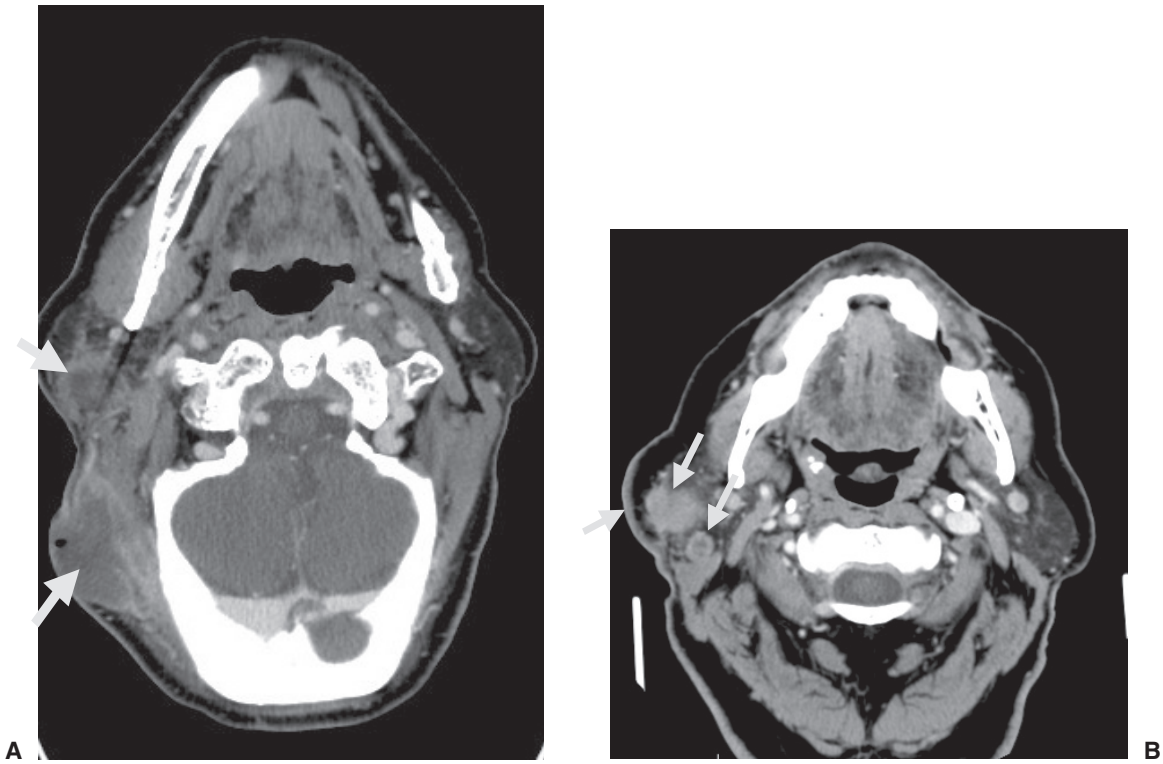
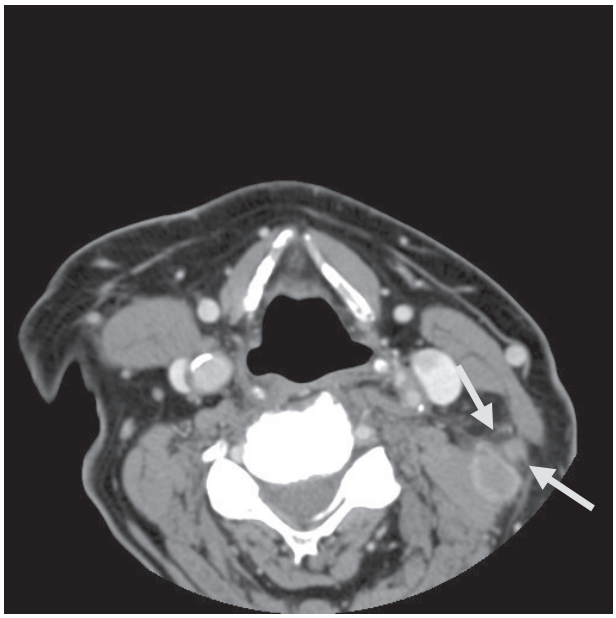



**FIGURE 23-27.** When to think of skin cancer: **A:** Axial contrast-enhanced computed tomographic (CT) image of the skull base shows a posterior scalp skin cancer (*large arrow*) demonstrating classic lymphatic spread resulting in a metastatic intraparotid lymph node (*short arrow*). **B:** Axial contrast-enhanced CT shows two metastatic intraparotid lymph nodes (*short arrows*) due to an overlying skin cancer (*long arrow*). **C:** Contrast-enhanced CT obtained at the level of the thyroid cartilage shows isolated level V lymph nodes one of which is invading the underlying trapezius muscle. Note the extracapsular penetration (*arrows*). These atypical isolated aggressive lymph nodes are the result of an adjacent skin cancer.



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C

**FIGURE 23-27.** *Continued*

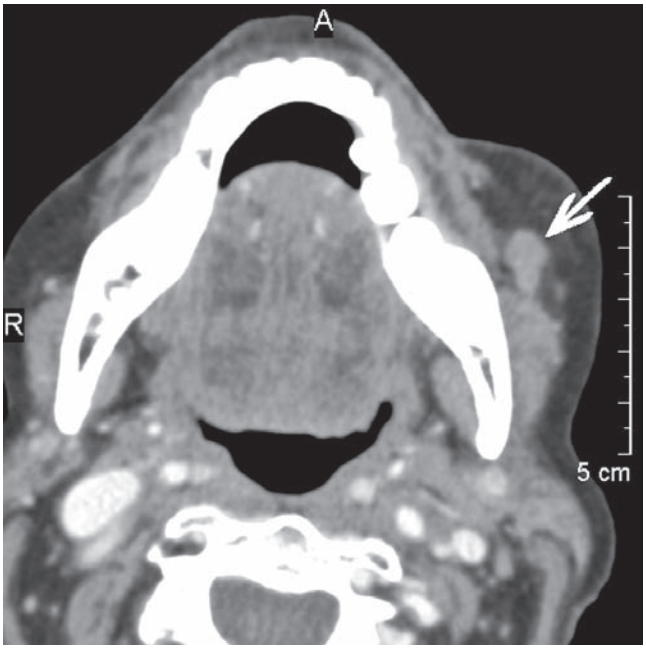
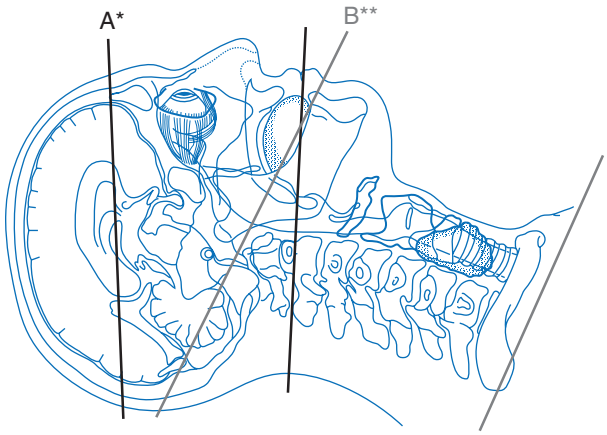


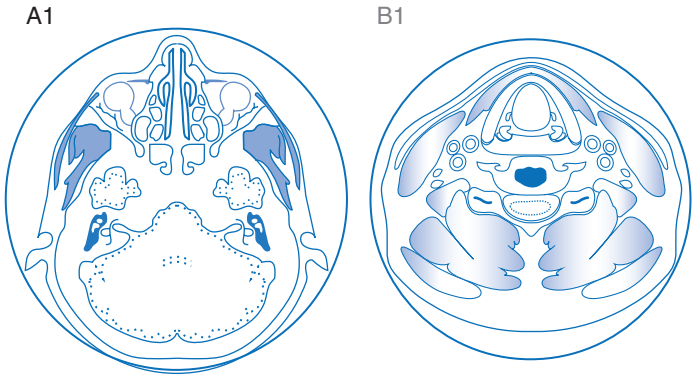

**Figure 23-28.** Axial postcontrast CT scan shows a positive facial lymph node. In this case, this was a metastasis from recurrent esthesioneuroblastoma.

ACQUISITION




| | | |
|---|---|---|
| | Patient position | Supine<br>Chin slightly elevated |
| | Contrast | 100 mL adult; 60 sec delay |
| | Injection rate | 1 mL/sec |
| | Respiration | Quiet, NO Swallowing |
| | Volume acquisition Specs | Appropriate to achieve images as specified in following reconstruction tables.<br>Head FOV. |
| A | Begin | Variable: start scan above area of interest |
| | End | Mid oral cavity |
| B | Begin | Mid oral cavity |
| | End | Clavicles |

RECONSTRUCTION




| | | |
|---|---|---|
| A2 | Algorithm | Soft |
| | Thickness | 1.5 mm |
| | Spacing | 1.5 mm |
| | F.O.V. | Cover skin |
| B1 | Algorithm | Soft |
| | Thickness | 2.5 mm |
| | Spacing | 2.5 mm |
| | F.O.V. | Cover skin |

**FIGURE 23-29.** Protocol for CT for skin cancer with intravenous contrast.

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| Acquisition | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Plane | Sagittal | Coronal | Coronal | Coronal | Axial | Axial |
| Sequence | T1 | T1 | T1 | T2-FSE | T1 | T2 |
| Contrast | None | None | Gd | Gd | Gd | Gd |
| SLT/SP | 3/0 mm | 3/0 mm | 3/0 mm | 3/0 mm | 3/0 mm | 3/0 mm |
| FOV | 16 cm | 16 cm | 16 cm | 16 cm | 16 cm | 16 cm |

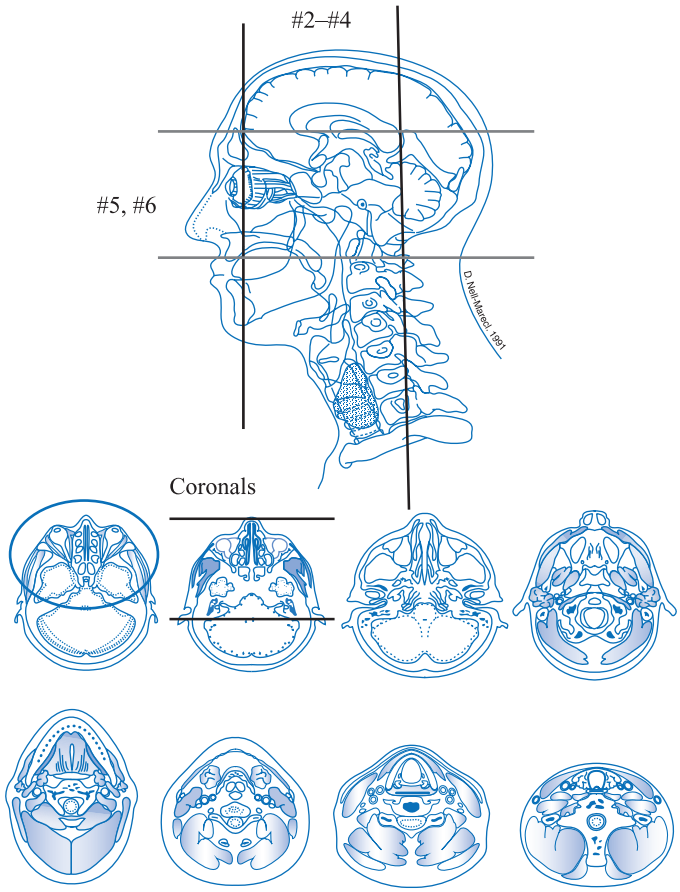



**FIGURE 23-30.** Protocol for MRI of the cavernous sinus with intravenous contrast.

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| Acquisition | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Plane | Sagittal | Axial | Axial | Axial |
| Sequence | T1 | T1 | T2-FSE | T1 |
| Contrast | None | None | None | Gd |
| Thickness/spacing | 4/1 mm | 4/0 mm | 4/0 mm | 4/0 mm |
| FOV | 24 cm | 16 cm | 16 cm | 16 cm |

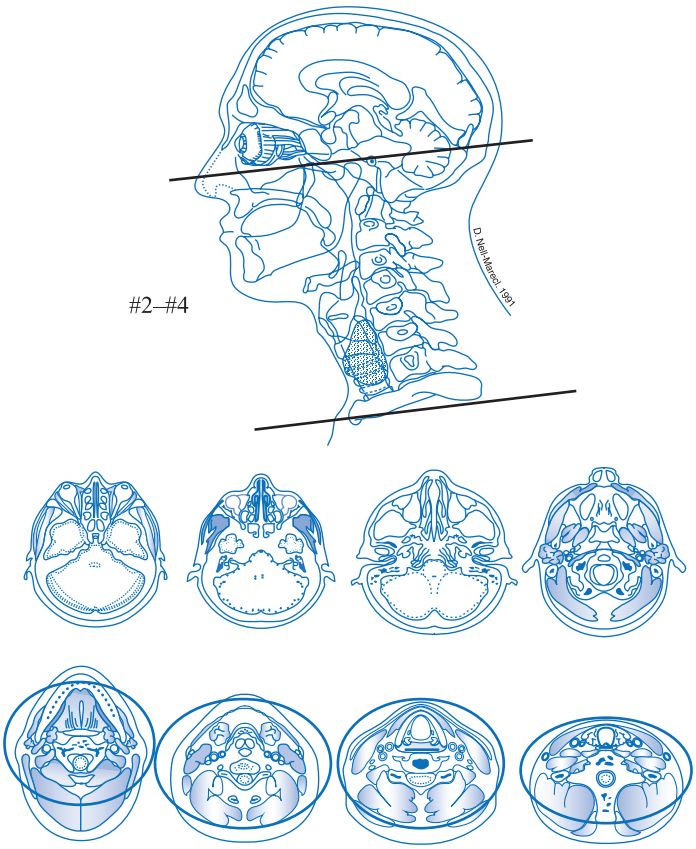



**FIGURE 23-31.** Protocol for MRI of the neck with intravenous contrast.

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# PART C:
# Radiation Therapy Technique

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Electron beam radiation therapy is the mainstay of treatment for skin cancers of the head and neck. It is important to carefully map out the extent of the lesion on the patient and add at least 1-cm margin. A larger margin up to 1.5 to 2.0 cm can be used if this does not encroach upon vital structures or if there is uncertainty about the edge of the lesion. Our practice is to place wires around the final margins, which correspond to the electron field edge. We also construct custom wax bolus of 0.5 to 1.0 cm to fit perfectly over the involved skin, to provide optimal dose distribution. This approach will satisfactorily deal with the majority of early or intermediate-sized lesions. Figures 23-32 and 23-33 show a clinical example.

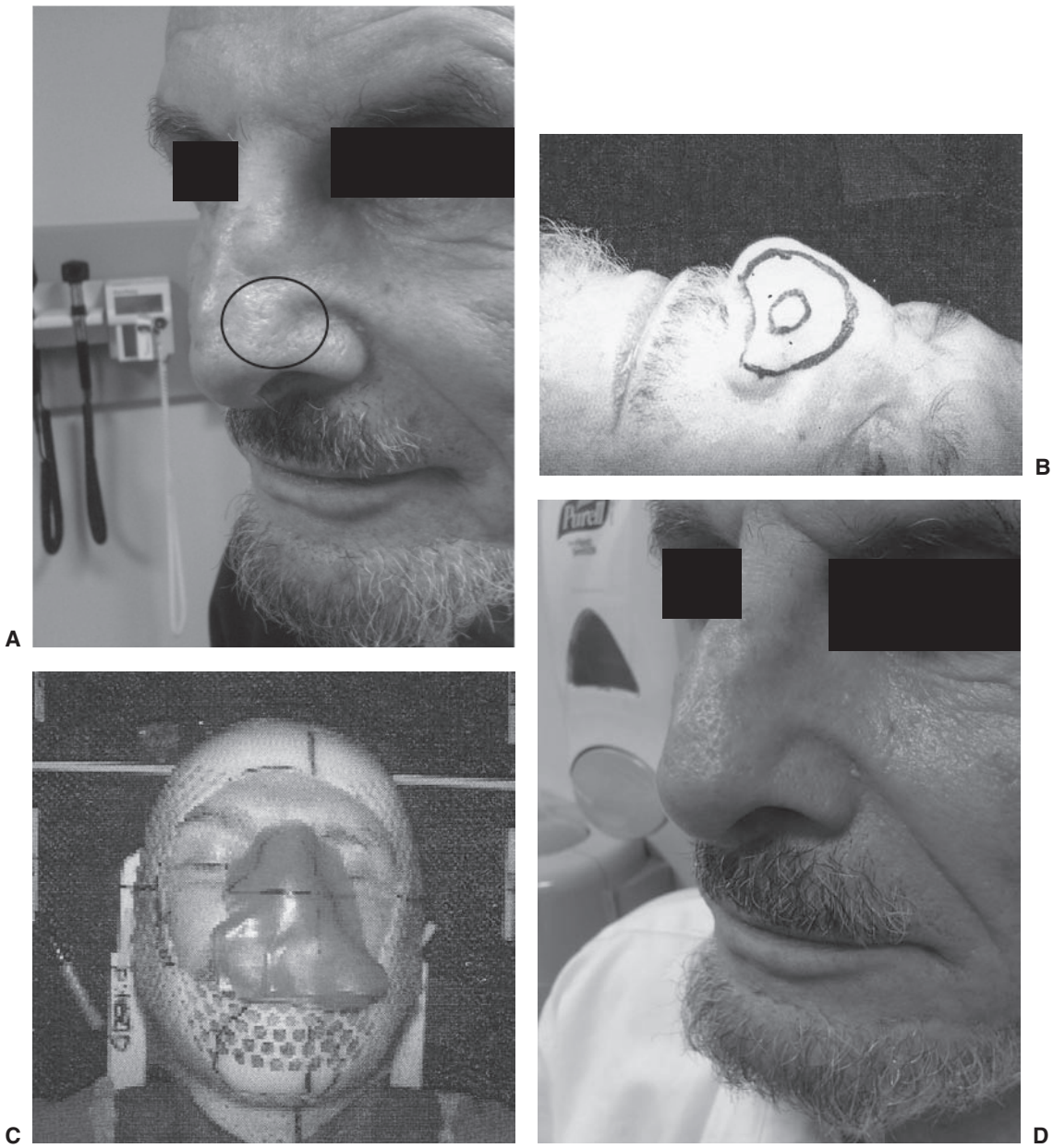



**FIGURE 23-32.** Basal cell carcinoma involving the skin of the left nasal ala. **A:** Before radiation therapy. **B:** Lesion mapped in inner circle and about 1.5 cm margin placed around lesion for electron field size. **C:** Custom was bolus placed over the nasal area, 1 cm thick. **D:** Patient received 5,100 cGy in 17 fractions using 6 MeV electrons with custom bolus. He remains without disease.

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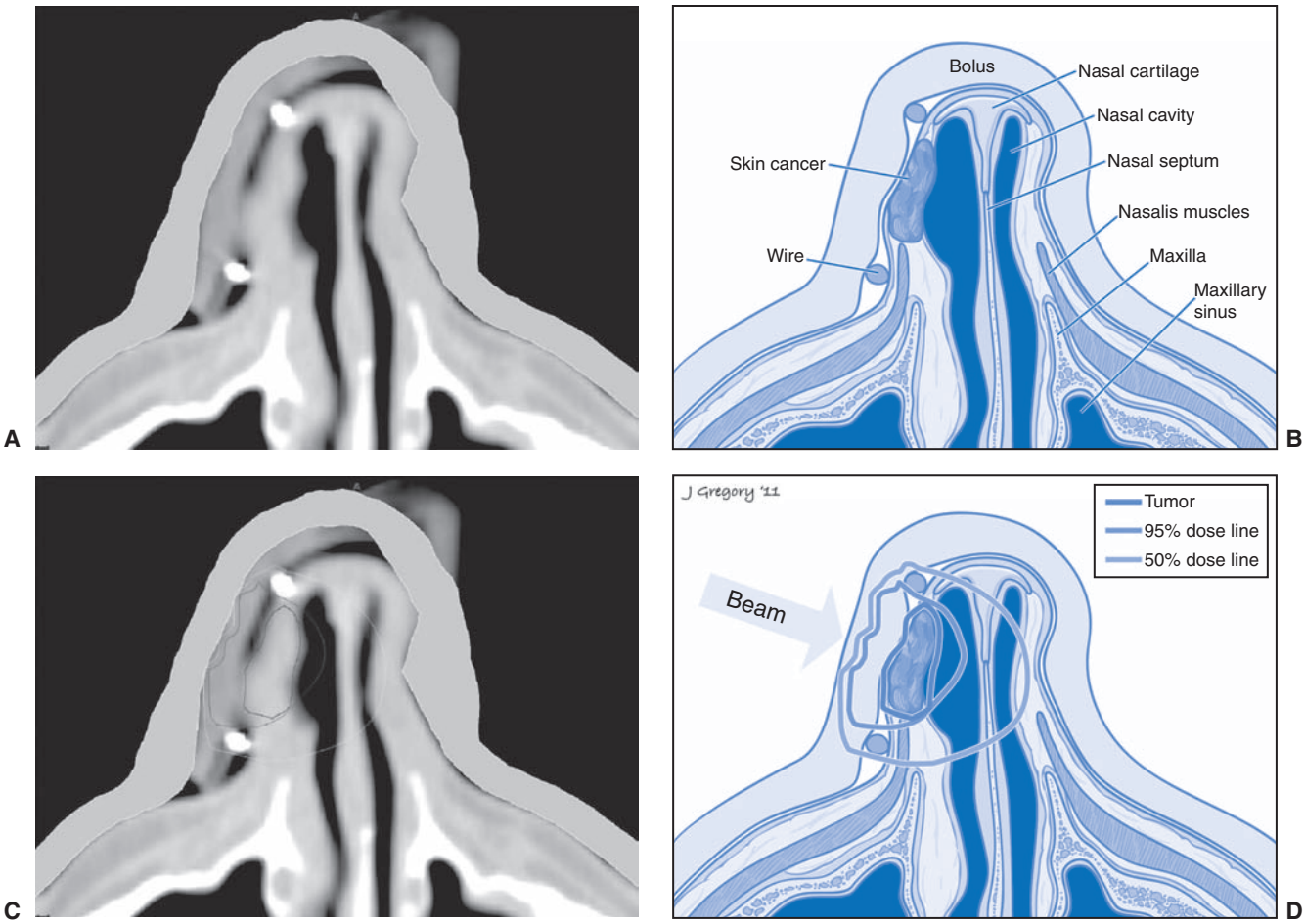



**FIGURE 23-33.** These are the images and drawing corresponding to the patient in Figure 23.32. **A:** CT planning image with custom bolus and wire around lesion visualized. **B:** Anatomical drawing corresponding to **A**. **C:** CT planning image with isodose distribution. **D:** Anatomical drawing corresponding to **C**. (See color insert.)

For more extensive lesions, more extensive planning is required. This will require CT-based planning and will often require combined photons and electrons. It is essential for the radiation oncologist to carefully assess the skin margins clinically and translate these into margins on the CT scan, as the radiologic assessment of the margins is impossible. Figure 23-34 shows a clinical example of an advanced basal cell cancer treated with definitive RT. Figure 23-35 shows a complicated recurrent squamous cell cancer of the forehead treated with combined photons and electrons to the forehead and ipsilateral neck.

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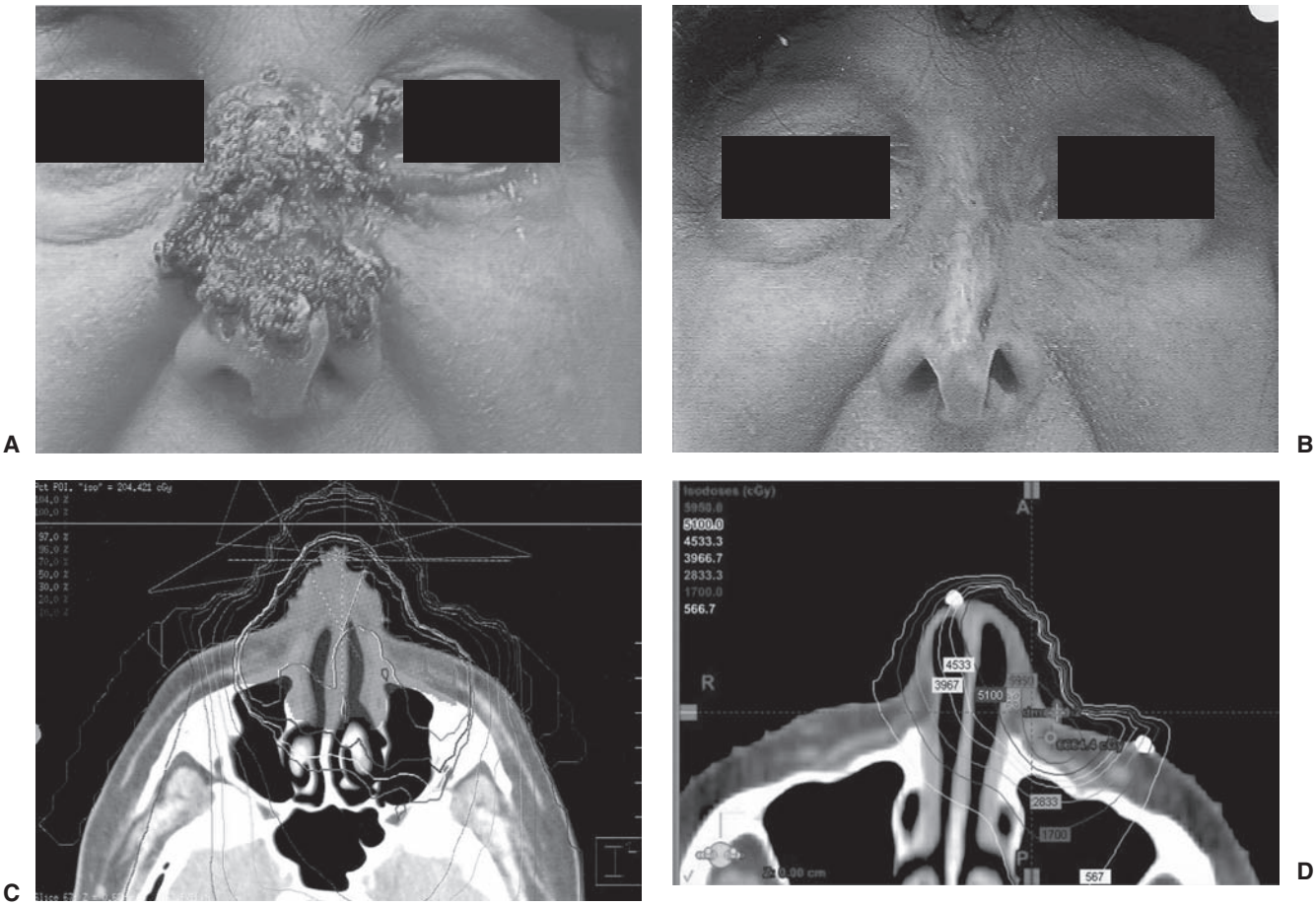



**FIGURE 23-34.** Patient neglected a basal cell cancer of the nose until it became massive, growing into both orbits, and destroying the nose. **A:** Before radiation therapy. **B:** After 6,000 cGy in 6 weeks. **C and D:** Isodose curves at 2 levels showing dose distribution of a combined 6 MeV electron and 6 MV photon plan.

*Source:* Photos courtesy of Dr. Harrison.

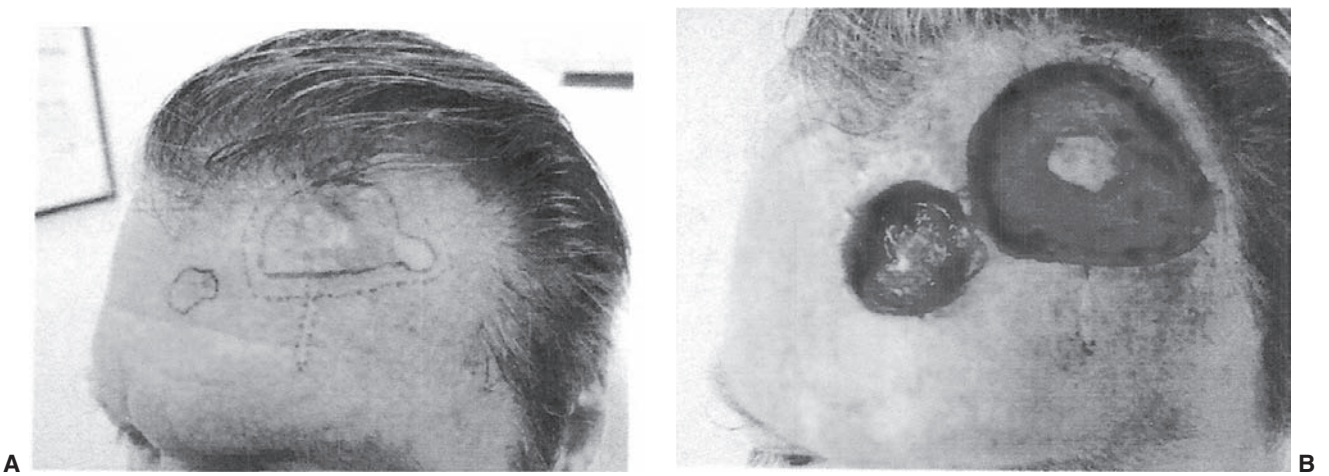
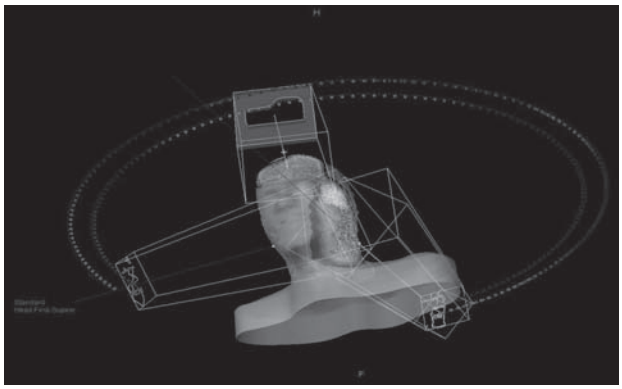


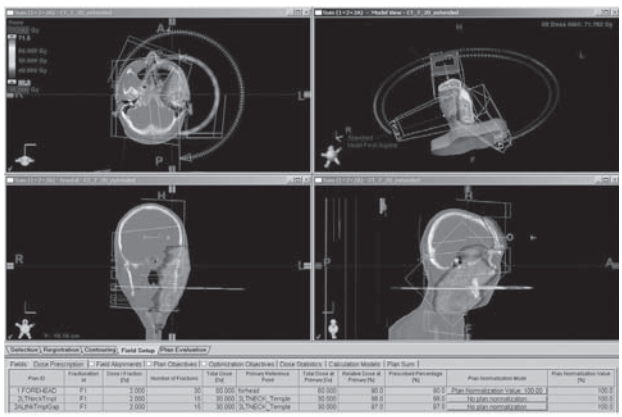

**FIGURE 23-35.** **A:** Multifocal recurrence of squamous cell cancer of the forehead status post Mohs surgery. **B:** Status post repeat Mohs resection. **C:** Patient had a sentinel node assessment revealing a positive periparotid node. We treated patient with postoperative radiation therapy to the forehead, left parotid bed, and upper neck using a combined electron and Rapid Arc photon plan. **D:** Patient received 6,000 cGy in 6 weeks to forehead and left upper neck. **E:** Patient remains disease free (no evidence of disease) in this region. NED.

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C



D



E

**FIGURE 23-35.** *Continued*

# PART D:
# Surgical Technique

Marc S. Zimbler

When analyzing facial soft tissue skin defects certain considerations are important, even before examining the defect itself. First and foremost, the reconstructive surgeon must be comfortable with the tumor extirpation itself. This is essential in cases where the reconstruction will involve the rearrangement of local tissue. Otherwise, concealing residual tumor can have devastating consequences. For many basal and squamous skin cancers of the face this means removing the lesion with Mohs micrographic surgery. In cases of melanoma, reconstruction should be delayed until permanent section analysis of surgical margins are completed. Other considerations prior to examining the defect include the patients' skin thickness, skin color and texture, and surrounding solar damage. Age and resultant skin laxity are also important when determining how much tissue advancement can be achieved and how long incisions should be made. Many skin cancer patients have had prior malignancies or recurrences, and scar tissue in the immediate or adjacent regions can influence reconstructive choices. Also, prior elective operations such as rhinoplasty or rhytidectomy can influence the surgeon's decision making. Consideration of comorbidities is also important. Many elderly skin cancer patients are on anticoagulants, have a history of diabetes, may not tolerate general anesthesia, or lack the ability to care for complex postoperative wounds. Cancer monitoring is always a major concern with more invasive tumors or recurrences. In many specific cases, a simple reconstruction is chosen initially, and then a more complex staged procedure can be performed once sufficient cancer monitoring has been obtained. The patient's own expectations are also essential to the surgeon's planning. For instance, does the patient require a complex staged surgery if his/her own aesthetic satisfaction is achieved with a simpler option. Many times the surgeon's level of aesthetic may not correlate with that of the patient. This is often a subtle distinction.

After considering these issues, it is now time to examine the defect. When examining the defect, several factors are determined initially before a reconstructive is designed. Relative to the defect three factors are essential—defect location, size, and depth. Ideally, each layer of absent tissue should be replaced by like tissue. When possible, the cutaneous defect should be closed with skin of similar thickness, color, and texture to that missing. Missing cartilage should be replaced by appropriately

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positioned, contoured, and sculpted cartilage. Facial location is critical because defects of the nose may be treated differently than others in which adjacent lax skin is abundant. Defect size is particularly important in determining whether a flap or skin graft is preferable. Depth of the defect is also considered because some are very superficial and can be treated by allowing secondary intention healing. On the other hand, deeper defects with exposed cartilage or bone may require flap coverage.

The location of the defect in relation to relaxed skin tension lines (RSTLs) and facial aesthetic subunits (Fig. 23-36A,B) is also an essential consideration in planning reconstruction. Scar orientation parallel to RSTLs or those camouflaged within facial aesthetic subunits create an optimal environment for wound healing and eventual scar formation. The importance of reconstructions utilizing these two key factors cannot be over emphasized.

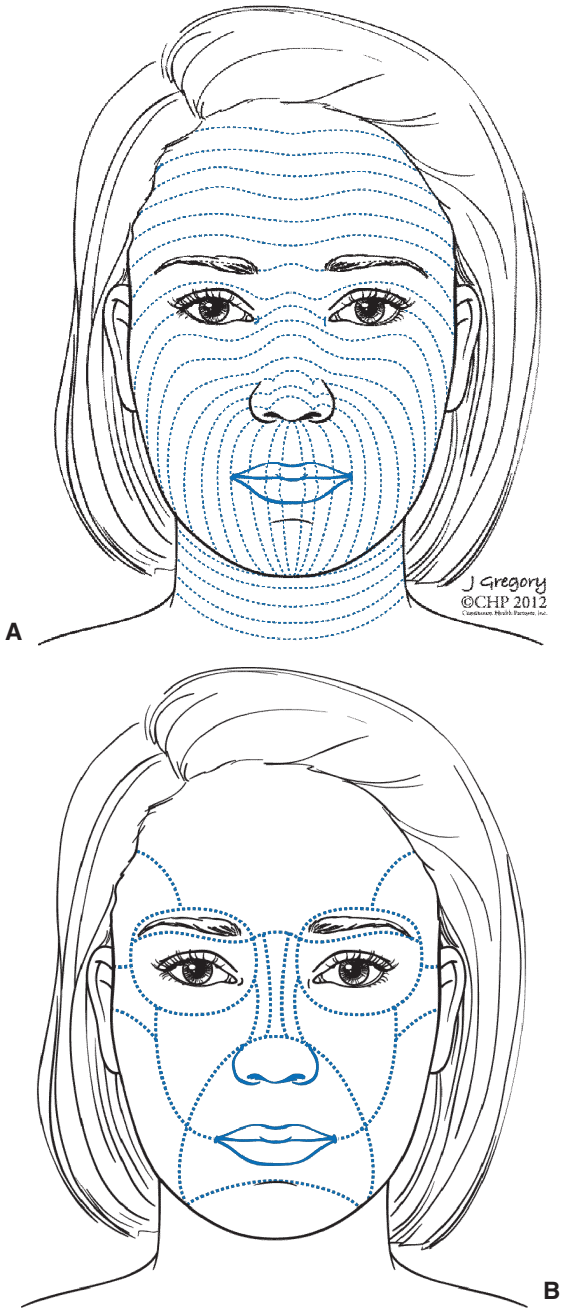



**FIGURE 23-36.** **A:** Relaxed skin tension lines (RSTLs) of the face. Incisions are designed parallel to RSTLs whenever possible. **B:** Facial aesthetic subunits. Incisions are designed at borders of facial aesthetic subunits whenever possible in order to camouflage scarring.

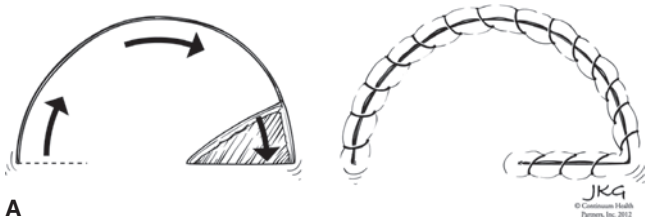
Generically speaking, options for repair include healing by second intention, primary closure, skin graft, and skin flaps—local, regional, or distal. Although most publications on reconstructive surgery concentrate on flap design, one should not underestimate primary closure as a viable source in the appropriately chosen regions. Key considerations to this method are wide subcutaneous undermining, defect size, and location. Primary closure should be the first consideration for reconstruction of a surgical defect, and especially in those patients in whom there is an abundance of adjacent lax tissue, it is often the method of choice. Many cheek and forehead defects can be closed primarily as long as they do not cause distortion of adjacent structures such as the lower eyelid and eyebrow. Key to this determination is defect size, proximity to the structure of concern, as well as laxity of the skin. Primary closure should be oriented parallel to relaxed skin tension lines or hidden within facial aesthetic subunits whenever possible. Except for small midline defects, primary closure is seldom possible on the distal nose. The size and midline location is critical to the outcome so as not to cause unilateral nasal distortion.

Skin grafts are also insufficiently discussed in the literature, even though they can play an essential role. Skin grafts on the face should be full thickness when possible. Compared with split thickness grafts, they have the advantage of creating a better color and texture match. They also create less contour irregularities, resist contraction, do not require special equipment to harvest, and are associated with less donor site morbidity. Typical donor sites for full thickness skin include postauricular, preauricular, and supraclavicular areas. Less commonly used sites are the upper forehead, upper eyelid, and nasolabial fold. When determining which site would be most appropriate to reconstruct, the surgeon must examine the defect for size, skin thickness, skin texture, and depth. Postauricular skin, which is often a first choice, is limited by amount of skin for harvest and thin nature, and often it is light colored. Preauricular skin is an excellent choice for thickness and color match, but is also limited by defect size. For larger defects, the supraclavicular region is excellent; however, skin match for the face may be suboptimal. When harvesting skin graft donor sites around the ear, prior facelift scarring can limit tissue availability. Adequate fat trimming from the skin undersurface and postoperative bolster placement are important in helping to maintain graft survivability after placement.

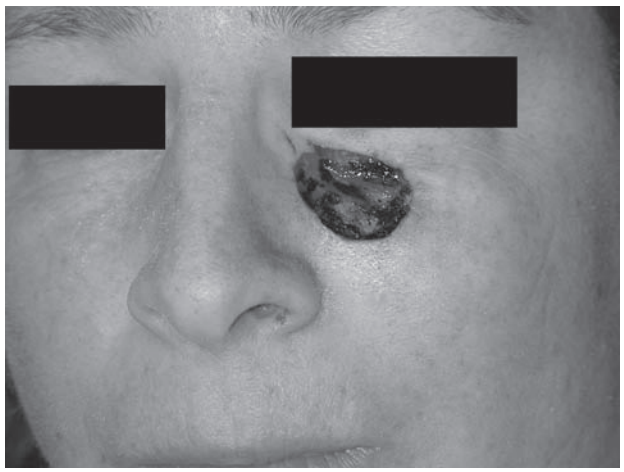
Flaps can be classified as local, regional, and distant. Local flaps are the most commonly used in facial cutaneous reconstruction and can be further divided into rotational, transposition, advancement, and island. Regional flaps include interpolated melolabial flaps, Abbe lip-switch flap, and paramedian forehead flaps. Distant flaps are usually microvascular free tissue transfer. Typically, a number of different flap designs can be considered for any given cutaneous defect. Surgical judgment is critical in the decision-making process. However, in the majority of cases, one or two flap designs are usually obviously preferable. Location and size of the defect are the two most critical factors in selecting facial flaps.

Rotational flaps are pivotal with a curvilinear configuration. They are designed immediately adjacent to the defect and are best used to close triangular defects. The "triangle" is covered by a portion of the standing cutaneous deformity, thus facilitating the pivotal movement of the flap (Fig. 23-37A). Typical examples include pivotal scalp flaps, dorsal glabellar flaps on the nose, and cervicofacial flaps (see Fig. 23-37B,C).

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A



B

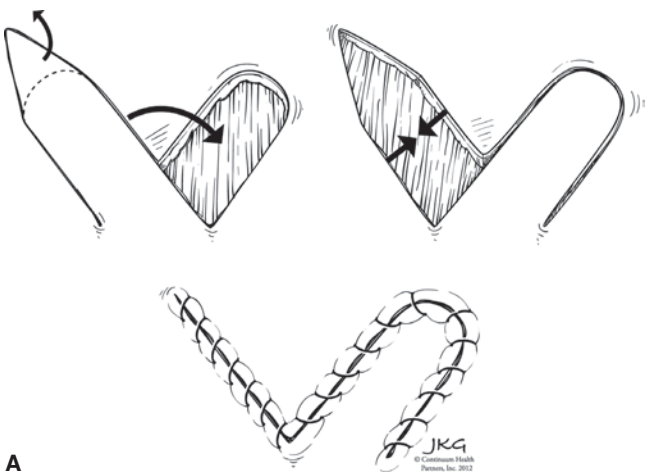


C

**FIGURE 23-37.** **A:** Rotation flap. **B:** 2.5 × 2.5 cm medial cheek Mohs defect. **C:** Closure of the Mohs defect with a rotation-advancement flap. Suture lines and standing cone deformities are designed at borders of facial aesthetic subunits.

Transposition flaps by definition cross over or transpose intervening tissue to reach their target location. Like rotational flaps, they are designed in such a way that one of the borders of the flap is also the border of the defect. Both rotational and transposition flaps develop standing cutaneous deformities at their base and have a pivotal point as movement (Fig. 23-38A). Typical examples of transposition flaps include nasolabial, rhombic, and bilobed (see Fig. 23-38B–D). For numerous reasons, this author does not perform the rhombus flap or its variations often.

Advancement flaps are the most common utilized for facial reconstruction. Advancement flaps have a linear configuration and move by sliding toward the defect (Fig. 23-39A). Stretching of the flap is the norm, and therefore they work best in areas of greater skin elasticity. Typical examples include uni -or bipedicle advancement, V-Y closure, and O-T plasty (see Fig. 23-39B,C).




A



B

**FIGURE 23-38.** **A:** Transposition flap. Flap transposes intact skin bridge. **B:** 1.5 × 1.0 cm lateral nasal Mohs defect with inferiorly based nasolabial transposition flap designed. **C:** Flap directly after closure. **D:** Postoperative result.

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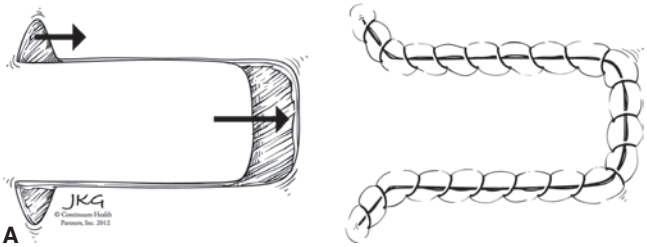


C



D

**FIGURE 23-38.** *Continued*




A



B



C

**FIGURE 23-39.** **A:** Advancement flap. Removal of Burow triangles at base of flap may be required. **B:** 2.0 × 2.0 cm forehead Mohs defect. **C:** Bilateral advancement flaps with horizontal incisions paralleling RSTLs.

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An island flap is incised on all borders so that there are no cutaneous attachments between the skin of the flap and the adjacent skin of the donor site. The pedicle of the flap consists only of subcutaneous tissue with its underlying vascular supply. Island flaps may be transferred by pivoting or stretching (Fig. 23-40A). Flap advancement length is limited with this type of flap; however, the deep vascular supply can be used to cover exposed bone or cartilage. Typical shapes for such island flaps include V-Y designs (see Fig. 23-40B–D).

Interpolated flaps, like the transposition flap is transferred by pivotal movement and has a linear configuration. However, it differs from transposition flaps in that its base is not contiguous with the defect. Thus, the pedicle must cross over intervening tissue and requires a second surgical procedure to divide and inset the flap (Fig. 23-41A). Typical interpolated flaps used on the face include the paramedian forehead flap, Abbe lip-switch flap, and melolabial flap. Melolabial flaps are excellent for reconstructing nasal alar defects and in certain situations may save the patient from having to undergo forehead flap reconstruction (see Fig. 23-41B–D). In the authors experience, forehead flaps are best utilized for complex nasal defects requiring more than just skin coverage. Both forehead flaps and melolabial flaps are excellent choices in combination with cartilage grafts to restore nasal form and function.

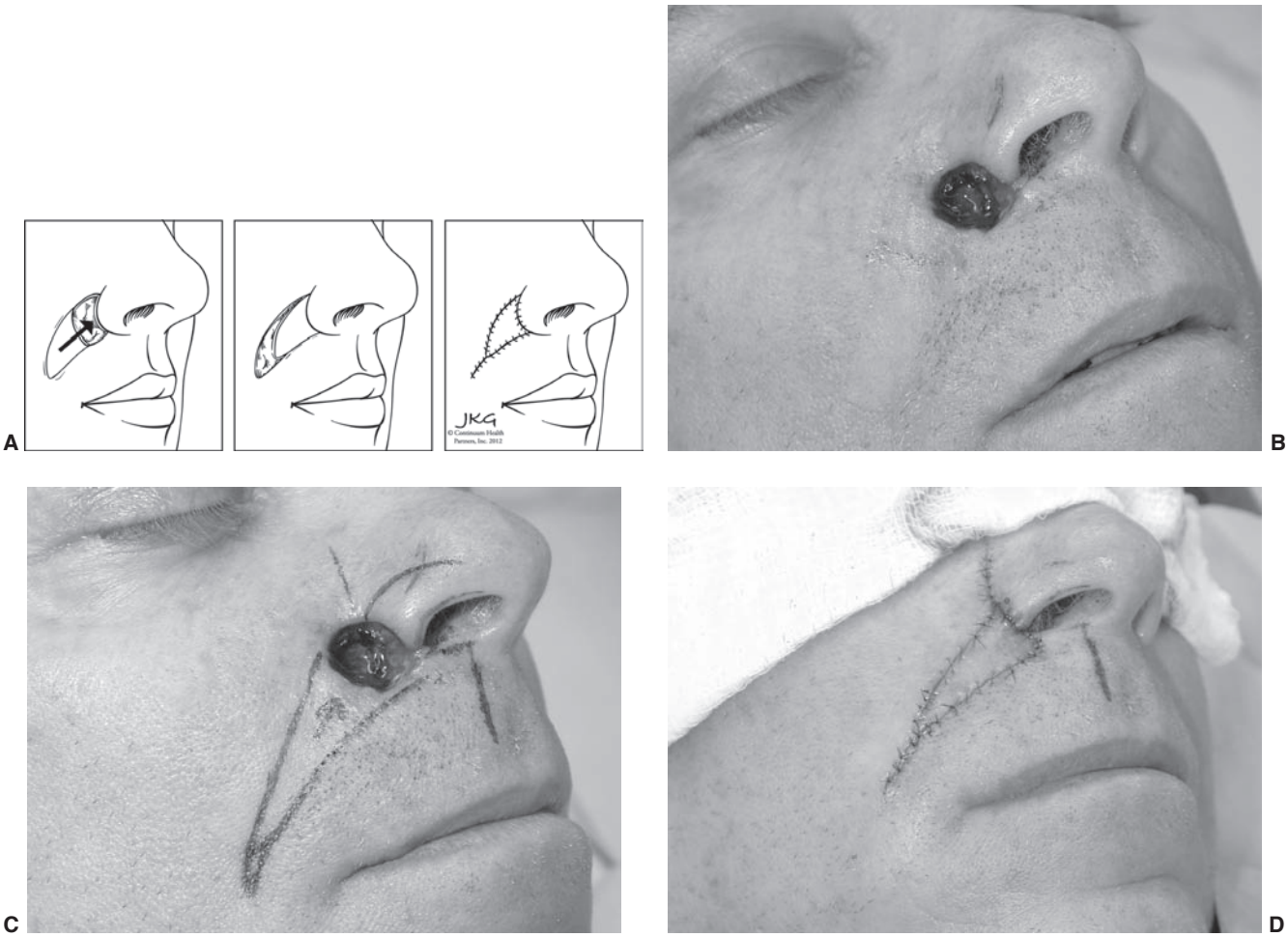
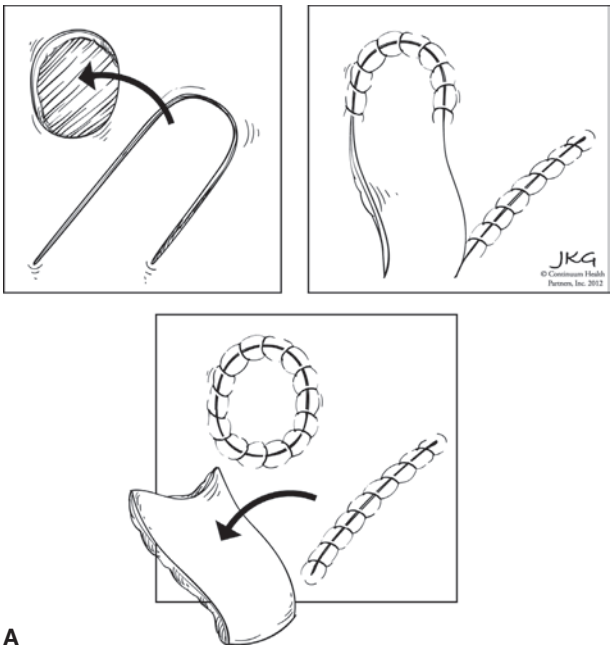



**FIGURE 23-40.** **A:** Melolabial V-Y island pedicled flap. **B:** 1.5 × 1.5 cm deep superior melolabial fold Mohs defect. **C:** V-Y island pedicle flap designed. **D:** Directly after closure of defect.

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A



B



C



D

**FIGURE 23-41.** **A:** Interpolated flap. Flap crosses intact bridge of skin, whereas pedicle is divided at a second staged procedure. **B:** Large nasal alar Mohs defect near rim. Auricular cartilage graft in place. Interpolated flap designed on cheek using melolabial fold and aesthetic facial subunit for donor scar. **C:** Pedicled flap in place directly after closure. **D:** Division of flap at 3 weeks during staged procedure.

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CHAPTER 24

# Melanoma of the Head and Neck

## PART A:
## General Principles and Management

Michael E. Kupferman and Michael A. Davies

### INTRODUCTION

More than 3.5 million new skin cancers are diagnosed every year. Although melanoma represents <5% of the cases, it is responsible for >75% of skin cancer–related deaths.[1] Thus, melanoma is the most aggressive form of skin cancer, and it is likely to be an increasingly prevalent problem in the future. An estimated 70,230 patients will be diagnosed with melanoma, and 8,790 will die from this disease, in the United States in 2012.[2] Currently, the lifetime risk of being diagnosed with melanoma is 1 in 37 for men and 1 in 55 for women. Concerningly, the incidence of melanoma has increased dramatically over the last several decades, with an increase of >200% in the age-adjusted incidence from 1975 to 2008.[3–8] The rise in incidence has been detected across all age groups and primary tumor thicknesses. The mortality rate has also increased approximately 60% over time, primarily due to increased mortality in patients ≥65 years of age, particularly among men.[3,7,8] However, many patients who die from melanoma are otherwise young and healthy, leading to melanoma being among the cancers with the highest life-years lost per fatality.[9,10]

Although melanoma is a highly aggressive cancer, patients can be cured of this disease if they are diagnosed early and managed appropriately. Carefully conducted studies over the last 20 years have defined the clinical and pathological criteria that define patient prognosis and guide current patient management.[11–13] Historically, melanomas have been grouped based on clinical and pathological features. However, recent discoveries about the molecular biology of melanoma have provided key insights into the molecular heterogeneity of this disease and are rapidly leading to new therapeutic approaches and improved clinical outcomes.[14] This chapter will review the existing standards for melanoma diagnosis and treatment and will discuss the recent advances in research and their implications for future patient management.

### ANATOMY

Melanomas of the head and neck most commonly present on the face, which corresponds to the area that has received the highest lifetime cumulative dosages of ultraviolet light. The scalp and ears are the next most common sites of presentation, followed by the skin of the neck. Due to the substantial cosmetic considerations associated with facial surgery, it is imperative that the operating surgeon has an understanding of the anatomic subunits of the facial structures and of lines of normal skin tension. On the nasal cavity, these include the dorsum, the nasal sidewalls, the nasal ala, the columella, and the tip. On the ears, these include the helix, the conchal bowl, the antihelix, and the lobule. On the eyes, these include the superior orbital rim, the inferior orbital rim, the medial canthal region, and the lateral canthal region. Placement of surgical incisions within the lines of normal skin tension will allow surgical reconstruction to proceed in a cosmetically appealing manner.

Of utmost importance in the management of head and neck melanoma is a concrete understanding of the surgical anatomy of the lymphatics, as the status of the regional nodes has the most impact on survival. For sentinel lymph node biopsy (SLNB), the identification of lymph nodes in the head and neck may be challenging due to their relationship to the cranial nerves. In particular, the lymphatics of the parotid gland may be superficial to the gland or may be embedded deep within the substance of the soft tissue, and surgical exploration for sentinel lymph nodes in this basin may place the facial nerve at risk for injury. Lymphatic drainage of regions such as the nasal skin, the lip, and the midface frequently drain to more than one nodal basin and may also drain in bilateral or contralateral directions.[15] Commonly, the facial lymph nodes that traverse the facial artery and vein are sites of SLN, and removal of these places the marginal mandibular branch of the facial nerve at risk.

Lesions of the scalp that are anterior to a line drawn along the coronal plane through the tragus oftentimes will drain to the



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parotid, the submental, or the anterior cervical lymph nodes.[16] Alternatively, melanomas that are posterior to this line will most often drain to either the suboccipital, the retroauricular, or the posterior triangle cervical lymphatics.[17] The removal of nodes that map to the posterior triangle places the spinal accessory nerve at risk for injury during the surgical excision. Thus, a precise understanding of the anatomy of the cervical lymphatics and of the cranial nerves is of critical necessity for surgeons managing patients with melanoma of the head and neck. Further elaboration of the anatomy of the cervical lymphatics may be found in other chapters in this text.

## RISK FACTORS

Improved awareness and screening are likely partially responsible for the marked increase in the incidence of melanoma over the last few decades. However, there is strong evidence that increased exposure to ultraviolet radiation (UVR) also plays a role.[18] Multiple studies support a causative role for UVR in cutaneous melanoma, including migration and epidemiologic studies.[3] A history of sunburns from natural UVR and the use of tanning beds (artificial UVR) are risk factors for melanoma, and public surveys have reported increasing prevalence of both behaviors among US adults.[19] Interestingly, while intermittent sun damage/exposure has consistently been identified as a positive risk factor, some studies suggest that chronic sun exposure is associated with a decrease in the risk of melanoma.[20] Other risk factors for cutaneous melanoma include a positive family history, multiple nevi, dysplastic nevi, freckled or fair skin, blue or green eye color, and red hair color.[21,22] The phenotype of fair skin, freckling, and red hair has been linked to polymorphisms in the *MC1R* gene, which encodes the melanocortin-1 receptor.[23] The polymorphisms in *MC1R* cause decreased signaling through the receptor, which ultimately results in decreased melanin production. The primary function of melanin is to absorb UVR, thus protecting cellular DNA from its damaging effects. Germline polymorphisms in other genes involved in melanin synthesis (*TYR*, *TYRP1*) have also been linked to an increased melanoma risk and further implicate the role of UVR in this disease.[23]

Approximately 10% of melanomas are familial (≥3 affected individuals). Familial melanomas are associated with a very early age of onset, frequently in areas without UVR exposure. The most common genetic feature in these families is germline deletion or inactivating mutation of the *CDKN2A* gene on chromosome 9.[23] Due to alternative splicing, *CDKN2A* is transcribed into two different proteins ($p16^{INK4A}$ and $p14^{ARF}$) which regulate cell cycle progression and cause cell cycle arrest in response to DNA damage. Inactivation of *CDKN2A* is detected in approximately 40% of melanoma-prone families. The critical role of DNA damage is also implicated by the identification of melanoma-prone families with germline mutations in the *CDK4* gene.[23] The detected genetic alterations result in a mutant CDK4 protein that is resistant to inhibition by $p16^{INK4A}$ and thus recapitulate loss of *CDKN2A*. Polymorphisms in a number of other genes involved in DNA repair have also been associated with increased risk of melanoma.[24]

## PATHOLOGY

Developmentally, melanocytes arise from the neural crest. The cells migrate most commonly to the epidermis of the skin, but they can also be found in the meninges lining the brain, the uveal tract of the eye, and the ectodermal mucosa. Melanomas can arise from each of these sites and are thereby clinically classified as cutaneous, primary meningeal, uveal, and mucosal melanomas. Cutaneous melanomas, which are by far the most common subtype, have been further subdivided into categories defined by a combination of pathological and clinical features. The majority of cutaneous melanomas fall into one of the following subtypes: superficial spreading melanoma (SSM), nodular melanoma (NM), lentigo maligna melanoma (LMM), and acral lentiginous melanoma (ALM). A rarer but clinically relevant subtype in the head and neck is desmoplastic melanoma (DM).

Superficial spreading melanomas, the most common subtype (~70%) of cutaneous melanomas, generally arise on any skin with intermittent sun exposure. Nodular melanomas (~15%) are characterized by vertical growth without a prior radial growth phase. Nodular melanomas are often highly aggressive and clinically appear as raised nodules. Lentigo maligna melanomas (~10%) appear as flat brown macules, often with hypopigmented areas. Lentigo maligna melanomas are associated with chronic sun exposure and are typically located on the head, neck, and arms. Acral lentiginous melanoma (~5%) is the least common subtype among Caucasians, but represents 30% to 70% of the melanomas diagnosed in African Americans and Hispanics. Acral lentiginous melanomas occur on the palms or soles, or underneath the nail plate, where exposure to UVR is relatively limited. DMs occur in areas with chronic sun exposure, particularly of the head and neck. DM are usually detected in elderly patients and are highly invasive, often presenting as lesions with significant (>5 mm) thickness. DMs often invade along neural tracks, which can result in significant symptomatology.

## MOLECULAR BIOLOGY

A variety of studies have demonstrated that there are significant molecular differences between the melanoma subtypes. Whole-genome copy number analyses have demonstrated that cutaneous, acral, and mucosal melanomas are characterized by distinct patterns of chromosomal gain and loss.[25] Furthermore, cutaneous melanomas with and without evidence of chronic sun damage (CSD) show distinct patterns of DNA copy number changes; tumors with evidence of CSD appear relatively similar to acral and mucosal melanomas. Uveal melanomas show a pattern of chromosomal aberrations that are distinct from the cutaneous and mucosal melanomas and are characterized by a high prevalence of isosomy of chromosome 3, which is associated with poor clinical outcomes.[26,27]

In addition to differences in the pattern of chromosomal changes, melanoma subtypes are characterized by differences in the prevalence of somatic mutations, a number of which are emerging as both prognostic markers and therapeutic targets (Table 24.1).[14,28,29] The most common somatic event in melanoma is alteration of the *BRAF* gene.[30] *BRAF* encodes serine-threonine kinase that is a key component of the RAS-RAF-MEK-ERK signaling pathway (Fig. 24-1). More than 90% of the alterations in *BRAF* that are detected in melanoma are missense mutations that affects the valine residue at position 600.[31,32] The most common mutation (~75% of *BRAF* mutations) results in substitution of a glutamic acid (V600E), which increases the catalytic activity of the BRAF protein >100-fold.[33] Melanoma cell lines with activating *BRAF* mutations demonstrate constitutive activation of MEK and ERK signaling and functionally depend on this pathway for growth and survival.[34] Mutation of *NRAS*, which also results in hyperactivation of MEK and ERK, is the second most common somatic event in melanoma and thus reinforces the critical role of the RAS-RAF-MEK-ERK pathway in this disease.[32]

Studies of the clinical correlates of *BRAF* mutations have found positive associations with both younger age and a lack of CSD.[35–37] Although activating *BRAF* mutations are detected in 45% to 50% of cutaneous melanomas without CSD, the

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**TABLE 24.1 Melanoma Subtypes: Genetic Mutations**

| | Cutaneous | Acral | Mucosal | Uveal |
|---|---|---|---|---|
| Clinical features | Most common subtype | Involving skin on palms, soles, or nailbeds | Mucosal surfaces of head and neck, gastrointestinal, or genitourinary tract | Arise from melanocytes in the ciliary tract of the eye |
| Regions of chromosome gain | 6p, 7, 8q, 17q, 20q | 6p, 7, 8q, 17q, 20q (Amp: 5p15, 5p13, 11q13, 12q14) | 1q, 6p, 7, 8q, 11q13, 17q, 20q (Amp: 1q31, 4q12, 12q14) | 6p, 8q |
| Regions of chromosome loss | 9p, 10, 21q | 6q, 9p, 10, 11q, 21q | 3q, 4q, 6q, 8p, 9p, 10, 11p, 11q | 3 (monosomy), 8p |
| *BRAF* mutations | 50% (CSD: ~30%) | 15% | 5% | <1% |
| *NRAS* mutations | 20% | 10% | 10% | <1% |
| *c-KIT* mutations | <2% in Non-CSD (CSD: 2%–17%) | 15% | 20% | <1% |
| c-KIT *amplifications* | 0%–7% in non-CSD (CSD: 6%) | 25% | 25% | <1% |
| GNαQ *mutations* | <1% | <1% | <1% | 45% |
| GNα11 *mutations* | <1% | <1% | <1% | 35% |

CSD, chronic sun-damaged.

*Source:* Adapted from Davies MA, Gershenwald JE. Targeted therapy for melanoma: a primer. *Surg Onc Clin N Am.* 2011;20:165–180, with permission from Elsevier.

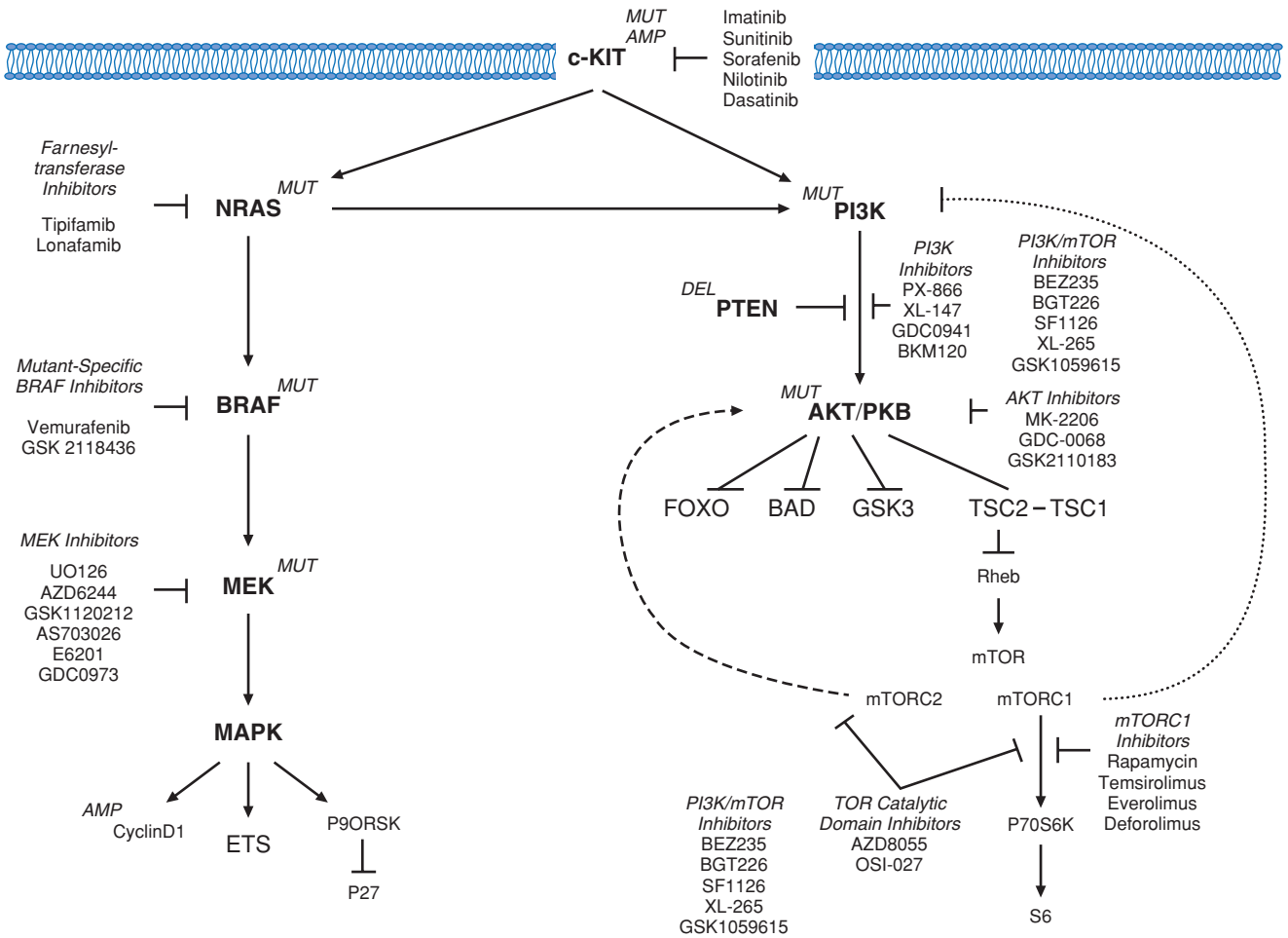



**FIGURE 24-1.** Molecular biology of melanoma. The figure illustrates pathways that are affected by somatic mutations in melanoma. MUT, activating mutation; AMP, gene amplification; DEL, loss of function.

*Source:* Adapted from Davies MA, Gershenwald JE. Targeted therapy for melanoma: a primer. *Surg Onc Clin N Am.* 2011;20:165–180, with permission from Elsevier.



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rate is lower (10%–30%) in tumors with histologic evidence of sun damage (i.e., solar elastosis).[25,38] *BRAF* mutations are also relatively rare in acral (10%–15%), mucosal (5%), and uveal melanomas (<1%).[25,32,39] *NRAS* mutations are associated with thicker primary tumors and shorter relapse-free survival (RFS) from initial melanoma diagnosis.[35,40] *NRAS* mutations appear to have a similar prevalence of approximately 20% in cutaneous melanomas with and without CSD, but a lower prevalence in acral (15%), mucosal (10%), and uveal (<1%) melanomas.[25,32]

The relative paucity of activating *BRAF* mutations in CSD-cutaneous, acral, and mucosal melanomas led to interrogations of regions of DNA copy number gain for additional oncogenic drivers in these subtypes. These studies resulted in the identification of frequent abnormalities in the *KIT* gene in these subtypes.[41] The *KIT* gene encodes a receptor tyrosine kinase that is also frequently activated genetically in gastrointestinal stromal tumors (GIST), testicular seminomas, and certain types of leukemia.[42] In addition to amplifications, initial studies identified somatic mutations in the *KIT* gene in melanomas. Overall, *KIT* mutation or amplification were identified in 36% of acral and 39% of mucosal melanomas. *KIT* alterations in cutaneous melanomas without CSD have consistently been reported to be quite rare (≤1%), but variable results (2%–28%) have been reported for cutaneous melanomas with CSD.[38,41]

A variety of other somatic alterations have been identified in melanoma (Fig. 24-1).[14,29] Inactivating mutations and deletions of *PTEN*, a negative regulator of the PI3K-AKT signaling pathway, have been identified in 10% to 30% of melanomas.[43] Loss of PTEN expression in the absence of detectable abnormalities in the *PTEN* gene has also been reported, consistent with epigenetic regulation of the gene.[44,45] Genetic inactivation of *PTEN* is mutually exclusive with the presence of activating *NRAS* mutations in melanoma, but frequently occurs in tumors and cell lines that have activating *BRAF* mutations.[46,47] Although *BRAF*, *NRAS*, and *KIT* mutations are very rare in uveal melanomas, these tumors frequently have activating mutations in *GNAq* (45%) or *GNA11* (35%).[48–50] Both *GNAq* and *GNA11* encode regulatory subunits of G-protein coupled receptors, which may activate many of the same pathways affected by the mutations that are common in other melanoma subtypes. Uveal melanomas also frequently have inactivating somatic mutations of the *BAP1* gene, which is located on chromosome 3, and may function as a tumor suppressor in this melanoma subtype.[51]

## PATTERNS OF SPREAD

The clinical course of cutaneous melanoma is highly variable. Cutaneous melanomas can spread locally through dermal lymphatic channels to form cutaneous satellite lesions (within 2 cm of the primary lesion), as well as in-transit lesions along the course of the draining lymphatics. More commonly, initial tumor progression presents as metastasis to draining regional lymph nodes. Distant metastases generally are diagnosed after the development of regional involvement, although some patients have their first relapse at distant sites. In addition, approximately 5% of melanoma patients present with metastasis(es) with no detectable primary tumor.[52] Melanoma can metastasize to virtually any distant organ, including skin, lymph node, lung, liver, GI tract, and bone, among others. One of the most common sites of distant metastasis is the brain. Approximately 60% of patients with distant metastases will develop brain involvement at some time during the course of their disease, and up to 80% of metastatic melanoma patients have evidence of brain involvement in autopsy series.[53,54]

Similar to cutaneous melanoma, mucosal melanomas tend to spread initially to regional lymph nodes and then subsequently to distant sites. In contrast to cutaneous and mucosal melanomas, uveal melanomas spread almost uniquely hematogenously, and thus lymph node involvement is quite rare. However, almost all uveal melanoma patients with distant disease have liver involvement (95%). Some patients also develop metastases to the lungs (25%), bone (15%), and skin (10%), but uveal melanomas almost never metastasize to the brain.[55]

## CLINICAL PRESENTATION

The majority of patients with cutaneous melanoma of the head and neck present in an early stage of disease, as it is uncommon for nodal metastasis to be present at the time of diagnosis. A pigmented lesion may have been present for many years, but it is not until one has undergone substantial change in its clinical appearance that prompts an evaluation with a biopsy. The classic mnemonic of "ABCDE" of pigmented lesions represents an important reminder in public awareness of the warning signs of melanomas, as the vast majority of melanomas (>70%) arise in a preexisting mole. These signs include ***A***symmetry, ***B***order irregularity, ***C***olor variegation, ***D***iameter >6 mm, and ***E***volution. These lesions may also present as areas that bleed after minor trauma, such as hair brushing or shaving, and patients may complain of itching at the site. Other clinical features associated with cutaneous melanomas include ulceration, regression, and nonpigmented lesions. It is important that the clinician evaluate the surrounding skin for the presence of satellitosis, which represents stage IIIB or IIIC disease, even when nodal metastases are absent (Fig. 24-2).

Nodal metastasis is often subclinical in early-staged patients yet is present in 20% to 30% of patients with T2 lesions, and the incidence of occult nodal metastasis increases substantially in thicker tumors. One of the more challenging areas of the management of melanoma of head and neck involves patients with a regionally metastatic melanoma with an unknown primary tumor. It is important that the treating team perform a careful and detailed clinical history to elicit a history of a regressed lesion or a previously biopsied "benign" nevus. DMs have a propensity for neurotropism, and eliciting signs and symptoms of this aggressive subtype is important in the evaluation of patients with head and neck melanoma.

### Diagnostic Staging and Evaluation

The evaluation of a suspected head and neck melanoma entails surgical biopsy, which may be performed as either an excisional biopsy or incisional biopsy, depending on the anatomical location and size of the lesion. Ideally, an excisional biopsy with 1 to 2 mm margins is preferred, which will allow adequate pathological analysis of the entire specimen for staging, without disrupting the lymphatics should an SLNB be necessary. It must be stated that an excisional biopsy does not suffice for surgical management of a melanoma; appropriate surgical margins should be taken at a separate procedure. An incisional or punch biopsy may be performed for large lesions and for those in cosmetically critical areas, such as the nose, eyelid, or ear. In these situations, a complete excision may require significant reconstruction and rotational flaps, which is best performed after definitive resection has been completed. The general principles for the biopsy for a suspected melanoma include representative lesion sampling, adequate depth, and proper specimen orientation. Shave biopsies are often performed for cutaneous lesions, but may not provide adequate representation of the depth of the lesion when performed for a pigmented lesion. This is primarily due to transection of the base of the melanoma, which will impact appropriate tumor staging of the patient. It is also

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**FIGURE 24-2.** Pigmented lesions of the head and neck. **A:** Melanoma *in situ.* **B:** Thin melanoma of the forehead. **C:** Thick melanoma of the midface. **D:** Satellitosis.

difficult for pathologists to provide a complete histopathological staging of a shave biopsy and thus an incisional biopsy or punch biopsy may be necessary for suspicious pigmented lesion of the head and neck that cannot be assessed with an excisional biopsy.

The appropriate histopathological staging criteria of a biopsied pigmented lesion are outlined in Table 24.2. The pathological reporting of these discrete criteria provides the treatment in the appropriate staging criteria and determines the need for any further evaluation and/or any diagnostic workup or treatment. Use of a pathology template for melanoma has been shown to improve proper staging of patients, particularly when performed as part of an established multidisciplinary group.[56]

***Updates to AJCC Staging.*** The staging evaluation for melanoma of the head and neck are based on the seventh edition of the TNM staging system of the American Joint Committee on Cancer (AJCC), which was published in 2009 and is provided in Tables 24.3 and 24.4.[12] Thin melanomas are defined as ≤1 mm in thickness, intermediate are 1.01 to 4 mm in thickness, and thick melanomas are >4 mm. Stage III patients are defined as those with any nodal metastasis or in-transit metastasis, and stage IV represents distant metastatic disease.

The updated staging system had several differences from previous editions. Substantively, the increasing recognition that mitoses are an adverse prognostic features has been incorporated in the definition of T1b lesions, which broadens the indications

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**TABLE 24.2 Key Histopathological Features of Melanoma Primary Tumors**

| Element | Comments |
|---|---|
| Histology | Lentigo maligna, superficial spreading, nodular, acral lentiginous, desmoplastic |
| Clark level | Used for defining lesions with BT ≤1 mm |
| Beslow thickness (BT)/ Depth of invasion | Cutoffs for staging: 1.0, 2.0, 4.0 mm |
| Growth phase | Vertical, radial |
| Ulceration | — |
| Lympho-vascular invasion | — |
| Mitotic figures (per $mm^2$) | Cutoff for staging: ≥1/$mm^2$ |
| Satellitosis | — |
| Margin status | Peripheral, deep |

for SLNB in early-staged patients and changes the prognosis for previously staged T1a patients. Clark levels are no longer used in the staging system with some exceptions (i.e., T1 lesions without information about mitotic rate), although pathologists continue to utilize it in pathology reports. Immunohistochemical analysis of sentinel lymph nodes with a melanoma marker (HMB-45, Tyrosinase, MART1, MelanA) is now considered standard of care in pathologically negative nodes, and immunohistochemically positive nodes are categorized as micrometastatic disease. The staging system also added serum lactate dehydrogenase (LDH) levels to the evaluation of patients with stage IV disease.

***Evaluation of Stages 0 to II Melanoma.*** The diagnostic evaluation of melanomas of the head and neck outlined in Figure 24-3 is based on the current National Comprehensive Cancer Network (NCCN) guidelines.[57] In patients with stages 0 to II melanoma, histological analysis of the primary tumor is the major diagnostic study, and for patients with thin melanomas without high-risk features, a thorough history and physical examination may suffice. For patients with ulcerated lesions, imaging of the head and neck may be beneficial, as this subset of patients are at a higher risk of harboring lymph node metastasis. This may be either with computed tomography (CT) of the head and neck or

**TABLE 24.3 2009 AJCC TNM Staging Categories for Cutaneous Melanomas**

| T Classification | Thickness (mm) | Ulceration/Mitoses |
|---|---|---|
| Tis | NA | NA |
| T1 | ≤1.00 mm | a: Without ulceration and mitoses < 1/$mm^2$<br>b: With ulceration or mitoses ≥ 1/$mm^2$ |
| T2 | 1.01–2.00 | a: Without ulceration<br>b: With ulceration |
| T3 | 2.01–4.00 | a: Without ulceration<br>b: With ulceration |
| T4 | | a: Without ulceration<br>b: With ulceration |
| **N Classification** | **No. of Metastatic Nodes** | **Nodal Burden** |
| N0 | 0 | N/A |
| N1 | 1 | a: Micrometastasis<br>b: Macrometastasis |
| N2 | 2–3 | a: Micrometastasis<br>b: Macrometastasis<br>c: In-transit metastases/satellites without metastatic lymph nodes |
| N3 | 4+ nodes, or matted nodes, or in-transit metastases/satellites with metastatic lymph nodes | |
| **M Classification** | **Site** | **Serum LDH** |
| M0 | No distant metastases | N/A |
| M1a | Distant skin, subcutaneous, nodes | Normal |
| M1b | Lung | Normal |
| M1c | All other visceral metastases<br>Any distant metastasis | Normal<br>Elevated |

N/A, not applicable; LDH, lactate dehydrogenase. Micrometastases are diagnosed after sentinel lymph node biopsy; macrometastases are defined as clinically detectable nodal metastases confirmed pathologically.

*Source:* From Balch CM, Gershenwald JE, Soong SJ, et al. Final version of the 2009 AJCC melanoma staging and classification. *JCO.* 2009;27:6199–6206. Reprinted with permission from the American Society of Clinical Oncology.

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**TABLE 24.4 2009 AJCC Stage Groupings for Cutaneous Melanomas Clinical Staging**

| | T | N | M |
|---|---|---|---|
| **Clinical staging** | | | |
| 0 | Tis | N0 | M0 |
| IA | T1a | N0 | M0 |
| IB | T1b or T2a | N0 | M0 |
| IIA | T2b or T3a | N0 | M0 |
| IIB | T3b or T4a | N0 | M0 |
| IIC | T4b | N0 | M0 |
| III | Any T | N > N0 | M0 |
| IV | Any T | Any N | M1 |
| **Pathologic staging** | | | |
| 0 | Tis | N0 | M0 |
| IA | T1a | N0 | M0 |
| IB | T1b or T2a | N0 | M0 |
| IIA | T2b or T3a | N0 | M0 |
| IIB | T3b or T4a | N0 | M0 |
| IIC | T4b | N0 | M0 |
| III | Any T | N > N0 | M0 |
| IIIA | T1–4a | N1a or N2a | M0 |
| IIIB | T1–4b | N1a or N2a | M0 |
| | T1–4a | N1b or N2b or N2c | M0 |
| IIIC | T1–4b | N1b or N2b or N2c | M0 |
| | Any T | N3 | M0 |
| IV | Any T | Any N | M1 |

Clinical staging includes microscopic evaluation of the primary tumor, and clinical and radiologic evaluation for metastases. Pathologic staging includes microscopic evaluation of the primary tumor, and microscopic evaluation of the regional lymph nodes after partial (SLNB) or complete lymphadenectomy. Pathologic stage 0 and stage IA do not require microscopic evaluation of regional lymph nodes for classification.

*Source:* From Edge SB, Byrd DR, Compton, CC, et al. *AJCC Cancer Staging Manual.* 7th ed. New York, NY: Springer-Verlag; 2010:326, with permission.

with an ultrasound (US) of the head and neck. The advantage of the US is the potential opportunity to perform a fine-needle aspiration of a suspicious lymph node, but it does not provide the same anatomic detail that actual imaging of the head and neck provides. However, staging can be personalized based on patient factors and physician preference. At our institution, the majority of patients with intermediate-thickness or thick melanomas will undergo imaging of the regional lymphatic basins with either a US or a CT, particularly if ulceration is present. Routine chest x-rays may optionally be performed for patients with IIB to IIC disease to evaluate for lung metastases. Chest x-ray, CT scans, or other imaging should also be performed if signs or symptoms are present that suggest the presence of distant metastases (i.e., pain, dyspnea, neurologic symptoms). Surgical staging of the lymph nodes will be discussed in forthcoming sections.

***Evaluation of Stages III to IV.*** Patients who are identified as harboring nodal metastasis, whether occult or clinical, should undergo baseline staging studies to exclude the presence of distant metastasis. These may include CT of the chest, abdomen, and pelvis; an MRI of the brain; and determination of serum LDH. More recently, the role of PET-CT for the evaluation of stage III melanoma has been explored and does provide effective baseline staging in this group of patients. The caveat to the use of PET for staging is the resolution for the detection of small metastases, as lesions smaller than 1 cm may be better appreciated on axial imaging. In similar manner, patients with in-transit metastasis require a formal metastatic workup. The timing of these studies should be at the discretion of the multidisciplinary team, but is often performed after local-regional treatment has been completed. Due to emerging therapeutic options, molecular testing for activating mutations in the *BRAF*, *NRAS*, and *KIT* genes should be strongly considered in patients with unresectable regional and distant metastases.[29]

***Role of SLNB.*** As the status of the lymph nodes remains the most powerful prognostic factor for patients with head and neck melanoma, proper staging of the lymphatics is one of the major diagnostic criteria for patients with melanoma of the head and neck.[58] Patients who are node negative generally do not require any adjuvant therapy. Conversely, those with nodal metastasis, even when present at microscopic levels, should be considered for adjuvant systemic therapy (discussed separately). Controversy regarding the management of regional lymphatics in melanoma has persisted for decades, and elective nodal dissection was frequently recommended for patients with melanoma in the past. However, as only approximately 20% of patients harbor occult metastasis, a substantial number of patients were subjected to unnecessary nodal dissections, which can result in significant morbidity.[59] Alternatively, observation alone is associated with adverse outcomes, compared with elective nodal dissection for certain groups of patients. With the increased recognition that most patients with intermediate-thickness melanomas do not benefit from elective nodal dissection, the staging philosophy for melanoma has changed substantially in the past decade.

Elective regional dissection has been supplanted by SLNB as the standard of care in the initial evaluation of the majority of patients with cutaneous melanoma. SLNB was first proposed as an effective staging tool by Cabanas in 1977 for the management of penile squamous cell carcinomas.[60] The technique was subsequently championed by Morton et al. for the diagnostic evaluation of metastatic melanoma, based upon the principle that melanoma metastasizes in an orderly fashion to the first-echelon draining lymphatic basin.[61] In the evaluation and staging of patient with melanoma, SLNB offers the following advantages: (a) increased sensitivity to detect regional metastases, (b) limited morbidity compared with elective nodal dissection, (c) identification of patients who may benefit from further therapies such as a neck dissection or systemic adjuvant therapy, and (d) potentially halting the regional progression of disease.

Although initially met with skepticism, SLNB is now the established approach for defining the presence of occult metastasis.[62] The rich and complex organization of the lymphatics of the head and neck make localization of the immediately draining nodes potentially more challenging, as compared with other sites. Moreover, initial published reports validating the role of this staging technique focused primarily on truncal and limb melanomas, with few studies having enrolled patients with lesions located in the head and neck.[63] One study has suggested that head and neck sites were associated with higher regional failure rates after a negative SLNB.[64] More recent studies with long-term follow-up of patients with head and neck melanoma suggest a regional failure rate of 4% to 8% after a negative SLNB, which is comparable to that for other anatomic sites.[65–67] Numerous studies

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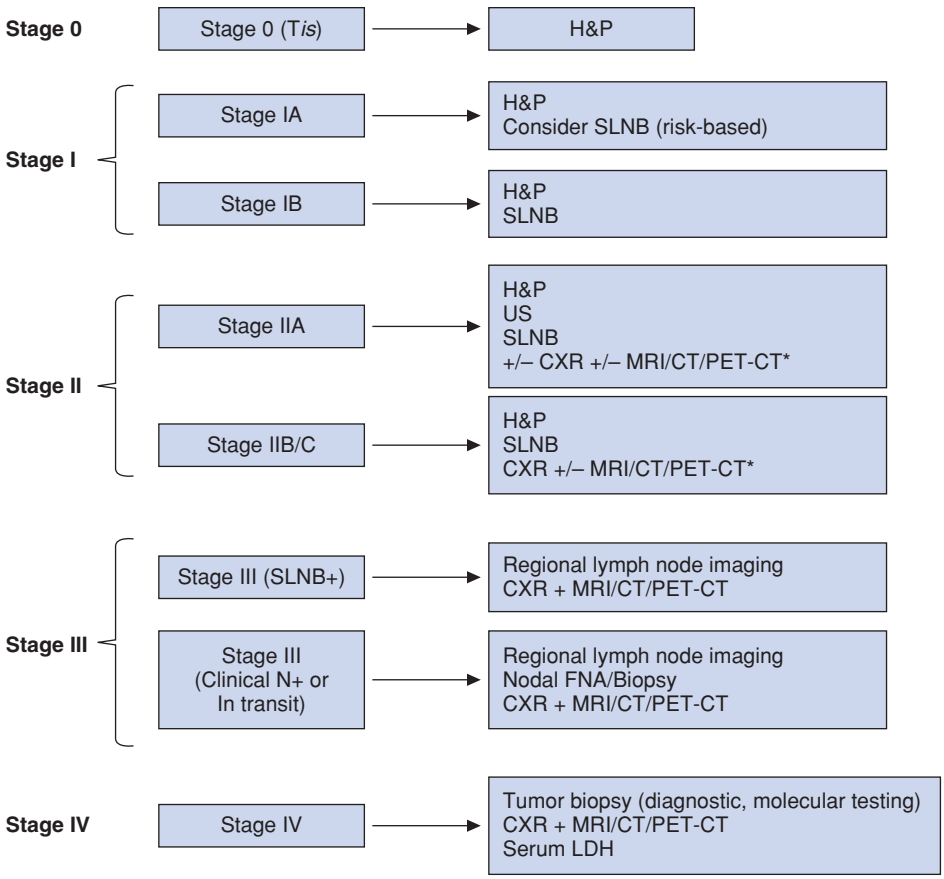



**FIGURE 24-3.** Diagnostic evaluation of cutaneous melanoma by clinical stage. H&P, history and physical; SLNB, sentinel lymph node biopsy; CXR, chest x-ray; US, ultrasound; FNA, fine-needle aspiration; LDH, lactate dehydrogenase. "*" indicates that the imaging decision and modality should be determined by presenting signs/symptoms.

have now validated SLNB for cutaneous melanomas of the head and neck, with a negative predictive value close to 98% and a false-negative rate of 5%.[68,69]

The benefits from SLNB have been established in both retrospective studies and in prospective multicenter trials.[70,71] It is clear that patients with intermediate-thickness melanomas, measuring between 1 and 4 mm in depth, have a 15% to 45% risk of harboring occult nodal metastasis. For most patients with lesions <1 mm, and thus less than a 5% risk of metastasis, an SLNB may not provide any further prognostic information. This risk increases with increasing thickness of the lesion, and those with melanomas measuring 2 to 4 mm have a risk of approximately 30% to 40% nodal positivity and nearly 50% for patients with lesions >4 mm. Multiple studies have demonstrated that patients who are sentinel lymph node negative had a substantial survival benefit compared with those who were sentinel lymph node positive, even when only micrometastases are present.[12] Moreover, the number of positive sentinel nodes and the size of the metastatic foci are factors that directly correlate with the risk of non–sentinel node metastases.[11–13] Thus, the status of the sentinel lymph nodes plays an important role in establishing the role of adjuvant therapy for patients with malignant melanoma. In 2006, Morton et al. established the prognostic role of SLNB in terms of impacting local-regional control and the importance of establishing the prognostic benefit of this staging procedure.[59]

One area of substantial controversy is the role of SLNB for patients with thin melanomas. Studies support that those with melanomas <1 mm thickness with the following risk factors may benefit from SLNB: mitotic figures >1/mm$^2$, the presence of ulceration, or tumors >0.7 mm in thickness.[72] The likelihood of identifying a positive sentinel node for all anatomic sites is in the range of 5% to 7%, although this rate is unclear in the head and neck. Consideration of performing an SLNB in this group must be placed in the context of the potential morbidity of cranial nerve injury and the cosmetic issues associated with surgical incisions in the face and neck region. Therefore, the decision to perform an SLNB for patients with thin melanomas should be made on an individualized basis.

***Radiographical, Surgical, and Pathological Considerations of SLNB.*** Preoperative lymphoscintigraphy utilizing technitium-99m sulfur colloid provides accurate identification of the sentinel nodes and correlates with the intraoperative findings in the vast majority of case. One of the limitations remains the planar aspect of the images, and distinguishing the depth of some of the nodes within the neck is challenging. For example, external jugular nodes, which are a common site for SLN, may be difficult to distinguish from the internal jugular nodes. Other anatomic areas that remain challenging to assess with planar imaging are the suboccipital nodes and those nodes located at the junction of level IIB and level V, which are in the vicinity of the spinal accessory nerve. A recent addition to the surgeon's armamentarium is the single photon emission CT with CT (SPECT-CT), which provides anatomic imaging in conjunction with the functional nuclear imaging (Fig. 24-4).[73] When performed together with planar lymphoscintigraphy, this technique provides greater presurgical detail for the intraoperative identification of SLN. Moreover, precise localization of the lymph nodes within the neck can facilitate placement of incisions and may decrease operative times.[74] At out institution, preoperative static lymphoscintigraphy and SPECT-CT are performed for all patients undergoing SLNB for melnomas of the head and neck.

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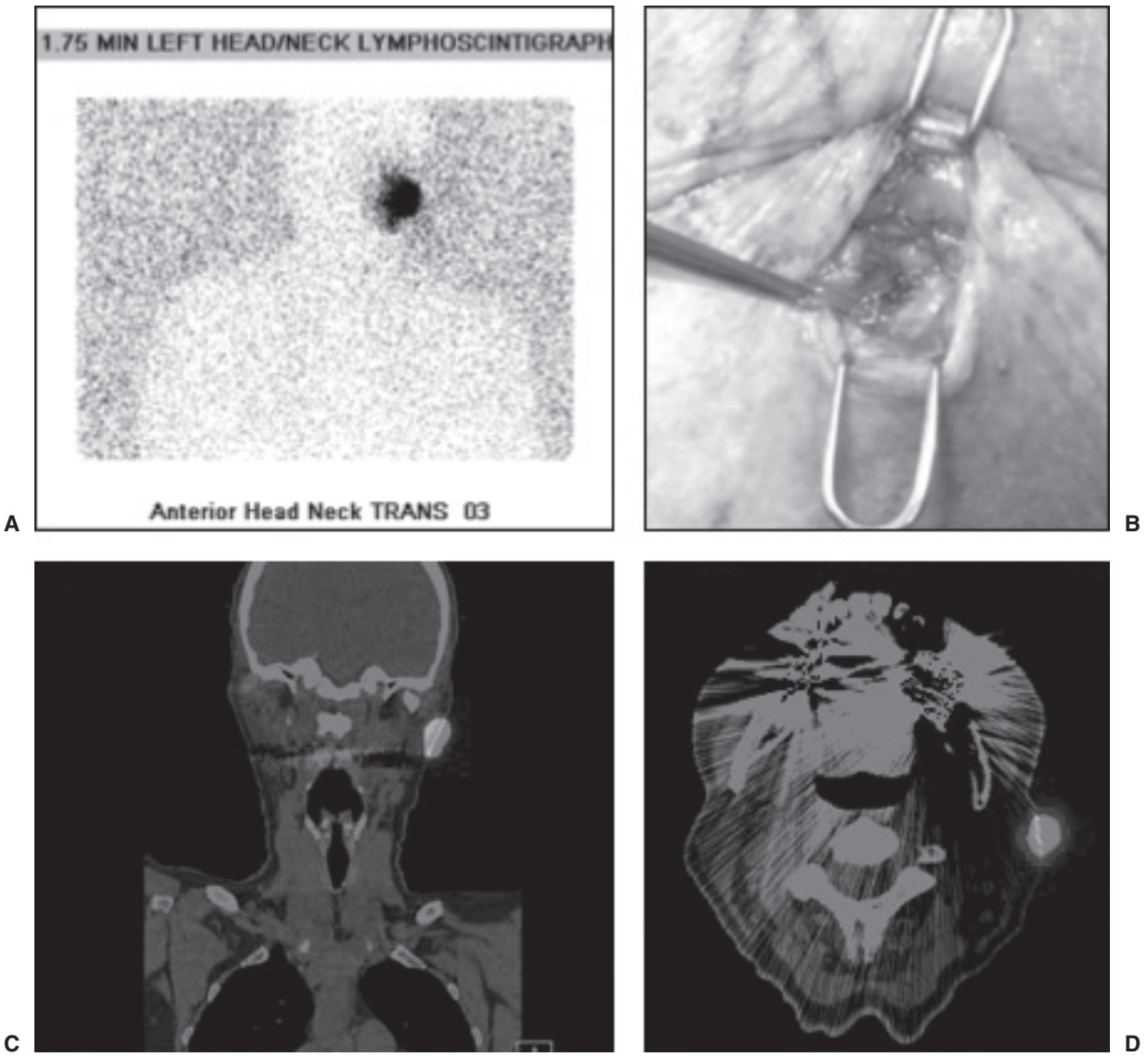



**FIGURE 24-4.** SPECT-CT in SLNB. **A:** Static lymphoscintigraphy demonstrates a lymph node inferior to the main lesion. It is difficult to discern the depth of the node and its precise level. **B:** Intraoperative findings reveal the SLN along the external jugular vein. Coronal **(C)** and axial **(D)** SPECT-CT images reveal the SLN to be located along the external jugular node, rather than in the deeper level II region.

A number of factors warrant discussion regarding the operative management of the sentinel nodes. The identification of the SLN with a gamma probe can be facilitated with the intraoperative injection of isosulfan blue 15 minutes prior to surgery. However, this injection must be placed intradermally, similar to the radioactive isotope, whereby improper placement of the injection can account for failed SLNB procedures. After measuring background counts, all radioactive nodes with counts within 10% of the highest recorded node should be excised. The addition of the isosulfan blue improves the detection with a visual cue, and all blue nodes should be removed as well.[75,76] It is not uncommon for melanoma to map to nonadjacent cervical basins, and multiple SLN are commonly identified. Reported nodal yields in the head and neck range are between 2 and 5 SLN per patient,[65,77] and discordance between the preoperative lymphoscintigraphy and the intraoperative SLN locations are not uncommon.[15]

Sentinel nodes are often found in proximity to the facial nerve and the spinal accessory nerve, and an iatrogenic injury is a surgical complication to be avoided. For melanomas in face and temporal scalp region, drainage to the parotid region is common, requiring dissection in proximity to the facial nerve. Thus, an understanding of the anatomy of this cranial nerve is of utmost importance. Initial concerns for removal of SLN from the parotid gland are unfounded, and careful dissection within the gland by an experienced surgeon can be safely performed without injury to the facial nerve.[68,78] This technique can obviate the need for removal of the parotid gland when this nodal basin is the site of SLN, although in some patients with deep nodes a formal parotidectomy with facial nerve dissection may be necessary. The aforementioned factors contribute to the complexity of surgical evaluation of occult disease.

The use of immunohistochemistry and step-sectioning of the SLN specimens increases the sensitivity of the SLNB technique

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for the detection of nodal disease. The role of frozen section analysis of SLN specimens remains controversial, and some institutions rely upon this approach for decision making vis-à-vis the complete nodal dissection.[69,79] However, there is a reported false-negative rate of 5% to 8% associated with frozen section of SLNs[80–82] due to the technical issues related to freezing artifact, tissue distortion, and tissue loss. Thus, in our practice, SLNs are not inspected with frozen sectioning, but rather are evaluated after formalin-fixation and paraffin-embedding of the entire block. Serial sectioning and immunohistochemical studies for HMB-45, Tyrosinase, MART1/MelanA increases the sensitivity for the detection of occult metastasis by approximately 20%.[83]

## CLINICAL MANAGEMENT

Surgery is the principle treatment for the management of malignant melanoma of the head and neck, with local excision of the primary tumor and operative resection of the involved lymphatic basins. Radiation therapy is offered to selected patients, and systemic therapies are indicated for selected stage II patients, most stage III patients, and for the majority of stage IV patients. This section will highlight some of the unique treatment principles that relate to the head and neck. General treatment algorithms are outlined in Figure 24-5.

### Stages 0 to II

***Surgery.*** Although debate has persisted regarding the extent of surgical resection for malignant melanoma, numerous randomized trials have demonstrated that for thin (<1 mm Breslow thickness) melanomas, margins of 1 cm are sufficient for local control.[84] For intermediate-thickness lesions, margins of 1 to 2 cm are adequate to prevent local recurrences, whereas margins of 0.5 cm are sufficient for melanoma *in situ* lesions.[85] These surgical principles have been validated in randomized trials both in the United States and internationally.[84,86,87] The current NCCN guidelines are outlined in Table 24.5 and serve as the standard approach for margin control in cutaneous melanoma. In the head and neck region, however, the recommended margins are not always feasible due to functional and cosmetic constraints. For example, resections near the eyelids may be limited due to ophthalmological morbidity, or nasal resections may result in substantial tissue loss and cosmetic deformities, and thus the extent of surgical resection is at the discretion of the operating surgeon. The excision should include the subcutaneous fat and underlying fascia of the neck, scalp, or face. The routine resection of sensory nerves and facial nerve branches is excessive. On the scalp, the pericranium can be left intact, whereas on the ear and nose, resections should include the perichondrium due to the thinness of the skin in these regions.

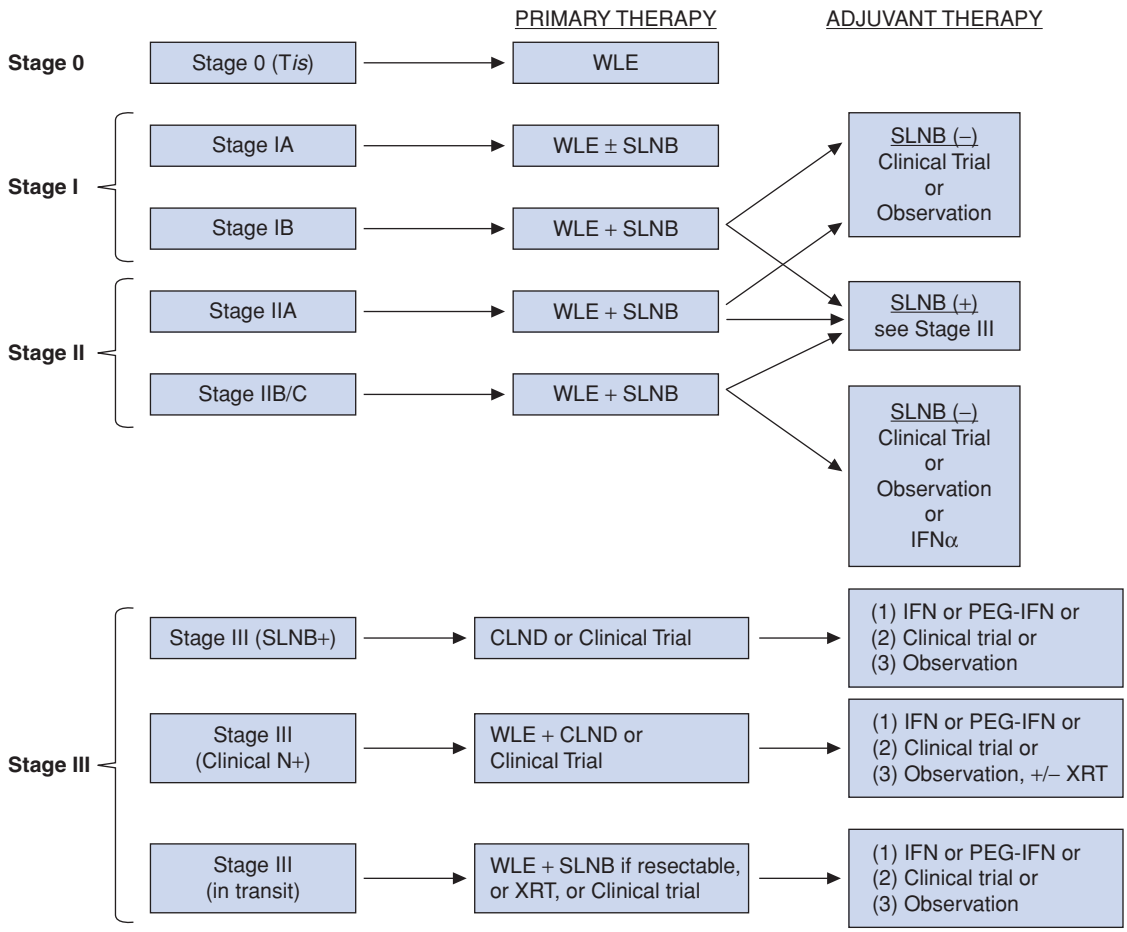



**FIGURE 24-5.** Management of stages 0 to III cutaneous melanoma. WLE, wide local excision; SLNB, sentinel lymph node biopsy; CLND, completion lymph node dissection; IFN, high-dose interferon α2b; PEG-IFN, pegylated interferon; XRT, radiation therapy.

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**TABLE 24.5 Recommended Primary Tumor Surgical Margins**

| Depth of Invasion | Recommended Surgical Margins |
|---|---|
| *In situ* | 0.5 cm |
| ≤2 mm | 1 cm |
| ≥2.01 mm | 2 cm |

Reconstruction of facial, nasal, otologic, and scalp defects are beyond the scope of this chapter, but the surgeon should obey certain principles. Unlike the truck and limb, facial and scalp defects can rarely be closed in a simple straight-line manner and often require complex grafting or local flap reconstructive techniques, which in our practice are often performed in a staged fashion once the pathological status of the margins are confirmed. The vast majority of dermatopathologists do not rely upon frozen section analysis of skin margins for patients with melanoma due to the risk of false-negative results from the tissue-fixation techniques. This is in contrast to the proponents of Mohs micrographic surgery for melanoma, who advocate immediate analysis of the resected margins at the time of excision. In our practice, pathological analysis of the entire paraffin block is performed to determine the margin status. Moreover, the need for regional dissection is dependent on the results of the SLNB, which may require 3 to 4 days for assessment, as detailed above in the prior section. Resection of the parotid gland and cervical lymphatics in the SLNB-positive patient may have a significant impact on the types of flaps available to the reconstructive surgeon. Therefore, most patients with stages 0 to II melanomas of the head and neck undergo surgical resection and SLNB as indicated, with reconstruction performed at a later date. As discussed above, elective nodal dissection is no longer performed for malignant melanoma, and for patients with thick lesions with a negative SLNB, observation of the neck is a sound management strategy.

***Radiation.*** In general, adjuvant radiation therapy is not indicated for stages 0 to II melanomas, although it may be used selectively in specific clinical scenarios. For example, DMs have a high propensity for perineural spread and thus have a high risk of local recurrence at the primary tumor site that can be reduced with postoperative radiation therapy (PORT).[88] Primary tumors that exhibit extensive lymphovascular invasion are also at high risk for local and in-transit recurrence and also are candidates for adjuvant radiation. Postoperative radiation therapy may also be used in the setting of close or positive margins in areas that are not amenable to more extensive or repeat resection. For patients with extensive areas of melanoma *in situ* or lentigo maligna, where surgical resection would lead to profound functional or cosmetic sequelae, local radiation is a reasonable treatment option.[89] Primary irradiation may be considered under exceptional circumstances, but is not the standard of care.

***Systemic Therapy.*** As described above, systemic therapies are generally not used as the primary therapeutic modality in early-stage melanomas, where surgery is highly effective. However, for patients that have primary tumors that are not amenable or are refractory to surgery and/or radiation, topical treatment with imiquimod may be considered.[90–92] Imiquimod is an immunotherapy that stimulates a local antitumor immune response by activating toll-like receptors on lymphocytes. Its use remains investigational at this time.

There is an established but somewhat controversial role for postoperative systemic therapies in patients with thick primary melanomas. Adjuvant treatment with interferon alpha 2b (IFN) was approved by the US FDA for high-risk melanoma patients in 1995 based on the results of the Intergroup E1684 study.[93] This study included patients with primary tumors >4 mm deep without lymph node involvement (T4 N0) and patients with microscopic or macroscopic lymph node (Tx N1–3). All patients underwent complete lymph node dissection and then were randomized to receive interferon or observation only. All patients were randomized within 56 days of their initial biopsy or 42 days of lymphadenectomy. The IFN treatment consisted of an induction phase of 20 MU/m$^2$/d given intravenously (IV) 5 days per week for 4 weeks, followed by 10 MU/m$^2$/d subcutaneously (SQ) 3 times per week for 48 weeks. A total of 287 patients were enrolled, randomized, and treated (IFN, $n = 143$; observation, $n = 137$). After a median follow-up of 6.9 years, the patients treated with IFN showed significant improvements in RFS (median 1.72 years for IFN, 0.98 year for observation, $p = 0.0023$), and overall survival (OS) ($p = 0.0237$). The IFN dosing regimen used in this trial, which is now commonly referred to as "high-dose IFN" (HDI), was subsequently approved by the FDA for use in patients with stage IIB to stage III melanoma.

Despite these initial positive results, subsequent analyses of E1684 and other adjuvant IFN trials have raised questions about the survival benefit of this therapy. Analysis of the patients in the E1684 trial after a median follow-up of 12.6 years continued to demonstrate a significant improvement in RFS with IFN treatment (hazard ratio [HR] 1.38 for observation vs. IFN, $p = 0.02$), but the difference in OS between the groups was no longer significant (HR 1.22, $p = 0.18$).[94] In addition, the E1690 study tested the efficacy of the HDI regimen versus a lower-dose regimen (LDI) (3 MU/m$^2$/d subcutaneously 3 times per week for 2 years) and observation in the adjuvant setting. The eligibility criteria in this trial were the same as the E1684 except that T4 N0 patients were not required to undergo lymphadenectomy (24% underwent elective lymph node dissection, and 5% underwent SLNB). In the initial analysis (median follow-up 4.3 years), HDI achieved a significant improvement in RFS versus observation (HR 1.28 for observation vs. HDI, $p = 0.05$), but there was no improvement in OS (5-year OS 52% vs. 55%).[95] A subsequent analysis performed at a median follow-up of 6.6 years found that IFN still showed a strong but nonsignificant trend for improved RFS (HR 1.24 for observation, $p = 0.09$), but there was no difference in OS (HR 1.0, $p = 0.98$).[94] A pooled analysis of the results for HDI from these two studies showed a significant improvement in RFS (HR 1.30 for observation, $p = 0.006$), but not in OS (HR 1.08, $p = 0.42$).[94]

The clinical benefit of adjuvant IFN must be weighed against the toxicity of the regimen. In the E1684, approximately 50% of patients experienced grade 3 or worse constitutional symptoms (98% any grade), which included fever, chills, and flu-like symptoms (fatigue, malaise, diaphoresis). Almost 30% of patients had neurologic toxicity of grade ≥3, including mood changes such as depression, and 15% had hepatotoxicity.[93] The administration and toxicity of the treatment is also made challenging by the 12-month duration of therapy.

## Stage III Melanoma

***Surgery.*** Surgery is the mainstay of treatment for patients with regionally metastatic melanoma of the head and neck. Wide excision of the primary tumor to negative margins should be performed, as described above, with the reconstruction dictated by the size and location of the defect. Clinically apparent nodal disease mandates a complete lymphadenectomy of the involved stations. For tumors involving the face, neck, and anterior scalp (as defined by the sagittal plane through the eternal auditory canals), a modified radical neck dissection to remove levels I to V, with preservation of the spinal accessory nerve,

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sternocleidomastoid muscle, and internal jugular vein, should be performed. The details regarding the technical aspects of the neck dissection are found elsewhere in this text. The decision to perform a superficial parotidectomy, with preservation of the facial nerve, should be based on the anatomic location of the tumor and the SLNB findings. In general, patients with disease in the parotid bed should undergo parotidectomy and neck dissection. For patients with regional metastasis and a lesion with first-echelon drainage to the parotid gland should be considered for parotidectomy (e.g., anterior lateral scalp melanoma, lateral cheek melanoma), even if the parotid gland is not the site of the metastatic disease. For patients with metastasis from a posterior scalp or posterior neck melanoma, a postero-lateral neck dissection, with removal of levels II to V suboccipital and retroauricular nodes, is necessary.

In the era of SLNB, controversy has arisen regarding the potential role of serial observation of the neck for patients with micrometastatic disease identified on SLNB (N1a, N2a). Approximately 20% of patients with a single positive SLN will harbor additional metastasis in the regional nodes at the time of completion lymphadenectomy, and thus 80% of patients will undergo regional dissection and not have other foci of metastasis in the specimen.[59] Certain risk factors are associated with non-SLN metastasis in melanoma, including age, ulceration, and tumor thickness, but the significance of these factors has not been completely elucidated in the head and neck region.[96,97] Specifically in the head, the incidence of nonsentinel metastatic nodes is observed in approximately 20% of patients.[68,98] Among patients who are not candidates for further surgery, elective nodal irradiation may be considered. The results of the MSLT-II trial, which randomized SNLB-positive patients to either immediate completion lymphadenectomy or observation with serial US and salvage neck dissection, will help address this uncertain clinical scenario. However, based on the current existing data, it is recommended that patients with stage III melanoma undergo completion lymphadenectomy.

For patients with satellitosis or in-transit metastasis, surgical resection should be performed when feasible, and sentinel node biopsy should be considered to stage the regional nodal basin. However, in situations where extensive dermal involvement is present and surgical extirpation would lead to substantial morbidity, systemic therapy or radiation should be considered as the primary treatment modality. The high risk of distant metastasis in such patients provides a strong rationale for the use of systemic therapy to try to achieve concurrent distant control.

***Radiotherapy.*** The indications for adjuvant radiotherapy in stage III disease are based primarily on the risk of regional recurrences after complete nodal dissection. Patients with bulky nodal metastases are at particularly high risk of failure, and, in contrast to the trunk and extremities, smaller volume neck/parotid disease warrants radiotherapy. For regionally metastatic melanoma of the head and neck, adjuvant radiation should be considered for patients with (a) extracapsular extension of disease (b) nodal stage at least N2 (>2 lymph nodes) (c) nodes larger than 2 cm, and (d) extensive dermal metastasis or satellitosis. The indications for radiotherapy vis-à-vis the primary tumor remain those as described above for stages I to II patients. Adjuvant irradiation in these settings offers durable control in the regional basin, although effects on distant metastasis and OS are less clear.[99–102]

***Systemic Therapy.*** As described above, HDI was approved for the adjuvant treatment of resected stage III melanoma in 1995 and should be considered in all patients with stage III disease. More recently, a pegylated form of interferon alpha 2b (PEG-IFN) was approved by the US FDA for the adjuvant treatment of patients with stage III disease (but not stage II). The approval was based on the EORTC 18991 phase III trial.[103] This trial, which included 1,256 patients who had undergone complete lymphadenectomy for positive lymph node involvement, randomized patients to observation or PEG-IFN, which was given for 8 weeks at a dose 6 $\mu$g/kg weekly subcutaneously, followed by 5-year administration of 3 $\mu$g/kg weekly. Similar to HDI, treatment with PEG-IFN resulted in a significant improvement in recurrence-free survival (HR 0.84, $p = 0.02$). However, it did not produce a significant improvement in distant metastasis–free survival (HR 0.90, $p = 0.20$) or OS (HR 1.00, $p = 0.98$). Preplanned subgroup analyses suggested that patients with microscopic N1 disease may have the most benefit from this therapy, but future randomized trials in this specific group of patients will be necessary for definitive conclusions and recommendations. Thus, both HDI and PEG-IFN are FDA-approved options for patients with stage III melanoma, but the relative risks and benefits of these therapies must be considered, and enrollment in clinical trials should be considered as an alternative.

## Stage IV Melanoma

***Surgery and Radiation.*** Surgery generally has a limited role for patients with stage IV disease. The potential benefits for surgical extirpation of local or regional disease in the face of distant metastases are primarily palliative and include (a) limiting the morbidity of continued tumor growth into local structures, (b) reducing nodal burden to lessen great vessel and muscular invasion, and (c) potentially decreasing the source of future metastatic foci. In the head and neck, uncontrolled tumor growth can lead to a substantial decrement in quality of life, and thus local-regional control of clinical disease should be offered when appropriate. The therapeutic role of distant metastectomy is controversial. It is clear that certain sites of metastasis harbor more favorable prognosis, such as the lungs, and video-assisted thoracic surgery to excise a limited number of metastatic sites can be performed in the setting of low burden of disease and/or slow-growing lesions.[104,105] Lesions in the brain should also be considered for locally directed therapies, due to both the general lack of efficacy of systemic therapies for these patients and the significant risks associated with mass effects and intracranial hemorrhage.[106] However, other than for palliative relief of symptomatic lesions, surgical resection of brain metastases is generally only appropriate when three or less lesions are present.[107] The decision to operate on distant metastases remains complex and may evolve in the near future due to the availability of increasingly effective systemic therapies. Ultimately, decision making regarding the role of surgery in this setting should take into account the patient's estimated survival, surgical morbidity, and the potential success with other available therapeutic modalities.

Similar to surgery, radiation may offer palliative benefit in patients with stage IV disease, but is generally not used with curative intent. Radiation therapy plays a prominent role in the management of brain metastases. Stereotactic radiosurgery (SRS) can be offered as an alternative to surgical resection for brain metastases, most effectively in tumors ≤2 cm in diameter. Traditionally whole brain radiation therapy (WBXRT) has been used for patients with >3 lesions, but there is growing data that stereotactic radiosurgery is a reasonable alternative in patients with multiple metastases and may be associated with less cognitive decline.[108]

***Systemic Therapy.*** Systemic therapies are the primary therapeutic modality for patients with stage IV disease. Although chemotherapy has been used for many years in melanoma, other modalities (immunotherapy, targeted therapy) also play a prominent role in the management of these patients.

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***Chemotherapy.*** The first agent approved by the FDA for the treatment of metastatic melanoma was dacarbazine (DTIC). The active metabolite of DTIC methylates guanine nucleotides, resulting in errors in DNA replication and ultimately strand breakage and cell death. Dacarbazine achieves clinical responses in only 10% to 15% of patients, and the overwhelming majority of clinical responses are transient. Temozolomide (TMZ) is an oral agent that spontaneously hydrolyzes to the same active metabolite as DTIC. Clinical testing demonstrated that TMZ was noninferior compared to DTIC, but not superior.[109] In addition to the convenience of oral dosing, TMZ, unlike DTIC, is able to cross the blood–brain barrier. Despite this pharmacologic advantage, treatment with TMZ achieves clinical responses in only 6% of patients with brain metastases.[110] A number of other chemotherapies have been tested as single agents in melanoma, but none have demonstrated significant improvements in outcomes versus dacarbazine.[111] Similarly, a variety of combination chemotherapy regimens have been tested in melanoma. The most widely used combinations initially were cisplatin, vinblastine, and dacarbazine (CVD), and the Dartmouth regimen of cisplatin, dacarbazine, carmustine, and tamoxifen. Although impressive clinical response rates were observed in nonrandomized trials of each combination, neither regimen significantly improved OS in comparison to DTIC in randomized trials and were characterized by increased toxicity.[111,112]

***Immunotherapy.*** The regulation of melanoma by the immune system was initially suggested by a number of different observations, including rare spontaneous regression of metastatic lesions, and the occurrence of disease relapses many years (i.e., >10) after initial melanoma diagnosis and resection. These observations led to efforts to treat and control metastatic melanoma through stimulation of the immune system, as opposed to the use of agents that act directly on the tumor cells.

Interleukin-2 is a cytokine normally produced by the body in response to infections. Treatment with high-dose bolus IL-2 (HD IL-2) achieves clinical responses in approximately 15% of patients.[113,114] Although this response rate overall does not appear very different from that achieved by dacarbazine, the majority of the patients who achieve a complete clinical response (~6%) have very durable responses, with disease-free intervals of >10 years.[115] Although HD IL-2 was never shown to improve OS in a randomized trial, it was approved by the FDA in 1998 due to its ability to cure some patients with stage IV disease. Unfortunately, HD IL-2 treatment is extremely toxic, with critical side effects resembling the physiology of sepsis. Virtually every organ system is affected, with prominent toxicities including hypotension, renal insufficiency, dyspnea, confusion, and liver dysfunction; early trials reported a treatment-related mortality rate of approximately 2%. A number of efforts have been undertaken to identify patients most likely to benefit from HD IL-2. The highest response rates are observed in patients with skin and subcutaneous involvement only; conversely, patients with brain metastases have very low response rates, and their treatment is complicated by the risk of cerebral edema that could ensue from the aggressive fluid resuscitation required by this treatment.[114]

Biochemotherapy regimens were designed with the goal of increasing the response rate of IL-2 by combining it with chemotherapy.[116] A variety of biochemotherapy regimens exist and have been tested, most with the backbone of the cisplatin, vinblastine, and dacarbazine chemotherapy, along with IL-2 and IFN. IL-2 is generally given as a continuous infusion instead of as boluses, which reduces the severity of many of the hemodynamic side effects of this agent. However, the combined effects of the agents still results in significant toxicities. Nonrandomized trials with various biochemotherapy regimens have reported clinical response rates of 30% to 50%, but in randomized trials no significant improvement in OS has been demonstrated compared with chemotherapy alone.[111,117,118] However, similar to HD IL-2 therapy, patients who achieve complete tumor responses with biochemotherapy frequently experience very durable disease-free survival.[118]

An improved understanding of the factors that regulate the antitumor immune response has recently led to new immunotherapeutic approaches. CTLA-4 is an immunoglobulin that is expressed on the surface of regulatory and effector T cells. After activation of the T cells induced by the binding of antigens presented to antigen presenting cells (APCs) to T-cell receptors (TCRs), CTLA-4 becomes concentrated on the cell membrane and competes with the co-stimulatory CD28 receptor to bind to B7. Engagement of CTLA-4 inhibits signaling from the TCR and thereby attenuates the function of the T cell. In order to overcome this inhibitory signal, antibodies were designed to recognize CTLA-4. The most well-characterized CTLA-4 blocking antibody is ipilimumab. After promising preclinical and early-phase studies, the efficacy of ipilimumab has now been demonstrated in two independent phase III studies. The first study tested the efficacy of ipilimumab alone and in combination with the gp100 peptide vaccine in previously treated metastatic melanoma patients, with results compared to the effects of gp100 alone.[119] Treatment with ipilimumab alone resulted in a modest clinical response rate of 10.9%, but it was significantly improved compared with the gp100 arm (1.5%, $p = 0.001$). Interestingly, many of the responses were delayed, and some responses were observed with continued treatment after initial evidence of disease progression. More importantly, treatment with ipilimumab resulted in a significant improvement in OS (median OS 10.1 vs. 6.4 months, $p = 0.003$), making it the first agent to ever demonstrate a significant improvement in this outcome in a phase III trial in melanoma. Another phase III trial in treatment-naive metastatic melanoma patients showed that the combination of ipilimumab and dacarbazine resulted in significantly improved OS compared with dacarbazine alone (11.2 vs. 9.1 months, HR 0.72, $p < 0.001$).[120] Based on these results, ipilimumab was approved by the FDA for the treatment of metastatic melanoma in 2011. In both the first- and second-line trials, approximately 20% to 25% of the ipilimumab patients were alive 3 years after starting treatment, compared with approximately 10% in the control treatment arms, suggesting that the survival benefit of ipilimumab may be durable, although additional follow-up will be needed to compare to the durability of HD IL-2 complete responses. While ipilimumab is similar to HD IL-2 in its basic mechanism of antitumor activity, it differs significantly in its toxicities. Unlike HD IL-2, ipilimumab is not associated with significant acute effects on hemodynamics or other organ systems. However, a variety of toxicities are observed with this treatment over time, generally reflecting manifestations of autoimmune attack of organs. Notably, autoimmune colitis leading to intestinal perforation can be a lethal event and must be recognized and treated early in patients. Common toxicities of ipilimumab include diarrhea (~35%), rash (30%), liver dysfunction (2%–30%), fevers (20%–35%), and endocrine insufficiencies (hypothyroidism, hypopituitarism, hypophysitis, adrenal insufficiency; total <5%).[119,120] Multiple studies are ongoing to identify biomarkers to identify patients who are most likely to benefit from ipilimumab.[121]

In addition to ipilimumab, a number of other experimental immunotherapies have shown promise in early-phase testing. PD-1 is another inhibitory receptor on the surface of T cells, similar to CTLA-4. Treatment with MDX-1106, an antibody against PD-1, in phase I testing achieved several clinical responses, including in melanoma patients.[122,123] Interestingly, the toxicity of the agent was very mild, with the most common toxicities being hematologic (~25% lymphopenia) and fatigue/musculoskeletal (15%); the incidence of autoimmune colitis (2.5%) and

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endocrinopathies (2.5%) were both very low. Another promising approach is the use of adoptive cell transfer of tumor-infiltrating T cells (called TIL).[124–126] In this modality, tumors are harvested from patients, and then lymphocytes are isolated from the resected tumors (the TIL). If the TIL can be grown to sufficient numbers, patients then undergo lymphodepleting treatments (high-dose chemotherapy or total-body irradiation), followed by infusion of their TIL. Patients are then treated with HD IL-2 to promote the activity and viability of the TIL. Although no randomized studies have been performed, single-arm studies have reported clinical response rates approaching 50%, and many of the responses are durable.[126,127] While the results are promising, the regimen is quite toxic, and it is only possible to administer for patients from whom the TIL are able to expand. In addition, the expansion of T cells to sufficient numbers for treatment requires 1 to 2 months, and thus it is not an appropriate first-line therapy for patients needing immediate treatment. However, TIL can be stored safely after their harvest for treatment later, and thus TIL harvest may become a consideration in the management of stage III melanoma in the future.[128]

***Targeted Therapy.*** The identification of frequent activating mutations in melanoma has led to the aggressive testing of targeted therapies in this disease. The first target to be addressed was *BRAF*, which was an attractive candidate due to both its high prevalence (~45% of melanomas) and the presence of a single activating hotspot (*V600E*), which facilitates both clinical testing and drug development. Initial clinical trials targeting BRAF in melanoma were performed with sorafenib (also known as BAY43-9006). Sorafenib is a small molecular inhibitor of many kinases, including BRAF, although it binds to several other targets with greater affinity.[129] While it showed activity against melanoma cell lines in preclinical models, sorafenib achieved clinical responses in <3% of patients in single-agent clinical trials.[130,131] More promising results were observed in a phase I trial in which sorafenib was combined with paclitaxel and carboplatin, as 40% of the melanoma patients achieved clinical responses, although clinical benefit did not correlate with *BRAF* mutation status.[132] However, a phase III, randomized, placebo-controlled trial of paclitaxel and carboplatin with or without sorafenib showed that the addition of sorafenib did not improve the response rate (12% with sorafenib, 11% with placebo) or progression-free survival (median 17.4 weeks with sorafenib vs. 17.9 with placebo).[133]

While these results were very disappointing, much more impressive results have been achieved with V600-mutant-selective BRAF inhibitors. Vemurafenib (also known as PLX4032 or RG7204) was the first such agent to enter clinical testing. Vemurafenib was selected for development based on the fact that it not only was a selective inhibitor of BRAF compared with other kinases, but also has approximately 10-fold greater affinity for BRAF proteins with the V600E substitution mutation compared with the wild-type sequence.[134] The potent ability of vemurafenib to inhibit the growth of melanoma cell lines with *BRAF V600* mutations was demonstrated in preclinical models both *in vitro* and *in vivo*.[135] Unexpectedly, additional studies demonstrated that vemurafenib treatment of melanoma cell lines without *BRAF* mutation resulted in increased tumor cell growth.[136–138] In phase I clinical testing, no responses were observed in metastatic melanoma patients with a wild-type *BRAF* gene, but 83% of patients with a *BRAF V600E* mutation achieved (unconfirmed) clinical responses.[139] Clinical responses were only observed when serum levels of the vemurafenib exceeded doses that correlated with tumor shrinkage in preclinical models, and pharmacodynamic testing showed a dose-dependent effect on MAPK pathway inhibition that correlated with the magnitude of clinical response.[139,140] The efficacy of vemurafenib was shown definitively in the BRIM-3 phase III trial. In this trial comparing the efficacy of vemurafenib against dacarbazine in previously untreated metastatic melanoma patients with a *BRAF V600E* mutation, treatment with vemurafenib significantly improved the overall response rate (48.6% vs. 5.5%, $p < 0.001$), progression-free survival (median 5.3 vs. 1.6 months, $p < 0.001$), and the risk of death from melanoma (HR 0.37, $p = 0.001$). The trial was stopped at its first interim analysis, when the median follow-up for all patients was <4 months, so the effects on OS were quite preliminary and will need to be followed over time. Consistent with earlier studies, the most common toxicities of vemurafenib are cutaneous, including the development of cutaneous squamous cell carcinomas or keratoacanthomas in approximately 20% of patients.[139,141] Such lesions must be removed, but to date there are no reports of metastasis from them, and treatment with vemurafenib may be continued safely after they are treated. Other toxicities include rash, arthralgias, fatigue, and fevers. Vemurafenib was approved for the treatment of metastatic melanoma patients with *BRAF V600* mutations in 2011. Significant antitumor activity has also been observed with GSK2118436, which is a structurally unrelated, selective inhibitor of V600-mutant BRAF proteins. GSK2118436 achieved confirmed clinical responses in approximately 60% of metastatic melanoma patients with *BRAF V600E* mutations in phase I and II clinical trials, with a preliminary median progression-free survival of 6.7 months, although final results of these trials are pending at this time.[142] A variety of other inhibitors against the RAS-RAF-MEK-ERK pathway are currently in various stages of testing and development.

Although the high clinical response rate of the selective BRAF inhibitors is impressive, the benefit derived from these agents is relatively short lived. The median duration of clinical responses with vemurafenib in its phase I and II clinical trials was approximately 7 months, which is very similar to the initial results with GSK2118436.[139,142] Many studies have been conducted using both resistant cell lines and clinical specimens to determine the mechanisms of resistance to BRAF inhibitors.[143] Surprisingly, to date all samples have shown the continued presence of the *BRAF V600E* mutation at the time of resistance and have failed to identify any secondary mutations in the *BRAF* gene.[144] However, a number of other changes have been identified that result in reactivation of signaling downstream of BRAF despite the continued presence of the inhibitor. The mechanisms include alternative splicing of the *BRAF* gene, mutations in *NRAS* and *MEK1*, and utilization of other RAF isoforms (CRAF, ARAF). However, resistance has also been observed despite continued inhibition of signaling by BRAF due to activation of other signaling pathways. Research is ongoing to determine the efficacy of combinatorial approaches to prevent and/or overcome resistance to BRAF inhibitors.

In addition to *BRAF*, genetic alterations in *KIT* present a therapeutic opportunity. Small molecule inhibitors of KIT are the FDA-approved standard of care in gastrointestinal stromal tumors, a disease in which approximately 80% of patients have activating mutations in the *KIT* gene. Based on this previous experience, a number of melanoma patients with *KIT* mutations have been treated with various KIT inhibitors, many of whom have achieved dramatic clinical responses and benefit.[145–147] These responses contrast to the results of phase II trials of the KIT inhibitor imatinib in unselected melanoma patients. These trials, which overwhelmingly consisted of patients with cutaneous melanomas, which are unlikely to harbor *KIT* mutations, overall reported a response rate of approximately 1%.[42] Similar to the experience with selective BRAF inhibitors, trials with KIT inhibitors are now ongoing that are restricted to melanoma patients with *KIT* mutations and/or amplifications. Initial results from two such trials with imatinib reported clinical response rates of 15% to 25% in these patients.[148,149] Although these results appear to be superior to those achieved in unselected melanoma patients, research is ongoing to

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determine why the response rate is lower than what is observed in gastrointestinal stromal tumor patients (>50%).[150] Additional investigations are being undertaken to identify factors that correlate with response to single-agent KIT inhibitors in melanoma.[148]

## OUTCOMES AND RESULTS

In addition to providing data regarding new staging criteria (mitotic rate, serum LDH), the 2009 AJCC cutaneous melanoma staging and classification system provided important information about outcomes in a contemporary cohort of >38,000 patients.[12] Perhaps most critically, the outcomes reflect the current era in which SLNB has become a standard part of the management of local disease and can result in upstaging of patients without clinically apparent lymph node involvement. The survival outcomes by TNM categories and clinical stage groupings are shown in Figure 24-6. Importantly, the findings validated the previously established prognostic markers (i.e., Breslow thickness) and validated new markers incorporated into the staging system (mitotic rate, serum LDH). For patients with primary tumors only (stages I–II), 5-year OS varied from 97% for patients with T1aN0M0 disease to 53% with T4bN0M0. The 5-year survival for patients with regional metastases ranged from 70% (T1–4N1aM0) to 39% (T1–4N3M0). As to date no systemic therapies have been proven to significantly improve OS in randomized trials in patients with stages I to III melanoma, these rates likely remain highly relevant at this time. For patients with distant metastases, the reported 1-year survival rates were 62% with M1a, 53% for M1c, and 33% for M1c. However, the recent development of two different systemic therapies (ipilimumab, vemurafenib) that result in significant improvements in the OS of patients with stage IV disease provides a strong impetus to reevaluate the outcomes in the near future.[119,120,141] Furthermore, as vemurafenib is only effective in patients with activating *BRAF* mutations, and based on emerging data about prognostic significance of activating mutations, it is likely that future estimates of survival will need to incorporate information about molecular markers as well.[35,36,40]

### Complications

***Surgery.*** Complications related to surgery can be divided into systemic and local complications. A discussion of systemic complications is beyond the scope of this chapter and can be found in numerous texts of perioperative management. Specifically for melanoma surgery of the head and neck, treatment sequelae may be functional or cosmetic. Injury to the cranial nerves during surgical resection and reconstruction can be devastating and may result in facial (VII) or tongue paralysis (XII), shoulder dysfunction (XI), or facial parasthesias (V). Injuries to other cranial nerves are uncommon, but transection of cervical rootlets during a neck dissection can result in injury to the phrenic nerve and sensory nerves of the skin, and injury to the thoracic duct during neck dissection can lead to a chyle leak. Poor cosmetic outcomes are usually the sequelae of inappropriately designed facial incisions or suboptimal local flap reconstruction. Management of ear and eye defects requires reconstructive expertise, and complications in these regions include ectropion, telecanthus, "cup ear" deformity, and external auditory canal stenosis. The removal of nasal lesions can result in nasal stenosis when reconstruction is suboptimal. Medical comorbidities such as diabetes mellitus, vasculopathy, and cigarette smoking are associated with an increased risk of wound infections and failed reconstructive efforts, such as rotational flap or skin-graft necrosis.

***Radiation.*** Complications from radiotherapy can be divided into acute and chronic complications. Hypofractionation strategies generally lead to minimal morbidity in the acute setting, although skin sloughing and mucositis can occur, particularly for lesions in proximity to mucosal surfaces. Unlike irradiation to mucosal tumors of the head and neck, radiotherapy for cutaneous melanoma in this area does not result in substantial trismus, pharyngeal stenosis, chronic dysphagia, or dysgeusia, particularly when laryngeal blocks are used. Irradiation of lesions that are located near the mandible or maxilla can lead to osteoradionecrosis, and thus a thorough dental evaluation is necessary before treatment. Other long-term morbidities may include carotid artery stenosis, xerostomia, hearing loss, or cranial neuropathies. Osteoradionecrosis of the parietal or frontal scalp may occur after surgery and radiotherapy for melanomas located in this region. This often occurs when a nonvascularized skin graft is utilized in the reconstruction of a scalp defect, and thus a vascularized rotation flap is recommended when a full-thickness scalp resection is performed. Bilateral neck irradiation is associated with substantial morbidity, and due to the poor survival of patients with bilateral nodal metastasis, should be avoided in patients who have indications for postoperative radiotherapy.[151]

***Systemic Therapies.*** A number of the new therapies that have demonstrated efficacy in melanoma have relatively unique sequelae and complications than are traditionally observed with chemotherapy. Immunotherapies, such as ipilimumab, may induce the immune system to attack not only tumors, but also normal organs and tissues. Thus, patients receiving these therapies must be monitored for organ dysfunction due to autoimmunity.[152] The most commonly observed autoimmune side effects include endocrinopathies (thyroiditis, hypophysitis), dermatitis, hepatitis, and colitis; rarer manifestations include uveitis, nephritis, and myositis. The recognition of the autoimmune etiology in symptoms related to these manifestations is important clinically in order to provide appropriate therapy (immunosuppression) and to avoid fulminant toxicities (i.e., gastrointestinal perforations).[119]

Although they are cytotoxic to tumor cells, the mutant-selective BRAF inhibitors (vemurafenib, GSK2118436) generally do not induce the broad toxicity that is observed with cytotoxic chemotherapies. However, approximately 10% to 20% of patients treated with these agents develop hyperproliferative cutaneous lesions, including keratoacanthomas and squamous cell carcinomas. Emerging data suggests that many of these lesions harbor activating *RAS* mutations.[153,154] Preclinical models support that the selective BRAF inhibitors induce the proliferation of these cells, but they do not actually induce those oncogenic events, thus defining the BRAF inhibitors as promoters but not initiators of these lesions.[153] Treatment with the selective BRAF inhibitors may be continued safely after the removal of these hyperproliferative lesions, and to date there are no reports of metastases arising from them.

### Management of Recurrence

***Local Recurrence.*** Melanoma will recur at the site of the primary excision in approximately 1% to 8% of patients with stage I or II melanoma and is associated with adverse prognosis.[86,87,155,156] The head and neck has one of the highest sites of local recurrence, and risk factors associated with primary site recurrence include age >60, >4 mm thickness, and ulceration.[86,157] It is important to distinguish a local recurrence from an in-transit metastasis or a new second primary tumor, and therefore a biopsy of any suspicious lesion near the surgical bed should be undertaken. Resectable lesions should be managed operatively, but it is important to evaluate the patient for regional and distant disease with appropriate radiographic and laboratory studies. These will often include a CT or US of the head and neck. The value of a

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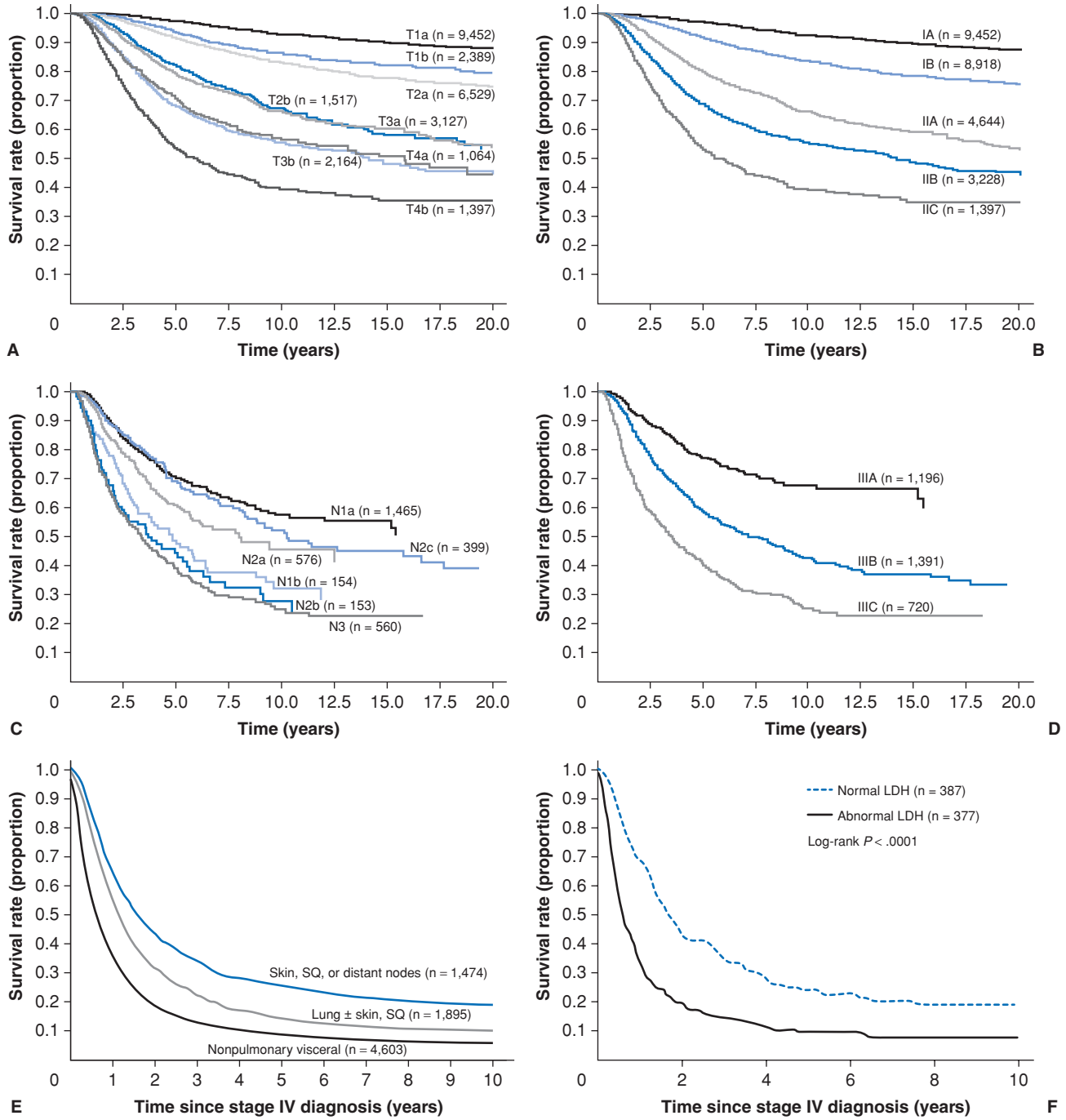



**FIGURE 24-6.** Overall survival in melanoma. Survival curves are shown for primary tumor **(A)** T categories and **(B)** clinical stages, for regional lymph node **(C)** N categories and **(D)** clinical stages, and for distant metastases by **(E)** anatomic location and **(F)** serum LDH. The number of patients in each curve is shown in parentheses. SQ, subcutaneous; LDH, lactate dehydrogenase.

*Source:* From Edge SB, Byrd DR, Compton CC, et al. *AJCC Cancer Staging Manual.* 7th ed. New York, NY: Springer-Verlag; 2010:329, 332–334, with permission.

sentinel node biopsy in the recurrent patient remains of questionable value, but if a patient has not had staging of the neck performed during prior treatment, the recurrent setting may be the appropriate time. However, the lymphatic drainage will likely be altered in this setting, and thus SLNB in this setting may lead to a false-negative result. For unresectable lesions, irradiation is a reasonable option to control local tumor growth, as progressive disease can lead to substantial cosmetic, functional, and neurological sequelae in the head and neck.

***Regional Recurrence.*** The incidence of regional recurrences in patients with malignant melanoma depends on numerous factors

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including age, tumor thickness, mitotic rate, ulceration, and LVI.[156,158,159] For stages I to II patients with negative SLNB, the reported regional recurrence rate is 2% to 7%,[64,69,155] which is distinguished from those with a false-negative SLNB. The risk of nodal recurrence among stage III patients is 10% to 15%. Clearly, the major concern in this population is the development of distant metastasis, and thus restaging studies should be performed. In the previously undissected neck, salvage lymphadenectomy is indicated as long as distant disease has not been identified. Regional control in the neck remains a high priority in this patient population due to the aforementioned issues surrounding morbidity. Whether to deliver adjuvant radiation in this situation is debatable and should be individualized and systemic therapy is indicated. Alternatively, the patient may be considered for a clinical trial.

## Special Issues/Future Directions

***Mucosal Melanoma.*** Melanoma of mucosal surfaces of the head and neck represents an aggressive form of the disease with a high propensity for regional spread and distant metastasis. At the molecular level, mucosal melanomas show a distinct pattern of chromosomal copy number gain and loss from the common cutaneous melanomas that lack evidence of CSD.[25] They also have a low prevalence of activating *BRAF* mutations (~5%), although the availability of effective therapies for those patients supports the rationale for testing for this abnormality (Table 24.1).[29] As discussed previously, mutations in the *c-KIT* gene are detected overall in 26% of mucosal melanomas, with specific studies in mucosal melanomas of the head and neck reporting mutation rates of 8% to 27%.[41,42] Clinical trials are ongoing to determine the overall efficacy of KIT inhibitors in melanoma patients with KIT mutations, but several case reports have described significant clinical responses to these agents.

Mucosal melanomas of the head and neck most commonly involve the oral cavity and sino-nasal tract. The lesions present as pigmented areas of the oral mucosa or as a polypoid mass of the nasal cavity that may be indistinct from a benign polyp. The general treatment paradigm entails surgical resection and adjuvant radiotherapy, although sentinel node biopsy is generally not utilized for the tumors. Margin control in these patients is difficult due to the proximity of the tumors to critical neurovascular and bony structures and is associated with adverse outcomes.[160] The addition of adjuvant irradiation improves local-regional control, but not OS.[161,162] In the paranasal sinuses, extension into the skull base is not uncommon. The outcomes for patients with paranasal sinus tumors are generally poor, with median 2-year survival of 65% for T1–T2 tumors and 20% to 30% for T3–T4 tumors.[163] For all mucosal sites in the head and neck, 5-year survival is approximately 25%.[164] A role for biochemotherapy is emerging for patients with unresectable disease or for those with distant metastasis.[165]

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# PART B:
# Radiologic Imaging Concerns

Jeffrey A. Bennett

Imaging of the head and neck for melanoma is usually performed as part of staging for metastatic lymph nodes and intracranial metastases. If the primary site is the skin of the scalp, face, or neck, imaging can be performed to determine depth of invasion. This topic is dealt with in detail in the chapter on skin cancers. The lymphatic drainage of primary melanoma of the skin tends to follow the expected pattern associated with squamous cell cancer, that is, parotid and facial nodes, as well as occipital and level 1 nodes, followed by cervical chain nodes. However, there are reports of more variability of lymphatic drainage with melanoma.[1–3] Therefore, bilateral nodes at all levels must be examined carefully on the scans. The sentinel node is typically mapped with nuclear medicine lymphoscintigraphy (Fig. 24-7) and has prognostic value.[4] An FDG-PET scan is usually performed for initial staging to determine distant spread of disease. FDG-PET typically shows marked radiotracer uptake,[5] but there is variability of uptake perhaps related to the histologic type of melanoma[6] (Figs. 24-7 and 24-8). FDG-PET is commonly used in surveillance scanning following treatment.

Melanoma lymph node metastases tend to be quite aggressive in appearance. There is often a solid enhancing portion with areas of necrosis (Fig. 24-9). Extracapsular spread is common. Early necrosis is often present, and, occasionally, almost purely necrotic nodes will be encountered (Fig. 24-10).

Extranodal sites of melanoma in the head and neck are rare, but can occur in the thyroid gland (Fig. 24-11) and mucosal surfaces of the head and neck. The sinonasal region and oral cavity are the most common sites of involvement along the

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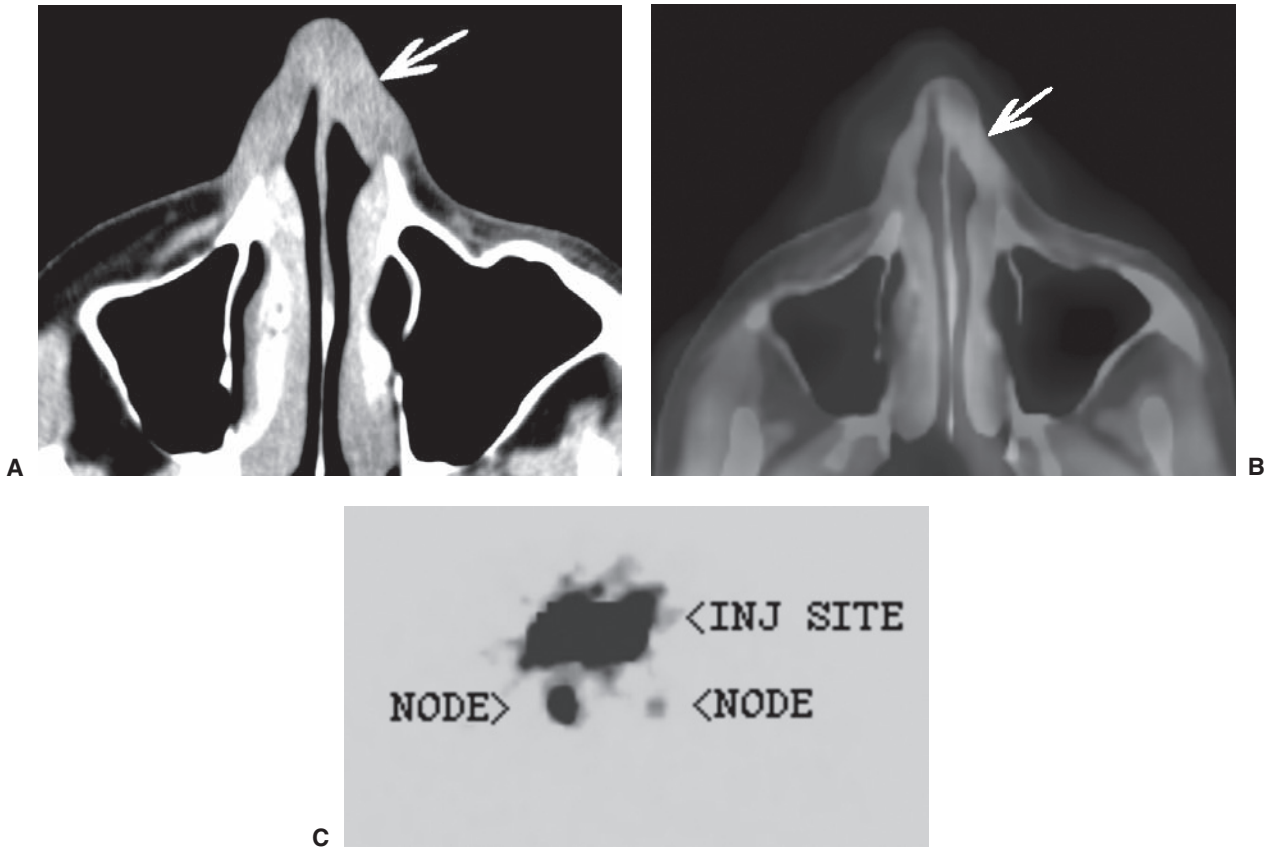



**FIGURE 24-7.** Axial contrast-enhanced CT scan **(A)** shows an enhancing mass on the left side of the nose (*arrow*). This showed only minimal uptake of radiotracer on the FDG-PET scan **(B)**. Prior to resection, nuclear medicine lymphoscintigraphy was performed **(C)**. 4 mCi Tc-99m sulfer colloid was injected in the skin around the primary site and imaging was performed over time-revealing sentinel nodes in the submandibular region.

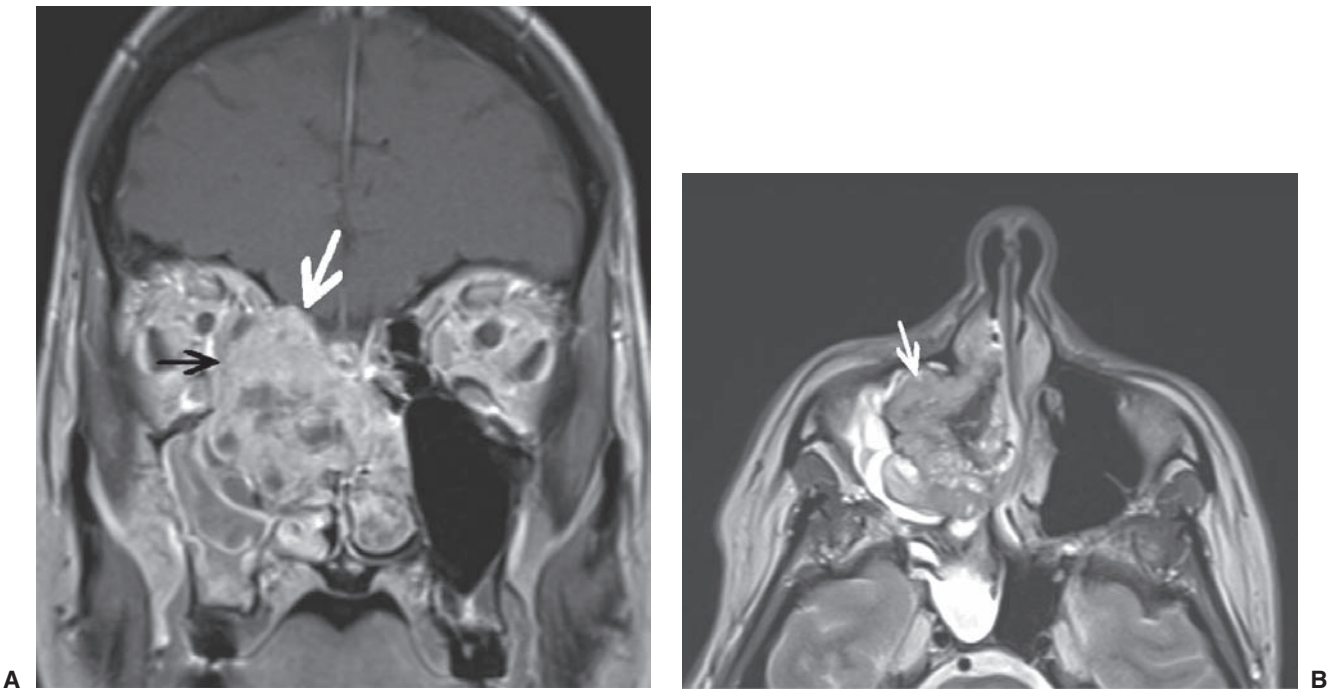
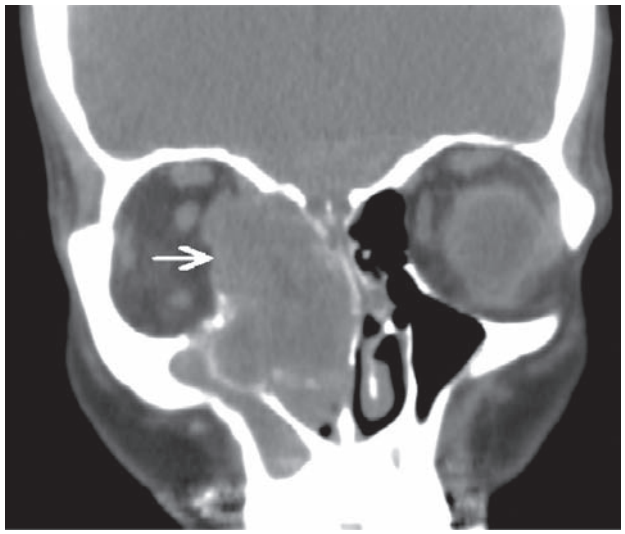


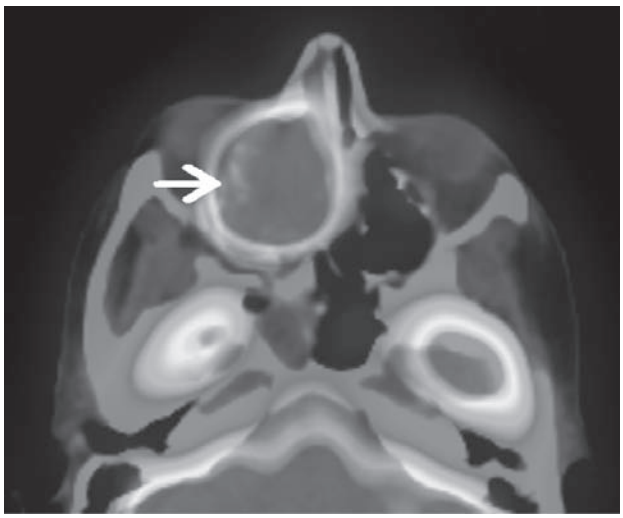

**FIGURE 24-8.** Sinonasal lymphoma. Coronal postcontrast T1-weighted MRI **(A)**, axial T2-weighted MRI **(B)**, and coronal noncontrast CT **(C)** show a very aggressive mass (*white arrows*) centered in the right nasal cavity. The mass shows avid enhancement and mixed signal on T2-weighted images. The mass had invaded the extraconal orbit (*black arrow* in **(A)**). The drainage of the right maxillary and shenoid sinuses has been obstructed and the ethmoid sinuses have been invaded. **D:** Accompanying FDG PET scan shows marked radiotracer uptake in the lesion (*arrow*) with an SUV of 7.1.



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C



D

**FIGURE 24-8.** *Continued*

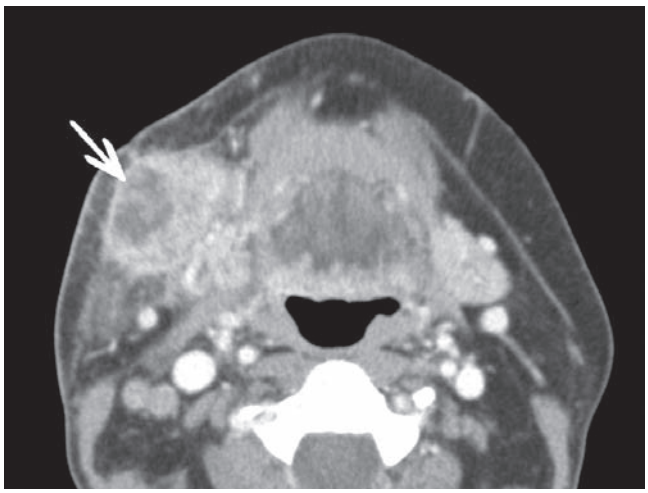


**FIGURE 24-9.** Axial CT scan shows a melanoma metastasis to a level 1b lymph node (*arrow*). This has an aggressive pattern with marked enhancement of the solid portion, an area of necrosis, and extracapsular spread.

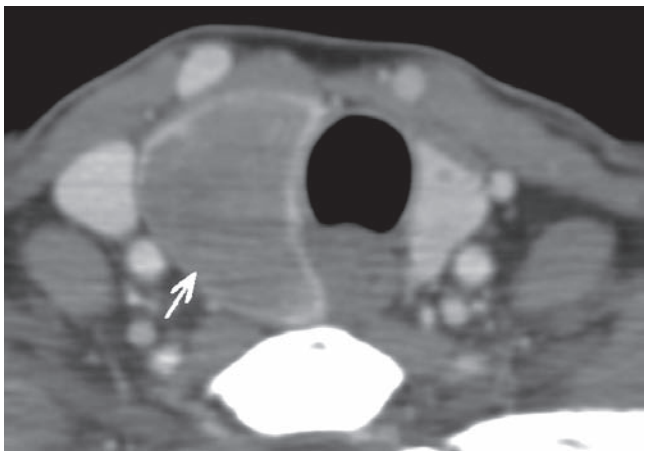


**FIGURE 24-10.** Axial CT scan shows a melanoma metastasis to a level 3 lymph node (*arrow*) that is predominantly necrotic with an enhancing rim. Extracapsular spread is present.

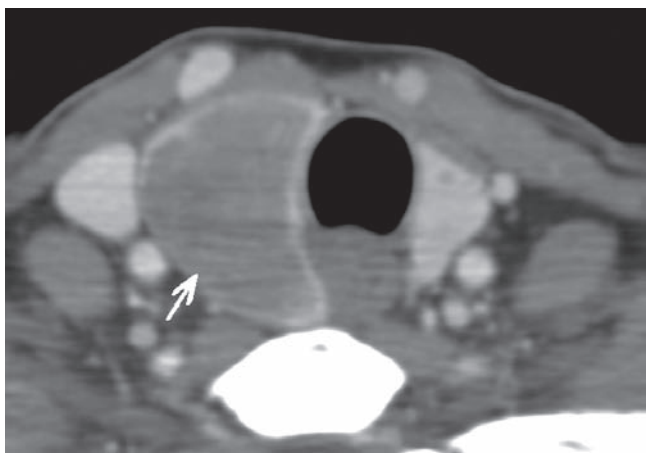


**FIGURE 24-11.** Rapidly growing low-density mass in the right lobe of the thyroid gland (*arrow*) shown on contrast-enhanced CT scan proved to be melanoma.

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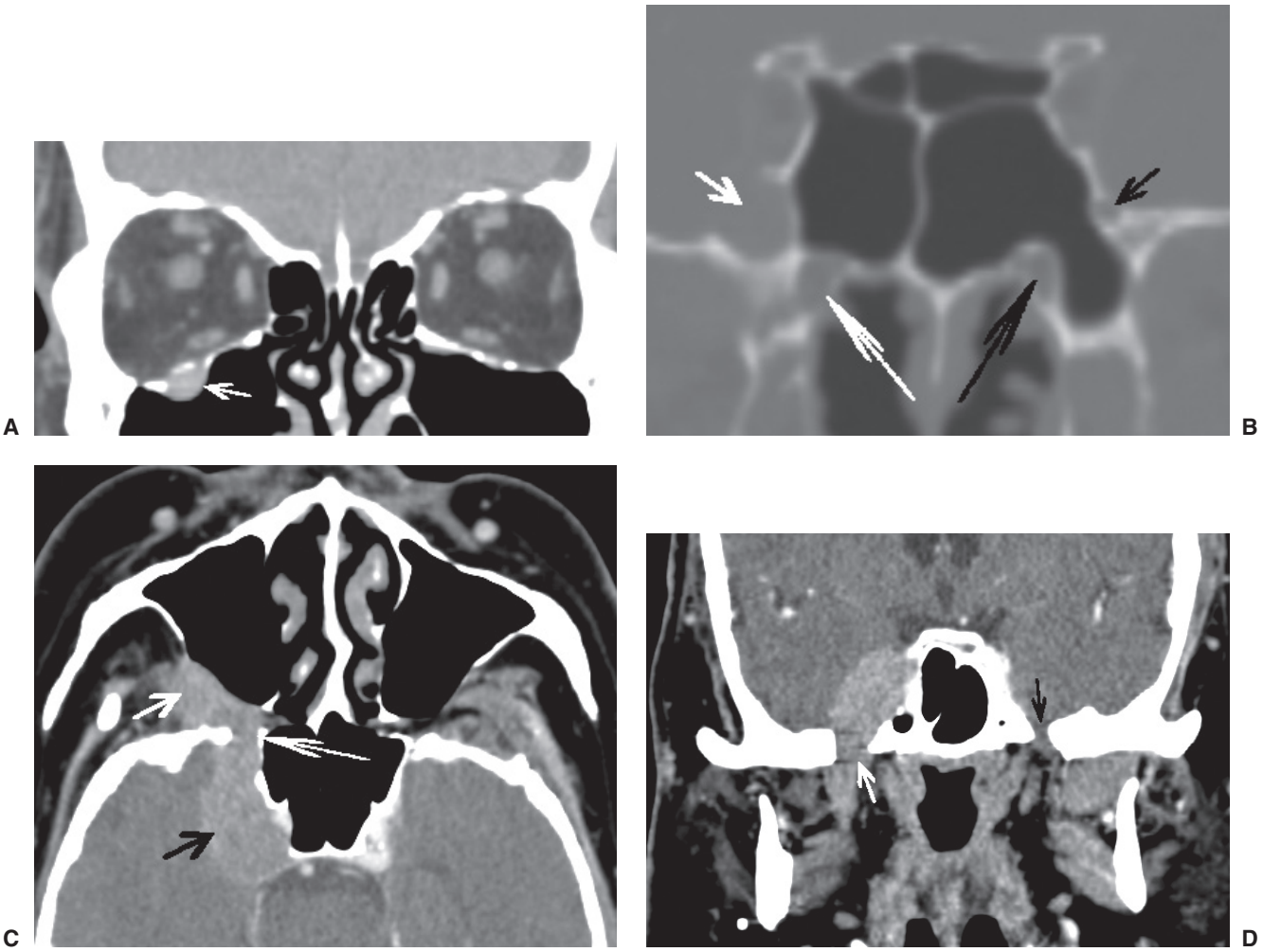



**FIGURE 24-12.** Perineural spread of melanoma in a single patient. **A:** Coronal postcontrast CT scan shows enlargement and enhancement of the infraorbital nerve from perineural spread of melanoma (*arrow*). **B:** Coronal CT scan with bone windows shows expansion of foramen rotundum on the right (*short white arrow*) as well as more subtle expansion and erosion of the vidian canal (*long white arrow*) secondary to perineural spread of cancer. Compare the normal foramen rotundum (*short black arrow*) and vidian canal (*long black arrow*) on the left. **C:** Axial post-contrast CT scan shows perineural spread along V2 into the pterygopalatine fossa (*short white arrow*), through foramen rotundum (*long white arrow*) into Meckel's cave and the cavernous sinus (*black arrow*). **D:** Coronal reformatted postcontrast CT scan shows perineural spread along V3 through foramen ovale (*white arrow*). Compare the normal foramen ovale on the left side (*black arrow*).

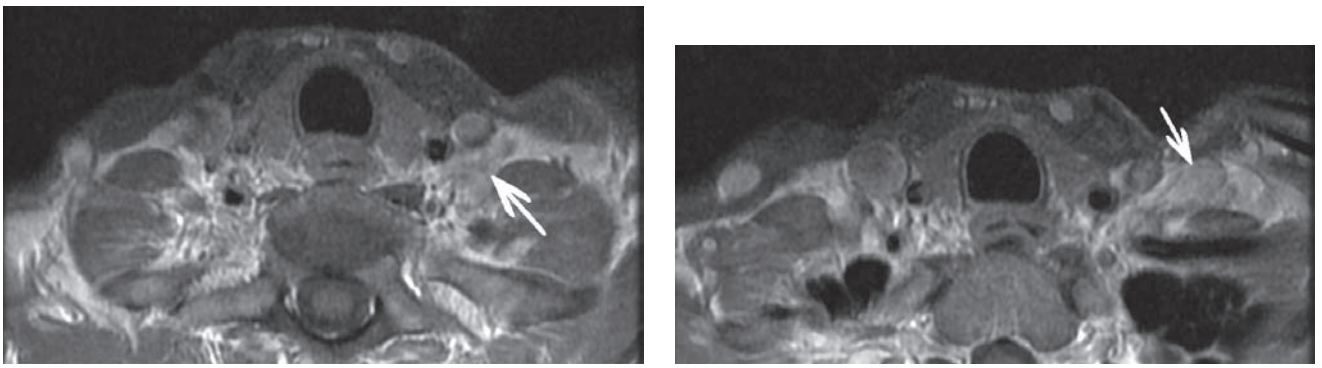


**FIGURE 24-13.** Axial contrast-enhanced T1-weighted MRI shows nodular enhancement along the brachial plexus (*arrows*).

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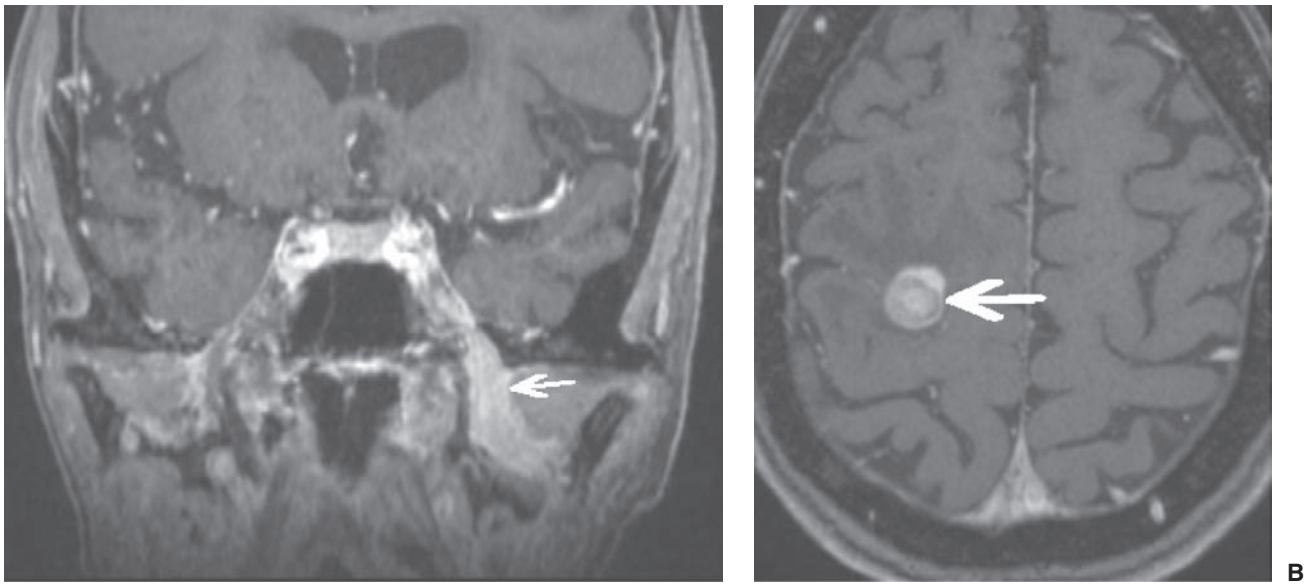


**FIGURE 24-14.** Perineural and hematogenous spread of melanoma. **A:** Coronal postcontrast T1-weighted MRI shows failure of treated melanoma along V3 (*arrow*). **B:** Also seen in the same patient on postcontrast T1-weighted MRI is a brain metastasis.

aerodigestive tract (see Fig. 24-8). Outcome remains poor, perhaps because of the dual lymphatic and hematogenous metastasis pattern, and the frequency of distant failure despite local/regional control.[7–9] Orbital melanoma is discussed separately in the chapter on cancer of the orbit.

Perineural spread of tumor is particularly common with desmoplastic melanoma,[10] and this finding should be anticipated and looked for on CT and MRI studies as this can affect the surgical extent of resection. Spread along the trigeminal nerve can be seen in facial melanomas (Fig. 24-12). A rare case of perineural spread along the brachial plexus is shown in Figure 24-13. Perineural spread of melanoma is often a site of failure in the head and neck following treatment (Fig. 24-14).

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# PART C:
# Radiation Therapy Technique

William M. Mendenhall

The technique employed depends on the site and extent of the melanoma. The most common indication for radiotherapy (RT) in head and neck melanoma is for postoperative RT after resection of a lesion associated with a positive regional lymph node(s).[1] A common site of lymph node metastasis is the parotid gland alone or combined with cervical lymph nodes. The parotid may be treated with an appositional electron field; the energy will depend on the depth-dose desired and is often 12-MeV electrons. If it is necessary to treat to 4 to 5 cm depth, higher-energy electrons may be "mixed" with 6 MV x-rays to reduce the skin dose. In this instance, the electron field is 1 cm larger than the x-ray field, except where it matches the low neck field, due to

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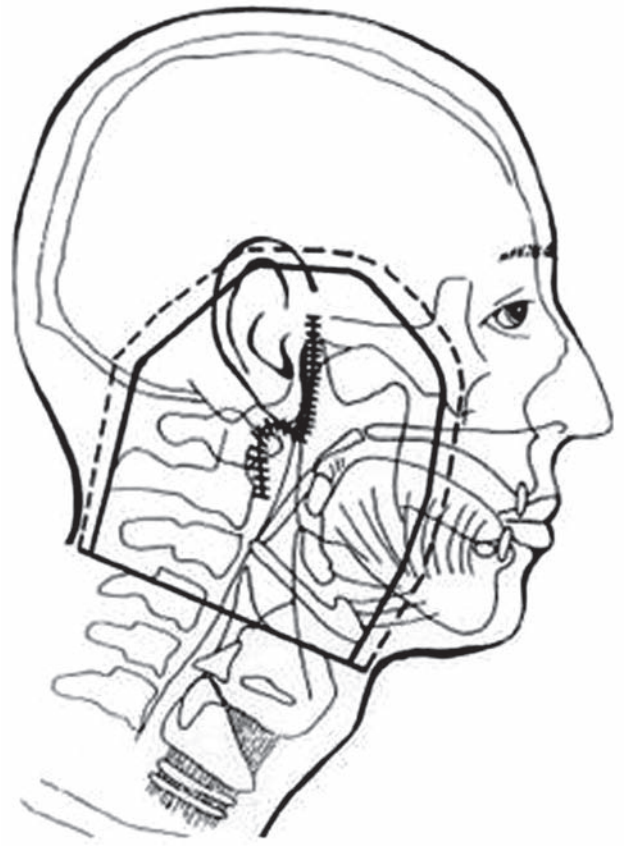


**FIGURE 24-15.** Appositional electron beam (*dashed line*) combined with 6-MV x-rays (*solid line*) to treat the parotid postoperatively.

beam constriction (Fig. 24-15). The anterior 6-MV x-ray field is matched with the parotid field(s) at the level of the thyroid notch. Alternatively, the parotid may be treated with intensity-modulated RT (IMRT).

Posterior cervical lymph nodes may be treated with opposed photon fields and reduced off the spinal cord once cord tolerance has been reached and the anterior aspect of the neck over the spine treated with 10-MeV electrons to the desired dose.

The primary site may be treated with orthovoltage RT or electron beam. The former is preferred (if available), unless the lesion is located in the scalp. Orthovoltage RT has several advantages compared with electrons: (a) there is less beam constriction; (b) it is easier to shield the eye; (c) the maximum dose is at the surface and bolus is not required; and (d) the dose distribution is not impacted as much by an irregular contour.[2] The orthovoltage beam energy is usually 250 Kvp. The field should be collimated on the skin surface with a customized lead mask for both orthovoltage RT and electrons.[2]

Lesions of the scalp associated with intransit metastases may require total scalp RT using a mixed pair of opposed 6-MV photon fields to treat the "rind" matched with lateral 6-MeV electron fields, a technique described to irradiate cutaneous angiosarcomas of the scalp.[3,4]

The dose-fractionation schedule is 30 Gy/5 fractions over 2.5 weeks with a reduction off the spinal cord and/or brain at 24 Gy.[1] Depending on the site treated, conventional fractionation may be employed if it is thought that a suboptimal cosmetic and/or functional outcome might be obtained with hypofractionation.[5]

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CHAPTER 25

# Management of Salivary Gland Tumors

## PART A:
## General Principles and Management

Daniel G. Deschler, Kevin S. Emerick, Lori J. Wirth, and Paul M. Busse

## ANATOMY

### Parotid

The exocrine salivary gland system of the upper aerodigestive tract is composed of two distinct classes of salivary glands. The major salivary glands consist of paired structures in the head and neck region with consistent anatomic drainage patterns within the oral cavity. The largest of these is the parotid gland followed by the submandibular gland and finally the sublingual glands. The minor salivary gland system consists of between 500 to 1,000 small glands located throughout the upper aerodigestive tract. Great density is noted in the region of the lips and the anterior oral cavity but extension of these glands into the oropharynx, tongue, larynx, sinonasal passages as well as the trachea is also demonstrated.

The primary function of the salivary gland system is the production of saliva which is a complex fluid composed of electrolytes, mucopolysaccharides, mucoproteins, immunoglobulins, and lysozymes. The primary digestive enzymes of the salivary gland system are amylase and lipase. The quality of saliva produced by specific glands can be quite variable from the relatively serous saliva produced by the parotid glands to the thicker more mucoid secretion of the minor salivary glands. Saliva plays numerous critical functions within the oral cavity with primary focus on those affecting digestion. Saliva is critical for bolus formation and subsequent lubrication of the bolus to allow the various critically timed stages of deglutition. Enzymatic digestion of food begins with the interaction of the digestive enzymes contained within saliva. Adequate hydration from saliva allows successful speech and articulation. Similarly, saliva plays critical roles in the immune system as well as in the maintenance of dental hygiene. Treatment modalities, whether they be surgical, radiation therapy based, or chemotherapeutic, can have significant impact on salivary production and saliva quality and therefore significantly and negatively impact these critical functions.

The parotid glands are the largest of the major salivary glands weighing between 15 to 30 g each. The parotid gland is a lobulated gland that has its location based in the lateral aspect of the face, anterior and inferior to the auricle. The lateral aspect of the gland is covered by the facial skin. The posterior aspect of the gland rests against the ramus of the mandible. The superior extent of the gland is the zygomatic arch as it continues inferiorly to overlie the posterior belly of the digastric muscle. Laterally, a dense fascia will cover the parotid gland and this fascia will extend all the way from the zygomatic arch inferiorly toward the sternocleidomastoid muscle. Anteriorly, this fascia is contiguous with the fascia overlying the masseter muscle and is referred to as the parotidomasseteric fascia. At the superior and posterior aspect of the gland are several fascial attachments which are critical in the subsequent surgical intervention in and around the gland.[1] Superiorly, thick fibrous attachments connect the gland to the zygoma. The fascia becomes thinner as the gland extends inferiorly in the pretragal region but then becomes quite dense again in the region of the tympanic bone and mastoid. This layer must meticulously be divided to allow access to the stylomastoid foramen and the identification of main trunk of the facial nerve. The most inferior aspect of the parotid gland is referred to as the tail of the parotid and overlies the angle of the ramus, extending down to the sternocleidomastoid muscle. This is the region in which the majority of benign tumors of the parotid gland are located. Final component of the parotid gland extends deeply behind the ramus of the mandible through the stylomandibular tunnel to enter the prestyloid component of the parapharyngeal space.

The primary arterial blood supply of the parotid gland is provided through branches of the extension of the external carotid artery as it continues under the digastric and stylohyoid muscles after giving off the facial artery branch which will course through the submandibular gland. The external carotid artery will then course through the deep parotid tissue to give off the superficial temporal artery. Further continuation of this vessel will give off the internal maxillary artery as it exits the gland. Of note is a



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consistent arterial branch, the posterior auricular artery, which will be located approximately 2 mm lateral to the main trunk of the facial nerve and can be a useful landmark during facial nerve identification and subsequent dissection.

The venous system for the gland begins with the superficial temporal and the deep maxillary veins which combine within the gland to form the retromandibular vein. The retromandibular vein will exit the inferior-posterior aspect of the gland and usually be contiguous with the external jugular vein as it drains into the lower neck. If there is no external jugular vein of significance, the retromandibular vein will usually drain into a deep facial vein at the lower aspect of the gland and continue into the internal jugular vein. A critical anatomic relationship provided by the venous anatomy of the gland is that the facial nerve branches will standardly run in a plane just superficial to the retromandibular vein. Therefore, with axial imaging assessment of masses of the parotid gland, the orientation and displacement of the retromandibular vein can give useful information in potential facial nerve branch location.

The primary drainage pathway for the parotid gland is via the parotid duct. This structure is approximately 4 to 7 cm long and exits from the anterior aspect of the gland in the plane along the line from the oral commissure to the lobule of the ear. Upon leaving the gland, the parotid duct will course over the masseter muscle and then make a sharp turn medially as it pierces the buccinator muscle to exit in the oral cavity as the Stensen duct. The Stensen duct is visible as a small papule located in the buccal mucosa opposite the upper second molar. Accessory parotid glands are noted in between 21% and 56% of patients and will be situated anterior to the gland along the course of the Stensen duct. In most cases, the accessory gland will have ancillary drainage into the parotid duct, but may also have independent drainage.

Critical to the management of any lesion within the parotid gland is a clear understanding of the motor neural supply to the face which is intimately related to the anatomy of the gland. The facial nerve (cranial nerve VII) provides the primary motor neural function to the muscles of facial expression. A thorough understanding of its anatomic course is critical to any surgical management of parotid gland lesions. Originating from the brain stem, the facial nerve has five distinct segments prior to exiting the temporal bone. These include the intracranial pontine segment, the meatal segment through the internal auditory canal, the labyrinthine segment, the tympanic segment, and finally the mastoid segment. The extratemporal component of the facial nerve begins upon its exit from the mastoid bone at the stylomastoid foramen. Familiarity with the intratemporal components of the facial nerve is critical as perineural involvement by tumor may extend proximally requiring resection of a nerve within these regions as well as grafting from the intratemporal nerve to its muscular branches.

The extratemporal facial nerve is directly addressed in most surgeries of the parotid gland, and a clear understanding of its anatomy is critical to successful treatment in this delicate anatomic region. The main trunk of the facial nerve will exit via the stylomastoid foramen which is located laterally and inferiorly to the styloid process at the intersection of the mastoid and the tympanic bones. The nerve will usually give off small branches just upon exiting the stylomastoid foramen to the stylohyoid muscle and the posterior belly of the digastric. At this point, the nerve will then enter the parotid gland and extend for a short course before beginning its branching pattern. The nerve is standardly identified in this region at the main trunk and then dissected in an antegrade fashion to expose its orientation to masses within the gland.

There are numerous critical landmarks which facilitate the location of the main trunk of the facial nerve as it exits the temporal bone (Table 25.1). The most consistent anatomic landmark is the tympanomastoid suture line. The main trunk of the facial nerve will standardly rest between 2 and 4 mm deep to this.[2,3] The tragal pointer, the apex of the triangle forming the deepest part of the tragal cartilage, is another useful landmark and is defined as the triangular component of the deepest aspect of the tragal cartilage. This will rest approximately 1 cm superior and superficial to the nerve but is a less consistent landmark than the bony landmark of the tympanomastoid suture line.

**TABLE 25.1 Anatomic Landmarks for Identification of the Facial Nerve during Parotid Surgery**

| | |
|---|---|
| Tragal pointer | Nerve ~1 cm medial and inferior to tip of pointer |
| Tympanomastoid suture line (TMS) | Nerve ~2–4 mm deep to TMS |
| Superior portion of posterior belly of digastric muscle (PBD) | Nerve 5–14 mm superior to PBD |
| Posterior auricular artery | Nerve 2–4 deep to this artery |
| Styloid process | Nerve will run superficial and inferior to the palpated styloid process |
| Mastoid bone | Nerve can be identified through otologic drill out |

In the dissection of the facial nerve, it is critical that a wide and broad exposure is achieved. This involves freeing the fascial attachments in the pretragal and pretympanic components of the gland as well as broad inferior dissection which allows mobilization of the gland off the digastric muscle. Dissection is then done superiorly toward the digastric ridge where the muscle will enter the mastoid bone, and this similarly gives a good indication of the level at which the facial nerve will rest. With this broad superior and inferior dissection, meticulous dissection can then be done in the region of the tympanomastoid suture line to expose the stylomastoid foramen and the main trunk of the facial nerve. Once in the gland, the main trunk of the facial nerve will demonstrate one of numerous variations in branching pattern to innervate the various muscles of facial expression. The first major split in the nerve is at the pes anserinus. Here the nerve will usually break into two major branches, an upper temporofacial branch and a lower cervicofacial branch. Through various branching patterns described in Figure 25-1, five major branches will be given off. These include the frontotemporal branch, the orbitozygomatic branch, the buccal branch, the marginal mandibular branch, and the cervical branch.

As noted, clear identification of the facial nerve and its branches is critical to the surgical management of parotid masses, both benign and malignant. If there is an inability to adequately identify the main trunk of the facial nerve and proceed with a standard antegrade dissection, then alternative approaches can be undertaken. A retrograde means of dissection identifies specific branches of the facial nerve distally, once they leave the parotid gland, and then proceeds with dissection in a retrograde fashion as these branches coalesce to form the main branches and the main trunk of the facial nerve. The marginal mandibular branch can be identified inferiorly along the superior and posterior aspect of the submandibular gland and its fascia. The buccal branch will have a consistent location in the midface

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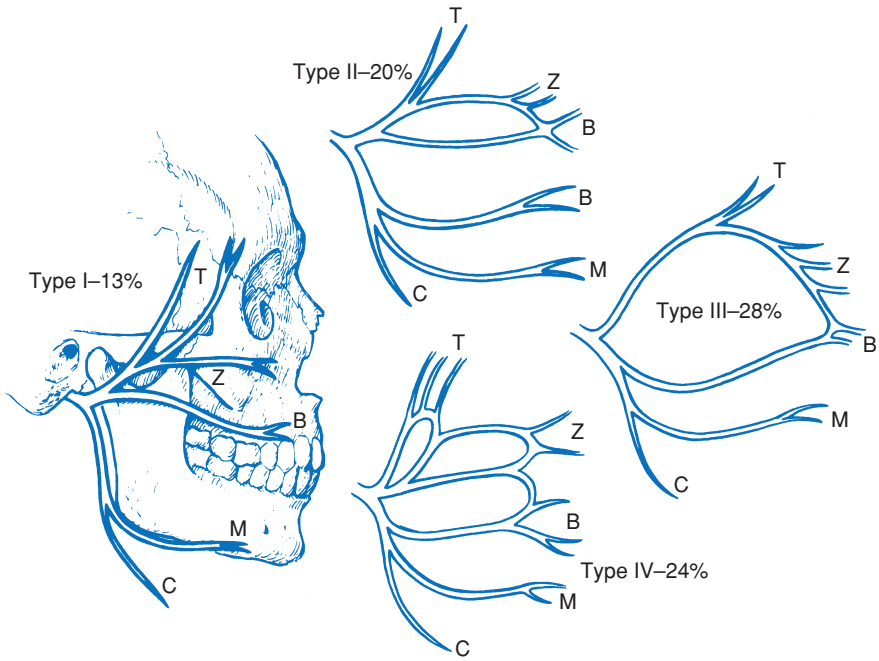



**FIGURE 25-1.** Anatomic variations of facial nerve branching. B, buccal; C, cervical; M, marginal mandibular; T, temporal; Z, zygomatic.

*Source:* From Johns ME, Kapan MJ. Malignant neoplasms. In: Cummings CW, Frederickson JM, Harker LA, et al., eds. *Otolaryngology—Head and Neck Surgery.* 2nd ed. St. Louis, MO: Mosby-Year Book; 1993:1048, with permission.

as it crosses the masseter in close relation to the parotid duct. Similarly, the orbitozygomatic branch is in a consistent position located on the line between the tragus and the lateral canthus of the orbit. Whichever means of dissection is utilized, be it antegrade or retrograde or some combination, clear identification of the nerve and its anatomy is critical to surgical success.

The sensory supply to the face and auricle surrounding the parotid gland is provided by the great auricular nerve which is formed from the cervical sensory plexus from rootlets C2 and C3. This nerve will course over the sternocleidomastoid muscle and then enter the parotid gland at a point that is usually 8 to 10 mm cephalad to the external jugular vein. The anterior branch of the great auricular nerve will course through the gland and supply the anterior facial skin whereas the posterior branch of the nerve will extend posterior to the lobule to innervate the ear. Preservation of the posterior branch of the great auricular nerve can be achieved with meticulous dissection of this branch through the posterolateral parotid parenchyma and maintenance of its course behind the lobule toward the ear, and studies have demonstrated potential benefit from the preservation of this nerve.

The secretomotor function of the parotid gland is controlled by the parasympathetic autoimmune system via the glossopharyngeal nerve (cranial nerve IX). Preganglionic parasympathetic fiber from the inferior salivary nucleus travel via cranial nerve IX through the jugular foramen where the tympanic branch will then turn back into the skull base via Jacobson nerve to enter the middle ear. These fibers will course along the roof of the middle ear becoming the lesser petrosal nerve which will then exit the skull base at the foramen ovale. The fibers then synapse at the otic ganglion located under the mandibular branch of cranial nerve V3. Postganglionic fibers exit the otic ganglion to join the auricular temporal branch of the trigeminal nerve in the inferotemporal fossa. These parasympathetic fibers supply the innervation for parotid salivary secretory function. Sympathetic innervation is modulated via the superior cervical ganglion sympathetic fibers, which travel along the external carotid system to innervate the gland.

The parotid gland is unique in its lymphatic anatomy. Through embryologic development, lymph nodes in the region of the parotid gland are incorporated into the gland itself and contained within the fascial borders. This is in distinction to the submandibular gland which contains no intraparenchymal lymph nodes. Ninety percent of the lymph nodes within the parotid gland will be located in the superficial lobe. The lymph nodes within the gland provide drainage from the scalp, face, ear, and orbit and primary tumors within these regions can lead to metastases within the parotid gland presenting as parotid masses. Similarly, lymphoma may occur within a lymph node in the parotid gland, presenting as a parotid mass.

## Parapharyngeal Space

The parapharyngeal space is the deep-neck compartment oriented as an inverted pyramid in the parasagittal plane bilaterally. The base of this pyramid is situated at the skull base abutting the petrosal bone. The apex of the pyramid is the hyoid bone. The lateral borders are formed by the medial pterygoid muscle and the ramus of the mandible, whereas the medial border is constituted by the lateral pharyngeal wall with its associated fascia and musculature. The anterior limit is the pterygomandibular raphe whereas the posterior limit is the spine.

The parapharyngeal space is divided into two distinct compartments by the styloid process and the stylomandibular fascia. The poststyloid compartment of the parapharyngeal space contains the neurovascular structures of the carotid sheath whereas the primary components of the prestyloid compartment are elements of the deep lobe of the parotid gland. Parotid masses may involve the parapharyngeal spaces in two distinct fashions. Tumors can arise within the deep lobe of the parotid gland and then extend into the parapharyngeal space through the stylomandibular tunnel. These masses will have a dumbbell shape constituted by a component within the deep lobe of the gland as well as in the parapharyngeal space. Alternatively, tumors may arise from salivary gland tissue distinctly within the parapharyngeal space and therefore present as an isolated mass within the prestyloid parapharyngeal space. Masses of the parapharyngeal space are often incidentally noted on imaging of the head and neck region obtained for other reasons. Similarly, they may be asymptomatic but physical exam of the oral cavity can demonstrate a distinct

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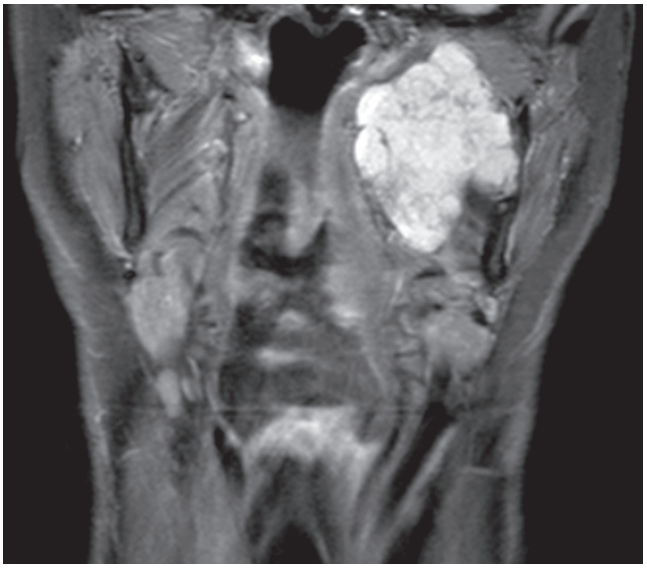


**FIGURE 25-2.** T2-weighted MRI demonstrated extension pleomorphic adenoma of the left parapharyngeal space.

fullness of the lateral pharyngeal region with displacement of the soft palate, tonsil, and lateral pharyngeal wall. Physical exam can also demonstrate a diffuse fullness in the region of the parotid gland secondary to the lateral displacement of the gland by the deeply situated mass (Fig. 25-2).

## Submandibular Gland

The second largest of the major salivary glands are the submandibular glands weighing 7 to 16 g each. These glands are located within the submandibular triangle that is bordered inferiorly by the anterior and posterior belly of the digastric muscle and superiorly by the lower border of the mandible. The majority of the submandibular gland is located below and posterior to the mylohyoid muscle with a smaller component anteriorly and superiorly, which extends deep to the mylohyoid muscle to abut the sublingual glands. This gives the gland a distinct horseshoe shape as it rests within the submandibular triangle. The submandibular gland is surrounded by the middle layer of the deep cervical fascia. This has importance as the marginal mandibular branch of the facial nerve runs in the plane immediately superficial to this fascia along the lateral and superior aspect of the submandibular gland. This becomes an important landmark in submandibular gland surgery designed to preserve the function of the lower branches of the facial nerve. As previously noted, there are no lymph nodes within the gland itself.[4] The majority of lymph nodes associated with the submandibular gland rest superiorly along the facial vasculature as it exits the gland and crosses the mandible. These perifacial nodes deserve a distinct consideration in the setting of cutaneous malignancies as well as oral cavity cancers. Lymph nodes can also rest along the posterior component of the gland where it abuts level IIA.

The arterial supply to the submandibular gland is from the facial branch of the external carotid artery. The facial artery will branch from the ECA and course medially under the digastric and stylohyoid muscle to enter the posterior aspect of the gland. The facial artery will then give off two to four branches to supply the gland and then exit superiorly from the gland over the border of the mandible. Often a small notch can be palpable in the lower border of the mandible where this artery will cross.

The venous supply to the submandibular gland can be quite variable but primarily consist of the anterior facial vein, which travels over the mandible with the artery and then courses on the anterior surface of the gland lateral to its fascia. It then will join the common facial vein and empty into the internal jugular system. On rare occasions, the anterior facial vein may empty into a prominent anterior jugular vein or the external jugular system. The facial vein does have anatomic importance as the marginal mandibular branch of the facial nerve will run in the plane just superior to the nerve and therefore this relationship can be utilized in nerve-preserving maneuvers during submandibular gland surgery. If the vein is located in the lower to mid portion of the gland and then elevated superiorly, this will allow the nerve to be rotated superiorly and provide a protective effect. The posterior venous system of the submandibular gland drains via the posterior facial vein which can be quite prominent. Specific situations that lead to this increased size are if the posterior facial vein provides drainage of the retromandibular vein in the setting of an underdeveloped external jugular system.

The ductal drainage system of the submandibular gland coalesces to form the submandibular duct, which exits the gland and then travels deep to the lingual nerve and medial to the sublingual gland. The duct then enters the floor of the mouth as Wharton duct, which exits at either side of the lingual frenulum in the anterior floor of mouth. The submandibular gland maintains an intimate relationship with the lingual nerve because of its anatomic proximity as well as the attachment of the nerve to the gland via the submandibular ganglion. The lingual nerve enters the submandibular triangle from posteriorly and superiorly as an extension of the mandibular branch of cranial nerve V3. The lingual nerve will then give off a small branch to the mylohyoid muscle which is standardly sacrificed in the majority of submandibular gland surgeries. Parasympathetic secretory fibers from the facial nerve and chorda tympani travel along the lingual nerve to synapse in the submandibular ganglion. From here, the sensory fibers of the lingual nerve will continue anteriorly into the floor of mouth to supply the somatosensory and taste functions of the anterior two-thirds of the tongue. The lingual nerve and submandibular ganglion are readily exposed during surgical exploration with inferior retraction of the gland and superior retraction of the mylohyoid muscle. This allows the gland to be severed from the nerve while maintaining sensory function. This maneuver likewise allows assessment of potential direct neural involvement.

During the same maneuver, the hypoglossal nerve will be evident running in a separate plane deep into the gland. Surrounded by the venae comitantes, the nerve will continue anteromedially to supply motor function to the tongue. The hypoglossal nerve will originate from the skull base exiting at the hypoglossal canal and then travel medially to the internal jugular vein and superficially to the external carotid system as it turns medially to enter the submandibular triangle. The hypoglossal nerve will enter the submandibular triangle inferior and posterior to the junction of the anterior and posterior belly of the digastric muscle at the lesser cornu of the hyoid bone. The submandibular tumors do not routinely directly involve the 12th cranial nerve. Care must still be taken to avoid injury during gland resection with resultant hypoglossal paralysis.

## Sublingual and Minor Salivary Glands

The smallest of the major salivary glands are the sublingual glands weighing between 2 and 4 g. The sublingual glands rest in the anterior floor of mouth superior to the mylohyoid muscle. Resting just lateral to the lingual frenulum and covered loosely by the oral cavity mucosa, the sublingual glands have a unique draining system via many small ductules (Rivinus ducts) which exit directly into the floor of mouth. Drainage may also occur via

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connections to the submandibular ductal system. The sublingual glands are innervated by the parasympathetic fibers from the seventh cranial nerve.

The minor salivary gland system consists of between 500 and 1,000 variably sized small glands located throughout the upper digestive tract. Ranging in size from 1 to 5 mm, these glands are found throughout the lips, tongue, soft and hard palate, buccal mucosa, pharynx, larynx, upper trachea, nasopharynx, and paranasal sinuses. The majority of the minor salivary glands are concentrated in the region of the lips, tongue, soft and hard palate as well as the buccal mucosa. Postganglionic parasympathetic secretomotor innervation to the minor salivary glands depends on the anatomic region that primarily is via the lingual nerve and branches from the sphenopalatine ganglion.

## EPIDEMIOLOGY

Salivary gland malignancies are not common. Considering that head and neck malignancies comprise only 5% to 6% of malignancies in the United States, the proportion of salivary malignancies overall is very small. They account for only 1% to 6% of head and neck cancer and only 0.3% of all cancers. The relatively small number of patients with salivary gland malignancy has made it difficult to thoroughly describe the epidemiology and prevalence of these malignancies. Additionally, with >20 histologic subtypes, which have undergone an evolution of classifications and limited data on the etiology and risk factors for these tumors, accurately defining the true epidemiology of these tumors has been very difficult. Large population-based data from SEER provides some insight. An early study from SEER shows a mean incidence of 0.89 per 100,000 per year.[5] A more recent SEER study using updated WHO histology classification found the incident rate to be 1.2 per 100,000 per year.[6] Smaller series from institutional databases and national tumor registries in Europe have reported a similar incidence.[7–9] The incidence appears to be very stable when compared over the last few decades.

There is a question of possible male predominance. The SEER data show a male predominance, with as much as a 51% increase in incidence rate compared with females.[9] However, other series have shown a much smaller difference in incidence rate which are effectively equal. Interestingly the SEER data identified a significant difference in the distribution of tumor histologies between men and women. For example, there are twice as many males with salivary ductal carcinoma, but there is no difference for adenoid cystic carcinoma (ACC). Depending on the makeup of tumor histology within a database, this could influence reported differences between males and females. There also appears to be a higher incidence rate among females <50; however, there is a higher rate among males >50.

Salivary glands malignancies typically present in the sixth decade of life. However, this too is likely impacted by histological subtype. Acinic cell carcinoma (AC), for example, has a mean age at diagnosis of 51 years, whereas squamous cell carcinoma has a mean age of >72 years of age. Some data have also suggested that more aggressive tumors tend to present at an older age, usually in the seventh decade.[7] Describing differences in race among such a small population has been difficult. Early SEER data also found a 1.4 times greater incidence in white patients than in black patients.[7,10] More recent data suggest this also may be histology driven.[9] The incidence rates are equivalent among all races for the two most common histologies, mucoepidermoid and ACC. However, most other subtypes have a higher rate in white patients.

Another consideration is the distribution of malignant tumors among the different salivary glands. More than half occur in the parotid gland. Thirty percent arise in the submandibular gland and the remaining 10% to 15% arise in the sublingual and minor salivary glands. These overall numbers are important to consider when assessing a neoplasm in each of these different sites. However, the parotid gland is also the most common site for benign salivary gland tumors as well. Benign neoplasm predominates in the parotid gland with only 15% being malignant. On the other hand, 50% submandibular neoplasms are malignant and 70% to 80% of sublingual gland and minor salivary glands are malignant.[11]

There is limited knowledge available regarding the etiology of these tumors. There are data demonstrating variable expression and mutations related to epidermal growth factor receptor (EGFR), c-kit, Ki-67, MUC1, antiapoptotic proteins (BIM, BAX, Bcl 2), and her-2 to name a few, but these findings are far from universal. Viral etiologies including cytomegalo virus has recently been reported as a possible etiology.[12] Altered p27/skp-2 expression has been reported as a key factor in differentiation and aggressiveness.[13] However, it is unclear what induces these changes. The embryology and ultrastructure of the salivary gland can provide a framework for understanding how the different histologies of tumors develop (Fig. 25-3). Major salivary glands have

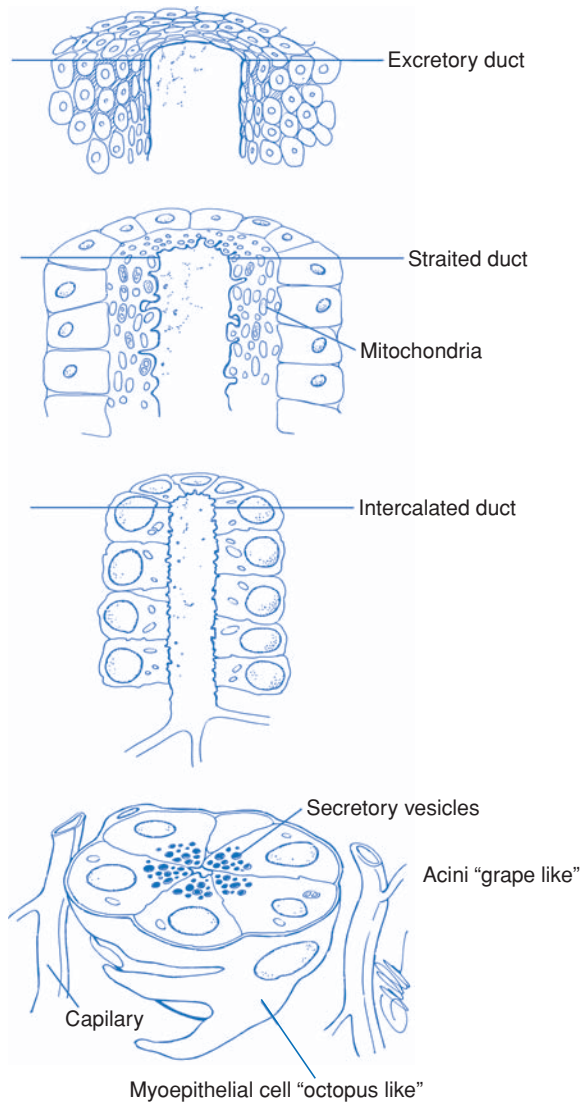



**FIGURE 25-3.** Histologic structure of salivary gland tissue.

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a ductal system through which both serous and mucinous cells drain. These are arranged into clusters called acini. The ducts are arranged in a series beginning with the acini, which drain into an intercalated duct which in turn drains into a striated duct and ultimately into the excretory duct.[14] These ducts are lined with an epithelium, and a layer of myoepithelial cells are present deep into the epithelium. From this histologic framework, there are two theories on how malignant neoplasm arise.[15] The multicellular theory suggests each type of neoplasm originates from a different cell type within the glandular unit, whereas the bi-cellular reserve cell theory suggests that all salivary neoplasm originate from either an excretory or intercalated duct cell which functions as a reserve cell with the ability to differentiate into different epithelial or epidermoid cells.

## PATHOLOGY

Although our understanding of histogenesis remains limited, there is a good descriptive knowledge of the different types of tumors classified as salivary gland malignancies. Additionally, this classification allows for tumors to be further subdivided into high grade and low grade (Table 25.2). The most common type overall is mucoepidermoid carcinoma (MEC) followed by adenoid cystic, acinic cell, adenocarcinoma, and carcinoma ex. However, the prevalence does vary based on age, gender, and anatomic location. The following is description of the key histologic subtypes.

### Mucoepidermoid Carcinoma

MEC is the most common salivary gland malignancy overall, yet only accounts for 15% of all salivary tumors. However, MEC alone accounts for nearly a third of parotid malignancies. Greater than 80% of MEC occur in the parotid gland, 10% in the submandibular gland, and <5% in minor salivary glands.[16] Palate is the most common minor salivary gland site for MEC, with rare occurrences on the retromolar trigone, floor of mouth, buccal mucosa, lip, and tongue. MEC is notably the most common malignant salivary gland tumor to arise in patients <20 years of age.

There is a variable composition of different cells in MEC: mucin-secreting, epidermoid, and intermediate. This variability has led to three distinct histological subtypes with different clinical courses.[17] The initial descriptions of these tumors came from Stewart et al. in 1945. Shortly thereafter, Foote and Frazell established a two-tier grading system, one grade thought to be benign and the other malignant.[16] However, it became clear to the authors that in fact all of these tumors were malignant, but in varying degrees of low, intermediate, and high grades. However, there has been a debate of the best way to consistently grade these tumors.

The two main grading systems were developed by Healey and modified by Batsakis[17] and the system developed by Goode et al. at the AFIP.[16] Each system grades tumors based on tumor architecture, pattern of invasion, cell type composition, histocytologic pleomorphism, and frequency of mitotic figures. Based on several studies using these grading systems, it has become clear there is a significant difference in the clinical behavior of these tumors depending on their grade. In addition to this focus on grade, there is also evidence for improved 5-year survival in stage I/II patients, 90%, compared with stage III/IV patients.[18] Ultimately, specific genetic changes may be identified that better define these and help predict clinical outcome and guide treatment.[14]

Low-grade MEC (Fig. 25-4) has an excellent prognosis ranging from a reported 92% to 100% 5-year survival. Batsakis reported these tumors are found in a young population with a strong female predominance and present at an early stage.[18,19] Surgical excision with negative margins yields an excellent local control rate, nearing 100%.[16,18,19] These tumors rarely metastasize to regional lymph nodes or to distant sites. A recent report showed that surgery even with positive or close margins had an excellent control rate when adjuvant radiation was given.[20]

High-grade MEC behave very differently than their low-grade counterparts.[21] Survival is very poor in this group, 22% to 43% 5-year survival. These tumors usually present in older patients, with a male predominance and present at stage III or IV[16–19,22] with up to 85% of these tumors having regional metastasis. Of patients with MEC who present or develop distant metastasis, they are nearly all high grade. Histologically, these tumors frequently have poorly differentiated epidermoid cells and rare mucin-positive cells. They can be confused with other high-grade carcinomas such as squamous cell carcinoma, salivary ductal carcinoma, adenocarcinoma, and malignant mixed tumors.

Intermediate-grade tumors have an intermediate clinical course, both in terms of presentation and outcome. Patients present with smaller tumors than high-grade MEC, but neck metastasis is relatively common, occurring in almost 20% of patients.[18]

**TABLE 25.2 Common Parotid Malignancies by Histologic Grade**

| Low Grade | High Grade |
|---|---|
| Low-grade mucoepidermoid carcinoma | High-grade mucoepidermoid carcinoma |
| Adenocarcinoma not otherwise specified (NOS), low grade | Adenocarcinoma NOS, high grade |
| Acinic cell carcinoma | Adenoid cystic carcinoma |
| Polymorphous low-grade adenocarcinoma | Salivary duct carcinoma |
| | Carcinoma ex-pleomorphic carcinoma |
| | Mixed malignant tumor |

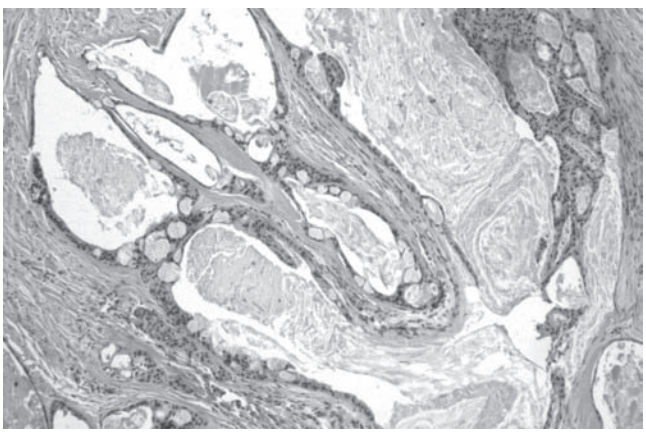


**FIGURE 25-4.** Classic low-grade mucoepidermoid carcinoma with predominantly cystic component. The cysts are line with both epidermoid cells and mucinous cells.

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The local and regional/distant recurrence rates are 22% to 30% and 39%, respectively, which fall in between the incidence reported for high-grade and low-grade tumors. Five-year survival is approximately, 70% for the group as a whole.[18,19] There appears to be a population of intermediate-grade MEC which does well, much like low-grade MEC, and a population which does quite poorly, behaving more like a high-grade MEC. Further studies into biochemical markers may help distinguish these tumors in the future. Not surprisingly, the variable clinical course has led to variable treatment among institutions. However, many favor an approach based on stage. Small, localized tumors with a benign clinical picture can be treated with wide local excision. However, large size, regional spread, and aggressive pathologic features should direct a more aggressive treatment course similar to a high-grade tumor.

## Adenoid Cystic Carcinoma

ACC is the second most common salivary gland malignancy. It was first recognized in 1854, but the term ACC was not used until 1953 by Foote and Frazell.[23] They tend to present in the fifth and sixth decades of life without a clear sex predilection. It occurs most commonly in the minor salivary glands, with a predilection for the oral cavity and hard palate in particular. However, it is well known to occur in any salivary gland as well as other unexpected sites such as the lacrimal gland, esophagus, and tracheobronchial tree. Overall, these tumors are characterized by slow local growth with rare spread to regional lymphatics. However, they are well known for their propensity for perineural invasion (PNI) and distant metastasis.[24–26] These tumors are also unique in that distant metastasis can also present in a very delayed fashion, years or decades later; therefore, long-term follow-up is important.[27]

The grading of ACC is much less controversial than other salivary gland malignancies. It is characterized by three histological subtypes: solid, tubular, and cribriform (Fig. 25-5). Most tumors possess components of two or three subtypes. The solid type demonstrates solid sheets and nests of atypical basaloid cells with an undifferentiated appearance and many mitoses.[28] Several large series have demonstrated that the solid type histology imparts a worse prognosis with 5-year survival as low as 17% in some studies.[24–26] Tubular histology has the best survival. The cribriform pattern is considered the classic ACC with a "Swiss-cheese" appearance and accounts for up to 64% of reported cases of ACC. It is considered an intermediate grade when comparing survival among all three of these subtypes.

Overall survival (OS) varies widely from different series and subsite. ACC is notable for its atypical survival curve. Unlike most head and neck malignancies, the survival for ACC does not plateau at 5 years. This is attributable to late local recurrences, late development of distant metastasis, and the slow growth of distant metastasis when they do occur. Clinical stage, solid histological subtype, and increased *p53* expression are independent significant prognostic factors for poor survival.[24] Age >45, paresthesias, pain, PNI and margin status also correlate with survival.[25]

ACC is usually treated with surgical resection followed by radiation therapy. Negative margins along nerves are a challenge to obtain because of extensive perineural spread and the presence of skip lesions along nerves. Despite the overall high-grade nature of this tumor, there is a low incidence of regional spread and elective neck dissection is not mandatory for the N0 patient. However, more recent data have reported rates as high as 23% for occult regional metastasis including a 17% rate for early-stage tumors.[29] Therefore, dissecting the first echelon of at-risk nodes may be considered. Given the margin issue discussed above, postoperative radiation is important for improving both local control and OS.[24] Because of the slow-growing nature of this tumor, neutron beam therapy has been investigated.[30] However, its overall benefit has yet to be determined in the postoperative setting and it is only available in a few sites worldwide.

## Adenocarcinoma

Adenocarcinoma previously referred to a very heterogeneous group of tumors. However, today there are several well-described classifications of adenocarcinomas. These include tumors such as salivary duct carcinoma, polymorphous low-grade adenocarcinoma, and epithelial-myoepithelial carcinoma. These tumors are classified based on the different salivary subglandular units such as the different cells within the acini or different salivary ducts cells from which they arise. Those tumors that do not fall into recently described classifications are still collectively referred to as *adenocarcinoma, not otherwise specified*.

As more tumors are classified, the number of adenocarcinomas becomes much fewer, such that adenocarcinoma, not otherwise specified now represents the least common salivary gland tumor. This remaining group is still heterogenous with variable cytoarchitecture ranging from low grade to high grade in differentiation, solid or cystic, and papillary and nonpapillary features. They occur in older patients in their seventh decade of

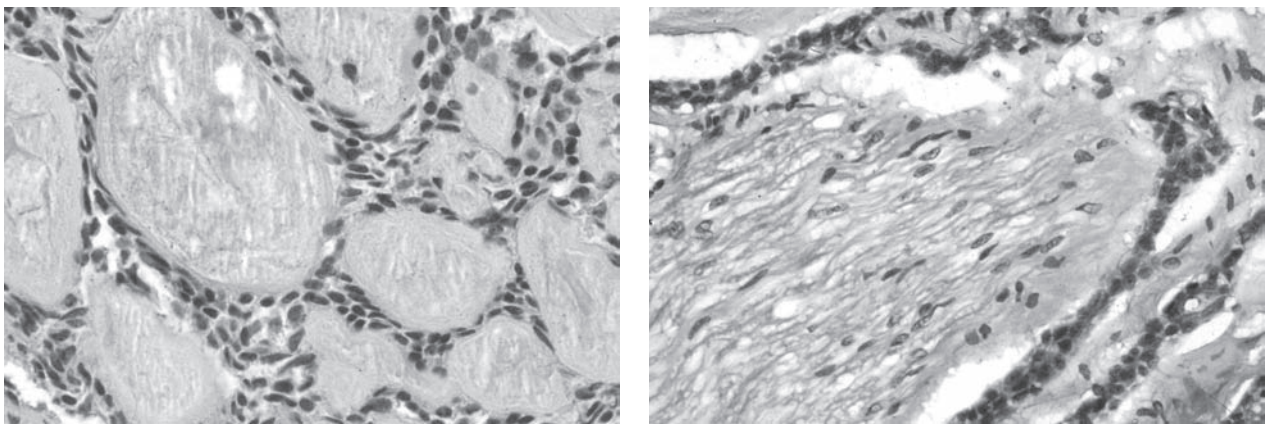



**FIGURE 25-5.** **A:** Cribriform type of adenoid cystic carcinoma with basaloid cells surrounding a myxoid matrix. **B:** Adenoid cystic carcinoma with extensive perineural spread. (See color insert.)

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life, with a 4:1 male predominance, and predominantly in major salivary glands.[31] Poor prognostic features have previously been described and include advanced stage, high histological grade, infiltrative growth factor, and tumor DNA content.[32]

Unfortunately, most of these tumors are high grade with a propensity for regional 23%, distant metastasis, 37%, and OS 10% to 60%.[31,33] Treatment is correspondingly aggressive with wide local excision, elective neck dissection, and postoperative radiation therapy.

## Acinic Cell Carcinoma

ACs account for up 17% of all salivary malignancies. However, it appears to have a higher incidence among children, where it is second only to MEC in incidence. These tumors are thought to arise from progenitor reserve cells of the terminal tubules and intercalated ducts of salivary tissue.[34] These tumors generally take the clinical course of a low-grade tumor. Batsakis did describe low- and high-grade histologic variants, with >90% of tumors considered histologically low grade.[34]

A recent National Cancer Data Base review of 1,353 cases has helped characterized this tumor.[35] It arises at a younger age than other salivary gland malignancies based on a median age of 52. This study also found a female predilection. It has been reported to occur in all salivary glands but is predominantly a tumor of the parotid gland, 86% of cases. This is likely attributable to the predominance of serous-type acini in the parotid compared with other salivary glands. It is notable for an incidence of bilateral tumors in up to 3% of cases, making it the second most common salivary neoplasm to occur bilaterally. Regional metastasis is not common. Studies report varying incidence from 0% to 17%, with most series reporting <10% and the National Cancer Data Base review identifying a 9.9% incidence.[35–37]

AC has an excellent 5-year disease-specific survival of >90%.[35] Clinicopathologic factors that predict a poorer outcome include high-grade histology, regional or distant metastasis at presentation, primary tumor in the submandibular gland, and age >30 years.[35] These patients likely have a 5-year survival around 30% to 40%. Interestingly, the overall recurrence rate from the Armed Forces Institute of Pathology series was 35%, yet within this group of recurrent disease only 16% died of this disease.[38] Other reports have also highlighted that prolonged survival is possible despite persistent disease. This has led many surgeons to consider palliative surgery for patients with incurable disease.

First-line treatment is surgical excision. Because the incidence of regional metastasis is <10%, routine elective neck dissection is not recommended. Adjunctive radiation therapy is reserved for high-grade tumors, recurrent tumors, positive margins, and stage III or IV tumors.[35–37]

## Salivary Duct Carcinoma

Salivary duct carcinoma is best known histologically for its resemblance to ductal carcinoma of the breast, from which it is indistinct.[39] Histologically, there are varying forms of cribriform, papillary, and solid growth patterns embedded in a sclerotic stroma. Comedonecrosis, PNI, and periglandular infiltration are common.

The clinical presentation is typical of a high-grade malignant tumor. It occurs most commonly in the parotid and is characterized by rapid onset, rapid progression, pain, and cranial nerve involvement. Advanced T and N stage are common as approximately half of patients present with stage IV disease, including up to 60% with regional metastasis.[39,40] Regional metastasis is common even in small T1 tumors. The presence of regional metastasis is a particularly poor prognostic indicator as up to 50% of patients with neck disease also had distant disease. Current treatment strategies provide good local regional control, unfortunately distant metastasis are not uncommon and make OS poor for these patients, 40% by 2 years and 20% by 5 years.[39,40]

All salivary duct tumors are treated as aggressive high-grade tumors. Aggressive surgical excision with facial nerve sacrifice, if clinically involved, and routine neck dissection are the standard first modality of treatment even for early T-stage tumors. Radiation to the primary and ipsilateral neck is also considered standard. Because of the poor survival and high incidence of distant metastasis, chemotherapy should also be considered. However, there is limited data on its efficacy, but a trial using cisplatin and 5-fluorouracil (5FU) is underway to investigate its use.[40]

## Mixed Malignant Tumor and Carcinoma Ex-pleomorphic Adenoma

There is a pathological distinction between these two tumors. The first is a true mixed malignant carcinoma arising *de novo* and consists of a malignant epithelial component and a malignant mesenchymal component. The second is an epithelial malignancy which arises from a benign pleomorphic adenoma. True mixed malignant tumors are very rare and are therefore difficult to characterize clinically.

Carcinoma ex-pleomorphic adenoma is an aggressive tumor with variable histology. Typically, pleomorphic adenoma can still be identified within the mass, but >50% of the mass shows malignant cells. This malignant component is most commonly adenocarcinoma (40%–44%), salivary duct carcinoma (25%–33%), adenoid cystic (14%), or adenosquamous cell carcinoma (7%).[41,42] Unfortunately, the exact pathogenesis of these tumors remains unknown, but there are DNA studies which show increasing anaploidy over time, which indicates the potential for malignant transformation.[43]

These tumors usually arise in a long-standing mass. When a change in the long-standing mass occurs, patients usually present with rapid growth, pain, skin changes, and cranial nerve involvement. However, an asymptomatic neck mass is also a common presentation. Neck metastasis occurs in 20% to 30% of patients and distant spread eventually occurring in more than 40% of patients.[40,41] As a group, survival is poor with 39% alive at 3 years and 30% at 5 years. There appears to be a subset which is particularly aggressive and progresses rapidly in the first year. These patients have approximately a 25% survival at 1 year.[41] This group has a high T stage and N stage, >50% of the mass is carcinoma, and invasion into surrounding structures.[41] Metastasis alone is a very poor prognostic factor. Spiro et al. reported only 1 of 31 patients with neck metastasis were alive at 10 years.[44]

## Polymorphous Low-grade Adenocarcinoma

Polymorphous low-grade adenocarcinoma is an appropriate name as it has a very low-grade clinical course and is an accurate histologic description. Grossly, they are well circumscribed but not encapsulated. Microscopically, a mixture of growth patterns can be seen: solid islands, glandular profiles, tubules, trabeculae, cribriform nests, and single file lines of infiltration. They have a characteristic perineural targetoid pattern of growth. When the diagnosis is not clear, immunohistochemistry (IHC) can be helpful. Glial fibrillary acidic protein, S100, and SMA are nonspecific but can assist in the diagnosis.[45]

This subtype is notable for its propensity to arise in minor salivary glands, specifically those in the oral cavity.[45] Within the oral cavity, the palate is the most common site, followed by the lip and the buccal mucosa. These tumors have a slow growth and

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indolent biology, such that the typical presentation is that of an asymptomatic mass in the oral cavity, which has often been present for years. Metastasis is uncommon. In a series of 164 patients from the AFIP, there was no cervical or distant metastasis.[45] Other series have reported up to a 12% neck metastasis incidence and 6% distant metastasis. The presence of a papillary component in these tumors may also be important. Some studies have shown a correlation with increased neck incidence of cervical metastasis when there is a prominent papillary component.[46] This all leads to an excellent prognosis with a >90% survival.

### Primary Lymphoma

Primary lymphoma of the salivary glands is uncommon, comprising only 1.7% to 3.1% of salivary neoplasm and only 10% of head and neck lymphomas.[47] Nearly all of them occur in the parotid gland. Greater than 85% are non-Hodgkin B-cell lymphomas, either nodular or diffuse. The remainder is nearly all Hodgkin disease. Parotid lymphomas can arise from intraglandular lymph nodes or can arise from the parenchyma itself. The latter is referred to as mucosa-associated lymphoid tissue and makes up the majority of cases. A previous history of underlying coexistent autoimmune disorder such as Sjogren syndrome or rheumatoid arthritis has been reported in up to 44% of patients. Approximately 5% of all Sjogrens patients will develop lymphoma. A mass occurring in a patient with a previous diagnosis of benign lymphoepithelial lesion, multiple masses in a unilateral parotid gland or bilateral parotid masses, or a mass associated with multiple, enlarged unilateral or bilateral cervical lymph nodes should all raise the suspicion of lymphoma.[48] The surgeon's role in this disease is to assist with diagnosis by providing adequate tissue in a safe manner. This can be accomplished with incisional or excisional biopsy, including parotidectomy, depending on the location and size.

## NATURAL HISTORY

Because of the varied locations for salivary glands, the presentation and natural history of salivary gland malignancies can vary. However, size, pain, nerve symptoms, symptoms related to invasion of nearby structures and evidence of metastasis are the common points of the natural history regardless of location.

The major salivary glands are relatively superficial in their location and therefore masses are often recognized on self-palpation by the patient and this is the most common initial presentation. These tumors will enlarge; however, the rate at which they grow is extremely variable based on histological subtype. Low-grade tumors as well as ACC tend to grow very slowly, similar to that observed for a benign pleomorphic adenoma. Patients may be aware of the mass for years before they seek medical attention because of this slow growth. However, high-grade tumors tend to rapidly grow. In the case of a carcinoma ex-pleomorphic, there may a long-standing slow-growing tumor that begins to rapidly change. However, a high-grade mucoepidermoid tumor may present initially with rapid growth.

Pain is an important component of the natural history. Up to a third of patients have pain on presentation. As the tumor grows into adjacent structures, other symptoms will develop such as trismus, fixation of mass, and overlying skin changes. Since all of the major salivary glands are adjacent to cranial nerves, tumors over time will ultimately involve these nerves either by direct invasion or perineural spread. In the parotid, this involves the facial nerve predominantly. The sublingual and submandibular glands are most likely to impact on the lingual and hypoglossal nerves. Trigeminal nerve involvement can be seen with tumors in any of these locations.

**TABLE 25.3 Incidence of Cervical Lymph Node Metastasis by Histologic Tumor Type**

| Tumor Type | Reported Incidence of Lymph Node Metastasis |
|---|---|
| Low-grade mucoepidermoid carcinoma | <5% |
| Adenocarcinoma, NOS | 20%–25% |
| Acinic cell | 5%–10% |
| Polymorphous low-grade adenocarcinoma | 10%–15% |
| High-grade mucoepidermoid carcinoma | 50%–85% |
| Intermediate-grade mucoepidermoid carcinoma | 20% |
| Adenoid cystic carcinoma | 4%–23% |
| Salivary duct carcinoma | 60% |
| Carcinoma ex-pleomorphic adenoma | 30% |

The natural history of metastasis is also quite varied based on histology (Table 25.3). Low-grade malignancies have a low risk of regional lymph node metastasis or distant spread.[18] However, high-grade MEC, for example, has an 80% incidence of regional metastasis in some series.[22] ACC, which is considered a high-grade malignancy, does not follow this trend and actually has a very low risk of regional spread. However, it has a very high risk of distant metastasis and unresectable perineural spread along the trigeminal and facial nerves.[24,26] AC and intermediate-grade MEC have a variable rate of regional spread, 10% to 20%. This can make lymph node management more challenging. Other clinical features may predict a higher risk of metastasis such as size and invasion of surrounding structures.

OS for salivary gland malignancies vary. Survival ranges from nearly 100% for low-grade MEC to as poor as 25% 1-year survival for carcinoma ex-pleomorphic. Other clinicopathologic features are likely important in the natural history as well such as margin status at resection and extracapsular spread.[49]

## STAGING

Table 25.4 summarizes the American Joint Committee on Cancer 7th edition staging for salivary gland malignancies.[50] Although much of the literature and discussion about treatment and prognosis of salivary gland malignancies focuses on histological grading, TNM staging remains an important and useful tool. Table 25.5 provides a review of survival based purely on histologic substype and Figure 25-6 highlights the impact of stage on survival. There is a clear incremental decrease in survival for each stage, such that at 5 years observed survival is 70% for stage I compared with 30% survival for stage IV.[50] This further demonstrates that stage and histology are important predictors of survival.

In the most recent update to the AJCC staging, there were a few changes. The most notable change to the staging in 2010 was the addition of stages IVA, B, and C. T4a tumors are now classified as stage IVA, T4b and N3 tumors are stage IVB, and patients with distant metastasis are stage IVC (Table 25.6).

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**TABLE 25.4 American Joint Committee on Cancer (AJCC) TNM Staging System: Salivary Gland Staging**

| | |
|---|---|
| **Primary tumor (T)** | |
| T1 | Tumor 2 cm or less in greatest dimension, without extraparenchymal extension[a] |
| T2 | Tumor >2 cm but <4 cm in greatest dimension, without extraparenchymal extension[a] |
| T3 | Tumor >4 cm and/or extraparenchymal extension[a] |
| T4a | Moderately advanced (tumor invades skin, mandible, ear canal, and/or facial nerve) |
| T4b | Very advanced (tumor invades skull base and/or pterygoid plates and/or encases carotid artery) |
| **Regional lymph nodes (N)** | |
| N0 | No regional lymph node metastasis |
| N1 | Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension |
| N2a | Metastasis in a single ipsilateral lymph node, >3 cm but not >6 cm in greatest dimension |
| N2b | Metastasis in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension |
| N2c | Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension |
| N3 | Metastasis in a lymph node >6 cm in greatest dimension |
| **Distant metastasis (M)** | |
| Mx | Distant metastasis cannot be assessed |
| M0 | No distant metastasis |
| M1 | Distant metastasis |

[a] *Note:* Extraparenchymal extension is clinical or macroscopic evidence of invasion of soft tissues. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.

*Source:* From the American Joint Committee on Cancer (AJCC). *TNM Staging System for the Major Salivary Glands.* 7th ed. New York, NY: Springer; 2010, with permission.

**TABLE 25.5 Estimate of 5-year Survival Based on Histologic Subtype**

| Histology | 5-yr Survival |
|---|---|
| Polymorphous low-grade carcinoma | >90% |
| Low-grade mucoepidermoid carcinoma | 92%–100% |
| Acinic cell carcinoma | 85%–90% |
| Intermediate-grade mucoepidermoid carcinoma | 70%–95% |
| Adenoid cystic carcinoma | 80%–92% (60% at 10 yr, 40% at 20 yr) |
| Adenocarcinoma | 10%–60% |
| High-grade mucoepidermoid carcinoma | 22%–51% |
| Salivary duct carcinoma | 20% |
| Carcinoma ex-pleomorphic carcinoma | 30% |

# EVALUATION

There are three key elements in the evaluation of a suspected salivary gland malignancy. Each has an important role in diagnosing a malignancy and helping direct treatment. These elements are the history and physical, imaging, and biopsy.

## History and Physical

Because of the varied locations for salivary glands, the history and physical examination appropriate for each site can also be quite varied. The major salivary glands are relatively superficial in their location and therefore masses are often recognized on self-palpation by the patient. As with any neck mass, it is important to ascertain the key elements of the mass: size, nature of the progression, firmness, associated pain, overlying skin changes, and previous presence of masses. Because of the critical location of the cranial nerves with respect to the major salivary glands, it is important to ask about symptoms associated with the cranial nerves. Since minor salivary glands are distributed throughout the aerodigestive tract, these patients may have a completely different presentation. They are more likely to present with symptoms typical of classic squamous cell carcinoma of the head and neck such as throat discomfort, change in voice and speech, otalgia, and blood in the saliva. The history should also ascertain information about potential systemic manifestations such as unintentional weight loss, fatigue, pulmonary symptoms, bone pain, and focal neurological deficits.

The physical exam such as the history should characterize the mass based on location, size, mobility, and involvement of surrounding structures. Evaluation should assess for facial twitching or facial asymmetry, dysarthria, limited tongue mobility, dysphagia, facial dysesthesia or hypoesthesia, and changes in the sensation of the tongue and floor of mouth. Cranial nerves II through XII should be fully assessed on examination in all patients with a suspected salivary gland neoplasm.

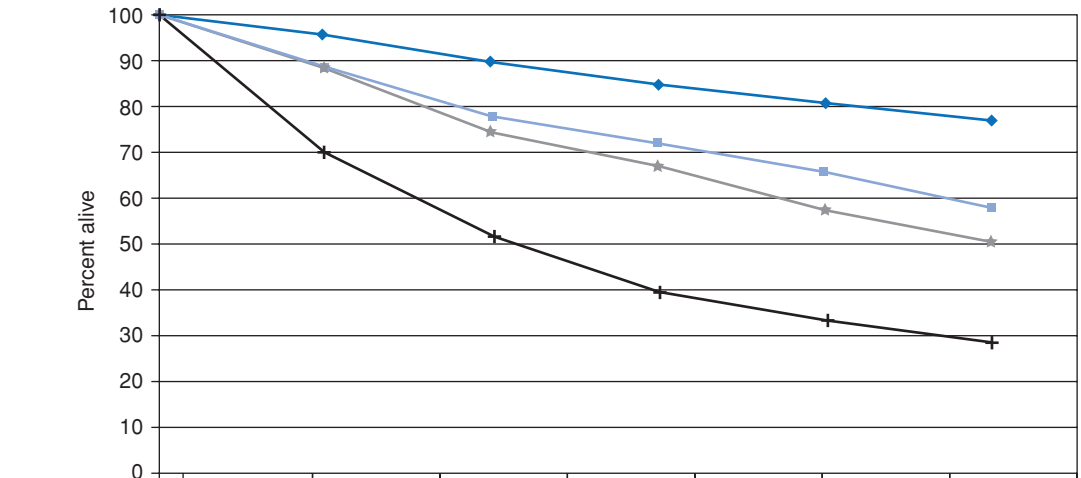
Although the most common presentation is an asymptomatic mass, other signs and symptoms will help alert the clinician of a possible malignancy. Up to one-third of malignancies have pain associated with the mass. Twenty percent have some cranial nerve symptoms and 10% have overlying skin involvement.[9]

## Imaging

Imaging studies are critical for evaluating and treatment planning for salivary gland malignancies in all sites. Computed tomography (CT) is most familiar to head and neck surgeons and is very useful for defining the presence of a mass as well as its relationship to boney structures such as the mandible and temporal bone. It is also an excellent modality for assessing lymph node statues. For minor salivary gland tumors or sublingual gland tumors, this remains an excellent first mode of imaging. However, in recent years MRI has become an important modality in salivary gland imaging.[51] Greater experience with MRI has helped define classic features of benign and malignant tumors, which makes this potentially a more specific test and sensitive imaging modality.

There are several important potentially diagnostic features on MR imaging that can be used in the preoperative assessment. Malignant lesions are hypointense on T2 imaging, which is helpful in distinguishing between benign tumors such as a pleomorphic adenoma. High-grade malignant tumors usually have an irregular border and can be seen infiltrating surrounding structures. Low-grade malignancies are usually well circumscribed but they are not encapsulated.[52,53] The hypointensity on T2 imaging and contrast enhancement should raise suspicion for

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| Observed survival | 1 | 2 | 3 | 4 | 5 | 95% CIs | Cases |
|---|---|---|---|---|---|---|---|
| 1 | 95.5 | 89.7 | 84.7 | 80.8 | 76.9 | 74.9–78.9 | 2,345 |
| 2 | 88.9 | 78.4 | 72.0 | 65.8 | 58.4 | 53.7–63.0 | 568 |
| 3 | 88.5 | 74.7 | 67.7 | 57.7 | 50.6 | 44.4–56.8 | 338 |
| 4 | 70.6 | 52.2 | 40.3 | 34.0 | 29.5 | 26.9–32.1 | 1,460 |

**FIGURE 25-6.** Observed survival by year based on stage.

a malignancy. Additional findings can be indicative of specific histological subtypes. Mucoepidermoid tumors may demonstrate a significant cystic component that has high intensity on both T1 and T2 imaging due to the mucin content.[53] Adenoid cystic tumors, which are predominantly solid type histology, have low signal intensity on T2 imaging whereas cribriform and tubular types have a higher intensity on T2 because of their lack of cellularity.[53] Primary salivary lymphoma can be distinguished when it arises in a periparotid lymph node. There is typically a distinct plane separating the mass from the gland. This is more difficult to assess when the node is intraparotid; however, it is usually low signal intensity on both T1 and T2 imaging with limited enhancement with contrast.[51,52]

In order to distinguish malignant from benign tumors, there are several characteristic features indicative of a likely benign lesion. Pleomorphic adenomas characteristically have a bright intensity on T2-weighted images with inhomogeneity and a well-defined capsule and margin. They also have a typical lobulated or bosselated contour, which occurs from the variable growth rate within the tumor. Vascular lesions such as hemangiopericytoma and hemangioma may also have this high signal intensity on T2. Benign cystic lesions generally have an enhancing peripheral rim with a smooth and well-defined border and may have intracystic fluid bright on T2.

Because of the importance of assessing perineural spread, a combination of MRI and CT may be helpful. MRI is considered more sensitive for this assessment, as the involved nerve may show a characteristic enhancement. However, CT may also be helpful by for detecting perineural spread by identifying a widened stylomastoid foramen, foramen ovale, or foramen rotundum. The assessment of fat in the foramina is also a key factor. Loss of this fat is very suspicious for nerve involvement. Lastly, one should assess the facial muscles and muscles of mastication. Loss of volume and asymmetry from one side to the other may be indicative of loss of neural input due to nerve involvement by tumor.

A last modality of consideration is PET/CT imaging. To date, there are limited data comparing its usefulness to MRI; however, there are several potential useful aspects. A primary benefit is the ability to detect distant metastasis. Salivary tumors appear to have a higher rate of nonlung distant metastasis such as bone and liver that could be missed with a standard chest CT assessment for distant metastasis. Similarly, PET may add information to CT imaging about more extensive local extension, which may show the tumor to be unresectable. However, there are limitations. PET/CT has been shown to be only 74% sensitivity, as there appears to be variability in PET avidity for different salivary gland tumors.[54] Additionally, its ability to accurately detect nerve involvement and the extent of involvement is unclear.

**TABLE 25.6 American Joint Committee on Cancer (AJCC) Staging for Salivary Gland Tumors by TNM Status**

| | N0 | N1 | N2 | N3 |
|---|---|---|---|---|
| T1 | Stage I | Stage III | Stage IVa | Stage IVb |
| T2 | Stage II | Stage III | Stage IVa | Stage IVb |
| T3 | Stage III | Stage III | Stage IVa | Stage IVb |
| T4a | Stage IVa | Stage IVa | Stage IVa | Stage IVb |
| T4b | Stage IVb | Stage IVa | Stage IVa | Stage IVb |

*Note:* Stage IVc is an T, any N and M1.

## Biopsy

Tissue acquisition is a key element of the evaluation. First, it is needed to confirm the diagnosis of malignancy. Second, it will help determine the histological subtype as this will likely impact on the management. Lesions suspicious for minor salivary gland tumors in the oral cavity, oropharynx, hypopharynx, or larynx can be biopsied in a traditional fashion in the office using injectable anesthetic and biopsy forceps or dermal punches, or in the operating room with direct laryngoscopy.

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Tumors in the submandibular and parotid regions are not quite as accessible. For these tumors, fine-needle aspiration (FNA) is the preferred method of biopsy. Several studies have now demonstrated FNA is a reliable technique achieving a diagnostic result in 88% to 98% of biopsies.[55–57] It has also been shown to be a safe and cost-effective diagnostic tool.

Additional work has shown these diagnostic specimens to have a consistent sensitivity, specificity, and accuracy. A summary of reported series shows a mean sensitivity of 81%, specificity of 95%, accuracy of 91%, and positive predictive value of 86%. For malignant tumors, specifically, there is a reported positive predictive value of 95%. Exact type-specific concordance with the histology was 81%. A last consideration involves lymphoma. FNA may provide this diagnosis or at least be suggestive of the diagnosis, which would likely change the management strategy.

There are a few additional considerations when evaluating the usefulness of FNA. Several studies show that the presence of a cytopathologist can decrease the number of nondiagnostic specimens, by providing immediate feedback while the patient is still present. There are a few diagnostic pitfalls that clinicians should be aware of with respect to FNA. Cystic lesions appear to be more difficult to accurately assess. AC and MEC in particular may have a cystic component which may appear benign on FNA. An ACC can be mistaken for pleomorphic adenoma because of their common basaloid appearance. Similarly, a lymphoma may be interpreted on FNA as a Warthin tumor due to the lymphoid component of these tumors.[58]

There are reported complications with FNA, which include hemorrhage, facial nerve injury, cellulitis, and parotitis, but all are considered rare.[59] When an experienced cytopathologist is available, FNA should be included in the evaluation. Accurate results from FNA of parotid tumors can allow for appropriate preoperative preparation, such as other services including reconstructive or otologic surgery, and operative intervention. This could range from a limited biopsy in the setting of a lymphoma to limited parotidectomy in the setting of a low-grade malignancy to potential radical parotidectomy with neck dissection and appropriate facial nerve reconstruction.

## SURGICAL TREATMENT OF SALIVARY GLAND MALIGNANCIES

The treatment of salivary gland malignancies has historically been surgically based. The bulk of treatment recommendations are driven by experience and reports focusing on parotid gland malignancies with extrapolation of this to the less common remaining salivary gland systems. Although most treatment plans begin with appropriate surgical intervention, studies have revealed the efficacy of adjuvant radiation therapy for advanced-stage disease and high-grade malignancies. Driven by experience with successful combined modality treatment for squamous cell carcinoma, experience in recent decades has demonstrated the increased utilization of radiosensitizing chemotherapeutic agents in the treatment of advanced salivary gland diseases. Initial experience was first recognized for the treatment of unresectable disease, but this principle has been gradually expanded to incorporate combined modality treatment for advanced-stage and high-grade malignancies, specifically those with poor prognostic features. There has likewise been interest in the utilization of biologic targeted agents to afford greater disease control.

Therefore, although surgical treatment remains the mainstay of any treatment algorithm for salivary gland malignancies, early multidisciplinary consideration is warranted and useful. This is specifically beneficial for patient education and perspective as well as formation of a multidisciplinary team to fully maximize adjuvant treatments. The National Comprehensive Cancer Network guidelines[60] for the management of salivary gland malignancies are outlined in Figures 25-6 and 25-7. Broken down by tumor size (T status) and tumor site, respectively, Figures 25-6 and 25-7 provide a useful framework for evaluation and treatment planning as well as the ultimate management of salivary gland malignancies. Yet, broken down into the most basic form, the management algorithm for the treatment of salivary gland malignancies is straightforward. Appropriate surgical resection with attempt for complete resection and functional preservation should be attempted. The addition of adjuvant radiation therapy based on the presence of high-grade histology, stage, and poor prognostic features such as positive margins, PNI, and nodal metastasis should be considered. Patients with unresectable disease or who are not surgical candidates may undergo nonsurgical treatment with radiation therapy or combination of chemotherapy and radiation therapy. Specific surgical intervention is based on the salivary gland site of origin of the malignancy with the primary goals being complete resection and functional preservation with inclusion of appropriate reconstructive efforts.

### Parotid Gland

Although the majority of parotid tumors are benign, 15% to 20% of these masses will have a malignant pathology. Malignancy may be suspected preoperatively based on the history, physical exam, preoperative imaging, or histology obtained with the FNA. Some parotid malignancies will only be diagnosed upon a frozen section or final pathology obtained upon parotidectomy or other surgical intervention for a parotid mass.

The management of parotid masses must adhere to the dictum of a complete resection with appropriate inclusion of adjoining parotid tissue and facial nerve preservation. The most efficient means of achieving these ends is the traditional approach of superficial parotidectomy with facial nerve identification, dissection, and preservation. Procedures such as enucleation or simple mass excision with nerve avoidance may only lead to unwanted and unwarranted findings of positive margins that could have been avoided and a potential higher risk of nerve dysfunction. Traditional descriptions of surgical procedures such as superficial and total parotidectomy can afford a simple framework to describe the degree of resection required in a parotidectomy. The most critical factor is that sufficient tissue surrounding the tumor be included with the resection. In the scenario of advanced disease, appropriate surgical extensions of the basic procedure may be warranted. These include facial nerve resection, resection of involved overlying skin, resection of the masseter muscle, resection of a portion of the mandible including the condyle, resection of major vessels such as the external carotid artery, resection of parapharyngeal space fat and dissection of adjoining structures, resection of the external auditory canal and possible inclusion of the auricle, and temporal bone resection. Yet, any extension of surgery must be consistent throughout the procedure avoiding morbid additional procedures when close or potentially microscopically positive margins are tolerated elsewhere, as with dissection and preservation of a functioning facial nerve. The planned extent of resection should be based on all available preoperative information from imaging, examination, and histology. The risks, benefits, and complications of the basic procedure should be discussed in detail as well as the necessity of potential surgical extensions to include total parotidectomy, neck dissection, mastoidectomy, mandibulectomy, skin resection, facial nerve sacrifice, and appropriate reconstruction.

The surgical approach in the setting of a defined mass with a functioning facial nerve begins with the creation of a cosmetically acceptable incision beginning in the pretragal skin crease. The incision extends around the lobule, over the mastoid, and

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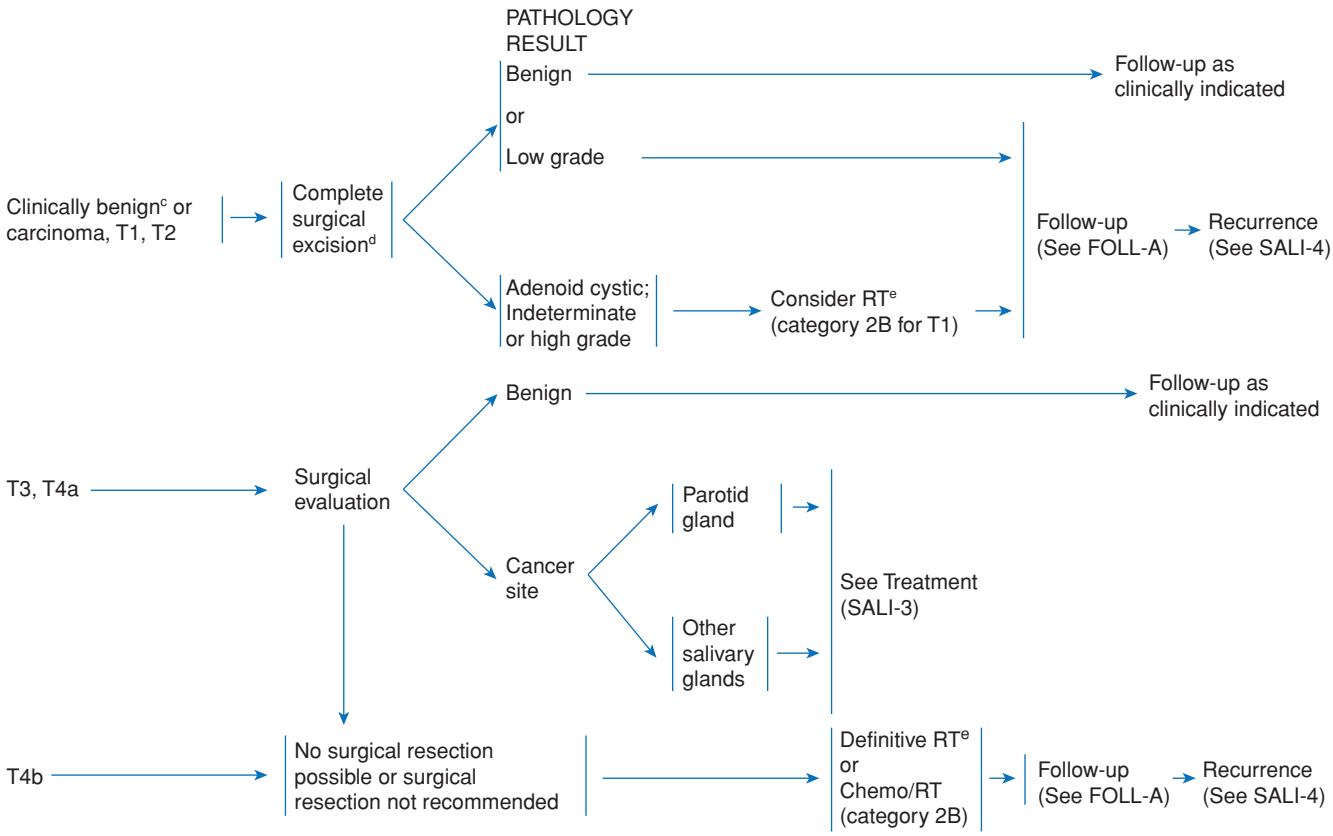



**FIGURE 25-7.** 2010 National Comprehensive Cancer Network guidelines for management of salivary gland malignancies based on tumor stage and histologic grade.

then inferiorly into a skin crease in the mid neck approximately 2 to 2½ fingerbreadths below the angle of the mandible. This incision can be extended forward in a skin crease to the submentum to facilitate extensions of the procedure such as neck dissection. Should a more complete neck dissection be required with dissections of levels IV and V, then the incision may be carried inferiorly into an Apron incision or a lower limb could be dropped to facilitate the exposure (Fig. 25-8). If a cervical advancement flap may be necessary for skin reconstruction, consideration of this should be given with initial incision planning. Facelift incisions have been advocated by many for the treatment of benign parotid tumors, but their use should be carefully considered in the setting of malignancy as limitations of exposure could be detrimental to ultimate resection.

The facial flap is then elevated forward in the deep plane just superficial to the parotidomasseteric fascia, unless contraindicated by tumor extension. During this maneuver, the great auricular nerve is identified as it crosses the sternocleidomastoid muscle and enters the parotid gland. At this point, it is usually taken and marked for a later use as a potential nerve graft. Preservation of the great auricular nerve in the setting of malignancy is not standard as this does require a dissection into the parotid parenchyma and may inadvertently cause a tumor disruption. The gland is now mobilized anteriorly by separating the fascial attachments at the digastric muscle and the mastoid tip. This facilitates exposure of the inferior aspect of the main trunk of the facial nerve. Gland mobilization is likewise completed anterior to the tragus and the external auditory canal exposing the tympanomastoid suture line. The main trunk of the facial nerve is now identified as it exits the stylomastoid foramen and enters the parotid gland. The key anatomic relationships previously discussed are critical in the identification of the main trunk at this level, and these are listed in Table 25.1.

Once the main trunk of the facial nerve is identified, dissection is carried forward in the plane directly overlying the nerve to identify the pes anserinus and the major branches of the facial nerve. Palpation of the mass during this component of the dissection is critical as it will indicate the position of the tumor relative to the branches of the facial nerve. The component of the parotid gland resting superficial to the facial nerve is now elevated by dividing the parotid parenchyma overlying the nerve while keeping the nerve under direct visualization. Dissection is usually completed through a combination of a superior to inferior as well as an inferior to superior dissection of the gland parenchyma. This allows superficial lobe of the gland to be elevated with the mass undisturbed. The approach likewise prevents filleting of the gland directly forward over the nerve during the dissection, which can lead to inadvertent disruption of the tumor. Should there be difficulty in identifying the main trunk of the facial nerve or if further identification of specific distal branches be necessary, retrograde dissection can be performed as described earlier (Fig. 25-9).

Division of the gland parenchyma can be completed with various techniques, each having specific advantages and disadvantages relative to hemostasis, cost, time, availability, and associated trauma. Whether utilizing sharp dissection, electrocautery, or devices such as the Hemostatix scalpel and Harmonic scalpel, the technique chosen is based on surgeon preference and experience.

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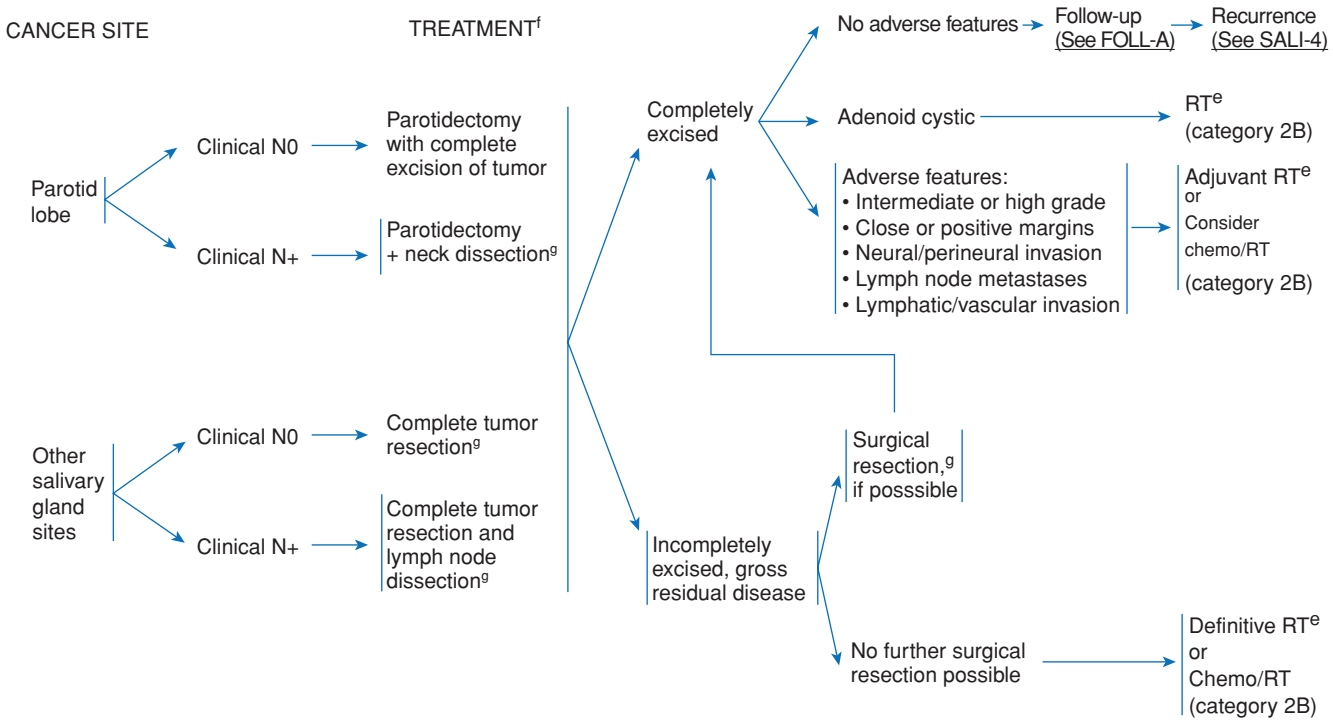



**FIGURE 25-8.** 2010 National Comprehensive Cancer Network guidelines for management of salivary gland malignancies based on tumor site.

Critical to any technique is the ability to minimize a neural trauma. This superficial parotidectomy approach should be sufficient for excision of a discrete mass without neural involvement.

Should superficial parotidectomy reveal a deep-lobe mass, complete mobilization of the superficial lobe should be undertaken to reveal the extent of the deep-lobe mass. Position of the tumor relative to the facial nerve branches as well as deep-lobe structures such as retromandibular vein, superficial temporal artery, deep temporal artery, and external carotid artery should be assessed. Dissection and delivery of the mass can then be undertaken if there is no discrete involvement of the nerve noted.

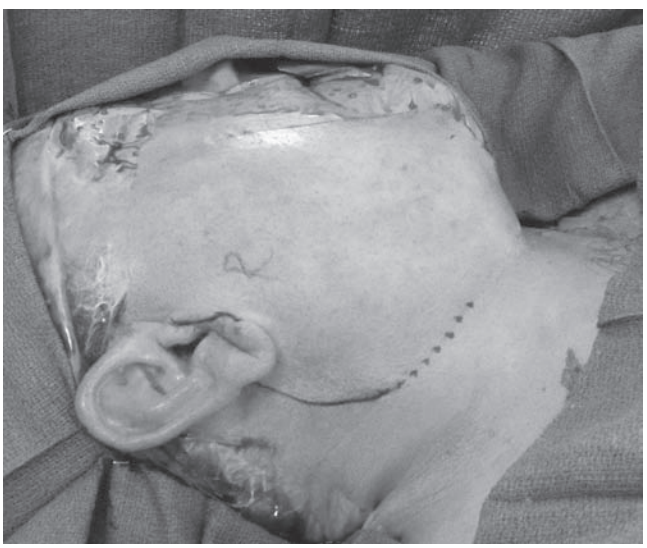


**FIGURE 25-9.** Pre-op incision planning for right parotidectomy, with dotted extension should selective neck dissection be warranted.

Once resected, the parotid tumor should be sent for frozen section analysis. Should a tumor previously noted to be suspicious for malignancy by FNA or imaging be found to be benign, closure can be undertaken as with standard parotidectomy for benign disease. If a low-grade malignancy is suspected, the closure may be undertaken, whereas if a high-grade lesion is noted, then consideration for selective neck dissection in the setting of an originally N0 neck can likewise be made.

During frozen section analysis, the wound is inspected and hemostasis is verified. Nerve integrity and function are verified and documented. A nerve stimulator, if used during any component of the procedure, facilitates this maneuver. The parotid bed is palpated for concerning lesions and associated lymph nodes, although the majority of parotid lymph nodes will be removed with the superficial parotidectomy. The level II lymphatic basin can likewise be palpated for any suspicious lymph nodes. Closure is then completed in a cosmetically acceptable fashion of surgeon choice over a closed suction drain.

## Management of the Facial Nerve

Intraoperative decision making relative to the facial nerve begins with thorough preoperative assessment of facial nerve function. Patients with paresis or paralysis of all or selective branches of the facial nerve system will require nerve sacrifice and appropriate reconstruction. Operative dissection should define distal nerve branches clear of tumor utilizing retrograde dissection. Similarly, the proximal nerve should likewise be cleared of tumor even if this should require mastoidectomy and clearance in the temporal bone. If nerve involvement by tumor is isolated to a discrete branch or system of branches such as the upper division or trunk, then preservation of the remaining facial nerve system can be undertaken with improved maintenance of function.

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Much more challenging is the scenario of normal facial nerve function with a mass suggestive for malignancy on preoperative evaluation. The critical factor determining the applicability and feasibility with the facial nerve preservation will be the direct relationship of the tumor to the nerve. Tumor should not be transected to attempt preservation of a normally functioning facial nerve or specific facial nerve branches. This only leads to tumor spillage, decreased control, and temporary, if not permanent, dysfunction of the dissected nerve. Distal and proximal branches should be dissected to reveal normal appearing nerve and the tumor appropriately resected with nerve sacrifice. Yet, prior to nerve sacrifice, confirmation of a malignant diagnosis by frozen section is recommended. This can be done by identifying a portion of the tumor away from the major nerve branches and creating a small window through the fascia overlying the tumor. This will expose the mass where biopsy can be obtained with either a scalpel or a dermatologic punch. The fascia overlying the biopsy site can then be reapproximated with a figure-of-eight stitch to limit any potential tumor spillage. With diagnostic confirmation of malignancy, the tumor dissection and nerve sacrifice can be undertaken.

In the somewhat rare scenario, that a malignant diagnosis cannot be confirmed, the surgeon may elect to close and delay ultimate resection until a definitive diagnosis of malignancy is confirmed. Utilization of tissue barriers such as cadaveric dermis or fascia that can be placed overlying the dissection bed will isolate the tumor until later resection is undertaken. This maneuver can prevent unnecessary nerve sacrifice for rare processes mimicking parotid malignancies such as infarcting or infected Warthin tumors, lymphomas, and atypical inflammatory processes, which may affect nerve function preoperatively, but ultimately be benign processes.

Although, facial nerve preservation is not advised if the nerve is grossly abnormal or dissection attempts to preserve the nerve leads to tumor spillage and grossly positive margins, nerve preservation can be attempted for tumors abutting the main trunk of the nerve and its branches. Meticulous dissection aided by loupe magnification can allow for oncologically safe separation of associated nerve branches from the tumor without direct tumor disruption. Even if final pathology indicates microscopically positive margins in the region of such dissection, final disease control with the addition of adjuvant radiation therapy is not adversely affected.

Ultimately, the surgical resection of parotid salivary gland malignancies should achieve wide local excision with negative margins and may include multiple extensions of the procedure in this anatomic region dense with critical structures. Yet, each extension of the basic surgical resection must be considered carefully under the basic tenant "the closest surgical margin will remain the closest surgical margin" regardless of how wide a resection margin may be achieved in another area. As an example, it may not be advisable to extend a resection to involve a mandibulectomy to avoid a close surgical margin in this region while tolerating a potentially microscopic-positive margin during the dissection and preservation of a functioning facial nerve. Likewise, if the morbidity of facial nerve resection has been accepted, appropriate extension of the procedure should be considered to achieve widely clear margins throughout the resection basin.

The use of facial nerve monitoring during parotid surgery deserves discussion. First, one must differentiate between the use of the facial nerve stimulation to facilitate dissection and real-time continuous electrical nerve monitoring as an injury-avoidance maneuver during surgery. Nerve stimulation should be considered in all cases and is relatively inexpensive irrespective of whether a reusable or disposable device is used. With nerve stimulation, current is directly applied to the structure in question and specific facial nerve muscle movements can be directly assessed. Nerve stimulation aids in the identification of the main trunk of the facial nerve, specific branch identification during tumor resection, and verification of nerve integrity upon completion of the surgery.

Continuous nerve monitoring devices assess select muscles of facial expression such as orbicularis oculi, orbiculari os, depressor anguli, and so forth with real-time interpretation of motor stimulation as noted on the monitoring device. Such real-time constant interpretation may be provided by a specified individual or by the surgeon. As both mechanical and electrical stimulation can be noted on the monitor, nerve stimulation related to potential dissection trauma can be noted as well as nerve identification by the use of electrical stimulation during surgery. Real-time nerve monitoring is used by many surgeons in standard practice but studies have yet to demonstrate significant improvement in ultimate outcome.[61] Considered as an adjunct parotid surgery, the nerve monitor does not supplant clear knowledge of the relevant anatomy, sound surgical technique, and thoughtful decision making. Consideration of continuous nerve monitoring use may be given for revision cases or in those in which a transmastoid approach is warranted and the use of a nerve monitor is part of standard otologic practice.

## Reconstruction

Reconstructive efforts associated with parotidectomy and facial nerve dissection should focus both on function and cosmesis and address each extension of the basic ablative procedure that is required. When facial nerve resection is required, primary nerve reconstruction can be considered. For limited nerve resection, primary anastomosis can be achieved if adequate mobilization of the remaining facial nerve branches is attainable such that a tension-free anastomosis can be completed. The neurorrhaphy is usually completed with interrupted sutures placed in an epineural fashion using 8-0, 9-0, or 10-0 monofilament sutures. Loupe magnification or an operating microscope is usually necessary to achieve optimal coaptation. Although, primary anastomosis is optimal, this is usually not achievable in most ablative cases. In this setting, a nerve graft will be required to fill the gap between the remnant facial nerve branches. Better function will be achieved in a small single-branch reconstruction as this will allow reinnervation with minimal synkinesis (Fig. 25-10A,B).

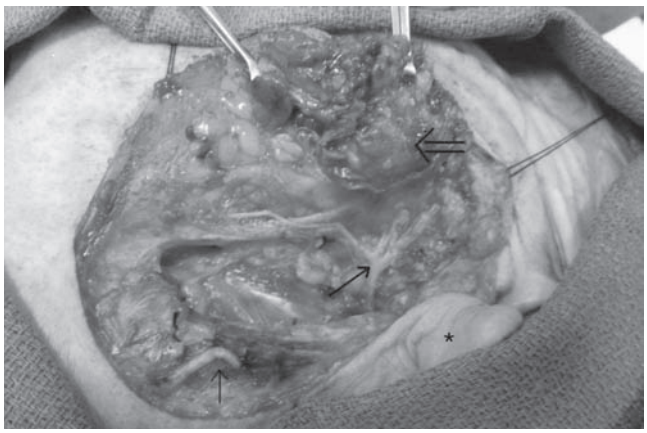


**FIGURE 25-10.** Dissected and preserved facial nerve system after during left superficial parotidectomy. Large single arrow at pes anserinus. Double arrow at Tumor. Small arrow at great auricular nerve dissected for potential nerve graft. Asterisk at earlobe.

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Nerve defects involving the main trunk and the pes anserinus will require nerve grafts with acceptable branching patterns and length to achieve a tension-free reconstruction of available branches. Although, success with synthetic nerve conduit has been reported,[62] autogenous nerve grafts remain the favored option for nerve reconstruction. Common graft donor sites include the great auricular nerve system, the ansa cervicalis, the sural nerve, the medial antebrachial cutaneous nerve, and nerves associated with free-flap reconstruction such as the motor nerves to the latissimus dorsi or vastus lateralis muscles (Table 25.7). Although, synkinesis is unavoidable with most nerve reconstruction, optimal function can be achieved by carefully selecting the distal branches with the greatest motor input to the desired facial nerve musculature. This can be easily assessed with the use of a facial nerve stimulator. Nerve margins should be histologically cleared of disease prior to reconstruction. Nevertheless, small series have reported functionally successful nerve grafts in the setting of microscopically positive nerve margins.[63]

Should nerve grafting not be achievable in the primary ablative setting, attention is focused on rehabilitation of the deficits created by the loss of the facial nerve function. Rehabilitative procedures such as eyelid weight placement (gold and platinum), lateral tarsal strip procedures for ectropion, browlifts, and static slings to the oral commissure and midface as well as dynamic slings using the temporalis or masseter muscles can be considered with the primary ablative procedure.[64] Often these procedures are completed in the secondary setting once postoperative or radiation therapy effects have stabilized the exact deficit. Likewise, procedures can be considered if primary nerve grafting fails to achieve exceptional functional outcome. Excellent functional restoration to the oral commissure can be achieved with microvascular muscle transfer utilizing the gracilis, latissimus dorsi, or serratus free-flap systems.[65]

Free tissue transfer techniques also provide excellent reconstruction options for large defects. The fibula, radius, and iliac osteocutaneous flaps are excellent options for necessitated mandibular reconstructions.[66] The anterolateral thigh flap, rectus abdominus flap, and radial forearm flap are versatile and dependable option for large cutaneous and auricular defects.[67] Smaller cutaneous defects may be reconstructed with local regional flaps such as a cervical facial advancement flap, the submental flap, and the supraclavicular flap.[68] In certain clinical scenarios, the pectoralis major flap also affords a dependable reconstructive option.[69]

Free-flap reconstructive techniques such as the lateral arm flap and the anterolateral thigh flap are also quite useful for addressing large contour defects created with total and subtotal parotidectomies and neck dissection.[70] Smaller contour defects can be addressed with sternocleidomastoid flaps, dermal graft, and free-fat grafts,[71] although care should be taken not to delay the initiation of radiation therapy or significantly alter the wound bed for subsequent treatment and follow-up.

Specific reconstructive efforts may also be undertaken to limit or control the effects of Frey syndrome at the time of the primary procedure. A thick-flap elevation technique, barrier methods such as cadaveric dermis, autogenous fascia, or vascularized fascial flaps have been shown to successfully limit Frey syndrome, but not completely prevent it.[72] Again, such efforts must be balanced with the ultimate adjuvant treatment plan.

**TABLE 25.7 Nerve Graft Donor Sites**

- Great auricular nerve
- Ansa cervicalis[a]
- Sural nerve
- Medial antebrachial cutaneous nerve
- Nerves associated with free-flap harvest
  - Lateral antebrachial cutaneous nerve (RFF)
  - Thoracodorsal nerve[a] (lat dorsi)
  - Nerve to vastus lateralis (ALT)

[a]Motor nerve.

## Treatment of Submandibular Gland Tumors

Tumors of the submandibular gland demonstrate a far greater likelihood of malignancy with up to 50% being malignant and therefore require caution in diagnostic workup and therapeutic intervention. Preoperative evaluation including history and physical exam findings suspicious for malignancy such as pain, cranial nerve impairment (V, VII, and XII), fixation to adjoining structures and prominent lymphadenopathy must all be taken into consideration. Imaging with CT or MRI and FNA are also critical aspects of the preoperative evaluation.

Treatment of submandibular gland tumors begin with appropriate resection similar to the management of parotid tumors with the goals of complete excision—after achieving clear margins—and with maximal achievement of function and cosmesis. The single greatest law in submandibular surgery is the attempt to achieve these goals through an inadequate incision without effective exposure to the gland, the tumor, and the adjoining structures. As demonstrated by Weber et al.,[73] submandibular malignancies are significantly better managed when approached as a formal level I neck dissection rather than through a simple "shelling out" of the gland which is utilized by many for benign inflammatory processes involving the gland.

Surgical resection begins with a curvilinear incision planned roughly two fingerbreadths below the angle of the mandible. This will create the initial incision in a plane inferior to the course of the marginal mandibular nerve branch of the facial nerve system. The incision should extend from the anterior border of the sternocleidomastoid muscle into the submental region overlying the anterior border of the digastric muscle. The superior flap is elevated in a subplatysmal fashion to the level of the mandible with the attention to the marginal mandibular nerve. This branch of the facial nerve system will be located just superficial to the fascia overlying the submandibular gland. A nerve stimulator can be an effective aid to this part of the surgery and nerve identification.

Dissection deep to the gland fascia as a means of nerve preservation is not advised as tumors may abut the fascia and such dissection may lead to tumor disruption. The facial vein can be ligated inferiorly as it crosses over the gland. As mentioned previously, elevating the superior stump will then elevate the marginal mandibular nerve system as it runs superficial to this vein. This maneuver can provide further nerve protection during dissection. All efforts should be made to preserve the function of lower facial nerve branches, which may be related to submandibular gland tumors. However, if these branches are directly involved by tumor, they should be resected and reconstructed in a similar manner to nerves involved in the treatment of parotid tumors.

Once the nerve has been mobilized, the gland is meticulously freed from the attachments to the lower border of the mandible. This is facilitated by ligation of the facial vessels as they exit the gland superiorly at the facial notch of the mandible. Any associated perifacial lymph nodes are also mobilized at this time and included in the dissection. The anterior aspect of the gland is mobilized off the anterior belly of the digastric muscle and the mylohyoid muscle. Smaller arterial and venous branches will pierce the mylohyoid muscle during this dissection and that will

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require attention. The mylohyoid muscle is retracted superiorly exposing the deep submandibular triangle and the course of the lingual nerve with its attachment to the gland at the submandibular ganglion.

The hypoglossal nerve and the prominent veins that accompany it will run in the plane just deep to the gland and the lingual nerve as the hypoglossal nerve enters the submandibular triangle from deep to the posterior belly of the digastric muscle. Care is taken to preserve these structures during dissection. The submandibular duct is now identified as it crosses under the lingual nerve and ligated as are the connections of the lingual nerve to the gland at the submandibular ganglion.

The posterior fascial attachments of the gland are released at the angle of the mandible exposing the posterior submandibular space and the proximal lingual nerve. The facial artery is identified as it travels under the posterior belly of the digastric muscle to enter the posterior aspect of the submandibular gland. With ligation of the facial artery, the submandibular gland can be fully mobilized off the further fascial attachments to the posterior belly of the digastric muscle completing the dissection of the gland and its associated lymphatics. Closure is completed in a similar manner to parotid surgery over a closed suction drain.

Extensions of the basic submandibular gland resection procedure may include a resection of involved nerve and reconstruction with applicable nerve grafting of motor nerves. All nerve margins should be histologically cleared with frozen section analysis prior to reconstruction. If the lingual nerve is sacrificed, a surgical clip may be placed on its proximal stump to aid with later adjuvant radiation therapy. More advanced disease with significant local involvement of the floor of mouth, tongue, mandible, and skin will necessitate resection of these structures as appropriate. Effective tissue flap reconstruction can likewise be completed in this primary setting. As with the parotid surgery, critical appraisal of potentially close surgical margins throughout the field must be taken into consideration prior to significant extensions of the operation.

As with parotid malignancies, salivary gland cancer of the submandibular gland should be considered for adjuvant radiation therapy based on the same criteria relative to stage and histology. Advanced-stage tumors, high-grade tumors, and tumors with poor prognostic pathologic features such as positive margins, perineural, perivascular and perilymphatic spread, parenchymal extension, and nodal metastases should receive adjuvant XRT.

## Treatment of Sublingual Gland, Minor Salivary Gland, and Parapharyngeal Space Tumors

Sublingual tumors present as submucosal masses in the floor of mouth. Because of the high propensity of malignancy in these glands, all noncystic sublingual masses should be considered malignant until resected and proven otherwise by histology. As ACC is the most common malignant tumor of the sublingual glands, particular care in the clearance of margins is warranted, but can be quite challenging. The diagnosis of sublingual tumors is facilitated by imaging and transoral FNA if achievable. Transoral open biopsy is acceptable as the ultimate treatment of these masses will involve resection that can easily include a carefully planned oral biopsy site.

Small tumors may be approached intraorally but every effort should be made to optimally clear margins and achieve nerve preservation. Because of the tight and dense anatomy of the region and proximity of other structures, a transcervical approach with ipsilateral submandibular gland resection may be required to provide adequate exposure for resection and nerve preservation. As sublingual gland resection adversely affects the submandibular ductal drainage system, submandibular gland resection may be mandatory for this reason.

The lingual nerve may also be involved by sublingual gland tumors mandating nerve resection with frozen section clearance. Because the mucosal defect involved in the resection can be significant, reconstruction may be required. Options include skin grafts, local regional flaps such as a submental island flap or free tissue transfer techniques such as the radial forearm flap. Tumors of the sublingual gland can be quite aggressive with significant tongue and mandibular involvement necessitating large resection and therefore appropriate soft tissue and bony tissue reconstructive efforts should be considered with appropriate preoperative discussion and preparation.[74]

Minor salivary gland cancers are among the most challenging in the upper digestive tract. These tumors can present with advanced-stage disease and be quite locally extensive. Minor salivary gland tumors will often present with infiltrating borders as well as perivascular and PNI that can make the clearance of margins challenging. Regardless, surgery remains the primary treatment modality for minor salivary gland tumors and should be considered initial treatment for all resectable disease regardless of the subsite. Resection techniques are determined by the standard techniques of the specific subsite involved: oral cavity, base of tongue, oropharynx, sinonasal, or larynx. Again the goals of clear surgical margins with optimal functional preservation are desired. As with resection planning, the optimal reconstructive methods which pertain to each subsite form the goal standard for reconstruction after the surgical ablation of minor salivary gland tumors (Figs. 25-11A,B and 25-12A,B).

The majority of parapharyngeal space salivary gland tumors are benign with the pleomorphic adenoma being the most common. The transcervical approach with submandibular gland resection and/or parotidectomy for increased exposure provides excellent access for the safe resection of well-circumscribed parapharyngeal space lesions. Utilization of mandibulectomy for increased exposure is well described but rarely needed. Complex and infiltrative masses of the parapharyngeal space require more careful consideration prior to attempted resection. Tissue diagnosis with FNA obtained in a transcervical or transoral manner can be beneficial. Because of the intimate relationship of the parapharyngeal space to critical surrounding structures such as cranial nerves IX, X, XI, and XII as well as the carotid artery and cranial base, careful and critical assessment of the true resectability must be undertaken. If the surgical resection is untenable, then nonsurgical treatments should be considered. As with the other subsites, adjuvant radiation should be recommended based on advanced-stage, high-grade histology and poor prognostic features on final pathology. Widely clear margins can be particularly challenging with the anatomic complexity of malignancies in sublingual, minor salivary gland, and parapharyngeal space tumors.

# MANAGEMENT OF THE NECK

Without debate, patients with clinically positive neck disease at the time of presentation should undergo neck dissection in conjunction with initial surgical therapy of the primary site. With the accordant increase in stage related to neck metastasis and the subsequent negative effect on survival, adjuvant radiation therapy should be strongly recommended to patients with positive neck disease. Yet, the neck dissection must remain a critical part of treatment in patients with N-positive disease for the somewhat radioresistant tumors. Extent of neck dissection is based on the extent of the disease, but should become sufficiently comprehensive to address all nodal basins at risk.

More challenging is the scenario of the clinically N0 patient. The bulk of data related to this question center on parotid

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**FIGURE 25-11. A and B:** Photos 1 year after resection and reconstruction of the marginal mandibular nerve branches for salivary gland carcinoma demonstrating acceptable restoration of function. Ansa cervicalis grafts used.

salivary gland cancers, but principles extractable from this experience are useful when approaching disease in other subsites. Historic series generally estimate the risk of cervical nodal metastasis in the clinically N0 parotid cancer patient to be 14% to 16%.[75] Although some series report higher rates of lymph node metastasis, these include intraparotid lymph nodes in their analysis, somewhat skewing the incidence.[76]

Factors associated with cervical metastatic disease include higher tumor grade, extraparotid extension, tumor size >4 cm (T3 and T4), pain, facial nerve involvement, and the presence of positive intraparotid lymph nodes.[77] The higher-grade histological subtypes for which elective neck dissection is generally recommended include high-grade MEC, malignant mixed tumor, salivary ductal carcinoma, squamous cell carcinoma, undifferentiated carcinoma, and adenocarcinoma not otherwise specified.[78] Interestingly, some recent reports note significantly higher rates of cervical metastasis for all salivary gland malignancies regardless of specific histologic subtype.[79] Histologically, low-grade

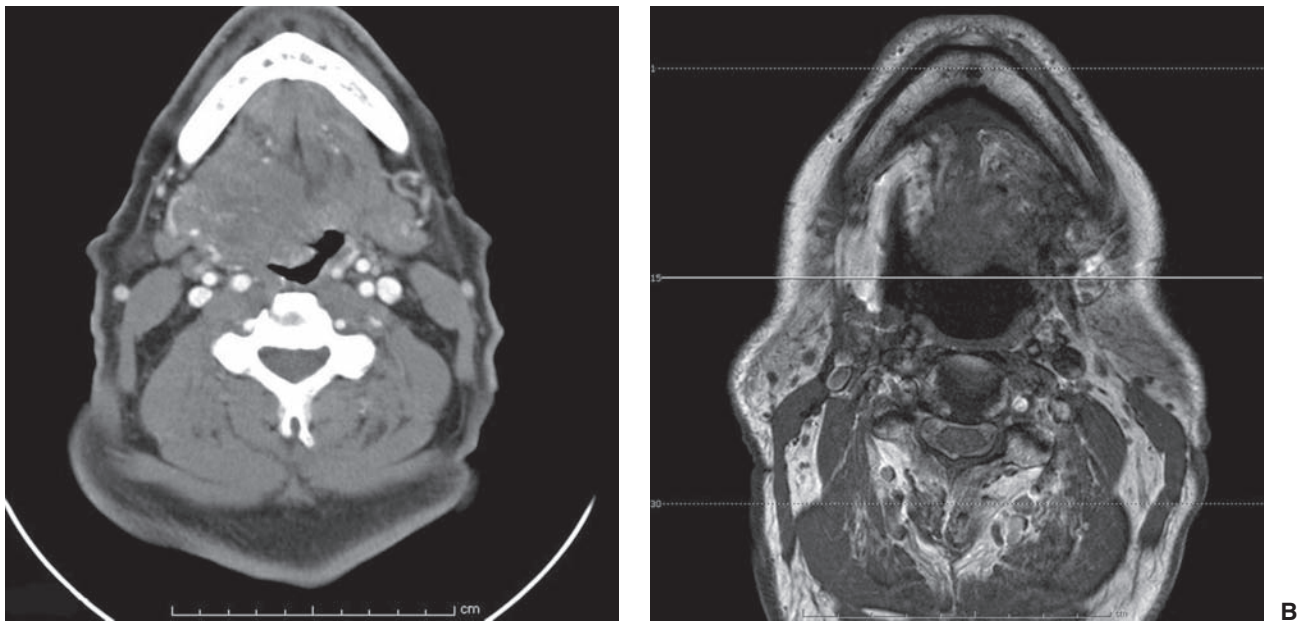



**FIGURE 25-12. A:** Soft tissue, axial CT with contrast of advanced adenoid cystic carcinoma of the base of tongue, subsequently treated with resection, through lingual release approach and radial forearm flap reconstruction, and postoperative XRT. **B:** T1-weighted MRI 3.5 years after resection demonstrating flap reconstruction and no evidence of recurrent disease. Patient has no tracheotomy and excellent speech and maintain a completely oral diet.

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lesions which are advanced in size or demonstrate aggressive features such as facial nerve involvement should likewise be considered for treatment of the neck, which may include elective neck dissection at the time of a primary surgical therapy.

The extent of elective neck dissection warranted in the N0 patients is also an issue of continued debate. Although, the modified radical neck dissection was traditionally advocated, selective neck dissections of the nodal basins at highest risk have been increasingly used, largely based on the favorable experience in the treatment of squamous cell carcinoma. With the concomitant use of radiation therapy for identified occult positive disease, excellent control rates have been demonstrated. Therefore, treatment of the neck nodal basins most at risk for each subsite should be considered for all tumors with advanced T stage and for tumors with aggressive local features regardless of histologic grade. Similarly, all high-grade carcinomas should be considered for neck treatment regardless of size. Elective neck dissection can be incorporated with initial surgical management in such cases, if information from pathologic assessment of the sampled lymph nodes affects therapeutic radiation planning.[80] A case can also be made that control may be improved, with the combination of neck dissection and XRT in these less radiosensitive malignancies. Elective dissections of levels 2 and 3 for early T-stage parotid malignancies can usually be completed through the same incision and with minimal morbidity. In the setting of low-grade histologic disease <4 cm, pathologic information demonstrating lack of occult metastatic disease and favorable histology can allow single modality treatment to be undertaken with more assurance. If elective neck dissection is not undertaken, for whatever reason, and final pathology of the primary site reveals evidence of high-grade histology or aggressive local features, therapeutic radiation to the neck should be advocated. As control rates with radiation therapy in the N0 neck are acceptable, neck dissection is not recommended as a secondary procedure.[80]

## Radiation Therapy for Salivary Gland Malignancies

***Major Salivary Gland Tumors.*** The most common setting for radiation therapy in the management of major salivary gland carcinomas is a surgical adjuvant following gross total resection. This is true for all histologies. Because of the location of the major salivary glands, there are limits to the extent of a surgical resection before morbidity overshadows additional gain and for this reason average local control rates have historically hovered around 60% following surgery alone. Risk factors for local recurrence following a complete resection include stage, a close (<5 mm) or microscopically positive resection margin, bone invasion, the presence of lymphovascular invasion (LVI), PNI, multifocal disease, adherence to a nerve or perineural involvement, and extracapsular extension (ECE).[81–88] A detailed analysis of risk factors associated with local and regional recurrence for all histologies following definitive surgery was reported by Chen et al.[89] Patients with T3–4 disease, positive surgical margins, high-grade histology, or lymphatic spread had 10-year actuarial recurrence rates of 37% to 63%. Another group looked at a large cohort of patients with parotid tumors of all histologies with the endpoint being disease-specific survival. The most important factors in this series were age, stage, tumor size, neural involvement, and degree of differentiation.[90] In most series, histology did not emerge as an independent risk factor for local recurrence when subjected to multivariate analysis.

Radiation in doses >56 Gy to the postoperative clinical target volume (CTV) following gross total resection in patients with risk factors for recurrence has routinely been demonstrated to reduce the rates of local and regional failure. Data from single institutions report long-term actuarial local control rates of 80% to 90% with acceptable morbidity.[26,81,90–95] Larger and more thorough studies from the Dutch Head and Neck Oncology Cooperative Group indicate that postoperative radiation is associated with a risk reduction of 9.7 for local regional failure.[88] More detailed data from this group demonstrate the 10-year local control rate between surgery plus postoperative radiation and surgery alone is 84% versus 18% for T3–4 tumors, 95% versus 55% for close margins, 82% versus 44% for incomplete resections, 86% versus 54% for bone invasion, and 88% versus 60% for PNI. An improvement was also seen in the postoperative neck for patients with N1–3 disease.[96] The greatest benefit of adjuvant therapy seen by the Dutch group and others is for more advanced disease and higher-grade tumors, as well as following resections that left an incomplete or positive margin.[94,96,97]

There may also be a survival benefit for a subset of patients with more aggressive tumors.[98] A study of SEER data restricted to 2,170 patients with high-grade and/or locally advanced malignant major salivary gland tumors did demonstrate adjuvant radiation was associated with a significant improvement in survival when subjected to multivariate analysis.[99] This improvement in survival has not been seen in many smaller series, possibly due to their inclusion of all histologies and stages.

Once a decision has been made to treat with adjuvant radiation, three-dimensional treatment planning is used to define a CTV that completely encompasses the original anatomic boundaries of the resected gland including a centimeter expansion to account for radial tumor spread and surgical manipulation. For tumors arising in the parotid gland, it is important to locate and include the deep lobe which can sometimes be underestimated with respect to its medial extension. Once a CTV has been defined, either a three-dimensional or intensity-modulated radiation therapy (IMRT) approach is used to conformally irradiate the CTV with limits placed on the spinal cord, contralateral parotid, esophageal constrictor muscles, oral cavity, and mandible. For most clinical situations where the margin is not microscopically positive, a dose of 56 to 60 Gray (Gy) is considered sufficient when delivered in 1.8 or 2.0 Gy fraction sizes.[81,83] A resected tumor with a positive margin or a situation with incompletely resected gross disease requires a higher dose, 66 Gy in the first situation and 66 to 72 Gy in the latter. Ideally, one would like to treat the entire resected tumor bed as an initial CTV to 60 Gy and then identify a secondary volume at higher risk and treat this smaller CTV to the target dose of 66 to 72 Gy. Occasionally, when an area of concern is appreciated during surgery, clips can be placed to help define a volume for higher dose. More commonly, however, a positive or close margin is discovered when the permanent sections are being reviewed, and it is impossible to retrospectively define the area where there is greatest risk. In this situation, the entire initial CTV has to be defined as high risk and irradiated to 66 Gy to assure adequate coverage. The question of the viability of a facial nerve graft following postoperative radiation is sometimes raised; however, this has not been an issue and should not affect the decision making regarding the advisability of adjuvant treatment.[100] An example of an IMRT treatment plan for a resected parotid tumor is seen in Figure 25-13. The dose is highly conformal and localized to the ipsilateral tumor bed minimizing unnecessary dose to uninvolved normal structures.

Histology can have a major impact on the design of an appropriate CTV. As described, the CTV for the resected primary site is essentially the same for all settings; however, the pattern of spread varies greatly and knowledge of the natural history of disease can avoid unnecessary treatment failures. Low-grade malignant tumors such as AC and low-grade MEC have minimal risk of lymphatic or perineural spread and the CTV is restricted to the salivary gland itself. A common clinical occurrence is a low-grade parotid tumor initially treated with a superficial parotidectomy.

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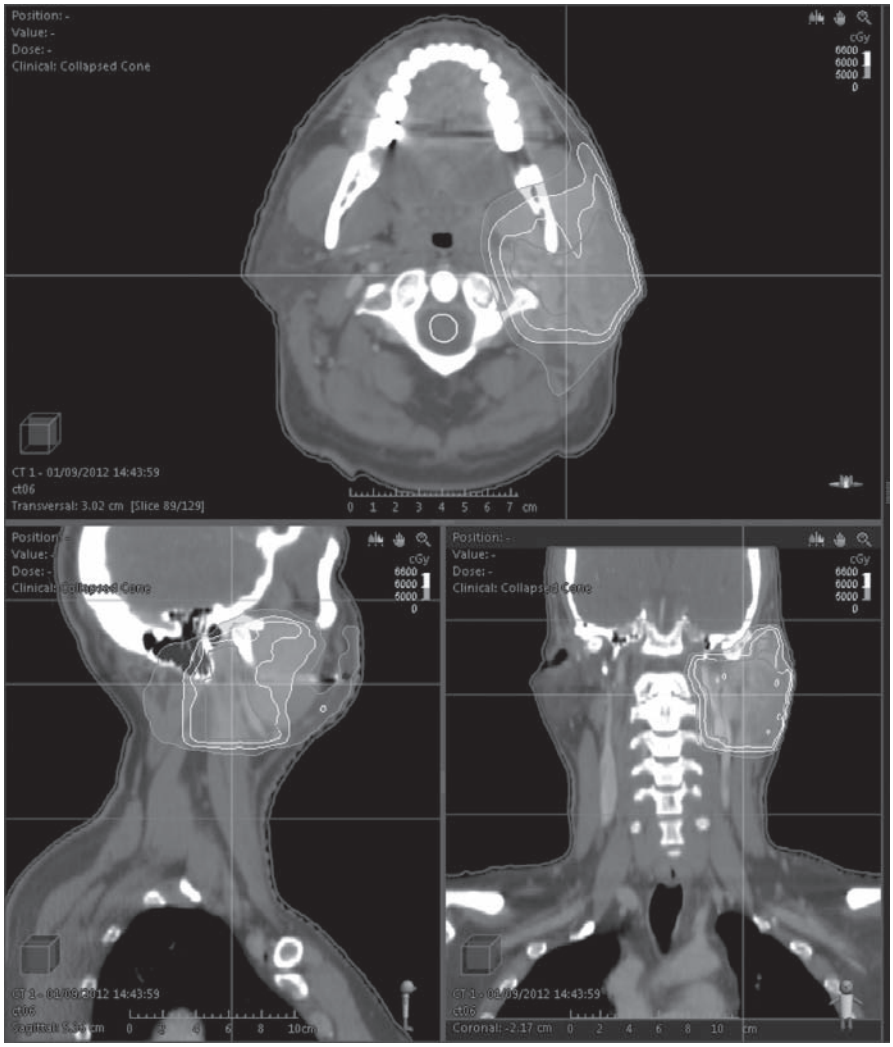



**FIGURE 25-13.** Postoperative IMRT plan for a parotid gland carcinoma. The CTV is the entire initial volume of the parotid gland including both superficial and deep lobes (magenta) and the 66-Gy, 60-Gy, and 50-Gy isodose volumes are shown.

These tumors can be well circumscribed and superficial enough so that no further therapy is needed; however, they can also be situated deeper into the gland where the facial nerve becomes a limiting factor in obtaining a comfortable resection margin. The risk of recurrence may still be relatively low, between 10% and 20%, however, should this occur; the consequences are high as salvage surgery would require sacrifice of at least part of the facial nerve. Postoperative radiation, 60 Gy to the primary CTV, should be considered in this setting.[101]

Higher grade tumors, most notably intermediate- or high-grade MECs, adenocarcinomas, and salivary gland duct carcinomas carry a substantial risk of involvement of the ipsilateral lymphatics, and this is a negative prognostic factor.[74,102,103] For N0 but high-risk disease, the CTV includes not only the resected salivary gland but lymphatic levels as well. For tumors that arise in the parotid gland, levels II, III, IV, and V are covered;[74] submandibular gland tumors should include level IB in addition to the above. The dose of radiation to the lymphatic CTV should reflect the risk of involvement; that is, the more proximal the lymphatic chain is to the salivary gland primary, the greater the risk and therefore, the higher the dose. Levels IB, II and III should receive 56 to 60 Gy whereas levels IV and V can be treated to 50 to 54 Gy. Almost always, irradiation of the neck is ipsilateral for N0 disease. Elective neck irradiation in this setting has proven to be very effective in preventing subsequent relapse in the neck;[103] however, it is very difficult to determine the true level of efficacy.[104] The role of radiation therapy in the management of an N1–3 neck is much the same as for squamous cell carcinoma of the upper aerodigestive tract.

Since the primary management of salivary gland tumors is surgery, a neck dissection is often performed at the time of primary resection and there is little emphasis on radiation as a single modality for gross disease as opposed to squamous cell carcinomas of the head and neck. Indications for postoperative radiation include the presence of gross or microscopic extracapsular extension, multiple lymph nodes, or N3 disease. The lymphatic CTV is similar to what is described above for the N0 neck; however, in the presence of level II disease, the CTV includes level Ib for parotid tumors.[105] The radiation dose is higher to account for the higher probability and/or extent of subclinical disease. The ipsilateral lymphatic levels of an involved neck are treated to a dose of 56 to 60 Gy and the area in the neck where extracapsular extension is noted can be treated for an additional 6 Gy to increase the likelihood of controlling minimal residual disease in the soft tissue or adjacent structures in the neck. Even with N2 disease, the contralateral neck is rarely treated[84] unless imaging demonstrates borderline contralateral adenopathy or if there is massive adenopathy in the ipsilateral low neck raising a concern for retrograde flow and collateral involvement.

ACC is a special case in all salivary gland sites as PNI and tracking along proximal cranial nerves is a significant pattern of spread. This has been associated with an increased risk for local

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failure and as a negative prognostic factor for survival especially if a named nerve is involved.[83] For tumors arising in the parotid gland, this is the facial nerve (cranial nerve VII); tumors arising in the submandibular gland can involve the lingual nerve (cranial nerve $V_3$) in addition to the hypoglossal nerve (cranial nerve XII) and facial nerve (cranial nerve VII). Whether or not perineural involvement is identified pathologically, its presence must be suspected and appropriate imaging needs be obtained prior to treatment planning. MRI is the preferred imaging and thin cuts should be obtained through the entire skull base and the brain stem as skip areas along an affected nerve are possible. In addition to the primary site CTV definition and doses previously described, an additional element to treatment planning for ACC is the course of the potentially involved cranial nerves to their respective foramina.

For potential subclinical perineural extension, 54 Gy is used. In the event of a completely resected primary tumor and radiographic findings of gross involvement of a proximal segment of a cranial nerve, the dose for treating subclinical disease along the path of the nerve should be higher, 56 to 60 Gy, and the gross disease needs to receive a dose of at least 66 to 70 Gy. The extension of the CTV does not always end at the neural foramina but may extend proximally to include the ganglion and even the afferent branch up to the anterior brain stem. Only advanced methods of radiation treatment planning and delivery such as IMRT can treat a complex CTV such as this and achieve the target doses while not excessively treating important normal structures. Concurrent chemotherapy may be considered in patients with multiple adverse or high-risk features.[106]

***Minor Salivary Gland Tumors.*** Any type of salivary tumor, benign or malignant, can arise from a minor salivary gland, and, like major salivary gland tumors, complete resection is the preferred treatment in many cases, followed by adjuvant radiation therapy.[107–109] The natural history and pattern of spread is determined by the histology rather than site of origin and the risk factors for recurrence share some overlap with those of the major salivary glands. As the anatomy is more complex for these tumors, so is the design of postoperative CTVs, which can range from the immediate tumor bed to the primary site and lymphatics and/or areas of potential perineural spread.

As with major salivary gland tumors, high-grade MEC and adenocarcinomas warrant additional attention to the lymphatic drainage; however, unlike major salivary gland tumors, the region at risk is not always ipsilateral. Centrally located primary sites such as the hard and soft palate, base of tongue, and larynx have the potential for bilateral lymph node involvement, and in these settings radiation is delivered to the bilateral neck as well as primary CTV. The same dose specifications elaborated in major salivary glands apply. Three-D planning and the use of IMRT are encouraged to develop an optimal treatment plan that avoids unnecessary irradiation to the parotid glands and other normal structures.

ACC of the minor salivary glands represents an even more complex challenge to the design of an appropriate CTV due to the nature of the innervations of the primary site and need to account for these along their proximate course. By the time each nerve is identified and traced back to its respective foramina, a CTV can become large and complex. For example, postoperative treatment of an ACC in the hard palate requires a CTV that not only includes the palate but also the course of $V_2$ and the parasympathetic chain to the pterygopalatine fossa and more proximally to the neural foramina of the skull base.

***Benign and Low-grade Tumors.*** Benign and low-grade tumors such as pleomorphic adenoma, grade 1 MEC, and low-grade pleomorphic adenocarcinoma often do not require additional therapy other than complete resection. For pleomorphic adenomas, the typical natural history is primary resection followed by a long disease-free interval and another resection. Each surgical iteration has a shorter interval[110] and adjuvant radiation is given after the second or third surgery, a decision governed by the degree of morbidity thought to be associated with the next round of surgery. A dose of 50 to 60 Gy has been shown to effectively prevent further recurrences with minimal morbidity or risk of malignant transformation or a second primary.[111] Pleomorphic adenoma can also arise in a minor salivary gland and even present as a submucosal parapharyngeal mass. In these settings, surgical resection is often incomplete and there is concern about a microscopic margin or even residual gross disease. Another concern is when there is tumor spillage during the course of the resection. Rather than wait until a recurrence manifests itself, radiation is offered after the initial resection since there will be little or no opportunity for surgical salvage. If given immediately after the initial resection, postoperative radiation is very effective in preventing the recurrence of this benign disease; however, if there is a delay and radiation is given after a second recurrence, often with incomplete resection the local recurrence rate goes from a negligible number (<1%) to 12.5%.[112]

Ideally, all margins are carefully documented and if part of the margin is positive or 1 mm or less and amenable to additional resection, it is preferable to undergo another course of surgery than use radiation at this step as the morbidity is often less. If the area of concern cannot be identified or if further surgery will lead to much higher morbidity, then postoperative radiation is advised. The CTV is the initial site of disease plus a centimeter if possible or the entire anatomic site to account for subclinical extension; a dose of 56 to 60 Gray (Gy) is considered sufficient; however, a positive margin requires a higher dose, 66 Gy. As mentioned, minor salivary gland tumors can arise in a myriad of anatomic sites, and not just the hard palate, and represent a more challenging problem in postoperative treatment planning. There is no one-size-fits-all approach to defining a CTV other than for radiographic and clinical documentation of the primary site and thoughtful consideration of potential patterns of subclinical spread.

***Unresectable Salivary Gland Tumors.*** Some salivary gland tumors are unresectable at presentation because of extensive involvement of adjacent structures such as the skull base, pterygoid muscles, or gross involvement of cranial nerves proximal to the neural foramina. It is more common to find a minor salivary unresectable than a major salivary gland. One reason for this is the submucosal nature of the malignant growth in a minor salivary gland, which can be asymptomatic and undetected unlike the presence of a mass in a major salivary gland. The initial clinical symptom is frequently numbness with a classic distribution pattern due to gross involvement of a branch of the trigeminal nerve.

Patients can also have disease that is technically resectable but have a high operative risk due to medical comorbidities, and in these cases, radiation becomes the primary modality,[108,113] often combined with concurrent chemotherapy.[114,115] Even though surgery and radiation therapy is the preferred approach, if surgery is not feasible, these cases are by no means simply palliative. If a sufficiently high dose is given, between 70 and 76 Gy, to gross disease, there is a reasonable chance of long-term control with 5-year actuarial local rates that range from 50% to 70%.[96,97,116,117] An experience using BID radiation was reported by Wang and Goodman with a local control rate of 85% but with relatively short follow-up.[118] It should be noted that these series contained some patients with T1 and T2 disease, a factor that could have contributed to the favorable outcome. The degree of the clinical response 3 to 6 weeks after the completion of

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radiation can have predictive value as to the ultimate outcome.[96] These cases are often complex and should be treated by IMRT with both CT and MRI imaging at the time of planning to assess the full extent of disease that includes bone involvement and perineural/soft tissue extension. As with any treatment plan involving the base of skull, dose constraints need to be placed on the optic nerves, optic chiasm, cochlea, brain stem, and temporal lobe in order to limit the likelihood of collateral damage to these structures. It is unclear whether resection of gross disease at the primary site in the setting of unresectable extension into the skull base is beneficial; it is most likely not, as the additional morbidity of debulking does not lead to a reduction in dose or translate into a higher likelihood for tumor control.

## Particle Therapy

Because of the complexity of cases with gross disease extending into the skull base and the need to deliver a dose in excess of 70 Gy, other radiation modalities have been studied in an attempt to achieve higher control rates than have historically been achievable with photons and to do so with an acceptable level of morbidity. Three different particle beams have been clinically examined, protons, fast neutrons, and carbon ions and a clinical experience exists for each.

Proton radiation for large-field radiation therapy has been studied at Massachusetts General Hospital since 1973, first with a fixed horizontal beam at the Harvard Cyclotron Laboratory and starting in 2001, with a fully rotational, gantry-based delivery system on the Massachusetts General Hospital campus. Unresectable salivary gland tumors were among the first disease sites to be studied and because of the favorable dose distributions attainable with protons and the sharpness of the penumbra, doses of 72 to 76 Gy have safely been delivered to gross disease close to the optic structures and the brain stem.[119] Currently, the practice is to treat complex cases such as these with once-daily proton radiation using conventional fraction sizes of 1.8 to 2.0 Gray Equivalent (an adjustment for an RBE of 1.1) to doses of 72 to 79 GyE. A review of an experience of 23 patients with unresected, incompletely resected ACC treated with this approach showed the actuarial local control rate at 5 years to be 93%, with minimal morbidity.[120] An example of one such case, a patient with ACC of the hard palate and gross involvement of V2, is presented in Figure 25-14.

Fast neutron radiation has been studied at several institutions in the US and Europe; the most extensive experience is at the University of Washington. The advantage of neutrons over photons is an RBE of 3, and according to investigators at University of Washington this can be as high as 8 for ACCs. A randomized trial conducted by the RTOG and MRC was conducted comparing neutron irradiation with conventional photon radiation for unresected salivary gland tumors. As reported by Laramore et al.,[121] there was a significant improvement in local control for the neutron arm of the study, 56% versus 17%. Additional single-institution studies were subsequently conducted at the University of Washington and primarily focused on patients with gross disease, either initially unresectable or with gross residual disease following primary resection. For all histologies, an actuarial 5-year local control rate of 59% was reported, 80% for patients with tumors <4 cm. A large cohort of patients with ACC experienced a similar, 57% local control rate.[122,123] Huber[124] reported a nonrandomized series of 75 patients with ACC treated with either neutrons, photons, or mixed beams where the 5-year actuarial local control rate was 75% for neutrons and 32% for all others. There are disadvantages to neutrons, however. The first is difficulty in collimation due to the lack of positive or negative charge. The second is poor tissue penetration leading to regions of underdosing for deep-seated sites of gross disease, such as the skull base. The third is the RBE of 3; although this can be advantageous to delivering more biologically effective radiation to a tumor, it also produces the same increased effectiveness in the irradiation normal tissue; for example, patients in the Huber study experienced more grade 3 and 4 late complications with neutrons alone (19%) than with mixed (10%) or with photons (4%).

An additional approach, still experimental and available only in a few centers in Europe and Japan is carbon-ion radiation. This particle has the dual properties of carrying a charge, like protons, so they can be effectively steered and collimated. They also have the advantage of a larger RBE than do protons. Preliminary results from a nonrandomized group of patients treated at the University of Heidelberg comparing either photon radiation to mixed photon–carbon-ion radiation showed 2- and 5-year actuarial local control rates of 72% and 25% for photons while the patients treated with mixed beam were 78% and 78%.[125] This regimen, 50 Gy with IMRT followed by a 24 Gy carbon-ion boost, is an ongoing phase II trial.[126] A companion study by the same group is evaluating cetuximab added to this regimen because of the high levels of EGFR seen in ACC and the opportunity for synergy.[127]

## Systemic Treatment of Salivary Gland Cancers

The rarity of salivary gland cancers, plus the fact that the majority of patients will be cured with initial treatment, makes the study of systemic therapy for salivary gland cancers challenging. Most salivary gland cancers are resectable at presentation. Thus, a major question in the field is the role for adjuvant therapy. As detailed above, the outcomes with surgery and adjuvant radiotherapy alone are generally quite favorable. Whether there is any additional benefit from the addition of chemotherapy to radiation has been studied in unresectable salivary gland cancers. Several small retrospective series are available, the largest of which reports on salivary gland cancers arising in the nasopharynx.[114,128–130] These series include patients with multiple primary sites and histologies and report upon various chemoradiotherapy regimens, though platinum-based approaches are most common. One additional series describes outcomes of salivary gland cancer patients receiving adjuvant IMRT with or without chemotherapy.[106] Adverse features in this series included histology, positive margins, neural or PNI, lymphovascular invasion, lymph node involvement, and extracapsular nodal extension. Overall, the reported toxicities of chemoradiotherapy are consistent with that expected, and the rates of locoregional control and OS are encouraging. A cautionary note should, however, be raised when considering chemoradiotherapy as a substitute for surgery, given the experience reported by Katori and Tsukuda on 17 salivary gland cancer patients treated with chemoradiotherapy followed by resection in the case of residual disease.[131] Although most patients experienced some tumor shrinkage, only 4 patients (24%) had a complete response. Definitive statements regarding the role of concurrent chemoradiotherapy in salivary gland cancers cannot be made without more prospective data; however, the data that are available indicate that concurrent chemoradiotherapy for salivary gland cancers is feasible and may be appropriate in select high-risk postoperative or unresectable SGC patients.

## Treatment of Recurrent or Metastatic Disease

Although the majority of patients with salivary gland cancer will have potentially curable disease at presentation, a significant percentage of patients will experience recurrence, particularly those with stage III or IV disease.[5,132,133] Distant metastasis is more common than locoregional recurrence, with lung, bone, and liver being the most frequent sites of disease. Metastases in low-grade tumors are rare, whereas metastases from ACC, salivary duct

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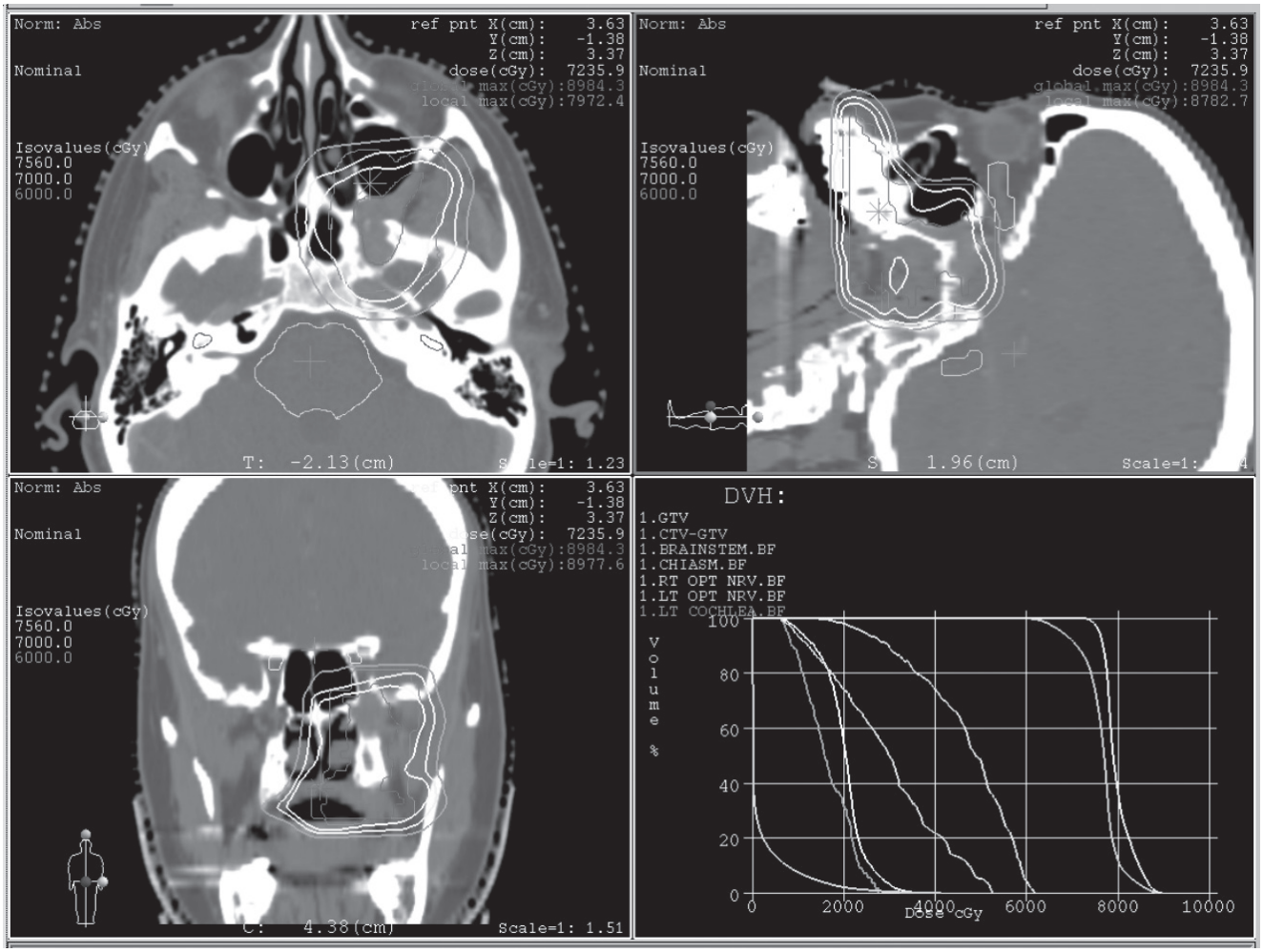



**FIGURE 25-14.** Definitive proton therapy for an unresectable adenoid cystic carcinoma of the hard palate with gross involvement of V2. Note the restriction of the irradiated volume to the defined CTV and relative sparing of the optic structures and the brain stem. There is no fall off or compromise of dose in the deepest part of the skull base. This patient is NED 6 years after 75.6 GyE to the GTV. (See color insert.)

carcinoma, high- or intermediate-grade MECs, ACs, and carcinoma ex-pleomorphic adenomas are more common.[85,134–138] Within ACCs, solid-type tumors are more likely to metastasize. Other risk factors include advanced stage, close or involved margins, vascular invasion, and histologic grade.[5–7,132–137] Fortunately, metastases from ACC tend to be asymptomatic and grow slowly over many years. The prognosis for other metastatic salivary gland cancers is less favorable.

A number of clinical trials investigating systemic therapies in recurrent/metastatic salivary gland cancer have been conducted over the last three decades; however, there are limitations to this body of work. The studies are generally small, noncomparator studies, and most have enrolled patients with varying baseline characteristics, including histologic subtype and lines of prior therapies. This heterogeneity makes comparison between studies impossible. In addition, the methodologies used, particularly in the older studies, have not been uniformly consistent with current standards.

One regimen for recurrent/metastatic salivary gland cancer that has been investigated in the largest number of patients is cyclophosphamide, doxorubicin, and cisplatin (CAP).[139–145] Overall response rates (ORRs) range from 27% to 100%, though the data must be interpreted with caution as most are from older studies with few patients. The largest series by Licitra et al. included 27 patients with various histologies, including ACC, salivary duct carcinoma, and adenocarcinoma.[144] Six patients (27%) achieved a partial response, with a median duration of 7 months. Responses were seen in multiple histologies, including ACC. The median OS was 21 months. Other combination chemotherapy regimens from older series include cisplatin; 5FU plus an anthracycline; cyclophosphamide plus doxorubicinr; and cisplatin, 5FU, cyclophosphamide, and doxorubicin.[146–149] The overall response and survival rates were similar to those of CAP; however, more toxicity was generally encountered with the more intensive regimens.

Single-agent chemotherapy has also been of interest. As combination chemotherapy is not necessarily superior to monotherapy, the toxicity of combination chemotherapy will be greater. Cisplatin has been studied in the phase II setting, showing an ORR of 16% and OS of 14 months.[150] More recently, single-agent vinorelbine has been compared with combined vinorelbine plus cisplatin in a randomized phase II study.[151] Thirty-six patients with recurrent/metastatic salivary gland cancer were enrolled. Responses were seen in patients with ACC and adenocarcinoma. ORRs were, respectively, 20% and 44%. The survival curves showed a trend of improved survival with the combination, but

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this was not statistically significant. The two most recent trials investigating cytotoxic chemotherapy in salivary gland cancer were phase II trials of paclitaxel run by the Eastern Cooperative Oncology Group (ECOG) and gemcitabine plus cisplatin run by the National Cancer Institute of Canada (NCIC).[152,153] The ECOG study showed an ORR of 26% in patients with mucopepidermoid or adenocarcinoma, but no responses were seen in 14 patients with ACC. Median OS was 13 months. The NCIC study showed an ORR of 24% to gemcitabine plus cisplatin, and responses occurred in all histologic subtypes. OS was 14 months. Taken together, these data indicate that several cytotoxic chemotherapies, including single-agent and doublet regimens, have modest activity in recurrent/metastatic salivary gland cancer, though there is no one clear best regimen.

Several phase II investigations of cytotoxic chemotherapy have limited enrollment to ACC. Given the unique, typically protracted course of ACC, it makes sense to study ACC as a separate entity.[154–157] Mitoxantrone, epirubicin, and gemcitabine have been studied as single agents. Mitoxantrone showed an ORR of 6% and 12%, respectively, in two phase II studies, the larger of which included 32 patients.[154,155] In this study, median OS was 18 months. Epirubicin showed similar activity, whereas gemcitabine yielded no objective response.[156,157] Combination regimens that have been studied in ACC include 5FU, cyclophosphamide plus vincristine; cisplatin plus 5FU; and epirubicin, cisplatin plus 5FU.[158–160] 5FU, cyclophosphamide plus vincristine yielded two responses in eight patients with recurrent/metastatic disease.[158] Cisplatin plus 5FU yielded no responses in 11 patients.[159] The most recent study investigating epirubicin, cisplatin plus 5FU was small, enrolling only eight patients, one of which experienced a partial response to treatment. In this group, OS was 27 months.[160] Thus, data on cytotoxic chemotherapy for ACC are sparse and activity is modest at best. For this reason, enrollment on a clinical trial for patients with ACC in need of treatment is currently preferred over the administration of cytotoxic chemotherapy, when available.[60,161]

## Molecular Targeting of Salivary Gland Malignancies

The diversity of salivary gland cancers is now an even more critical factor in treatment decisions, as molecularly targeted therapies are becoming available for the treatment of recurrent/metastatic disease. To date, evidence of overexpression of EGFR, human epidermal growth factor receptor 2 (HER2), c-kit, and vascular endothelial growth factor receptor (VEGFR) in various salivary gland cancers has led to the study of newer targeted agents in recurrent/metastatic disease.

EGFR has been found to have intermediate to high expression in the majority of salivary gland cancers, across all subtypes.[162] Three EGFR targeted therapies have made it to phase II study: gefitinib, an EGFR tyrosine kinase inhibitor; cetuximab, a monoclonal antibody directed against EGFR; and lapatinib, a dual EGFR, and HER2 tyrosine kinase inhibitor.[163–165] All three studies enrolled ACC and non-ACC patients. There were no responses seen.

HER2 overexpression by immunohistochemistry has been described in several salivary gland cancer subtypes, most commonly in salivary duct carcinoma.[164] When examined by fluorescence *in situ* hybridization, gene amplification was found in 10 of 10 salivary duct carcinomas, 2 of 3 adenocarcinomas, and 1 of 4 poorly differentiated carcinomas.[164] Trastuzumab, the monoclonal antibody directed against HER2, has been investigated in a phase II study of salivary gland cancers overexpressing HER2 by IHC.[166] The study closed early after the majority of tumors screened did not overexpress HER2; however, 14 patients were enrolled and treated. Of these, only one patient with an MEC experienced a response. There have since been several case reports since detailing results of trastuzumab plus cytotoxic chemotherapy in various subtypes with HER2 overexpression, some of whom did experience durable responses to treatment.[167–171] Thus, trastuzumab as a single agent does not appear as promising as the drug in combination with chemotherapy, though more definitive trials are needed.

Identification of c-kit expression in a single adnexal ACC, as well as the success of targeting this proto-oncogene in leukemias and gastrointestinal stromal tumors with the c-kit inhibitor, imantinib, led to larger studies of c-kit expression in ACCs. KIT protein expression was found in 90% of ACCs.[172] KIT expression has been found in several other salivary gland cancers subtypes, as well.[173] Six small phase II trials of imantinib in ACC have been conducted, two of which limited treatment to ACCs expressing KIT.[174–179] Of the 64 patients enrolled across these studies, only 2 responses were reported. An additional study investigated imantinib as a single agent first, then added cisplatin after 2 months of imantinib alone.[180] In the 28 patients enrolled, there were no responses to imantinib alone; however, 2 responses were seen after cisplatin was added. The lackluster activity of imantinib most likely reflects the fact that KIT is not an oncologic driver in ACCs, consistent with the absence of c-kit mutations in this disease.[181]

Lastly, efforts targeting angiogenesis have been studied in ACCs, in part due to high expression of VEGF and other angiogenesis factors found in ACCs.[182] Sunitinib, an oral multikinase inhibitor of VEFGR and c-kit, has been investigated in a phase II study of ACC.[183] Fourteen patients were enrolled, but no responses were seen. The proteosome inhibitor, bortezomib, has also been studied in ACC, given the idea that inhibiting proteosome degradation of key regulatory proteins involved in regulating the cell cycle and angiogenesis may have anticancer efficacy.[184] Twenty-five patients were enrolled in a phase II study. There were no responses to single-agent bortezomib; however, one patient out of 10 given bortezomib plus doxorubicin experienced a partial response.

## Ongoing Trials/Future Efforts

Although clinical trials of targeted therapies in salivary gland cancers have not yet led to major progress in the treatment of recurrent/metastatic disease, several clinical trials of new drugs are underway. Current studies are primarily enrolling patients with ACC and include phase II studies of the histone deacetylase inhibitor, vorinostat, the c-kit inhibitor, dasatinib, and the fibroblast growth factor receptor and VEGFR inhibitor, dovitnib.

Moreover, recent findings regarding the molecular underpinnings of salivary gland cancers offer new opportunities for more specific targeted therapies.[162,185] One example is the recent identification of the *MYB-NFIB* translocation common in ACCs, which leads to overexpression of Myb, as well as downstream mediators of apoptosis, cell cycle control, and growth. This provides new targets for rationale drug development for the management of ACC.[186–188] Beyond ACCs, salivary duct carcinomas are another histologic subtype in which recent advances are expected to translate into more effective therapies. Salivary duct carcinomas harbor frequent molecular abnormalities, including mutations in PIK3CA and BRAF as well as the overexpression of HER2 and androgen receptor, all potentially targetable with drugs that are currently available or in development.[162,189–191] More discoveries identifying critical oncogenic pathways that drive specific salivary gland cancers are expected. As the future unfolds, the new challenges will emerge. It is most likely that molecularly driven therapies will offer the greatest benefit, but demonstrating this in these uncommon, histologically and molecularly diverse cancers will require new approaches in clinical trial design.

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In conclusion, the study of systemic therapy for salivary gland cancers has been primarily confined to recurrent/metastatic disease. In addition to the small number of patients that develop recurrent/metastatic disease, investigations of systemic therapy are further limited by the heterogeneity in histology and trial design. Cytotoxic chemotherapies have modest activity in recurrent/metastatic salivary gland cancers. Recent advances in the understanding of the biology of various salivary gland cancers has, however, brought us closer to developing effective systemic therapies. If these advances can be coupled with broad cooperation across multiple institutions to study new agents in well-designed clinical trials, real progress in the systemic treatment of salivary gland cancers will be within reach.

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# PART B:
# Radiologic Imaging Concerns

Jeffrey A. Bennett

MRI is generally preferred over CT for the imaging of salivary gland neoplasms. This is because of its ability to better characterize the internal morphology of the tumor, its boundaries, and to determine perineural spread. For example, benign mixed tumors often appear very bright on T2-weighted images with variable enhancement (Fig. 25-15). However, imaging cannot confidently predict whether the lesion is benign or malignant.[1] Features that suggest a benign mass are sharp margins of the lesion and no lymphadenopathy or signs of perineural spread. A malignant lesion is suggested by indistinct margins, enhancement, and edema of the facial nerve suggesting perineural invasion, and lymphadenopathy (Fig. 25-16). Nevertheless, many benign and malignant salivary gland tumors will appear to be well circumscribed both on CT and MRI.[2] Suggested protocols are given in Figures 25-17 and 25-18.

Imaging is often performed to plan an approach for biopsy, as therapy is different depending on whether the mass is a primary salivary gland tumor, or lymphoma, or other metastasis such as squamous cell cancer from a skin primary site. Fine-needle aspiration has proven to have reliable sensitivity and specificity for salivary gland neoplasms.[3] Ultrasound guidance is usually excellent for more superficial parotid and submandibular gland lesions. CT is often better for biopsy of lesions in the deep lobe of the parotid, as a transfacial approach (Fig. 25-19) can often be used to avoid crossing the facial nerve. In most cases, a core biopsy can be safely obtained when FNA is not diagnostic and is often helpful in the workup of lymphomas or sarcomas. Core-needle biopsies can be obtained either with ultrasound guidance or CT guidance.[4]

MRI is particularly useful for evaluating the presence of perineural spread. This is very common in certain types of neoplasm such as adenoid cystic carcinoma. Intravenous contrast is essential for making this diagnosis, and the use of fat suppression often makes perineural spread more apparent. The axial plane is excellent for demonstrating perineural spread of cancer along the auriculotemporal nerve, which is a connection between the facial nerve and mandibular nerve (Fig. 25-20). The coronal plane is better for demonstrating tumor spread along the descending facial nerve canal (Fig. 25-21).

In the recent past, surface coils were very useful to obtain high-resolution MR images of the superficial parotid gland. The prevalence of multichannel head coils and 3T magnets has made surface coils unnecessary.

It has been found that dynamic contrast-enhanced MRI may be useful in the identification of Warthin tumor as this tumor demonstrates rapid enhancement and rapid attenuation.[5] Presumably, this enhancement pattern could be detected with dynamic contrast-enhanced CT as well. Other investigators have found the detection of low-signal areas in a parotid tumor on short tau inversion recovery and T2-weighted sequences, as well as low apparent diffusion coefficient values on diffusion-weighted imaging suggested Warthin tumor.[6,7]

Posttreatment imaging for tumor recurrence is challenging because of the difficulty in differentiating scar from recurrent tumor.

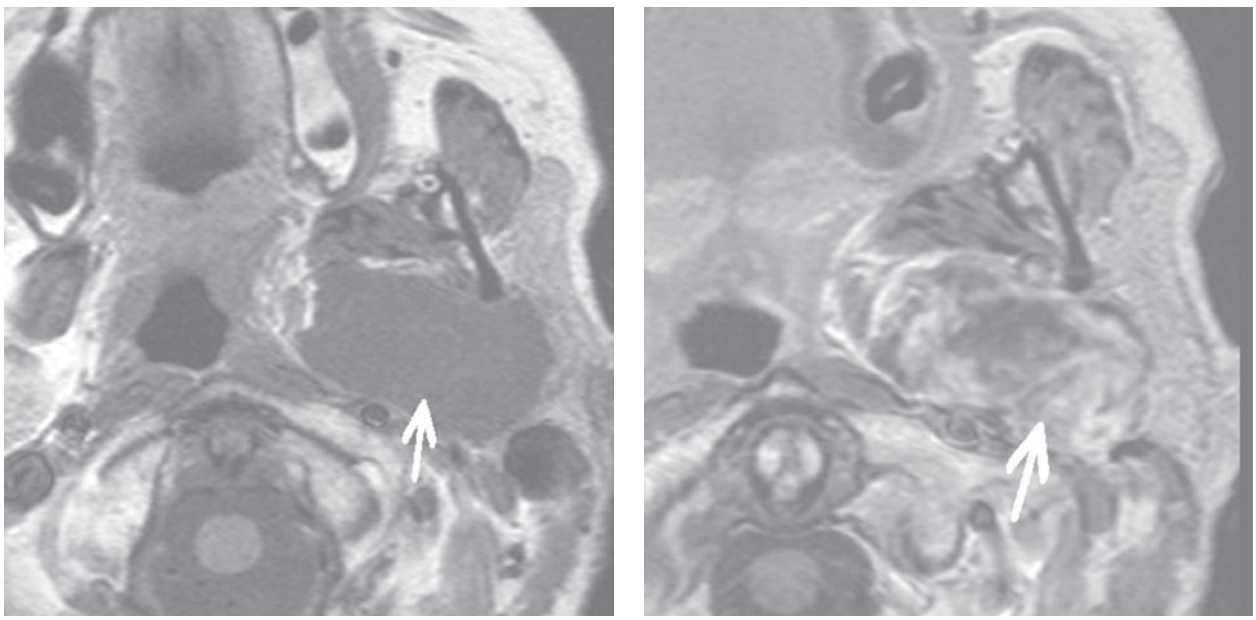
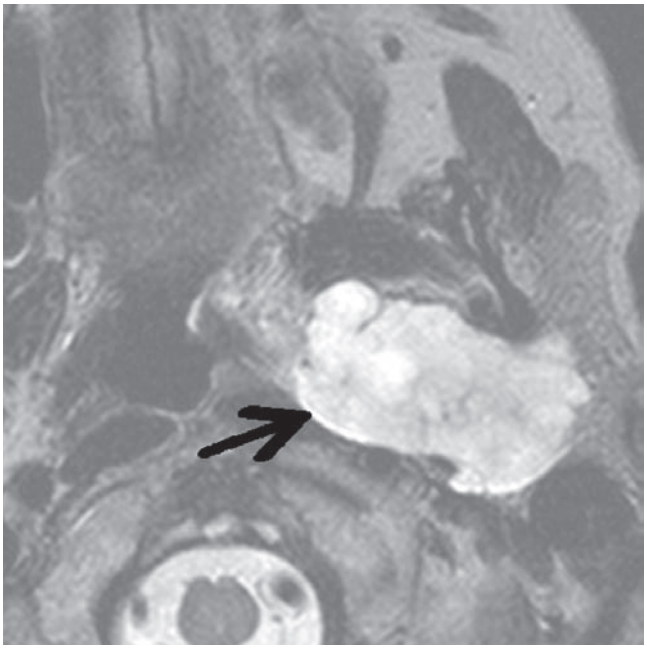



**FIGURE 25-15.** Axial noncontrast T1-weighted MRI **(A)**, axial postcontrast T1-weighted MRI **(B)**, and axial T2-weighted MRI **(C)** show a large mass (*arrows*) in the deep lobe of the left parotid gland. The mass demonstrates homogeneous low signal on T1-weighted images, is very bright on T2-weighted images, and shows irregular patchy enhancement. This tumor was determined on pathology to be a benign mixed tumor.

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C

**FIGURE 25-15.** *Continued*

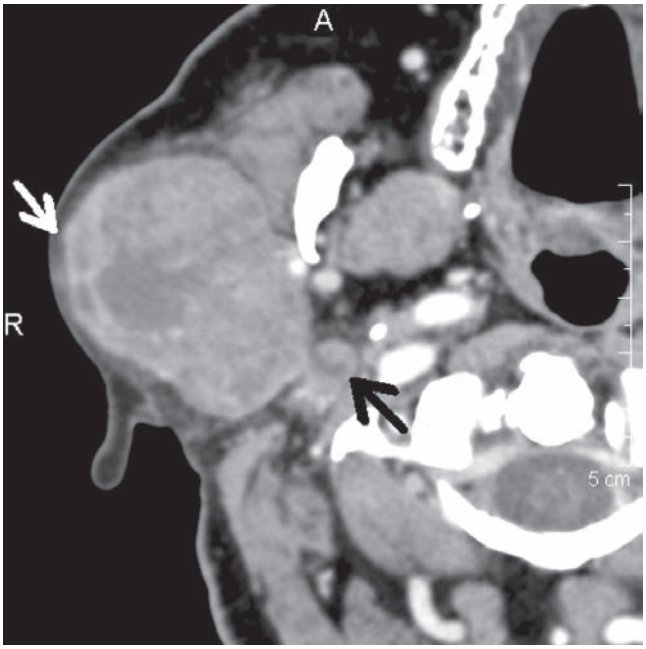
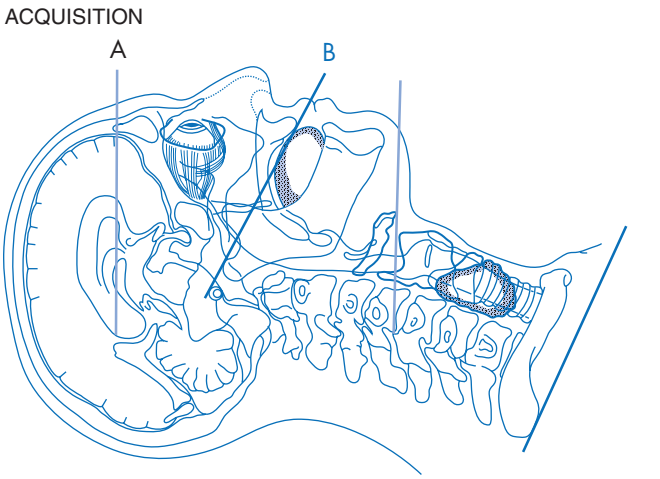



**FIGURE 25-16.** Axial postcontrast CT scan shows a large superficial lobe parotid mass with aggressive features including an indistinct margin (*white arrow*) and associated intraparotid positive lymph nodes (*black arrow*). At pathology this tumor was a mucoepidermoid carcinoma.



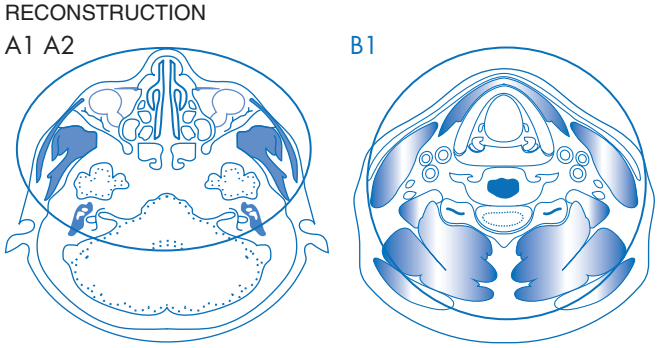




**FIGURE 25-17.** Protocol for CT of the maxillofacial region and neck with intravenous contrast.

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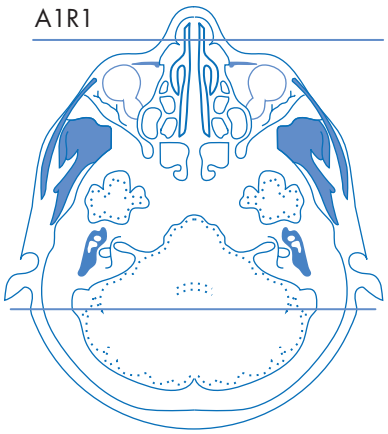
| | | |
|---|---|---|
| | Patient position | Supine<br>IOML perpendicular to tabletop |
| | Contrast | 100 mL adult |
| | Injection rate | 1 mL/sec; 60 sec delay |
| | Respiration | Quiet, NO swallowing |
| | Volume acquisition specs | Appropriate to achieve images as specified in following reconstruction tables.<br>Head FOV. |
| A | Begin | Above frontal sinus |
| | End | Through mandible |
| B | Begin | Mid oral cavity |
| | End | Apices |

| | | |
|---|---|---|
| A1 | Algorithm | Soft tissue |
| | Thickness | 1.0 mm |
| | Spacing | 0.8 mm |
| | F.O.V. | Approx. 170–190 |

| | | |
|---|---|---|
| A2 | Algorithm | Bone |
| | Thickness | 1.0 mm |
| | Spacing | 0.8 mm |
| | F.O.V. | Approx. 170–190 |
| B1 | Algorithm | Soft tissue |
| | Thickness | 2.5 mm |
| | Spacing | 2.5 mm |
| | F.O.V. | Approx. 160–180 |

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REFORMATION




| | | |
|---|---|---|
| A1R1 | Algorithm | Soft tissue |
| | Thickness | 1.0 mm |
| | Spacing | 1.0 mm |
| | F.O.V. | Approx. 180 |
| | Plane | Coronal |
| | Begin | Frontal sinus |
| | End | Through IAC |

**FIGURE 25-17.** *Continued*

| Acquisition | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Plane | Sagittal | Axial | Axial | Axial | Axial | Coronal |
| Sequence | T1 | T1 | T2-FSE (FS) | T1 | T1 (FS) | T1 |
| Contrast | None | None | None | Gd | Gd | Gd |
| SLT/SP | 4/0 mm | 3/0 mm | 3/0 mm | 3/0 mm | 3/0 mm | 3/0 mm |
| FOV | 16 cm | 16 cm | 16 cm | 16 cm | 16 cm | 16 cm |

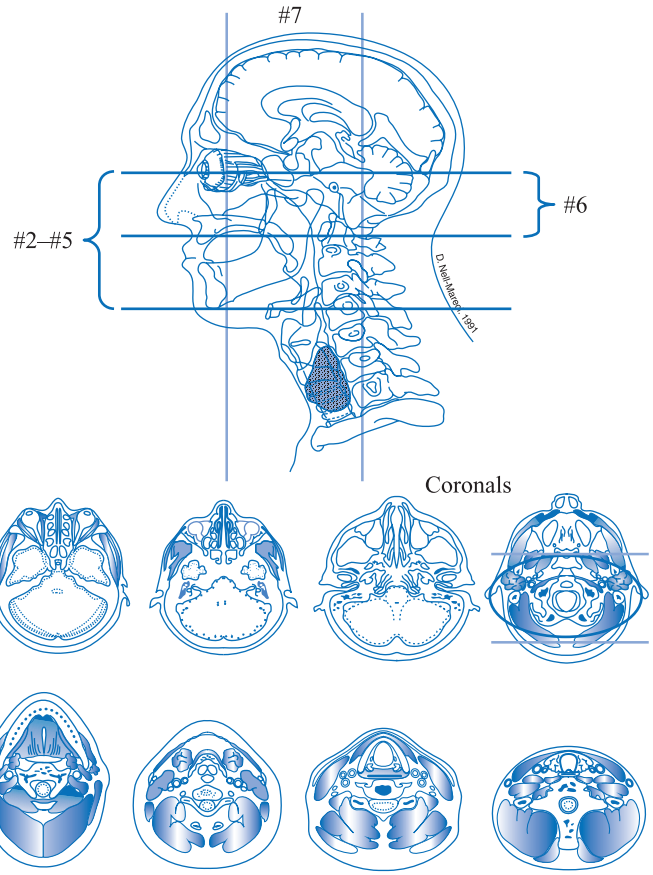



**FIGURE 25-18.** Protocol for MRI of the parotid with intravenous contrast.

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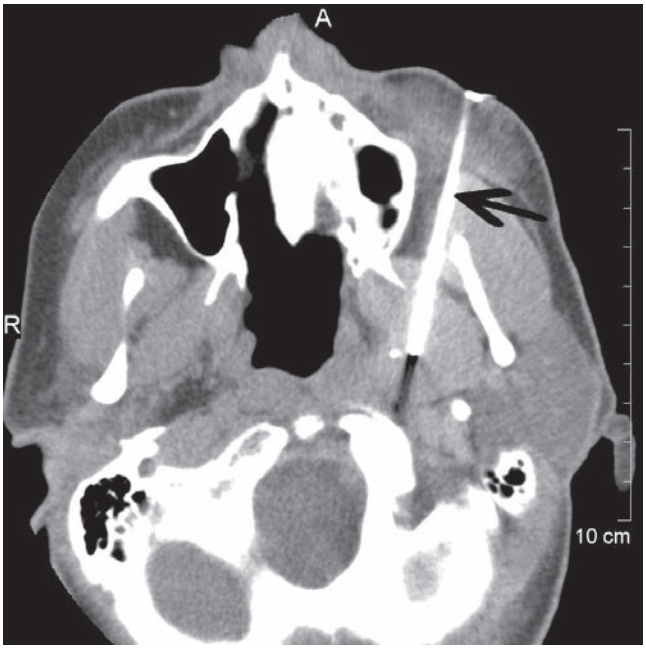



**FIGURE 25-19.** Axial CT scan shows a transfacial approach for biopsy of a deep-lobe parotid mass. The needle in this case is a 16G guide needle (*arrow*) through which fine-needle aspirates or core biopsy can be performed using a coaxial technique. The transfacial approach is a useful safe approach to deep-lobe parotid lesions, which avoids potential damage to the facial nerve.

T2-weighted images are useful in those cases where tumor, such as benign mixed tumor, is high signal, differentiating it from scar which is dark (Fig. 25-22). FDG-PET normally shows uptake in the salivary glands. Nevertheless, increased FDG uptake has been demonstrated in both benign and malignant salivary gland neoplasms and thus may be helpful in cases of recurrent cancer (Fig. 25-23).[8–11] Image-guided biopsy is often necessary when recurrent tumor is suspected.

Submandibular gland lesions are infrequently imaged, as they usually present early and are easily palpated. Large parotid tail lesions can sometimes be mistaken for submandibular lesions because they can extend down into the submandibular space (Fig. 25-24). Lesions of the sublingual gland are often imaged to see if there is involvement of the lingual neurovascular bundle (Fig. 25-25).

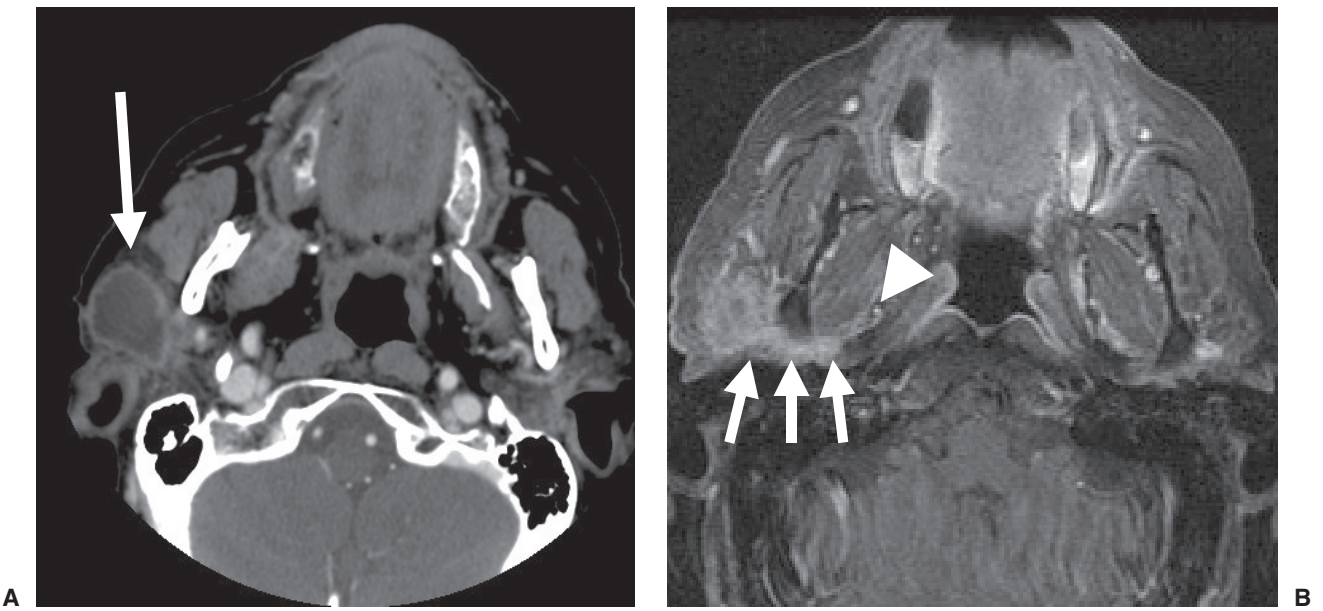



**FIGURE 25-20.** Perineural spread of parotid metastases along the auriculotemporal nerve. **A:** Contrast-enhanced computed tomography (CT) shows a necrotic tumor involving the right parotid gland. **B:** Contrast-enhanced T1-weighted (T1 W) sequence with fat suppression shows the enhancing tumor extending posteriomedially behind the posterior portion of the mandible (*small arrows*) toward V3 (*arrowhead*).

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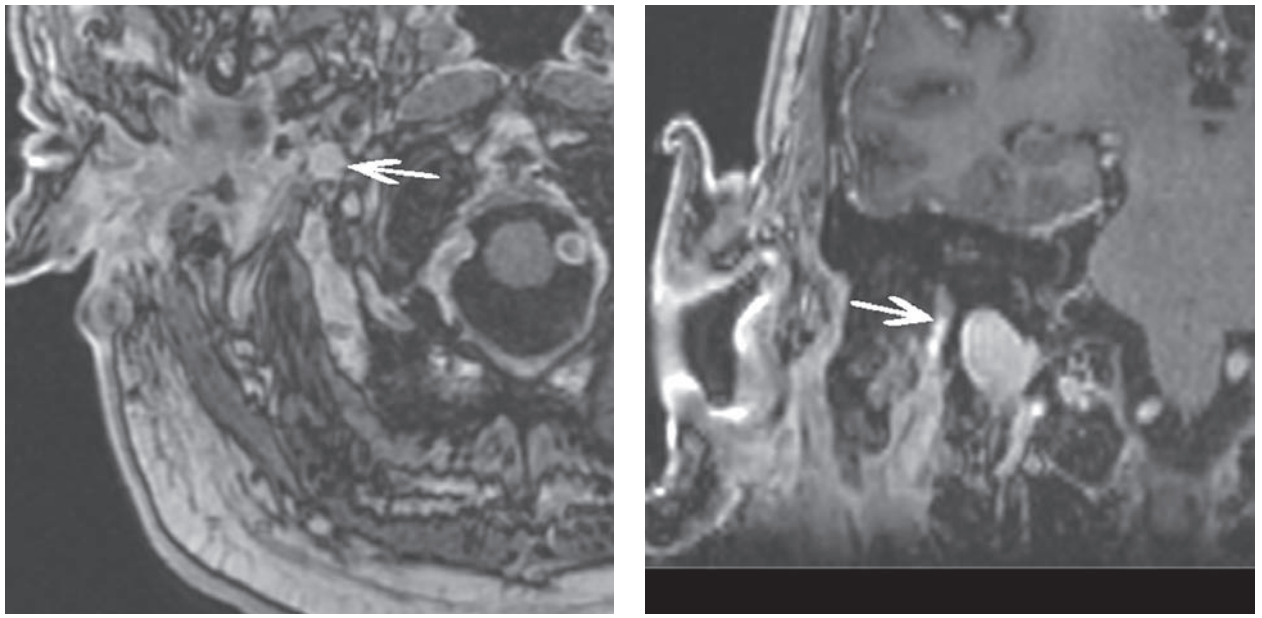


**FIGURE 25-21.** Axial **(A)** and coronal **(B)** postcontrast T1-weighted thin section gradient MR images show a deep-lobe parotid mass with retrograde perineural spread along the facial nerve. Enhancing tumor is seen at the stylomastoid foramen (*arrow in* **A**) with extension up the descending facial nerve canal (*arrow in* **B**).

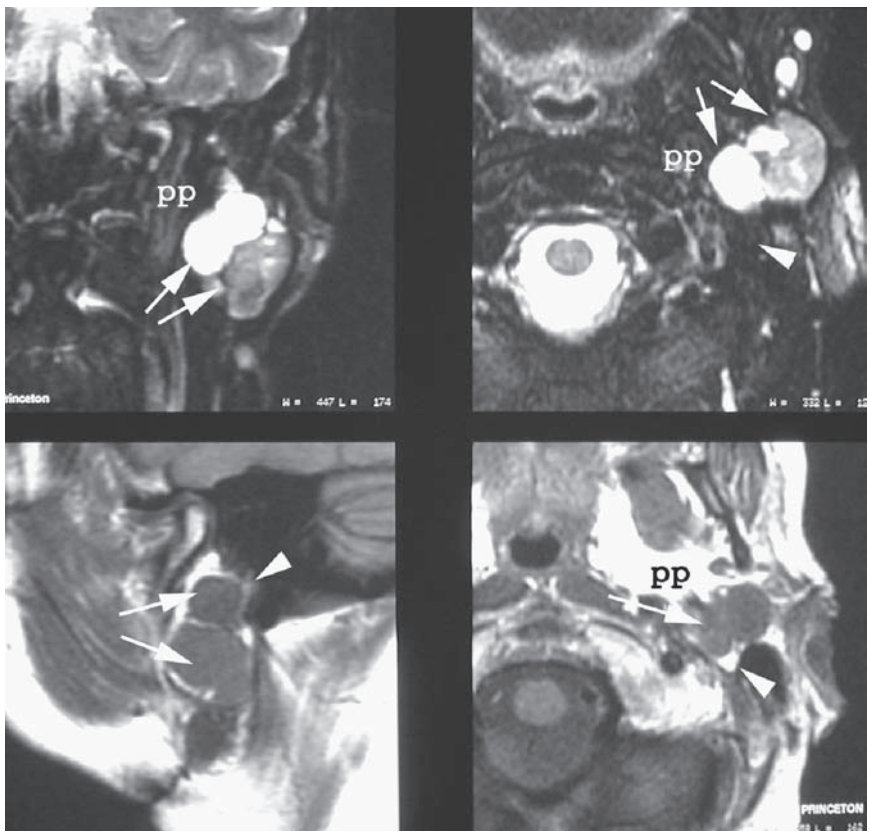



**FIGURE 25-22.** Recurrent pleomorphic adenoma, deep-lobe recurrence. Magnetic resonance imaging collage, clockwise from **top left**: coronal T2, axial T2, axial T1, and sagittal T1 images show the deep-lobe recurrence (*white arrows*) involving the parapharyngeal space (*pp*), approaching, but not infiltrating the stylomastoid foramen (*white arrowhead*).

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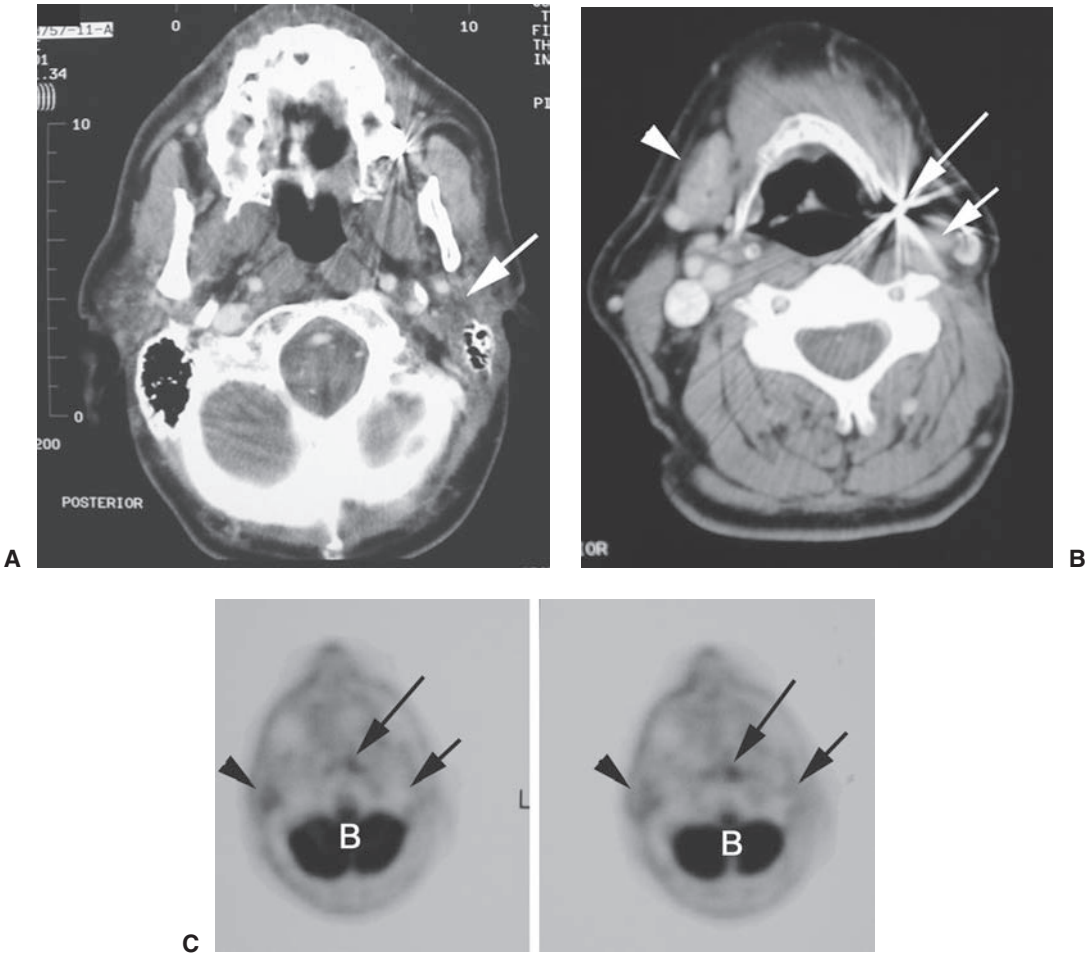
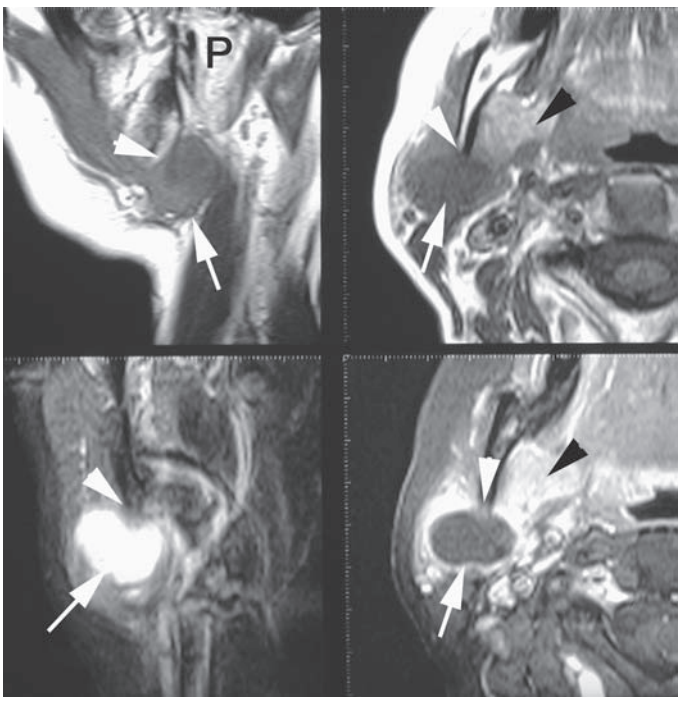



**FIGURE 25-23.** Fluorodeoxyglucose-positron emission tomography (FDG-PET) salivary follow-up. Enhanced axial computed tomographic images through **(A)** parotid bed show operative changes status post enucleation of the left parotid mass (*white arrow*) and **(B)** level II of the neck show poor visualization of the left neck dissection (*short arrow*) due to artifact from operative clip (*long arrow*). Normal submandibular gland (*arrowhead*). **C:** Axial FDG-PET images through the parotid beds show absent metabolic activity in operative bed (*short arrows*), physiologic activity in remaining right parotid bed (*arrowhead*), and asymmetric muscle activity (*long arrow*).

**FIGURE 25-24.** Tale of the tail. Magnetic resonance imaging collage, from **top left**, includes sagittal T1, axial T1, contrast axial T1, and coronal T2. The tail of parotid mass (*white arrows*) appears remote from the parotid gland (*P*) and pushes down against the submandibular gland (*black arrowhead*) contacting the edge of the mandibular ramus (*white arrowheads*).






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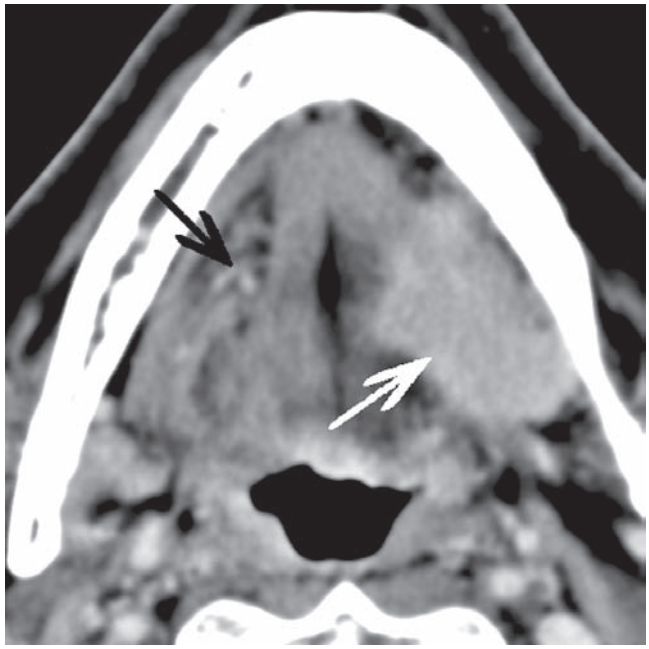


**FIGURE 25-25.** Axial contrast-enhanced CT scan shows a high-grade mucoepidermoid carcinoma of the left sublingual gland (*white arrow*) which has markedly indistinct margins. The tumor encases the distal lingual neurovascular bundle. The normal distal lingual neurovascular bundle on the right is shown for comparison (*black arrow*).

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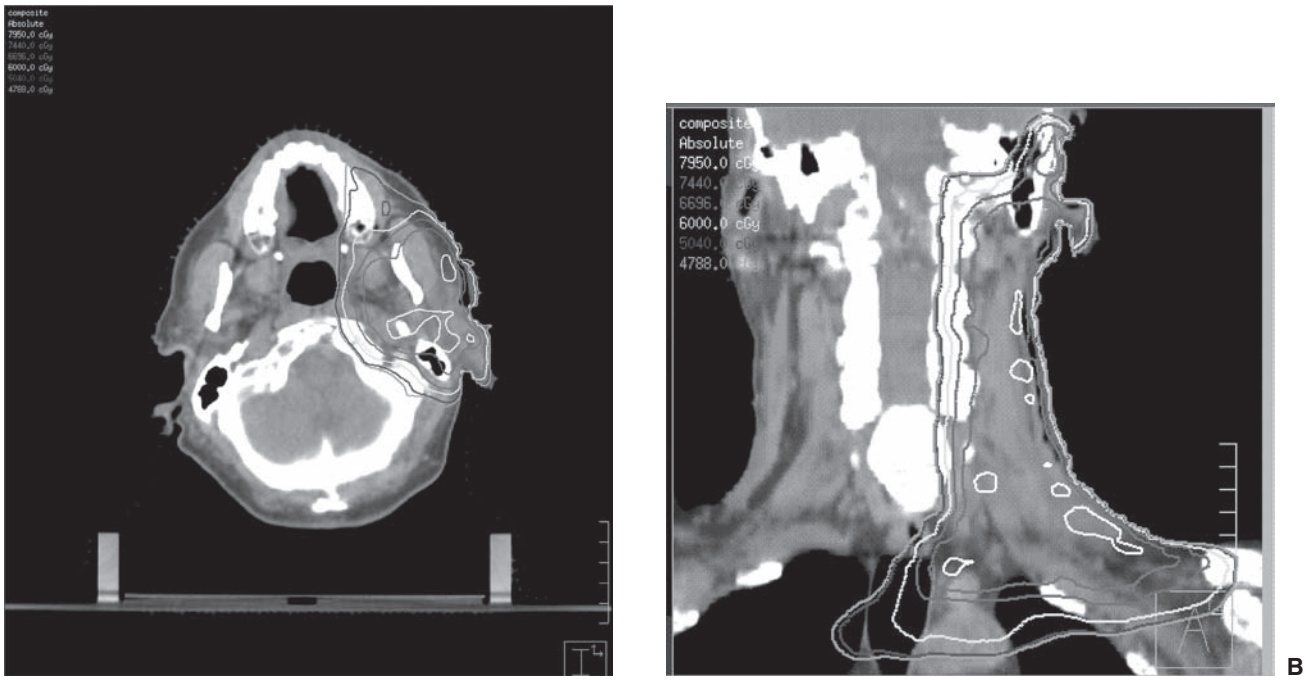

# PART C:
# Radiation Therapy Technique

William M. Mendenhall

The irradiation techniques employed for salivary gland tumors varies with the primary site, histology, and whether the patient is being treated with postoperative irradiation or definitive radiotherapy (RT). Surgery is the preferred initial step in essentially all patients, unless the tumor is incompletely resectable, resection that would be associated with an unacceptable cosmetic or functional deficit, the patient is medically inoperable, and/or the patient refuses surgery.

Patients with pleomorphic adenoma are treated with surgery alone, unless the margins are positive, and/or the tumor is recurrent, and is multifocal. Postoperative RT is unemployed in the latter circumstances; the dose-fractionation schedules are the same as those employed for carcinomas.[1] Low-grade carcinomas, such as low-grade mucoepidermoid carcinomas, are usually treated with surgery alone. Postoperative RT is indicated for positive or close (<1–2 mm) margins. High-grade carcinomas are treated with surgery and postoperative RT. High-grade carcinomas include high-grade mucoepidermoid carcinomas, poorly differentiated adenocarcinomas, salivary duct carcinomas, carcinoma ex-pleomorphic adenomas, and lymphoepitheliomas.[2] Patients with adenoid cystic carcinomas usually are treated with surgery and postoperative RT.[3] An exception would be the patient with a grade I $T_1N_0$ lesion with widely negative margins. Patients with adenoid cystic carcinomas undergo magnetic resonance imaging

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A B

**Figure 25-26.** The patient underwent a left parotidectomy and neck dissection for a $T_3N_{2B}$ high-grade mucoepidermoid carcinoma of the left parotid gland. Although a gross total dissection was achieved, margins were microscopically positive. Postoperative IMRT was used to treat the left parotid bed and neck to 74.4 Gy in 62 twice-daily fractions. **A:** Axial dose distribution. **B:** Coronal dose distribution. (See color insert.)

prior to surgery to detect gross perineural invasion. The regional lymph nodes are electively irradiated in patients with high-grade lesions and a clinically negative neck. The ipsilateral neck is irradiated for lateralized primary sites, such as the parotid. Both sides of the neck are treated if the lesion arises in a middle structure, such as the base of tongue.[4]

Parotid carcinomas are treated with a wedge-pair technique; an anterior low neck field is matched to the parotid fields at the level of the thyroid notch if the neck is to be irradiated. Alternatively, intensity-modulated radiation therapy (IMRT) may be employed to reduce the dose to the ipsilateral temporal lobe and cerebellum (Fig. 25-26). Submandibular gland neoplasms may be treated with an ipsilateral mixed beam composed of photons and high-energy electrons. Intensity-modulated radiation therapy may be employed, particularly if there is perineural invasion and it is necessary to irradiate the "at risk" nerves to the skull base. Patients with skull base involvement due to perineural invasion may benefit from treatment with proton beam RT to reduce the dose to adjacent structures, such as the optic nerves and the brainstem.[5,6] The techniques used to irradiate minor salivary gland tumors varies with the site and is similar to those described for squamous cell carcinomas, depending on the risk of regional node involvement and perineural invasion.

Patients are treated at 2 Gy per once-daily fraction to 50 Gy for electively undissected nodal basins, 60 Gy for negative margins, 66 Gy for positive margins, and 70 Gy for gross disease. Alternatively, patients with positive margins or gross disease are treated to 74.4 Gy in 62 twice-daily fractions.

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CHAPTER 26

# Primary and Recurrent Disease of the Lateral Skull Base

## PART A:
## General Principles and Management

Esther X. Vivas, Andrew A. McCall, Paul A. Gardner, and Carl H. Snyderman

### INTRODUCTION, NATURAL HISTORY, PATHOLOGY, AND PATHOGENESIS

Lateral skull base malignancy is rare. The lateral skull base is an ambiguous term that denotes the area lateral to the central skull base and is generally congruous with the middle cranial fossa and its adjacent areas. It includes the infratemporal skull base and extends from the lateral cavernous sinus to the temporal bone. It encompasses the temporal bone, petrous segment of the internal carotid artery (ICA), the Eustachian tube, and branches of the trigeminal nerve. The lateral skull base can be approached from multiple directions, each approach requiring a different understanding of complex anatomical relationships.

Carcinoma of the temporal bone, including the external auditory canal (EAC), middle ear, and mastoid, is thought to affect approximately one to six people per million in the United States.[1–3] The true incidence of disease, however, is unknown and varies depending on the publication cited. This problem is compounded by absence of a centralized data-collecting system for temporal bone carcinoma, which is available for other malignancies such as through the Surveillance Epidemiology and Surveillance Results (SEER) database. The SEER database, maintained by the National Cancer Institute, collects information on incidence, prevalence, and survival from specific geographic areas of the US population and reports cancer mortality. Unfortunately, it does not support a category for lateral skull base or temporal bone carcinoma. In addition, there is no standardized staging system for temporal bone cancer. Neither the American Joint Committee on Cancer (AJCC) nor the International Union Against Cancer (IUAC) have published staging guidelines. Currently, the modified University of Pittsburgh staging system (2000) is the most accepted and validated system in use.[3–6]

To date, there is no large prospective study on the treatment and outcomes of lateral skull base malignancies. The bulk of peer-reviewed literature consists of retrospective analyses. As a result, information on incidence and prevalence is dominated by reports of independent institutional experiences. Due to these limitations and the inherent rarity of the disease, some larger studies have reported their experience using pooled data from various tumor histology subtypes.[5]

Overall, primary cancer of the temporal bone is thought to account for <0.2% of all tumors in the head and neck.[7] Squamous cell carcinoma (SCCA) is the most common primary tumor type to affect the temporal bone. In following with the overall incidence of SCCA of the upper aerodigestive tract, temporal bone malignancies affect more men than women. Certain reports, however, have shown an approximate even gender distribution.[8] Caucasians are much more affected than are Blacks and Hispanics. Primary temporal bone cancer typically arises during the fifth and sixth decades of life.

Primary neoplasms of the lateral skull base include cancers that arise from the bone and cartilaginous tissues of the skull base. The lateral skull base is secondarily involved by neoplasms that arise in skin appendages, the parotid glands, the paranasal sinuses, and the nasopharynx and spread along natural corridor tissue planes. SCCA is by far the most common malignancy to affect the temporal bone, though basal cell carcinoma, adenocarcinoma, adenoid cystic carcinoma, and melanoma have all been reported as possible tumor types in adults.[5] Etiology of the disease is not entirely known. For SCCA, correlations with exposure to ultraviolet radiation, frostbite, prior radiation therapy, and even chronic infection have been reported in the literature.[3] Aside from SCCA, reports vary on the next most frequent tumor type, with adenoid cystic carcinoma, adenocarcinoma, or basal cell carcinoma coming in as second depending on the particular study.[3,9–11] In the pediatric population, rhabdomyosarcoma is a rare, but aggressive malignancy that can be encountered in the temporal bone. Basal cell carcinoma is the most common cancer of the pinna and as such is often misleadingly included in reports of primary lateral skull base malignancies. Much more common than primary malignancies of the temporal bone are secondary malignancies from locoregional spread. Upper aerodigestive tract,



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parotid gland, and cutaneous cancers comprise the bulk of locoregional disease.

Primary bone and mesenchymal tumors can also affect the lateral skull base. Chordomas are malignant tumors that are thought to arise from embryologic remnants of the notochord. Outside the spine, the clivus is the most common site. These tumors typically present as midline tumors, but can extend laterally to involve the temporal bone and occipital condyles. Chondrosarcomas of the skull base typically arise in the region of the petroclival synchondrosis and have a more parasagittal location than do chordomas. Patterns of growth are similar with concentric destruction of bone and lateral extension to the temporal bone, occipital condyles, and craniocervical junction.

Metastatic disease can involve the temporal bone and lateral skull base. Spread to the temporal bone can occur hematogenously or through meningeal carcinomatosis, which pathognomonically presents with multiple cranial neuropathies. Primary tumor sites that metastasize to the temporal bone can be from the breast, lungs, kidney, stomach, and prostate.[12] When metastatic disease involves the temporal bone, widespread hematogenous metastases to other body sites are often present, and prognosis is poor.

## RELEVANT ANATOMY AND PATTERNS OF SPREAD

The lateral skull base is a complex anatomic structure that houses important neurovascular structures. The temporal bone articulates with the sphenoid, parietal, occipital, and zygomatic bones. It has four main anatomic components: the squamous, mastoid, petrous, and tympanic parts. It has a pyramidal shape and contributes to the lateral skull base. The squamous part forms the lateral wall of the middle cranial fossa. The mastoid portion houses the mastoid air cell system and vertical segment of the facial nerve to its exit point from the skull base at the stylomastoid foramen. The petrous temporal bone contains the petrous portion of the carotid artery, the otic capsule, petrosal nerves, and the internal auditory canal. The tympanic part houses the bony component of the EAC and at its anterior edge forms the tympanosquamous suture line. The posterior edge of the tympanic ring terminates at the tympanomastoid suture line. The medial two-thirds of the EAC is composed of bone and the lateral third is cartilaginous. The bony-cartilaginous junction is the narrowest segment of the EAC. This junction is an important structure as it serves as a potential pathway for spread of malignant disease. Other potential sites of tumor spread beyond the confines of the temporal bone, including the foramen of Huschke and the fissures of Santorini. The foramen of Huschke refers to a defect in the anterior inferior tympanic ring that usually closes by 5 years of age, but persists in 7% of adults.[13] It is a structure that opens into the infratemporal fossa due to incomplete ossification of the anterior bony canal and can allow for tumor extension into the deep lobe of the parotid. The fissures of Santorini are found within the cartilaginous canal and can also allow tumor spread into the parotid gland and periparotid tissues. Nasopharyngeal cancer may spread along the Eustachian tube to gain access to the temporal bone and floor of the middle cranial fossa. Figure 26-1 provides a more comprehensive review of potential avenues for tumor spread. Neoplasms that have a predilection for perineural growth such as adenoid cystic carcinoma and SCCA may track along branches of the facial nerve along its course and extend intratemporally or intracranially. Similarly, perineural invasion by tumor can track along branches of the trigeminal nerve for long distances to reach the middle cranial fossa through Meckel cave or by connections with the facial nerve.

The course of the ICA is a key landmark that defines different surgical approaches to the lateral skull base. The parapharyngeal ICA enters the carotid canal medial to the glenoid

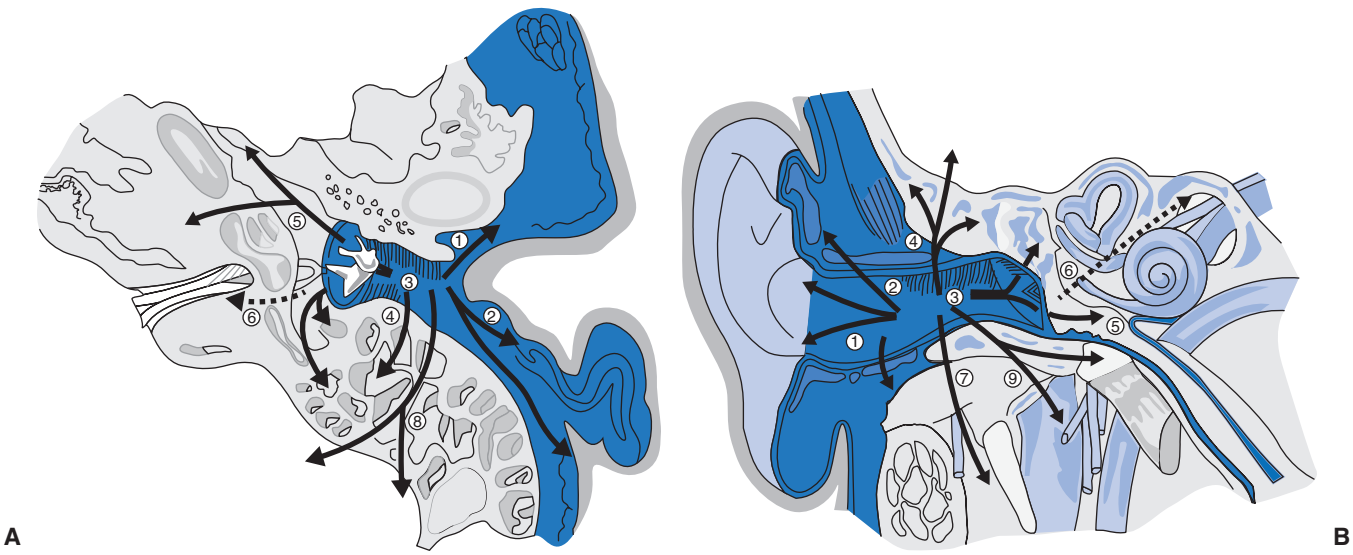



**FIGURE 26-1.** Axial **(A)** and coronal **(B)** temporal bone anatomy, identifying pathways of the spread of cancer. Cancer can spread (1) anteriorly through the cartilaginous ear canal into the parotid gland; (2) through the concha into the postauricular sulcus; (3) through the tympanic membrane into the middle ear; (4) posteriorly into the mastoid; (5) into the anterior mesotympanum to the carotid artery and the Eustachian tube; (6) into the inner ear through the round window or otic capsule; (7) along the facial nerve into the infratemporal fossa; (8) through the mastoid, posterior fossa dura, and sigmoid sinus; and (9) beneath the skull base to the jugular fossa, carotid artery, and lower cranial nerves.

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fossa and courses horizontally (in an anteromedial direction) as the petrous segment. The petrous segment of the ICA is situated deep to the Eustachian tube, which runs obliquely across the ICA. Thin bone separates the ICA from the Eustachian tube, measuring about 2 mm at the level of the foramen ovale.[14] The lateral pterygoid plate, foramen ovale, foramen spinosum, and spine of the sphenoid are oriented in a line that is superficial to the Eustachian tube. These are useful landmarks for lateral skull base approaches to the petrous ICA. Medially, the petrous segment continues as the paraclival (vertical) segment at foramen lacerum. The pterygoid canal transmitting the Vidian nerve and sometimes artery is a useful landmark for identifying this second genu of the ICA. The Vidian artery is present in a minority of patients, but the Vidian nerve reliably courses superolaterally over the petrous ICA to join the greater superficial petrosal nerve (GSPN) and deep petrosal nerve. Meckel cave and the trigeminal ganglion are bounded by the petrous and paraclival segments of the ICA, the temporal lobe, and the lateral cavernous sinus (Fig. 26-2). The sixth cranial nerve courses superolaterally behind the midportion of the vertical paraclival ICA to Dorello

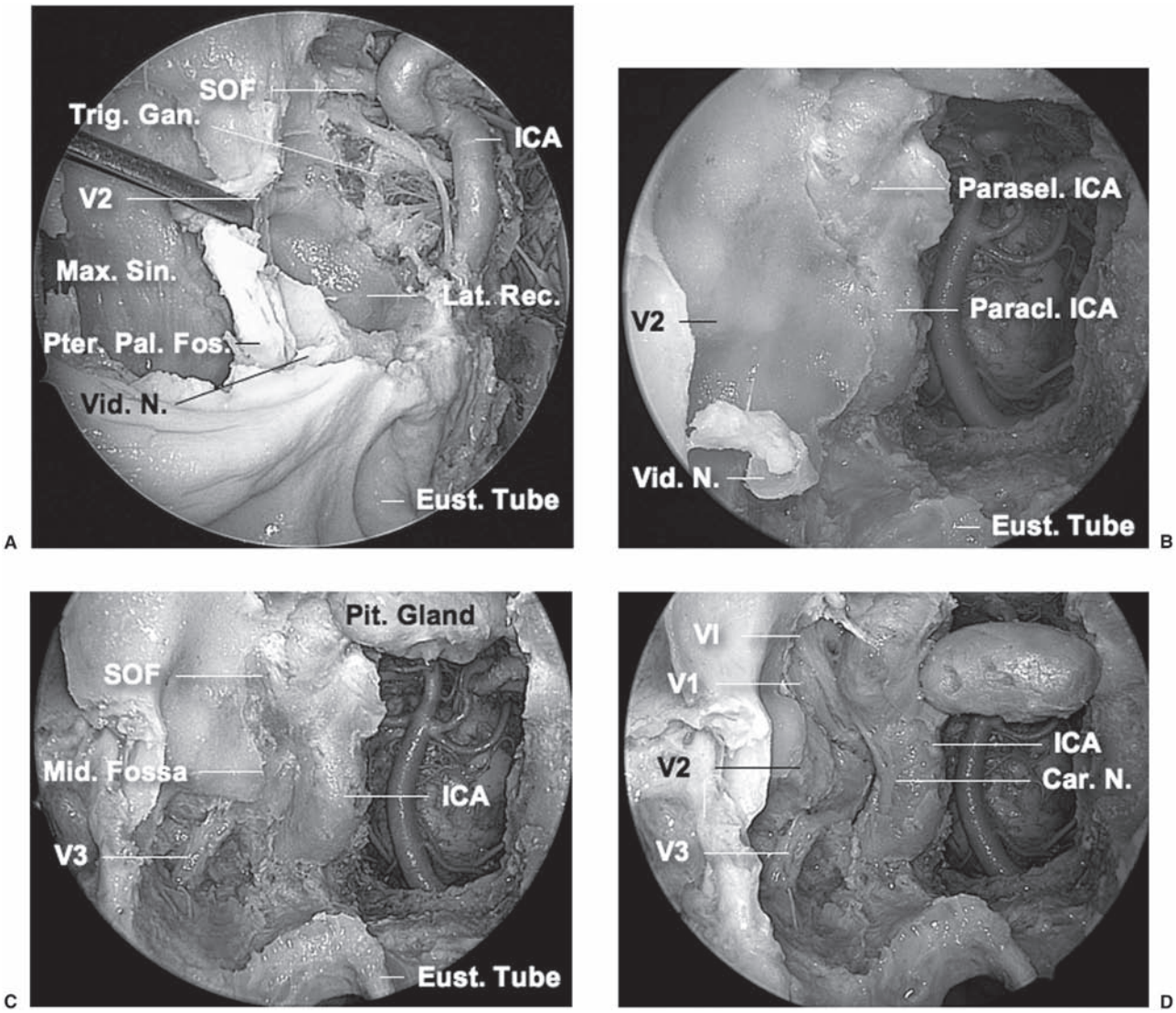



**FIGURE 26-2.** A right-sided Meckel cave approach. **A:** A general overview of the endonasal approach to Meckel cave. **B:** Stepwise approach. **C:** Drilling now continues lateral to the paraclival carotid artery, exposing the dura of the middle fossa. **D:** The dura of the middle fossa has been opened to expose the three branches of the trigeminal nerve. The abducens nerve runs medial to the ophthalmic nerve (V1) from the cavernous sinus to the superior orbital fissure. **E:** Further drilling has been performed at the anterolateral triangle of the middle fossa (between V2 and V3), whereas the osseus covering of the anteromedial triangle has not been removed. **F:** Close-up view of Meckel cave. The dura that lies over the trigeminal ganglion has been opened to expose the medial aspect of Meckel cave. Ant, anterior; Car, carotid; Cav, cavernous; Eust, Eustachian tube; For, foramen; Fos, fossa; Gan, ganglion; ICA, internal carotid artery; Lac, lacerum; Lat, lateral; Max, maxillary; Med, medial; Mid, middle; N, nerve; Pal, palatine; Paracl, paraclival; Parasel, parasellar; Pit, pituitary; Pter, pterygoid; Sin, sinus; SOF, superior orbital fissure; Tr, triangle; Trig, trigeminal; Vid, Vidian.

*Source:* Reprinted with permission from Prevedello DM, Kassam AB, Carrau RL, et al. Suprapetrous approach to Meckel cave and temporal fossa. In: Stamm AC, ed. *Transnasal Endoscopic Skull Base and Brain Surgery* (pp. 327–331). New York, NY: Thieme; 2011.

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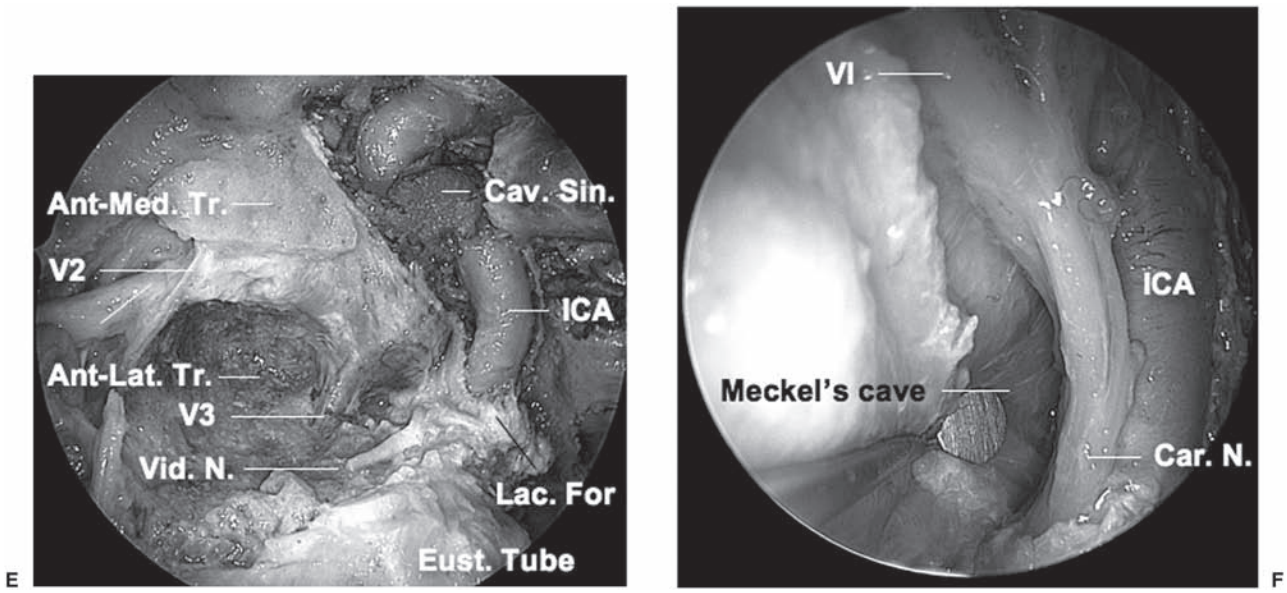



**FIGURE 26-2.** *Continued*

canal on the superior surface of the temporal bone. It traverses the lateral cavernous sinus just superior to Meckel cave.

The cavernous sinus surrounds the sella and encompasses the cavernous segment of the ICA, the nerves to the extraocular muscles, and the first division of the trigeminal nerve. The nerves are all lateral to the ICA and run in the lateral wall of the cavernous sinus before entering the superior orbital fissure. From superior to inferior, the order of the cranial nerves within the lateral wall of the cavernous sinus is III, IV, and V1. The sixth cranial nerve lies medial to the first division of the trigeminal nerve (V1) and runs obliquely through the cavernous sinus lateral to the ICA after exiting Dorello canal. The cavernous sinus can be divided into four compartments based on the course of the ICA: medial, lateral, postero-superior, and antero-inferior. Tumors of the lateral skull base are more likely to involve the lateral (perineural invasion of head and neck malignancy) and antero-inferior (chordomas, chondrosarcomas) compartments.

## CLINICAL PRESENTATION

The clinical presentation of incident lateral skull base malignancies can be elusive. It can masquerade as a chronic otitis externa or suppurative otitis media. As a result, the diagnosis of temporal bone malignancies is often delayed until the disease is at an advanced stage. An average 6-month delay in diagnosis has been reported.[15] Gidley et al.[5] reported a series of 124 patients with SCCA of the temporal bone, of which 71 had incident disease. Within this group, 62% of the patients presented with otorrhea, followed by otalgia (52%), hearing loss (43%), and facial nerve dysfunction (15.5%). Additionally, a mass can be frequently seen in the EAC on examination.[3] The presence of persistent, deep-seated, unrelenting pain despite adequate treatment for chronic otitis media is an ominous sign and should raise a care provider index of suspicion. This type of pain must be discriminated from other nonmalignant causes; deep otalgia, along with coexistent otorrhea, and abducens nerve palsy is seen with petrous apicitis (Gradenigo syndrome) and deep ear pain that is exacerbated with swallowing or face pain can be seen with Eagle syndrome or geniculate neuralgia, respectively. Spontaneous bloody otorrhea is an unusual presentation of infectious ear disease and as such raises concern for the presence of a more threatening cause. Trismus and pain are ominous signs and indicate tumor extension into the pterygoids and masticator space. Temporal bone carcinoma initially presenting as malignant otitis externa (MOE) has been reported, thus underscoring the importance of early biopsy in suspicious cases.[16] Temporal bone involvement by malignancies of salivary gland origin can present with tumors developing insidiously and relatively asymptomatically, with 75% manifesting with a painless mass and only 6% to 13% manifesting with facial nerve palsy.[17] Chondromatous skull base lesions, chordoma, and chondrosarcoma commonly present with headache and diplopia secondary to abducens nerve palsy. Inferolateral extension can result in dysarthria, hoarseness, dysphagia, and aspiration from involvement of the lower cranial nerves.

Metastatic disease to the temporal bone commonly occurs in the setting of more widespread metastatic disease. Temporal bone metastatic lesions can remain clinically silent when tumor is located within the petrous temporal bone because the otic capsule is relatively resistant to neoplastic invasion. If tumor involves the internal auditory canal, or if the otic capsule is breached, symptoms of hearing loss, dizziness, or facial paralysis may ensue.

Perineural extension to the lateral skull base typically involves branches of the trigeminal nerve and may be associated with facial hypesthesia, or pain, or weakness of mastication (Fig. 26-3). If tumor gains access to the lateral cavernous sinus, diplopia secondary to loss of function of extraocular muscles may develop. Most commonly, decreased abduction from a sixth nerve palsy is observed, but ptosis, pupillary dilation, and restriction of gaze in other directions may result from a third nerve palsy.

## DIAGNOSTIC EVALUATION AND CLINICAL STAGING

As with any malignancy, a thorough physical examination should be the initial phase in the diagnosis and staging algorithm. A complete head and neck examination is performed with microscopy, assessment of cranial nerve function, and palpation of the parotid gland and cervical lymph nodes. The examiner should also look and test for any temporal lobe or cerebellar signs,

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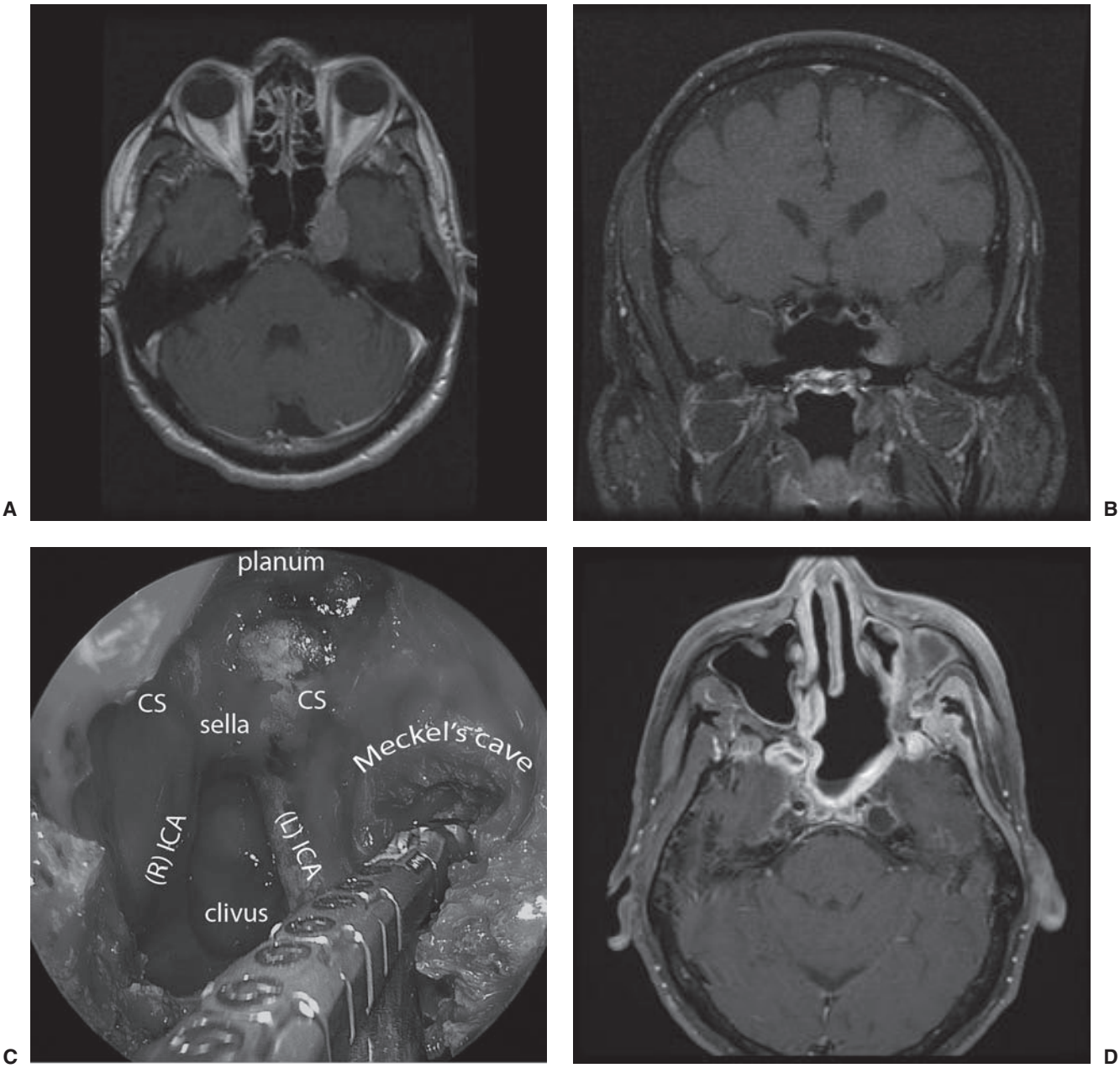
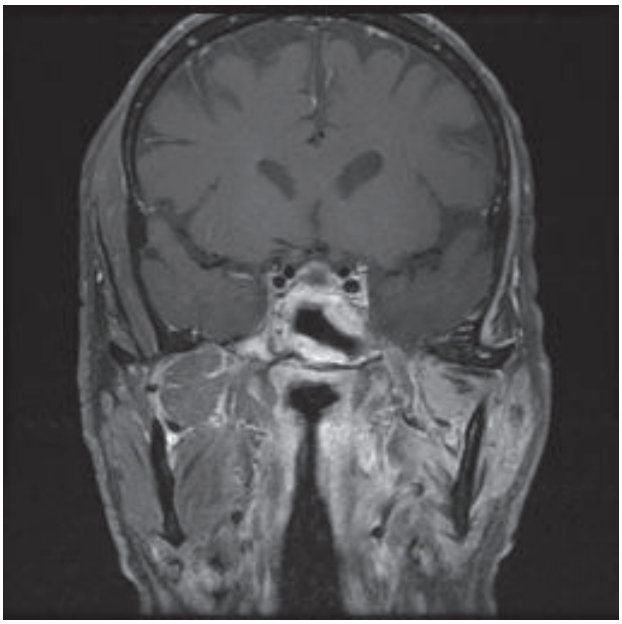



**FIGURE 26-3.** A 59-year-old man with new onset paresthesias in a left V1 and V2 distribution. Preoperative imaging revealed extensive perineural spread of neoplasm along the course of V2 and proximal V3 with tumor extending along the greater palatine nerve, within the pterygopalatine in fossa, and extending along the foramen rotundum and infraorbital nerve and within the Vidian canal. **A:** Preoperative T1 axial scan with gadolinium. **B:** Preoperative T1 coronal scan with gadolinium. Superiorly, tumor extended to the level of the inferior orbital fissure and inferiorly to the level of the foramen ovale. Extensive bulky tumor was noted along the lateral margin of the left cavernous sinus and filling the Meckel cave, with tumor bulging into the prepontine cistern. Endonasal biopsy revealed adenoid cystic carcinoma. The patient underwent a left Caldwell-Luc approach for excision of the infraorbital nerve and a left endoscopic transpterygoid approach to the middle cranial fossa for excision of the carcinoma. Reconstruction consisted of an abdominal fat graft in the Meckel cave and a septal mucosal flap. **C:** Intraoperative image during endoscopic endonasal transpytergoid surgery for resection of adenoid cystic carcinoma with trigeminal nerve involvement in the left Meckel cave. The bone overlying the Meckel cave has been removed, the dura has been incised, and the tumor has been identified and partially resected. Identification of the anatomical landmarks, as specified in the image, is important to proceed with safe tumor resection. **D:** Postoperative T1 axial scan with gadolinium. **E:** Postoperative T1 coronal scan with gadolinium. The postoperative changes reflect debulking of tumor with postsurgical expansion of the left Meckel cave. There is extensive abnormal enhancement within the muscles of mastication on the left most compatible with denervation atrophy. CS, cavernous sinus; ICA, internal carotid artery.

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E

**FIGURE 26-3.** *Continued*

which can be indicative of very advanced disease. New onset seizures likely represent intracranial spread of cancer. A complete audiometric evaluation is required. This provides an objective assessment of the functional status of the middle and inner ear, which is useful during surgical planning and preoperative patient counseling. Conductive losses can be seen with lesions in the external or middle ear, whereas anacusis, tinnitus, and vertigo suggest inner ear involvement.

Preoperative histologic confirmation of cancer should be obtained whenever possible. However, aside from lesions found in the EAC, access to tissue for biopsy and diagnosis is limited by the anatomic constraints and relative inaccessibility of the lateral skull base. As a result, radiographic imaging has become an integral part of the diagnosis and staging of these malignancies. CT and MRI provide complementary information for most skull base neoplasms. Arriaga et al. determined that preoperative CT can accurately diagnose the pathologic extent of tumor, but not without limitations.[18] Some limitations include differentiating fluid and inflamed mucosa from tumor in the middle ear or mastoid, as well as distinguishing inflammation from tumor in the absence of adjacent bony erosion.

Fine-cut CT images are used to evaluate the presence and extent of bone erosion, whereas MRI is more apt for evaluation of the soft tissues. CT images should be obtained in axial and coronal cuts with and without contrast. Iodinated contrast is used to evaluate tumor extent, nodal metastasis, carotid involvement, patency of the sigmoid, transverse, petrosal, and cavernous sinuses and to assess for intracranial extension. It is important to evaluate all lymph nodes in the drainage echelon of the lateral skull base, which include the facial, parotid, and jugulodigastric chains. Noncontrast bone window cuts demonstrate the presence of bony erosion or remodeling, two findings reflective of tumor invasion. MRI is optimal for the evaluation of soft tissue invasion, particularly perineural spread. High-resolution T1 and T2 images in axial and coronal planes are essential. T1 sequences should be obtained with and without gadolinium. T1 images are used for spatial relationships and bone marrow involvement, whereas T2 images can help to define differential diagnosis, especially of hyperintense, heterogeneous tumors such as chordomas or chondrosarcomas. Postgadolinium T1-weighted images with fat saturation can help to delineate tumors that enhance brightly and are used for evaluation of perineural involvement, which can manifest as foraminal widening or enhancement, replacement of fat density, or increased signal intensity.[17]

It is important to carefully evaluate known pathways for tumor spread on pretreatment imaging as overlooked tumor spread can result in treatment failure. For example, when assessing the medial extent of disease, special attention is paid to the course of the facial nerve. Proximal invasion can lead to involvement of the geniculate ganglion and greater superficial petrosal nerve, whereas distal spread toward the stylomastoid foramen can involve the digastric and sternocleidomastoid musculature, parotid, or the adjacent skull base. Perineural spread can also occur via cranial nerves V and VIII. As described earlier, the fissures of Santorini and foramen of Huschke are routes to the parotid gland and infratemporal fossa, respectively. Extension via the petrotympanic fissure can reach the carotid canal, carotid artery, and Eustachian tube.

Posterior involvement can affect the sigmoid sinus or jugular bulb and can be seen as sinus or venous compression, occlusion, or thrombosis. CT and MRI are used in conjunction to evaluate for intracranial extension via perineural spread, transdural invasion, and bone marrow invasion. Metastasis from a primary lateral skull base malignancy is rare, but if suspected, a metastatic evaluation consisting of chest radiography and liver function testing is adequate. Positron emission tomography (PET)/CT scanning has made identification of metastasis more accurate. Positron emission tomography imaging can be used as part of an initial metastatic work up and can also be used in posttreatment surveillance for recurrent or persistent disease. It is limited, however, in its ability to differentiate inflammatory and malignant disease. When diagnostic imaging suggests involvement of the carotid artery, preoperative angiography with a balloon test occlusion (BTO) should be considered in preparation for possible ligation during tumor extirpation.[17] Consideration should also be given to embolization when intraoperative hemorrhage is a concern.

Chondromatous neoplasms such as chordoma and chondrosarcoma can be difficult to differentiate radiographically. Both demonstrate bone destruction on CT with varying amounts of calcification. They are heterogeneous on MRI and are characteristically bright on T2-weighted images due to increased water content. The apparent origin, sagittal versus parasagittal, can provide helpful clues as to the suspected origin of the tumor.

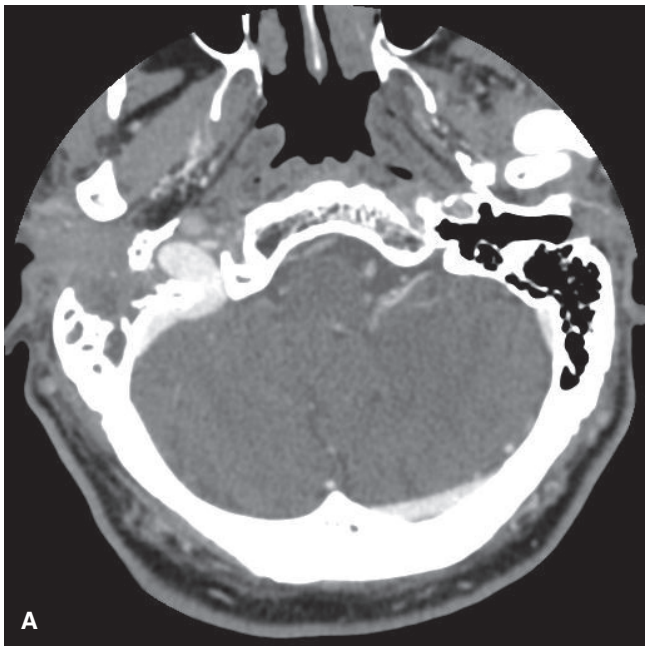
Although there have been multiple templates proposed and used over the years to stage primary temporal bone malignancies, the University of Pittsburgh Staging System is the most widely used and accepted. It was proposed initially by Arriaga et al. in 1990[17] and then modified by Moody et al. in 2000.[6] In the modified version, facial palsy was recognized to be a poor prognostic factor and as such placed the patient in T4 status as opposed to T3. Multiple studies have validated the original and modified staging system.[4,5,10] In 2010, Higgins and Moody-Antonio performed a pooled data survival analysis where they demonstrated that preoperative facial palsy carried a significantly worse survival prognosis and therefore validated classification into a T4 status that was reflected in the modified 2000 staging system.[4]

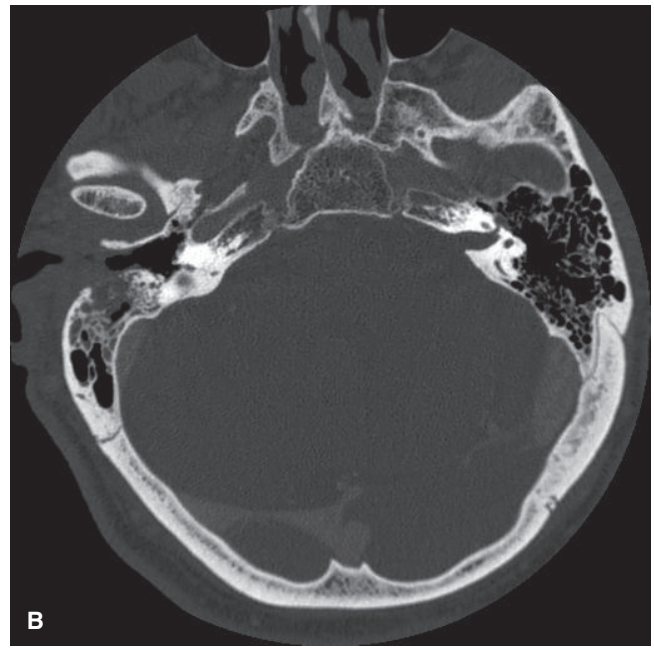
The staging system relies on preoperative CT radiography and uses bone erosion, location of the tumor, soft tissue extension, and facial paralysis as the major factors in determining T status and survival prognosis as outlined in Table 26.1. T1 tumors are those limited to the EAC without bony erosion or soft tissue extension. T2 tumors are also limited to the EAC, but with some bony erosion or for radiographic evidence of soft tissue extension (<0.5 cm). T3 tumors are those with full-thickness bony canal erosion and limited (<0.5 cm) soft tissue extension or if the tumor involves the middle ear and/or mastoid (Fig. 26-4). T4 status is allocated to anyone presenting with facial paralysis.

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**TABLE 26.1 University of Pittsburgh Staging System for Squamous Cell Carcinoma of the Temporal Bone**

| Status | Description |
|---|---|
| T status | |
| T1 | Tumor limited to the external auditory canal without bony erosion or evidence of soft tissue extension |
| T2 | Tumor with limited external auditory canal bony erosion (not full thickness) or radiographic finding consistent with limited (<0.5 cm) soft tissue involvement |
| T3 | Tumor eroding the osseous external auditory canal (full thickness) with limited (<0.5 cm) soft tissue involvement, or tumor involving middle ear and/or mastoid |
| T4 | Tumor eroding the cochlear, petrous apex, medial wall of the middle ear, carotid canal, jugular foramen or dura, or with extensive (>0.5 cm) soft tissue involvement; patients presenting with facial paralysis |
| N status | Lymph node involvement is a poor prognostic sign and places the patient in an advanced stage (i.e., T1 N1 [stage III] and T2, 3, 4, N1 [stage IV]) |
| M status | M1 disease is stage IV and is considered a very poor prognostic sign |



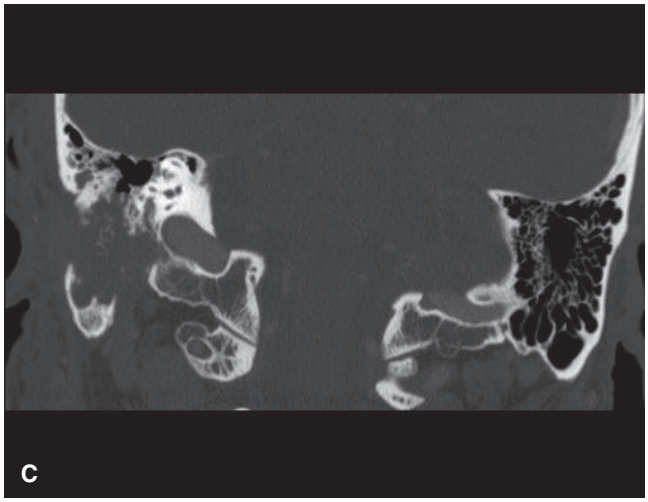




**FIGURE 26-4. A–C:** Axial and coronal CT images in bone and soft tissue windows from a patient with squamous cell carcinoma of the external auditory canal with bony canal erosion on the right. This represents a T3 lesion under the Pittsburgh staging system.

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T4 tumors can alternatively involve the cochlea, petrous apex, medial wall of the middle ear, carotid canal, jugular foramen, or dura, or if there was extensive extratemporal soft tissue involvement (>0.5 cm). Lymph node involvement is a very poor prognostic sign and places the patient in an advanced stage as does metastatic disease.

Chondrosarcomas are staged by their histologic appearance and presence of metastases. The histologic grade (scale from 1 to 3) is one of the most important predictors of biological behavior and prognosis and is based on factors such as mitotic rate, cellularity, nuclear size, and staining pattern.[19–21] Low-grade tumors can be very indolent and often have a favorable prognosis.

Assessment of tumor involvement of the cavernous sinus is best done with an MRI scan. This can differentiate displacement of the wall of the sinus from true invasion as well as assess encasement or involvement of the ICA. MRI is also superior for demonstration of perineural extension.

## MANAGEMENT STRATEGIES AND TREATMENT PLANNING GUIDELINES

Surgical resection is the gold standard for primary temporal bone malignancies and is obtained with a lateral temporal bone resection (LTBR), subtotal temporal bone resection, or a total or radical temporal bone resection (Fig. 26-5). Total temporal bone resection is rarely performed because of the high level of morbidity and a lack of well-documented survival benefit, except with specific histology such as verrucous squamous carcinoma, an entirely local and indolent disease.[17] A negative tumor margin at the initial intervention is of paramount importance. Positive margins are associated with a very poor prognosis. An *en bloc* resection is advocated for LTBR. For subtotal and total temporal bones resections, there is still ongoing debate on whether piecemeal as opposed to *en bloc* resection compromises survival. It has been reported that *en bloc* resection of the EAC with surrounding soft tissue structures followed by piecemeal resection of tumor and structures medial to the middle ear provides better operative control and probably does not negatively influence the cure rate.[22,23]

Treatment modality is dictated by the extent of disease, with medial extension indicative of aggressive pathology, and therefore requiring aggressive intervention. Radiation as a single modality is not adequate for the treatment of temporal bone cancer, but is readily used as adjuvant therapy, particularly for advanced tumors. In general, the use of adjuvant radiation should be anticipated whenever the middle ear is involved with disease. The University of Pittsburgh group routinely recommends postoperative radiation of 50 to 60 Gy delivered to the primary site, parotid region, infratemporal fossa, and ipsilateral neck.[23] An exception would be small lesions in the EAC with very limited or no bone erosion and complete surgical resection. As with radiotherapy, chemotherapy is not effective as single modality treatment for these cancers. In general, chemotherapy is usually reserved for palliation in patients with distant metastases or recurrences. The role of chemotherapy is evolving, however. A group of patients treated by preoperative chemoradiation therapy and temporal bone resection had better survival than did patients treated by surgery or radiation therapy alone.[24] A group out of Japan recently reported their experience with superselective intra-arterial cisplatin and radiotherapy for patients with T3 and T4 SCCA of the temporal bone.[25] For those patients who are not surgical candidates because of poor state of health, chemoradiation is offered as a palliative alternative.

Concomitant parotidectomy with selective neck dissection has been increasingly advocated and has become common practice for T1 and T2 lesions, whereas a total parotidectomy is performed for more advanced disease with facial nerve invasion.[6,26] Ideally the parotid is removed *en bloc* with the temporal bone specimen. In regard to the neck, it is well known that lymph node metastasis carries a very poor prognosis. Moffat et al. reported on 39 patients with SCCA of the temporal bone, 9 (23%) had positive nodes in the neck and all died of the disease within 27 months.[27] A supraomohyoid neck dissection is recommended, although the survival benefit is unclear.[23] In the clinical N0 neck, this practice allows for assessment of the first echelon of drainage and assists with staging and determining adjuvant therapy. An additional benefit is to have cervical access and control of the great vessels, should the intraoperative need for control arise.

### T1 and T2 Disease

T1 and selected T2 lesions of the temporal bone should always be treated surgically by an LTBR. A true LTBR is now accepted

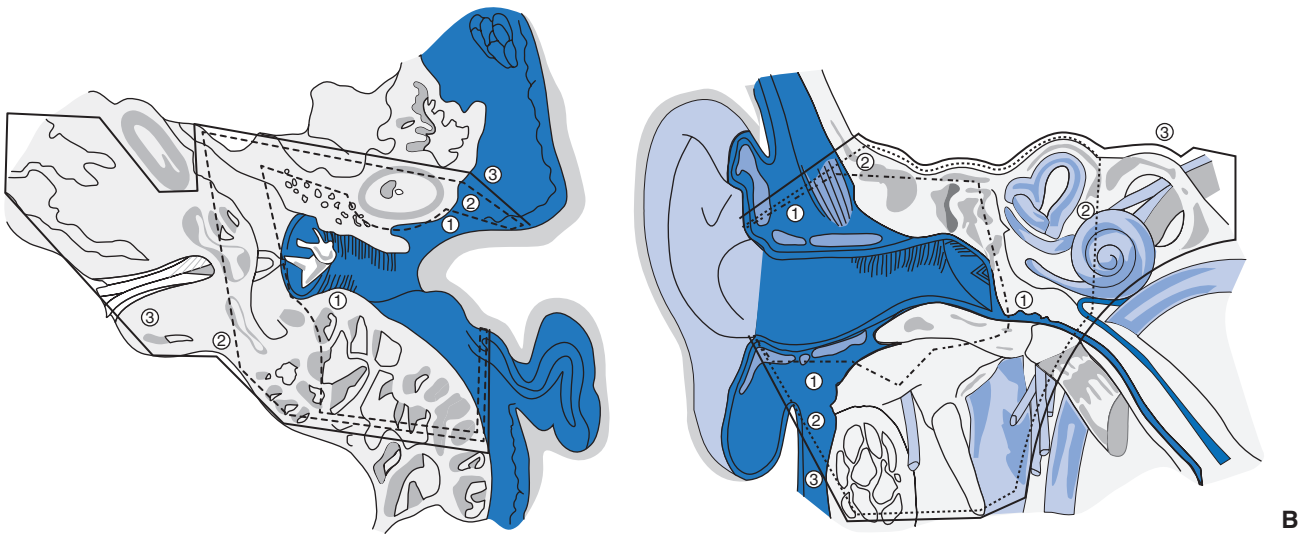



**FIGURE 26-5.** Axial **(A)** and coronal **(B)** illustrations demonstrating (1) lateral resection of the temporal bone, (2) subtotal resection of the temporal bone, and (3) total resection of the temporal bone. The carotid artery is preserved in this illustration.

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as the standard of care. In the past, so-called sleeve resections were employed. Sleeve resections became an umbrella term for procedures that ranged from simple transcanal circumferential excisions of canal skin with attached tumor to more extensive resections resembling a modified LTBR. Because of such variability, reports provided a wide range of disease-specific surgical outcomes, complications, morbidity, and mortality. As previously discussed, a superficial parotidectomy with selective neck dissection should be performed in conjunction with an LTBR.

## T3 and T4 Lesions

For lesions that extend to the middle ear or mastoid cavity (T3 or T4), a subtotal temporal bone resection is required. A total or radical temporal bone resection is indicated when disease extends to the petrous apex. A superficial parotidectomy with selective neck dissection should be performed unless the facial nerve is to be resected, when a total parotidectomy is then warranted. Postoperative radiation is advocated, and the results of the lymph node dissection can help guide its use.[6] Zanoletti and Danesi felt that nodal disease can be considered a marker of the aggressiveness of the tumor, and as such a prophylactic selective neck dissection played a role.[26] Adjuvant chemoradiotherapy has been driven by surgeon and institutional experience, and a consensus on its effect on disease-free survival has not been reached.

There is a limited role for surgery for the treatment of high-grade neoplasms with extensive secondary involvement of the lateral skull base. Extension of epithelial cancers to the cavernous sinus, carotid canal, and brain generally makes them unresectable, and primary treatment with radiochemotherapy is preferred with possible surgical salvage. Surgery does play a role, however, in the diagnosis and palliation of these neoplasms. Resectable tumors with perineural extension can be followed to Meckel cave in an attempt to achieve a clear margin. This may provide immediate relief from neuropathic pain and improve the response to radiotherapy.

On rare occasions, sacrifice of the ICA may be considered in order to obtain a clear margin or for palliation of symptoms. Tumors that are in close proximity to the ICA may increase the risk of intraoperative injury and subsequent stroke. Preoperative evaluation of collateral cerebral flow is helpful in determining the best strategy for management of the ICA in such situations.[28,29] If 4-vessel cerebral angiography demonstrates good collateral cross-fill through the communicating vessels, it is likely that the patient, especially if young, would tolerate sacrifice of the ICA without risk of a stroke. Approximately 15% of patients, however, are at risk for a delayed stroke due to watershed areas of ischemia in the distribution of the middle cerebral artery. Preoperative balloon occlusion testing prior to ICA sacrifice can be performed to better stratify patients into high-, intermediate-, and low-risk groups. Cerebral perfusion is assessed using clinical monitoring of neurological function during balloon occlusion and is followed by measurement of cerebral perfusion with CT perfusion or nuclear imaging (single-photon emission computed tomography [SPECT]). Clinical changes in the neurological examination or significant drops in cerebral perfusion on the side of occlusion would generally preclude sacrifice of the ICA without a vascular bypass operation.

# SURGICAL TECHNIQUE

The selection of the optimal surgical approach depends on multiple factors including the diagnosis, extent of disease, age, and comorbidities of the patient, surgical morbidity, prior therapy, and the training and experience of the surgeon. The introduction of endoscopic endonasal approaches to the skull base has added another option (especially for midline tumors with lateral extension), and multiple corridors may be utilized to provide optimal exposure with the least morbidity for the patient. Intraoperative frozen sections are essential and will guide the extent of resection for advanced disease. The following descriptions of surgical techniques have been predominantly adapted from the second edition of Myers' *Operative Otolaryngology: Head and Neck Surgery* book where the details of the dissection are available.[23]

## Temporal Bone Resection

***Lateral Temporal Bone Resection.*** A LTBR removes the conchal meatus, cartilaginous, and bony portion of the EAC and intact tympanic membrane with an attached malleus. Boundaries of resection include the middle ear cavity medially, the TMJ capsule anteriorly, the zygomatic root superiorly, the mastoid cavity posteriorly, and the infra temporal fossa (ITF) inferiorly. Laterally, the resection can include the concha, as well as portions or entire pinna, depending on the extent of the disease. Briefly, a postauricular incision is made 3 cm behind the postauricular sulcus and extended superiorly toward the temporal area, and inferiorly past the mastoid tip, and into the neck to allow for a neck dissection. The skin is raised briefly and dissection is then directed medially through the fibro-periosteal layer, followed by development of a soft tissue flap over the mastoid cortex. This allows for a tight three-layer closure should CSF be encountered. The lateral part of the EAC is sutured closed to prevent tumor spillage. The skin flap is dissected superficially to the deep temporalis fascia, the sternocleidomastoid fascia, and the parotid fascia, until the masseter muscle is identified and the entire parotid gland bed is exposed. At this point, a complete mastoidectomy is performed. The sinodural angle, tegmen mastoideum, posterior bony ear canal wall, and the digastric ridge all need to be well exposed. The lateral semicircular canal is identified and used for orientation. The zygomatic root is drilled to expose the epitympanum and tegmen tympani up to the capsule of the TMJ. The vertical portion of the facial nerve is exposed and followed to the second genu and stylomastoid foramen. The facial recess is then opened and the middle ear inspected for cancer that has penetrated the tympanic membrane. The incudostapedial joint is disarticulated, incus removed, and tensor tympani tendon transected. The facial recess is then extended inferiorly through the chorda tympani nerve to expose the posterior hypotympanum, and the inferior portion of the tympanic ring is drilled toward the anterior wall of the EAC. The limit of this dissection is the periosteum between the temporal bone, the ITF, and the capsule of the TMJ. Once the bony dissection has been completed, the EAC is attached anteriorly by anteromedial section of bone just lateral to the Eustachian tube. An osteotome is inserted through the extended facial recess lateral to the Eustachian tube orifice and with gentle taps, the EAC is dissected from the TMJ capsule. It is important to avoid injury to the ICA with the osteotome. The ICA lies just medial to the Eustachian tube. At this point, the specimen is attached only to the parotid gland, the superficial lobe of which can be removed in continuity with the specimen and the facial nerve preserved. The Eustachian tube should be plugged with the incus and/or a soft tissue plug. If the surgical defect is large and deep, the posterior half of the temporalis muscle can be rotated into the surgical defect and secured with sutures. An abdominal fat graft can also be used to fill part of the cavity. Hemovac drains are recommended.

Further reconstruction options will be discussed later in this chapter.

## Subtotal Temporal Bone Resection

A subtotal temporal bone resection (STBR) is undertaken when cancer has extended medial to the tympanic membrane into the middle ear or mastoid. This procedure can be performed in an

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*en bloc* or discontinuous fashion, as previously described. The procedure begins in the same manner as an LTBR. If facial nerve function is normal preoperatively and intraoperative assessment is without evidence of tumor invasion, the surgeon has to decide, based on the extent of the disease, whether the nerve is to be preserved. If the nerve is to be preserved, piecemeal resection of tumor is undertaken, and the facial nerve skeletonized along the labyrinthine, geniculate, horizontal, and vertical segments down to the stylomastoid foramen. The tegmen and posterior fossa plates of bone are thinned and resected piecemeal after dural elevation and sent for permanent section, avoiding dural and superior petrosal sinus injury. Translabyrinthine dissection exposes the IAC and jugular bulb, and if cancer is not present at the jugular bulb, the dissection stops over the bulb. If the facial nerve is to be preserved, the dura of the IAC is opened to allow mobilization of the facial nerve at the porus acusticus. The greater superficial petrosal nerve is transected from the geniculate ganglion, and the facial nerve is gingerly dissected out of the bony canal and mobilized posteriorly. If the facial nerve is to be sacrificed, the IAC dura is still opened and the facial and vestibulocochlear nerves transected. The remaining tympanic ring inferiorly is then drilled to the periosteum of the skull base, which should not be resected unless it is invaded by tumor because it protects vascular and neural structures in the ITF. The mandibular condyle need not be taken if the cancer has not infiltrated into the protympanum. The bone lateral and posterior to the vertical portion of the ICA above the jugular bulb is drilled until the artery from the otic capsule is exposed, at which point the remainder of the otic capsule is drilled. The vaginal process between the jugular bulb and the ICA is also drilled out. At this time, only the petrous apex is left. If cancer involves the lateral wall of the sigmoid sinus and jugular bulb, residual tumor resection can be achieved with an ITF approach similar to the Fisch type A. The subtotal temporal bone resection is completed once dissection and isolation of the internal jugular vein (IJV) and cranial nerves IX, X, XI, and XII in the neck is accomplished.

## Total Temporal Bone Resections

A subtotal temporal bone dissection needs to be completed, followed by proximal control of the ICA at either the skull base or neck, and distal control achieved in the floor of the middle cranial fossa via middle fossa craniotomy. The carotid artery posterior to V3 is exposed so that a clip can be placed for distal control if necessary. The bone lateral to the ICA at the genu is removed, and the ICA is dissected free from its canal from the skull base to the foramen ovale. The petrous apex is drilled to complete the total resection of the temporal bone. The Eustachian tube can be resected anteriorly to the level of the foramen ovale. If cancer is found anterior to this area, nasopharyngeal resection and possibly cavernous sinus dissection may be necessary. In order to prevent CSF rhinorrhea, the transected end of the Eustachian tube should be sutured closed. Should disease involve dura, it needs to be resected and repaired in conjunction with a neurosurgeon, and additional exposure may be necessary via craniotomy. The reader is encouraged to review the classic description by Sataloff and Myers published in 1987 as it offers much more details than what is relayed above.[30] Only minor modifications have been implemented since its publication date.

In terms of reconstruction, consideration should be given to the probable need for postoperative radiation. Small defects of the pinna can be repaired with a split-thickness skin graft. Skin grafts can also be used to line the mastoid and middle ear and sutured to the remaining soft tissue of the meatus. The surgical defect can be partially filled with a vascularized flap such as with temporalis muscle or fat as previously mentioned. A posterior scalp or cervicofacial advancement flap can be used for resections involving the pinna, and this would close the external canal. Alternatives include a lower island trapezius or pectoralis major myocutaneous flap. A free flap with microvascular anastomosis, with rectus abdominis muscle or anterolateral thigh, may be necessary for more extensive defects. A head and neck reconstruction team should aid in this part of the procedure. Facial nerve reconstruction via cable graft should be performed when the facial nerve is sacrificed. The greater auricular nerve, cervical cutaneous nerve, accessory nerve, or sural nerve can be used. Gold weights for corneal protection should be used when the facial nerve has been sacrificed. Should excessive lid edema preclude placement at time of the oncologic resection, a temporary tarsorrophy is performed and the gold weight placed at a later date. Hearing rehabilitation should also be considered in time.

***Infratemporal Skull Base Approach.*** An infratemporal skull base approach provides wide access to the lateral skull base and may be combined with other transtemporal and transfacial approaches. A hemicoronal scalp incision with extension to the preauricular skin crease is made and the scalp is elevated superficial to the cranium and deep temporal fascia. The temporal branches of the facial nerve are preserved by incising the superficial layer of the deep temporal fascia above the zygomatic arch and elevating the fat pad that is superficial to the temporalis muscle with the scalp. Periosteum is elevated from the zygomatic arch and lateral orbit, and the masseter muscle is detached from the inferior margin of the zygomatic arch. The temporalis muscle is elevated from the underlying cranial bone and reflected inferiorly. A frontotemporal craniotomy is performed to provide access to the floor of the middle cranial fossa and facilitate orbitozygomatic osteotomies. The dura is elevated from the orbital roof and a reciprocating saw is used to transect the orbital rim and roof at the margin of the craniotomy. The zygomatic arch is transected at its posterior attachment and a cut is made across the zygomatic bone from the lateral limit of the inferior orbital fissure. The orbital contents are protected while remaining bone is drilled across the orbital walls to connect the bone cuts. The orbitozygomatic bone segment is removed in one piece and saved for reattachment with titanium microplates at the end of the case. If exposure of the petrous ICA is necessary, the bone of the glenoid fossa is included. This requires dissection of the temporomandibular joint capsule. The bone cuts must be placed carefully to avoid injury to the ICA deep to the glenoid fossa and the cochlea posteriorly. A subtemporal craniectomy is then performed with removal of bone up to foramen ovale and foramen spinosum. This provides access to the floor of the middle cranial fossa. If necessary, the mandibular nerve and the middle meningeal artery are sacrificed to gain access to the petrous ICA and the Eustachian tube. The petrous ICA runs deep to the Eustachian tube. The lateral recess of the sphenoid sinus can be accessed between the second and the third divisions of the trigeminal nerve.

***Endoscopic Endonasal Approach.*** Meckel cave can be approached using an endonasal suprapetrous approach (Figs. 26-2 and 26-3). A transpterygoid approach is first performed with exposure of the contents of the pterygopalatine space. The sphenopalatine and palatosphenoidal branches of the sphenopalatine artery are sacrificed and the posterior wall of the maxillary sinus is removed. A wide sphenoidotomy is performed and the landmarks of the lateral sphenoid wall are identified. In a well-pneumatized sinus, the paraclival ICA is visible lateral to the clival recess. The lateral recess is bounded by the foramen rotundum superolaterally and the Vidian canal inferolaterally. The contents of the pterygopalatine space are dissected from the base of pterygoid bone to gain full access to the lateral sphenoid recess. The Vidian nerve is followed to the plane of the petrous ICA, but must be sacrificed to fully access Meckel cave. The Vidian nerve and maxillary nerve

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converge on Meckel cave. The bone lateral to the paraclival ICA is carefully drilled to expose the dura. The dura is incised to expose the trigeminal nerve. Foramen ovale with the mandibular nerve is located inferior to the second division and lateral to the paraclival ICA. Meckel cave is bounded superiorly by the lateral cavernous sinus and the cranial nerves V1 (ophthalmic branch of trigeminal) and VI.

## OUTCOMES AND RESULTS

Reports vary a great deal on survival outcomes for temporal bone malignancies. As previously discussed, this is in part due to the lack of a standardized staging system, variable surgical interventions, and the inherent rarity of the disease, thus making it impossible to carry large prospective trials. Most reports are from institutional experiences and consist of relatively small series. In addition, some reports include patients with histology other than SCCA or with cancer that has secondarily involved the temporal bone. Attempts have been made to analyze data that only includes primary SCCA of the temporal bone. Pooled data from various studies has been analyzed by several groups and findings reported in the literature. Brackmann et al.'s analysis noted that T1 lesions successfully treated with surgery alone had a 95% 5-year survival, with no benefit from the addition of radiation. Some T2 and T3 lesions treated with radiation after complete surgical removal showed an 85% 5-year survival. The 5-year survival of patients with more advanced lesions decreased to <50%. Cancer requiring a total temporal bone resection carried a dismal prognosis, with a 50% 1-year survival and reports of 0% 2-year survival.[17] Moody et al. reported a 2-year survival of 100% for T1 lesions, 80% for T2 lesions, 50% for T3 lesions, and 7% for T4 lesions. Survival for T3 tumors was 75% with postoperative radiotherapy, compared with 0% with surgery alone in a series of 32 patients with SCCA. Positive margins decreased survival from 75% to 32%.[7] Chi et al. studied 72 patients with SCCA of the temporal bone. All patients were treated surgically. The 5-year survival for patients with T1 disease was 100%, 67% for T2 disease, 21% for T3 disease, and 14% for T4 disease. In their series, patients with histopathology of poorly differentiated SCCA had significantly worse survival than those with well or moderately differentiated SCCA (0%, 37.5%, and 35.3%, respectively).[10]

In summary, several factors are clearly associated with decreased survival, and they include facial nerve paralysis, positive margins, dural involvement, and lymph node involvement. Goodwin and Jesse felt incomplete resection was the primary cause of failure and that postoperative radiation was of no benefit if the cancer could not be resected completely.[31] Arriaga et al. found that patients with negative pathologic margins had a 63% survival rate compared with 25% in those with positive margins.[32,33] Morris et al. reported on 31 patients with squamous cell cancers of the EAC seen between 1994 and 2010.[6] They felt the strongest negative prognostic factors in the study were neck metastasis, positive surgical margins, and extratemporal spread of disease, especially to the mandible, parotid gland, or brain/dura. The 5-year overall survival was 63.2%, disease-specific survival was 67.7%, and recurrence-free survival was 53.5%. Their 5-year rate of local failure was 33.5%, regional failure 0%, and distant failure 6.3%. The 5-year disease-specific survival was 80.8% in node negative patients, and 18.8% in node-positive patients ($p < 0.0001$). The 5-year survival in node-negative patients was 90.5% versus 29.4% in those with nodal disease. Zanoletti and Danesi reported on 51 patients with SCCA of the temporal bone treated between 1983 and 2004. There was an overall survival of 47% and a disease-specific survival rate of 60% at 5 years of follow-up. The disease-free rate in the positive neck cases was 25% and in the negative neck cases was 70%. All the failures in their study were local recurrences at the primary tumor site.[26]

## COMPLICATIONS

Vascular complications represent the most common risk in temporal bone resection. Hemorrhage from venous structures is not uncommon and can occur from injury to the sigmoid sinus, superior petrosal sinus, inferior petrosal sinus, jugular bulb, or internal jugular vein. Significant bleeding most commonly occurs at the inferior petrosal sinus. The excessive use of packing at the jugular foramen can result in injury to CN IX, X, and XI, so this should be done with caution.[17] The vein of Labbé is an important route of venous outflow from the temporal lobe and, if damaged, can lead to temporal lobe infarction with aphasia, if it occurs on the dominant side. It can be injured where it inserts into the transverse sinus. Seizures can also develop with venous infarct or temporal lobe retraction. Arterial bleeding can occur from injury to the middle meningeal or carotid artery. The middle meningeal can simply be controlled with coagulation, but carotid injury is much more challenging. This can be managed with direct pressure and placement of temporary clips, followed by primary repair. Intra-arterial and systemic heparin should be administered. If the artery cannot be repaired, the surgeon has to decide on the risk of ligating the vessel. Results of the preoperative balloon occlusion test will guide management. Consultation with vascular and neurosurgical services is encouraged.

Cerebrospinal fluid leaks can occur postoperatively and put the patient at risk of developing meningitis. They occur with inadequate closure of the dura, and an existing path for egress into the soft tissues and into the external environment. Typical sites are the Eustachian tube, incision site, and remnant of the EAC. Prevention is maximized with good dural repairs, adequate Eustachian tube plugging, and a water-tight wound closure. Leaks can be managed conservatively with bed rest, head of bed elevation, stool softeners, and a lumbar drain. Should these measures fail, surgical exploration is warranted. Postoperative paralysis of CN IX and X can occur with tumors that extend to the jugular foramen, and this carries high morbidity. These patients suffer dysphagia, vocal cord paralysis, and inability to protect the airway with subsequent aspiration. A tracheotomy may be needed as well as a gastrostomy tube. Aspiration pneumonia carries a high morbidity. Wound infections do not occur more frequently than with other head and neck procedures and are typically managed with local care and antibiotics as needed.

Less common complications include stroke from an emboli on ICA manipulation or repair or from intentional sacrifice. Intracranial bleeding can occur when resection or repair of dura takes place, and this in turn can lead to intracranial hypertension. Management should be immediate and in conjunction with a neurosurgeon.

## MANAGEMENT OF RECURRENCE

Recurrent disease carries a grave prognosis. Local and locoregional recurrences can be addressed on a case-by-case basis. These are typically managed with chemoradiation. Prasad and Janecka reported the site of recurrence in 54 patients to be local in 45, local and regional in 5, regional in 3, and local and metastatic in 1. Salvage surgery is not typically offered for recurrent temporal bone cancers as an attempt to improve survival, but can play a role in palliation. Surgery does have a role in management of recurrent chondromatous neoplasms. Recurrences usually occur in the first 2 to 3 years postoperatively.[3,26]

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## SPECIAL ISSUES AND FUTURE DIRECTIONS

As mentioned earlier, primary cancer of the lateral skull base is rare. With lack of a standardized staging system, reporting surgical and survival outcomes is challenging. Transpharyngeal approaches to the parapharyngeal space and infratemporal skull base are being explored in the context of robotic surgery and may provide another corridor for surgical therapy.

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# PART B:
# Radiation Therapy Technique

William M. Mendenhall

Malignancies involving the lateral skull base are treated with techniques similar to those described for parotid neoplasms. A wedge-pair technique may be employed; the low neck is irradiated with an anterior field matched at the level of the thyroid notch for those with high-grade malignancies.

Alternatively, intensity-modulated radiation therapy (IMRT) may be used to reduce the dose to the adjacent brain. Proton beam RT may be used to further reduce the RT dose to critical adjacent normal tissues without compromising target volume coverage.

Patients are treated at 2 Gy once-daily to 50 Gy for undissected subclinical disease, 60 Gy for negative margins, 66 Gy for positive margins, and 70 Gy for gross disease. Alternatively, patients with positive margins or gross disease are treated to 74.4 Gy in 62 twice-daily fractions.

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CHAPTER 27

# Paragangliomas of the Head and Neck

## PART A:
## General Principles and Management

Spiros Manolidis, Kenneth S. Hu, and Mark S. Persky

### INTRODUCTION

Paragangliomas represent highly vascular neoplasms that embryologically arise from the paraganglia of neural crest origin and most commonly occur in the head and neck region. These tumors are closely associated with either blood vessels (carotid artery, jugular bulb) or nerves (vagus, tympanic plexus), and their clinical presentation may involve a wide spectrum of signs and symptoms. A slowly enlarging neck mass and/or findings consistent with cranial nerve dysfunction are the hallmarks of presentation. A familial history of these tumors may be present, and there is a significant incidence of multicentric tumors, both in familial and sporadic cases. Malignant paragangliomas are uncommon and their diagnosis can only be confirmed by the presence of metastatic disease, usually within regional lymph nodes. There are no strict histologic criteria within the primary tumor that can differentiate between benign and malignant paragangliomas.

Computed tomography (CT) and magnetic resonance imaging (MRI) usually establish the diagnosis. $^{111}$Indium pentetreotide imaging can also be used to evaluate paragangliomas, define multiple tumors, and detect the possible presence of metastatic disease.[1] Angiography defines the vascular supply and may visualize vessel involvement (invasion) and paves the way for preoperative embolization, if surgery is contemplated.

Paragangliomas are highly vascular, and they characteristically have early blood vessel and neural involvement, in addition to skull base and potential intracranial extension. These factors all contribute to the challenging nature of effectively treating these tumors. Traditionally, surgery has been the preferred method of treatment, especially with the evolution of more sophisticated skull base approaches, safer embolization protocols, and advanced vascular bypass procedures.[2,3] Postoperative cranial nerve dysfunction is anticipated in patients with tumors characterized by early neural involvement, larger tumors, and skull base involvement, therefore, a focus on rehabilitation efforts is necessary.

Radiation therapy was traditionally relied upon for treating unresectable paragangliomas or tumors in elderly or debilitated patients. However, advances in radiation oncology and long-term experience have demonstrated high tumor control with low rates of chronic complications, such that primary radiation treatment of paragangliomas has assumed a prominent role in treatment algorithms.

### ANATOMY AND PHYSIOLOGY OF PARAGANGLIA

Paraganglia are part of a system of cell clusters that facilitate the baroreceptive and chemoreceptive reflexes of the cardiovascular system. They are diffusely distributed throughout the upper body. They contain cells that are capable of secreting neuropeptides that have the capability to influence vascular reflexes.

These structures are part of the diffuse neuroendocrine system (DNES) and are either neural crest origin cells or neuroectodermally derived. The former, neural crest derivatives, produce the C cell of the thyroid gland, the melanocyte, and the paraganglia. Paraganglia are found in the adrenal medulla or diffusely distributed as the extra-adrenal paraganglia.[4,5] The diffusely distributed extra-adrenal paraganglia are divided into branchiomeric paraganglia and vagal paraganglia. The branchiomeric are distributed along arteries and cranial nerves in the head and neck. The jugulotympanic paraganglia arise from the second branchial arch, whereas the carotid paraganglia arise from the third branchial arch. The intravagal paraganglia do not follow this embryologic pharyngeal pouch distribution and are thus classified separately. Even so, unusual paraganglioma locations have been recorded that do not fit this classification: larynx, orbit, thyroid, nasal cavity, and sinuses, as well as intracranial (Fig. 27-1).[6]

The carotid body is a chemoreceptor that senses changes in arterial oxygen pressure, pH, and carbon dioxide. Along with the cardiac and aortic bodies, these are the only chemoreceptors in



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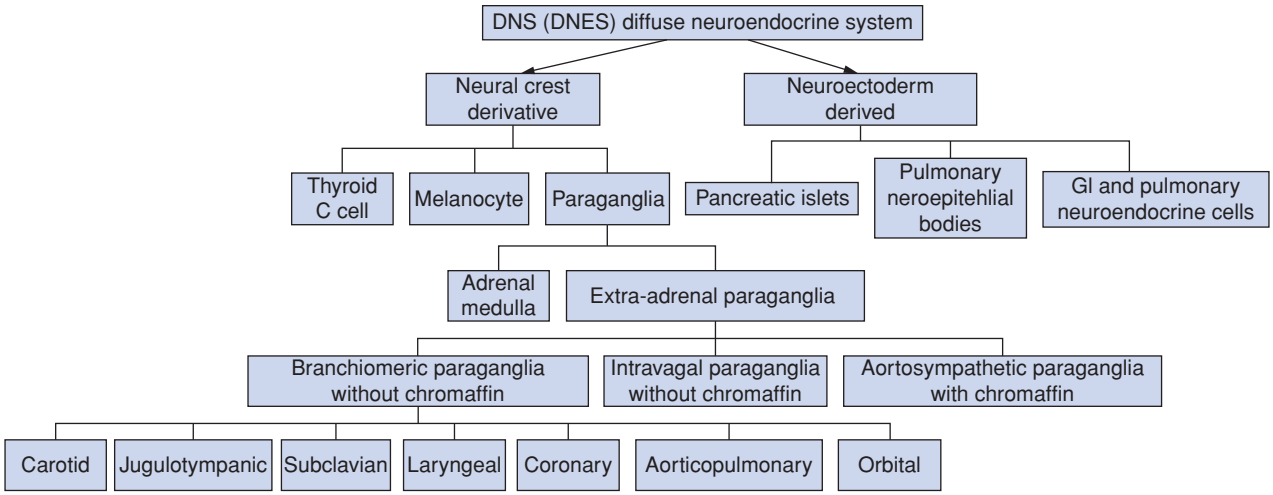



**FIGURE 27-1.** Classification of the diffuse neuroendocrine system. GI, gastrointestinal.

the paraganglia. The carotid body is a discrete oval structure situated behind the carotid bifurcation and receives blood supply directly from the carotid bifurcation via the glomic arteries. The afferent reflex is mediated by a branch of the glossopharyngeal nerve (nerve of Hering) (Fig. 27-2).[7]

The jugulotympanic paraganglia are distributed within the temporal bone in close association with the tympanic branch of the glossopharyngeal nerve (Jacobson nerve) and the auricular branch of the vagus nerve (Arnold's nerve). The majority of the temporal bone paraganglia are located in the jugular fossa and the rest are located in the bony canal that transmits Jacobson's nerve or in the submucosa of the tympanic cavity. There is a marked difference in the clinical behavior of tumors arising from the jugular paraganglia versus the tympanic paraganglia, a fact that has significant therapeutic implications (Fig. 27-3).[8]

The vagal paraganglia are distinctly different from the jugulotympanic paraganglia. They do not form discrete bodies and are incorporated within the vagus nerve underneath the perineurium or interspersed within the vagal nerve fibers in the pars nervosa of the jugular foramen (which transmits the lower cranial nerves IX, X, and XI). The superior vagal ganglion is found at the level of the jugular foramen. The nodose vagal ganglion lies just below the jugular foramen. Both ganglia are in close proximity to cranial nerves IX through XII, the pars venosa of the jugular foramen, as well as the ascending portion of the petrous internal carotid artery (ICA).[9] Thus, vagal paragangliomas have distinct therapeutic implications based on their close association with the superior portion of the vagal nerve and their adjacent neurovascular structures.

The microanatomy of normal paraganglia is that of clusters that contain chief cells (type I cells) surrounded by sustentacular cells (type II). These clusters are interspersed by a web of blood vessels. The equivalent structures seen in paragangliomas are termed Zellballen cells, and they retain part of this structural arrangement. The sustentacular cells do not secrete catecholamines and are similar in nature to the Schwann cells enveloping autonomic ganglia. The chief cells have abundant secretory granules—typical of secreting cells. The biochemistry of paraganglia chief cells is characterized by catecholamine production.[10] This sequence is characterized by enzymatic conversion of tyrosine to dopamine, norepinephrine, and epinephrine. Extra-adrenal paraganglia lack the methyltransferase required for the conversion of norepinephrine to epinephrine. The metabolic breakdown of catecholamines to metanephrine (from epinephrine) and normetanephrine (from norepinephrine), as well as vanillylmandelic acid (VMA), each can be detected in the urine. Actively secreting paragangiomas can, therefore, be detected with appropriate urine and serum analysis (Fig. 27-4).

## PARAGANGLIOMA EPIDEMIOLOGY AND PATHOPHYSIOLOGY

### Incidence

Paragangliomas are neoplasms of the paraganglia. Paragangliomas of the head and neck are rare tumors, comprising about one in 10,000 of all tumors in the head and neck area excluding intracranial tumors. A review by the surgical pathology department at Memorial Sloan-Kettering Cancer Center showed an incidence of head and neck paragangliomas accounting for 0.012% of all head and neck tumors.[11] The annual incidence of extra-adrenal paragangliomas is estimated at 1 in 300,000.[12] The carotid body is the most common site for paraganglioma. Carotid body tumors and jugulotympanic tumors account for approximately 80% of these, and vagal paragangliomas add another 5%. Nasal, orbital, laryngeal, and other head and neck sites are much more rare.[13] Significant referral pattern distortions make these numbers less reliable. Multiple paragangliomas are present in up to 22% of all patients with a paraganglioma, and these are frequently hereditary in nature with a family history of such tumors.

### Multicentricity

Approximately 10% of sporadic cases will have a concurrent second paraganglioma.[14–16] Multicentricity may be present in up to 22% of those with a genetic predisposition. The most common pattern of a synchronous secondary paraganglioma is a second carotid body tumor, and occurrence is present in 20% of carotid body tumors. Bilateral carotid body tumors, as well as an additional paraganglioma ipsilaterally or contralaterally present significant and challenging treatment problems due to the potential for cranial nerve deficits and loss in baroreceptor function, which results in labile hypertension.[17–19] Multiple tumors may be metachronous, and this has implication for surveillance for

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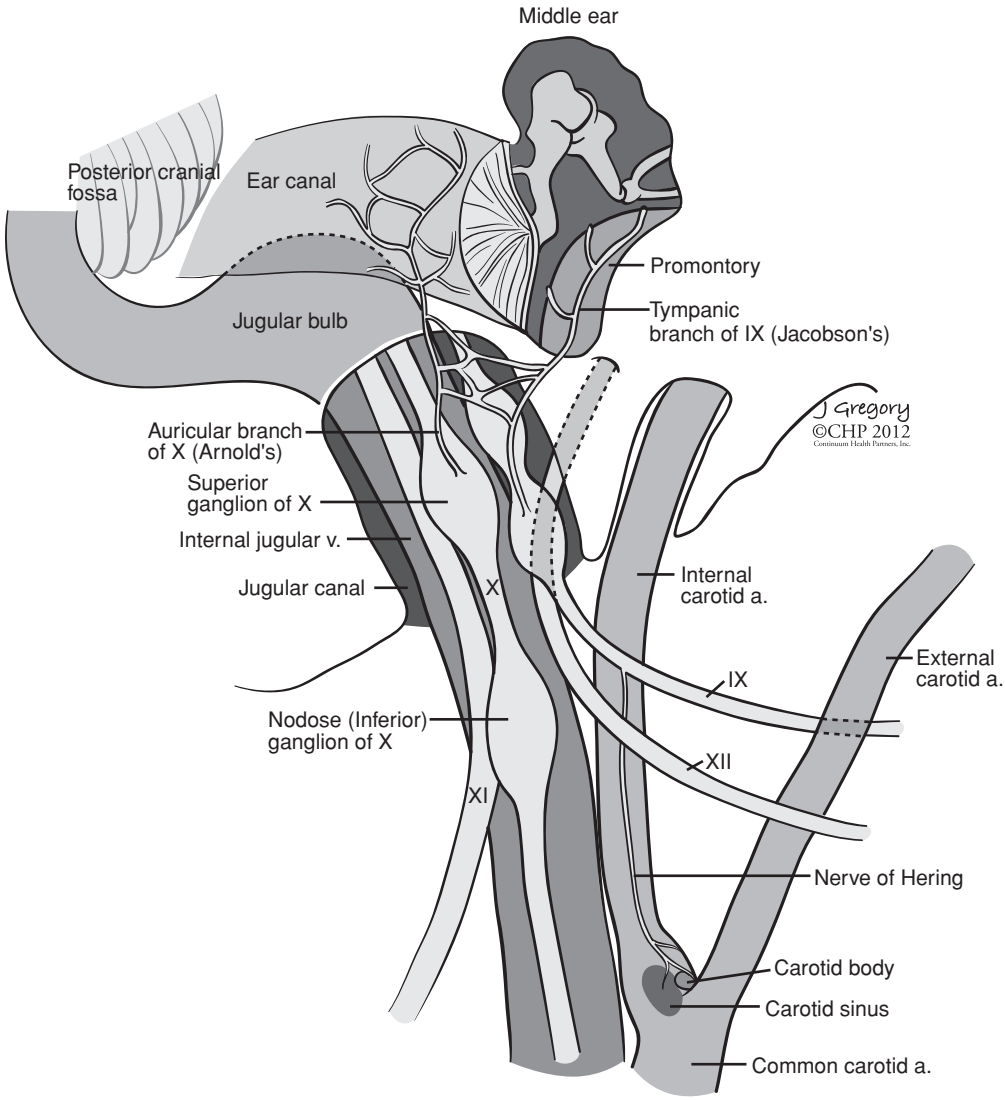



**FIGURE 27-2.** Schematic representation of lower cranial nerves at the level of jugular foramen. (See color insert.)

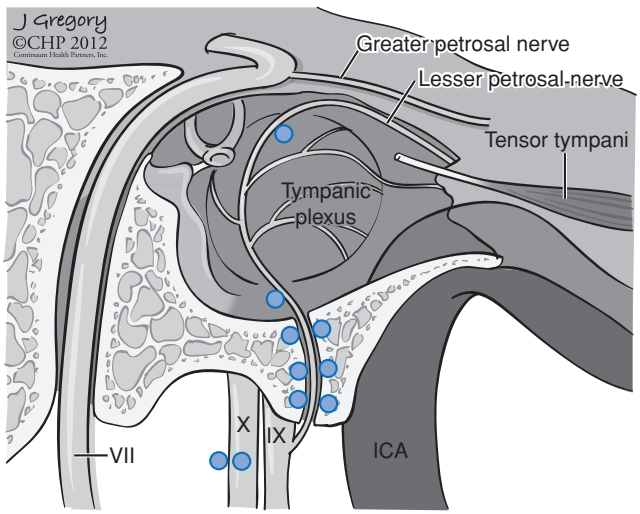



**FIGURE 27-3.** Distribution of frequent locations for glomus bodies in the temporal bone. (See color insert.)

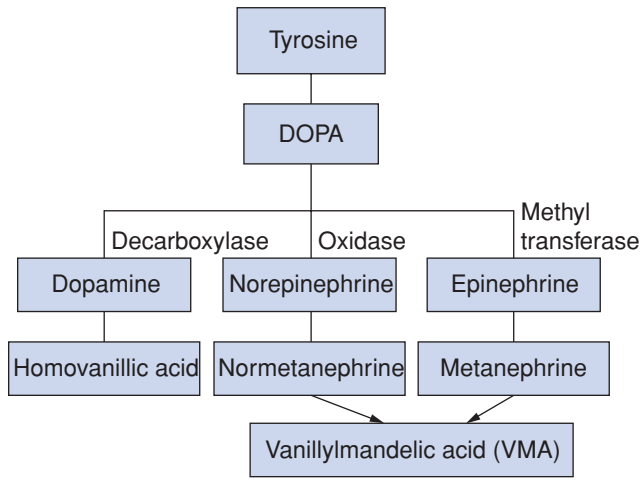



**FIGURE 27-4.** Biochemical pathway for catecholamine metabolism. DOPA, dopa dihydroxyphenylalanine.

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patients with a paraganglioma. Since multicentric tumors may be metachronous, routine follow-up MRI, $^{111}$indium pentetreotide (Octreoscan$^{R}$) or (18)F-DOPA positron emission tomography imaging is indicated.

## High Altitude

Other than genetics, the only known predisposition for a paraganglioma is high-altitude living associated with chronic hypoxemia. Several studies show that there is an increased incidence of these tumors with high-altitude living, a 9-fold increase for those living between 2 and 3 km and 12-fold increase for those living between 3 and 4.5 km above sea level. Patients forming these tumors at higher altitude show a lower rate of bilaterality and a lesser degree of familial history of paragangliomas.[20–22] Rodriguez-Cuevas et al. reported a retrospective analysis of 120 cases of carotid body tumors occurring in inhabitants living at a high altitude (>2,200 m above sea level). As compared with cases occurring in populations living below 1,500 m above sea level, they noted a higher female predominance (8.3:1 vs. 2:1), a lower rate of bilaterality (5% vs. 10%–20%), and a less frequent familial history (1% vs. 7%–25%).[23] High-altitude paraganglioma has a prevalence of up to 1 in 10 in humans and 1 in 2 in bovines compared with an estimated 1 in 500,000 prevalence in humans at low altitudes.[24,25] A higher incidence of carotid body hypertrophy and carotid body tumors has also been noted in patients with chronic obstructive pulmonary disease, perhaps related to chronically low $pO_2$ levels.[26]

## Functioning Paragangliomas

Approximately 1% to 3% of paragangliomas secrete catecholamines. A five-fold increase in catecholamines is sufficient to produce symptoms. Symptoms consistent with a functioning tumor are tachycardia, excessive sweating, weight loss, and hypertension. Secreting paragangliomas account for approximately 2% of all instances of secondary hypertension. Twenty-four hour urine collection in these patients will show elevated levels of the catecholamine metabolites, metanephrine, and VMA. Serum catecholamines will show elevated levels of norepinephrine in functioning extra-adrenal paragangliomas. Elevated serum epinephrine is indicative of a concurrent pheochromocytoma.[6,27] Paraganglioma familial syndrome subtypes 1 and 4 (PGL1 and PGL4) are associated with a higher incidence of concurrent pheochromocytoma. Conversely, multiple endocrine neoplasia type IIA (pheochromocytoma, medullary thyroid carcinoma, and parathyroid hyperplasia) and type IIB (pheochromocytoma, medullary thyroid carcinoma, parathyroid hyperplasia, and mucosal neuromas) are associated with head and neck paragangliomas.[28]

## Malignant Variant

Malignant paragangliomas represent a small subset of extra-adrenal paragangliomas that have a propensity for regional lymph nodes and distant metastatic disease, primarily to the lungs, liver, and bones. Sporadic paragangliomas have a higher rate of malignancy than familial type paragangliomas, except for PGL4 syndrome that is associated with a rate of malignancy as high as 54%, and importantly, the likelihood is site specific. Orbital and laryngeal paragangliomas have the highest rate of malignancy, approximately 25%. With vagal paragangliomas, the rate is up to 10%, followed by jugulotympanic paragangliomas with a malignancy rate of 5%, and carotid body tumors being last at 3% to 6%. Unfortunately, there are no histologic criteria by which primary tumor malignancy can be diagnosed, and that determination depends on tumor present in lymph nodes or distant metastatic sites. The presence of malignancy has profound implications in the treatment of these tumors.[29–31] In a review of 43 cases of malignant carotid body tumors, the best locoregional control was achieved by primary resection combined with neck dissection, and followed by adjuvant radiation therapy. The interval to recurrence is long, ranging from 20 months to 20 years.[32]

## Genetics

Overall, germline mutations can be identified in approximately 30% of patients with head and neck paragangliomas.[33,34] Familial glomus tumors constitute approximately 20% of affected patients, for which the genetic defects are known. One subgroup (10% of all glomus tumors) appears to be caused by sporadic mutations in SDHB and SDHD.

Hereditary susceptibility to paragangliomas, mainly of the head and neck region, was recognized at least two decades ago, and led to the identification through linkage analysis of three loci on chromosomes 11 and 1, named PGL1 on 11q23, PGL2 on 11q11.3, and PGL3 on 1q21–23. Following the discovery of succinate dehydrogenase (SDH) subunit D gene (*SDHD*) as the gene responsible for PGL1 in familial head and neck paragangliomas, it was thereafter recognized that two other subunits of this mitochondrial enzyme, SDHC (PGL3) and SDHB (PGL4, 1p36) were associated with heritable pheochromocytoma and/or paraganglioma. To date, the gene for PGL2 has not been identified.[20,35–38]

At present, causative gene mutations are identified in about 32% of paragangliomas-pheochromocytomas.[39] In the hereditary tumor syndromes: MEN2A, MEN2B, Von Hippel-Lindau and NF-1, in which a pheochromocytoma or paraganglioma presents, a causative gene mutation is seen in 17% of cases. Within the mitochondrial SDH complex, paragangliomas account for 15% of mutations.

The molecular basis for tumorigenesis in paragangliomas resides in mutations, germ line, and somatic for the most part in the genes that control SDH. The product of these multiple genes is a 4-dimer protein that catalyzes succinate to fumarate in mitochondria as the first step of oxygen-dependent glucose breakdown via the respiratory pathway. The enzyme is composed of 4 dimers, namely, SDHA, SDHB, SDHC, and SDHD, and is anchored in the internal bilipid membranes of the mitochondria. SDHA and SDHB are the proteomic components that anchor the enzyme in the membrane, while SDHC and SDHD are the proteomic components that catalyze the reaction from succinate to fumarate. This reaction is crucial to entering glucose breakdown from anaerobic to aerobic metabolism.[34] SDH or succinate-ubiquinone reductase is the complex II of the mitochondrial respiratory chain located in the mitochondrial matrix. SDH couples the oxidation of succinate to fumarate in the Krebs cycle with electron transfer to the terminal acceptor ubiquinone, thus leading to the generation of ATP.[40]

SDH is an enzyme complex composed by four subunits encoded by four nuclear genes (*SDHA*, *SDHB*, *SDHC*, and *SDHD*). *SDHC* (cybL, 15 kDA, 169 amino acids) and *SDHD* (cybS, 12 kDa, 159 amino acids) subunits are hydrophobic and provide membrane anchor and the binding site for ubiquinone. *SDHA* (flavoprotein, 70 kDa, 664 amino acids) and *SDHB* (iron–sulfur protein, 27 kDa, 280 amino acids) are hydrophilic, with the former involved in substrate binding and oxidation and the latter in electron transfer. Both *SDHB* (35.4 kb, 8 exons) and *SDHC* (50.3 kb, 6 exons) genes are located on chromosome 1, in the short and long arm, respectively. *SDHD*, located on 11q23.1, spans 8.9 kb and contains four exons whereas *SDHA* lies on the short arm of chromosome 5 (5p15) and is composed of 15 exons spread in a genomic region of 38.4 kb. Whereas homozygote germline mutations affecting *SDHA* cause Leigh syndrome, a subacute necrotizing encephalomyelopathy during infancy, *SDHD*, *SDHB*, and *SDHC* heterozygous mutations cause a genetic

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predisposition to head and neck paragangliomas and adrenal/extra-adrenal pheochromocytomas.[41] This inherited tumorigenic predisposition is transmitted in an autosomal dominant fashion with age-dependent and incomplete penetrance. However, for *SDHD* located on chromosome 11q, a parent-of-origin effect is revealed as the disease is manifest almost exclusively when the mutation is transmitted from the father. A maternal imprinting has therefore been postulated, but despite the pattern of inheritance, *SDHD* shows bi-allelic expression in normal tissues and neural crest-derived tissues.[20,31]

All of these genes are tumor-suppressor genes showing loss of heterozygosity (LOH): the loss of the normal allele in the tumor, in conjunction with germline mutation. This results in loss of a protein subunit that destabilizes the SDH complex and alters or abolishes its enzymatic activity.[42]

Inactivation of the SDH complex leads to a hypoxic state with accumulation of succinate resulting in the stabilization of HIF1a (hypoxia-induced factor 1a). Oxygen normally facilitates the degradation of HIF1a through prolyl hydroxylases. As oxygen levels decline HIF1a enters the nucleus and initiates the transcription of a host of genes known to be involved in tumorigenesis, including Vascular endothelial growth factor (VEGF).[43] VEGF and platelet-derived endothelial growth factor (PD-ECGF), as well as endothelin-1, has been found in the majority of specimens examined. It has been postulated that this was consistent with a paracrine mechanism for tumor development.[44,45]

Recent hypotheses for the mechanism of a tumorigenesis link a decrease in apoptosis and the activation of a pseudohypoxic pathway via these mechanisms.[46] This peudohypoxia is known as the Warburg effect and is the basis for tumor imaging by F-16 PET/FDG.[47]

***Paraganglioma Syndrome 1: SDH Subunit D.*** SDH Subunit D (SDHD) is the second anchoring peptide for mitochondrial complex II in the inner mitochondrial membrane. The gene resides at 11q23 and was the first mitochondrial gene to be linked to tumorigenesis.[20] The proportion of mutation carriers at *SDHD* gene that will develop a tumor is 87% to 100% (very high penetrance).[48] *SDHD* is responsible for PGL1 syndrome. Patients with PGL1 commonly have multifocal tumors and very rarely malignant ones. Maternal imprinting (absence of disease transmitted by the mother) suggesting sex-specific epigenetic modifications.[34] Higher altitudes in SDHD/PGL1 patients show increased phenotypic severity as well as increased likelihood of developing a pheochromocytoma.[49] In a similar manner, nonsense/splicing mutations show earlier presentation of head and neck paragangliomas as well as increased incidence of pheochromocytomas.[48] It has been proposed that *SDHD* is a critical component of a cellular oxygen-sensing system. Mutations in *SDHD* may incapacitate the oxygen-sensing mechanism, leading to an apparent or real hypoxic state accompanied by chronic hypoxic stimulation and cell proliferation. Support for hypoxia-induced hyperplasia comes from evidence obtained in high-altitude physiological studies. Cows, guinea pigs, rabbits, and dogs experience carotid body hyperplasia when living at high altitudes, which exposes them to a hypoxic condition, and this has also been described in humans. Another clinical observation lending support to these theories is the finding that patients suffering from conditions resulting in hypoxemia, such as cystic fibrosis, cyanotic heart disease, and chronic obstructive pulmonary disease, experience carotid body hyperplasia, and those suffering from chronic obstructive pulmonary disease have a higher rate of carotid body tumors.[20,21,35–38]

***Paraganglioma Syndrome 2: SDH Assembly Factor 2.*** SDH Assembly Factor 2 (SDHAF2) is essential for the correct flavination of *SDHA* and thus the function of the SDH complex.[40] This is referred to as the PGL2 locus. Mutations in SDHAF2 have been described to produce only head and neck paragangliomas, and these make a small contribution to the genetic burden of this condition.[50] *SDHAF2* gene maps to chromosome 11q13 and as with the *SDHD* mutations there are parent-of-origin effects on expression, such that tumor development only occurs after paternal inheritance. A striking aspect of mutations on *SDHAF2* is the very high level of penetrance and the development of tumors at an early age.[40]

***Paraganglioma Syndrome 3: SDH Subunit C.*** SDH Subunit C (SDHC) is one of two peptides anchoring mitochondrial complex II in the inner mitochondrial membrane. The gene resides at 1q23.3. Only 10 index cases of families with head and neck paragangliomas have been identified worldwide.[51] It accounts for <1% of all head and neck paragangliomas and is responsible for PGL3 syndrome.[39]

***Paraganglioma Syndrome 4: SDH Subunit B.*** SDH Subunit B (SDHB4) is the iron sulfur protein catalytic subunit of complex II. The gene resides at 1p36.1-p35.[52] It has been identified as the susceptibility gene for PGL4 (paraganglioma syndrome 4—OMIM: #115310). Patients with head and neck paragangliomas due to mutations of *SDHB* gene show a high rate of malignancy at 20% to 54%. These mutations have a low level of penetrance of 25% to 40%.[21,40,53] Only 37% of *SDHB* mutation–positive index cases report a family history at presentation.[34] *SDHB* is known to be a significant cause of adrenal pheochromocytomas.

## Succinate Dehydrogenase Subunit A

SDHA is a flavoprotein and the main catalytic subunit of SDH. Head and neck paragangliomas had not been associated with mutations in the gene for SDHA. However, recently a patient with an SDHA mutation and a catecholamine-secreting abdominal paraganglioma was described.[54] Congenital deficiency due to homozygous recessive mutations of *SDHA* gene have been described, and these patients are severely affected with early cardiomyopathy, but no development of paragangliomas.[52,55,56] Other *SDHA* mutations produce Leigh syndrome, a mitochondrial encephalopathy.[55] These mutations are generally missense.[52] It has been postulated that complete loss of *SDHA* function as would occur with a truncating mutation would not be compatible with life.

Neurofibromatosis type 1 is also associated with both pheochromocytomas and jugulotympanic paragangliomas. Pheochromocytomas are also associated with multiple endocrine neoplasia type II with *RET* gene mutations, and with Von Hippel-Lindau syndrome and mutations in *VHL* gene.

In patients with successive generations of a family harboring the mutations, tumors develop at progressively younger ages. This finding is a good example of genetic anticipation, in which the mutation appears to be more severe with succeeding generations.

***Succinate Dehydrogenase Complex Assembly Factor 2 (SDHAF2).*** This protein is responsible for the addition of the flavin–adenine dinucleotide (FAD) prosthetic group to form the SDHA flavoprotein. Studied mutations in the gene that codes for SDHAF2 show that this is related to high penetrance for head and neck paragangliomas.[20]

In summary the genetic associations in these paraganglioma syndromes are as follows:

- Patients with paraganglioma develop tumors at a younger age than sporadic cases
- In PGL1, PGL2, and PGL3, the genetic transmission is autosomal dominant, with highly variable expressivity and reduced penetrance. Genomic imprinting is seen in PGL1: the

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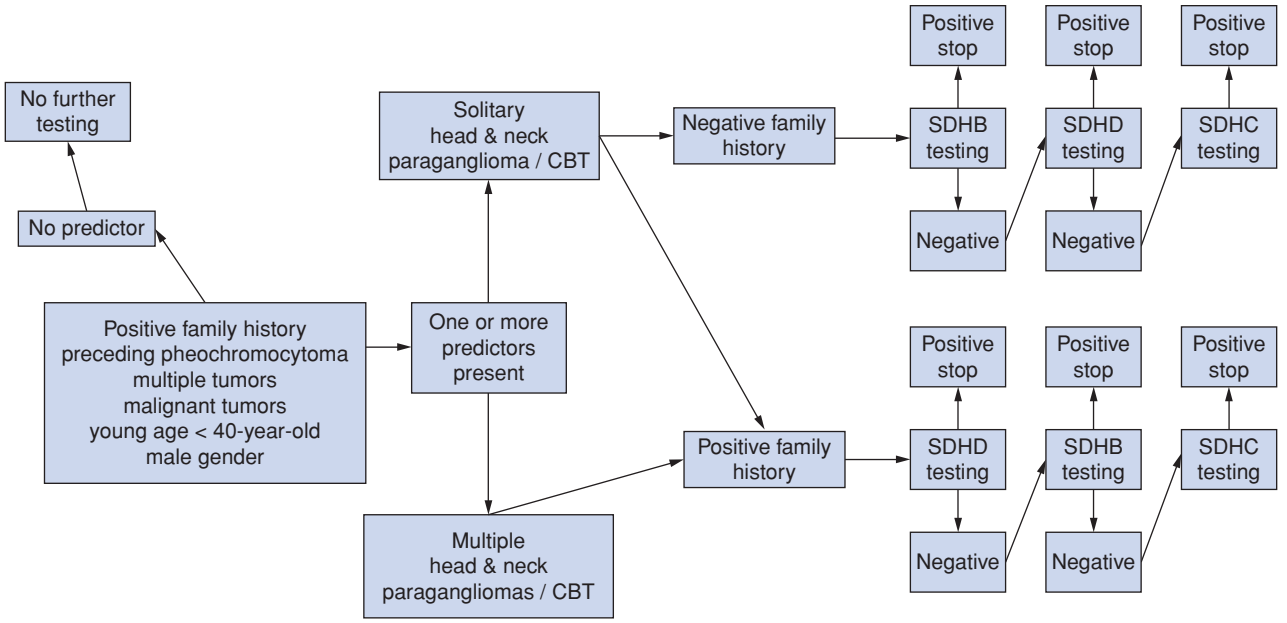



**FIGURE 27-5.** Algorithm for genetic testing for patients with head and neck paraganglioma. CBT, carotid body tumor.

paternally transmitted genes lead to tumor development and the maternally transmitted gene gives carrier status without developing tumors

- PGL1 and PGL4 show multicentricity and pheochromocytomas
- PGL1 has a high degree of penetrance whereas PGL4 shows moderate penetrance
- PGL4 shows a marked increase in malignant paragangliomas
- PGL3 present exclusively as benign paragangliomas with no multifocality and has no association with pheochromocytomas
- Other tumor syndromes: Neurofibromatosis type 1, MEN type 2, and Von Hippel-Lindau predispose to paragangliomas

## Genetic Testing

Head and neck paragangliomas are associated primarily with PGL1, PGL3, and PGL4 syndromes which correspond to the SDH genes: *SDHD*, *SDHC*, and *SDHB*. Multiple endocrine neoplasia and Von Hippel-Lindau that can be associated with head and neck paragangliomas correspond to the *RET* and *VHL* genes, respectively. In one study, these five genes produce 25 at-risk exons and the cost of testing all five was estimated at US$4,100/patient.[57] The same study developed an algorithm on the basis of clinical/history predictors for efficient genetic testing in head and neck paragangliomas (Fig. 27-5) (Table 27.1).

**TABLE 27.1 Genetics of Paraganglioma: SDH- and SDH-related Genes**

| Gene | Locus | Protein | Mechanism | Syndrome | Anatomic Location |
|---|---|---|---|---|---|
| SDHD | 11q23 | Membrane anchoring Protein of complex II | Autosomal dominant | Paraganglioma Pheochromocytoma | Head and neck |
| SDHB | 1p36.1–p35 | Iron sulfur catalytic Subunit of complex II | Autosomal dominant | Paraganglioma Pheochromocytoma | Abdominal thoracic paraganglia adrenal |
| SDHC | 1q23.3 | Membrane anchoring Protein of complex II | Autosomal dominant | Paraganglioma Pheochromocytoma | Head and neck |
| SDHA | 5p15 | Flavoprotein catalytic subunit of complex II | Autosomal recessive | Mitochondrial encephalopathy Leigh syndrome | Systemic |
| SDHAF2 | 11q12.2 | Assembly factor 2 for SDHA | Autosomal dominant | Paraganglioma Pheochromocytoma | Head and neck |
| SDHAF1 | 19q11.12 | Assembly factor 1 for SDHB | Autosomal recessive | Infantile leukoencephalopathy | Systemic |

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## CLINICAL PRESENTATION AND CLASSIFICATION

The clinical presentation(s) of paragangliomas is (are) location specific. As these tumors enlarge, they tend to produce cranial neuropathies. Additionally, secreting tumors can produce hypertension, tachycardia, sweating and nervousness, secondary to catecholamine release.

### Carotid Body Tumors

Carotid body tumors typically present as a slowly enlarging asymptomatic deep neck mass at the level of the carotid artery bifurcation. In a small minority of patients, pain is present around the tumor. Because of the association with the carotid artery, the tumors are laterally mobile, but are cephalic-caudally fixed on examination. As the tumor enlarges, a bruit may be detectable and parapharyngeal extension can result in the lateral displacement of the soft palate. Cranial nerve paralysis symptoms are unusual and present in very large tumors with superior extension toward the jugular foramen. Shamblin's classification is commonly used to stage carotid body tumors and though this is based on intraoperative findings, it can be applied to radiologic findings prior to treatment (Table 27.2) (Fig. 27-6).

**TABLE 27.2 Shamblin's Surgical Classification of Carotid Body Tumors**

| | |
|---|---|
| Type 1 | Relatively small tumor with minimal attachment to the carotid vessels |
| Type 2 | Larger tumor with moderate attachment to carotid vessels, but resectable with preservation of the carotid vessels |
| Type 3 | Tumor encases the carotid vessel requiring arterial sacrifice with reconstruction |

### Jugulotympanic Paragangliomas

Jugular and tympanic paragangliomas occur predominantly in the fifth and sixth decades of life with an overwhelming female predominance. They are slow growing and their pattern follows pathways of least resistance in the temporal bone and surrounding skull base structures. Although tympanic and jugular paragangliomas differ in presentation in the early stages, both types produce similar symptoms related to consistent cranial nerve deficits in their later stages. Tympanic paragangliomas present early with pulsatile tinnitus and conductive hearing loss. Tympanic membrane exam suggests a red-blue middle ear mass that blanches with positive pressure on pneumatic otoscopy (Brown's sign). With subsequent growth, there is expansion in the middle ear cleft and ossicular erosion. Extension through the tympanic membrane produces an ear canal polypoid mass that can spontaneously produce bloody otorrhea. Extension to the mastoid can occur through a number of pathways. Involvement of the facial nerve (usually in the mastoid) can produce paralysis as a presenting sign. Anterior growth toward the pericarotid air cells can involve the petrous carotid artery and occupy the Eustachian tube. Medial growth into the infralabyrinthine air cells can reach the petrous apex and petroclival area, as well as cavernous sinus. Intracranial extension is possible with extension through the jugular foramen and/or petrous apex. More infrequently, there is involvement of the otic capsule and the inner ear with attendant sensorineural hearing loss and vertigo at presentation.

Because of their site of origin within the jugular bulb, jugular paragangliomas have the capacity for early and extensive skull base invasion with involvement of cranial nerves IX through XII.

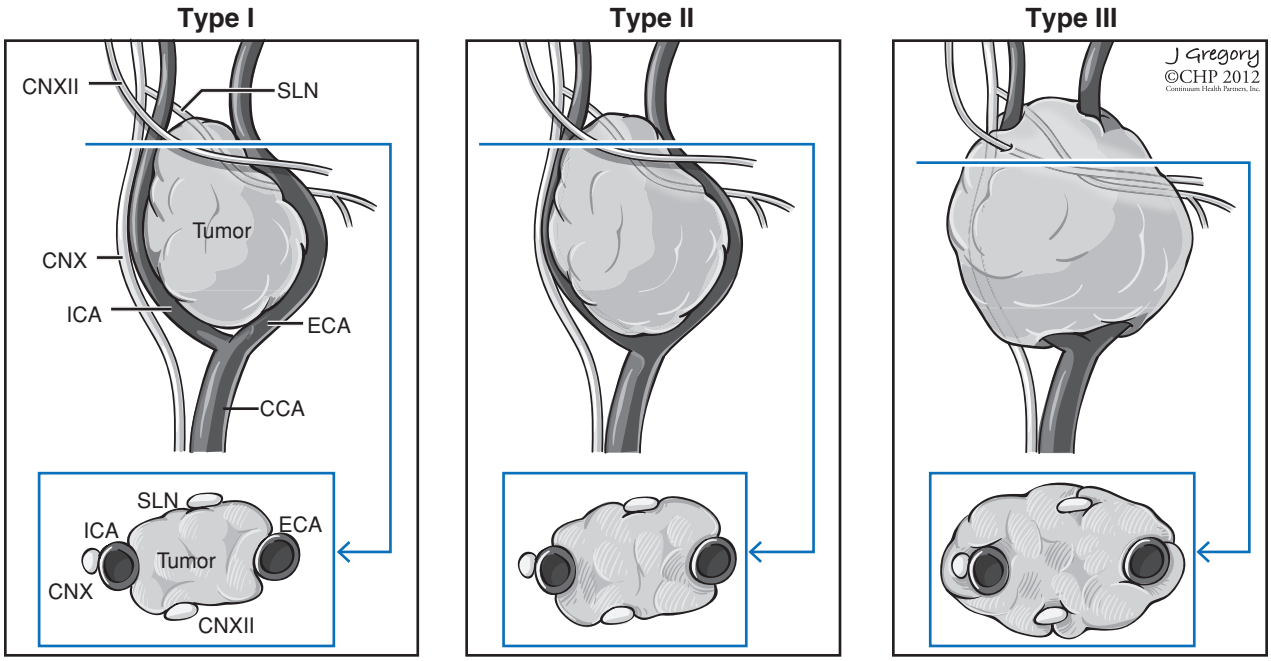



**FIGURE 27-6.** Shamblin's classification of carotid body tumors. CCA, common carotid artery; CN, cranial nerve; ECA, external carotid artery; ICA, internal carotid artery; SLN, sentinel lymph node.

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Growth through Jacobson nerve canal and the hypotympanic air cells leads to involvement of the middle ear and mastoid bone leading to conductive hearing loss, tinnitus, and facial paralysis. Intracranial involvement through the jugular foramen is frequent. Erosion of the jugulocarotid spine leads to involvement of the vertical petrous carotid artery, and further anterior extension leads to involvement of its horizontal portion. More medial extension to the infralabyrinthine air cells lead to involvement of the petrous apex. Further medial extension along this pathway leads to involvement of the clivus and cavernous sinus. Occasionally, jugular paragangliomas will escape the confines of the temporal bone and involve the infratemporal fossa and parapharyngeal space. Lower cranial nerve involvement is frequent and ranges from 38% to 58%.[58,59] Multiple cranial nerves are frequently involved in Vernet syndrome (paralysis of CNs IX, X, and XI) or Collet–Sicard syndrome (paralysis of CNs IX, X, XI, and XII). In at least 10% of jugular paragangliomas, one of these sequences is present (Fig. 27-7). The attendant symptomatology is hoarseness, swallowing difficulty, hemipalatal dysfunction with nasal air escape, shoulder motion restriction, and dysarthria due to tongue hemiparalysis. Two surgical classification systems are in wide use today. Both can be used preoperatively based on radiographic findings. The Fisch classification system makes no distinction between tympanic and jugular paragangliomas and is predicated on detailed patterns of progressive disease extension, whereas the Glasscock-Jackson system treats tympanic and jugular paragangliomas differently[27,58] (Tables 27.3 and 27.4).

Vagal paragangliomas account for 5% of all head and neck paragangliomas and originate in that nerve where the paraganglia are diffusely distributed in the superior, middle, and inferior vagal ganglia. There is a female preponderance of 3:1. Tumors originating superiorly will often present with a dumbbell appearance, with an intracranial component in the posterior cranial fossa. Tumors originating inferiorly will extend into the poststyloid compartment of the parapharyngeal space. Vagal paragangliomas are frequently associated with multiple cranial neuropathies at presentation in up to 50% of patients. The vagus nerve is affected most commonly, followed by the hypoglossal and the spinal accessory nerves (Fig. 27-8).[60]

## WORKUP FOR PARAGANGLIOMAS

Patients presenting with signs and symptoms of a paraganglioma should undergo a thorough history and physical examination to evaluate cranial nerve dysfunction, evidence of signs and symptoms related to catecholamine secretion, and signs of malignant

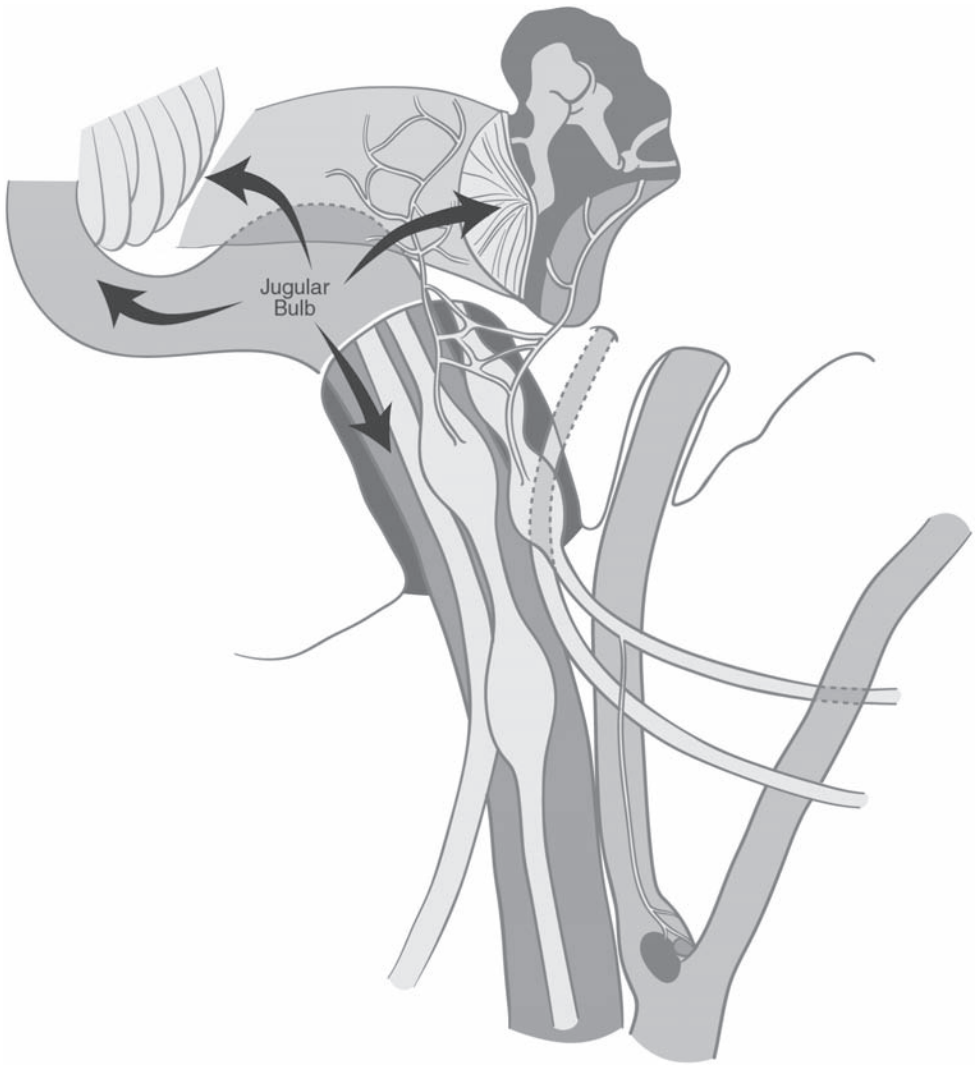



**FIGURE 27-7.** Modes of spread for jugular paragangliomas.

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**TABLE 27.3 Fisch Classification of Jugulotympanic Paragangliomas**

| | |
|---|---|
| Class A | Tumors arising on the tympanic plexus confined to the middle ear |
| Class B | Tumors arising from the inferior tympanic canal in the hypotympanum with middle ear and/or mastoid invasion, but jugular bulb and carotid canal intact |
| Class C | Tumors arising in the dome of the jugular bulb and involving the overlying cortical bone |
| C1 | Tumors eroding the carotid canal, but not involving the carotid artery |
| C2 | Tumors involving the vertical petrous carotid artery |
| C3 | Tumors involving the horizontal carotid canal, but not foramen lacerum |
| C4 | Tumors involving the foramen lacerum and cavernous sinus |
| Class D | Tumors with intracranial extension |
| De1 | Extradural extension of <2 cm medial dural displacement |
| De2 | Extradural extension of >2 cm medial dural displacement |
| Di1 | Intradural extension of <2 cm |
| Di2 | Intradural extension of >2 cm |
| Di3 | Neurosurgically unresectable tumors |

*Source:* Modified from Fisch V, Mattox D. *Microsurgery of the Skull Base.* New York, NY: Thieme Medical Publishers; 1988:149–153, with permission.

**TABLE 27.4 Glasscock–Jackson Classification of Jugulotympanic Paragangliomas**

| | |
|---|---|
| **Glomus tympanicum** | |
| Type 1 | Small mass limited to the promontory |
| Type 2 | Tumor completely filling the middle ear |
| Type 3 | Tumor filling the middle ear and mastoid |
| Type 4 | Tumor completely filling the middle ear, extending into the mastoid or through the external auditory canal. May also extend anteriorly to involve the carotid artery |
| **Glomus jugulare** | |
| Type 1 | Small tumor involving the jugular bulb, middle ear and mastoid |
| Type 2 | Tumor extending under the internal auditory canal. May have intracranial extension |
| Type 3 | Tumor extending to the petrous apex. May have intracranial extension |
| Type 4 | Tumor extending beyond the petrous apex into the clivus or infratemporal fossa. May have intracranial extension |

transformation. Attention should be focused on a familial history of paragangliomas, MEN type 2, and Von Hippel-Linday syndromes. Genetic testing for PGL gene should be done if there is a positive family history, and other members of the family should be screened for paragangliomas.

Twenty-four-hour urine screening as well as serum catecholamine screening for norepinephrine, epinephrine, and their metabolites should be performed to exclude a functioning tumor. A fine-needle biopsy is not indicated in most tumors because the radiographic studies are virtually diagnostic.[17,18,27,61]

## DIAGNOSTIC IMAGING STUDIES

### Computed Tomography

CT with contrast is an excellent imaging choice for the diagnosis and delineation of paragangliomas. Since these tumors are highly vascular, early and intense contrast enhancement is seen. The relation of the tumor to the external and internal carotid arteries, as well as the jugular vein makes this modality essentially diagnostic.[62] The delineation of the pattern of invasion of the temporal bone and skull base is indispensable in treatment, especially preoperative planning. Carotid body tumors display the characteristic splaying of the internal and external carotid arteries by a circumscribed mass occupying the carotid bifurcation. These tumors displace the ICA posterior and laterally. Vagal lesions typically displace the ICA anteriorly and occupy the high parapharyngeal space, with or without involvement of the skull base. Jugulotympanic paragangliomas can be distinguished in their early phases, especially when a tympanic paraganglioma is confined to the tympanic cavity. Characteristic patterns of bone destruction occur with jugulotympanic paragangliomas. These include erosion of the jugulotympanic spine, enlargement of the jugular foramen with bone destruction, and involvement of the middle ear and mastoid.[62,63] Multiplain reconstruction of high-resolution CT scans—axial, sagittal, and coronal—is of great assistance in the planning of operative management of these tumors. Middle ear and/or Eustachian tube involvement will create obstructive fluid accumulation in the aerated spaces of the temporal bone, including the mastoid (Fig. 27-9).

### Magnetic Resonance Imaging

MRI is a complementary and equally important imaging modality in the evaluation and treatment of head and neck paragangliomas. MR with gadolinium contrast serves three purposes: delineation of the tumor in question, surveillance and detection of concurrent paragangliomas of the head and neck, and confirmation of the diagnosis of paraganglioma. The classic, "salt and pepper" appearance of paragangliomas on T2-weighted images is due to the high-flow vascular voids that are essentially pathognomonic. Paragangliomas show intense signal enhancement with gadolinium contrast.[64] Fat-suppressed sequences are exceptionally useful in delineating the extent of the tumor. Patterns of carotid artery displacement can be accurately determined distinguishing carotid body tumors from vagal paragangliomas.[64] More importantly in tumors with intracranial extension, intradural versus extradural involvement can be appreciated, and the relationship of the tumor to important intracranial structures can be delineated. Specialized techniques such as MR angiography and contrast time-of-flight three-dimensional angiography increase the sensitivity of the diagnosis of concurrent tumors, but do not supplant selective angiography in the preoperative planning setting (Figs. 27-10 and 27-11).[65,66]

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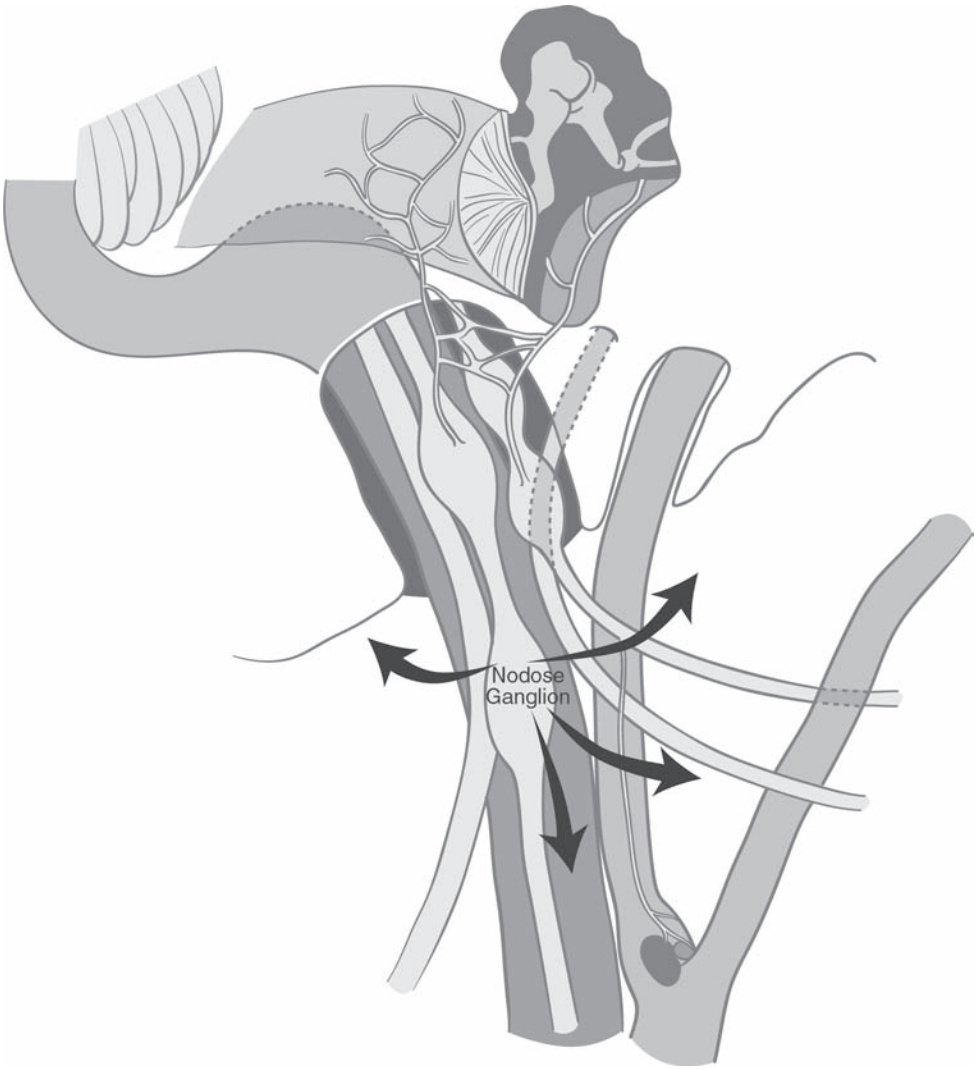



**FIGURE 27-8.** Modes of spread for vagal paragangliomas.

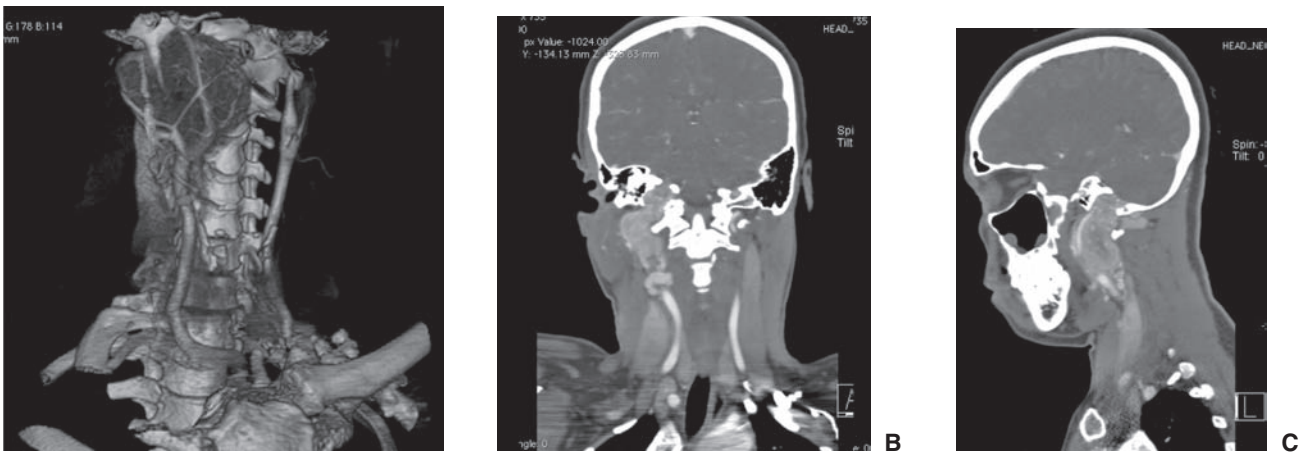


**FIGURE 27-9.** Computed tomography angiogram of a patient with a large paraganglioma. **A:** Volumetric surface rendering shows anterolateral displacement of the internal carotid artery and narrowing of its lumen. Note the filling of the internal jugular vein with contrast posterior to the common carotid artery, demonstrating the high flow within this tumor. **B:** Coronal reformat demonstrates involvement of the jugular foramen as well as the hypoglossal canal by tumor. **C:** Sagittal reformat demonstrates circumferential involvement of the internal carotid artery with anterior displacement, with extensive involvement of the jugular foramen to its intracranial portion. (See color insert for part **A**.)

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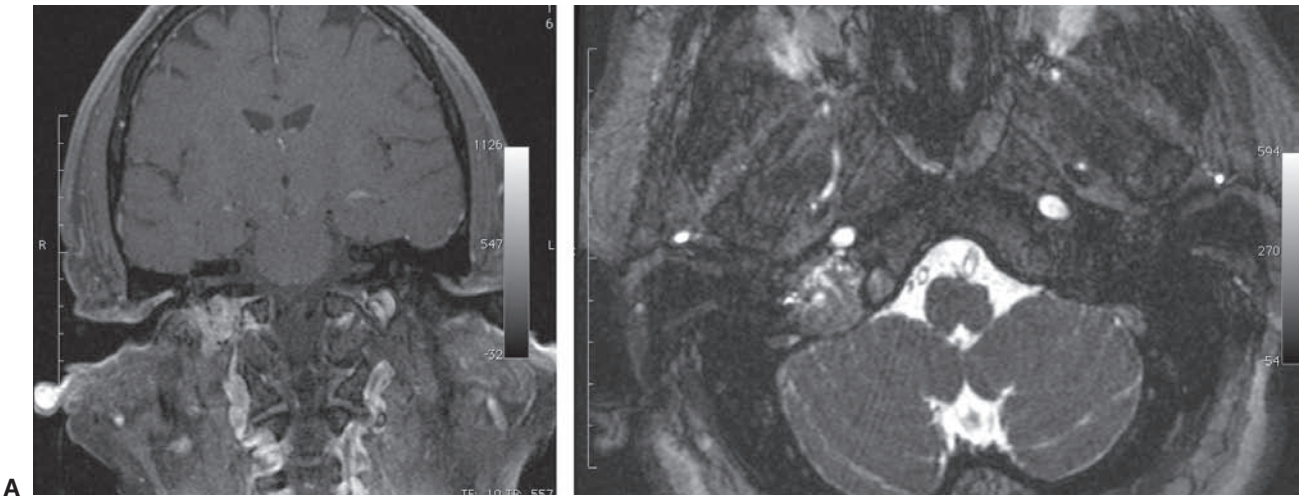



**FIGURE 27-10.** Jugular paraganglioma. **A:** Coronal enhanced fat-suppressed T1-weighted image shows avid enhancement with focal round flow voids indicating large feeding vessels. **B:** Axial fat-suppressed T2-weighted image demonstrates the proximity of the tumor to the vertical portion of the petrous internal carotid artery as well as the intracranial but extradural component of the tumor in the jugular foramen posteriorly.

## Angiography

With the evolution of detailed MR and CT techniques, angiography plays a much more limited role in the diagnosis of head and neck paragangliomas, but is still very important in preoperative planning of these tumors. Angiography provides a detailed map of tumor blood supply and venous drainage, demonstrates the tumor-flow dynamics, and details the general vascular anatomy of the head and neck and intracranial space. Importantly, four-vessel cerebral angiography provides qualitative and quantitative flow studies of the cerebral circulation. This angiographic information creates the ability and access for the preoperative preparation provided by superselective embolization of the feeding arterial supply to the tumor. Bleeding is thus decreased intraoperatively.

Arterial supply of carotid body tumors is derived directly from the feeding vessels to the carotid body that is typically hypertrophied in the presence of a tumor.[27,58,67] Arterial supply of jugulotympanic tumors is well defined when these tumors are early in their development and invariably involves the ascending pharyngeal artery. As these tumors grow, they recruit additional blood supply that comes from the internal carotid circulation via the caroticotympanic arteries. With invasion of the posterior fossa and medial extension of the tumor toward the cavernous sinus, additional vascular recruitment is possible through the posterior circulation by means of the vertebral arteries through the clival anastomoses, as well as the cavernous sinus microcirculation. This is especially important in the preoperative embolization of these tumors. Assessing tolerance to interruption of the ICA is of paramount importance for extensive paragangliomas

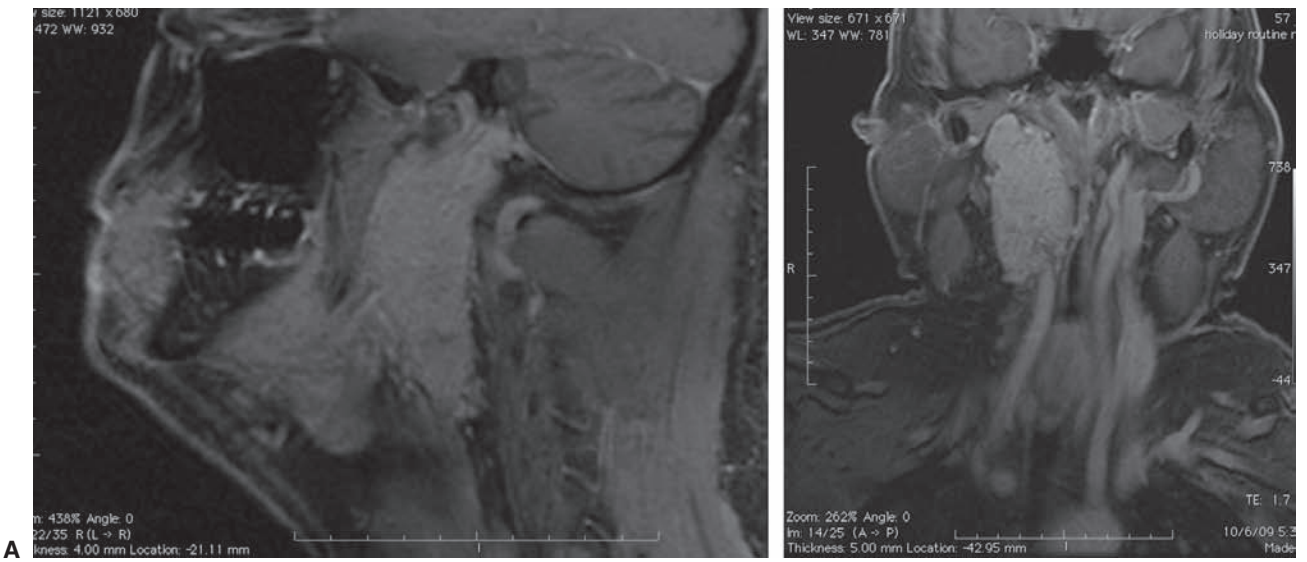



**FIGURE 27-11.** Vagal paraganglioma. Sagittal **(A)** and coronal **(B)** enhanced fat-suppressed T1-weighted images demonstrate typical rostrocaudal growth. The internal carotid artery is displaced anteriorly.

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that involve the ICA because of its vulnerability to injury during surgery, or where a planned internal carotid resection is contemplated. An angiographic balloon occlusion test involves the use of a femoral-artery-introduced catheter guided ultimately into the internal carotid, which is temporarily occluded usually at the carotid siphon within the cavernous sinus. This helps to determine whether there will be neurologic deficit.[17,19] During occlusion, several methods of neurologic monitoring testing can be utilized. In order of decreasing sensitivity, they are clinical neurologic examination, electroencephalography (EEG), and quantitative blood-flow examination through xenon CT concurrent examination. Xenon CT angiography is a precise quantitative study with the best sensitivity, but is rarely available and cumbersome (Fig. 27-12).[68,69]

## Radionuclide Imaging

Radionuclide imaging of paragangliomas targets the biochemical pathways of catecholamine synthesis, storage, and secretion by chromaffin tumor cells. A variety of different imaging techniques exist: $^{123}$I-metaiodobenzylguanidine (MIBG), $^{18}$F-3,4 dihydroxyphenylalanine ($^{18}$F-DOPA-PET), $^{18}$F-fluorodopamine ($^{18}$F-FDA-PET), $^{18}$F-fluoro-2-deoxyglucose ($^{18}$F-FDG-PET), and Indium octreotide scanning ($^{111}$In-octreoscan).[70,71]

Different functional imaging agents target paraganglioma tumor cells through different mechanisms. $^{123}$I- and $^{131}$I-labeled MIBG and $^{18}$F-FDA are actively transported into neurosecretory granules of catecholamine-producing cells via the vesicular monoamine transporters after uptake into cells by the norepinephrine transporter. In contrast, $^{18}$F-DOPA enters the cell via the amino acid transporter, a biochemical phenomenon based on the capability of paraganglioma and other neuroendocrine tumors to take up, decarboxylate, and store amino acids along with their biogenic amines. Instead of targeting catecholamine pathways, $^{18}$F-FDG enters the cell as the glucose transporter, and its accumulation is an index of increased glucose metabolism. While $^{111}$In octreoscan images indicate somatostatin type 2 receptors that are expressed in paragangliomas.[17,18]

$^{111}$Inoctreoscan specificity and sensitivity is approximately 90% in head and neck paragangliomas, a fact that makes it a very effective screener for secondary tumors as well as a postoperatively screen for recurrent disease when structural studies like CT and MRI may be compromised. $^{123}$I-MIBG shows similar sensitivities and specificities. Malignant and metastatic paragangliomas are best imaged with $^{18}$F-FDG-PET, which shows sensitivities of 74% to 88%.[17,18]

It is increasingly understood that there is a link between genotype-specific tumor biology and imaging. For example $^{18}$F-FDG-PET has an excellent sensitivity for paragangliomas due to *SDHB*-associated mutation. The *SDHB* gene encodes for subunit B of the mitochondrial SDH complex II that catalyzes the oxidation of succinate to fumarate in the Krebs cycle and feeds electrons to the respiratory chain, which ultimately leads to the generation of ATP (oxidative phosphorylation). Higher glucose requirements for anaerobic metabolism explains the increased $^{18}$F-FDG uptake by malignant *SDHB*-related paragangliomas.[71]

# TREATMENT

Surgical resection has been the traditional treatment for paragangliomas of the head and neck. Microsurgical skull base techniques such as the Fisch infratemporal fossa approaches were developed to specifically resect temporal bone paragangliomas (Fig. 27-13). The refinement of these elegant surgical techniques, especially when aided by preoperative embolization, have significantly reduced morbidity and have minimized mortality associated with surgery. However, with complete tumor extirpation, lower cranial nerve resection or inadvertent injury to the lower cranial nerves can result in significant morbidity affecting phonation and deglutition, along with the risk for aspiration.

Radiation therapy—initially used only for the treatment of unresectable tumors or for surgical treatment failures—has become an established treatment modality in untreated lesions and has been incorporated into the treatment algorithms for head and neck paragangliomas. External beam radiation, intensity-modulated radiation therapy, and, more recently, stereotactic radiation, all have been used with excellent results.

In deciding what modality of treatment to select, the following factors should be taken into account: the patient's age and

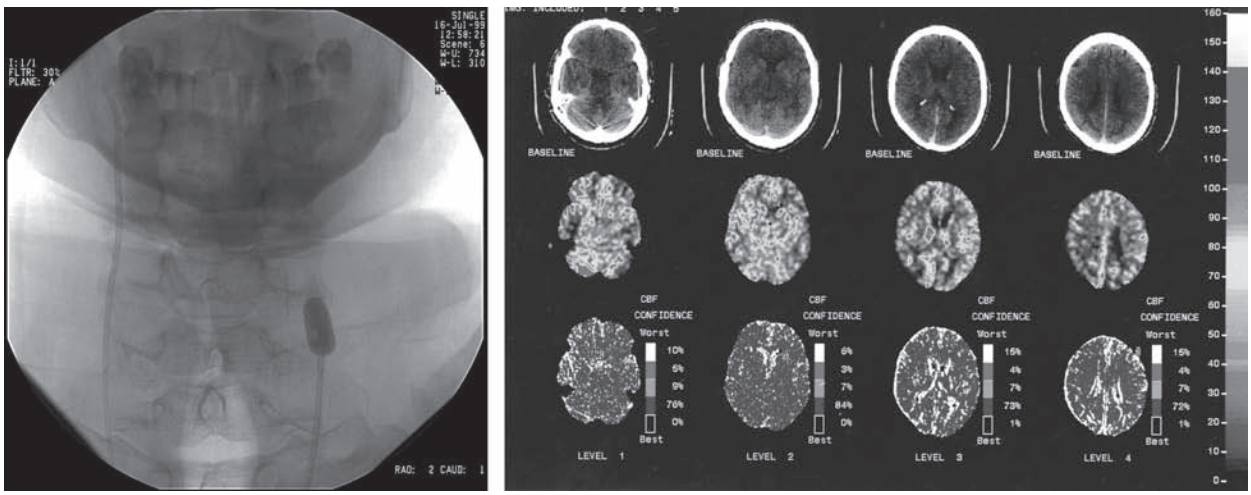



**FIGURE 27-12.** Balloon occlusion testing. **A:** Frontal angiographic image shows the inflated radiodense balloon in the proximal left internal carotid artery, occluding flow. **B:** Quantitative cerebral blood flow images created by inhaling xenon gas during dynamic CT. The color images reveal reduced flow (blue instead of red) in the left MCA distribution.

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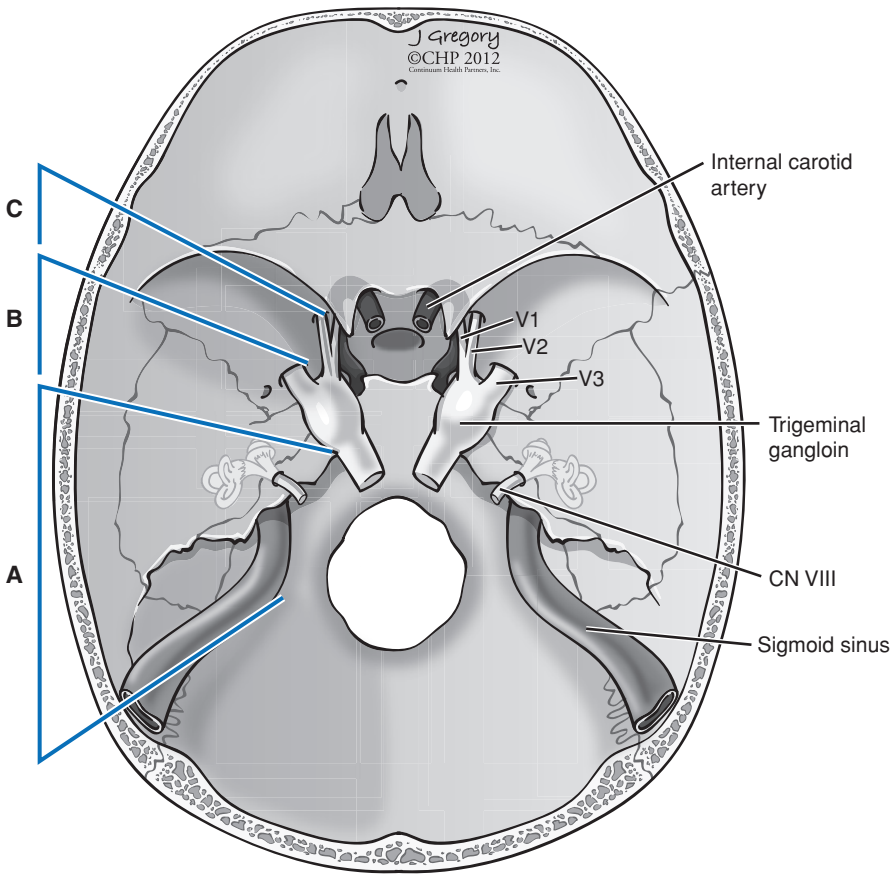



**FIGURE 27-13.** Fisch classification of infratemporal fossa approaches. Type A, exposure to the level of the anterior Eustachian tube, middle meningeal artery/foramen spinosum. Type B, exposure to the foramen ovale, V3. Type C, exposure to the foramen rotundum, V2. CN, cranial nerve.

medical comorbidities, the type of paraganglioma in question (vagal, tympanic, jugular, carotid body), the presence of concurrent paragangliomas, the extent of the tumor, as well as any preoperative cranial nerve deficits, whether partial or complete. When surgery is contemplated, the availability of a surgical team with experience in lateral skull base methods, as well as an experienced interventional neuroradiology team, is sought.

## SURGERY

Preparation for surgery requires angiographic evaluation for most paragangliomas. Anesthesia requirements should take into consideration tumors that may be actively secreting catecholamines, which will require alpha and beta adrenergic blockade. Continuous arterial pressure monitoring is required, and transfusions may be necessary. Central venous pressure monitoring may be required depending on the underlying comorbidities.

### Angiographic Evaluation

Superselective angiography is invaluable in surgical planning for paragangliomas. This sophisticated technology provides an arterial map that not only identifies the feeding blood vessels, but also provides the flow dynamics of the tumor. This is especially useful with larger tumors in which multiple feeding vessels from both the internal and external circulation may be present with anastomoses between the external and internal carotid systems.[72] Similarly, the ICA can be evaluated for structural integrity and areas of constriction or irregularity that might suggest vessel involvement and the potential need for its sacrifice. The venous phase of angiography is equally important in identifying the draining vessels and especially in jugulotympanic paragangliomas, the degree of occlusion of the jugular bulb, sigmoid sinus, and jugular vein.

Equally important is the angiographic evaluation of adequate cerebral circulation in the event of ICA disruption or sacrifice. There are many methods for assessing for adequate contralateral cerebral circulation. Xenon CT scanning with concurrent balloon occlusion is a quantitative analysis of cerebral flow and is the most precise method of cerebral circulation evaluation though it is cumbersome and not readily available.[68,69] Temporary balloon occlusion of the carotid with monitoring of the clinical neurologic examination in the presence of a patent circle of Willis is easier to perform and also very reliable. EEG monitoring can be performed during balloon occlusion, as well as hypotensive challenge during the period of balloon occlusion. Approximately 93% of patients can tolerate sacrifice of the carotid artery based on the appropriate angiographic evaluation. It should be noted that intraoperative conditions may be different in terms of cerebral delivery of oxygen than those in the angiographic suite.[19] Tolerance with temporary internal carotid occlusion does not predictably avoid the possibility of a delayed postoperative cerebrovascular ischemic event. The venous outflow of the ipsilateral and contralateral sigmoid and jugular systems should be noted, especially in jugulotympanic paragangliomas. Because of the possibility of a postoperative venous stroke, a contralateral hypoplastic or absent jugular system constitutes a contraindication (Fig. 27-14).[73–75]

### Embolization

Embolization is a very useful adjunct to surgery of large paragangliomas, and when done by an experienced endovascular team, carries a very low morbidity rate. The obvious risk of embolization

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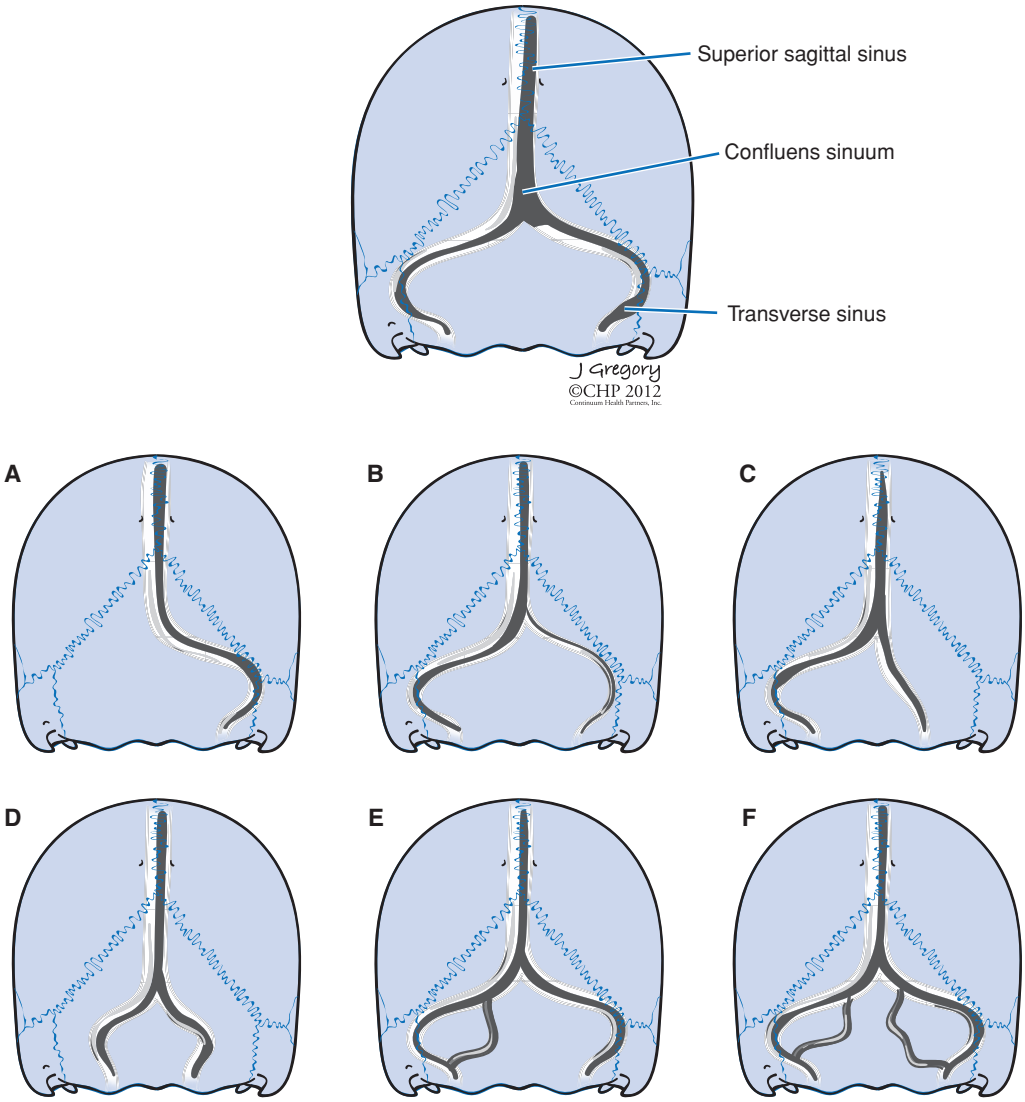



**FIGURE 27-14.** Variations of the intracranial posterior venous outflow system at the level of the transverse sinus, sigmoid sinus, and jugular bulb. Variations A and B would have a high surgical significance if a lesion were to involve the dominant side.

is the escape of embolizing particles into the cerebral circulation with all risk of stroke. This can occur through external–internal carotid circulation anastomoses or flow reversal from the arterial supply of the tumor. The advantages of embolization are tumor shrinkage and decreased blood flow that in large tumors have profound benefits. Less intraoperative bleeding is generally associated with a much easier dissection—more obvious tissue planes and less risk to normal anatomic structures, especially cranial nerves. Importantly, such a circumstance lessens the likelihood of requiring transfusion. Larger paragangliomas have multiple arterial feeding vessels that require superselective angiography. Using these methods, each successive embolization devascularizes additional compartments of the tumor until an absence of a tumor "blush" is achieved. It is essential that surgery be performed within 48 hours of embolization to avoid recruitment of collateral circulation. The inflammatory tumor reaction that has been reported following embolization is countered somewhat by the administration of steroids (Fig. 27-15).[72,76]

## Surgery

***Carotid Body Tumors.*** Smaller carotid body tumors can be approached through a transverse neck incision, but the removal of larger ones is facilitated by an oblique/vertical incision along the anterior border of the sternocleidomastoid muscle. Proximal and distal tumor dissection identifies the common, internal and external carotid arteries and jugular vein. Vessel loop control is achieved on the appropriate vessels. Carotid bypass precautions should be readily available. The cephalic extent of the large tumors can make control at the skull base substantially more difficult. The entire course of the ICA is then exposed, and usually it is noted to be displaced posterolaterally. A subadventitial plane of dissection must be done with extreme care. The tumor may require splitting in configurations in which it encases the ICA. In a similar fashion, the external carotid artery is then addressed. Encasement and infiltration of the external carotid artery may necessitate vessel sacrifice, although this should be avoided when possible. Ligation of this artery for control of blood flow to the tumor is ineffective since it usually does not alter the main supply, and, additionally, the collateral circulation is not infrequent (Figs. 27-16 and 27-17).

The dissection of the tumor at the bifurcation of the carotid is done as a last step since this site is the most vulnerable breaching the artery. As the site of origin (carotid body) of these tumors, the association with the arterial wall is its most intimate. The surrounding cranial nerves associated with carotid body

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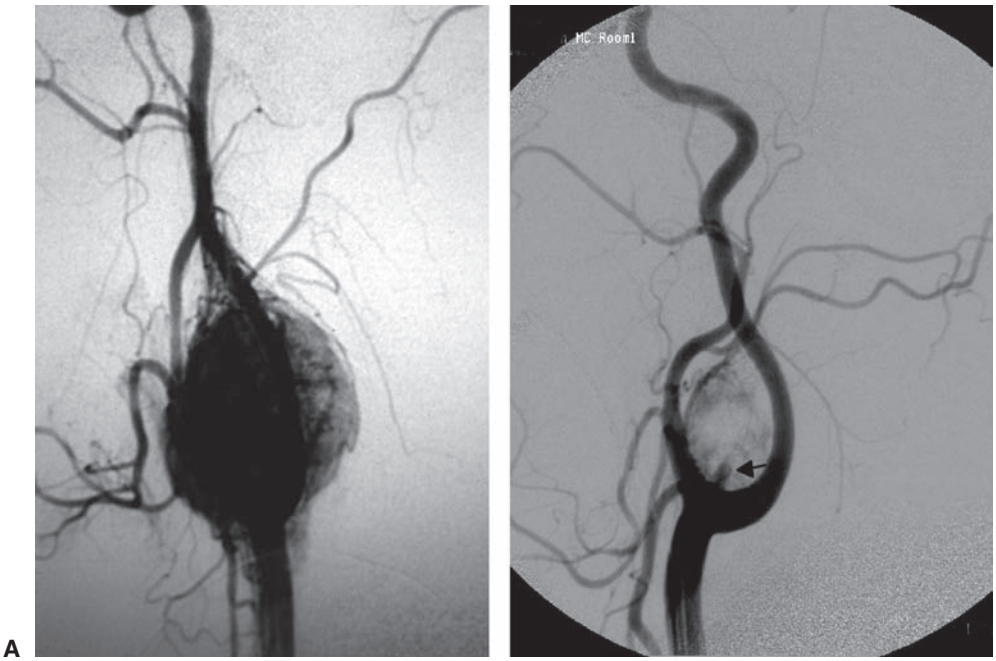



**FIGURE 27-15.** Preoperative embolization of a carotid body tumor. **A:** Preembolization lateral angiogram shows early, intense blush reflecting high vascular flow with multiple collateral feeding vessels. **B:** Postembolization frontal angiogram shows marked reduction in vascularity. The primary feeding vessel (*arrow*) terminates abruptly.

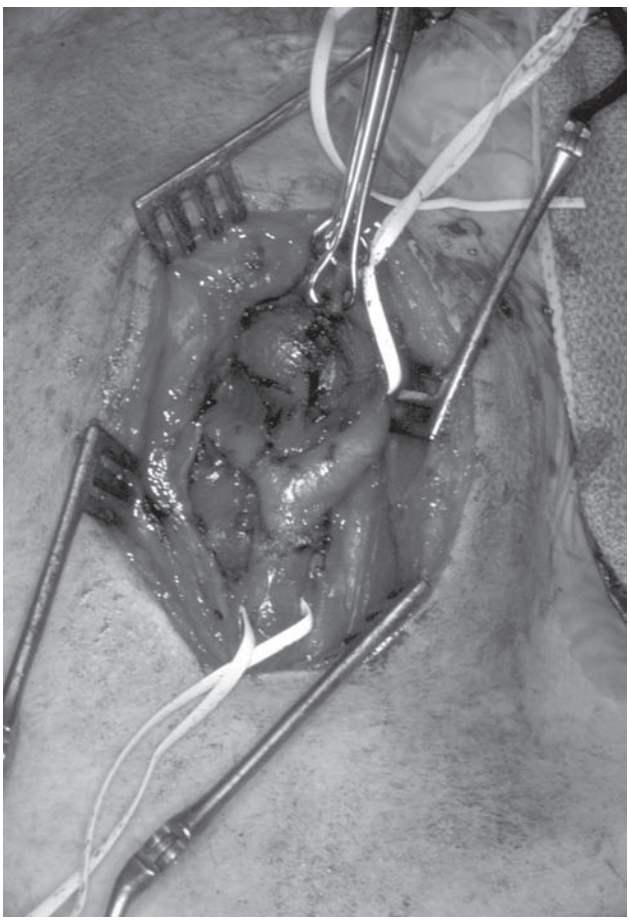


**FIGURE 27-16.** Intraoperative picture of a carotid body tumor. Tenaculum is on the lateral tumor surface. Vessel loops are around the common carotid artery (inferiorly) and internal carotid artery (superiorly).

tumors usually show marked hyperemia of the vasa nervosum of the sheath. In larger tumors, these nerves—vagus, hypoglossal, and glossopharyngeal—may be intimately involved and their dissection can cause dysfunction.

***Jugulotympanic Paragangliomas.*** Small tympanic paragangliomas (Glascock–Jackson type I, Fisch Class A) can be approached through a transcanal/inferiorly based tympanomeatal flap. Embolization of these tumors is not required. Bipolar electrocautery microforceps can be used to shrink the tumor and resect it. Larger tympanic paragangliomas confined to the middle ear and/or mastoid, but that do not breach the bone overlying the jugular bulb or the jugulocarotid spine, can be exposed through a combined postauricular/endaural approach with a canal-wall-up mastoidectomy and extended facial recess approach inferiorly that sacrifices the chorda tympani and removes the vaginal process of the tympanic bone to expose the hypotympanum.

When the jugular bulb is involved, a combined temporal/cervical approach is required. An extended mastoidectomy and extended facial recess approach is performed with skeletonization of the sigmoid sinus and exposure of the jugular bulb through the retrofacial air cells. The ICA is dissected superiorly and controlled. Cranial nerves IX, X, and XI are identified and traced proximally and distally. The internal jugular vein is then ligated superiorly and dissected toward the jugular bulb in the neck. The sigmoid sinus is occluded and ligated above the tumor extension. Contralateral venous outflow should be verified through preoperative studies. When occlusion of the sigmoid sinus is performed, this should be done in a manner that avoids interfering with the outflow from the anastomotic vein of Labbe, which drains the temporoparietal cortex and thereby avoids the risk of a venous stroke.[77] Once the sigmoid sinus is opened and the jugular vein is ligated inferiorly, hemostatic agents can be injected to gently occlude the inferior petrosal veins. This provides blood-free visualization of the jugular bulb and improves the microsurgical dissection at the pars nervosa of the jugular bulb, the site most likely to sustains cranial nerve injury. Dissection of the tumor should proceed with irrigating bipolar electrocautery. At the level of the jugular bulb, the dissection should be undertaken with extreme

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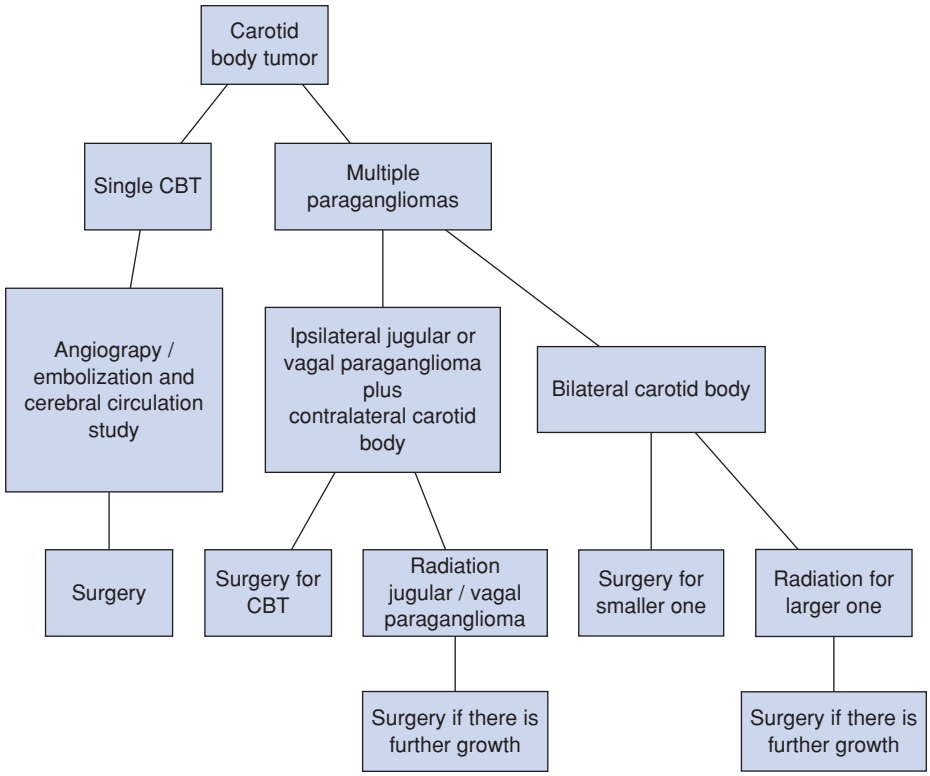



**FIGURE 27-17.** Decision analysis tree for the treatment of carotid body tumors (CBTs).

caution since the cranial nerve rootlets of the glossopharyngeal and the vagus are at their most vulnerable. In jugulotympanic paragangliomas, these rootlets are displaced medially and are thus in a favorable position. If the tumor does not extend into the pars nervosa/medial jugular bulb compartment, preservation of the cranial nerves is desirable.[78]

Those more advanced tumors that involve the vertical and/or horizontal petrous carotid artery and possible intracranial extension require a postauricular infratemporal fossa approach. These approaches begin with an extended mastoidotomy, removal of the external auditory canal, tympanic membrane, malleus, and incus. The external canal is permanently closed, which condemns the patient to a profound ipsilateral conductive hearing loss. The peritubal and pericarotid air cells are removed and the intrapetrous carotid artery is skeletonized proximal to the tumor extent. This may involve sacrifice of the middle meningeal artery and removal of the foramen spinosum as well as the foramen ovale if the tumor has extended toward the cavernous sinus. Tumor is removed from the carotid, middle ear, and sigmoid/jugular bulb/jugular vein (Fig. 27-18). Tumor extension to the medial jugular bulb compartment and/or intracranially places the nerve rootlets of cranial nerves IX, X, and XI in a vulnerable position, and more frequently than not, it is necessary to sacrifice them. If there is no such extension, an effort is made to gently dissect the tumor away from the nerves. The Eustachian tube should be permanently occluded to avoid postoperative cerebrospinal fluid rhinorrhea. Intracranial extension is addressed by opening the dura in the presigmoid area down to the tumor extension at the level of the jugular bulb. Tumor extension toward the petrous apex and clivus may necessitate a translabyrinthine/transcochlear approach. In these approaches, the facial nerve is mobilized out of the fallopian canal in its vertical and horizontal portion to the geniculate ganglion. This will result in temporary facial paralysis due to interruption of the blood supply to the nerve as well as the retraction anterosuperiorly.[27,58,79] Incomplete recovery of facial nerve function is a possible outcome. Reconstruction with temporoparietal fascia flap or temporalis muscle alone is done at the conclusion to assist healing and prevent a cerebrospinal fluid leak. Lumbar drainage for a limited period of time in the immediate postoperative recovery may be indicated for the prevention of a cerebrospinal fluid leak. When cranial nerves have been sacrificed, immediate surgical amelioration with a concurrent vocal cord medialization and a pharyngoplasty with cricoesophageal myotomy at the same sitting have been recommended.

Technical refinements include the juxtacondylar approach as well as the transjugular craniotomy.[78] These modifications both shift the surgical angle of approach posteriorly. The advantages are that they obviate the need for facial nerve transposition and improve the control and preservation of the lower cranial nerves in the jugular foramen. The limitation is that they cannot address tumor involvement in the petrous carotid artery area.

***Vagal Paragangliomas.*** Most vagal paragangliomas originate in the nodose (inferior) ganglion that is situated 2 cm below the jugular foramen. Their bidirectional growth along the vagus results in involvement of the jugular bulb superiorly and postyloid parapharyngeal space inferiorly. The ICA is displaced anteriorly.[60] Vagal paragangliomas originating in the superior and middle ganglia that are situated within the jugular foramen cause early skull base invasion with intracranial extension. The surgical techniques to approach these tumors are identical to those for jugulotympanic paragangliomas when the skull base is involved. The inferior extent of vagal paragangliomas requires detaching the digastric muscle from its origin and removing the styloid process to access the parapharyngeal space extension. Sacrifice of the vagus nerve in these tumors is inevitable. With involvement of the jugular foramen and skull base, additional cranial

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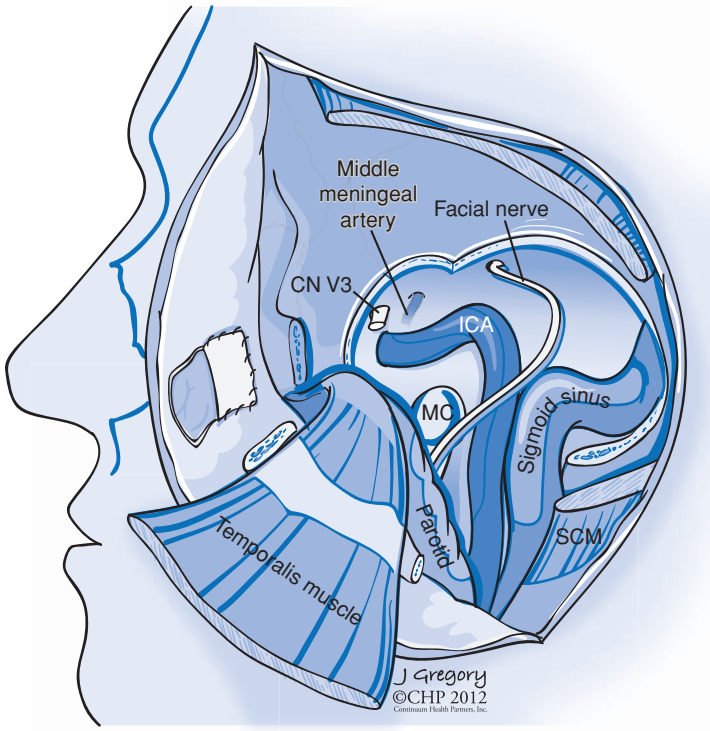



**FIGURE 27-18.** Schematic representation of a type B infratemporal fossa approach. Lateral temporal bone has been removed exposing the petrous carotid artery, jugular vein, jugular bulb and sigmoid sinus. Facial nerve has been mobilized in its horizontal and vertical portions. The third division of the trigeminal nerve (V3) has been divided as well as the middle meningeal artery right behind it. CN, cranial nerve; MC, mandibular condyle; SCM, sternocleidomastoid muscle; ICA, internal carotid artery.

nerve deficits are to be expected as these tumors extend medial to the cranial nerve rootlets, within the pars nervosa of the jugular foramen.

## POTENTIAL COMPLICATIONS

### Vascular Injury

Early series of paraganglioma surgery reported a stroke rate of 10% to 20%; recent series report rates of 0% to 2%. Because of contemporary diagnostic methods, preoperative planning, and microsurgical techniques, the risk of injury or need for internal carotid sacrifice is minimal. For carotid body tumors, the risk of injury and need for vessel sacrifice is size specific with tumors larger than 5 cm likely requiring carotid reconstruction. In addition, preoperative findings of stenosis and irregularity on angiography and/or circumferential involvement on MRI with loss of the pericarotid adventia make preoperative preparation for carotid resection and reconstruction critically important.[80–83]

Vagal paragangliomas differ from carotid body tumors and jugulotympanic tumors because they are not intimately associated with the carotid artery. In advanced vagal and jugulotympanic lesions, however, the ICA can be completely encased by tumor within the petrous portion. With adequate surgical exposure and microsurgical technique, injury should be infrequent in experienced hands. Internal carotid sacrifice in this location is fraught with problems; therefore, if sacrifice is contemplated, consideration for alternate treatment in these instances is important. If the vessel is at high risk for injury within the petrous carotid portion, and the patient has safely passed balloon occlusion testing, permanent preoperative occlusion of the carotid distal to the tumor should be considered.

Reported more recently, a novel approach to the artery that is particularly at risk for injury is to place a vascular endoprosthesis and then perform the surgery several weeks later. Fibrosis around the self-expanding stent creates a leak-proof artery. This has the advantage of reducing blood flow to the tumor, as well as preventing vascular injury.[84]

### Baroreflex Failure

Surgery for removal of bilateral carotid body tumors results in loss of the baroreceptor reflex with bilateral denervation of the carotid sinus. In the immediate postoperative period, this results in labile refractory hypertension, tachycardia, diaphoresis, and headache that is treated with sodium nitroprusside. Long-term treatment is control with clonidine.[85] This complication is more than theoretical, and in this bilateral circumstance, alternative therapy should be considered for one of the tumors.

### Cranial Nerve Injury

The risk to the lower cranial nerves in surgery for paragangliomas is location and tumor size specific. In decreasing order of risk these tumors pose to injury: vagal, jugulotympanic, and carotid body paragangliomas. Size of lesion is especially important in vagal and jugulotympanic paragangliomas. Tumors with extensive skull base involvement, intracranial and/or infratemporal fossa extension are likely to have extensive involvement of the lower cranial nerves with at least one nerve involved, and oftentimes, multiple nerve deficits preoperatively. Involvement of the facial nerve with preoperative paralysis is a sign of such extensive involvement.[27,58,59,86,87]

Single cranial nerve deficit most commonly results postoperatively in temporary deglutition, dysphonia, tongue motion abnormalities, and/or aspiration problem. Because of the complex interactive physiology of swallowing, and speaking, multiple cranial nerve deficits have additive effects and are poorly tolerated in older patients. In this population, recovery is often very difficult, and permanent aspiration requiring management with a gastrostomy and tracheostomy is a real possibility, especially in

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high vagal nerve injuries. Bilateral lower cranial nerve paralysis, especially of the vagus nerve, as a result of therapy or progression of tumor in bilateral disease is a devastating injury that can results in significant dysphagia and dysphonia.

The clinical manifestations of vagal nerve injuries reflect the level of the insult, whether from tumor or from surgical trauma. Injuries distal to the origin of the superior laryngeal nerve will result in vocal cord paralysis that is generally easily managed. Higher vagal injuries, such as those at the nodose ganglion or at the level of the jugular foramen, result in vocal cord paralysis, anesthesia of the ipsilateral supraglottic and hemilarynx, and paralysis of the ipsilateral soft palate. These deficits result in aspiration and dysphagia. In addition, air and food escape into the nasopharynx because of the paralysis of the soft palate. Vagal nerve injuries at the jugular foramen are often associated with glossopharyngeal nerve injuries that add ipsilateral pharyngeal anesthesia, an occurrence that further compromises swallowing function. Superior vagal injuries require prompt and intensive swallowing therapy in addition to surgical management of the vocal cord paralysis (Fig. 27-19). Most injuries at the level of the jugular foramen are permanent, and early surgical management helps mitigate the over effects of the deficits. Vocal cord medialization with a thyroplasty combined with cricopharyngeal myotomy will improve phonation and deglutition, as well as minimize the risk of aspiration. An ipsilateral palatal adhesion procedure can mitigate the hypernasality in speech and nasality during deglutition. Additional lower cranial nerve injuries are seen in 30% to 50% of patients with a vagal nerve injury. When this occurs, overall recovery is significantly more complicated.[88–91]

Accessory nerve injury results in loss of trapezius and/or sternocleidomastoid muscle function. Physical therapy is required for this to avoid pain secondary to shoulder "drop" as well as limitation of motion. If the nerve is injured below the jugular foramen, it may be amenable to primary repair by a nerve graft.[90]

Injury to the hypoglossal nerve results in ipsilateral tongue paralysis and long-term hemi-atrophy of that structure. When this is combined with additional cranial nerve injuries, swallowing becomes even more difficult and physical therapy becomes essential in preventing aspiration. Swallowing therapy is directed at teaching the patient to move the bolus to the functioning side.[90]

Injury to the sympathetic chain is seen in approximately 25% of patients postoperatively as a result of interruption of the sympathetic ganglia. This results in partial or complete Horner syndrome. The resultant ptosis can be easily rectified through a Müller muscle eyelid tightening procedure. "First bite syndrome," which is intense pain with the first bite, can develop as a result of denervation hypersensitivity of the myoepithelial cells of the parotid gland. This problem improves gradually and spontaneously in most patients.

Following the manipulation of removal, up to 40% of patients with carotid body tumors demonstrate cranial nerve deficits, the majority of which are transitory. Vagal nerve injury is the most common of those so affected. More specifically, in jugulotympanic paragangliomas the most common nerve deficit is also vagal (27%), followed by the glossopharyngeal (18%), the accessory and the hypoglossal (8%) on account of older surgical series.[17–19,59,90]

## Results of Recent Surgical Experience

The oncological outcomes from surgical management of advanced-stage jugulotympanic and vagal skull base paragangliomas have significantly improved in the last two decades. Surgical control ranges from 72% to 98%, results that are associated with a very low perioperative mortality and morbidity.[92] Tumors that were previously considered inoperable such as lesions that completely engulf the carotid artery, and those with extensive intracranial extension are now technically resectable.[93,94] A review

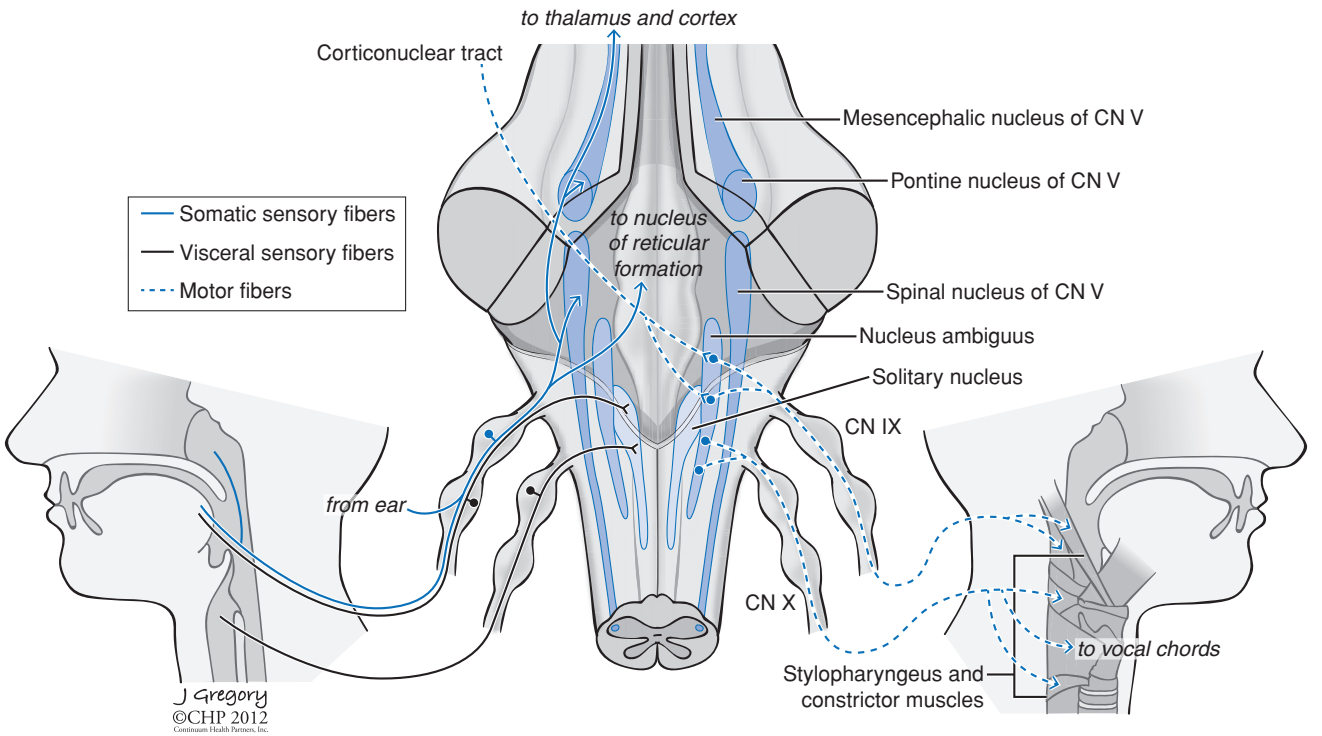



**FIGURE 27-19.** Schematic representation of the afferent and efferent swallowing reflex. CN, cranial nerve.

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of 9 publications of surgically managed temporal bone paragangliomas of advanced stage (Fisch C and D), with a substantial proportion of these patients having intracranial extension of their tumors showed tumor control in 84% to 100%, with a mortality of 1.7%, and morbidity from cerebrospinal fluid leaks ranging from 1.6% to 14.9%. In these largest series, new cranial nerve deficits were 15.9% to 17.6%.[92,95–102]

Sanna et al. reported on 121 cases surgically managed, with extensive tumors including 55.4% of which demonstrated intracranial extension. There were no deaths in the series, but morbidity was as follows: cerebrospinal fluid leak was 1.6%; cranial nerve dysfunction for CN IX was from 29.8% preoperatively to 54.5% postoperatively (24.7% additional); CN X dysfunction was from 47.1% preoperatively to 47.1% postoperatively (15.0% additional); CN VII dysfunction similarly was an additional 19%, with most of these being transient due to the nerve transposition. The same study reports that all but 4 patients (3.3%) required a secondary intervention for aspiration or dysphagia at 6 months.[92] Similar results are presented in a series of advanced tumors reported by Al-Mefty; 91.6% tumor control and a 7.1% new cranial nerve deficit as a result of treatment.[97] Moe and Tra Ba Huy also report recent series with similar patient profiles and outcomes.[95,97]

The keys to these encouraging results are the preoperative management of the ICA either by stenting or by preoperative occlusion when necessary, as well as the evolution of surgical techniques toward a safer tumor dissection; hence, a lesser mobilization of the facial nerve as well as proper management of the lower cranial nerves in their exit from the jugular foramen and the hypoglossal canal.

The common denominator for such outcomes in the surgical management of temporal bone paragangliomas is the interaction of a multidisciplinary team that includes expert preoperative interventional radiology and wide-ranging experienced surgeons.

## RADIATION THERAPY

Historically, radiotherapy has been considered for treatment of subtotally resected, technically unresectable paragangliomas (e.g., extensive skull base involvement or intracranial extension) or those considered inoperable because of age or medical comorbidities. However, with long-term experience reporting the efficacy of CT-based planning and modern radiation therapy delivery techniques, definitive radiotherapy has become recognized to be a highly effective treatment for paragangliomas. The most commonly treated site has been jugulotympanic paragangliomas followed by carotid body or vagal paragangliomas. Both conventionally fractionated radiotherapy and stereotactic radiosurgery have been utilized. Successful treatment of paragangliomas with radiotherapy must be defined since there is rarely total resolution of the tumor after treatment. Thus, "local control" usually means stability (or regression) of tumor size and nonprogression (or improvement) in neurologic symptoms.

### Radiation Effects

***Histopathologic Changes.*** The basis by which radiation prevents tumor growth and reduces symptoms is not completely understood. Essentially, the chief cells can be present long after radiation.[103–106] Few studies have reported the actual radiobiologic effect of radiation on paragangliomas.[103–105] Gardner studied 6 irradiated tumor specimens resected 4 to 6 weeks postradiation.[106] The distinctive finding was of vascular endarteritis with mural thrombi when compared with nonirradiated specimens. One of six specimens showed a necrotic infarct, whereas two cases showed changes in tumor cells consistent with pyknotic cellular death. No significant difference in fibrosis was noted between the irradiated and nonirradiated specimens. However, Rosenwasser and others have noted a 6-month postradiation dramatic increase in stromal fibrous connective tissue with wide separation of tumor nests and diminished vascularity.[103,107–109] Chief cells are present, but may develop nuclear pleomorphism with coarse chromatin clumping and irregular nuclear outlines. Others have described similar histopathologic findings in irradiated specimens.[106–108]

***Radiographic Changes.*** On postradiotherapy radiographic evaluation, the majority of lesions demonstrate unchanged size or modest tumor regression.[110–112] Mukherji reported the University of Florida experience of 17 patients with 18 paragangliomas that were treated with definitive radiation. These patients had been studied with pretreatment CT or MRI, and following radiation, were restudied with the same imaging.[113] Sixty-one percent showed a decrease in tumor size with an average reduction of 23% (range 8%–45%) at a median follow-up of 2½ years. All tumors persisted, but none showed an increase in size. Postradiation MRI findings included reduction in flow voids, decreased heterogeneous enhancement, and reduced T2 signal. CT detected improvement in skull base erosion in rare cases (1/8 patients).[110,111] Other smaller studies demonstrate regression in 57% to 73% of patients followed by CT.[114,115] Angiographic follow-up after radiation might not show significant change in patients, even in those in whom there has been no evidence of clinical tumor progression. Maruyama reported the results of three paragangliomas followed by serial angiography over several years and though tumors were clinically controlled, only minimal reductions in vascularity was detected angiographically.[116] In summary, paragangliomas show modest radiographic change or stable tumor in the majority of cases.

Based on these findings, it seems that radiation induces an obliterative endarteritis with resultant fibrosis that probably prevents regrowth in addition to promoting partial tumor involution.[103,117] Even though radiation exerts a primary effect on chief cells, it is difficult to determine whether morphologically persistent cells have lost reproductive capability.[118]

### Local Control with External Beam Radiation Therapy

The first major review demonstrating the efficacy of radiation was reported by Alford and Guildford (1962), on 106 cases of paragangliomas.[119] Although more advanced lesions were treated with radiotherapy, local control was comparable to surgery, 72% versus 78%, respectively. Unfortunately, follow-up was relatively short for a disease with a long natural history. Since then, numerous reports with follow-up as much as 35 years have demonstrated the effectiveness of radiation in control of head and neck paragangliomas (Tables 27.5 and 27.6). The accumulated data represent a wide variety of dose levels (30–70 Gy), radiation techniques (electrons, photons, radium implant) and beam energies (superficial, cobalt, 4–6 megavolts). Overall, local control rates range from 65% to 100% with an average of 90% based on >1,000 tumors from 37 series (985/1,094) (see Table 27.5).[103,110,111,114–116,120–151]

No obvious difference in local control is detectable between those primarily involving the temporal bone (jugular and tympanicum) versus the carotid body tumors and vagal paragangliomas (local control 97%—61/63) (see Table 27.6).[121,126,138,152–154] Mean or median follow-up was at least 10 years[110,115,121,123–125,129,137,139,145,148] in multiple series with a maximum follow-up of >30 years in some.[121,125,126,130,137,148] Kim reported a local control of 90% on

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**TABLE 27.5 Radiotherapy for Head and Neck Paragangliomas**

| Institution | Number of Patients | Median Follow-up | RT Dose (Range) | Local Control | Disease-specific Survival | Overall Survival | Time to Local Failure |
|---|---|---|---|---|---|---|---|
| UF: Hinerman et al. (2001)[121] | 71 (80 tumors) | 11.1 yr (7 mo–32 yr) | 45 Gy (22–60 Gy) | 94% (75/80) | 98% | NS | 3, 5, 8, and 19 yr |
| UF: Evenson et al. (1998)[122] | 15 (23 tumors) | 5 yr | 45 Gy (35–70 Gy) | 96% | 89% | NS | 5 yr |
| WF: Mumber and Greven (1995)[123] | 15 | 11 yr | 50 Gy (45–60 Gy) | 100% | NS | NS | NS |
| Geisenger: Cole and Beiler (1994)[124] | 38 | 10 yr | (35–45 Gy) | 87% | 89% | 59% | 2, 3, 5 yr, and 2 after 10 yr |
| UVMC: Larner et al. (1992)[125] | 29 | 16.2 yr (5–31 yr) | 30–60 Gy | 86% | 93% | — | 8, 8, 12, and 17 yr |
| Mayo: Schild et al. (1992)[114] | 10 | 7.5 yr | 46 Gy (16–52 Gy) | 100% | 100% | 100% | NS |
| RMH: Powell et al. (1992)[126] | 46 | 9 yr (1)–(32) | (35–66 Gy) | 85% | NS | NS | NS |
| Netherlands Cancer Institute: Verniers et al. (1992)[115] | 22 (44 tumors) | 10 yr (mean) | 50 Gy (50–60 Gy) | 88% (10 yr) | NS | NS | 2 and 9 yr |
| Krakow: Skolyszewski et al. (1991)[127] | 24 | 7 yr | 60 Gy (30–60 Gy) | 96% | 100% | 92% | NS |
| University of Arizona: Boyle and Shimm (1990)[128] | 10 | 2–9 yr | 45–54 Gy | 100% | 100% | 80% | NS |
| Hoogenhout (1990)[129] | 31 | 11 yr | 40–50 Gy | 97% | — | — | — |
| Methodist and CTRC: Pryzant et al. (1989)[110] | 20 | 11 yr | 45 Gy | 94% | NS | NS | 8 yr |
| Iowa: Wang et al. (1988)[130] | 19 | 5–35 yr | 58 Gy (29–68 Gy) | 84% | NS | 71% (10 yr) | NS |
| UF: Friedland (1988)[131] | 26 | 2–18 yr | 45 Gy (40–50 Gy) | 96% | NS | NS | NS |
| Copenhagen: Hansen and Thomsen (1988)[132] | 39 | 7 yr | 40–60 Gy | 92% | 95% | 82% | Both failed at 1.5 yr |
| Washington University: Konefal et al. (1987)[133] | 26 | Minimum 4 yr | 24 to >60 Gy | 86% | 73% | NS | NS |
| Royal Victory Hospital: Dawes et al. (1987)[134] | 55 (58 tumors) | — | 50 Gy/20 fractions | 83% | 95%, DFS, 77% | 94% (20 yr) | NS |
| Johns Hopkins: Zinreich and Lee (1986)[135] | 15 | 2–10 yr | 45 Gy/5 wk | 100% | NS | NS | NS |
| Wessex Regional: Mitchell and Clyne (1985)[136] | 12 | 6–7 yr (1.5–15 yr) | 34.5–60 Gy | 92% | 92% | 83% | Persistent after treatment |
| St. Bartholomew's Sharma et al. (1984)[137] | 42 | 11 yr (0–35 yr) | 50–65 Gy | 83% | 93%; DFS, 77% | NS | NS |
| Rotterdamsch RT I: Lybert et al. (1984)[138] | 28 | 1.5–18 yr | 40–60 Gy | 100% | NS | NS | NS |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| PMH: Cummings et al. (1984)[139] | 45 | 10 yr (3–23 yr) | 35 Gy/3 wk | 93% | 100% | 76% | 1, 7, and 16 yr |
| University of Kansas: Reddy et al. (1983)[140] | 11 | >10 yr | 22–56 Gy | 100% | 100% | NS | NS |
| UF: Dickens et al. (1982)[141] | 14 | 8 yr (3–12 yr) | 47 Gy (38–56 Gy) | 100% | 100% | 100% | NS |
| UVA: Kim et al. (1980)[111] | 40 | 5–30 yr | 12–60 Gy | 83% | NS | NS | NS |
| MGH: CC Wang | 45 | 1–26 yr | NS | 96% | NS | 93% | 6 and 11 yr |
| University Hospital of Wales: Gibbin and Henk (1978)[143] | 14 | 8.7 yr (mean) (1–16 yr) | 45 Gy (42–50 Gy) | 86% | 86% | 86% | Both within 2 yr after RT |
| Washington University/Swedish/Virginia Mason: Simko et al. (1978)[144] | 14 | 7.7 yr (mean) (1.3–17 yr) | 28–65 Gy | 86% | 92% | 92% | NS |
| Queen Elizabeth: Arthur (1977)[145] | 20 | 13 yr | 45–50 Gy | 95% | 100% | 75% | 3 yr |
| Washington University: Spector et al. (1975)[103] | 20 | 8 yr (2–27 yr) | 46–60 Gy | 65% | NS | NS | NS |
| MDAC: Tidwell and Montague (1975)[146] | 17 | 4–18 yr | 42–50 Gy | 100% | 100% | 94% | NS |
| UCSF: Newman et al. (1973)[147] | 14 | — | 46–55 Gy | 93% | 93% | 93% | Persistent |
| University of Minnesota and UK: Marayuma (1972)[116] | 14 | NS | 45 Gy (30–60 Gy) | 93% | 65% | 100% | NS |
| MGH: Hatfield et al. (1972)[120] | 23 | 5 yr (minimum) | >40 Gy (30–45 Gy) | 74% | NS | NS | 1–18 yr |
| Mayo: Fuller et al. (1967)[148] | 69 | 10–15 yr (1–32 yr) | — | 88% | 95% | 88% | NS |
| University of Michigan: Grubb and Lampe (1964)[149] | 14 | 4 yr (0–10 yr) | 40 Gy (22–50 Gy) | 86% | 100% DFS, 86% | 79% | NS |
| Total | 967 (1,009 tumors) | | | 90% (907/1,009) | | | |

RT, radiation therapy; UF, University of Florida; NS, not stated; WF, wake forest; UVMC, University of Virginia Medical Center; RMH, Royal Marsden Hospital; CTRC, Cancer Therapy and Research Center; DFS, disease-free survival; PMH, Princess Margaret Hospital; UVA, University of Virginia; MDAC, M.D. Anderson Cancer Center; UCSF, University of California, San Francisco; MGH, Massachusetts General Hospital; UK, University of Kentucky.

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**TABLE 27.6 Local Control after Radiotherapy for Carotid Body Tumors and Vagal Paragangliomas**

| Institution | Number of Patients | Median Follow-up | Median Dose | Local Control |
|---|---|---|---|---|
| Centro oncologico (Valdagni) | 7 (13 tumors) | 2.5 yr (1–19 yr) | 50 Gy (46–60 Gy) | 100% |
| Rotterdamsch RT I (Lybeert) | 9 (11 tumors) | 1.5–18 yr | 4–60 Gy | 100% |
| Wessex Regional (Mitchell and Clyne) | 6 | 6 | 37–55 Gy | 83% |
| RMH (Powell) | — | 4 | 9 yr | 100% |
| UF (Mendenhall) | 4 (6 tumors) | 3 yr (2–4.5 yr) | 45 Gy (41–49 Gy) | 100% |
| UF (Hinerman) | 18 (25 tumors) | 9 yr (mean) | 45 Gy (35–70 Gy) | 96% |
| Total | 48 (63 tumors) | — | — | 97% (61/63) |

RMH, Royal Marsden Hospital; UF, University of Florida.

225 temporal bone tumors from 11 radiotherapy series published from 1965 to 1980.[111] Schild updated the analysis by including studies published from 1965 to 1992.[114] Local control was obtained in 91% (337/370) after radiotherapy. In his report, Kim demonstrated a dose–response relation between local control and total radiotherapy delivered.[111] The optimal dose appeared to be >40 Gy. Local failure was 1% versus 25% if patients received >40 Gy ($n$ = 142) versus <40 Gy ($n$ = 83), respectively.

In general, a dose of 45 Gy/5 weeks is recommended; however, a Canadian schedule of 35 Gy/3 weeks has also shown to be effective.[139] The high rates of local control after radiotherapy led Rosenwasser to conclude that "radiation failures occur, but perhaps they are not so much failures in the sense that irradiation is not effective, but that irradiation may not have reached the tumor in its entirety."[155] Paralleling such high rates of control are disease-specific survivals ranging from 65% to 100% with the majority of series reporting rates between 90% and 100%, as well as high rates of overall survival of 65% to 100% (see Table 27.5).

## Toxicity of Fractionated Radiotherapy

Severe complications after radiotherapy have been reported in 30 series involving 795 patients, and are summarized in Table 27.7.[110,114,115,120–128,130,131,133,134,136–149] This review involves 37 years of literature (1964–2001) with a wide variation in techniques and doses. The incidence of severe complications is 6% (49/795), and treatment-related mortality is 0.6% (5/795). Four of the five reported deaths resulted from brain complications including necrosis and abscess. Several of these deaths resulted from overdosage of radiation with external beam radiation (66–70 Gy), obsolescent brachytherapy techniques using radium implant, or large-volume brain irradiation. Severe morbidity consisted primarily of osteoradionecrosis ($n$ = 12 [1.5%]), chronic otitis ($n$ = 8 [1%]), brain necrosis ($n$ = 6 [0.8%]), radiation-related cranial neuropathy ($n$ = 4 [0.5%]), radiation-induced sarcoma ($n$ = 3 [0.4%]), external auditory canal stenosis ($n$ = 2 [0.3%]), and trismus ($n$ = 2 [0.3%]). The majority of such complications were related to treatment using excessive doses, outdated treatment techniques (orthovoltage, which is preferentially absorbed in the bone or radium implant), or reirradiation. For example, of the four cranial neuropathies related to radiotherapy, three occurred after 64 to 66 Gy. Cole and Beiler[124] reported that all severe complications in their series occurred in the orthovoltage-treated patients and none in those treated with megavoltage. Of importance is the low incidence (0.4% [3/795]) of radiation-induced secondary malignancy, including two fibrosarcomas occurring 15 and 25 years posttreatment, and one osteosarcoma occurring 5 years later. One fibrosarcoma developed after a radium implant; the other two malignancies occurred after treatment with 50 and 62 Gy (see Table 27.7). Common complications that can occur include epilation, skin dryness, fibrosis, and cerumen buildup in the external auditory canal.

With modern treatment planning and appropriate dosing, definitive radiotherapy for paragangliomas should be well tolerated. In the acute setting, patients may experience dermatitis, alopecia, mucositis, epilation, and alterations in taste and saliva, along with either otitis externa or media. The potential complications vary according to the radiation technique and treatment site. At standard doses, most of these side effects are transient, and treatment-related mortality is exceedingly rare. Care must be taken to minimize dose inhomogeneity and volume of treated normal tissues, especially brain (Fig. 27-20).

## Stereotactic Radiosurgery

Stereotactic radiosurgery (SRS) has been explored in the primary treatment of paragangliomas and salvage of surgical failures. The first published report for SRS was in 1995, and numerous reports have subsequently followed. SRS offers the possibility of a single, highly focused small-field treatment with a steep dose gradient to maximally spare surrounding normal tissue. The radiobiologic rationale of delivering one large dose is to effectively treat tumors that may be radioresistant while minimizing the amount of normal tissue in the treatment field. Two methods of delivering stereotactic radiation involve (a) the use of radioactive cobalt sources (gamma-knife) or (b) the generation of radiation from a linear accelerator (LINAC). Typically, all imaging (e.g., CT scan or MRI), planning, and treatment are completed in a one-time treatment session, and the radiation is delivered with the highest precision of all current radiation-delivery techniques.

Multiple series have reported success using this approach to treat primarily jugular paragangliomas with high local control (Table 27.8).[112,156–160] A wide range of median doses have been reported delivering from 15 to 32 Gy with 15 Gy being the most common dose prescribed. Tumor regression is noted in 36%.[161] Treatments appear to be well tolerated, with no reported iatrogenic lower cranial neuropathies, and low incidence of transient facial neuropathy, hearing impairment, and vertigo. Limitations of SRS include eligibility restrictions, lesion size, and location, as well as a greater risk for geographic miss due to the sharp dose gradient.[156] Tumors may be no >4 cm to achieve tight dose conformality.

A population-based meta-analysis of 19 studies comprising 335 glomus jugulare patients treated with radiosurgery was reported by Guss et al.[162] For all studies, tumor control was 97%, while among the 8 studies with median follow-up of >36 months,

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**TABLE 27.7 Severe Complications after Radiotherapy for Paraganglioma**

| Author | Number of Patients | Severe Chronic Complications |
|---|---|---|
| Hinerman et al. (2001)[121] | 71 | One transient CNS syndrome preirradiation<br>One transient CN VII palsy 10 mo after RT resolved spontaneously<br>One otitis media requiring myringostomy<br>One severe dental caries<br>One external otitis |
| Evenson et al. (1998)[122] | 15 | One transient CNS lethargy |
| Mumber and Greven (1995)[123] | 15 | One osteosarcoma of occipital bone 5 yr p pt received 62 Gy |
| Cole and Beiler (1994)[124] | 38 | Three osteoradionecrosis (all treated with orthovoltage)<br>One recurrent tumor hemorrhage (treated with orthovoltage)<br>No serious complications in megavoltage-treated patients |
| Larner et al. (1992)[125] | 29 | None reported |
| Schild et al. (1992)[114] | 10 | None reported |
| Powell et al. (1992)[126] | 46 | Two facial nerve palsy p 64–66 Gy |
| Verniers et al. (1992)[115] | 22 | One perforation due to otitis media |
| Skolysweski et al. (1991)[127] | 23 | One brain cortical atrophy |
| Boyle et al. (1990)[128] | 9 | None reported |
| Pryzant et al. (1989)[110] | 20 | None reported |
| Wang et al. (1988)[130] | 19 | EAC stenosis p 67 Gy<br>One encephalopathic death p 66 Gy |
| Friedland (1988)[131] | 15 | One revision sequestrectomy for cholesteatoma<br>One revision mastoidectomy and sequestrectomy for bony sequestrum 10 yr p RT<br>One trismus |
| Konefal et al. (1987)[133] | 26 | One osteoradionecrosis after 54 Gy to the right ear and bilateral mixed beam treatment<br>One encephalopathy<br>Two labyrinthitis |
| Mitchell and Clyne (1985)[136] | 12 | One mastoid sequestrectomy for persistent ear crusting 16 yr p RT |
| Sharma et al. (1984)[137] | 42 | Four cases of osteoradionecrosis (three after reirradiation to doses of 80–88 Gy in two cases and one radium implant) |
| Lybert et al. (1984)[138] | 28 | One possible CN VIII palsy p 65 Gy |
| Cummings et al. (1984)[139] | 45 | Four chronic otitis externa<br>One chronic otitis media<br>One EAC stenosis<br>One fatal brain necrosis p 70 Gy accidentally delivered<br>One osteoradionecrosis 10 yr p 58 Gy using electrons |
| Reddy et al. (1983)[140] | 11 | None reported |
| Dickens et al. (1982)[141] | 14 | Two cholesteatoma<br>One bony sequestrum<br>One trismus |
| Wang (1990)[142] | 45 | Two patients with osteoradionecrosis |
| Gibbin and Henk (1978)[143] | 14 | None reported |
| Simko et al. (1978)[144] | 14 | One temporal bone necrosis p 57 Gy |
| Arthur (1977)[145] | 20 | None reported |
| Tidwell and Montague (1975)[146] | 17 | One fatal with C45 brain necrosis p 50 Gy to large volume (hot spot 63 Gy in brain) |
| Newman et al. (1973)[147] | 14 | One lethal fibrosarcoma 15 yr p 50 Gy |
| Hatfield et al. (1972)[120] | 23 | One brain abscess |
| Fuller et al. (1967)[148] | 69 | One fibrosarcoma 2t yr p radium implant<br>One death from abscess due to necrotic mastoid process p radium implant |
| Grubb and Lampe (1964)[149] | 14 | None reported |
| Total | 795 | |

CNS, central nervous system; CN, cranial nerve; EAC, external auditory canal; RT, radiation therapy; 2t, 20; p, post (after); pt, patient.

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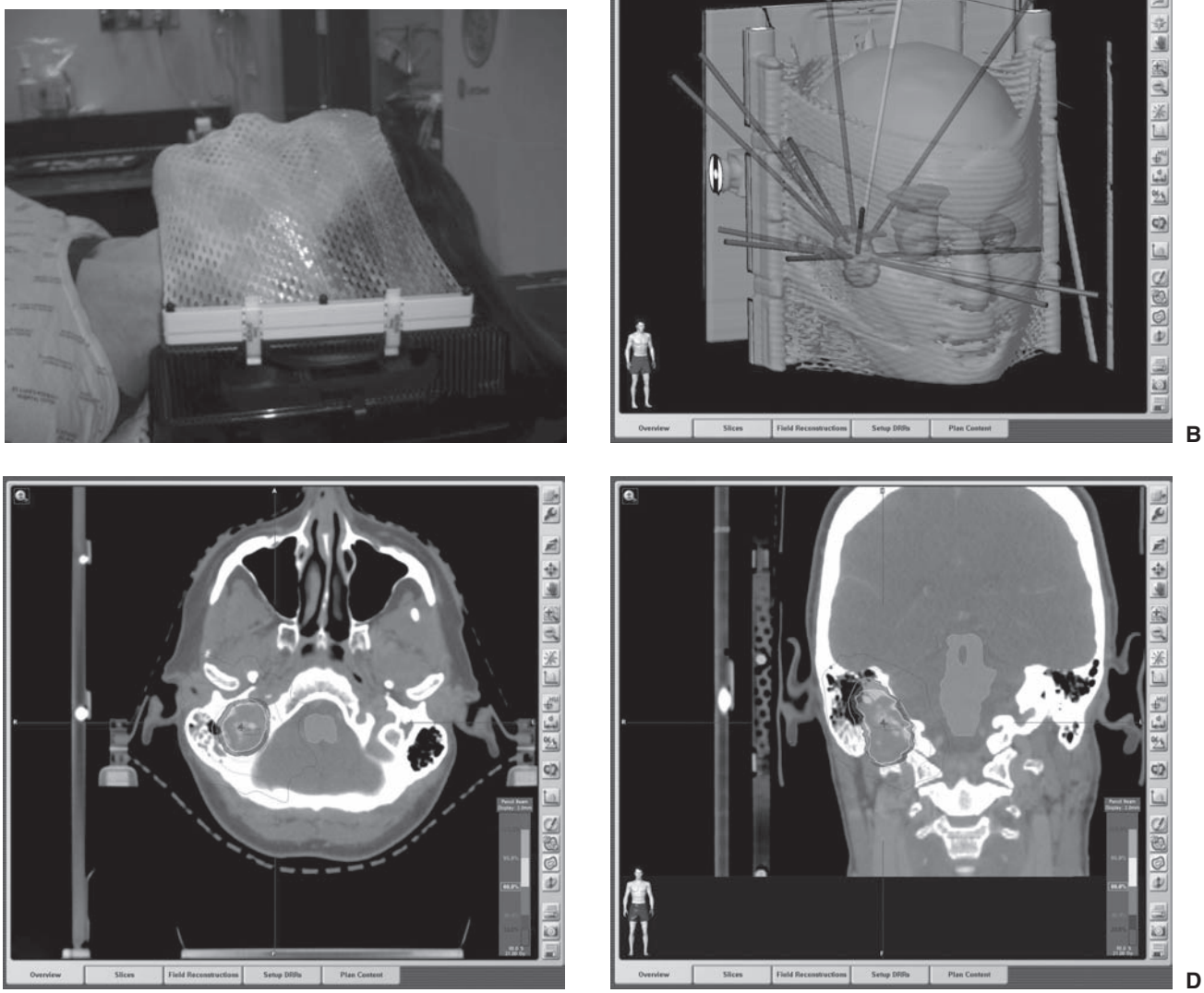



**FIGURE 27-20.** Fifty-year-old female with an incapacitating jugulotympanic paraganglioma causing tinnitus and dizziness causing gait instability and nausea. Due to the size of the lesion and proximity to the seventh and eighth cranial nerve, a stereotactic fractionated radiation therapy approach was recommended to minimize risk of iatrogenic neuropathy. **A:** The patient was immobilized with a frameless stereotactic mask. **B:** Multiple noncoplanar beams were used to deliver 21 Gy in 3 fractions. Dosimetry is seen in axial **(C)** and coronal views **(D)**. (See color insert for Parts **C** and **D**)

95% achieved control. No difference in outcome was reported by SRS technique whether by LINAC, gamma-knife, or cyber-knife approaches.

### Toxicity of Stereotactic Radiosurgery

Toxicity after stereotactic radiosurgery is detailed in Table 27.8. Based on a weighted series of 6 studies of radiosurgery for 133 jugular paragangliomas, the neurologic deterioration related to SRS was 4%, whereas there was improvement or stability in 96%. Reported complications included radiation-induced transient cranial neuropathy, impaired hearing, and chronic vertigo.[163] Others report a worsening of neurologic deficit after SRS in 8%, with 6% transient and 2% permanent. No patients experience new cranial nerve deficits.[161]

## IMPACT OF RADIATION THERAPY ON NEUROLOGIC FUNCTION

The most frequent symptoms associated with temporal bone paragangliomas are hearing loss and tinnitus, which are noted in 55% to 58% and 56% to 66% of patients, respecti vely.[110,123,126,128,136,139] After radiotherapy, tinnitus commonly improves or resolves in up to 88% of cases.[126,139] Among temporal bone tumors treated with radiation with a median follow-up of 10 years, Cummings demonstrated complete subsidence in 79% of 38 reported cases and stable or partial decrease in 21%.[139] Of the 40 patients with initial hearing impairment, 5% reported a return to normal hearing, 30% reported some improvement and 62% were unchanged. Christie Hospital reported

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**TABLE 27.8 Experience with Stereotactic Radiosurgery**

| Institution | Number of Patients | Median Follow-up (mo) | RT Dose: Mean Peripheral Dose | Local Control (%) | Complications |
|---|---|---|---|---|---|
| Liscak | 14 | 20 | 19.4 Gy (10–25 Gy) | 100 | Acute: headache and nausea in two patients Chronic: hearing decreased in three patients |
| Austria (Eustacchio) | 10 | 38 | 13.5 Gy | 100 | — |
| Mayo (Foote) | 9 | 20 | 15 Gy (12–18 Gy) | 100 | No reported chronic or acute toxicities |
| University of Texas, southwestern (Jordan) | 8 | 27 | 16 Gy (12–20 Gy) | 88 | Chronic: intractable vertigo requiring cane resolved in one patient |

| Institution | Number of Patients | Median Follow-up | RT dose to Periphery (Gy) | Local Control | Complications |
|---|---|---|---|---|---|
| Liscak et al. (1998)[157] | 66 | 24 | 16.5 | 100% | 5%, permanent facial nn palsy in two patients, temporary tinnitus in one patient |
| Pollock (2004)[163] | 42 | 39 | 15 | 98% (hearing preserved in 81%) | 15% experienced hearing loss, facial nn palsy and temporary vertigo |
| Eustacchio et al. (2002)[a] | 25 | 37 | 14 | 100% | One transient vertigo |
| Gerosa et al. (2006)[b] | 20 | 51 | 17.3 | 100% | Two with hearing deterioration. Five with improved CN function |
| Varma et al. (2006)[c] | 17 | 48 | 15 | 82% | No new CN deficit with 8/17 with improvement of CN palsy |
| Maarouf et al. (2003)[d] | 14 | 4 yr | 15 | 100% | Neurologic improvement in 25% |
| Saringer et al. (2001)[e] | 13 | 4.2 yr | 12 | 100% | One transient worsening dysphagia 1 1 transient facial paralysis |
| Lim et al. (2004)[f] | 13 | 27 mo | 17 | 100% | Two transient neuropathies resolved by 8 mo |
| Sheehan et al. (2005)[g] | 8 | 28 mo | 15 | 100% | No transient neuropathies; 57% showed decrease in size |
| Jordan et al. (2000)[112] | 8 | 27 mo | 16.3 | 88% | One transient intractable vertigo requiring cane |
| Poznanovic et al. (2006)[118] | 8 | 18 mo | 15 | 100% | One transient neuropathy and one permanent vertigo |
| Willen et al. (2005)[177] | 5 | 19 mo | 15 | 100% | None reported |

[a]Eustacchio S, Tummer M, Unger F, et al. The role of gamma knife radiosurgery in the management of glomus jugular tumours. *Act Neurochir Suppl*. 2002;84:91–97.
[b]Gerosa M, Visca A, Rizzo P, et al. Glomus jugulare tumors: the option of gamma knife radiosurgery. *Neurosurgery*. 2006;50:561–569.
[c]Varma A, Nathoo N, Neyman G, et al. Gamma knife radiosurgery for glomus juglare tumors: volumetric analysis in 17 patients, *Neurosurgery*. 2006;59:1030–1036.
[d]Maarouf M, Voges J, Landwehr P, et al. Stereotactic linear accelerator-based radiosurgery for the treatment of patients with glomus jugulare tumors. *Cancer*. 2003;97:1093–1098.
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[g]Sheehan J, Kondziolka, D, Flickeinger J, et al. Gamma knife surgery for glomus jugulare tumors: an intermediate report on efficacy and safety. *J Neurosurg Suppl*. 2005;102:241–246.
RT, radiation therapy.

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their outcomes using external beam radiotherapy (EBRT) in 49 patients with jugular or tympanicum tumors.[164] The median age was 55 years. Twenty-seven patients presented with deafness, 25 with tinnitus, 10 with facial nerve palsy, 14 with otalgia, 8 with bleeding, and 6 with other cranial nerve palsies. Patients were treated with a median dose of 45 Gy. At a median follow-up of 7.4 years, complete clinical response was noted in 78% (39/49) and the 5- or 10-year local control was 92%. Others have also reported an 8% to 85% incidence of hearing impairment as a presenting symptom,[110,123,126,128] but do not detail a follow-up response to radiotherapy as measured by audiologic testing.

The incidence of other lower cranial neuropathy at presentation is usually about 40% for temporal bone tumors, but may range from 8% to 60%.[110,114,115,123,125,126,136] Often, the presenting cranial nerve symptoms are long-standing with only a modest possibility of improving after radiotherapy. The probability of improvement is most likely inversely related to the duration of cranial neuropathy.[126,138] The reported rates of improvement vary from 0% to 83% with an average of 35% for all series that document response (Table 27.9).[110,114,123,126,128,131,134,136,138,139,141] Complete restoration of cranial nerve function can occur in about 10% (range 8%–20%); however, no change is noted in the majority. Importantly, only about 1% of cranial neuropathies worsen after radiotherapy. Radiation-induced cranial neuropathy is rare, and those reported have been associated with doses above what is currently recommended. Four such cases have been reported; two cases of CN VII palsy, one CN VIII dysfunction occurring after high dose of radiotherapy (64–66 Gy),[126,138] and one case of CN VI palsy, which the authors stated had an "unclear etiology."[134]

**TABLE 27.9 Cranial Neuropathy Response after Definitive Radiotherapy**

| Author | Improved | Complete Resolution | Worse |
|---|---|---|---|
| Friedland et al. (1988)[131] | 33% (19/57) | 9% (5/57) | 4% (2/57) |
| Cummings et al. (1984)[139] | 100% (26/26)[a] | 8% (2/26) | 0% |
| Dawes et al. (1987)[134] | 28% (16/57) | NR | 0% |
| Boyle et al. (1990)[128] | 50% (2/4) | NR | 0% |
| Mumber and Greven (1995)[123] | 50% (3/6) | NR | 0% |
| Lybert et al. (1984)[138] | 17% (1/6) | 0% | 0% |
| Dickens et al. (1982)[141] | 47% (14/30) | 20% (6/30) | 0% |
| Mitchell and Clyne (1985)[136] | 66% (2/3) | NR | 0% |
| Pryzant et al. (1989)[110] | 0% (0/9) | 0% | 0% |
| Powell et al. (1992)[126] | 19% (5/26) | NR | NR |
| Schild et al. (1992)[114] | 83% (5/6)<br>33% (67/204) | NR<br>10% (13/128) | 0%<br>1% (2/204) |

Three cases of new cranial neuropathy [two cranial nerve VII after radiation therapy (64–66 Gy) (Powell), and one reported a cranial nerve VI with unclear cause (Dawes)]. NR, not reported.
[a]Cranial neuropathy stable or improved, excluded from total analysis of those improved.

## Fractionated Radiotherapy Compared with Surgery

Extraction of meaningful data from retrospective studies is inherently fraught with difficulty. Single-institution retrospective series often report conflicting results based on small patient numbers and selection bias. For example, Ogura et al.[165] reported a cure rate of 80% (39/49) after surgery alone for jugular paragangliomas versus 25% (3/12) after radiotherapy alone, and 64% (7/11) with combined surgery and radiation. In this series, and those from Glasscock et al.,[166] surgery was recommended as the treatment of choice for resectable tumors, and radiotherapy was proposed for large, inoperable tumors. Moore et al.[167] reported successful control in 88% (7/8) of tympanic paragangliomas treated with surgery alone, and 25% (1/4) of petrosal/extrapetrosal tumors treated by surgery alone versus 100% (5/5) of similar tumors treated with radiotherapy alone, and 88% of tumors treated with surgery followed by radiotherapy. Other series have demonstrated no obvious differences between surgery and radiotherapy.[117] Carrasco and Rosenman[168] reported a large series showing similar local recurrence rates after surgery versus radiotherapy occurring in 7% versus 8% (19/283 vs. 24/299), respectively. The mortality rate from progressive disease was low after treatment with either modality, 2.5% (7/283) with surgery versus 6% (18/299) with radiation. Due to the retrospective nature of the data, the impact of selection bias on such an analysis cannot be determined.

In an effort to extract meaningful data, one may compare outcomes based on a common staging system. Few studies report their results based on a staging system that can be used for cross-modality and interinstitutional comparison. However, several series report results based on the McCabe/Fletcher staging system, which categorizes temporal bone paragangliomas into the tympanic, tympanomastoid, and petrosal/extrapetrosal categories (Table 27.10).[110,111,121,125,130] Although this staging system is based on the use of outdated radiographic examinations, such as plain x-ray films and retrograde jugulography, it is similar in principle to the Fisch and Glasscock/Jackson systems, which are currently preferred. A combined analysis of five studies reporting the results of surgical or radiotherapeutic treatment of temporal bone tumors staged according to the McCabe/Fletcher system is presented in Table 27.10.[110,111,121,125,130] Patients were treated with radiotherapy alone ($n$ = 94), surgery alone ($n$ = 45), or surgery and radiation ($n$ = 39). Patients in the last cohort received radiation, usually in the postoperative setting, for gross residual disease. Median follow-up ranged from 11 to 16 years. The average local control was 93%, 78%, and 85% for patients treated with radiotherapy, surgery, or combined surgery and radiation, respectively. Despite a selection bias against the radiotherapy group (65% were group III paragangliomas) compared with the surgery alone (13% were group III), or combined surgery and radiation (51% were group III), local control appeared at least as good after radiotherapy alone compared with the other two treatment groups. Local control

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**TABLE 27.10 Local Control after Primary Radiation Therapy versus Surgery versus Surgery and Postoperative Radiation in Temporal Bone Paragangliomas**

| McCabe-Fletcher Stage | RT[a] | Sx[a] | Sx + RT[b] | All Patients |
|---|---|---|---|---|
| I | 93% (14/15) | 87% (27/31) | 78% (7/9) | 87% (48/55) |
| II | 100% (18/18) | 88% (7/8) | 70% (7/10) | 89% (32/36) |
| III | 92% (56/61) | 17% (1/6) | 95% (19/20) | 87% (76/87) |
| Total | 93% (88/94) | 78% (35/45) | 85% (33/39) | 87% (156/178) |

[a]RT, radiation therapy; Sx, surgery. Based on pooled analysis of five series that reported results by a common staging system (Wang, Larner, Pryzant, Kim, Hinerman).

[b]Note the majority received radiation therapy in conjunction with surgery as upfront definite treatment rather than as salvage.

for group III tumors was better after definitive radiotherapy (92%) or combined modality treatment (95%) versus surgery alone (17%). Patients with early or intermediate group tumors did well regardless of treatment approach. Although McCabe and Fletcher recommended surgery alone for tympanic tumors, combined treatment for tympanomastoid tumors, and radiotherapy alone for petrosal or extrapetrosal tumors,[137] the combined analysis suggests that surgery or radiotherapy are equally effective alternatives for group I and II tumors of temporal bone paragangliomas (local control 87% and 88% vs. 93% and 100% after surgery and radiation therapy for group I and II tumors, respectively), and radiotherapy is the preferred treatment option for advanced tumors (local control 92% for group III tumors) (see Table 27.10). Moreover, a combined approach does not appear to improve local control compared with radiotherapy alone. Kim et al.[111] also emphasized that there is no obvious benefit of a debulking subtotal resection in conjunction with definitive radiotherapy. The pooled analysis is based on retrospective data on 174 patients and is subject to selection/reporting bias; nevertheless, it represents a comparison based on a common staging system with reasonably long-term follow-up. Unfortunately, the respective morbidities of the different treatment groups were not detailed in these studies.

## Surgery Compared with Stereotactic Radiosurgery

A meta-analysis of tumor control rates and treatment-related morbidity was performed for glomus jugulare patients.[169] One hundred nine studies with 869 patients were collected for the analysis. Four groups of patients were compared—(a) those undergoing gross total resection (GTR), (b) subtotal resection (STR), (c) subtotal resection combined with stereotactic radiosurgery (STR + SRS), and (d) stereotactic radiosurgery alone (SRS). The median follow-up and tumor control were as follows: (a) GTR 88 months, 86%; (b) STR 72 months, 69%; (c) STR + SRS 96 months, 71%; and (d) SRS 71 months, 95%. The patients undergoing SRS alone had the best tumor control rates ($p < 0.001$). Regarding morbidity, those undergoing GTR had worse cranial IX to XI deficits compared with the SRS group although CN XII deficits were comparable.

A comprehensive literature review comparing stereotactic radiosurgery versus conventional surgery for the treatment of jugular paraganglioma in 576 patients was reported by Gottfried.[161] Eight radiosurgery series reporting outcomes on 142 patients and seven conventional surgical series detailing outcomes on 374 patients were reported. The mean patient age undergoing surgery was about 10 years younger (47 vs. 57 years, respectively) than those treated with stereotactic radiosurgery. Five of the eight series on radiosurgery had used gamma-knife whereas three were LINAC based. Patients were treated between 1990 and 2001 with 48% receiving radiosurgery as primary treatment and 52% undergoing salvage or adjuvant radiosurgery. Shrinkage of tumor was reported in 36% treated with radiosurgery, whereas 61% remained unchanged. With regard to neurological symptoms, 39% showed improvement, 58% showed no change, and 3% showed worsening. Most patients experiencing neurologic improvement did so within the first 12 months. The neurological complication rate was 8.5% with 6.4% transient and 2.1% permanent. Transient complications include exacerbation of preexisting cranial nerve deficits, tinnitus, or vertigo. The permanent complication rate was worsening facial nerve function in three patients, worsening vertigo in one patient, and progressive hearing loss to deafness in one patient. No patients experienced new lower cranial nerve deficit. No treatment-related deaths were reported. With regard to the surgically treated cohort, gross total resection was obtained in 83% to 86% of complex tumors; that is to say, those with tumors having catecholamine secretion, malignancy, multiple paragangliomas, and those with previous treatment with adverse events such as sacrifice of the ICA and 88% of 288 noncomplex tumors. The major surgical morbidities were cerebrospinal fluid (CSF) leak in 8.3%, aspiration 5.5%, wound infection/ischemia 5.5%, pneumonia 2.3%, and meningitis 2.1%. New cranial nerve deficits reported in several surgical series were noted in the seventh cranial nerve in 4% to 11%, in the ninth 26% to 42%, tenth 13% to 28%, eleventh 25% to 26%, and twelfth 5% to 21%[161,170–172] and occurs in 22% to 83%% of all surgical patients.[161,172–176] Surgical mortality was 1.3%. Additional surgical procedures included vocal cord injection (10%–25%), thyroplasty (8%–10%), eyelid weights, cricopharyngeal myotomy (4%), tracheostomy (0%–5%), tarsorrhaphy (20%), and nasogastric tube feeding (8%–20%). At a follow-up of 49 and 39 months (20–86.4 months) for the surgical and radiosurgical groups, respectively, the surgical local control was 92% and radiosurgical control was 98%.

## Stereotactic Radiotherapy

To minimize treatment morbidity, an alternative is stereotactic radiotherapy. Wegner reports an early experience of 18 glomus jugulare patients treated with LINAC-based stereotactic radiation therapy (SRT). Eight of the patients had persistent tumor after previous surgery, and one recurred after external beam radiation, whereas two were treated with combined extracranial stereotactic radiation therapy with intracranial gamma-knife radiotherapy. The median prescribed dose was 21 Gy in 3 fractions (16–25 Gy/1–5 fractions) to the 80% isodose line. At a median follow-up of 22 months, the local control rate was 100%. No patients experienced any new or worsening neurologic deficits. No patients experienced iatrogenic cranial neuropathy.

## Salvage Therapy

Late recurrences have been reported up to 19 years after radiotherapy[121] with the majority recurring within 10 years after radiotherapy (see Table 27.5), highlighting the need for continued long-term surveillance. If local failure occurs after definitive

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radiotherapy or surgery, Carrasco concluded that salvage rates are high based on a review of 24 series from 1964 to 1987 comprising 582 patients treated with surgery and/or radiation.[168] Four percent (25/582) died of disease (2.5% [7/283] of surgery patients and 6% of radiation patients [18/299]), and salvage was obtained in 88% in patients failing initial treatment with either surgery or radiotherapy. Of 62 patients recurring after initial resection, 95% (56/59) were salvaged with definitive radiation and 100% (3/3) with additional surgery with an overall salvage rate of 95% (59/62). Salvage of radiotherapy failures with surgery or additional radiotherapy was successful in 95% (19/20) and 71% (25/35), respectively, for an overall rate of 80% (44/55). Thus, the use of either surgery or radiotherapy as initial treatment does not preclude the success of salvage surgery or radiation for tumor recurrence.

For jugulotympanic tumors recurring after previous resection, radiation therapy represents the preferred option. Elshaikh reported the Cleveland Clinic experience comparing surgery versus radiation therapy to salvage 29 recurrent paragangliomas having undergone previous resection.[177] Median time to recurrence from initial surgery was 36 months. Sixteen were jugular, 7 carotid body, 5 tympanic, and 1 thyroid. Radiation was used in 12 patients deemed unresectable or who refused surgery (9 jugular, 2 tympanicum, and 1 thyroid), whereas surgery was used in 17 patients (7 jugular, 7 carotid body, and 3 tympanicum). Radiation consisted of SRS in 7 patients and 5 with external beam radiation. Surgery was effective in controlling all carotid body recurrences. However, in patients with jugular or tympanicum paragangliomas, radiation was more effective with local control of 100% versus 62% ($p = 0.0124$), respectively, at a median follow-up of 55 months. No significant side effects were reported from radiation while postsurgical complications occurred in 47% including lower cranial nerve palsy, CSF leak, and meningitis.

## Malignant and Catecholamine-secreting Paraganglioma

Metastatic disease is often indolent and asymptomatic. The standard treatment of malignant paragangliomas is resection of the primary and regional node dissection followed by postoperative radiation. These tumors may demonstrate more aggressive local behavior and surgery, especially of paragangliomas involving the temporal bone, may have an increased rate of complications.[113] Data regarding outcome of malignant paraganglioma after definitive radiation is rare. Hinerman reported on 3 patients with malignant carotid body tumors and neck metastases who underwent definitive radiation (64.8–70 Gy) who were without evidence of disease at 15 months, 4 years, and 6 years.[121] Catecholamine-secreting tumors should be treated with resection as case reports indicate poor functional control in patients treated with radiation therapy despite lack of tumor progression.[178]

## Treatment Strategies

Ideal treatment for a patient with paraganglioma is one that offers a high chance of cure with single-modality treatment without debilitating morbidity and with preservation of cranial nerve function. The concept of "cure" must be defined and accepted by the treating physician and, of course, the patient. Certainly, the surgical definition of "cure" is total tumor resection and long-term confirmation of tumor absence. The radiation therapy literature defines "cure," in the paraganglioma patient, as nonprogression of tumor as documented by appropriate long-term imaging follow-up. Only infrequently is there appreciable tumor regression as is often seen in the successful treatment of malignant neoplasms of the head and neck.[105,124] Therefore, the concept of "cure" in a paraganglioma patient should be modified to include stabilization or nonprogression of tumor growth.

Based on such definitions, surgery and radiation therapy demonstrate equal cure rates[121] for nonmalignant paragangliomas. Thus, in selecting a treatment modality, the focus should center on the treatment morbidity, the potential to improve symptoms, and the likelihood to preserve existing cranial nerve function. Refinements in surgery, interventional radiology, and medical care have resulted in significantly lower rates of surgical morbidity/mortality and cranial nerve dysfunction. Primary surgery should be considered for patients with small to moderate-size carotid body tumors and tympanic paragangliomas without cranial nerve dysfunction. These tumors can usually be totally excised without significant morbidity.[179] Bilateral carotid body tumor surgery should be avoided since the resulting baroreflex failure syndrome would require long-term and occasionally difficult-to-control symptoms.[180] Patients undergoing surgery for vagal paragangliomas almost always require sacrifice of the vagus nerve and, often, additional adjacent cranial nerves.[181] Primary surgery may be considered for patients with jugular or vagal paragangliomas in the presence of lower cranial nerve dysfunction (CNs VII, IX–XII), whereby resection of the tumor would not result in additional significant functional deficits, especially in younger and middle-aged patients without coexisting medical problems. For patients with catecholamine-secreting or malignant tumors, upfront surgery is recommended. In patients with an associated PGL4 mutation, surgery should be considered as the first line of treatment because of the marked increase in incidence of malignant paragangliomas.

Primary radiation therapy should be considered in jugular and vagal paragangliomas, which have a natural history for skull base or cranial nerve involvement, especially those with minimal symptoms as such tumor may be controlled with high rates of cranial nerve function preservation. For jugulotympanic tumors presenting with tinnitus, radiation therapy offers a high likelihood for improvement/resolution of such symptoms. Improvement of cranial nerve dysfunction is less likely, especially in those with a long history of deficit. Primary radiation therapy should also be

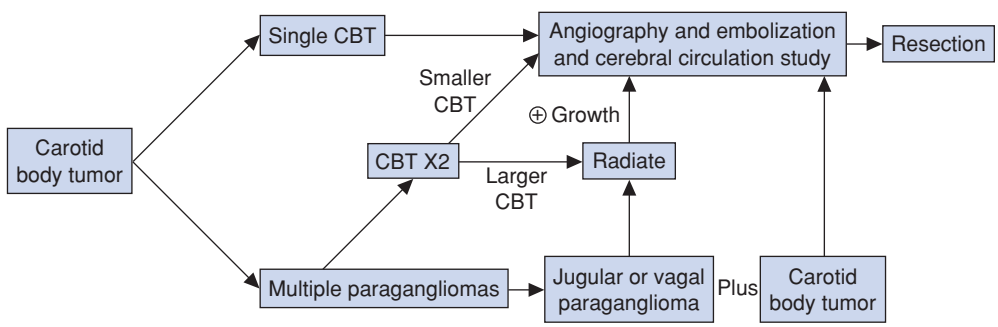



**FIGURE 27-21.** Decision analysis tree for the treatment of carotid body tumors (CBTs).

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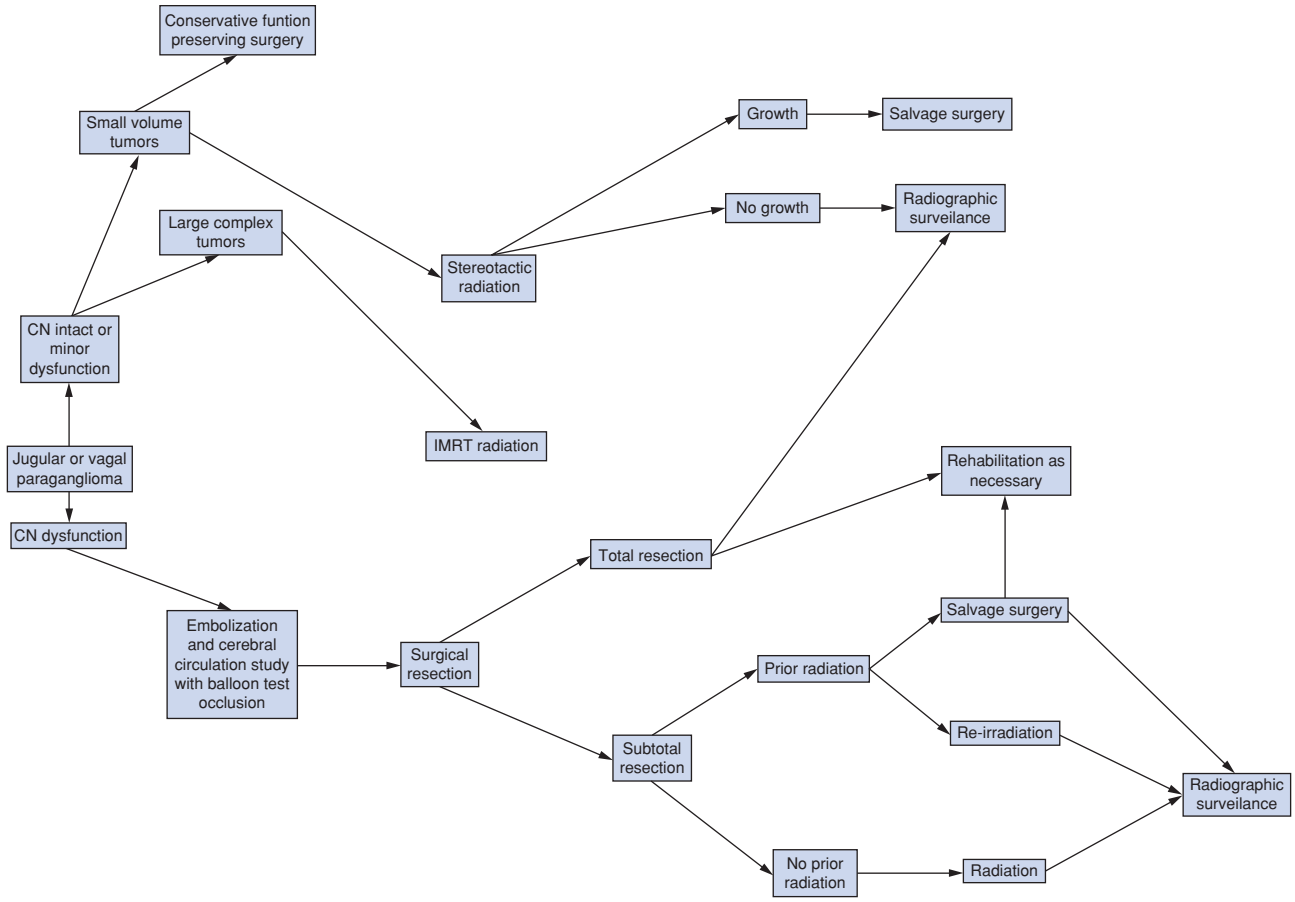



**FIGURE 27-22.** Decision analysis tree for the treatment of vagal and/or jugular paragangliomas. CN, cranial nerve.

considered in the treatment of the elderly, patients with multiple or severe medical conditions, and patients with extensive skull base or intracranial involvement.[12,76,106,107,158,176,182,183] In patients with bilateral carotid body tumors, primary radiation therapy to the larger tumor should be considered. Adjuvant radiation therapy is recommended in patients with malignant tumors and subtotal resection.

Primary radiation therapy may be delivered with conventional fractionation or with ablative stereotactic radiation doses. Typically, a dose of 45 Gy in 5 weeks is given with conventional fractionation and 15 Gy with stereotactic dosing. Excellent outcomes have been attained with both approaches, with a modestly increased risk of worsening of cranial nerve dysfunction and additional cranial nerve morbidity from stereotactic radiosurgery. Fractionated stereotactic radiation therapy may represent the optimal approach, but the experience to date is limited with shorter follow-up. In general, smaller tumors are better suited for stereotactic approaches where dose in homogeneity is lessened and volume of normal tissue at risk is smaller.

Observation without treatment is also an option for older patients and patients with a high operative risk due to medical comorbidities who can be closely followed in the setting of these slowly growing tumors.[108,109]

The appropriate treatment algorithms are shown in Figures 27-21 and 27-22 with emphasis based on multiple factors, including the patient's age, type and extent of paraganglioma, status of pretreatment neural dysfunction, comorbidities, and support network for possible treatment morbidity in determining the appropriate mode of treatment. Despite advances in surgical treatment and radiation techniques, these tumors have the potential for significant morbidity. Overriding factors such as the patient's wishes, the patient's lifestyle, and family support structure may alter the treatment choices. Regardless of the modality of treatment, long-term follow-up with serial scanning is indicated.

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# PART B:
# Radiation Therapy Technique

William M. Mendenhall

The treatment technique depends on the location of the tumor, the number of lesions (1 or ≥2), and whether the tumor is malignant. The vast majority of tumors are single and benign.

Temporal bone tumors may be treated with stereotactic radiosurgery or fractionated radiation therapy. Stereotactic radiosurgery is performed with either a linear accelerator-based system or a gamma knife; the results with either technique are equivalent.[1]

Fractionated radiation therapy may be delivered with stereotactic radiation therapy, intensity-modulated radiation therapy (IMRT), or a wedge pair technique using three-dimensional (3D) conformal treatment planning (Figs. 27-23 and 27-24).[2] The lesion is treated with a 1-cm margin of normal tissue to a dose of 45 Gy in 25 fractions over 5 weeks. The disadvantage of the wedge pair technique is that a larger volume of normal tissue is treated. However, even very large tumors can be treated with an ipsilateral technique that will result in a very low dose to the contralateral parotid gland and minimize the risk of xerostomia.

Glomus vagale and carotid tumors are not suitable for stereotactic radiosurgery and are better treated with IMRT or three-dimensional treatment planning using a wedge pair technique.

The technique used for patients with multiple tumors is variable and depends on the location and extent of the lesions. Very large bilateral tumors may require parallel-opposed fields. Alternatively, resection of one lesion and irradiation of the contralateral

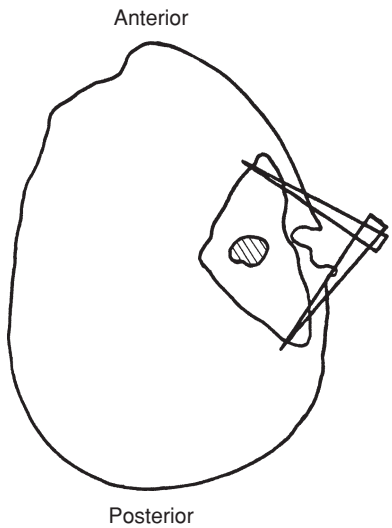
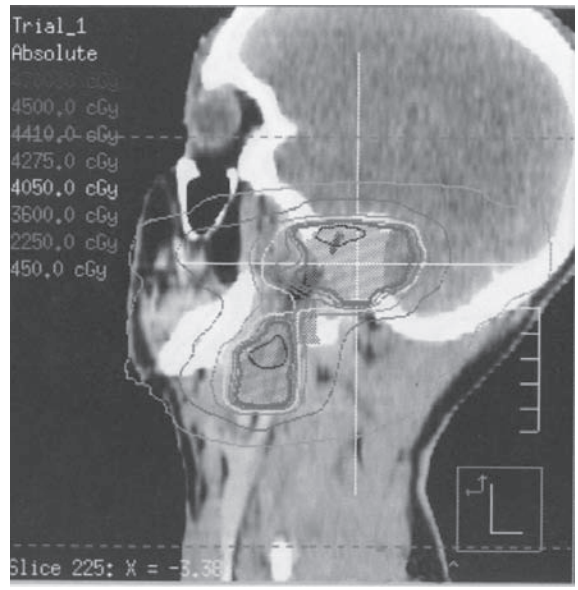
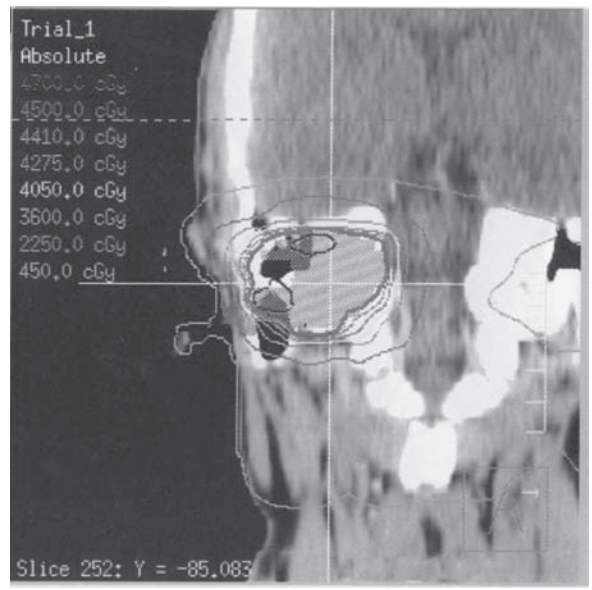



**FIGURE 27-23.** Axial contour of skull through the temporal bone depicting the dose distribution for the wedge pair technique. This consists of oblique 6-mV x-ray fields with wedge compensating filters. The fields enter anteroinferiorly and posterosuperiorly so that the beams enter and exit below the eyes. The 93% isodose line encompasses the temporal bone chemodectoma (hatched area).

*Source:* From Mendenhall WM, Friedman WA, Parsons JT, et al. Radiation therapy and stereotactic radiosurgery for temporal bone tumors. *Oper Tech Otolaryngol Head Neck Surg.* 1996;7:208–218, with permission. (Fig. 1, p. 209)




A




B

**FIGURE 27-24.** Intensity-modulated radiation therapy (IMRT) for ipsilateral tumor. The patient is a 34-year-old man found to have a right glomus vagale and a right glomus tympanicum. The patient was treated with IMRT and received 45.0 Gy in 25 fractions. The mean right parotid dose was 21.5 Gy and the mean left parotid dose was 3.0 Gy. Follow-up with magnetic resonance imaging (MRI) revealed the paragangliomas to be stable 1 year after IMRT (**A:** sagittal; **B:** coronal). (See color insert.)

*Source:* From Mendenhall WM, Million RR, Parsons JT, et al. Chemodectoma of the carotid body and ganglion nodosum treated with radiation therapy. *Int J Radiat Oncol Biol Phys.* 1986;12(12):2175–2178, with permission.

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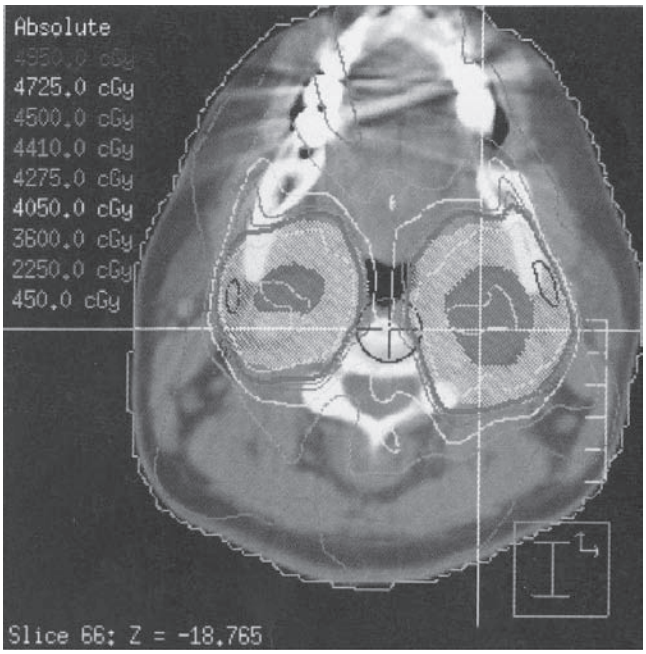



**FIGURE 27-25.** The patient is a 33-year-old woman with bilateral glomus vagale paragangliomas. She received 45 Gy in 25 fractions with 6-mV x-rays using intensity-modulated radiation therapy (IMRT). The mean parotid doses were 18.4 Gy and 20.2 Gy, respectively. Follow-up computed tomography (CT) at 1 year revealed no evidence of progression. (See color insert.)

*Source:* From Mendenhall WM, Million RR, Parsons JT, et al. Chemodectoma of the carotid body and ganglion nodosum treated with radiation therapy. *Int J Radiat Oncol Biol Phys*. 1986;12(12):2175–2178, with permission.

tumor may minimize the long-term morbidity of treatment if one of the lesions can be resected with acceptable morbidity. Relatively small bilateral paragangliomas may be treated with IMRT with adequate sparing of one or both parotid glands (Fig. 27-25).

There is little information pertaining to radiation therapy for malignant paragangliomas. The diagnosis of malignancy is based on the presence of metastatic disease. The author's philosophy has been to resect lesions that can be resected with acceptable morbidity and to add postoperative irradiation depending on the pathologic findings. In practice, most patients who are operated on for malignant paragangliomas receive adjuvant postoperative irradiation at the author's institution. The dose fractionation schedules are similar to those employed for other malignancies. Because (by definition) the regional lymph nodes are involved, the ipsilateral lymph nodes must be included in the target volume.

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CHAPTER 28

# Cancer of the Thyroid and the Parathyroid

## PART A: General Principles and Management

Bruce J. Davidson, Kenneth A. Newkirk, and Kenneth D. Burman

## THYROID CANCER

### Introduction

***Epidemiology—Increasing Incidence of Thyroid Cancer.*** According to cancer statistics, there has been a substantial rise in thyroid carcinoma in the United States in recent years. Cancer statistics for 2012 estimate 56,460 new cases of thyroid cancer will occur. This is more than three times the number of thyroid cases reported 15 years earlier (Fig. 28-1).[1] The mortality is increasing at a slower rate, with 1,780 deaths expected due to thyroid cancer in 2012.[1] Were thyroid cancer outcomes more ominous, the public awareness of this significant trend would be widespread. In fact, the rise in incidence is of uncertain significance. Although this increased incidence may represent a true increase in disease, there are other possible explanations including reporting variability, increased diagnostic effort, and improved technology.

Although the reported incidence of thyroid cancer is alarming, these figures must be assessed in the context of data implying a much larger prevalence of these tumors. Several autopsy series around the world have suggested that the prevalence of occult papillary cancer (typically defined as tumors <1 cm in diameter) in patients dying of other causes ranges from 6% to 28%.[2] In the United States, studies have shown the incidence of occult papillary cancer to be 6% to 13% in patients dying of other causes.[2–4] If one were to make a very conservative estimate of occult thyroid cancer in the United States at 1% of adults, it could be estimated that there are currently >3 million undiagnosed thyroid cancers. The Surveillance, Epidemiology, and End Results (SEER) database estimated a prevalence of thyroid cancer of 458,403 in 2010; therefore, it would appear that what is seen is only a minority of the total number of thyroid cancers in cancer statistical data.[5]

There are several suspected reasons for the increased incidence of thyroid cancer. These reasons include (a) an increased reporting of occult tumors, (b) an increased diagnostic suspicion due to increased awareness by clinicians, (c) an improvement in diagnostic skills through increased ultrasound surveillance, (d) an increased use of fine-needle aspiration (FNA), and (e) the growing use of ultrasound-guided FNA to evaluate small lesions of the thyroid. If any or all of these reasons were the cause of the increase in thyroid cancer incidence, one might expect that there would be an increase in the proportion of cancers diagnosed at lower stage.

Using SEER data from 1975 to 2002 and historical staging, there has been no change in the proportion of thyroid cancer that is confined to the thyroid, so it would not appear that increases are of low-stage tumors only.[6] However, improvements to the SEER database beginning in 1988 lend further insight. First, it has been shown that the entire increase in incidence of thyroid cancer consists of papillary carcinomas. Secondly, as primary size has been better reported by SEER since 1988, 49% of the increased incidence between 1988 and 2002 consists of tumors <1 cm diameter, and 87% of the increase consists of tumors <2 cm.[6] Therefore, a significant portion of this "epidemic" of thyroid cancer would appear to be a reflection of increased investigation and assessment of small thyroid lesions. The controversy about this is not resolved as more recent analysis of SEER data shows that although the majority of the increase in thyroid cancer is among low-stage tumors, a measurable increased incidence can be shown for higher stage tumors as well.[7]

Although the diagnosis of small papillary cancers appears to be responsible for the majority of increase in thyroid cancer incidence, it is difficult to predict the natural history of even small papillary thyroid cancers and clinical judgment is important in the monitoring of such patients.[8] Mazzaferri has cautioned that even patients with micropapillary cancer have a cancer-related mortality of approximately 1%, a risk of distant recurrence of approximately 2.5%, and a risk of local node recurrences of approximately 5.0%. These figures are why clinicians are uneasy as they try to address this epidemic.

***Worldwide Epidemiology.*** The worldwide incidence of thyroid cancer varies as shown in Figure 28-2, with the highest reported incidence in Polynesia, followed by North America. In general, the



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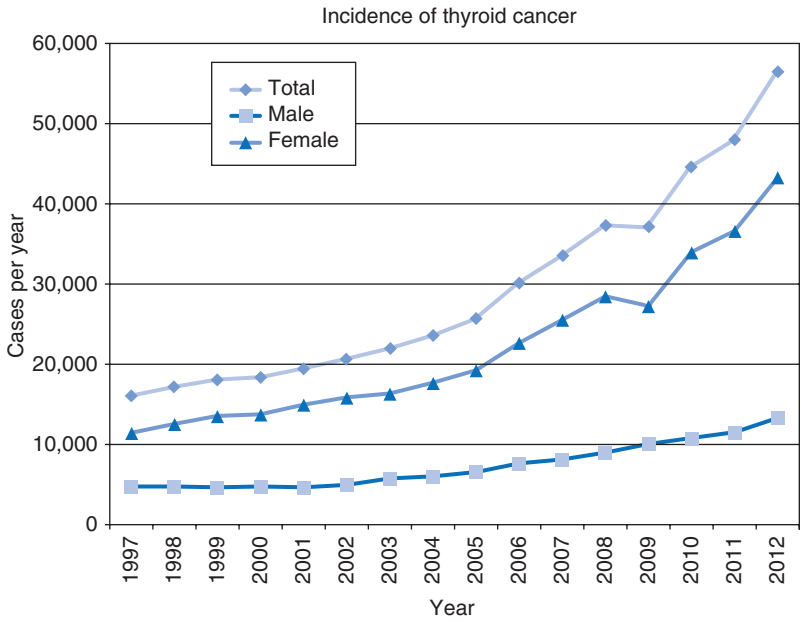



**FIGURE 28-1.** Incidence of thyroid cancer in the United States, 1997–2012 (estimated).

*Source:* Adapted from American Cancer Society. *Cancer Facts and Figures 1997–2012.* Atlanta, GA: American Cancer Society; 2012, with permission.

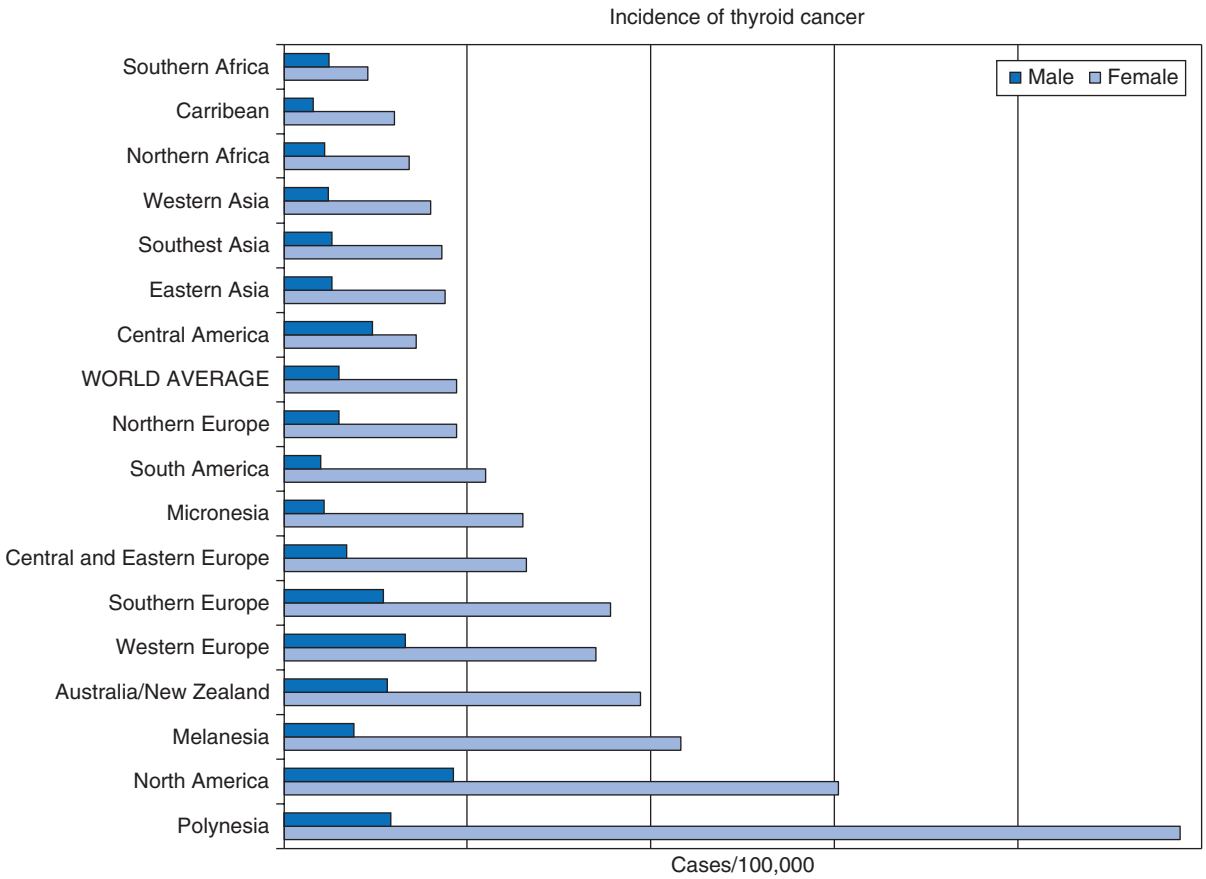



**FIGURE 28-2.** World age-standardized thyroid cancer incidence by gender and region.

*Source:* Adapted from Ferlay J, Shin HR, Bray F, et al. *GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 10 [Internet].* Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr, Accessed January 1, 2012, with permission.

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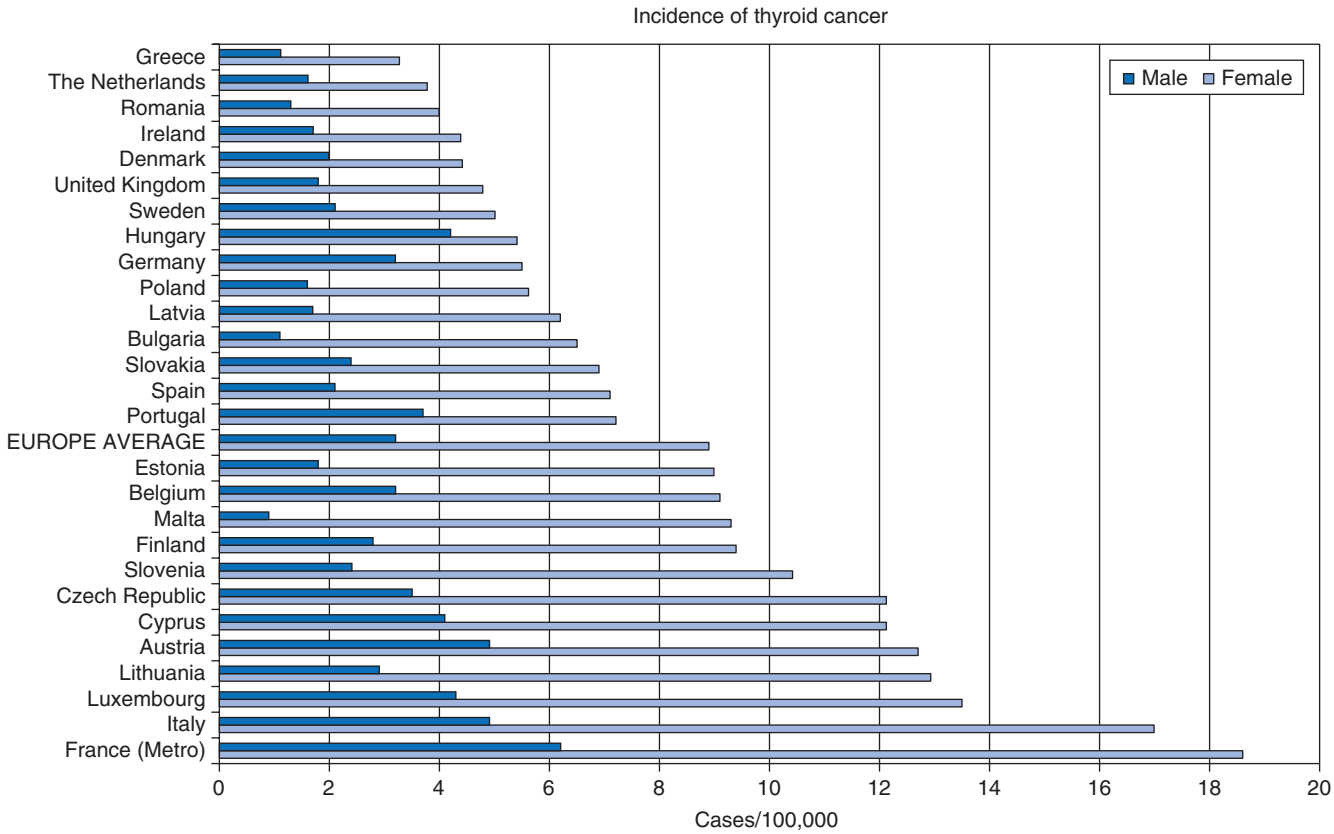



**FIGURE 28-3.** European Union age-standardized thyroid cancer incidence by gender and country.

*Source:* From Cancer Research UK. http://info.cancerresearchuk.org/cancerstats/types/thyroid/incidence/. Accessed January 1, 2012, with permission.

incidence in more developed countries is higher than that in less developed countries.[9] Worldwide incidence varies considerably, and even within Europe (Fig. 28-3), wide variations are seen.[10]

With such a wide variation in incidence of thyroid cancer, the impact of environmental exposures may be considered. For the countries surrounding the Chernobyl nuclear facility, an increase in thyroid cancer incidence has been shown and more will be written on this later in the chapter.[11] However, similar to the U.S. experience, multiple studies have demonstrated an increase in thyroid cancer incidence throughout the world. A relationship to the Chernobyl incident or to other radiation or environmental exposures has not been suspected in this increase.[12] Instead, the increase in thyroid cancers has been explained by a changing management strategy in thyroid disease. A French multi-institutional study demonstrates a relationship to both the increased use of diagnostic ultrasound and to rigorous cytologic evaluations. The result has been an increase in the proportion of surgical cases that result in malignant pathology.[13]

Lithuania introduced ultrasound-guided FNA in 1997 and a recent retrospective evaluation shows a significant increase in the incidence of thyroid cancer beginning in 2000. Before this, the annual increase in thyroid cancer incidence was approximately 5% per year. Since 2000, the annual increase in thyroid cancer is 28% per year. The increased incidence is seen in both papillary and follicular cancers, but is confined to stage I disease only.[12]

***Changes in Histology.*** Over the last 50 years, there has been an increase in the frequency of papillary cancers primarily, with a decrease in follicular cancers and anaplastic cancers and essentially no change in medullary cancers.[14] It has been proposed that the difference in the proportion of tumors of each histology is partly explained by variations in environmental iodine exposure. Iodine-deficient areas are associated with an increased risk of goiter and an increased proportion of follicular cancer and anaplastic cancer. Iodine-sufficient areas are associated with increased autoimmune thyroid disease and an increased proportion of papillary thyroid cancers with a decrease in follicular and anaplastic cancers. A dose–response relationship is indicated with the proportion of papillary to follicular cancers changing from approximately 5:1 in high iodine-intake areas, to 2.5:1 in moderate iodine areas to 1:1 in iodine-deficient areas.[15]

Changes in pathologic interpretation of thyroid cancers over time may confound our ability to make generalizations about the proportion of cancer histology over time and about the relationship between iodine and thyroid cancer histology. A review of previous thyroid cancer cases entered in the Geneva Cancer Registry over a 30-year period demonstrated that 45% of follicular cancers diagnosed between 1970 and 1979 were reclassified as papillary cancers. Cases entered more recently, 1990 to 1998, were less likely to be reclassified, but the rate of reclassification was still 25%. The possible explanation for this high rate of reclassification is not known but could relate to the development of stricter guidelines for microscopic characterization.[16]

***Etiology.*** A relationship between ionizing radiation and thyroid cancer was first described in 1950 by Duffy and Fitzgerald.[17] A dose–response relationship has been established for lower doses of radiotherapy, particularly in individuals exposed in childhood.[18] Between approximately 1920 and 1960, the use of low-dose irradiation was practiced for benign diseases of childhood

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including acne, tinea capitis, impetigo, sinusitis, adenoid hypertrophy, thymic enlargement, and keloids. The practice has now been discontinued since the recognition that this practice contributed to an increased risk papillary thyroid cancer development. However, the risk of developing thyroid cancer in patients treated with low-dose radiotherapy is increased, even for doses as small as 0.1 Gy, and although the risk begins to decline at 30 years, it remains elevated far longer. The risk is greatest for those irradiated at younger than 15 years of age with an estimated relative risk of 7.7 per Gy.[18] The risk of nodules in patients irradiated for benign disease has been reported at 38%[19] and approximately a third of these nodules will be malignant.[20–22] While the risk is significant for those patients irradiated, the numbers of irradiated patients is not felt to be large enough to explain the increase in cancer incidence across populations discussed earlier.

While childhood radiation for benign conditions is no longer used, there remains a cohort of patients who are treated in childhood for malignancy with radiation therapy. This is a population that has been shown to be at increased risk of thyroid cancer. Estimates of increased risk ratio (RR) of 4.6 to 14.6 have been reported.[23,24] The risk increases with increasing thyroid radiation dose up to about 20 Gy and then tapers off.[24] The risk is greater with younger age of treatment and in females. Subsequent thyroid cancer risk is most often associated with Hodgkin and non-Hodgkin Lymphoma[23] and neuroblastoma.[24] For lymphomas, the field of radiation includes the thyroid bed whereas for the latter tumor the early age of treatment is a major factor influencing thyroid cancer risk. The relative risk of developing thyroid cancer peaks at 20 years after treatment,[23,24] but lifelong monitoring is recommended.[23]

There has been evidence of increased rates of differentiated thyroid cancer (DTC) in areas downwind from nuclear test sites.[24] Following atomic testing in the United States between 1950 and 1958, the estimated average cumulative dose of radiation from environmental iodine-131 ($^{131}$I) has been estimated to range from 1 to 4 rads per individual across the United States. Some areas are estimated to have had exposures up to 16 rads. In contrast, the average annual background radiation is 0.1 rad.[26] A careful evaluation of thyroid cancer rates attributable to atmospheric nuclear testing found that the risk of thyroid cancer was only suggested for individuals exposed before the age of 1. Older children and adults did not demonstrate an increased risk.[26]

The risk of environmental exposure from radiation has been clearly documented following the Chernobyl nuclear disaster in the Ukraine in 1986.[27–29] The pattern of development, however, is quite different from that seen in childhood therapeutic radiation exposure. In childhood low-dose therapeutic radiation exposure, the risk of thyroid cancer rises after a latency of approximately 10 years and peaks at 25 to 30 years as shown in Figure 28-4.[30] Following Chernobyl, the increase in thyroid cancers was seen as early as 1989, only 3 years after the accident.[27–29] The impact of the Chernobyl disaster may not be yet fully known. Data from Belarus (whose border is <20 miles from Chernobyl) indicate a significantly higher incidence of thyroid cancer in high-exposure areas when compared with low-exposure areas. The rate of thyroid cancers continues to increase in individuals who were between 0 and 15 years of age at the time of the disaster.[11]

Other environmental factors that might lead to an increase in thyroid cancer development are not clear. In a thorough case-control study using the Swedish Cancer Registry and an extensive review of lifetime diagnostic radiograph exposures, there was no evidence of an increased exposure to diagnostic radiographs in patients with DTC.[31] Similarly, there is no strong indication that irradiation from the use of therapeutic $^{131}$I leads to an increased risk of thyroid cancer.[32–35] One exception is work by Franklyn et al. which evaluated patients with hyperthyroidism given $^{131}$I and found a higher incidence and mortality rate of thyroid cancers as well as a higher incidence of small bowel tumors, although the absolute incidence rates were low.[36]

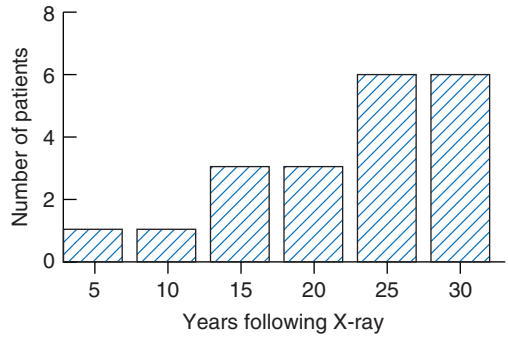



**FIGURE 28-4.** Incidence and timing of papillary thyroid carcinoma in patients exposed to ionizing radiation during childhood.

*Source:* Adapted from DeGroot M, Sternberg T. *The Thyroid and Its Diseases*. 5th ed. New York, NY: Churchill Livingstone; 1984, with permission.

Associations between thyroid cancer and other exposures have been investigated. Owing to the fact that thyroid cancer is a relatively common disease in young women and the increased incidence of thyroid cancer is greatest in women, multiple studies have investigated the relationship between thyroid cancer and reproductive history and exogenous hormone use. The data are mixed but describe an increased risk of thyroid cancer with early menarche,[37] early first pregnancy,[38] late first pregnancy,[39] and late last pregnancy.[39,40] Other studies show no relationship to reproductive history.[41,42] The relationship between oral contraceptive use and thyroid cancer has been positive, negative, or unrelated depending on the study,[37,43,44] although there is a suggestion from pooled data that oral contraceptives can act as a promoter of thyroid cancer.[43] The risk of oral contraceptive use appears to be eliminated after the hormone is discontinued.[43]

Genetic causes of thyroid malignancy are well known for medullary cancer, and this will be discussed in detail later in the chapter. For papillary cancer, there are a handful of syndromes that manifest this cancer. These include Gardner syndrome, Cowden disease, and Carney complex, all autosomal dominantly inherited.[45,46]

## Relevant Anatomy

***Embryology.*** The thyroid gland develops from the endodermal tissues of the primitive gastrointestinal tract. The site of origin ultimately is the foramen cecum at the tongue base and descent of the thyroid occurs by the seventh gestational week to lie anterior to the cricoid and cervical trachea. The thyroid is able to concentrate iodine and form thyroid hormone by the 11th gestational week. It reaches its full size of 15 to 25 g in adulthood.

The descent of the thyroid through the anterior midline neck explains several anomalies that relate to thyroid pathology. These include ectopic thyroid located at the tongue base, termed a *lingual thyroid*. Lingual thyroid tissue has been reported in up to 10% of children.[47,48] When noted, this may represent the only thyroid tissue in patients and evaluation of the neck for additional thyroid tissue is important. Along the pathway of thyroid descent, a cyst of ciliated pseudostratified epithelium and variable amounts of thyroid tissue may remain. These thyroglossal duct cysts are usually closely related to the central portion of the hyoid bone, and it is generally accepted that this bone must be resected to successfully remove the cyst. The cyst, or similarly located ectopic thyroid tissue, may give rise to thyroid neoplasia

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on occasion. The most inferior point on the pathway of normal thyroid descent would be represented by the pyramidal lobe, thyroid tissue located just cephalad to the thyroid isthmus.

Other ectopic locations of thyroid tissue have been noted including mediastinum, heart, liver, esophagus, larynx and trachea, and ovary.[49–54] These structures are obviously beyond the range of the typical descent of thyroid tissue and represent true ectopic locations. Thyroid rests in cervical lymph nodes deserve special mention. Although these have been described previously in cervical lymph nodes,[55] the concern when thyroid tissue is identified in these nodes is that this represents well-DTC metastatic to that node. As a general rule, thyroid rests in nodes along the jugular chain (i.e., lateral neck nodes) are considered diagnostic for thyroid malignancy. On the other hand, thyroid rests in central compartment lymph nodes are felt to represent benign thyroid rests if no suspicion of malignancy is noted in the thyroid itself. These guidelines may not apply to all patients and each patient's context should be reviewed to determine when additional testing for the presence of malignancy must proceed.

While the thyroid follicular tissue develops from the embryologic foregut, the calcitonin producing (C or parafollicular) cells of the thyroid develop from neural crest ectoderm related to the fourth and fifth branchial pouches. These tissues, known as the *ultimobranchial body*, migrate anteriorly and merge with the descending follicular thyroid tissues, thus explaining their designation as parafollicular cells. Analysis of thyroid tissues has shown that these C cells lie in greater concentration in the superior and posterior aspect of the thyroid, a location similar to the superior parathyroid, which also arises from the fourth brachial pouch.

The parathyroid glands develop as two paired structures from the third and fourth branchial pouches. The third pouch gives rise to the inferior parathyroid and the more inferior thymus gland. This relationship explains the fact that ectopic parathyroid tissues may be located within the thymus. As stated, the superior parathyroid develops from the fourth branchial pouch along with the ultimobranchial body, which gives rise to the C cells.

## Anatomy

The thyroid consists of two lobes, each approximately 8 to 10 mL in size connected by a thin isthmus lying over the trachea. A pyramidal lobe of any significant size is present in a minority of cases. The average gland weighs 15 to 25 g. The thyroid isthmus is often easily palpated, just below the cricoid cartilage. The thyroid lobes are palpable lateral to this, with the examination made easier when the patient swallows. The left and right lobes of the thyroid lie just deep to the sternothyroid muscles. The gland is encased by a thin layer of fascia, but the posterior attachment of the gland to the trachea is quite dense and lies just medial to the area where the recurrent laryngeal nerve enters the cricothyroid membrane. It has been estimated that up to two-thirds of thyroid glands may have a tubercle of Zuckerkandl, a posterior, lateral extension of the thyroid lobe that may be an important landmark in identifying the recurrent laryngeal nerve and the superior parathyroid gland.[56–58]

***Vascular and Lymphatic Anatomy.*** The vascular anatomy of the thyroid is described as two paired arteries and three paired veins. These include superior and inferior thyroid arteries and superior, middle, and inferior thyroid veins. Although this is true, the practical application of this information is significantly limited by the surgical anatomy of the thyroid. The superior thyroid vein, and to a lesser extent the artery, anastomose with the thyroid through several small branches. The superior laryngeal nerve may be intertwined with these branches, so meticulous dissection of individual branches of the superior thyroid artery and vein is required when dissecting the superior pole of the thyroid. Likewise, the inferior vein is always divided into multiple branches at the margin of the thyroid gland. Individual ligation of these branches is required due to the fact that the inferior parathyroid is often located on the thyroid capsule in this area. Finally, the inferior thyroid artery has been shown to contribute the major blood supply to both the inferior and superior parathyroid glands. Preservation of the vascularity of these glands is felt to be important in order to preserve their function after thyroidectomy. Therefore, dissection and ligation of only the distal branches of this artery as they enter the thyroid has been felt to be most judicious. Regarding the last point, however, there may be some debate as two randomized studies looking at subtotal thyroidectomy found no difference in postoperative hypocalcemia whether or not the inferior arteries were ligated at the main trunk.[59,60] Whether these studies apply to the performance of total thyroidectomy is unclear.

The superior thyroid artery arises as the first branch of the external carotid artery in the vast majority of individuals. From this point, it descends to the upper thyroid pole by passing deep to the omohyoid muscle and superficial to the superior constrictor muscle and cricothyroid muscle. The superior laryngeal nerve arises from the vagus nerve high in the neck and passes deep to the carotid artery to reach the larynx. The internal branch of the superior laryngeal nerve enters the thyrohyoid membrane just inferior to the hyoid whereas the external branch travels parallel and deep to the superior thyroid artery and then passes medially to the cricothyroid muscle.

The relationship between the superior thyroid artery and nerve is variable. This variability was emphasized in a recent anatomic study that included review of previous data. In this, the nerve was shown to cross the plane of the superior thyroid artery over 1 cm above the superior thyroid pole in 18% to 68% of cases. The nerve crossed within 1 cm of the superior thyroid pole in 11% to 60%. However, the more important, and most consistent, anatomic relationship for surgical dissection was the finding that the nerve crosses the artery below the upper pole of the thyroid in 14% to 20% of patients.[61] In addition to this study, recent work has shown that in almost half of all thyroidectomies the superior laryngeal nerve may be located below the superior pole of the thyroid gland and be at risk for injury,[62] with oversized glands having a higher risk.[63]

The inferior thyroid artery is a branch of the thyrocervical trunk and passes deep to the common carotid artery to reach the thyroid. In this orientation, it is roughly perpendicular to the recurrent laryngeal nerve. The relationship between the inferior thyroid artery and this nerve is variable, but is stated to demonstrate the nerve as deep to the artery in 70% of cases. A distinction has been suggested between the two sides of the larynx with the right nerve most often passing between branches of the inferior thyroid artery and the left nerve most often passing behind the artery.[64]

Lymphatics of the thyroid consist of a rich intraglandular network as well as extraglandular drainage. The intraglandular network has been thought to explain the high rate of multifocality in papillary thyroid cancers by allowing tumor emboli to travel through the thyroid and metastasize to other intrathyroidal sites. The extraglandular network passes through the medial compartment of the neck and also follows the arterial supply in a retrograde manner as it exits this medial compartment. The medial or central compartment of the neck, shown in Figure 28-5, represents the primary echelon nodal drainage from the thyroid gland. Surgical dissection of the central compartment in the treatment of thyroid papillary carcinoma has been shown to yield an average of eight nodes per patient.[65]

Secondary echelon nodal drainage is to the lateral neck compartment and posterior triangle lymph nodes. The retrograde lymphatic drainage following the arterial supply to the thyroid

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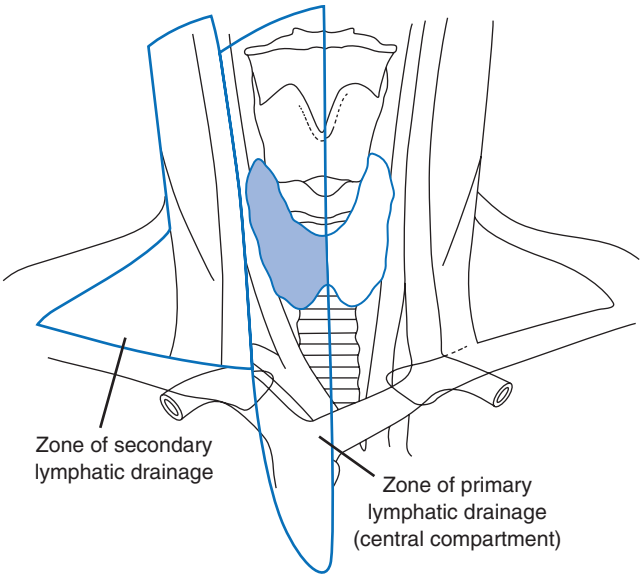



**FIGURE 28-5.** Primary and secondary echelon lymphatic drainage from the thyroid gland.

is demonstrated by work on subcentimeter papillary thyroid cancers. Small tumors of the upper portion of the thyroid are as likely to spread to level II in the upper jugular chain (presumably through lymphatics along the superior thyroid artery) as to lower neck nodes.[66]

***Neuroanatomy.*** The nerves important in thyroid anatomy and thyroid surgery are those of the larynx. The superior laryngeal nerve and recurrent laryngeal nerve are branches of the vagus nerve. This nerve exits the skull base at the jugular foramen, and just below this point, the superior laryngeal nerve branches off to pass deep to the carotid artery and medially toward the larynx. The internal branch of this nerve enters the thyrohyoid membrane to supply sensory innervation to the supraglottic larynx. The superior location of this branch means that is it not at risk in thyroid surgery unless a large cephalad extension of the thyroid is present. The external branch of the nerve is of greater concern in thyroid surgery. This branch innervates the cricothyroid muscle, a nerve important in vocal fold stretch and in vocalizing at high pitch. The nerve travels to this muscle along the superior thyroid artery, to which it lies deep. Near the upper pole of the thyroid and occasionally between branches of the superior thyroid artery, the nerve travels medially to the cricothyroid muscle. *En route*, the nerve may penetrate the inferior constrictor muscle and, in fact, has been shown to travel deep to this muscle throughout its course in 10% of patients.[61] The nerve is quite small and even with significant effort can prove difficult to identify. In fact, one study reported an effort to identify the nerve in 50 cases using a nerve stimulator and was only able to identify the nerve in 20% of cases.[67] Other surgeons have been more successful and have reported success in identifying the nerve in >90% of cases.[68]

The recurrent laryngeal nerve branches from the vagus nerve in the thoracic cavity. On the left side, the nerve passes around the aortic arch and then superiorly up along the tracheoesophageal groove to the Berry ligament. On the right side, the nerve passes around the subclavian artery and then passes in a more oblique direction toward the larynx. The nerve passes deep to the inferior thyroid artery in most cases (Fig. 28-6). As the nerve proceeds cephalad, small branches may be seen that enter the

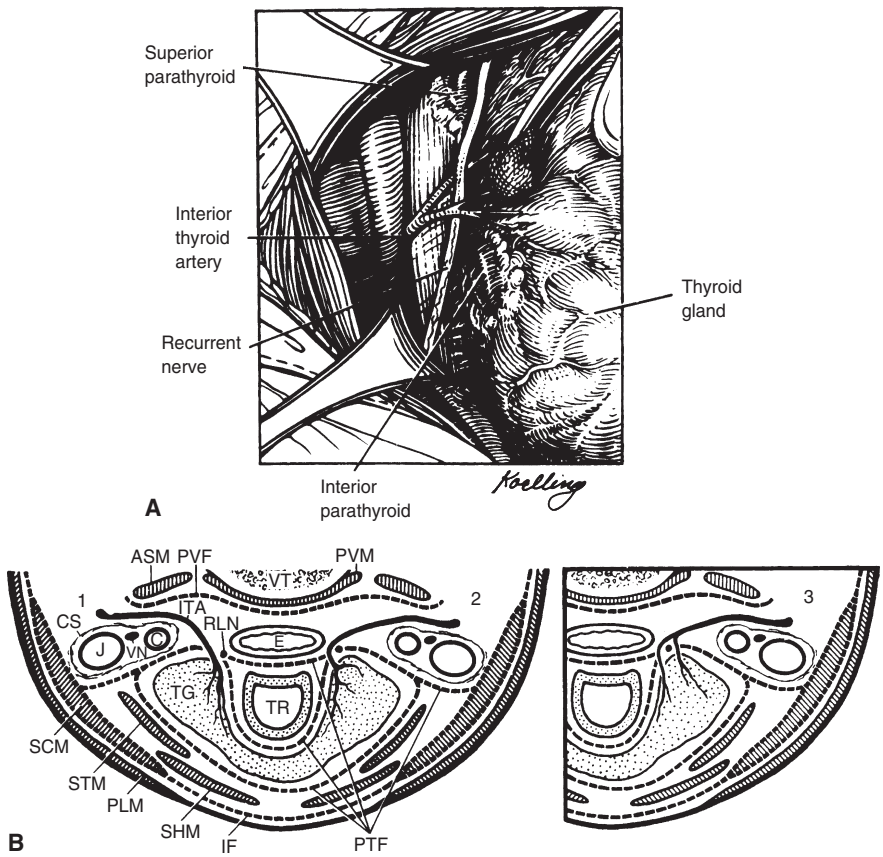



**FIGURE 28-6.** The various relationships of the inferior thyroid artery to the recurrent laryngeal nerve. **A:** View of the right neck with the inferior artery dividing to straddle the recurrent laryngeal nerve. **B:** Cross-sectional diagram of the neck showing the various relationships between the inferior thyroid artery and the recurrent laryngeal nerve (*1*, artery superficial to nerve; *2*, artery deep to nerve; *3*, artery dividing around nerve). ASM, anterior scalene muscle; PVF, prevertebral fascia; PVM, prevertebral muscle; CS, carotid sheath; ITA, inferior thyroid artery; RLN, recurrent laryngeal nerve; J, jugular vein; VN, vagus nerve; C, carotid artery; E, esophagus; TG, thyroid gland; TR, trachea; SCM, sternocleidomastoid muscle; STM, sternohyoid muscle; PLM, platysma; SHM, sternohyoid muscle; IF investing fascia; PTF, pretracheal fascia.

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trachea and esophagus. These include sensory branches to the upper trachea and subglottic larynx. The motor component of the recurrent laryngeal nerve may divide into a posterior and anterior division below the level of the Berry ligament. Katz describes branching of the nerve over 5 mm below the lower border of the cricoid cartilage in 63% of >1,100 thyroidectomies.[69] In addition, recent work suggests that in 1% of cases the recurrent nerve or its branches may enter the larynx in a higher-than-expected location making the nerve more prone to injury.[70] It is important to recognize this branching of the nerve during thyroid surgery. Failure to recognize this anatomy may result in injury to a branch of the nerve. The function of the motor branches of the recurrent laryngeal nerve is to supply all of the muscles of the larynx except the cricothyroid. These include both the abductors and the adductors of the larynx. Injury to the nerve can result in significant laryngeal incompetence. When disruption of those sensory fibers from the recurrent laryngeal nerve to the upper trachea and subglottic larynx occurs in conjunction with motor injury to the recurrent nerve, the combination of vocal cord incompetence and hemitracheal anesthesia can make the postoperative course of such a patient much more problematic.

The anatomy of the recurrent laryngeal nerve results in some specific risks during thyroid surgery. The nerve can be placed under significant stress during the surgery as dissection proceeds along the lateral aspect of the thyroid and the gland is retracted medially to expose the path of the nerve. During this medial retraction of the gland, the nerve may become compressed by a distal branch of the inferior thyroid artery or by a fascial band stretched across the nerve. At the ligament of Berry, the nerve courses posteriorly to enter the larynx behind the cricothyroid joint. This fixed relationship between the nerve and the cricothyroid joint and the medial traction of the gland described earlier can also contribute to stretch on the recurrent laryngeal nerve during the dissection. Inadvertent transection of the recurrent laryngeal nerve is not a significant risk for an experienced thyroid surgeon. However, stretch injuries of the nerve may still occur. Almost all of these are temporary. The use of intraoperative recurrent nerve monitoring has been suggested to decrease the risk of injury. However, in recent review of the literature, Dralle et al.[71] found that in six studies comparing intraoperative recurrent nerve monitoring with postoperative laryngoscopic findings, nerve monitoring had a high negative predictive value (NPV; 92%–100%), but relatively low and variable positive predictive values (PPVs; 10%–90%), potentially limiting the role of nerve monitoring. International study guidelines have recently been published on the role of intraoperative nerve monitoring.[72]

A special anatomic relationship should be mentioned in the case of the right recurrent laryngeal nerve. This nerve may be nonrecurrent in a small number of patients, typically estimated at well below 1%. This occurs when there is an aberrant takeoff of the right subclavian artery. This anomaly represents an anomaly of the fourth branchial arch resulting in the right subclavian to arise from the aorta and pass deep to the esophagus. The recurrent laryngeal nerve will then pass deep to the carotid and directly toward the larynx. The authors have seen nonrecurrent nerves that travel parallel (and deep) to the superior thyroid artery and others that resemble a recurrent nerve except that they travel behind the carotid at the level of the inferior thyroid artery.

***Parathyroid Anatomy.*** Normal parathyroid glands are each approximately 40 to 70 mg in weight, meaning a size of approximately 4 × 6 mm at surgery. The location of these glands is variable. The typical location of the superior parathyroid gland is behind the thyroid at the cricoid level, lateral to the recurrent laryngeal nerve. The inferior glands are located on or adjacent to the lower pole of the thyroid in 50% of cases. The inferior glands may lie within thymic tissue in up to 40% of cases.

In the treatment of primary hyperparathyroidism, the surgeon must be familiar with various ectopic locations of parathyroid tissue in order to identify and resect adenomas or hyperplastic glands in these locations. The treatment of malignant diseases of the thyroid does not typically require direct application of this knowledge. However, the surgeon should be aware that 4% of parathyroid glands are found embedded within the thyroid gland.[73] Figure 28-7 shows such a case where both inferior parathyroid glands were identified within the thyroid on pathologic study. This case emphasizes both the possibility of intrathyroidal parathyroid gland and the symmetry often seen when searching for parathyroid glands at surgery. Beyond identification and preservation of parathyroid glands while dissecting the thyroid gland, the treatment of thyroid malignancy will often require a medial compartment neck dissection. Here, the parathyroid glands are at significantly greater risk of devascularization or inadvertent removal during the dissection process and surgeons must be facile at parathyroid gland identification, dissection, and preservation of the parathyroid vascular pedicle, and when necessary, perform parathyroid autotransplantation, usually into an adjacent muscle.

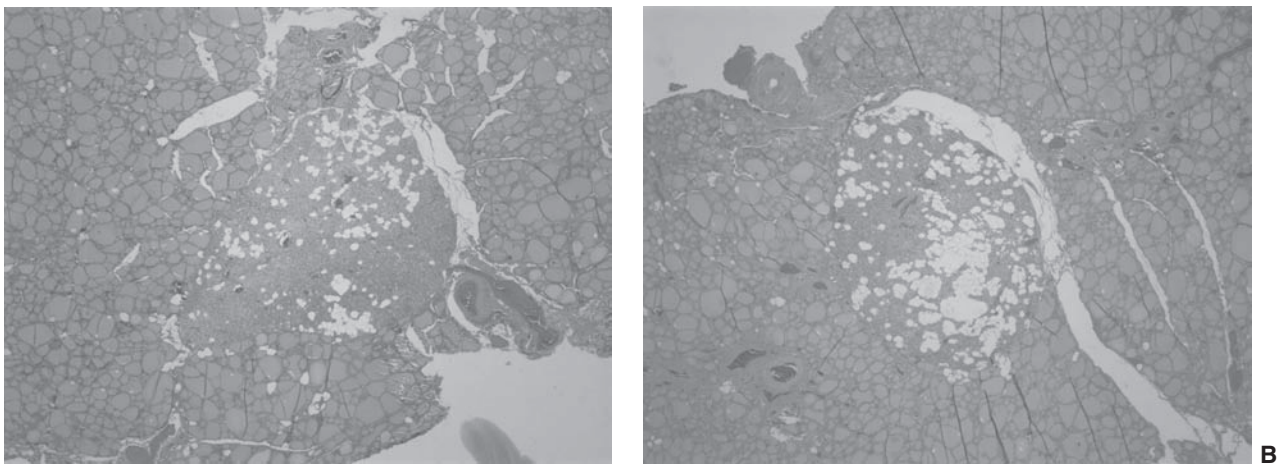



**FIGURE 28-7.** Pathologic evaluation following thyroidectomy revealed that this patient's left **(A)** and right **(B)** inferior parathyroid glands were both located within the thyroid parenchyma. This example demonstrates the relative symmetry that may be seen in parathyroid anatomy.

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## Physiology

The application of thyroid physiology in the treatment of patients with thyroid cancer is one of the basic tools of the clinician. These applications include the possible use of exogenous thyroid hormone to suppress stimulation of benign and malignant thyroid tissue, withdrawal of thyroid hormone to allow intrinsic stimulation to be maximized in anticipation of radioactive iodine, and, more recently, the use of exogenous thyroid stimulation to prepare patients for radioactive iodine without the need for exogenous thyroid hormone withdrawal.

The basic functional unit of the thyroid is the thyroid follicle, which consists of a space filled with colloid and lined by thyroid follicular cells. These cells avidly trap iodide molecules through sodium iodide symporter channels and transport this iodide to the follicular lumen. Meanwhile, follicular cells also synthesize thyroglobulin (Tg), a glycoprotein that serves as the backbone and storage molecule for thyroid hormone. On the luminal side of the follicular cell plasma membrane, iodide molecules are oxidized and attached to tyrosyl peptides of the Tg molecule. Subsequent coupling of iodinated tyrosyl residues leads to the formation of the functional thyroid hormones, still embedded within the Tg glycoprotein through these tyrosyl residues.[74] The two active thyroid hormones, thyroxine (T4) (3,5,3',5'-tetraiodothyronine) and 3,5,3'-triiodothyronine (T3), are stored in this manner within the thyroid colloid until released into circulation. Release of active hormone occurs by reverse pinocytosis from the intrafollicular space back through the follicular cell where the Tg molecule is cleaved to release the T3 and T4 hormones into the plasma.

Tg itself may leak out or be released from follicular cells into the circulation, and the serum measurement of Tg has become an important tumor marker. The molecule is present in serum in normal and pathologic conditions. Increased serum Tg concentrations may be seen in the hyperthyroid phase of silent or subacute thyroiditis; multinodular thyroid disease; and in papillary, follicular, and anaplastic thyroid cancers. The use of serum Tg measures in previously untreated patients (with intact thyroid glands) is limited by its lack of specificity to distinguish benign from malignant conditions. However, in patients previously treated for DTC, in whom there is little or no residual normal thyroid tissue, Tg has become an essential indicator of residual or recurrent DTC (i.e., papillary or follicular thyroid cancer).

In plasma, T3 and T4 are bound to thyroxine-binding globulin (TBG) as well as prealbumin and albumin. Thyroxine-binding globulin is a protein made in the liver and is the dominant thyroid hormone–binding protein. T4 mainly acts as a prohormone and is metabolized to the active form of thyroid hormone, T3, in the liver and kidney primarily. Actions of thyroid hormones influence growth, development, and metabolism. In adulthood, the major effects of thyroid hormone are in the regulation of metabolism, including changes in oxygen consumption and protein, carbohydrate, lipid, and vitamin metabolism.[75]

Iodine and thyroid-stimulating hormone (TSH) are the major influences on thyroid hormone secretion and thyroid stimulation. TSH is excreted from the anterior pituitary and is in turn regulated by thyrotropin-releasing hormone (TRH) from the hypothalamus. Both TSH and thyrotropin-releasing hormone excretion are influenced by feedback from serum levels of thyroid hormones (Fig. 28-8). TSH has been shown to increase thyroid hormone production through multiple mechanisms, from increasing iodine uptake by the sodium–iodine symporter to expediting Tg reuptake by thyrocytes as well as multiple steps in thyroid hormone production.[74]

TSH also stimulates thyrocyte proliferation. It is this effect that has led to the use of TSH suppression as an adjunct in the treatment of thyroid malignancy. Consistent TSH suppression therapy, interrupted only for short periods of TSH stimulation, in order to perform diagnostic studies or ablative treatment with radioactive iodine has long been the mainstay of papillary and follicular thyroid cancer treatment. TSH stimulation has traditionally required withdrawal of exogenous thyroid hormone for several weeks. More recently, however, this stimulation can be obtained through the use of recombinant human TSH (rhTSH) injections without the need for thyroid hormone withdrawal.

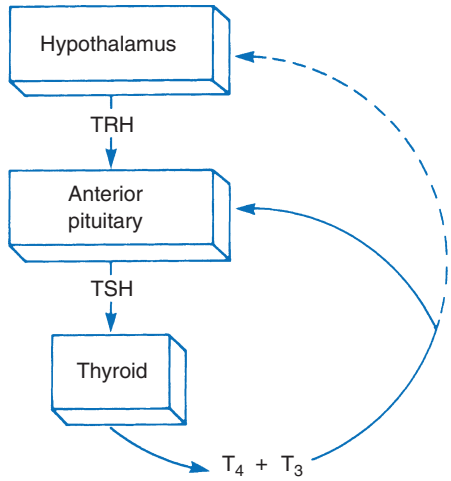



**FIGURE 28-8.** Autoregulatory feedback system for thyroid activity. TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

## NATURAL HISTORY, PATHOLOGY, PATHOGENESIS, AND PATTERNS OF SPREAD

Papillary thyroid cancer, and to a lesser extent follicular thyroid cancer, generally grows as an intraglandular mass before developing lymphatic and distant disease. For this reason, most patients will be alerted to the possibility of the presence of cancer by the discovery of a thyroid mass. Most thyroid masses are, in fact, benign, so the level of clinical suspicion may impact upon the discovery of a malignancy.

A myriad of pathologic processes might present with a mass in the thyroid. Among the benign thyroid masses are adenomatoid nodules, follicular adenomas, and thyroiditis. Adenomatoid nodules are the most common finding to present as a thyroid mass. These may occur as individual masses, but are commonly seen in multinodular glands. Follicular adenomas are benign, but due to the limitations of cytologic evaluation cannot reliably be distinguished from follicular carcinomas. Patients with autoimmune thyroiditis are at risk of developing thyroid lymphomas.

Malignant thyroid masses include papillary and follicular cancer, medullary and anaplastic cancer, lymphoma, squamous cell carcinoma, metastatic tumors to the thyroid, and other rare malignancies. Most of these tumors arise from follicular epithelium. The exceptions are medullary cancer, which arises from parafollicular cells and lymphomas, which arise from intrathyroidal lymphoid cells.

Papillary cancer is the most common thyroid malignancy and makes up approximately 80% of all thyroid cancers.[76,77] Follicular cancer makes up approximately 10% of thyroid cancers and the remaining 10% of tumors are medullary, anaplastic, and other tumors. The distribution of these cancers changes with age. Papillary cancer is more common in patients younger than 40 years of age,

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and follicular cancers more common in older patients. Anaplastic cancers are almost exclusively seen in older patients.

## Papillary Cancer

Papillary architecture is the histopathologic feature that is characteristic of papillary cancer. However, there are multiple additional features that may be seen. The tumors consist grossly of a firm mass within the thyroid gland. Papillary fronds and areas with laminated calcified structures known as *psammoma bodies* may be present. Crowded follicular epithelial cells with cleaved nuclei, nuclear clearing, prominent nucleoli, and mitotic figures define this cancer.[78] Many of these nuclear features can be identified easily in cytologic specimens, making the diagnosis of this tumor by FNA quite accurate.

Earlier in this chapter, the authors reviewed the frequency of occult thyroid cancer and estimated that a large proportion of occult cancers of the thyroid are currently undiscovered. These occult tumors are papillary cancers and are defined by a diameter of <1 cm. The term *papillary microcarcinoma* has been used to describe these tumors. Their natural history is statistically inconsequential, given that most will go undiscovered and never cause any clinical disease. However, whether these occult tumors are biologically distinct from clinically apparent papillary cancers is unknown. There is recent retrospective data from Hong Kong that suggests that only clinically apparent microcarcinomas are of clinical importance due to the fact that, when compared with occult microcarcinomas, only the overt tumors demonstrated a risk of extrathyroidal or lymphovascular invasion, nodal metastases, and postoperative recurrence.[79]

The natural history of clinically apparent thyroid tumors consists of progressive enlargement, intraglandular metastases, involvement of adjacent structures, regional lymphatic disease, and distant metastatic disease. This series of events is not thought to necessarily occur in a stepwise manner; intraglandular metastasis and regional nodal involvement are the most common clinical findings for this tumor type.

A common pathologic feature in papillary thyroid cancers is for multiple foci of tumor to occur within the gland.[80] It has not been clear whether these are intraglandular metastases or true multifocal tumors. Previous literature suggested that this was more commonly a feature seen in irradiated glands.[81] Others found support for a mechanism of intraglandular metastatic spread.[82] However, recent investigations have found genotypic distinctions between multifocal tumors in 40% to 50% of patients with papillary cancer.[83,84] These data indicate that a significant portion of multifocal tumors arise independently in a gland at risk as opposed to intraglandular spread of tumor.

Others, however, have shown evidence of clonal origin in >85% of these multifocal tumors.[85] The papers showing genotypic differences between tumor foci utilized single gene comparisons whereas the paper demonstrating clonality utilized multiple loci in a loss of heterozygosity investigation. Given that tumor development is a multistep process, with multiple genetic events, additional genetic events may occur after intraglandular dissemination. The prognostic impact of multifocality seems to predict an increased risk of recurrence without an impact on survival.[86]

Regional lymphatic metastases are the second most common pathologic feature of papillary thyroid cancer. These occur in >35% of adults with papillary cancer[87] and an even higher proportion, 40% to 75%, in patients older than 40 years of age at diagnosis.[88–90] The risk of regional lymph node metastasis has been shown to be higher in patients with multifocal disease and in those with intratumoral lymphatic vessels.[91,92] The risk of nodal disease is not confined to those with macroscopic primary tumors as some series of microcarcinomas have shown metastatic nodal disease in approximately 50% of patients.[93]

The prognostic impact of nodal disease is unclear. Although there is a high rate of nodal disease in young patients, these patients have an excellent prognosis. The impact of age on prognosis is so dominant that the overall significance of nodal disease has been debated. However, in multivariable analyses and in age-matched case-control studies, a worse prognosis emerges for patients with nodal disease.[91,94] This is shown for both cancer recurrence and disease-specific survival.[86] The greatest impact of nodal disease on survival may be seen in patients older than 60 years of age, a cutoff significantly older than is reflected in the current staging system (where age 45 is thought to be determinant).[95]

Between 10% and 20% of papillary thyroid cancers will show evidence of local invasion. When this extends beyond perithyroidal fat, adjacent structures may be invaded. Most commonly, extension to strap muscles anterior to the gland may be seen. The clinical significance of this is minimal as these muscles may be resected without significant postoperative sequelae. Tumor or medial compartment nodes may also invade the recurrent laryngeal nerves, the hypopharynx, the esophagus, the larynx, or the trachea. Invasion may range from microscopic to gross invasion of these structures. Preoperative indications of involvement include voice change, dysphagia, and respiratory compromise.

Distant metastatic disease from papillary thyroid cancer is most commonly seen in the lungs. Other distant sites include bone, brain, and, less commonly, other locations. Distant metastases are shown in 2% to 3% of papillary thyroid cancers at diagnosis.[96,97] Microcarcinomas have been suggested to have an equivalent likelihood of distant metastasis at the time of diagnosis.[98] In follow-up, another 3% developed lung metastases. The risk is greater when follicular variant papillary cancer is present and even higher for macroinvasive follicular carcinoma.[97] The prognostic impact of distant metastatic disease is significant with a worse survival when disease is macroscopic and does not concentrate radioiodine.[99,100] Adults with macrometastases have been reported to have a 50% survival at 1 year,[101] but this can depend significantly on the number and location of the distant metastases.

Distant metastases from DTC appear to be more common in children than in adults. The prognostic impact, however, is less. Children younger than 21 years of age will present with distant disease in approximately 25% of cases, but 10-year cause-specific survival approaches 100%. The need for ongoing management of these cases is indicated by a progression-free survival rate of 66% at 10 years.[102]

A growing body of evidence shows the high frequency of BRAF mutation in PTC. Next to melanoma, papillary thyroid cancer has the highest frequency of this mutation, ranging from 27% to 81%.[103] The result of these mutations is activation of the mitogen-activated protein kinase (MAPK) pathway leading to tumorogenesis. Other pathways leading to activation of this kinase include ras mutations (more common in follicular thyroid cancers). These pathways to MAPK activation appear to be mutually exclusive mechanisms within individual tumors. There are >40 different BRAF mutations reported, but >90% consist of a T to A transversion at nucleotide 1,799 and lead to an amino acid change at residue 600. This mutation is described as BRAFV600E and causes constitutive activation of the protein, thus driving the MAPK pathway.[104]

There may be geographic variability in BRAF mutations in PTC with the highest rates shown in Korea (63%–81%).[103] The lowest reported rates are in Southern Europe (27%–60%). Interestingly, data from University of California, San Francisco (UCSF) describes an increase in BRAF mutations in papillary cancers treated at that institution over time with a rate of 43% to 51% prior to 2001 and a rate of 88% since that time.[105] The prognostic impact of BRAF mutations is under study.[104]

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## Follicular Variant of Papillary Thyroid Cancer

The World Health Organization reports 15 variants for papillary thyroid carcinoma.[106] The most common of these variants are the follicular, tall cell, and diffuse sclerosing variants (DSVs). In a series of >1,000 cases in 30 years, reviewed with present day diagnostic criteria, classic papillary cancer was seen in 46%, microcarcinoma in 28%, follicular variant in 18%, tall cell in 4%, and diffuse sclerosing in 2%. Other variants, including insular, oncocytic, and others were seen <1% of the time.[107]

While several variants of papillary thyroid cancer exist, the follicular variant of papillary thyroid cancer (FVPTC) is most common. According to Livolsi, this variant was first described in 1960, but was not widely recognized until approximately 20 years later.[78] The hallmarks of this tumor are a predominantly follicular pattern with the nuclear features of papillary cancer. The tumors may be encapsulated or unencapsulated, with the encapsulated version difficult to distinguish from follicular neoplasms.[78] Although the architecture may resemble a follicular neoplasm, the diagnosis is made on the nuclear features that the tumor presents, most commonly intranuclear inclusions, nuclear grooves, and ground glass nuclei. There is inconsistency seen among pathologists when evaluating thyroid specimens for the presence of FVPTC. In fact, in a series of >85 cases of FVPTC, there was complete agreement by 10 pathologists in <40% of cases.[108]

Although FVPTC is considered to be the most common subtype of papillary thyroid cancer, recent molecular investigations indicate that this tumor may be distinct from papillary cancer.[109] Ras mutations are more common in the FVPTC than in classic papillary cancer and are thought to be associated with the follicular differentiation of these tumors.[110] The peroxisome proliferator–activator receptor-γ alteration can also be seen in these tumors and in follicular neoplasms, but not in papillary thyroid cancers of the classic type.[109] In addition, BRAF mutations, which are very common in classic papillary cancer, are seen in as few as 12% of FVPTC cases.[111] Recent data indicate the FVPTC phenotype may vary with the molecular signature of the tumor.[112]

The clinical presentation of FVPTC is similar to other thyroid neoplasia. Grossly, the tumor differs from classic papillary thyroid cancer by the presence of a tumor capsule in most cases. The diagnosis is confirmed, however, by nuclear features as opposed to capsular invasion, thereby following a pattern for papillary cancer. Some series indicate that this tumor presents in a manner that is intermediate between papillary and follicular cancers with respect to extrathyroidal extension, lymph node metastases, and distant metastases. Extrathyroidal extension and nodal disease has been shown less commonly in these tumors than in papillary cancers, but still more commonly than in follicular tumors.[96] A greater prevalence of multifocality in FVPTC has been shown when compared with papillary cancer.[113] Depending on the study, distant disease can be found more commonly in FVPTC than in papillary cancer, but neither tumor has distant metastases as commonly as follicular cancer.[96,113] In the authors' own experience, it was found that although FVPTC tumors are larger at diagnosis, the behavior demonstrates less likelihood for local invasion and a lower recurrence rate.[114]

Owing to the fact that the diagnosis of FVPTC is made by the nuclear features of the tumor, it is suspected that previous cases have been overlooked. In an effort to evaluate the outcome of these cases, a series of FVPTC cases including those previously classified as follicular adenomas and carcinomas has been performed. This leads to the assessment that most (~80%) FVPTC are encapsulated tumors, some of which are invasive and some not invasive, but both groups show low incidence of lymph node metastasis and excellent outcomes. The 20% of FVPTC cases that are unencapsulated appear to represent those with a poorer prognosis, although their behavior was shown to be similar to papillary cancer, not worse. Therefore, even within this tumor type there appears to be subtypes that may have distinct behaviors.[115] Recent investigation of BRAF mutations in these tumors correlates genotypic findings with histologic appearance and clinical behavior (Fig. 28-9).[112]

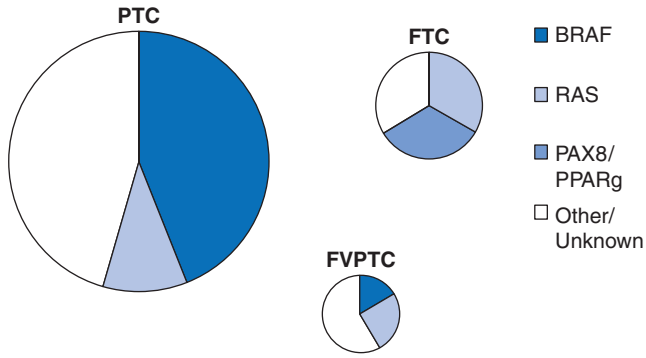



**FIGURE 28-9.** Proposed molecular relationship between phenotype and genotype in follicular variant of papillary cancer.

*Source:* From Rivera M, Ricarte-Filho J, Knauf J, et al. Molecular genotyping of papillary thyroid carcinoma follicular variant according to its histological subtypes (encapsulated vs. infiltrative) reveals distinct BRAF and RAS mutation patterns. *Mod Pathol.* 2010;23:1191–1200, with permission.

Given that the diagnosis of FVPTC is made by cellular and nuclear features, one might expect that diagnosis of this tumor may be afforded by FNA biopsy. Unfortunately, the sensitivity of cytology is low, estimated as low as 9% by researchers at the University of Pennsylvania. Intraoperative pathology is better, but still less than optimal at 36%.[116] Others have reported more favorable sensitivity with FNA, but still <50%.[117]

The pathogenesis and presentation of FVPTC may be distinct from classic papillary cancer. However, most reports reflect an overall survival that is similar to classic papillary thyroid cancer.

## Other Variants of Papillary Cancer

The third most common variant of papillary cancer, after the classic type and the follicular variant, is the tall cell variant (TCV). This is diagnosed based on the appearance of the follicular cells making up the tumor. Diagnosis is made when >70% of the follicular cells are found to be twice as tall as their basal width. These are often large, locally aggressive tumors and vascular and lymphatic invasion may be seen.[78] The diagnostic prevalence of TCV appears to vary between institutions. A review of cases in Sweden found that in a series of papillary cancers, the diagnosis was made in 2% of cases read by a local pathologist. However, further review by "expert" pathologists led to diagnosis in another 5% of cases.[118] The presentation of these tumors is more often in males and in older patients and show increased likelihood of extrathyroidal extension.[119] The authors have found that tall cell cancers were more likely to be smaller than 1.5 cm in diameter, but more likely to be extrathyroidal and of higher stage than typical papillary cancers.[120] One factor that might impact on this tendency for extrathyroidal extension is a higher rate of expression of c-MET, a tyrosine kinase that influences cellular invasiveness.[121]

Decreased disease-specific survival has been shown in most series with a mortality as high as 25%.[119,122] The authors' review of survival was more favorable with a mortality of 5% although the mean follow-up was <4 years.[120] A recent matched-pair analysis comparing tall cell to classic PTC was performed using the

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SEER database. Controlling for demographics, extent of disease, and treatment, this found worse disease-specific 5-year survival (82% vs. 91%) in tall cell cancer.[123]

The features of the DSV of papillary cancer include diffuse involvement, numerous micropapillary structures with lymphatic permeation, extensive squamous metaplasia, numerous psammoma bodies, marked lymphocytic infiltration, and prominent fibrosis. When compared with classic papillary cancer, the clinical features of these tumors reveal a similar predilection for women, a younger age at the time of diagnosis, a greater incidence of cervical metastases, increased incidence of lung metastases, and decreased disease-free survival on follow-up.[124] Others have confirmed that this variant is associated with increased lymph node involvement, increased regional recurrence, increased distant metastases, and decreased survival.[125]

Tall cell and DSVs of papillary thyroid cancer would appear to have a more aggressive behavior and worse prognosis than classic papillary thyroid cancer. Unfortunately, the surgeon is still limited by incomplete knowledge at the time of surgical treatment of thyroid cancers. This is due to overlapping cytologic features among the various papillary cancer subtypes. While some cytologists have retrospectively determined cytologic features that indicate tall cell cancers, the ability to distinguish these subtypes on biopsy or frozen section in practice is limited.[126,127] Surgeons, therefore, are usually required to make decisions about surgical treatment based on clinical features and intraoperative findings.

While subclassification can indicate prognostic differences between various patients with papillary carcinoma, tumor grading may be a more important prognostic factor in multivariable analysis. This may be due to the relative infrequency of each particular papillary variant. However, when taken together, patients presenting with high-grade tumors, represented by nuclear atypia, tumor necrosis, and vascular invasion, do demonstrate decreased survival.[128]

## Follicular Carcinoma

Follicular thyroid cancer represents the second most common thyroid cancer type. Approximately 10% to 15% of thyroid cancers are classified as follicular. These tumors are typically encapsulated, solid neoplasms with minimal colloid, microfollicle formation, and variable degrees of nuclear atypia. This histologic pattern is similar in benign and malignant follicular neoplasms; therefore, the distinction between the adenoma and carcinoma hinges on identification of vascular and/or capsular invasion by tumor.

The behavior of follicular cancer is thought to be somewhat worse than papillary carcinoma. However, this may be secondary to an older age and more advanced stage at diagnosis when compared with papillary cancer.[87,129] When controlled for age, gender, and stage, the prognosis of follicular and papillary cancer are similar.[129] Mazzaferri and Jhiang report similar 30-year survival and recurrence rates for these tumors types after eliminating those patients found to have distant metastatic disease at diagnosis.[87]

Tumor stage appears to be critically important in comparing these tumor types, and inherent biologic differences are probably indicated by the 11% to 18% rate of distant metastatic disease in follicular cancer at the time of diagnosis, more than twice that of papillary cancer.[130,131] However, this difference in distant metastatic disease may be partly explained by tumor size at diagnosis. The prevalence of distant disease appears to correlate with tumor size and when tumors of similar size are compared, no difference is seen between follicular and papillary cancer and the likelihood of distant disease.[131]

The pattern of capsular invasion merits further discussion. Limited invasion into (but not through) the fibrous capsule surrounding the tumor is termed *minimally invasive follicular carcinoma*. More complete extension through the capsule represents classic follicular carcinoma. The behavior of these two types of follicular cancer differs and some favor an approach to minimally invasive cancer that utilizes conservative surgical treatment only. With regard to vascular invasion, it is associated with a higher rate of distant metastasis.[132]

Pathologists attempted to define minimally invasive follicular carcinoma as follows: "an encapsulated follicular tumor (not papillary), with only small to medium vessel invasion within or immediately adjacent to the tumor capsule and/or up to full-thickness capsular transgression without accompanying extension into the thyroid parenchyma."[133,134] Unfortunately, there is significant discordance between pathologists as shown in a study from France where diagnostic interpretation was discordant in >50% of minimally invasive follicular carcinomas when reviewed by a group of experienced pathologists.[135] Although the excellent outcomes of patients with minimally invasive carcinoma are encouraging, the authors favor a similar approach to all follicular carcinomas given the limitations of pathology and the potential negative prognostic impact of vascular invasion.

While the pathology of papillary cancer is made in large part on the cellular and nuclear features of the tumor, follicular tumor diagnosis is determined by the tumor architecture, specifically capsular invasion. Cytologically, therefore, papillary cancers are typically diagnosed by FNA biopsy. This is not true for follicular cancers. The cytologic distinction between follicular carcinomas, follicular adenomas, and some cellular adenomatoid nodules is not possible and requires surgical resection to establish the precise tumor pathology. Recent efforts to define the immunohistochemical or genetic distinctions between these various entities hold promise, but are not yet sufficiently sensitive for clinical use.[136] Because it is not possible to establish a firm diagnosis of follicular carcinoma preoperatively, it would be helpful to be able to obtain this assessment by intraoperative frozen section. However, capsular invasion may only involve a small portion of the capsule, making the diagnosis of follicular cancer very difficult using standard frozen-section analysis. A diagnostic accuracy of 98% has been reported when the pathologist is able to process multiple[5–12] frozen sections.[137] However, this is a significant undertaking and pathologists in the United States have repeatedly emphasized the difficulty in establishing a diagnosis of these cancers on frozen section.[138,139] For this reason, most surgeons will try to avoid decision making based on a frozen section in follicular neoplasia.

Invasion of the tumor capsule in follicular carcinoma should be distinguished from extension beyond the thyroid parenchyma. This is an important difference that can confuse the student of thyroid neoplasia. Invasion of the tumor capsule defines the disease of follicular carcinoma but tumor may still remain entirely intrathyroidal. Extension beyond the thyroid parenchyma can occur in a tumor of any histology, and may result in invasion of adjacent structures such as the larynx, trachea, or esophagus. Invasion of these structures demonstrates a biologically aggressive tumor and portends a worse prognosis.[140–142]

The two most common sites of distant disease in follicular cancer are bone and lung. This tumor is more likely than papillary cancer to involve bone, and, not uncommonly, the first manifestation of a follicular cancer will be a bone metastasis. However, because of the greater overall incidence of papillary cancers, that tumor type is more common than follicular in series of metastatic thyroid cancer to bone. In a series from Memorial Sloan-Kettering Cancer Center (MSKCC) with bone metastases from thyroid cancer of various histology, the prognosis was generally poor with survival estimated at 29% after 5 years. Although survival was worst among those with anaplastic and medullary cancer with no 5-year survivors, other histologies revealed a 5-year survival approaching 40%. This rate did not vary between papillary, follicular, or other histologies nor by tumor differentiation.[143]

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## Hurthle Cell Carcinoma

Hurthle cell carcinoma is considered to be a variant of follicular carcinoma. These tumors demonstrate large cells with granular cytoplasm and abundant mitochondria. The Hurthle cells themselves are felt to represent a metaplastic response of follicular cells and may be seen in inflammatory as well as neoplastic lesions.[78] Although distinguishable from follicular cancer, Hurthle cell carcinoma typically shows a similar histologic pattern and a similar behavior.

The finding of Hurthle cells in cytologic specimens can raise concern for a Hurthle cell neoplasm, but in fact these cells are seen with regularity in benign thyroid nodules. When these cells predominate, then concern for a Hurthle neoplasm is raised. Like other follicular lesions, cytologic diagnosis cannot distinguish malignancy and surgical resection is required. According to experience from the University of Michigan, the likelihood of malignancy in those Hurthle cell lesions undergoing surgical resection is approximately 30%, similar in their experience to that for follicular lesions.[144] Other experienced pathologists have indicated a rate of malignancy of 45% in nodules diagnosed as Hurthle cell lesions by FNA, a higher rate of malignancy than for follicular lesions.[145]

There has been previous concern that Hurthle cell cancers carry a worse prognosis than follicular cancers. Larger nodules are more likely to be cancer with Hurthle cell cancer in 55% of those over 4 cm versus 13% in smaller lesions.[146] A recent report has used a smaller cut point and integrated age as well. Using these criteria, a lesion >1.5 cm in a patient older than 45 was cancer in 63% versus 10% in younger patients with a smaller lesion.[147]

There has been previous concern that Hurthle cell cancers carry a worse prognosis than follicular cancers. An assessment of SEER data, however, does not show a statistical difference between the two. For a group of >900 patients, 20% were Hurthle cell and 80% were follicular cancer. Ten-year survival was 73% in Hurthle cell carcinoma and 83% in follicular cancer. Multivariate analysis revealed that a worse survival was associated with older age (50 years or older), male gender, larger tumor size (>5 cm), nodal metastases, and distant metastases. The histologic type (Hurthle vs. follicular), presence of local extension, extent of thyroidectomy, and radioactive iodine use did not impact the mortality rate.[148]

## Insular Carcinoma

Insular carcinoma is a form of thyroid cancer with aggressive behavior that is intermediate in behavior between the differentiated papillary and follicular cancers and anaplastic carcinoma. An insular pattern may be seen to a variable degree in papillary or follicular cancers, but the prognostic impact of this finding is not significant.[149] However, tumors of pure insular pattern are more aggressive than both papillary and follicular cancers. It has been pointed out that the current thyroid cancer staging system distinguishes between differentiated and anaplastic cancer; it does not allow for independent staging of these intermediate-grade tumors.[150] Insular cancer is associated with nodal disease in 50% of cases and with distant metastases in an even greater proportion of cases.[139] Disease-specific death rates range from 38% to 62% in recent series.[151,152]

## Medullary Carcinoma

Medullary thyroid carcinomas (MTCs) arise from the parafollicular or C cells of the thyroid. These cells, derived from neural crest and part of the diffuse neuroendocrine system, secrete calcitonin and the cancers that derive from these cells also secrete calcitonin. The cancers occur in a sporadic form in approximately 75% of cases. The other 25% occur in a familial form, most commonly associated with an autosomally dominant transmitted syndrome.

Medullary cancers present clinically as firm, encapsulated tumors, often with nodal metastases at presentation. In sporadic cases, the primary tumor is usually unilateral, whereas in familial cases it is typically bilateral. This is explained by the fact that familial susceptibility to medullary cancer leads first to C-cell hyperplasia, and the development of medullary cancer follows this. Multifocal tumors are common in familial medullary cancer.[153] The embryologic location of C cells in the upper two-thirds of the thyroid makes this the most common site of MTC.

The pathology of medullary cancers demonstrates a variety of growth patterns. Most often, tumors show a nested, trabecular, or solid growth pattern that invades adjacent thyroid tissue. Cells may be round or spindle shaped.[78] Amyloid has long been noted as a common feature in MTC, present in 60% to 80% of tumors.[154] Amyloid consists of the fully formed protein of calcitonin hormone.[155]

Calcitonin can be seen in MTC tumors using immunohistochemical staining. Calcitonin can also be measured in serum, and this is a reliable tumor marker with which to measure the presence or absence of disease. There are few other tissues in the body that secrete calcitonin, and none to any significant amount leaves calcitonin as an accurate serum tumor marker for this disease. Data in the U.S. and Europe suggest that routine screening of serum calcitonin is a cost-effective means of screening for MTC, with a basal serum calcitonin level of >20 pg/mL necessitating further work-up. Recommended preoperative tests for patients with known or suspected MTC include serum calcitonin, calcium, carcinoembryonic antigen (CEA), and RET analysis.[156]

The familial form of medullary cancer is inherited through autosomal dominant transmission. When it occurs without any other neuroendocrine feature, it is termed *familial medullary thyroid cancer* (FMTC). When other neuroendocrine tumors are associated, then these tumors form one of the multiple endocrine neoplasia (MEN) type II syndromes. These are listed in Table 28.1. MEN 2A is the most common syndrome and represents >75% of familial MTC. This syndrome presents with MTC in 90% of patients with a smaller proportion of carriers developing pheochromocytoma (50%) and parathyroid hyperplasia/adenoma formation (20%–30%). The inclusion of FMTC under the heading of MEN 2 is deliberate due to the fact that some kindred of MEN 2 may be incorrectly diagnosed as FMTC due to incomplete history and inadequate follow-up for additional neuroendocrine tumors.[157]

Familial MTC is associated with a germline mutation of the RET oncogene, located on chromosome 10. This oncogene encodes for a tyrosine kinase that has both intracellular and extracellular components. These germline mutations are usually point mutations in one of the exons 10 to 16 and cause tyrosine kinase activation.[157]

Extensive work has been done in recent years to characterize the most common mutations in order to predict the clinical behavior of patients with MEN 2.[157] This information correlates to the observed clinical behavior of hereditary MTC. It has been observed that MTC, arising as part of MEN 2B, is more aggressive than MTC in MEN 2A or FMTC. MEN 2B is associated with mutations at 918. Cancers with this mutation arise early in life, at a mean age of 3, according to data by Machens et al.[158] and may be associated with higher local recurrence and lower survival.[156] Mutations associated with MEN 2A (Fig. 28-10) will tend to manifest later in childhood or young adulthood. The most common of these mutations are at codons 618, 620, 634, 790, 791, and 804. The mutations at 768 and 804 appear to be associated with an onset of C-cell hyperplasia and progression to MTC that

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**TABLE 28.1 Multiple Endocrine Neoplasia 2 (Men 2) and Its Clinical Variants or Syndromes**

| Syndrome | Characteristic Features |
|---|---|
| FMTC | MTC |
| MEN 2A | MTC<br>Adrenal medulla (pheochromocytoma)<br>Parathyroid hyperplasia |
| MEN 2A with cutaneous lichen amyloidosis | MEN 2A<br>Pruritic cutaneous lesions (upper back) |
| MEN 2A or FMTC with Hirschsprung disease | MEN 2A or FMTC<br>Hirschsprung disease |
| MEN 2B | MTC<br>Adrenal medulla (pheochromocytoma)<br>Intestinal and mucosal ganglioneuromatosis<br>Characteristic habitus, marfanoid |

FMTC, familial medullary thyroid carcinoma; MTC, medullary thyroid carcinoma.

*Source:* Adapted from Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of men type 1 and type 2. *J Clin Endocrinol Metab.* 2001;86:5658–5671, with permission.

occurs at a somewhat later age than many of the other mutations, and MTC with nodal disease is typically not seen before the age of 50.[158]

Although the age of onset of MTC is variable depending on the specific RET mutation, there may be differences in penetrance related to specific mutation as well. For instance, RET mutation C634Y, causing cysteine to be replaced by tyrosine at that codon, leads to a highly active transformation in the RET gene. This is associated with a high penetrance of MTC (79% by age 30).[159] Mutations at this codon are also associated with a 50% penetrance of pheochromocytoma and 10% penetrance of parathyroid hyperplasia.[146] In contrast, a mutation such as E768D, which causes glutamate to be replaced by aspartate, has a lower penetrance for MTC (36% at 45 years) and seldom leads to pheochromocytoma or parathyroid hyperplasia.[160]

Patients presenting as putative sporadic MTC may, in fact, harbor germline mutations. All patients diagnosed with sporadic MTC should be tested due to the fact that previously unrecognized kindreds may emerge or that these patients might harbor spontaneous germline mutations. In a large series of patients thought to be sporadic on clinical grounds, approximately 6% were found to harbor germline mutations.[161] Tumor tissue can also be assessed for RET mutations occurring within the thyroid tissue itself. More than 40% of tumors demonstrate these mutations, usually of codons 918 or 634. A worse outcome has been reported for these patients. Of course, only familial cases will have a germline defect in the RET oncogene (e.g., seen in white blood cells) whereas both familial and sporadic disease may harbor a RET oncogene mutation within the thyroid tissue.[162]

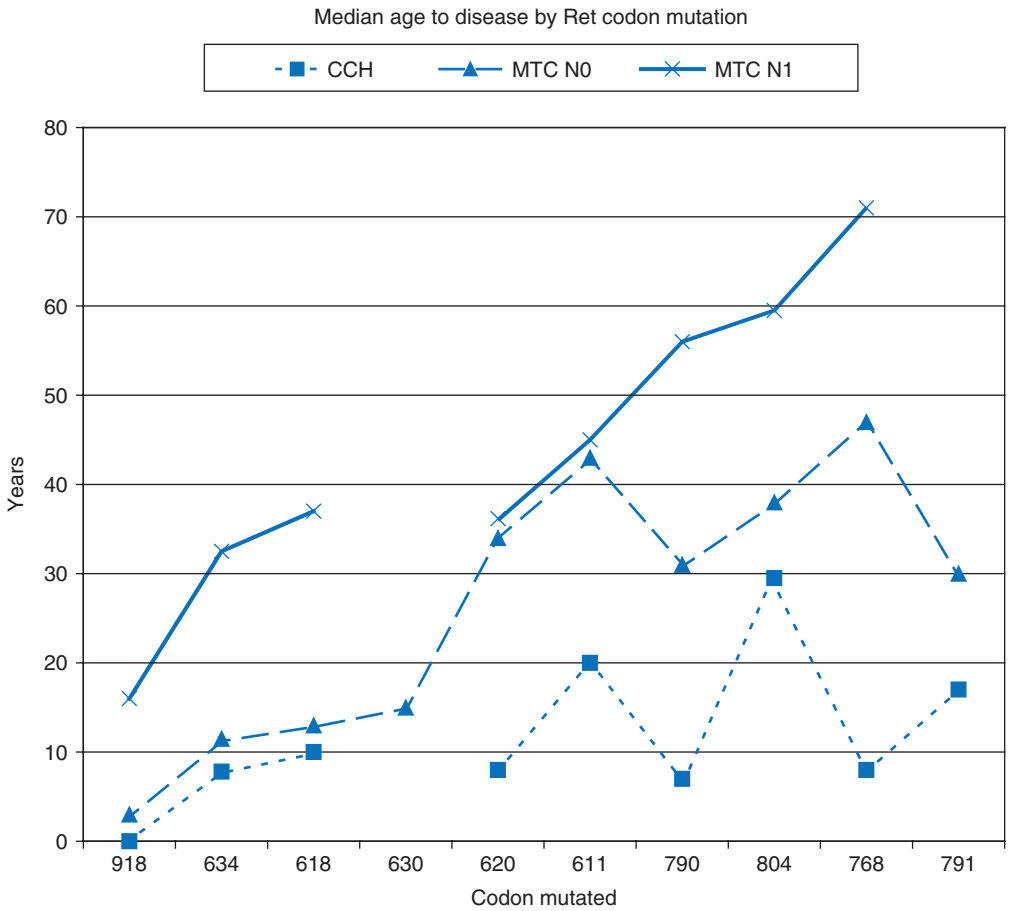



**FIGURE 28-10.** Age of onset of C-cell hyperplasia (CCH), and medullary cancer varies by the specific germline mutation of the RET oncogene. MTC, medullary thyroid carcinoma.

*Source:* Adapted from Machens A, Holzhausen H-J, Thanh PN, et al. Malignant progression from C-cell hyperplasia to medullary thyroid carcinoma in 167 carriers of RET germline mutations. *Surgery.* 2003;134:425–431, with permission.

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Although the primary tumor in MTC is often well circumscribed and encapsulated, lymph node metastases are common. These nodal metastases tend to first occur in the central compartment, but lateral neck nodes are also common and may require treatment.[163] Mediastinal lymph nodes are less accessible for primary surgical sampling, but this area is also frequently involved in more advanced MTC. Data suggest that at the time of thyroidectomy, measurement on intraoperative serum calcium levels 30 minutes after thyroid removal may be a predictor of persistent or distant disease even in patients with no clinical or radiographic evidence of disease.[164] However, these data warrant further study. While lymphatic spread is more common, hematogenous spread may occur and result in distant metastases to the lung, liver, and other organs.

When MTC presents clinically, approximately 50% to 80% of the patients will have medial compartment lymph node metastases. A similar proportion will have ipsilateral nodal disease in the jugular nodes. Contralateral nodal metastases will be seen in approximately 20% to 40%.[163,165] These high rates of nodal disease have a significant impact on treatment recommendations in MTC and on the ability to normalize serum calcitonin levels after surgical therapy. Detection of lateral neck disease may present a challenge. Ultrasound imaging of the lateral neck has been controversial as up to one-third of scans of the neck may be falsely negative. Some data exist that biochemical marker analysis may be a more sensitive means of determining the need for lateral neck dissection, with serum calcitonin levels >200 pg/mL being suggestive of contralateral neck metastasis and >400 to 500 pg/mL suggestive of distant metastasis.[156]

In spite of the common feature of nodal disease in MTC and a reduced cure rate when significant nodal disease is present, the natural history of this disease typically manifests slow growth and metastatic spread. Patients with persistent hypercalcitoninemia after definitive treatment may live for many years with no appreciable worsening of their disease. There are exceptions to this rule, typically when more aggressive variants of MTC are seen, and a rapidly fatal course may be seen. These aggressive tumors may be recognized by necrosis, pleomorphism, and multiple mitoses on pathology analysis.

## Thyroid Lymphoma

The lymphoid tissues within the thyroid gland can be the tissue of origin for a primary lymphoma of the thyroid. These are unusual, constituting between 1% and 5% of all thyroid tumors. Less than 2% of all extranodal lymphomas will present in the thyroid.[166] Most of these will be either mucosa-associated lymphoid tumors, known as *MALT lymphomas,* or *diffuse large B-cell lymphomas*. Other lymphoid malignancies present in the thyroid more rarely and include Hodgkin lymphoma, T-cell and other lymphomas, and extramedullary plasmacytomas.

Primary thyroid lymphomas show a female predominance and typically present with painless thyroid enlargement in an elderly female. Approximately 50% will present with aerodigestive tract compressive symptoms.[167] Hoarseness is often present and appears to be related to laryngeal edema rather than vocal fold paralysis (Fig. 28-11).[168]

Preexisting autoimmune disease of the thyroid is commonly seen in thyroid lymphomas according to most series[169,170] but more rarely in others.[167] The preexistence of autoimmune thyroiditis in these cases not only has pathogenetic implications for lymphoma development, but also creates a dilemma in diagnosis (clinically, cytologically, and pathologically). The development of thyroid lymphoma occurs in most cases with thyroid enlargement over a few months. FNA will demonstrate lymphoid tissue in both Hashimoto thyroiditis and lymphoma, but determining monoclonality of lymphoid cells is critical in order to make the diagnosis of lymphoma. Obtaining adequate material for biopsy may require an open surgical procedure, and depending on the presentation, thyroidectomy may be appropriate, although most frequently chemotherapy without a thyroidectomy represents appropriate management. Jonak et al. have reported good chemotherapy responses with Rituximab plus dose-reduced mitoxantrone, cyclophosphamide, vincristine, and prednisolone.[171]

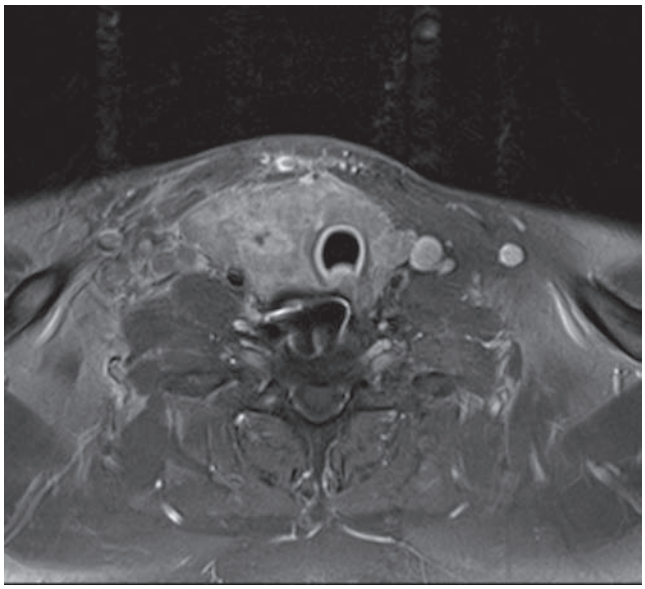


**FIGURE 28-11.** MRI demonstrating extensive thyroid lymphoma. Note displacement without invasion of the airway. Recurrent laryngeal nerve function was normal.

There is a female predominance in patients with thyroid lymphoma. Recent efforts to demonstrate monoclonality using polymerase chain reaction methods show promise to improve the diagnostic sensitivity of FNA biopsy for these lymphomas.[172]

MALT lymphomas are typically indolent, and when diagnosed while still contained within the thyroid parenchyma, stage IE, surgical resection alone may be curative. Diffuse large B-cell lymphoma is more aggressive than MALT lymphoma. It is reported to develop from a transformed MALT lymphoma approximately 40% of the time. At diagnosis, however, disseminated disease is seen in >50% of these cases. These tumors will most often require chemotherapy and radiation with the role of surgery limited to biopsy and airway palliation.[173]

While this section describes primary lymphoma of the thyroid, it should be recognized that systemic lymphoma may involve the thyroid tissues secondarily. In fact, autopsy series report thyroid gland involvement in 15% of systemic lymphomas[174]; thus, all patients with lymphoma in the thyroid merit a complete staging evaluation.

## Anaplastic Carcinoma

Among the most aggressive of human malignancies, anaplastic thyroid cancer typically presents in the elderly with a rapidly growing neck mass, and compression of the trachea and the esophagus.[175] Only 8% of cases present with intrathyroidal disease. Extrathyroidal extension is the rule, making surgical intervention difficult without sacrificing vital structures. Although >40% of patients present with distant metastatic disease, the disease process is so rapid in the locoregional area, that the natural history is one of progressive aerodigestive tract compromise.

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It is suspected that frequently anaplastic carcinoma develops from preexisting thyroid disease. In support of this, 80% of cases have a history of a preexisting goiter.[176] These cancers may develop from transformation of a DTC.[177–179] In fact, the vast majority of anaplastic tumors will show some component of papillary, follicular, or Hurthle cell carcinoma, indicating the likely original tumor.[168,180] Anaplastic cancer cells are distinct from DTCs in their lack of thyrotropin receptors and in their inability to transport iodine or produce Tg[181] and they do not seem to respond to radioactive iodine therapy. Among anaplastic cancers, it has been shown that a low serum thyroxine level is associated with a worse prognosis, but whether this indicates biologic differences between anaplastic tumors or simply reflects total thyroidal tumor burden is not clear.[182]

In an evaluation of the anaplastic thyroid cancers reported to the National Cancer Institute's SEER database between 1973 and 2000, 516 cases of anaplastic thyroid cancer were evaluated. Surgical resection was performed in 64% of these cases and radiation therapy was used in 63%. Patients younger than 60 years, patients with intrathyroidal tumors, and patients treated with surgery followed by radiation were independent predictors of increased survival in multivariate analysis. However, as a whole, the prognosis was poor with 81% of patients dead of disease at 1 year.[183] Even in studies demonstrating improved locoregional control, most patients died of distant metastasis.[184,185] There is some evidence that an aggressive treatment plan with surgery, chemotherapy, radiation sensitizers, and IMRT may be of benefit.[186,187]

Anaplastic tumors typically are composed of varying proportions of spindle, polygonal, and giant cells.[188] Papillary cancers may also contain areas with these same cellular features. Although not diagnostic of anaplastic cancer, these papillary cancers are more aggressive and show a lower survival than typical papillary thyroid cancers.[189,190] Of more concern, however, is the situation where, within a differentiated tumor, an area shows complete transformation to an anaplastic tumor. These tumors merit aggressive treatment due to a behavior that follows a typical anaplastic pattern. The pathologic diagnosis of even a small focus of poorly differentiated or anaplastic features in a thyroid sample should be considered seriously and treated appropriately. The American Thyroid Association (ATA) is formulating guidelines for the management of anaplastic thyroid cancer that will soon be published.

### Metastases to the Thyroid

Microscopic metastases to the thyroid are common when evaluated in autopsy specimens of patients dying with a disseminated cancer of any type. Up to 24% of these specimens reveal thyroid metastases.[191,192] The presentation of clinically apparent metastases in the thyroid is significantly less common than this. However, when a thyroid mass presents in a patient with a known malignancy, metastatic cancer should be considered. FNA should be used to evaluate such a lesion. Typically, diagnosis of such a metastasis will lead to an approach to treatment that is systemic, such as chemotherapy, rather than surgery directed at the thyroid gland. Exceptions may be seen in slow-growing tumors such as renal cell carcinoma that present with a resectable thyroid metastasis,[192] where surgical resection can be expected to promptly and effectively reduce the risk of future aerodigestive tract compromise. Renal carcinoma, pulmonary carcinoma, and malignant melanoma seem particularly prone to metastasize to the thyroid gland.

## CLINICAL PRESENTATION

The most common presenting sign of thyroid cancer is a thyroid nodule. Although the vast majority of thyroid nodules are benign, all nodules merit careful evaluation for malignancy. Elements of the history and specific clinical symptoms and signs can increase the suspicion of malignancy.

The age and gender of the patient should be considered. Children with nodules present a risk of malignancy that ranges from 15% to 60%.[193–195] Similarly, nodules in patients older than 60 years of age present an increased risk of malignancy.[196,197] The risk of malignancy in a nodule is between two and three times greater in a male than in a female patient.[197–199]

A history of a rapidly enlarging thyroid nodule usually indicates hemorrhage, and this can occur in both benign and malignant disease. These patients usually have thyroid tenderness, discomfort, or pain. Increasing thyroid-related pain should raise concern for malignancy. Hoarseness can be present due to tumor effects on the recurrent laryngeal nerve. This can be seen in benign disease on occasion, but is typically felt to indicate a malignant process. Dysphagia is a common symptom in large multinodular goiters and is gradual at onset in these cases. Dysphagia which increases over several weeks in the setting of a small- or moderate-sized thyroid mass should raise concern for a malignant process involving the inferior constrictor or cervical esophageal musculature. Airway compromise can result from tracheal involvement by tumor or by bilateral recurrent laryngeal nerve paralysis. Both would indicate a likely malignancy.

A personal history of low-dose irradiation is a major consideration when attempting to assess a thyroid nodule. This is associated with an increased risk of both benign and malignant thyroid nodules. The concern for malignancy is significant, and a high degree of suspicion for malignancy should be entertained in these cases.

A family history of thyroid malignancy should be integrated into the assessment of patients with thyroid nodules and trigger the exploration for both papillary thyroid carcinoma and familial medullary carcinoma. For papillary thyroid carcinoma, Cowden syndrome and Gardner syndrome should be considered. Cowden syndrome is associated with hamartomas, breast lesions, gastrointestinal polyps, ovarian cysts, uterine fibroids, and thyroid tumors. Gardner syndrome is associated with colonic polyps and other benign tumors, including osteomas of the facial skeleton. A personal or family history of these related diseases should lead to further evaluation.

The patient suspected of presenting with a familial medullary carcinoma might report chronic diarrhea, which is probably related to the hypercalcitoninemia (or related chemokines). Patients with MEN may report a personal or family history of hypercalcemia, hyperparathyroidism, renal stones, or pheochromocytoma. A history of severe hypertension or symptoms of sweats, flushing, palpitations, and headaches should raise concern for a pheochromocytoma. The fact that, in the past, pheochromocytoma was a major cause of mortality in patients with MEN 2B should be kept in mind while pursuing this history. The possibility of a pheochromocytoma should be excluded in patients with possible or definite MEN 2 before consideration of thyroid or parathyroid surgery.

Examination of the thyroid should focus on the number, size, and laterality of thyroid nodules. Firm nodules are the hallmark of malignant disease. Benign disease tends to be softer on examination, but these physical findings are not considered to be sufficiently accurate to determine management. Benign nodules with hemorrhage may be both firm and tender. Autoimmune thyroiditis may be associated with a diffusely enlarged, rubbery gland, but these glands can harbor DTC and can also give rise to thyroid lymphomas.

Cysts may be evident on examination. Cysts are typically thought to be low risk for malignancy, but cystic cancers do occur. The risk of malignancy in thyroid cysts is 2% to 9%.[200] However, the ultrasonographic characteristics of the cyst are important. A stepwise rise in malignancy has been shown between

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pure cysts (7%), complex cysts (12%), and solid nodules (21%).[201] This relationship emphasizes the importance of ultrasonographic evaluation in thyroid disease.

The distinction of solitary versus multinodular thyroid disease has been useful in assessing the likelihood of malignancy. As a general rule, solitary nodules are thought to present a greater risk of malignancy than the nodules in a multinodular goiter. However, in a recent, large, retrospective study, the risk of malignancy was found to be approximately 15% for glands with either solitary or multinodular glands when nodules of >10 mm diameter were present. For the individual solitary nodules, the risk of malignancy was greater than for the individual nodules in a multinodular goiter.[202] The multinodular glands revealed that the cancer occurred in the largest nodule approximately 70% of the time and that approximately 45% of the multinodular glands with cancer harbored multifocal cancer.[202] The number of nodules may be helpful in predicting malignancy. In patients selected for thyroidectomy at the University of Pennsylvania, the risk of malignancy was approximately 40% in glands with one or two thyroid nodules, but this risk was reduced by half when more than two nodules were present.[203]

Assessment of the mobility of the thyroid mass with respect to neck musculature and the laryngotracheal complex is critical and may trigger assessment for local tumor extension by imaging studies. A loss of tissue planes on examination, especially in a rapidly growing mass, should raise concern for anaplastic carcinoma.

Following assessment of the thyroid, the cervical nodes should be evaluated. A delphian node refers to midline adenopathy and may be seen in either thyroid carcinoma or advanced laryngeal cancer. Medial compartment lymph nodes can be difficult to appreciate on examination due to the overlying thyroid tissue and the proximity of the sternoclavicular joints inferiorly. These nodes, however, constitute the primary echelon nodal basin for thyroid cancers. The lateral cervical nodes include those along the jugular vein and in the posterior triangle. The jugular nodes are typically involved before the posterior triangle lymph nodes. High jugular nodes will typically be seen in aerodigestive infections and malignancies. However, thyroid metastases may occur in high jugular nodes, particularly with primary tumors of the upper thyroid pole. These nodes, therefore, should be assessed carefully in patients with thyroid cancer.

Examination of the larynx is critical in thyroid disease. Malignant lesions, and benign lesions less commonly, can result in laryngeal paralysis. Usually, the patient is aware of a recent voice change. Occasionally, however, this paralysis is gradual at onset, and the patient has spontaneously compensated for the paralysis without calling it to the attention of a physician. A preoperative examination on the awake patient is the most sensitive way to discover the paralysis. The authors feel strongly that it is important to document the preoperative laryngeal examination before any thyroid surgery. Preoperative paralysis will increase the concern for malignancy in the assessment of thyroid masses and may also influence intraoperative decisions during thyroid surgery.

The assessment for aerodigestive tract compromise on clinical examination may include indirect or flexible laryngoscopy, and palpation and auscultation of the laryngotracheal complex. If the tumor is compressing or invading the hypopharynx or cervical esophagus, distortion of the hypopharynx may be seen on office laryngoscopy. Pooling of saliva in the hypopharynx may indicate invasion of the pharyngoesophageal junction. Invasion of the laryngotracheal complex may be indicated by immobility of the tumor with respect to these organs, and significant airway compromise may result in stridor, sometimes best appreciated on auscultation of the midline neck.

The remainder of the physical examination in patients under evaluation for thyroid cancer can be directed by symptoms. The lungs are the most common site of involvement by metastatic disease in papillary thyroid cancer, but evidence of this on physical examination is exceedingly rare. New bone pain or discomfort should be fully investigated.

## DIAGNOSTIC EVALUATION AND CLINICAL STAGING

When patients present with thyroid nodules following a routine clinical and laboratory examination, the basic workup begins with thyroid function testing and FNA. Ultrasonography is the basic imaging test and provides information of nodule location and architecture as well as an objective measurement of the nodule size. For nodules that are difficult to palpate, ultrasonography is essential in obtaining an accurate FNA. Figure 28-12 describes an algorithm for assessment of thyroid nodules. In the multinodular gland, the largest of the nodules is most likely to reveal cancer, if present in the gland.

### Laboratory Testing

When evaluating thyroid nodules, thyroid function testing should include TSH with or without free T4. These tests are almost always normal in patients with thyroid malignancy, so confirmation of normal thyroid function does not reduce the need for cytologic evaluation of the thyroid nodule. One utility of thyroid function tests is in determining whether a patient is presenting with a toxic nodule. These nodules can cause suppression of TSH and typically have a very low rate of malignancy.[204,205] The discovery of a suppressed TSH therefore should reduce the clinician's suspicion of malignancy. In fact, although controversial, some reports suggest that toxic nodules may show cellular abnormalities that can confuse the cytologist; individual circumstances must be considered in the decision whether to perform an FNA on an apparent toxic nodule.

Thyroid antibodies are not routinely obtained in patients with thyroid nodules, but are recommended to a patient suspected of having Hashimoto thyroiditis; these laboratories may support the diagnosis. However, rapid thyroid growth in such a patient may indicate lymphoma, so this should be factored into the assessment.

Tg is normally present in serum at concentrations of approximately 20 to 40 ng/mL. Tg elevation in a previously untreated patient is nonspecific and may be seen in thyroiditis and in hyperthyroidism.[206] A markedly elevated Tg may be suggestive of carcinoma, but is not diagnostic.[207] This is in distinction to patients followed up for a previous history of differentiated thyroid carcinoma (who have had a thyroidectomy) in whom Tg is a useful tumor marker. When ordered, Tg testing should include simultaneous measurement of anti-Tg antibodies because the presence of antibodies limits the utility of Tg measurement. Tg antibodies commonly interfere in a chemiluminescent Tg assay causing an artifactual lowering of apparent serum Tg levels (frequently being interpreted as undetectable). Radioimmunoassays for serum Tg can report a falsely elevated serum Tg level in the presence of Tg antibodies. In summary, reported serum Tg levels in patients with Tg antibodies are extremely difficult to interpret.

Calcitonin serum measurement is essential when medullary carcinoma is suspected. Elevation indicates either C-cell hyperplasia or MTC. False-positive elevation has been reported in Hashimoto thyroiditis, hyperthyroidism, and goiter,[208] so the laboratory test itself is not considered diagnostic without further pathologic confirmation. However, in benign thyroid disease, these calcitonin elevations are usually mild.

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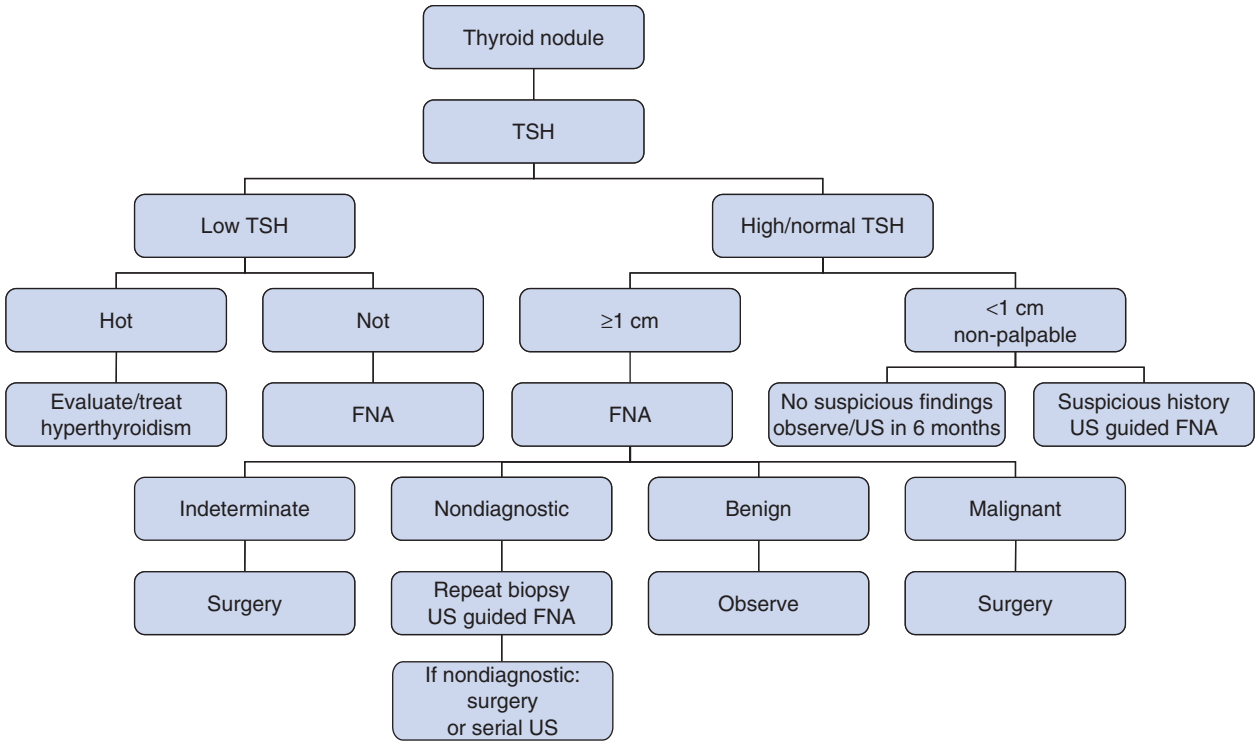



**FIGURE 28-12.** Algorithm for evaluation of thyroid nodules. FNA, fine-needle aspiration. US, ultrasound. FNA with onsite verification preferred. US guidance preferred for small nodules, nodules located in the posterior aspect of the thyroid and nodules >50% cystic. Indeterminate lesions such as "follicular lesions of undetermined significance" may be considered for repeat FNA with molecular testing for mutations of *raf* or *ras* and for PAX8/PPAR gamma rearrangements.

Over the last few years, different centers have begun to advocate routine calcitonin testing in patients with thyroid nodules. In a large study from Italy, >10,000 patients were evaluated with routine calcitonin screening. Calcitonin was elevated in 47 patients, 44 of whom were later shown to harbor MTC, resulting in an MTC prevalence of 0.4%.[209] This has not been widely used in screening in the United States,[210] and in 2006, the ATA Guidelines Taskforce could neither recommend for nor against routine calcitonin testing.[211]

When medullary carcinoma is suspected, there are other laboratory tests that must be considered (Fig. 28-13). Most importantly, MEN 2A and 2B are associated with pheochromocytoma, so urine (e.g., 24-hour urine vanillylmandelic acid [VMA], total metanephrines, catecholamines) and/or serum evaluation (e.g., catecholamines, free metanephrine, free normetanephrine) should be obtained before any surgical intervention. It is presently controversial whether urine or serum measurements are more sensitive in detecting a pheochromocytoma, but it is extremely important to perform as complete an evaluation as necessary to exclude the presence of a pheochromocytoma. Occasionally, an adrenal imaging study (e.g., computed tomography [CT] of adrenal glands or magnetic resonance imaging [MRI]) may be useful. Hyperparathyroidism should also be ruled out for MEN 2A, so that surgery can address both the thyroid and parathyroid disease as appropriate. All patients with MTC merit testing for RET oncogene mutations. This can be done after a verified diagnosis has been obtained and does not need to be obtained before surgery for the thyroid malignancy.

## Fine-needle Aspiration and Cytologic Evaluation

The single most useful study in the assessment of a thyroid nodule is an FNA biopsy. Cytologic assessment is highly accurate and can indicate whether surgical intervention is required. FNA has historically been used to assess solitary nodules and in the dominant nodule of multinodular goiters. With increased use of ultrasound (US), the ATA has defined an array of indications for FNA based on size, US appearance, and clinical suspicion.[212] While the need for thyroid surgery has long been determined by clinical information, ultrasonographic, and nuclear medicine studies, the introduction of FNA has led to a 35% to 75% decrease in the number of patients requiring surgery.[213–216] As a result, there has been a substantial increase in the proportion of malignant lesions in surgical cases.[217–219] Also, FNA has led to a reduction of approximately 25% in the overall cost of managing thyroid nodules.[220]

Results of FNA are typically categorized as benign, malignant, suspicious, or insufficient for diagnosis. In most studies, aspirates are interpreted as benign, typically adenomatoid nodule, Hashimoto thyroiditis, or cysts. The actual percentage of benign aspirates reported has varied from 45% to 82% in reported series.[221–223] For benign biopsies, a false-negative rate of <5% is reported. Traditionally, this has led to a recommendation that benign lesions should be reaspirated at some point in order to confirm the initial diagnosis. This recommendation is in evolution with multiple reports now showing an even smaller false negative and therefore less need for routine reaspiration.[224–227] These series demonstrate a false-negative

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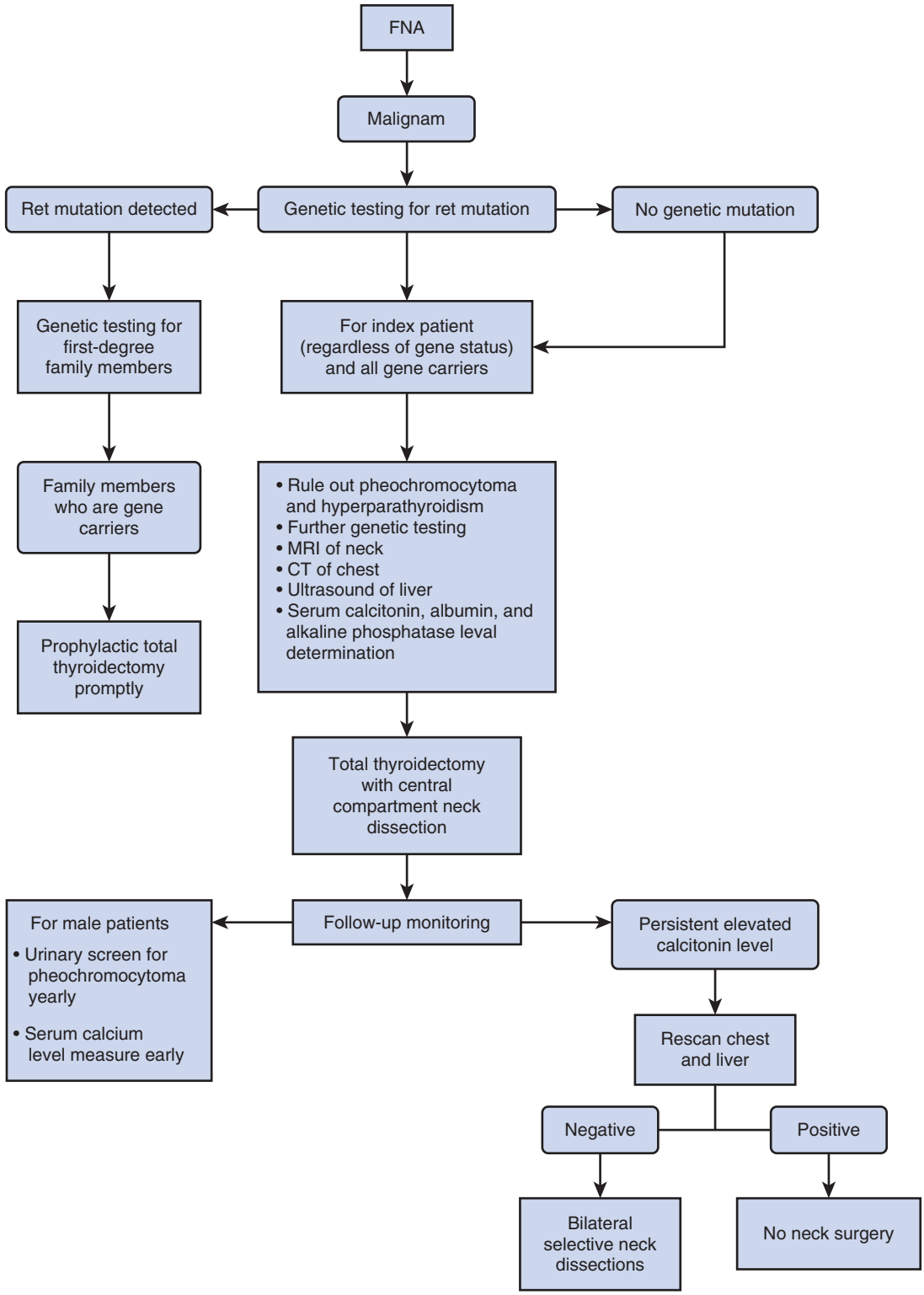



**FIGURE 28-13.** Fine-needle aspiration (FNA) suspicious for medullary carcinoma should trigger additional testing as outlined in this algorithm. MRI, magnetic resonance imaging; CT, computed tomography.

rate of 0% to 1.5% with papillary thyroid cancer diagnosed subsequently in most circumstances. These data are reassuring, but individual clinical circumstances, including physician and patient suspicion, imaging characteristics, and follow-up, will determine the role for reaspiration after an initial benign aspiration.

The primary reason to evaluate thyroid nodules is to determine whether they represent cancer. Malignant diagnoses are

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often obtained for papillary cancers with identification of papillary fronds, psammoma bodies, nuclear grooves, intranuclear inclusions, and other nuclear and cellular features. The false-positive rate in these cases approaches 0% in most reports, and the surgeon can proceed to address the surgical treatment without additional biopsies or frozen-section analyses. When a less common malignancy, such as medullary cancer, is present, cytology may be accurate, but calcitonin staining of the thyroid FNA specimen can aid in the diagnosis. Similarly, malignant diagnoses of anaplastic carcinoma or lymphoma may be made on cytologic criteria, but the need for immunohistochemistry, flow cytometry, and even open biopsy is common in these circumstances.

A "suspicious" cytologic diagnosis may represent a number of different circumstances. This terminology may be used to describe follicular lesions. These biopsies are typically highly cellular, with little colloid and with or without nuclear atypia. Microfollicles may be described. These lesions may represent simply cellular adenomatoid nodules, follicular adenomas, or follicular carcinomas. Hurthle cell lesions would also fall into this category. For both of these lesions, the ability to distinguish benign from malignant tumors requires surgical pathology in order to visualize vascular or capsular invasion. The likelihood of cancer in these suspicious lesions ranges between 15% and 22% in recent series.[221,228,229] The rate of malignancy in Hurthle cell lesions has been reported to be higher at 32%.[228]

Other suspicious lesions include those that have some nuclear features of papillary carcinoma, but insufficient in degree to make a malignant diagnosis. This raises the issue about variability between cytologists and the increased accuracy seen with increased experience by the cytologist. The University of Pennsylvania reports this group as a subset of their follicular lesions. These constitute approximately 25% of the total number of follicular lesions in their group.[229] At surgery, between 40% and 72% of these lesions will malignant, and more than half will be diagnosed as follicular variant of papillary cancer.[229,230] Unlike typical follicular lesions, these lesions may merit frozen-section assessment in order to determine the extent of surgery.[230]

Aspirates that are insufficient for diagnosis are reported 15% to 20% of the time.[221,231] In many cases, reaspiration will lead to a diagnostic specimen. The use of ultrasound guidance has been shown to reduce the rate of insufficient aspirates from 16% to 7%.[231] The authors encourage that aspiration be done with a cytologist on site to verify the adequacy of the sample obtained. This is true for both palpation-guided and ultrasound-guided biopsies.

When a cyst is encountered on aspiration, a dilemma arises. Most often, cysts represent degeneration of an adenomatoid nodule. Palpation-guided aspiration of the cyst may provide symptomatic relief, allow resolution of the "nodule" by removing the cystic fluid and allowing sclerosis to occur, and provide cytologic assessment. Although cysts are typically found to have a lower chance of harboring malignancy than a solid nodule, cystic changes may be seen in both papillary and follicular cancers, and an accurate cytologic interpretation requires cellular material to be seen. Accurate sampling of the cyst wall can be difficult, and this is a circumstance where ultrasound guidance can be helpful. Repeated reaccumulation and recurrence of a drained cyst should lead to the consideration of surgery.

## Imaging

The evaluation of the typical thyroid patients with thyroid cancer may differ from the patient undergoing workup for a thyroid nodule. In the case of a thyroid nodule, ultrasonography is typically the most revealing single-imaging study. In thyroid cancers, ultrasonography is also useful, but additional studies may include chest x-ray, CT, MRI, and positron emission tomography (PET) scans.

Ultrasound is able to determine whether the thyroid nodule is isolated or part of a multinodular goiter. Imaging characteristics of the nodule can provide information that can aid in the prediction of malignancy. Regarding the risk of cancer in a uninodular versus multinodular goiter, the overall risk of malignancy is similar—approximately 15%. However, the risk of cancer in each individual nodule in a multinodular goiter is less.[232] Nodule characteristics that increase the concern for malignancy are an irregular shape, a jagged border, the presence of internal echoes, and the absence of peripheral echoes.[233]

A major advantage in ultrasound imaging over palpation alone in thyroid evaluations is the improvement in objective measurements. These can be helpful in follow-up of nodules in that objective measures can be compared over time. An additional application of ultrasonography is in FNA. As compared with palpation-guided FNA, ultrasound-guided FNA has shown an increase in diagnostic yield on biopsy and also on cancer yield on final pathology when patients undergo subsequent surgery.[231]

Ultrasound in workup of thyroid malignancy has been extended beyond the thyroid bed to the cervical nodes. An ultrasound of the neck in cases of documented thyroid malignancy is a routine component of the preoperative workup in order to assess lymph nodes. This includes imaging of the central and lateral necks. Given that the initial ultrasound may focus primarily on the thyroid gland itself, the nodal assessment usually requires a separate study requisition. The goal of this study is to avoid overlooking identifiable nodal metastases at the initial thyroid surgery.

Routine radiography does not have a significant role in evaluation of thyroid nodules except in larger lesions where tracheal deviation, substernal extension, and tracheal compression may be seen. Occasionally, calcification of the thyroid or cervical lymph nodes may be seen of chest x-ray. Calcification in cervical nodes may suggest papillary thyroid carcinoma, but other causes include tuberculosis, previously treated lymphoma, adenocarcinoma, or squamous carcinoma.[234]

Calcification of the thyroid on ultrasonography or chest x-ray raises concern for thyroid malignancy. However, calcification is a nonspecific finding and degenerated adenomatoid nodules will frequently form calcifications. Degenerated nodules are more likely to form peripheral calcifications or large, so-called chunk, calcifications. Malignancies are more likely to be associated with smaller calcifications. Microcalcifications have the highest association with malignancy.[235] Calcifications may also be seen in MTCs, but have no diagnostic or prognostic value.

CT and MRI are helpful in defining the three-dimensional anatomy in thyroid disease. In benign thyroid disease, these are used in the evaluation of substernal goiters. In thyroid malignancy, these studies may indicate regional adenopathy or local extension. It is very important that the decision to use iodinated contrast be carefully considered in the workup of DTC when CT evaluation is required. The large iodine load can persist for several weeks after contrast is given. The result can be reduced radioactive iodine uptake and less effective radioactive iodine treatment after surgery. Delayed treatment with radioactive iodine is usually required in these cases. As an alternative, an MRI with gadolinium contrast can be used for preoperative imaging, as this compound does not contain iodine. CT and MRI are useful in thyroid cancer when invasion of the visceral structures is suspected. Laryngotracheal and esophageal invasion are better visualized on these studies than on ultrasonography.

PET scan has emerged as a useful tool in the management of patients with thyroid cancer. In follow-up, these studies may localize metastatic disease when $^{131}$I scans are negative, apparently due to dedifferentiation of these cancers. In the workup of preoperative patients with thyroid disease, the role for PET scan is less clear and it is not typically used. When all lesions are considered,

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PET scans may distinguish benign from malignant tumors and a standard uptake value (SUV) of 5.0 has been proposed as a cutoff value distinguishing malignancy.[236] For lesions with indeterminate cytology and for follicular lesions, studies differ on whether PET can distinguish benign from malignant lesions.[236–238] The authors have shown that digital merging of PET scan and MRI images is useful in identifying suspicious cervical lesions in patients being examined for recurrent thyroid cancer.[239]

It is quite common that patients undergoing evaluation for nonthyroid conditions will be found to have thyroid lesions in an imaging study. These incidental findings may be identified as thyroid calcifications on radiographs, or thyroid nodules on ultrasonography, CT, MRI, or PET scan. The incidence of malignancy in these incidental lesions is estimated to be between 8% and 17%.[240–241] When incidental lesions are found on routine radiographs, CT, or MRI, a follow-up ultrasonography is recommended due to improved detection of suspicious morphology and a greater sensitivity for multinodular disease. The true incidence of these small lesions may in fact be underestimated by routine radiology review. In a study of 200 consecutive CT scans and equal number of MRI scans, the initial reading identified incidental lesions in 6% of cases. However, rereview of these scans found incidental lesions in 16% of the patients.[242]

Incidental lesions found on PET scan may present a greater risk of malignant tumors. In large studies, such lesions are found in 2% to 4% of PET scans. Because these patients may undergo PET scan due to the presence of other malignancies, not all patients get further evaluation, but most patients do. Cancer is identified in approximately 40% of incidentally discovered discrete thyroid lesions on PET scans.[243,244]

Not all incidental lesions merit an extensive workup. If the incidental thyroid lesion was discovered on CT, MRI, or PET, then an ultrasonography should be ordered to evaluate the thyroid for single versus multinodular disease and to document the characteristics of the lesion. Biopsy should be strongly considered for incidental lesions >1 cm in diameter. For smaller lesions, workup should be considered if there is a history of radiation exposure, a family history of thyroid disease, or symptoms or physical findings worrisome for malignancy or if the sonographic characteristics of the lesion are worrisome. Otherwise, lesions <1 cm in diameter should be evaluated by thyroid function tests and followed with serial ultrasonographic examinations.

## MANAGEMENT STRATEGIES AND TREATMENT PLANNING GUIDELINES

The previous section described the approach and diagnostic evaluation of patients suspected of having thyroid cancer. Given the limitations of FNA and other diagnostic studies, a significant number of patients undergo thyroid surgery without a diagnosis of malignancy. This group includes those who have a lesion suspicious but not diagnostic of cancer on needle aspiration, patients with follicular lesions, and other patients operated upon for benign conditions who are found on surgical pathology to have a thyroid malignancy. Before proceeding with a stage-by-stage review of treatment for thyroid cancer, the physicians must therefore begin with a description of the surgical approach to the patient with an uncertain diagnosis of malignancy.

Much has been written about various surgical approaches to the thyroid in the past. These approaches range from the rarely appropriate excision of a thyroid nodule to total thyroidectomy. Between these lies a confusing array of possible procedures: lobectomy, lobectomy and isthmusectomy, subtotal thyroidectomy, and near-total thyroidectomy. This range can be extended as well to include various neck dissections that may be used in thyroid malignancy.

The minimal surgery in thyroid disease is typically considered to be a thyroid lobectomy. This removes all of the thyroid tissue from one side of the trachea, preserves the superior and recurrent laryngeal nerves and parathyroids, and includes an assessment for abnormal cervical lymph nodes in the ipsilateral central neck. Performing a lesser surgery such as excision of a thyroid nodule causes scarring around the thyroid lobe, which may increase the risk of complications from any subsequent surgery on that same lobe. In selected circumstances, excision of a small thyroid nodule may be appropriate, such as discovery of a small nodule in the thyroid at the time of parathyroidectomy, or resection of a small nodule in the thyroid isthmus. By performing a thyroid lobectomy as the minimal surgical intervention, the surgeon can be relatively certain that an adequate oncologic surgery was performed on that half of the thyroid. A subsequent completion thyroidectomy can be done safely because the contralateral lobe has not been dissected.

Most thyroid lobectomies extend to about the midline, so some refer to their basic surgery as thyroid lobectomy and isthmusectomy. Extension beyond that point into the contralateral thyroid lobe is described as a subtotal thyroidectomy. In this procedure, the surgeon preserves some portion of the opposite thyroid lobe. Some prefer to save a layer of thyroid tissue along with the posterior capsule of the gland. Others may save the contralateral superior pole. In the former group, the dissection is done with the intention of leaving the contralateral recurrent laryngeal nerve protected by a layer of thyroid tissue, but significant bleeding from the remnant of the thyroid gland can occur and obscure visualization. In the latter group, the upper lobe is preserved with the suggestion that this will avoid injury to the superior parathyroid gland and reduce the risk of hypocalcemia. For any patient undergoing thyroid surgery because of potential malignancy, neither of these operations is favored by the authors. In the former, the risk of contralateral recurrent laryngeal nerve injury remains, particularly where the nerve rises to pass close to the Berry ligament. In fact, the rate of nerve injury has been reported to be higher in subtotal than in total thyroidectomy.[245] In the latter surgery, the risk of superior parathyroid injury remains due to its unpredictable location ranging from the uppermost extent of the superior thyroid pole to a position adjacent to the recurrent laryngeal nerve. These surgeries may have a role in the surgical treatment of thyrotoxicosis in which the intention is to render the patient euthyroid without the need for medication after surgery.

Total and near-total thyroidectomy are the procedures typically recommended for the treatment of malignant disease. The authors prefer these surgical approaches in bilateral benign thyroid disease as well. The distinction between these two procedures is unclear, but "near-total" recognizes a reality confronted by thyroid surgeons. At the posterior thyroid ligament, variable amounts of tissue may extend over or under the recurrent laryngeal nerve. It is here that the surgeon will weigh the risks of leaving a small amount of normal thyroid tissue versus skeletonization of the recurrent laryngeal nerve. As long as there is no concern about tumor extension in this area, leaving this small amount of tissue is considered safe. It is usually this small amount of tissue that will be seen in radioactive iodine scans following total thyroidectomy. The difference in surgical dissection between total and near-total thyroidectomy is otherwise negligible. Both procedures should involve identification and preservation of the recurrent laryngeal nerve and preservation of any parathyroid glands. Except for tissues immediately surrounding the Berry ligament, the understanding that total and near-total thyroidectomy differ is erroneous and therefore, in this chapter, these two procedures will be described as total thyroidectomy.

The decision to perform a total thyroidectomy in a patient who is not yet diagnosed with a malignancy of the thyroid will

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depend on a number of factors, including the preference of the patient. Some surgeons favor total thyroidectomy in any patient undergoing thyroid surgery. Many patients favor a procedure that will allow them to go without thyroid replacement following surgery, so will choose thyroid lobectomy. For patients with multinodular disease, particularly if it is bilateral, the authors favor a total thyroidectomy. For patients with a single small nodule found to be a follicular lesion, a lobectomy will be performed. When follicular lesions are larger, the risk of invasion is greater, so a total thyroidectomy is favored.

Therefore, the array of thyroid procedures to be considered in a patients presenting with a potential thyroid malignancy is reduced to just two, thyroid lobectomy or total thyroidectomy. With these two interventions, the thyroid surgeon can be certain to perform an oncologically sound surgery for every patient encountered.

## Treatment by Stage

The staging system for papillary and follicular thyroid malignancy is unique in that patient age (younger than 45 years vs. older than 45 years) is the dominant factor in assigning stage. In younger patients, the stage for differentiated cancer is either stage I or stage II depending on the presence of distant metastatic disease. Although this overall staging definition can help in predicting survival, it is less helpful in defining the treatment required. For that distinction, the tumor, node, metastasis (TNM) definitions can be more useful. The fact that all patients (younger than age 45) without distant metastatic disease are defined as stage I emphasizes the excellent outcomes that can be expected in these patients. The 50-year-old patient with a small tumor isolated to the thyroid and a 30-year-old patient with multiple enlarged cervical metastases are both stage I tumors. However, the treatment of these two stage I tumors will differ markedly.

In 2002, the distinction between T1 and T2 thyroid cancers was revised. Previously, the distinction point between these two T stages was a primary tumor diameter of less than or greater than 1 cm. The revision in 2002 changed this to less than or greater than 2 cm. The previous T stage allowed for a clear distinction between occult or microcarcinomas as T1 tumors and the higher T-stage tumors. Now, T1 tumors will include both the occult cancers (T1a) and multiple other tumors up to 2 cm (T1b) in diameter. For older patients with differentiated carcinoma and for patients with medullary carcinoma, the staging system is more familiar with stages I through IV represented. In addition, the present 2010 staging system has been changed descriptors to subdivide the T-stage categories into solitary (s) and multifocal disease (m).[246] All anaplastic cancers are considered as stage IV (Table 28.2).

# DIFFERENTIATED THYROID CANCER (PAPILLARY, FOLLICULAR, AND HURTHLE CELL CARCINOMA)

## T1–3N0 (Stage I Younger than 45 Years, Stages I to III Older than 45 Years)

***Surgery.*** For tumors confined to the thyroid, the initial treatment of a thyroid cancer is surgery. If cancer is identified before surgery by FNA, the authors feel that a total thyroidectomy is indicated and evaluation and removal of abnormal medial compartment lymph nodes should be included. For tumors extending beyond the thyroid capsule into the perithyroidal soft tissues (T3), effort should be made to resect all gross disease. This may require resection of the strap muscles anteriorly or a shave of tracheal perichondrium or esophageal musculature posteriorly to obtain adequate margins.

Treatment guidelines by the ATA and the National Comprehensive Cancer Network (NCCN) agree that total thyroidectomy is appropriate for these differentiated thyroid cancers. However, both guidelines suggest that treatment by thyroid lobectomy is equally effective in certain circumstances. These "low-risk" patients are those with cancers confined to the thyroid, with no cervical metastases or distant disease, with no aggressive histologic variant, and with no previous radiation exposure and ages 15 to 45 years. A major difference between these two guidelines is the definition of "small." The ATA suggests that only tumors smaller than 1 to 1.5 cm would merit this approach whereas the NCCN guidelines include cases up to 4 cm in diameter. The NCCN guidelines acknowledge that most patients with these favorable characteristics do undergo total thyroidectomy and also suggest that a completion thyroidectomy is indicated if final pathology after lobectomy demonstrates more aggressive features than initially thought.[212,247]

The question of performing a completion thyroidectomy is most often encountered when lobectomy is performed for benign disease and a microscopic (<1 cm) papillary carcinoma is discovered by the pathologist. The NCCN guidelines provide a framework for the evaluation of these patients. These guidelines suggest that evaluation of the pathology for multifocal disease and that ultrasound imaging of the opposite lobe and the medial and lateral compartments compartment may indicate patients who require completion thyroidectomy. Most patients without any of the above poor prognostic findings require no additional surgical treatment and some can be followed up without suppressive therapy with thyroxine postoperatively, although many may need thyroxine replacement to maintain normal TSH. The longer such a patient is monitored, the more likely they will require L-thyroxine replacement, especially considering the newer interpretations of what is considered a "normal" serum TSH.

The role of medial compartment neck dissection in patients with DTC who are clinically N0 is unclear. A recent consensus statement on the terminology, classification, and indications for central compartment neck dissection has been published in the last few years.[212] For papillary thyroid cancer, the prevalence of nodal disease ranges from 20% to 90% of cases.[248,249] These nodes are often not clinically suspected on preoperative evaluation or imaging. However, preoperative ultrasound may identify suspicious nodes in 20% to 30% of cases and may potentially alter the surgical approach in 20% of cases.[250] Present ATA guidelines recommend central and lateral neck ultrasounds for all patients undergoing thyroidectomy for malignant cytologic findings on biopsy (Recommendation 20).[212] The discovery of enlarged lymph nodes at surgery merits medial compartment neck dissection. However, the authors find it quite common that metastatic nodes appear normal in size, but firm to palpation at surgery.

The extent of medial compartment neck dissection needed in DTC is also unclear. At its most extensive, this is an *en bloc* dissection that includes the nodes between the hyoid and innominate vein and from one carotid sheath to the other. It includes skeletonization of both recurrent laryngeal nerves with preservation of their fibers to the cervical esophagus if possible and preservation of all parathyroid glands *in situ*. Although this is technically safe, the rate of temporary hypoparathyroidism has been reported to be 21%.[251] Given the fact that prognostically favorable papillary thyroid cancers can be treated by lobectomy alone, it seems overly aggressive to treat these same cancers with routine medial compartment neck dissection. The authors prefer to evaluate the medial compartment nodes carefully, perform a limited dissection of the ipsilateral tracheoesophageal groove, and extend this to a complete medial compartment neck dissection

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## TABLE 28.2 Thyroid Staging Table

**Definitions**

**Primary tumor**

Differentiated and Medullary tumors

TX: Tumor cannot be assessed

T0: No evidence of primary tumor

T1: Tumor <2 cm

T1a: 1 cm or less limited to the thyroid

T1b: 1–2 cm limited to the thyroid

T2: Tumor >2 cm and <4 cm

T3: Tumor >4 cm limited to the thyroid or any size with limited (sternothyroid muscle or perithyroidal soft tissue) extrathyroidal extension

T4A: Moderate Advanced Disease

Tumor extending beyond the thyroid to subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve

T4B: Very Advanced Disease

Tumor extending to prevertebral fascia, encasing carotid, or mediastinal vessels

Anaplastic Cancers

T4a: Intrathyroidal—surgically resectable

T4b: Extrathyroidal—unresectable

**Regional nodes**

NX: Nodes cannot be assessed

N0: No regional nodal metastases

N1a: Medial compartment nodal metastases

N1b: Unilateral, bilateral, retropharyngeal or mediastinal nodal metastases

**Distant metastases**

MX: Distant metastases cannot be assessed

M0: No distant metastases

M1: Distant metastases

**Staging**

**Papillary or follicular thyroid cancer**

**Age <45 years**

Stage I
Any T, any N, M0

Stage II
Any T, any N, M1

**Papillary or follicular thyroid cancer**

**Age >45 years**

**Or Medullary cancer**

Stage I
T1, N0, M0

Stage II
T2, N0 M0

Stage III
T1–3, N0–1a, M0

Stage IVA
T1–3, N1b, M0
T4a, N0–1b, M0

Stage IVB
T4b, any N, M0

Stage IVC
Any T, any N, M1

**Anaplastic cancer (all are stage IV)**

Stage IVA
T4a, any N, M0

Stage IVB
T4b, any N, M0

Stage IVC
Any T, any N, M1

Staging scheme for thyroid cancer. Note the impact of age upon staging in papillary and follicular cancers. Also note the distinction between T1 and T2 tumors at 2 cm diameter, a change from earlier TNM definitions which used 1 cm as the cutpoint.

*Source:* From American Joint Committee on Cancer. Thyroid. In: *AJCC Cancer Staging Manual.* 7th ed. New York, NY: Springer; 2010:77–87, with permission.

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if obvious metastatic disease is identified. This approach would appear to be validated by data from Toronto where a group of patients with microscopic disease in medial compartment lymph nodes who did not undergo medial compartment neck dissection showed a 7% risk of medial compartment nodal recurrence on follow-up. This risk of medial compartment recurrence was similar to those patients undergoing medial compartment neck dissection.[252]

Determining the need and utility for prophylactic medial neck dissection in papillary thyroid cancer has been a subject of debate in recent years. Studies typically demonstrate no survival advantage for patients undergoing limited neck dissection.[253] Exceptions to this are studies showing both a survival and locoregional control advantage for patients undergoing a compartment-oriented approach to papillary cancer[254] and studies showing a survival advantage only for older patients older than 60 years who undergo neck dissection.[90]

Recent work raises an additional issue beyond survival and locoregional control. A retrospective evaluation compared a large series of patients undergoing thyroidectomy and ipsilateral medial compartment neck dissection to those undergoing thyroidectomy alone. A significant difference in stimulated Tg was demonstrated with the rate of an undetectable stimulated Tg at 6 months at 72% in the dissected group versus 43% in those who had thyroidectomy alone.[255] These results will need to be confirmed in larger series with longer follow-up. However, if it is possible to reliably reduce the proportion of patients with detectable Tg after treatment, there should be a decrease in the downstream financial and emotional costs of continued evaluation and monitoring of patients. For some patients with clinically N0 necks, central compartment neck dissection may upstage patients to N1a and upstaging patients over the age or 45 from stage I or II to stage III.[256] Recent ATA consensus guidelines suggest that prophylactic central compartment neck dissection may be performed in the N0 neck for advanced primary tumors (T3 and T4), but it may be appropriate to forgo prophylactic dissections for small (T1 and T2) papillary tumors and most follicular tumors (Recommendation 27).[212]

***Radioactive Iodine.*** The use of radioactive iodine treatment in thyroid malignancies varies depending on the surgical pathology. Guidelines by both the ATA and the NCCN have recommended radioactive iodine treatment if an aggressive variant is identified. These include tall cell, columnar cell, insular, oxyphilic, or poorly differentiated carcinoma. According to the NCCN, the indications for radioactive iodine in cases where no nodal disease is present include macroscopic multifocal disease, extrathyroidal extension (T3 or T4), and positive margins. The ATA guidelines recommend radioactive iodine treatment in multifocal disease, except when all foci are <1 cm, and does not recommend it for unifocal or multifocal disease <1 cm in the absence of other high-risk features (Recommendation 32d).[212] Further adding to the cautions about the use of radioactive iodine in low-risk (T1N0) disease, recent data have shown an increasing incidence of second primary malignancies (including salivary gland malignancy and leukemia in particular).[257] Additionally, the guidelines recommend treatment for those with extrathyroidal extension or vascular invasion. Although Hurthle cell tumors are less radioistope avid than papillary and follicular cancers, the indications for radioactive iodine are similar.

To summarize, not all patients younger than 45 years of age with T1-2N0M0 tumors require radioactive iodine. T3 tumors will merit radioiodine. Patients older than 45 years of age require radioiodine except in those cases where the disease is of limited size. Also, while the ATA recommends ablation in all patients with a postsurgical indication except patients with nodules <1 cm (unifocal or microscopic multifocal), the NCCN guidelines allow for no radioactive iodine treatment if a stimulated Tg is <1 ng/mL and the postoperative radioactive iodine scan shows no residual uptake.

If a total thyroidectomy has not been performed, and radioactive iodine treatment is indicated, a completion thyroidectomy will simplify and expedite treatment, but ablation of the thyroid remnant may be considered if a small volume of thyroid tissue remains. Therapeutic radioactive iodine treatment will then be possible 6 to 12 months after ablation of the thyroid remnant.

To be most effective, patients treated with radioactive iodine should be prepared for the treatment with TSH stimulation. This may consist of thyroid hormone withdrawal, allowing the TSH to rise accordingly, or by administering rhTSH. During withdrawal, the serum TSH at the time radioiodine administration should be >30 $\mu$U/mL. Patients should also be instructed to adhere to a low-iodine diet in the 2 weeks before the radioactive iodine treatment. Excess iodine, either through dietary intake or as a result of a recent dose of iodinated contrast such as would be given for a diagnostic CT scan, will reduce the uptake of iodine and potentially reduce the effectiveness of radioactive iodine therapy, and therefore, should be avoided.

Recent ATA guidelines suggest that remnant ablation can be performed effectively after thyroxine withdrawal or rhTSH stimulation (ATA Recommendation 34).[212] Studies have shown that thyroxine withdrawal and rhTSH equally prepare patients for remnant $^{131}$I ablation, with rhTSH studies showing an improvement in the subjective quality of life[258] and similar short-term recurrence rates.[259]

Currently, it is controversial which patients should have $^{131}$I administered under levothyroxine withdrawal conditions or with rhTSH stimulation. The authors' view at present is that most patients can be administered radioactive iodine following rhTSH stimulation rather than during levothyroxine withdrawal. Withdrawal is associated with severe symptoms of hypothyroidism that can be avoided by using rhTSH. On the other hand, rarely rhTSH administration may result in rapid enlargement of some thyroid cancer lesions with particular attention to those in the brain or skull where such mass changes could have deleterious effects. Radioactive iodine therapy following rhTSH injections has not yet been demonstrated to have the same long-term benefit in all circumstances as has $^{131}$I therapy after levothyroxine withdrawal. Nevertheless, most comparative studies published thus far show these different methods to be of equivalent benefit in ablating residual thyroid tissue and possibly in treating metastatic lesions. Current approaches will be modified as more relevant studies are performed and reported.

The dose of iodine administered will vary depending on the indications and the desired goal of therapy. If iodine is being administered for ablation of the thyroid remnant only, then the dose of radioactive iodine is typically between 30 and 100 mCi. If there is concern about residual cancer, such as in cases where extrathyroidal extension is identified, or aggressive histology is documented, the dose will typically be 100 to 200 mCi. Some institutions favor the use of dosimetry in selected patients with aggressive or recurrent disease in order to help determine radioiodine retention in an individual patient, which then allows calculation of a more specific radioiodine dosage.[260,261]

***TSH Suppression.*** The use of thyroxine as a mechanism to provide TSH suppression is commonly used after thyroid cancer treatment. The concept is that TSH is a growth factor for thyroid cells and that decreasing its level may have a beneficial effect on thyroid cancer growth or recurrence. When an occult papillary cancer is discovered after lobectomy, this is typically not required. However, the TSH should be monitored in an effort to

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detect subclinical hypothyroidism, and, if identified, thyroxine replacement should be initiated.

For larger stage I tumors, and for microscopically invasive follicular cancers, TSH suppression is often utilized after surgical treatment. However, the goals of TSH suppression are typically modest and values in the low normal range are adequate. Stages II and III tumors merit greater TSH suppression although a recent study by Jonklaas failed to show significant benefit of aggressive suppression therapy even in stage II tumors.[262] Stage III tumors should be treated with a goal of keeping TSH 0.1 to 0.5 $\mu$U/mL for 5 to 10 years after treatment. Present ATA Guideline recommendations (Recommendation 40) suggest that TSH suppression below 0.1 mU/L is appropriate for intermediate-risk and high-risk tumors, whereas maintenance levels of 0.1 to 0.5 mU/L may be appropriate for low-risk patients, whether they have undergone remnant thyroid ablation or not.[212]

## T4N0M0 (Stage I Younger than 45 Years or Stage IV older than 45 Years)

***Surgery.*** For tumors with extension beyond the thyroid into trachea, esophagus, larynx, recurrent laryngeal nerve, prevertebral fascia, carotid, or mediastinal vessels, surgery remains the recommended first-line therapy in DTC. For tumors adherent to the larynx or trachea, a shave resection may be possible but if intraluminal extension is identified, tracheal resection or partial laryngectomy is indicated.[263–266] A total laryngectomy is rarely indicated in DTC and in the patients in whom this is considered, a subtotal resection and external bean radiotherapy would be an appropriate alternative. Esophageal invasion may be limited to the muscular layers of the esophagus, allowing a submucosal resection to be accomplished. The recurrent laryngeal nerve can often by dissected away from the tumor capsule, but encasement or invasion of the recurrent laryngeal nerve may require nerve sacrifice. This tumor involvement usually is suspected preoperatively because vocal fold motion is abnormal or absent.

***Radioactive Iodine.*** Tumors of such aggressiveness should be treated with radioactive iodine unless they are proved to be noniodine avid. Doses of radioactive iodine may be near 100 mCi if no uptake beyond the thyroid bed is detected, but usually higher doses will be administered.

***External Beam Radiotherapy.*** Not typically used for routine management of thyroid cancer, external beam radiotherapy is appropriate in T4 tumors. Radiotherapy doses will typically be administered in standard fractionation to doses of approximately 60 Gy. The fields chosen for treatment will typically include the thyroid bed, central compartment, and mediastinal nodes. Recent ATA Guidelines recommendations (Recommendation 41) suggest that external beam radiation (EBRT) should be considered in any patient above the age of 45 with gross visible extrathyroidal extension with a high likelihood of microscopic disease, in those patients with gross residual disease in whom RAI or further surgery would not be beneficial. NCCN Guidelines provide similar recommendations. EBRT has also been suggested for those patients with extensive pT4 disease above the age of 60 even in the absence of evident residual disease.[267] Recent data suggest that PET may play a role in evaluating the posttreatment response following EBRT and should be part of the management algorithm, especially in noniodine avid (RAI scan-negative) tumors (Recommendation 48d).[212]

The timing of EBRT and radioactive iodine needs some comment. It is preferred that radioactive iodine precedes external radiotherapy. This avoids the potential for reduced radioactive iodine uptake in tumor tissue previously subjected to external radiotherapy. In addition, if a radioiodine-avid tumor is shown by radioactive iodine treatment, then there is a theoretic advantage in waiting for some period of time (e.g., 3 months) before EBRT commences.

***Thyroid-stimulating Hormone Suppression.*** These high-risk tumors should be treated with thyroxine with a goal of maintaining TSH at or <0.1 $\mu$U/mL. Medical contraindications such as atrial fibrillation and osteoporosis will need to be considered with aggressive TSH suppression.

## T1–4N1M0 (Stage I Younger than 45 Years, Stage III or IV Older than 45 Years)

***Surgery.*** The treatment of patients with clinical neck disease starts with surgery. All patients merit total thyroidectomy and a neck dissection. Neck dissection is associated with better outcomes than management of clinical nodal disease by "berry picking." The extent of neck dissection should be determined by the extent of neck disease. In cases with medial compartment nodal disease, a complete medial compartment dissection is warranted. For patients with nodal disease along the jugular chain or in the posterior triangle, both a medial compartment neck dissection and a lateral neck dissection should be performed. To address the levels of neck disease at risk, levels II through V should be dissected in most cases. Preservation of the spinal accessory nerve, the sternocleidomastoid muscle, the jugular vein, and even the cervical sensory nerves is usually possible. Levels II to IV are the most common levels involved. Level I is rarely involved in thyroid disease and can be omitted. Levels I and V are never involved in isolation.[268]

The importance of level II in the management of neck disease in thyroid cancer merits further discussion. Whereas levels III and IV have the highest prevalence of nodal metastasis, the rate of level II disease has been reported at approximately 50% by Sivanandan and Soo.[268] Even in papillary microcarcinomas, when lateral neck dissections are performed routinely, level II involvement ranges from 15% to 30% depending on the location of the tumor within the thyroid gland. The finding that upper lobe and multifocal cancers metastasize to level II in 30% of the cases argues for careful attention to this level of the neck.[66] Level II can be reached by a low transverse incision in many cases although access to tissues posterior to the spinal accessory nerve (level IIb) can be difficult. Ridge et al. have reported a 21% incidence of nodal involvement of level IIb (above the spinal accessory nerve) in their series of neck dissections for thyroid cancer.[269]

***Radioactive Iodine.*** For patients with DTC identified as having lymph node metastases, treatment guidelines differ. ATA guidelines recommend postsurgical radioactive iodine in all patients with follicular cancer and all patients with papillary thyroid cancer larger than 1 cm. NCCN guidelines provide for options in therapy with no treatment when postoperative stimulated Tg is low and radioactive iodine scan is negative. The NCCN guidelines acknowledge the fact that a high number of papillary thyroid cancers will harbor occult nodal disease, but that the historical behavior of these tumors remains favorable.

***Thyroid-stimulating Hormone Suppression.*** Patients with nodal disease at diagnosis merit TSH suppression therapy following surgery. However, as noted by Jonklaas, young patients in this group are stage I tumors and the benefit of TSH suppression is not clear.[262] Typically all patients with nodal disease are treated, but more aggressive TSH suppression goals are used in older patients and in those with documented metastatic disease on post-therapy radioactive iodine scans. The clinical context must also be considered especially with regard to the possibility of aggravating or precipitating atrial fibrillation or bone loss.

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### T1–4N1M1 (Stage II Younger than 45 Years, Stage IV Older than 45 Years)

***Surgery.*** Patients with distant metastatic disease at presentation merit thyroid surgery both to provide control of the primary site and to allow the use of radioactive iodine to treat the distant disease. In this circumstance, neck dissections may be limited to grossly positive nodal disease, again to reduce the tumor burden and allow effective treatment with radioactive iodine.

***Radioactive Iodine.*** For patients with M1 disease, radioactive iodine is given in most cases. Dosimetry may be used to maximize the tolerable dose; however, there is not clear evidence that this form of treatment is better than empiric radioactive iodine dose selection. Micronodular pulmonary metastases respond well to radioactive iodine and treatment should be repeated until there is no further tumor response. Macronodular lung disease is less responsive but treatment is appropriate as long as tumor nodules uptake radioactive iodine.

Other sites of metastatic disease merit radioactive iodine treatment as well. Possible exceptions include solitary brain metastases, or bone metastases that threaten spinal cord integrity, or involves weight-bearing bone. Instead, these metastases should be considered for resection or treated by local irradiation. The reader is referred to both the ATA and NCCN guidelines[212,247] for a description of treatment options for various metastatic situations.

***Thyroid-stimulating Hormone Suppression.*** Patients with metastatic disease merit aggressive TSH suppression therapy with a goal of maintaining TSH at <0.1 $\mu$U/mL. Again, the exception would be a young patient with minimal evidence of metastatic disease such as radioavid microscopic lung metastases. Ideally, these situations should be individualized.

## MEDULLARY THYROID CARCINOMA

### Sporadic or Inherited Presenting with Clinical Disease (Stages I–IV)

***Surgery.*** Surgery is essential in the treatment of MTC; however, a sporadic tumor may be the index tumor of a pedigree with MEN, and it is therefore important that an effort to evaluate for both pheochromocytoma and hyperparathyroidism be undertaken before surgery. If present, the former may require surgery before the thyroid surgery.[247]

For medullary cancer, a total thyroidectomy is recommended along with at least a medial compartment neck dissection. The threshold for performing lateral neck dissections is low, and some authors have recommended that all patients undergo bilateral neck dissections in addition to the thyroidectomy and medial compartment dissection. NCCN guidelines favor thyroidectomy and medial compartment neck dissections in all patients. Ipsilateral lateral neck dissection is recommended for clinical or radiologic evidence of nodal disease. In addition, prophylactic lateral neck dissection should be considered when there is significant central neck disease. Dissection of the contralateral neck is recommended when clinical or radiologic disease is identified there. The neck dissections done in medullary carcinoma should be as thorough as possible in the regions dissected because these tumors are not responsive to radioactive iodine and are considered less responsive to external beam radiotherapy as well.[247]

***Surgery with RET Germline Mutation.*** RET mutations may be seen in familial medullary carcinoma and in MEN 2A and 2B. Patients with these germline mutations require special consideration regarding the management of the thyroid. RET mutations of codons 883, 918, and 922 are associated with MEN 2B. This aggressive syndrome merits surgical intervention in the first year of life in order to prevent the emergence of clinical disease.[157,247] A central neck dissection should also be performed in these cases. If a tumor >5 mm is detected, the NCCN guidelines advise consideration of an ipsilateral neck dissection as well.[247]

RET mutations of codons 609, 611, 618, 620, 630, 634, 768, 790, 791, 804, or 891 are associated with MEN 2A and FMTC. Patients with these mutations merit surgery at age 5 or when the mutation is identified in older individuals.[247] Previous guidelines had distinguished patients with mutations at codons 611, 618, 620, and 634 from the other MEN 2A hotspots. These guidelines had advised surgery before age 5 in the former group with the possibility of later surgery (before age 10) in the latter group. These strategies are still undergoing modification and should be individualized.[157]

Surgical preparation should include measurement of parathyroid hormone level in order to be able to address parathyroid disease at the time of surgery, if hyperparathyroidism is present. Surgery should consist of total thyroidectomy with central compartment neck dissection in those patients with elevated calcitonin or CEA and in those with thyroid nodules identified by ultrasonography or at surgery. Lateral neck dissection should be considered for those with primary tumors >1 cm diameter[247] (NCCN guidelines).

If the preoperative parathyroid hormone level was elevated (or high normal in the context of hypercalcemia), then parathyroid disease should be managed at surgery. This will consist of excision of a parathyroid adenoma, if present, or subtotal parathyroidectomy and preservation of the equivalent of one parathyroid gland *in situ* or autotransplanted when hyperplasia is identified.[247]

***Radiation Therapy.*** There probably is no role for radioactive iodine in MTC. If radiotherapy is indicated, external beam radiotherapy is required. The role for radiation therapy as an adjunct in the treatment of medullary thyroid cancer is unclear. There are no randomized trials supporting its use, but institutional reports demonstrate activity against this tumor type when compared with historical controls. For disease that has been completely resected, with clear margins and minimal nodal disease, there does not appear to be any role for radiotherapy. The NCCN guidelines recommend that radiation be considered in T4 tumors (NCCN guidelines). The authors feel that those patients with close or positive surgical margins or multiple nodal metastases, especially if extracapsular extension is noted, should be considered for postoperative radiotherapy.[270]

## ANAPLASTIC CARCINOMA

### Surgery

Typically, anaplastic carcinoma presents so aggressively that surgery is not feasible because of extensive infiltration of surrounding structures. In these cases, surgical intervention is limited to biopsy and, if indicated by airway compromise, tracheotomy. Biopsies in this disease may be obtained by core needle biopsy although some cases required additional tissue by open biopsy to complete the pathologic assessment. Tracheotomy may require resection of the thyroid isthmus and adjacent tumor to provide unobstructed access to the airway.

Rare cases of anaplastic cancer may present early enough to allow surgery to be considered. However, even small anaplastic tumors may show extensive tumor infiltration, so the decision to pursue surgery should be made with care. Total thyroidectomy with resection of involved regional nodes and structures should be considered. The authors would not consider resection of

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aerodigestive tract structures due to the quality-of-life effects and no expectation of therapeutic benefit. For those patients selected for surgery, the therapeutic goal is to allow for locoregional control of disease and preservation of voice, airway, and swallowing with recognition that distant disease is highly likely to present. Occasionally, a diagnosis of anaplastic thyroid cancer emerges on final pathology. There is no role for completion thyroidectomy or neck surgery in these cases.

### Radiation Therapy

Anaplastic cancer does not concentrate radioiodine, so radioactive iodine treatment is not recommended. External beam radiotherapy to the thyroid bed and neck is commonly utilized in an effort to establish locoregional control of tumor. Standard fractionation and hyperfractionation regimens have been utilized. Radiation doses in the range of 60 Gy are more effective than lower doses. Toxicity is a major limiting factor in twice-daily fractionation schemes, but seems to show more responsiveness than once-daily regimens.[271]

### Chemotherapy

As part of the standard care for anaplastic cancer, chemotherapy is used in combination with radiotherapy. Doxorubicin is considered the single most effective agent.[184,272] This can be combined with cisplatin in a manner that yields relatively favorable responses.[181,272] Other agents, including paclitaxel, have also been utilized.[273]

## OUTCOMES AND RESULTS

### Differentiated Thyroid Cancer

Owing to the similar outcomes in papillary and follicular thyroid cancer, many series report these two cancer types together. Although differences may be seen in the presentation and behavior of these two tumor types, the outcomes of this group as a whole will first be discussed and distinctions will then be made between the two tumor types as required. It is generally accepted that the vast majority of patients with DTC do well, with overall survival in excess of 90% in multiple series. In the largest series of thyroid cancers reported, Hundahl utilized the National Cancer Data Base (NCDB) to evaluate outcomes of >53,000 patients treated between 1985 and 1995. This series shows the value of American Joint Committee for Cancer (AJCC) staging as a predictor of prognosis. Table 28.3 shows the outcome of papillary cancer by stage and Table 28.4 shows the same data for follicular cancer. What is most notable here is both the excellent outcome of low-stage tumors and also the low prevalence of high-stage tumors. These two factors have contributed to the general understanding that patients with differentiated cancer do well.[76]

**TABLE 28.3 Papillary Carcinoma Stage Distribution and Survival**

| Papillary Cancer Stage (16% Unknown Stage) | I | II | III | IV |
|---|---|---|---|---|
| 5-yr survival | 100% | 100% | 94% | 48% |
| Proportion of cases | 57% | 14% | 10% | 2% |

There is both an excellent outcome of low stage tumors, but also a low prevalence of high stage tumors.

*Source:* Adapted from Hundahl SA, Fleming ID, Fremgen AM, et al. A national cancer data base report on 53,856 cases of thyroid carcinoma treated in the United States, 1985–1995. *Cancer.* 1998;83:2638–2648, with permission.

**TABLE 28.4 Follicular Carcinoma Stage Distribution and Survival**

| Follicular Cancer Stage (18% Unknown Stage) | I | II | III | IV |
|---|---|---|---|---|
| 5-yr survival | 99% | 99% | 82% | 47% |
| Proportion of cases | 41% | 27% | 7% | 7% |

Similar to papillary cancer, there is both an excellent outcome of low stage tumors, but also a low prevalence of high stage tumors.

*Source:* Adapted from Hundahl SA, Fleming ID, Fremgen AM, et al. A national cancer data base report on 53,856 cases of thyroid carcinoma treated in the United States, 1985–1995. *Cancer.* 1998;83:2638–2648, with permission.

Tables 28.3 and 28.4 describe 5-year survival data. At 10 years, similar outcomes are seen for patients younger than 45 years. In contrast, older patients begin to show poorer survival. This is clearly demonstrated in the data from Hundahl represented in Figure 28-14. Increased age at the time of diagnosis corresponds to worse 5-year survival, but 10-year survival is markedly worse in older patients. These data also emphasize the need for long follow-up in thyroid cancer studies. It is generally felt that, when possible, 20-year survival figures should be compared in this disease to determine optimal therapy.

Although it is generally understood that patients with DTC will do well following treatment, there are cases that fail treatment and a small number of patients who die of disease. Determining which patients will do well and which patients will do poorly has been an area of debate in thyroid cancer study. Those patients with an excellent prognosis may be managed with less aggressive therapy than those with a more ominous prognosis. As an example, studies have shown that patients who die of DTC often have distant disease at presentation. In a study from Germany in which 38 of 484 patients with DTC died of thyroid cancer, 20 had distant disease at presentation.[274] Similar data are seen from Toronto, where 10 of 522 patients with DTC died of disease and 5 of these had distant metastases at presentation.[275]

Efforts to define prognosis in DTC have led to risk stratification criteria. Shaha describes an experience from Memorial Sloan-Kettering Cancer Center of >1,000 DTCs. In his analysis, using criteria echoing the age, metastases, extent, and size (AMES) risk criteria, he differentiates low-risk, intermediate-risk, and high-risk cancers. The definitions of these risk groups are shown in Table 28.5. Cancers are equally distributed between low-risk (39%) and intermediate-risk (39%) groups with high-risk cancers seen in only 22% of patients. Patients with high-risk cancers show a 57% 20-year survival with recurrences predominantly being distant in 34% and lesser risks of local in 18% and regional in 17%. Intermediate-risk tumors on the other hand show an 85% 20-year survival with almost equal distribution between local (10%) and regional (14%) and distant (12%) recurrences. Low-risk cancers show a 99% 20-year survival with low risk of local (5%), regional (10%), and distant (2%) recurrences. Because of the low risk of recurrence and negligible risk of death in the low-risk group, Shaha has recommended that thyroid lobectomy alone be considered, perhaps with suppression of TSH, in this group.[276]

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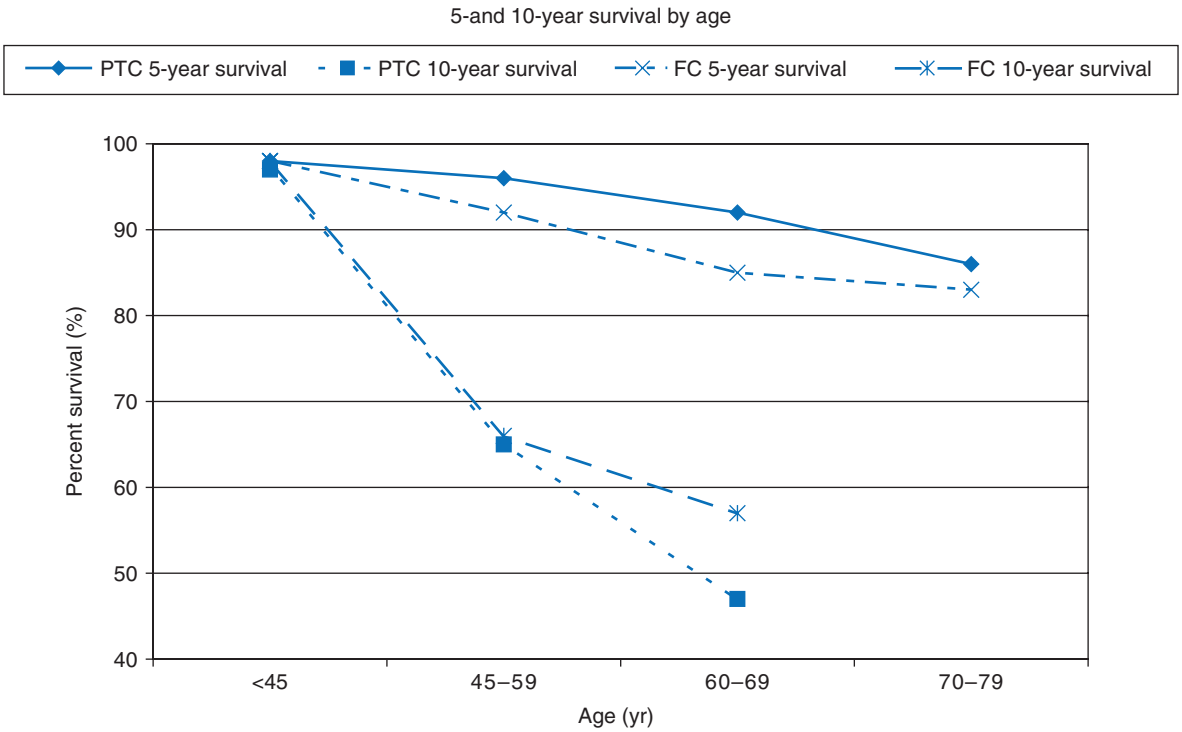



**FIGURE 28-14.** Five-year survival and 10-year relative survival for young patients are similar for both papillary and follicular cancer. However, a difference in survival is seen in older populations when comparing 5- to 10-year survival. PTC, papillary thyroid carcinoma; FC, follicular thyroid cancer.

By utilizing three risk groups instead of two, these data select out the very low-risk patients who may be appropriate for partial thyroidectomy. Not all clinicians agree with this approach, and if the previously reported NCDB data are a reflection of accepted practice, most T1 papillary thyroid cancers (63%) were treated by total or near-total thyroidectomy between 1985 and 1990. Two issues are worth noting here. One is that this era was one in which T1 was defined by tumors <1 cm in diameter, as opposed to the more recent staging cut-off point of 2 cm. Second, the Memorial Sloan Kettering and the NCBD data are derived from a period when neither serum Tg nor relevant radiologic studies such as cervical sonograms were used routinely in follow-up; therefore, residual or recurrent disease may have been underestimated.[76]

## Papillary Cancer

It is difficult to determine survival differences in treatment options for DTC because patients typically do well. Differences, however, do emerge relative to treatment and locoregional control. In an often quoted series of papillary thyroid cancers published by Mazaferri, 576 patients were followed for a median of >10 years. There was no difference in the risk of death from

**TABLE 28.5 Risk Group Stratification in Differentiated Thyroid Cancer**

**Differentiated Cancer of Thyroid: Risk Group Definitions**
**Risk Groups**

| | Low | Intermediate | Intermediate | High |
|---|---|---|---|---|
| Age (y) | <45 | >45 | <45 | >45 |
| Distant metastasis | M0 | M1 | M0 | M1 |
| Tumor size (cm) | T1/T2 (<4) | T3/T4 (>4) | T1/T2 (<4) | T3/T4 (>4) |
| Histology and grade | Papillary | Follicular and/or high grade | Papillary | Follicular and/or high grade |
| Frequency | 39% | 39% | | 22% |

Table shows definitions of risk groups and the typical frequency seen.

*Source:* Adapted from Ashok R, Shaha MD. Implications of prognostic factors and risk groups in the management of differentiated thyroid cancer. *Laryngoscope.* 2004;114:393–402, with permission.

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disease whether a total (0.6%) or less than total (1.5%) thyroidectomy was performed. There was, however, a significantly lower risk of recurrence in the total thyroidectomy group (11% vs. 19%).[141] The Mayo Clinic has described a series of papillary cancers followed up for a median of 23 years and indicates no difference in cause-specific mortality or risk of distant metastases between patients treated by total thyroidectomy or lobectomy. There was a significant decrease in local recurrence (2% vs. 14%) and nodal recurrence (6% vs. 19%) when total thyroidectomy was performed versus lobectomy.[277] An analysis of the SEER database looking at patients who have undergone surgery for papillary thyroid cancer has confirmed the above findings. In this study of 22,724 patients, increased tumor size, extrathyroidal extension, positive nodal status and increased age were associated with worse disease-specific and overall survival. When controlling for tumor size in multivariate analysis, there is no survival difference between patients undergoing total thyroidectomy and lobectomy.[278]

For follicular variant of papillary thyroid carcinoma, the survival appears no worse, possibly even better, than classical papillary carcinoma with survival at 21 years reported as 86% and 80%, respectively, in one series.[279] Reports, including the authors' own, comparing papillary cancer and follicular variant of papillary cancer have indicated a higher chance for local invasion (10% vs. 0%)[104] and distant metastasis (4% vs. 0%) in papillary cancer[103] as well as a higher chance of local recurrence.[104] Recently, data have indicated that FVPTC may consist of both encapsulated and invasive forms and that the encapsulated form has essentially no risk of local recurrence or death, even when treatment is limited to hemithyroidectomy.[105] In the same SEER database review mentioned previously, follicular variant of papillary was not associated with worse DSS or OS. These results will need to be confirmed by others, and therefore at this time the authors recommend that this variant be treated using the same protocol that one would use to treat the classic form of papillary cancer.

One issue in determining the outcome in papillary thyroid cancer is the use of serum Tg as a tumor marker. This is a highly sensitive test, estimated at 80% to 100% sensitive, with a negative predictive value of 99% when measured under thyroid hormone withdrawal following previous thyroidectomy and radioiodine treatment.[280] The test does, however, lack specificity and false-positive readings can be seen. Furthermore, these comments only apply to patients who do not have Tg antibodies, which may interfere in the accurate measurement of serum Tg.

Although it is logical to assume that an elevated serum Tg following previous thyroidectomy and radioactive iodine would indicate residual gland or recurrent tumor, there are many situations in which tumor is suspected but cannot be verified clinically. Studies from France and Italy both indicate that patients with low-risk papillary cancer need to be evaluated judiciously for mild increases in Tg. When patients have been treated by thyroidectomy and radioactive iodine and undergo Tg determination under TSH stimulation, 30% to 67% of those with Tg elevations of 1 to 10 ng/mL will normalize without further treatment.[280,281]

Utilizing ultrasound, metastatic disease is often identified in the neck when recurrence has been indicated by elevated Tg. When Tg is 1 to 10 ng/mL, 19% of patients will be found to harbor cervical metastases. When Tg is >10 ng/mL, the likelihood of cervical lymph node metastases increases to >50%.[281]

Despite the caveat that false-positive Tg levels may be seen and lead to unnecessary testing, a consensus panel concluded that this form of evaluation was appropriate follow-up testing in low-risk papillary cancer patients and that radioactive iodine diagnostic scans were not required to search for recurrent disease. Specifically, this panel reviewed 784 patients with no clinical evidence of cancer and low serum Tg (<1 ng/mL) on thyroxine replacement. These patients were evaluated by both rhTSH stimulated Tg and rhTSH stimulated or withdrawal radioactive iodine whole body scans. Twenty-one percent of patients had Tg stimulated to >2 ng/mL after rhTSH and 36% of these were found to have metastases. Thyroid radioiodine scans found only 19% of these recurrences, and the consensus panel concluded that rhTSH stimulated Tg was adequate follow-up in low-risk patients.[282] Present ATA guidelines on low-risk patients who have remnant thyroid ablation recommend that in the setting of a negative cervical ultrasound and undetectable TSH stimulated may be followed with a thyroxine withdrawal or rTSH stimulated Tg at 12 months after ablation (Recommendation 45a) and thereafter may be followed with annual clinical exams and Tg measurements on hormone replacement (Recommendation 45b).[212]

Indications for PET scanning in well-differentiated cancers is expanding beyond previous recommendations of follicular histology with an elevated suppressed Tg and a negative diagnostic whole body RAI scan. Possible indications include use in the initial staging of poorly differentiated carcinomas, as a prognostic tool for predicting disease specific mortality risk in patients with metastatic disease and in the evaluation of posttreatment response of systemic or local treatment for metastatic or locally aggressive disease (Recommendation 48).[212]

A proportion of papillary thyroid cancers are poorly differentiated, and these tumors have a more ominous prognosis. Among the poorly differentiated papillary thyroid cancers, tumors with trabecular, insular, and solid (TIS) pattern predominate. Outcomes for these cancers have been described by a report from the University of Turin. Overall, 10-year survival was worse for these tumors (67%) than for either papillary thyroid cancer or follicular cancer (90%). The data allowed a scoring system to be developed which rated necrosis, mitoses, and patient age in order to subclassify these trabecular, insular, and solid tumors into three classes. Class I tumors showed a prognosis similar to papillary and follicular cancers. The 10-year survival for these three classes of trabecular, insular, and solid cancers was 83%, 74%, and 48%.[283] In addition, the previously mentioned TCV and the DSV of papillary have also been shown to have a worse prognosis compared to classic papillary type.[284] In a review of 43,738 patients from 1988 to 2008, the incidence of TCV and DSV increased by 126% compared with papillary cancer for the same time period. In addition, the DSV and TCV were associated with higher rates of extrathyroidal extension, multifocality, and nodal (more common with DSV) and distant (more common with TCV) disease. Overall survival was less for DSV (5-year OS 87.5%) and TCV (80.6%) compared with classic papillary (93.5%, $p < 0.001$).

## Follicular Cancer

Although the outcomes for minimally invasive follicular carcinoma are typically excellent, a worse prognosis can be seen in macroscopically invasive follicular cancer. Among 215 follicular thyroid cancers reported from Hong Kong in which total thyroidectomy was done in 80.5% and radioactive iodine was used in 81.4%, a 10-year cause-specific survival of 81% was seen with multivariate analysis showing significantly worse survival with extrathyroidal extension, gross residual disease after surgery, metastatic disease at presentation, or lack of radioactive iodine treatment. This series included minimally invasive follicular cancers as defined by complete encapsulation and invasion noted only on pathologic evaluation. For these minimally invasive cancers, the cause-specific survival was significantly better at 97.6% at 10 years. Most of the 52 patients with minimally invasive cancer underwent total thyroidectomy and radioactive iodine treatment. Although there were no locoregional recurrences among the minimally invasive cancers, three (5.8%) patients developed bone metastases, two of whom were treated with radioactive iodine previously, and one patient died of diffuse bone metastases.[285]

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In another series from Hong Kong, the excellent outcomes in minimally invasive follicular carcinoma are shown. This series of 156 patients with follicular cancer were followed up for an average of 14 years and included 49 (31%) classified as minimally invasive, 23 (15%) others showing angioinvasion, and 84 (54%) with widely invasive tumors. Seventeen (11%) presented with distant disease and half of these died of disease. In the entire series, a total of 17 (11%) died of disease, and death from disease was limited to those with widely invasive follicular cancer. No patients with minimally invasive cancer or angioinvasion alone died of disease.[130]

Although the first of these two series from Hong Kong tended to treat all follicular cancer with total thyroidectomy and radioactive iodine, regardless of the degree of invasion, the second recommended hemithyroidectomy alone for minimally invasive follicular cancers. Paradoxically, the first series resulted in subsequent distant metastatic disease in 6% whereas the second, more conservative, approach reported no risk of distant disease in follow-up.[130,285] A series from the AFIP also supports lobectomy as adequate treatment for minimally invasive follicular carcinoma. In this series of 95 cases of minimally invasive follicular carcinoma, all recurrences were local and only one patient died of disease.[134]

Comparing the outcome between those minimally invasive tumors with capsular invasion alone versus those with angioinvasion demonstrates a higher cause-specific mortality (28% at 10 years) among tumors with angioinvasion.[286] The terms *angioinvasive* or *moderately invasive* follicular cancer has been proposed to describe the worse outcome in angioinvasive tumors compared with tumors with capsular invasion alone.[130] A stepwise decrease in 5-year survival is seen between tumors with capsular invasion alone (98%), versus those with angioinvasion with or without capsular invasion (80%) versus those with macroscopic invasion (38%).[287] These results may be interpreted to suggest that treatment of minimally invasive follicular cancer by hemithyroidectomy alone may be best limited to those cases with capsular invasion alone and more comprehensive treatment advised in cases with angioinvasion.

## Hurthle Cell Cancer

Hurthle cell cancer is considered to be a variant of follicular cancer, with similar behavior. In a study from M.D. Anderson, evaluating outcomes in 127 Hurthle cell neoplasms (89 adenomas and 38 carcinomas), Hurthle cell carcinoma showed a 62% disease-specific survival at 20 years. In contrast, there was a 100% disease-specific survival in patients diagnosed with Hurthle cell adenoma, an area that had been controversial.[268] The NCDB data show a difference in outcome between follicular and Hurthle cell carcinomas with longer follow-up. In this series, there were >1,585 cases of Hurthle cell cancer reported versus 6,764 follicular cancers. At 5 years, survival was equivalent at 91%, but at 10 years, Hurthle cell cancer survival was 76% versus 85% for follicular cancer.[76]

## Medullary Thyroid Cancer

The NCDB data show 80% survival at 5 and 10 years despite the fact that only 38% of these patients were treated by total thyroidectomy and lateral neck dissection.[76] This same database has indicated that when medullary cancer occurs in a patient with a positive family history, 50% of cases are stage I whereas only 8% of those without a family history are stage I. In fact, in the absence of a family history, patients are most commonly stage II (40%). The prevalence of higher stage (III or IV) tumors is roughly similar between those cases with and without a family history, 39% and 44%, respectively. These data show that there is a significant incidence of higher stage tumors regardless of family history.[77]

Nodal disease has a critical impact on the ability to render patients with medullary cancer disease-free, at least as indicated by a normalized calcitonin. Following total thyroidectomy, medial compartment neck dissection, and bilateral neck dissection, calcitonin has been shown to normalize in 70% to 95% of those without pathologic nodes, but only 20% to 32% of those with nodal disease.[289] Similar relationships can be seen when numbers of nodes and numbers of involved compartments are evaluated. Compartments refer not to neck levels, but to the medial compartment, the two lateral compartments, and the mediastinal compartment. Biochemical cure is achieved in 32% of patients with one to nine nodal metastases, but in no patient with 10 or more positive nodes. Similarly, cure is achieved in 33% of those with one involved nodal compartment, 23% of those with two involved compartments, and 0% of those with more than two compartments.[290] Therefore, the role of mediastinal dissection is controversial. Typically, mediastinal dissection is limited to those patients with radiologic suspicion of mediastinal adenopathy.[247] Machens has demonstrated associations between both extrathyroidal extension and cervical adenopathy and positive mediastinal adenopathy.[291] However, although biochemical cure is rare, Machens has shown significant palliation of symptoms when recurrent MTC requires mediastinal dissection.[292]

For many years, there were conflicting data whether sporadic or hereditary forms of medullary thyroid cancer had a worse prognosis. Initially through intensive biochemical screening of kindred at risk and now with the advent of RET testing, the data have pointed toward worse outcomes in sporadic forms of medullary cancer.[293] Early intervention in hereditary forms of the disease can be assumed to account for this difference. For example, a 40-year experience at University of California, San Francisco described a 95% survival when patients with hereditary medullary were discovered by genetic or biochemical screening. Unfortunately, only one-third of these hereditary patients were discovered by screening. Overall, only 49% of patients (hereditary and sporadic) were cured with recurrence in 12% and persistent disease after treatment in 38%.[294] Survival in medullary cancer has been shown to be equivalent to that of a general population when one of the following is present: patients with a family history discovered by screening or patients with tumors <1 cm in diameter whose tumors are stage I or II.[295]

MEN 2B has a poorer prognosis than MEN 2A with a biochemical cure shown in 56% of those medullary cancer patients with MEN 2A and 0% of those presenting with cancer in the setting of MEN 2B.[293] This clinical experience, from the Mayo Clinic, reflects a series of cases before widespread genetic testing and supports the current recommendations for prophylactic thyroidectomy in carriers of RET germline mutations. A recent report describes an experience with 50 patients treated by prophylactic thyroidectomy due to demonstration of a RET gene mutation. At 5 and 10 years after treatment, no patient had evidence of clinical medullary cancer. Forty-four (88%) had undetectable basal and stimulated serum calcitonin levels; two patients had elevated basal and stimulated calcitonin levels and four had a rise in stimulated levels, but remained within the normal range for serum calcitonin.[296]

The persistence of hypercalcitonemia following thyroidectomy is a common occurrence in medullary thyroid cancer. Despite this finding indicating residual medullary cancer following treatment, often there is no clinically demonstrable tumor and patients can survive for many years with occult medullary cancer. In fact, a Mayo Clinic case series with hypercalcitoninemia after treatment for medullary cancer reports 5- and 10-year survival rates of 90% and 86%, respectively.[297]

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It has been reported that outcomes in patients with medullary thyroid cancer who are discovered by routine screening is better than that in an historical cohort who presented clinically. The detection of MTC was noted in 0.4% of the >10,000 patients screened. Screened cases were of lower stage and following treatment were more likely to be rendered biochemically free of disease by serum calcitonin measurement (59%) than those presenting clinically (2.7%). Survival was also significantly better in the screened group. Screening for medullary cancer remains controversial due to the low yield of cases identified, but this group estimated a cost per MTC discovered of US$12,500 assuming a calcitonin test cost of US$50/sample (probably low by U.S. standards).[209] This group, from Pisa, Italy, favors calcitonin screening in all patients with thyroid nodules.

The utility of calcitonin screening remains controversial. This is due to the low prevalence of medullary cancer in patients with nodular disease, 0.5% to 1.5%. However, the likelihood of finding an abnormally elevated serum calcitonin level in patients with nodular thyroid disease is 3.8% to 5.1%, with most patients having a nonspecific elevation of serum calcitonin not believed to be related to the presence of medullary thyroid cancer. The degree of elevation of serum calcitonin level can be predictive of medullary thyroid cancer with a level >100 pg/mL being relatively diagnostic. While measurements after pentagastrin stimulation may eliminate false-positive readings on baseline studies, pentagastrin is not available in the United States. Therefore, the issue of whether to recommend universal serum calcitonin screening universally must take into consideration the lack of availability of pentagastrin as well as the costs of serum calcitonin measurements and pentagastrin stimulation where available (including the expense of the medication and personnel time) versus the ability to detect medullary thyroid cancer in unsuspected patients with nodular disease. The measurement of serum calcitonin in a patient with an FNA suggestive of medullary thyroid cancer should, of course, be performed. Furthermore, a clinical history of palpitations, severe or chronic diarrhea, episodes of diaphoresis, headache, hypertension, or hypercalcemia may increase suspicion for the presence of an MTC. Marfanoid habitus, neural crest-derived mucosal skin or gastrointestinal lesions, and a family history of other neuroendocrine tumors or medullary thyroid cancer should also trigger the consideration of appropriate testing including a serum calcitonin level. The present controversial issue focuses solely on the diagnostic evaluation and cost-effectiveness of screening patients with thyroid nodular disease with a serum calcitonin level and not on the appropriateness of measurement when clinically suggestive.[210]

## Anaplastic Cancer

The survival of patients with anaplastic cancer is extremely poor. NCDB data describe a 10-year survival of 14% with the vast majority of these patients dying in the first year after diagnosis.[76] In fact, this survival rate is surprisingly high, particularly considering that this is an observational database. Others have reported lower survival, including a 10% to 21% 1-year survival,[192,193,298] a 6% to 11% 2-year survival,[298,299] and a 5% 5-year survival.[298] A recent report of 37 patients treated at Memorial Sloan-Kettering Cancer Center using doxorubicin and radiotherapy reveals locoregional control of 45% and overall survival of 28% at 1 year.[300]

The most favorable series reported in the literature utilized surgery, chemotherapy, and hyperfractionated radiotherapy and described a 27% 3-year survival. In this series of 30 anaplastic thyroid cancers treated over a 10-year period, 17 of the 24 patients without distant metastatic disease underwent surgical resection. Subsequent treatment included two cycles of doxorubicin and cisplatin followed by b.i.d. radiation therapy. Adjuvant chemotherapy was then followed for an additional 6 months. Three additional patients underwent surgery following chemotherapy and radiotherapy. With this protocol, 3-year actuarial survival was 27% overall and 35% among patients without distant metastases at diagnosis.[301]

# COMPLICATIONS

## Surgical

Surgical complications consist of infection, hematoma, laryngeal nerve injury, hypoparathyroidism, and other rare complications. Complications recorded from a prospective cohort study of >5,500 patients treated in the United States in 1996 and German prospective study of >5,800 patients in 1998 both showed that the most common complication was transient hypocalcemia, which occurred in 12% to 24% of patients undergoing total thyroidectomy.[77,302] In the U.S. study, significant voice change was interpreted to mean recurrent laryngeal nerve paralysis and was shown in approximately 1% of thyroid surgeries, slightly lower in lobectomies. However, this probably underestimated the incidence of nerve injury because routine laryngoscopy was not performed.[77] The German study reports a rate of 2.3% permanent vocal fold paralysis for total thyroidectomy.[303] Other complications reported are airway problems, bleeding, and infection, all below 1%.[77]

Complications have been correlated to the volume of thyroid surgery performed by the operating surgeon. In a report on 5,680 various thyroidectomies performed in the state of Maryland between 1991 and 1996, the complication rate for the 1,144 total thyroidectomies was volume dependent with surgeons performing >100 cases/year showing 75% fewer complications than those performing <10/year (4.3% vs. 16.1%). Although this difference is significant, the data included a wide variety of complications, ranging from recurrent nerve injury to drug reactions to cardiac events. The specific difference in the rate of recurrent laryngeal nerve injury in total thyroidectomy was not reported, but the rate between the highest and lowest volume surgeons was 0.4% versus 1.5% for all thyroid surgeries. No information was provided to assess transient versus permanent paralysis.[304] Others have reported on the safety of thyroid surgery in the setting of residency education.[305,306] In addition, the prospective German trial reported earlier showed a correlation between surgical volume and permanent recurrent laryngeal paralysis but failed to show any significant correlation with transient laryngeal paralysis or transient or permanent hypocalcemia.[302] In a review of 21,270 thyroid surgeries listed in the Maryland Health Service Cost Review Commission Database from 1990 to 2009, Gourin et al. concluded that high-volume surgeons had a lower incidence of recurrent nerve injury and hypocalcemia.[307]

## Laryngeal Nerve Paralysis

Among patients, one of the most feared complications is a loss of voice after thyroid surgery. Although the authors acknowledge that the rate of laryngeal nerve injury can be underreported depending on the extent of laryngeal examination postoperatively, the concern about the risk of voice loss after surgery is typically unfounded. The degree of voice alteration after laryngeal nerve injury is highly variable, as some patients detect no voice change when a postoperative paralysis is present and others are highly symptomatic. It is extremely rare to have a complete loss of voice, even with recurrent laryngeal nerve paralysis. Detailed preoperative discussions are warranted with all patients, especially those who use their voice professionally such as singers.

The nerves at risk in thyroid surgery include the superior laryngeal nerve and the recurrent laryngeal nerve. The incidence

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of superior laryngeal nerve paralysis is almost certainly underreported because this results in only a mild voice change, typically consisting of a loss of upper range vocalization and some voice fatigue. A large Italian study estimated the rate of superior laryngeal nerve paralysis after thyroid surgery at 3.7%.[308] Recurrent laryngeal nerve injury is the injury of more concern. The most significant problem regarding recurrent laryngeal nerve paralysis is the rare occurrence of bilateral paralysis, which results in airway compromise due to the inability to abduct the two vocal folds during inspiration. The incidence of bilateral paralysis has been noted to be 0.2% to 0.4%.[308,309] In spite of the airway issue, the postoperative voice can be quite good in these situations because the two vocal folds are in a paramedian position.

In an excellent review by Sulica, the incidence of recurrent laryngeal nerve injury was tabulated for recent series. Eighteen studies, each with at least 100 patients, published between 1991 and 2005 were included. The total number of patients reported was >28,000. In these series, the rate of vocal fold paralysis was 1% to 8.6% with 1% to 5.1% of cases being reported as temporary paralysis and 0% to 2.9% reported as permanent paralysis.[310]

Malignant pathology typically presents higher risk of nerve injury at surgery than benign pathology[311–313] and lower rates of injury have been shown when the nerve is identified at surgery.[311,314–316] Similarly, techniques that utilize subtotal thyroidectomy have been shown to have a higher rate of recurrent laryngeal nerve injury (3.6%) than cases that include complete removal of the thyroid lobe (0.9%).[245] Nerve monitoring during thyroid surgery has become more commonplace in the last several years, despite a lack of evidence that this practice reduces laryngeal paralysis.[317–320] The authors have typically used monitoring in patients who have undergone thyroidectomy or who they feel are at higher risk of nerve injury based on information available preoperatively (e.g., reoperations, preoperative nerve weakness, medial compartment nodal disease, history of radioactive iodine, history of Graves disease, and history of thyroiditis), but their experience suggests only a small (~1%), reduction in temporary paralysis.

As indicated earlier, most vocal fold paralyses after thyroidectomy will be temporary, caused by stretch or devascularization injury to the nerve. Over several weeks, these will typically resolve. Management of patients with these injuries may include laryngeal electromyography to demonstrate the nerve or nerves that have been injured (although this is typically indicated by the examination) and to help define the potential for recovery. Intervention typically includes speech therapy in an effort to maximize contact between the paralyzed vocal fold and the functional vocal fold. Medialization of the paralyzed vocal fold can be done either with absorbable material if a symptomatic paralysis is deemed to be temporary, or permanent medialization in the case of a permanent paralysis (e.g., sacrificed nerve or an unrecovered paralysis after a period of observation).

## Hypoparathyroidism

Less well understood by patients is the risk of hypocalcemia following thyroidectomy. This is the most common complication of thyroidectomy and is limited to those patients undergoing bilateral dissection. The NCDB series placed the risk of hypoparathyroidism at 12% to 14% of total thyroidectomy and 3% of near-total thyroidectomy.[77]

In a large prospective German study, hypocalcemia after total thyroidectomy was transient in 24% and permanent in 9%. Similarly, the rates for primary treatment of thyroid cancer were 19% and 5%, respectively, and 26% and 9% for treatment of recurrent thyroid cancer.[302] Lower rates were seen in benign thyroid disease, perhaps related to the fact that malignant disease was more likely to be treated by total thyroidectomy. Using multivariate analysis, total thyroidectomy (vs. surgery where a thyroid remnant of >4 mL remained) was the greatest risk factor for both transient and permanent hypocalcemia. Other significant factors in transient hypocalcemia were bilateral ligation of the inferior thyroid artery near the carotid sheath, female gender, and thyroid surgery for Graves disease. Additional significant factors for permanent hypocalcemia were bilateral ligation of the inferior thyroid artery at the carotid sheath and the visualization of less than two parathyroid glands.[302] Table 28.6 shows several studies reporting the rates of hypocalcemia after total thyroidectomy.[303,245,321–323]

Given that hypocalcemia is the most common complication of thyroid surgery and that this complication often determines whether patients can be managed in a short-stay postoperative unit, much effort has been made to try to predict or to avoid symptomatic hypocalcemia in patients undergoing thyroidectomy. Routine serum parathyroid hormone measurement is not typically required, but some have shown that a parathyroid hormone level >10 pg/mL at 4 hours after surgery predicts with 98% accuracy that the serum calcium will remain >2 mmol/L (8 mg/dL).[324] More typically, patients are followed by serum or ionized calcium levels and for symptoms of hypocalcemia. Rising calcium levels demonstrate that the risk of hypocalcemia is essentially zero. Nahas reports a 13% incidence of symptomatic hypocalcemia when calcium levels are not rising but calcium is >8 mg/dL. In contrast, the rate rises to 75% when nonrising calcium levels are seen along with calcium levels <8 mg/dL.[325]

In an effort to avoid symptomatic hypocalcemia and reduce hospitalization, the routine use of calcium and vitamin D in the perioperative period has been proposed. Randomized comparisons of calcium (3 g/day) and vitamin D (1 $\mu$g/day) therapy for 2 weeks versus no supplementation show that symptomatic hypocalcemia is reduced from 24% to 7% and overall rates of hypocalcemia are reduced from 36% to 13%.[326] Similar favorable results have been shown by others.[327,328] However, the optimal dosing and length of calcium and vitamin D replacement is not clearly defined and a higher dose of calcitriol (1 $\mu$g b.i.d.) has been indicated by some.[327] Studies that have included postoperative parathyroid hormone measurements do not appear to justify the concern that routine calcium supplementation will reduce the recovery of parathyroid gland function.[328]

**TABLE 28.6 Transient and Permanent Hypocalcemia after Total Thyroidectomy**

| Author (Ref) | Year | *N* | Transient Hypocalcemia | Permanent Hypocalcemia |
|---|---|---|---|---|
| Tartaglia et al. (287) | 2003 | 1,636 | 2% | 0.9% |
| Pisunu et al. (293) | 2003 | 310 | 11.9% | 0.9% |
| Bellantone et al. (294) | 2002 | 526 | NA | 3.4% |
| Thomusch et al. (275) | 2003 | 88 | NA | 12.5% |
| Rosato et al. (295) | 2002 | 9,599 | 14% | 2% |

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## Completion Thyroidectomy

Reoperation in thyroid disease is associated with increased risks of complications. The risk will depend on whether the specific area that requires reoperation has been previously dissected. When lobectomy has been performed on one side, a completion thyroidectomy to remove the residual lobe is usually safe, although careful attention to parathyroid preservation is warranted due to concerns about the effects of the first surgery on parathyroid tissues.

Kupferman et al. describe a single-institution experience in which both the initial and compilation surgeries were done at the University of Pennsylvania. Completion thyroidectomies were associated with a 14% incidence of temporary hypoparathyroidism and no cases of permanent hypoparathyroidism. There were no recurrent laryngeal nerve injuries. One hematoma and one seroma were reported among the 36 cases described.[329] Similar favorable results for hypoparathyroidism and for permanent recurrent laryngeal nerve injury are reported by others,[330,331] although temporary recurrent laryngeal nerve injury rates of up to 4% are described.[331] Wu et al. showed a 4.4% incidence of overall complications in 204 patients undergoing completion thyroidectomy in 2,034 patients over a 10-year period. Transient, clinically symptomatic hypocalcemia was seen in 2% of the study population, whereas transient laboratory hypocalcemia was seen in 1.5%. No cases of vocal cord paralysis were reported, and there was no difference in the complication of patients before or after 4 hours of observation.[332]

## Neck Dissection

Complications following neck dissection for thyroid cancer vary depending on the extent of neck dissection. Medial compartment neck dissection places the patient at greatest risk of hypoparathyroidism whereas lateral neck dissection is more likely to be associated with temporary trapezius muscle weakness due to effects upon the spinal accessory nerve.

In an evaluation of complications after medial compartment neck dissection with or without lateral neck dissection for papillary cancer, Roh showed a significantly higher rate of hypocalcemia (31%) in these patients as compared with patients undergoing total thyroidectomy alone (10%). The rate of permanent hypoparathyroidism was 5% and 0%, respectively. Overall rates of complication were also higher in the neck dissection group (50% vs. 12%).[333]

Kupfermen et al. described a mixed group of thyroid cancer patients undergoing various neck dissections for thyroid cancer with or without simultaneous thyroidectomy. This series reported that complications were greatest when medial compartment dissection was included and demonstrated a 21% rate of temporary hypoparathyroidism, but no cases of permanent hypoparathyroidism. Of patients undergoing lateral neck dissection, 27% demonstrated postoperative shoulder weakness.[334]

# MANAGEMENT OF RECURRENCE

Thyroid cancer is one of the few malignancies in which recurrence may be noted simply from serologic results, elevated serum Tg levels in differentiated carcinoma, and serum calcitonin levels in medullary cancers. As an overall rate of recurrence, Mazaferri reports a 40-year recurrence rate of 35% for DTCs. Approximately two-thirds of recurrences occur in the first 2 years after treatment and approximately two-thirds of all recurrences are in the neck. For the most part, cervical recurrences are successfully managed as long as extensive soft tissue recurrence is not present. Distant metastatic disease is associated with a 30-year survival of 43%.[335]

In low-risk cancers, there is an association between the initial serum Tg levels at the time of remnant ablation and the risk of recurrence. Tg <2 ng/mL is associated with a recurrence rate in follow-up of <2%, whereas a level of 2 to 10 ng/mL is associated with an 8% rate of recurrence and a level >10 ng/mL with a 42% rate of recurrence.[336] Similarly, a single Tg measurement after rhTSH stimulation can predict recurrence rates with Tg levels of <0.5 ng/mL associated with a recurrence rate of 1.6%, Tg 0.6 to 2 ng/mL associated with a recurrence rate of 5.5%, and Tg levels >2 ng/mL associated with an 80% recurrence rate. This astounding rate of recurrence was derived from a small number of patients (16 of 20 patients in the last group recurred). However, the data were derived prospectively.[337]

The presentation of recurrent disease may occur in a number of ways. Clinical symptoms and signs of disease will depend on whether this is local, regional, or distant disease. Local or regional recurrence may present with a palpable mass or an abnormality on ultrasound. More aggressive disease may manifest vocal fold paralysis or tracheal or esophageal invasion with their attendant symptoms. Distant disease most often occurs in lung, bone, or central nervous system and may be discovered during routine imaging or due to symptoms.

In the past, the radioactive iodine scan was considered the single most effective tool in following up patients treated for DTCs. This has more recently been found to be less sensitive than rhTSH stimulated Tg levels. With most recurrences in the neck, imaging of the neck by ultrasound has gained a greater role in follow-up.

The discovery of an elevation in stimulated Tg will lead to further investigation in an effort to identify the site of recurrence. If there has been no recent neck ultrasonography, then this is a simple next step. If a radioactive iodine scan has not recently been done, then this will typically follow in an effort to identify a site of recurrent disease and potentially to treat that disease with further radioactive iodine treatment.

## Locoregional Recurrence

In many cases, it is difficult to tease out local recurrence from medial compartment nodal recurrence. The use of ultrasound may be able to distinguish the recurrence as nodal or thyroidal. Once a recurrence is imaged, if it is of any significant size and if surgery can be done, this will usually follow. This allows for both a resection of all known disease and allows for less volume of disease to be treated by subsequent radioactive iodine treatment.

Small-volume nodal disease may be nonpalpable and of insignificant size on ultrasonography, but still visualized on radioactive iodine diagnostic scans. In these circumstances, radioactive iodine has been used as the primary treatment with surgery held for salvage cases. Iodine uptake can be abolished in approximately two-thirds of cases in which nodal metastases <1 cm in diameter were treated by a single dose (100–150 mCi) of radioactive iodine.[338] When repeated doses of $^{131}$I are used for small-volume neck disease, surgical resection of residual nodal disease is needed in only 16% of cases.[339] Partial response is typically seen when nodes are >1 cm in diameter, so surgery is recommended in these cases.

The complexity of surgery in the neck for recurrence will depend in large part on the extent of previous surgery. Recurrence in the thyroid bed or in medial compartment lymph nodes will usually be managed by a medial compartment neck dissection. While bilateral medial compartment dissection is ideal, concerns about the risk of hypoparathyroidism and recurrent laryngeal nerve injury may cause the surgeon to limit dissection to one side of medial compartment neck only if oncologically possible. These surgical risks have been shown to be minimal in a series of >200 central neck dissections for recurrent disease recently

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reported by Clayman. This study includes a heterogeneous group of patients with a large proportion undergoing simultaneous lateral neck dissection and 2 of 3 receiving postoperative $^{131}$I. However, the series shows excellent disease control with undetectable Tg in 66% and central neck clinical control in 76% of patients. In fact, although some patient needed additional surgery for recurrent disease of the central neck, there was ultimately a 98% control rate.[340]

When disease recurs in the thyroid bed, there may be involvement of aerodigestive tract structures. These require a surgical approach similar to that described in the section describing primary surgery. However, more aggressive surgical techniques may need to be considered if there is evidence that the recurrent disease is not likely to take up radioactive iodine.

Lateral neck recurrence is much more straightforward because most patients will not have had a lateral neck dissection previously. In these cases, a neck dissection that includes levels II to V is recommended with sparing of the jugular vein, sternocleidomastoid muscle, and spinal accessory nerve. In addition, the cervical nerve roots can often be spared as well. Figure 28-15 shows a left lateral neck node confirmed to be metastatic cancer by FNA. In the recurrent setting, neck dissection is associated with clinical neck control in 95%.[341] Tg can become undetectable in these cases and two recent series employing central and/or lateral neck dissections and median follow up of at least 5 years have been reported. Clayman reports undetectable Tg in 66% and no evidence of clinical or biochemical disease in about half.[340] A group from Ohio State found that stimulated Tg was undetectable in 27% of their patients.[342]

The frequency of level II involvement in thyroid cancer merits some discussion. This has been shown to be associated with primary tumors of the upper thyroid pole, likely related to retrograde lymphatic drainage along the superior thyroid artery. The rate of level II metastasis has been shown to be 40% to 56% when there is lateral neck disease, thus arguing that all lateral neck dissections include level II. The need for inclusion of level IIb is controversial,[269,343,344] but is recommended if nodal disease at IIa is identified. Level Vb is involved in 20% to 40% of cases, but the incorporation of level Va is very rare and appears to be unnecessary.[341,343]

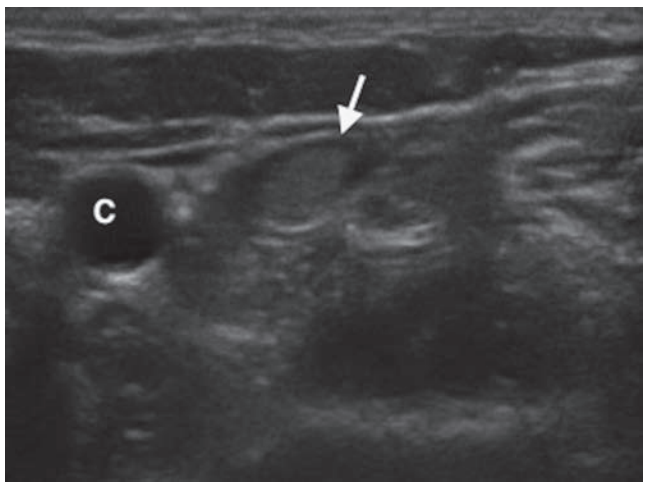



**FIGURE 28-15.** Ultrasound of the left lateral neck at level IV. Arrow indicates a lymph node showing loss of fatty hilum and heterogeneous density. Metastatic cancer was confirmed on FNA prior to neck dissection. C, Carotid artery.

The use of radioactive iodine in the treatment of locoregional recurrence will vary. All patients merit evaluation for further treatment. If a high-dose ablation has not previously been performed, an empiric dose may be given at this point in an effort to visualize (and treat) other foci of metastatic disease that may not be revealed on diagnostic scans. However, when after surgery there is no uptake in the surgical bed, the effectiveness of further radioactive iodine treatment is unknown. Oftentimes, patients will be treated empirically at that point, but the effectiveness of this treatment is debated.

One interesting approach to cervical nodal recurrence has been utilized at the Institute Gustave Roussy. This involves treating with 100-mCi radioactive iodine preoperatively and undergoing surgery 4 to 7 days later using a gamma probe intraoperatively to improve the detection of nodes that harbor metastatic disease. This is reported to have a 92% cure rate.[345] Follow-up radioactive iodine scans have demonstrated that most uptake after surgery was behind the sternoclavicular joint and this region probably merits close attention whenever surgery is performed for recurrent disease in the neck.[346]

The impact of locoregional recurrence upon survival is variable. Mazzaferri describes a mortality of 12% at 30 years whereas Rouxel et al. report a mortality of approximately 50% at 10 years.[335,347] In multivariate analysis, the following factors were associated with worse survival after locoregional recurrence: age older than 45 years at diagnosis of primary tumor, a follicular histology, extrathyroidal extension of the primary tumor, distant metastases before locoregional recurrence, absence of radioiodine ablation after initial surgery, recurrence in the thyroid bed, and the absence of radioiodine uptake of the recurrence.[347] Some of these factors would be associated with higher risk stratification at the time of initial treatment.

## Distant Recurrence

When distant metastatic disease is found, the site of disease will impact the management strategy. Brain metastases will often be managed with surgery due to the concern that radioactive iodine may cause edema and compromise neurologic function. External radiation therapy or focused radiation (e.g., GammaKnife, Cyberknife) may be used alone or following surgical resection. Bone metastases can be treated with radioactive iodine, but response is limited when the bone metastasis is large enough to be causing symptoms. Surgery may be required in weight-bearing bones. External beam radiation therapy may be used to control metastatic lesions in bone. Radiofrequency ablation and cryotherapy represent newer adjuvant techniques that have been used to address bone metastases. It is important to consider the entire clinical context in helping to decide whether a biopsy of a metastatic lesion is warranted to confirm the source of as thyroid cancer. In general, if a lesion (e.g., osseous) is the initial site of appearance (of the original tumor or the first metastases), then a biopsy may be indicated. However, if a new osseous lesion occurs in the setting of multiple of other sites of known metastatic thyroid cancer a biopsy may not be routinely required. Patients with osseous metastases should be considered for intravenous zolendronic acid therapy or subcutaneous Denosumab therapy. An international committee has recommended bisphosphonate therapy in patients with osseous metastases from solid tumors. The committee noted that there was more literature regarding the effectiveness of intravenous bisphosphonates regarding their ability to delay cancer-related skeletal events.[348] Preliminary studies suggest that in patients with thyroid cancer intravenous zolendronic acid may decrease osseous complications.[349] Possible complications of bisphosphonate therapy, especially when given intravenously, include hypocalcemia, an acute phase reaction, and in unusual circumstances osteonecrosis or atypical femoral

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fractures.[350] Recent studies have also indicated that Denosumab, an inhibitor of Receptor Activator of Nuclear Factor B Ligand (RANK Ligand), may also be effective in decreasing skeletal events in patients with osseous metastases.[351] Clinicians administering these agents should be familiar with their indications, contraindications, and possible adverse effects. The frequency and long-term duration of treatment of each of these treatments is controversial given the generally relatively prolonged survival of DTC patients and the potential adverse effects of these treatments to include jaw osteonecrosis and atypical hip fracture.

Overall, approximately one-third of cases with distant metastases will be controlled with radioactive iodine. This will typically involve $^{131}$I treatments every 6 months until uptake is abolished on posttreatment scans, although other centers will treat these patients only once or twice with radioactive iodine as many of these lesions do not trap or respond to radioactive well. The most success is seen when pulmonary metastases are visualized only on radioactive iodine scans. This will be controlled by radioactive iodine in 83%. Approximately half of the cases with pulmonary metastases <1 cm will be controlled whereas only 14% of patients with larger pulmonary metastases will be rendered disease free.[352] Survival after diagnosis of distant metastases in DTC is actually relatively favorable with one recent report describing overall survival of 88% and 77% at 5 and 10 years after the diagnosis of metastatic disease. There was no significant difference in survival between papillary and follicular cancers with distant metastases.[353]

## Radioactive Iodine As It Pertains to Distant Thyroid Carcinoma

When treating residual or recurrent distant thyroid carcinoma (DTC), there are often competing issues that impact the use of radioactive iodine. These include limits on cumulative radioactive iodine dose given to the patient previously and long-term risks of radioactive iodine exposure on the bone marrow. At the same time, disease that has persisted in spite of previous radioactive iodine can be suspected to be less iodine avid than untreated tumors. Decreased avidity of tumor tissue can theoretically be addressed by increasing the dose of radioactive iodine given. However, this effort to increase the total dose of iodine is associated with increased side effects of treatment, such as bone marrow suppression, xerostomia and epiphora, or increased tearing. These latter two complications can remarkably affect the quality of life and bone marrow suppression can have important clinical implications. There is also evidence that radioactive treatment is associated with a higher risk of certain malignancies, such as salivary gland tumors and leukemia.[354]

There are three ways to address metastatic disease with radioactive iodine. Empiric therapy is the most common method with historical experience used to guide dosing. Most metastatic disease would be treated with 150 to 200 mCi of $^{131}$I. However, this may underdose tumor tissue and a higher dose might be possible if one could measure the patient's potential for systemic complications. A more scientific approach uses quantitative tumor dosimetry in which the dose delivered to the tumor itself can be calculated and adjusted. The risk of systemic complications requires blood or whole-body dosimetry to determine the safe dose of iodine that can be given without exposing the bone marrow or lung tissue to excessive radioactivity. When large doses of radioactive iodine are given, there is a greater need for medical follow-up in the posttreatment period to evaluate for anemia and leucopenia.[335] Long-term follow-up studies assessing the benefit of dosimetry as compared with empiric dosing need to be performed, but at present the approach seems rational in patients with aggressive or metastatic disease. Empiric dose $^{131}$I therapy may exceed standard limits of radiation exposure to the patient or more commonly, may underestimate the appropriate dose.[355–357] A recent study compared empiric radioactive therapy versus a dosimetrically determined dose in patients with known metastatic thyroid cancer. Dosimetry was found to increase progression-free survival.[358]

## Management of Tg Positive, Scan Negative Patients

Often, patients in follow-up will be found to have an elevated serum Tg concentration without evidence of disease on whole-body radioactive iodine scanning (or physical examination). The management of these cases is a matter of debate. Even when diagnostic radioiodine scans are negative, a posttreatment scan can be positive and demonstrate the site of recurrent disease. This is especially true for microscopic pulmonary metastases. However, the yield of posttreatment diagnostic scans in this setting has been estimated to be as low as 5% to 6%.[359,360] On the other hand, others have found that 80% to 94% of diagnostic scan negative patients will show disease on a posttreatment scan.[335,361] This remains controversial with advocates on both sides. In a compilation of previously published studies, a rate of posttreatment scans being positive was placed at 62% and 63% of patients showed a drop in Tg following treatment. These writers advocate empiric dosing in these cases when the Tg is >10 ng/mL or in age, metastases, extent, and size high-risk cases.[362] This issue has become even more controversial with the use of cross-sectional imaging or PET scans, which can detect lesions that may or may not concentrate radioactive iodine.

## Recurrent Medullary Thyroid Cancer

Recurrent medullary cancer is a relatively common event, and most often this is manifest by an elevated serum calcitonin after completion of treatment. The serum half of human calcitonin is measured in minutes (estimates vary but the half-life is probably ~10 minutes). However, perhaps because of prolonged thyroid and extrathyroidal storage with slow release, because of thyroidal release at surgery, or possibly because some calcitonin assays may show interference with calcitonin precursors, serum calcitonin levels obtained within several days or even weeks after thyroidectomy may be elevated and falsely indicate residual disease. In most cases, at least 3 months should be given before evaluating posttreatment calcitonin levels. Management of this finding will include efforts to identify treatable residual or recurrent disease. In this effort, neck ultrasonography may be the single most useful test. Beyond this, multiple other imaging studies may be considered, including MRI of the neck, CT scans of the head, neck, chest abdomen, and pelvis, FDG-PET scans, and MDP bone scans. In selected circumstance, a brain MRI may be useful. However, the sensitivity of any particular test is limited and the yield of these investigations in asymptomatic patients is low.

PET sensitivity is 62% to 86% in patients with recurrent MTC. The higher sensitivities are shown for patients with calcitonin >1,000 pg/mL. The sensitivity is low with PET scanning when the calcitonin level is <500 pg/mL.[363,364]

One of the major problems in managing patients with residual or recurrent MTC is determining whether liver metastases are present. The rate of hepatic metastases in this population is approximately 25% and CT and MRI imaging studies are not sufficiently sensitive in the detection of these metastases. Laparoscopy and hepatic angiography have shown greater sensitivity for detection of these metastases.[365,366] A hepatic MRI may also be useful.

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When recurrent disease is discovered or suspected in the neck, then surgery may be considered. Reoperation in the neck has been evaluated and advocated by Tissell and others.[367] In a series by Moley from Washington University, 45 of 115 patients with recurrent MTC were treated with curative intent by medial compartment and lateral neck dissections as well as mediastinal dissections. Thirty-eight percent showed normalization of stimulated calcitonin.[368] The selection of patients is probably one of the most important determinants of success. Others have not shown such favorable results. The experience reported in a similar-sized group of patients at UCSF describes that only 4% showed normalization of even basal calcitonin.[369]

In addition to selection, the clinical presentation of these patients can determine the success of reoperation. Patients with normal imaging studies will obtain normal serum calcitonin levels in 29% whereas those with evidence of nodal disease on imaging studies show normalization in only 6%.[370] Similarly, in the primary treatment of MTC, the finding of disease in the neck contralateral to the tumor and/or disease in the mediastinum is correlated with the likelihood of calcitonin normalization and with the rate of distant metastases. When one of these compartments is involved, the rate of calcitonin normalization is 10%, but when two are involved the rate is zero. The rate of distant disease is 61% when both compartments are involved.[371]

Beyond surgery for cure of recurrent MTC, palliative surgery may be required in some cases of incurable disease. In a group of 16 patients treated for symptomatic recurrent disease with palliative procedures ranging from neck mass excision to liver resection, symptomatic improvement was demonstrated in all patients. The median time to recurrence of these symptoms was over 8 years, indicating significant palliation in the face of incurable disease.[372] In the face of recurrent medullary cancer, it is important to realize and to help patients understand that the survival is favorable with 5- and 10-year survival rates of 90% and 86%.[296]

When recurrent medullary cancer is not resectable, and if radiotherapy has not previously been given, this may be considered. The response rate to radiotherapy is difficult to quantify and verify. However, in retrospective series, an improvement in locoregional control has been suggested.[373]

Chemotherapy may be used for distant metastatic medullary cancer, however, with low response rates. The slow-growing nature of this tumor is reflected in a 10-year survival of 20% even with distant disease. Typical chemotherapeutic regimens may include cisplatin and doxorubicin. A recent report describes a prolonged, objective response without toxicity using capecitabine.[374] In a series of 20 patients given alternating cycles of doxorubicin-streptozocin and 5-fluourouacil (5FU)-dacarbazine, only 3 showed a response, although 10 had stability of their disease.[375]

Some medullary cancers will express CEA and efforts to target this with antibodies to CEA have shown some responses when used with doxorubicin.[376] More notable is a French trial that demonstrated improved survival in patients undergoing therapy with a bispecific monoclonal antibody able to attach $^{131}$I to anti-CEA targeted cells. With this trial, the median survival was 61 months in untreated patients and 110 months in patients given the radioimmunotherapy.[377] Recently, targeted specific therapy (i.e., multikinase inhibitors) has been used[378] and one agent, Vandetanib, has recently been approved for use for aggressive medullary thyroid cancer by the FDA (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm250168.htm). However, multikinase inhibitors have potential adverse effects to include fatigue, leukopenia, nausea, hand-foot syndrome, hypertension, proteinuria, interaction with other concurrently administered medications (e.g., P450 inhibitors), and prolongation of the QT interval.[378] Prolongation of the QT interval seems particularly applicable to this agent and specific training is required for the health care personnel desirous of utilizing this agent. (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm250168.htm). Close monitoring of these patients is required.

## SPECIAL ISSUES AND FUTURE DIRECTIONS

### Pregnancy

Thyroid nodules and thyroid cancer that occur during pregnancy deserve special consideration. With regard to thyroid nodules, thyroid sonography and FNA should be performed when appropriate in a pregnant patient with a thyroid nodule. If the FNA is benign, and there are no worrisome clinical parameters or a large suspicious thyroid nodule (>2–3 cm), then these patients usually can be monitored during pregnancy. If the nodule is growing and the clinician is concerned or if the FNA is diagnostic of papillary cancer, then a thyroidectomy can be performed, preferably during the second trimester of pregnancy. More controversial is the circumstance in which the FNA is suspicious but not diagnostic for papillary thyroid cancer or if the FNA shows follicular neoplasm. Individual considerations must be taken into account as to whether to recommend surgery and regarding its timing. As a general approach, the authors tend to recommend surgery during the second trimester if the FNA shows papillary thyroid cancer, and in most cases if the FNA is suspicious for papillary thyroid cancer or shows follicular neoplasm. The type of surgery may vary based on the clinical context and the experience of the surgeon, but the authors generally favor a lobectomy rather than a total thyroidectomy because of the possible risks of hypocalcemia and its treatment on the developing fetus. If further thyroid surgery is required it may be performed following delivery. There are no approaches to these issues that are evidence based and further studies are required. $^{131}$I must be avoided during pregnancy and during breast-feeding. Radioactive iodine in the breast may persist for several weeks or months following the discontinuation of breast-feeding. If a patient is taking exogenous levothyroxine for the treatment of hypothyroidism (surgically induced or due to primary hypothyroidism), it is recognized that the requirements for levothyroxine may increase during pregnancy, and close monitoring and dose modulation are required.

### Renal Failure

$^{131}$I is excreted mainly by the kidneys and its dose should be altered in patients with renal failure or more importantly in patients on chronic hemodialysis. The authors have reviewed this topic and concluded that it seems reasonable to perform dosimetry to estimate the retention of radioiodine and calculate a more rational $^{131}$I therapeutic dose. The $^{131}$I is also removed rapidly by hemodialysis and special radiation precautions need to be taken by dialysis personal. The physicians recommended giving tracer radioiodine doses and therapeutic doses immediately following hemodialysis. The radioiodine given would then be largely retained without removal (except for small nonsensible losses) until the next hemodialysis session in 1 to 2 days. Therefore, the radioactive exposure of the patient and the tumor are difficult to estimate empirically without dosimetry.[379]

### Targeted Chemotherapy

Major advances in the understanding of the development and progression of thyroid cancer have occurred mainly with recognition of relevant oncogenes. Specific agents have been developed to inhibit these oncogenes and some have already reached clinical trials. Tyrosine kinase inhibitors serve as the prototype for this type of therapy. Specific kinase inhibitors, such as sorafenib

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(an inhibitor of Raf kinase) or axitinib (an oral tyrosine kinase inhibitor which also inhibits vascular endothelial growth factor [VEGF] receptors 1, 2, and 3) are being utilized in trials of thyroid cancer.[380] Many different types of targeted therapy are being attempted and various clinical trials are available. A current listing is found on Clinicaltrials.gov.[381–384] As noted above, Vandetanib has been approved by the FDA for treatment of advanced medullary thyroid cancer (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm250168.htm).

### Future Directions

Further studies assessing the utility of molecular thyroid cancer markers will be helpful in the preoperative differentiation of benign from malignant thyroid nodules. In addition, identification and characterization of oncogenes and other biochemical factors that are important in the development and progression of thyroid cancer of all types will help in the development of specific targeted therapy. Clinical studies in the areas of dosimetric analysis of $^{131}$I, attempts to prevent the possible adverse effects of $^{131}$I, and the proper algorithm to monitor patients with thyroid cancer will also be important. Identification of which patients would benefit from additional doses of $^{131}$I and attempts to identify the avidity of residual thyroid cancer for $^{131}$I should also be performed.

## PARATHYROID CANCER

### Introduction

Parathyroid cancer is a rare event. Among cases of primary hyperparathyroidism, <1% will be attributable to parathyroid cancer.[385] These statistics are similar worldwide except for Japan where a significantly higher proportion of patients with hyperparathyroidism are found to have parathyroid cancer.[386]

Within the last several years, two cancer registry reports of parathyroid cancer have been published. The largest of these describes 286 patients with parathyroid cancer registered in the NCDB between 1985 and 1995.[387] The second of these is a report from the SEER database, which includes 224 cases presenting between SEER 1988 and 2003. This report demonstrates an increase in the incidence of parathyroid cancer over time. The incidence in the first 3 years of this series was 3.58 cases/100,000 whereas the incidence for the last 3 years was 5.73 cases/100,000. A significant upward trend was shown. The increase has been attributed to the increased in frequency of surgeries done for primary hyperparathyroidism because routine calcium screening has become more common, and surgical guidelines for primary hyperparathyroidism were liberalized after 2002.[388]

The etiology of parathyroid cancer is unknown. One risk factor is previous radiation therapy that is associated with later development of parathyroid cancer in five cases in the literature.[385] Approximately 2% of parathyroid cancer cases have been reported to have a family history of primary hyperparathyroidism. This relationship appears to be more common than the relationship between parathyroid cancer and MEN type I, although this too is reported to be associated with an increased risk of parathyroid cancer.[389]

Hyperparathyroidism-jaw tumor (HPT-JT) syndrome is a rare disorder consisting most often of hyperparathyroidism and ossifying fibromas of the maxilla and mandible, and less commonly renal cysts, hamartomas, or Wilms tumors. Although benign primary hyperparathyroidism is the most common finding in this syndrome, there is a 15% incidence of parathyroid cancer.[389]

Secondary and tertiary parathyroid hyperplasia is thought to be a risk factor as well with 18 cases reported in the literature.[390] Parathyroid cancer in these patients has occurred approximately 6 years after the start of hemodialysis. Unfortunately, these cases of parathyroid cancer in end-stage renal disease do not appear to differ significantly in clinical presentation from patients with benign secondary hyperparathyroidism, so preoperative suspicion is usually limited.[391]

Whereas benign hyperparathyroidism is more common in women by approximately 3 to 1, parathyroid cancer occurs with equal frequency in men and women. The disease also appears to present at a mean age that is 10 years younger than patients with benign hyperparathyroidism.[385]

### Relevant Anatomy

Anatomy in parathyroid disease is essentially that reported in the section on thyroid disease. Koea reports on a large review of the world literature that the left inferior gland is the site of presentation of parathyroid cancer in about half of all reported cases. However, any gland, including those in ectopic positions, may develop carcinoma.[385] This can result in the rare presentation of parathyroid cancer beyond the thyroid bed to the carotid sheath, retropharyngeal tissues, or mediastinum.[385,392]

## NATURAL HISTORY, PATHOLOGY, PATHOGENESIS, AND PATTERNS OF SPREAD

### Pathology

The intraoperative findings that raise suspicion for parathyroid cancer include a gray-white, firm, spherical tumor with a thick capsule adherent to adjacent structures. Most of these cancers weigh between 2 and 10 g. The appearance of these lesions differs from the red-brown, soft characteristic of parathyroid adenomas.[393] Unfortunately, the intraoperative findings are often not suspicious for carcinoma and frozen sections are not particularly reliable for this disease either. In fact, frozen section is contraindicated due to the concern for tumor seeding. In some cases, the diagnosis of cancer may be made only after a recurrence of parathyroid disease.[390] In Koea's review of 358 cases from the literature, approximately half were suspected to be cancer at the time of surgery. Local invasion is the typical feature indicating cancer. The structures invaded are the thyroid (89%), the strap muscles (71%), the recurrent laryngeal nerve (26%), the esophagus (18%), and the trachea (17%).[385]

The pathologic criteria for the diagnosis of parathyroid cancer were established by Schantz and Castlemen. These include the presence of a fibrous capsule, a trabecular or rosette architecture, mitotic figures, and vascular or capsular invasion.[394]

### Pathogenesis

Parathyroid cancers have been associated with alterations in the *CDC73* (also known as *HRPT2*) tumor suppressor gene on chromosome 1 in addition to the alteration of the tumor suppressor genes *RB1* and *BRCA2*. The *CDC73* has been found to exist in hyperparathyroidism-jaw tumor syndrome, with 10% to 15% of these patients developing parathyroid cancer.[395] *HRPT2* is a tumor suppressor gene encoding for the protein parafibromin. This gene has also found to be mutated in cases of apparently sporadic parathyroid carcinoma, so a role in the pathogenesis of some case of parathyroid cancer is suspected. The role of parafibromin in normal and malignant tissues is not yet known. It has been suggested that patients with parathyroid cancer undergo testing for HRPT2 mutations and that familial screening may be considered, if mutations are discovered.[389]

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Other genes thought to be significant in parathyroid cancer are the retinoblastoma (RB) gene, and the *BRCA2* gene, both on chromosome 13.[389] The role of the RB protein in parathyroid cancers may be further implicated by the frequency of PRAD1/cyclin D1 overexpression in 91% of parathyroid cancers. The cyclin D1 protein has been shown to inactivate the *RB* gene product.[396]

### Patterns of Spread

A small number of patients will be found to have nodal metastases or distant metastases at presentation, both estimated at 3% by Koea. When left untreated, patients typically succumb to their disease in approximately 14 months.[385]

The typical difficulty in managing parathyroid cancer is in obtaining local control. Koea shows that *en bloc* resection should be favored over parathyroid gland excision. This is in part due to the fact that the mortality after local recurrence is 90%.[385]

## CLINICAL PRESENTATION

The hallmark of parathyroid cancer is a markedly elevated serum calcium level. Most cases of primary hyperparathyroidism are discovered when routine screening shows mildly elevated serum calcium, and patients are often asymptomatic. In contrast, patients with parathyroid cancer will present with serum calcium in the range of 14 mg/dL or more and severe symptoms of hypercalcemia including nephrolithiasis, nephrocalcinosis and impaired renal function in 80% of patients and severe bone involvement in 90%.[397] This high level of calcium leads to symptoms of fatigue, weakness, nausea, anorexia, polydipsia, and polyuria.

Less than 5% of patients with parathyroid cancer will be asymptomatic. Also in contrast to benign hyperparathyroidism, the frequency of a palpable neck mass, renal disease, or bone disease are each estimated to be >35% to 40%.[385] Recurrent laryngeal nerve paralysis is also relatively common. Parathyroid hormone levels are higher in carcinoma than in hyperparathyroidism. Alkaline phosphatase levels are also elevated.[391]

Approximately 2% of all reported cases have been nonfunctional parathyroid cancers. Because these do not cause hypercalcemia, they tend to present later in their course, and this probably explains the worse survival seen in this subgroup.[385]

Because intraoperative suspicion usually is the most critical point in proper diagnosis and treatment of parathyroid cancer, familiarity with the intraoperative appearance of parathyroid cancer is essential. These cancers are firm to rock hard as compared with the typical softer consistency of parathyroid adenomas.[391] As stated previously, these are often gray-white, firm, spherical tumors with a thick capsule adherent to adjacent structures.

When cancer is recognized, the surgeon should proceed to a bilateral neck exploration with examination of all four parathyroid glands to exclude the presence of parathyroid hyperplasia. *En bloc* resection should include the ipsilateral thyroid and adjacent strap muscles. Formal lymphadenectomy is rarely indicated as lymph node involvement is present in <5%.[389]

## DIAGNOSTIC EVALUATION AND CLINICAL STAGING

There is no agreed-upon staging system for parathyroid cancer. This is due in part to the rarity of parathyroid cancer. Another reason why staging is typically not done is that tumor size and lymph node status do not correlate with survival. For these reasons and due to the fact that many cases are not diagnosed preoperatively or even intraoperatively, there is no specific staging workup.[388]

When there is preoperative suspicion, ultrasonographic scanning may be helpful in assessing parathyroid anatomy preoperatively. In addition to demonstrating larger benign parathyroid tissues, ultrasound can identify features that may be indicative of malignancy, such as lymphadenopathy or erosion into adjacent structures. Imaging using sestamibi scanning may demonstrate metastatic disease.[393] Data suggest that 4-D CT scanning may play an increasing role in the localization for benign parathyroid disease and potentially have a role in parathyroid carcinoma.[398] There is no utility in preoperative FNA due to the difficulty in establishing a histologic diagnosis. Another reason to avoid FNA is that this may weaken the parathyroid capsule and make capsule rupture more likely. This raises a risk of seeding into the soft tissues of the neck.

## MANAGEMENT STRATEGIES AND TREATMENT PLANNING GUIDELINES

The ability to predict parathyroid cancer based on preoperative findings is lacking. In a large Swiss series in which nine parathyroid cancers were discovered among 311 patients with primary hyperparathyroidism, the factors associated with parathyroid cancer were high serum calcium, high parathyroid hormone level, and gland weight, but the positive predictive value of any one of these indicators is <20%. This series does seem to support the negative predictive value of parathyroid hormone level less than four times the normal and gland weight <1.9 g. When these two factors are present, the likelihood of parathyroid cancer was zero.[399]

Surgery is the primary treatment modality for parathyroid cancer and suspicion of disease appears to be a major driver in assuring optimal care for these patients. The recommended treatment for parathyroid cancer is *en bloc* resection of the parathyroid gland, the ipsilateral thyroid lobe and strap muscles as well as recurrent laryngeal nerve, trachea, or esophagus if involved.[385] A bilateral exploration is recommended in order to evaluate for parathyroid hyperplasia.[389] Prophylactic lymphadenectomy is not recommended due to the low rate of nodal disease, estimated to be 6% in the SEER data.[388]

If disease is suspected, then *en bloc* surgery should proceed as noted earlier based on clinical appearance. A frozen section or partial resection to obtain a histological diagnosis only risks tumor seeding and is contraindicated.[393] Unfortunately, distinguishing parathyroid cancer from an atypical parathyroid adenoma is difficult at surgery. An atypical parathyroid adenoma may have fibrous bands, trabecular growth pattern, mitoses, and nuclear atypia, but has essentially no chance for recurrence after parathyroidectomy. Parathyroid cancer, on the other hand, has a chance of recurrence >50% even with *en bloc* resection according to one recent report.[400]

During the immediate postoperative period, there is a significant risk of hypocalcemia due to hungry bone syndrome from the hyperparathyroid bone disease, and serum calcium levels should be followed closely. When hungry bone syndrome with hypocalcemia does occur, the treatment with calcium and vitamin D usually needs to be vigorous.[393]

Some patients are found to have carcinoma only on final pathology after parathyroid gland excision. In these circumstances, a prompt return to the operating room for *en bloc* resection is controversial. Those in favor report that this will allow a complete resection of at-risk tissues before postsurgical inflammation affects the surgical bed.[385] Others feel that cancers not apparent at initial surgery do not require reoperation and can be followed clinically. Those with gross residual disease should be operated upon, whereas those with no demonstrable disease can be followed up.[389]

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Radiotherapy for bulky disease has not shown effectiveness, although has been reported anecdotally to be effective in controlling microscopic disease in the adjuvant setting. Chemotherapy has been used for unresectable or recurrent disease with dacarbazine appearing to be the single most effective agent.[385]

When metastatic disease can be resected, it probably should be because this is associated with a 5-year survival approaching 25% as compared with no survival in the patients treated nonsurgically. This undoubtedly is a reflection of selection bias as well as extent of metastatic disease.[385]

## OUTCOMES AND RESULTS

In the literature reviewed by Koea, approximately 40% of patients were treated by *en bloc* resection and the remainder by parathyroid gland excision. The difference in outcomes is notable. When treated by parathyroid gland excision, local recurrence occurred in 51% of patients and the mortality in this group was 90%. The cause of death was equally divided between uncontrolled neck disease and distant metastatic disease. When *en bloc* resection was used, the recurrence rate was only 8%. The mortality in those few patients in this group who recurred locally was still 88%, and another 4% of patients died of distant disease. However, at 15 years, Kaplan-Meier survival is estimated at 70% for those undergoing *en bloc* resection and only 20% in those undergoing parathyroid excision. The key appears to be intraoperative suspicion because only those cases suspected to be cancer were subjected to *en bloc* resection.[385] By multivariate analysis, the treatment by simple parathyroid excision, the presence of metastatic lymph nodes, distant metastases, and nonfunctional cancers were all independent predictors of worse survival.[385]

This experience described in the previous literature is quite different from the recent SEER database experience. In that, most patients underwent simple parathyroidectomy (78.6%) with *en bloc* resection in a small minority of cases (12.8%). With this, the 10-year cause-specific survival is excellent at 87.6%. Multivariate analysis revealed that older age, male gender, and distant metastases at diagnosis were associated significantly with a worse overall survival rate. In addition to these factors, cases diagnosed in the early part of the series did worse. This could indicate that the earlier cases presented with more advanced disease, but there was no evidence that earlier cases presented with tumors of greater size.[388] Other data also appear to indicate a high rate of local recurrence in spite of *en bloc* resection. Rates as high as 69% have been reported.[401,402]

## COMPLICATIONS

Surgical complications are similar to the thyroid cancer portion of this chapter. As noted earlier, patients should be followed up for hungry bone syndrome after surgery. Most deaths in this disease are related to the complications of uncontrolled hypercalcemia, and this will be further reviewed in subsequent text.

## MANAGEMENT OF RECURRENCE

Following treatment, serum calcium levels are followed as a tumor marker. If these become elevated, then a search for tumor recurrence is indicated. Recurrence is most commonly a local problem. When tumor recurs at a distant site, the lungs are most commonly involved. Other distant sites are liver and bone.[393] Imaging of recurrent disease may utilize sestamibi scanning. One recent report was able to use an intraoperative gamma probe to successfully resect a tumor recurrence providing long-term palliation,[403] and PET scanning may have a role in the diagnosis of metastatic disease.[404]

When local recurrence or metastatic disease is identified, patients should be evaluated for surgical resection. This is indicated for four reasons: (a) these tumors are relatively slow growing, (b) these tumors rarely cause mortality due to the physical effects of the local or metastatic disease, (c) the tumors are not particularly responsive to radiotherapy or chemotherapy, and (d) the mortality of this cancer is most often related to the effects of severe hypercalcemia.[393] Prolonged survival rates of up to 70% have been shown despite disease recurrence.[389]

When resection is no longer feasible, then the treatment should be directed at lowering the serum calcium.[390] This may involve treatment with bisphosphonates to control both hypercalcemia and bone disease.[390]

Acute hypercalcemia is managed in the standard manner and includes IV hydration, loop diuretics, calcitonin, bisphosphonates, and even calcimimetic agents. The latter (e.g., Cinacalcet) act on calcium receptors on parathyroid cells and increases the sensitivity of these receptors to circulating calcium. This leads to a decrease in parathyroid hormone secretion.[389] Cinacalcet has been shown to be effective in the management of inoperable parathyroid carcinoma and intractable hypercalcemia.[405]

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# PART B:
# Radiologic Imaging Concerns

Jeffrey A. Bennett

Thyroid nodules are detected frequently on physical examination and are found even more commonly on imaging studies of the neck, including computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound, performed for reasons other than evaluation of the thyroid gland. There remains controversy over how to manage these nodules as their initial workup and surveillance poses a considerable economic burden on society, and the vast majority of the lesions will never pose a threat to the patient's life. Ultrasound is the main imaging modality used to evaluate and triage lesions for biopsy and/or follow-up. Recommendations have been made concerning imaging features that suggest a nodule might be biopsied or followed, depending on the clinical scenario.[1–8] If a nodule is >75% cystic, it is probably benign. Nodules <1 cm in diameter are usually not biopsied. A dominant nodule that is >1 cm in diameter and is >25% solid is usually biopsied. Other ultrasound features that suggest malignancy are nodules with central rather than peripheral hypervascularity and nodules with irregular margins. Palpable nodules can be biopsied without image guidance. Ultrasound guided biopsies are performed when the nodule is not palpable (Fig. 28-16). Biopsy is almost always performed with fine-needle aspiration. A 25 or 27 gauge needle should be used as larger needles produce inferior samples with more blood.

New techniques in ultrasound are now being applied to the evaluation of thyroid nodules. Acoustic radiation force impulse imaging is being used to evaluate the elasticity of nodules. Two methods termed Virtual Touch tissue imaging and Virtual Touch tissue quantification (Siemens Medical Solutions, Mountain View, CA) have shown the elastic parameters of malignant nodules to be significantly higher than those of benign nodules.[9] It remains to be determined whether this type of imaging can reduce the need for fine-needle aspiration.

Nuclear medicine imaging studies with radioactive iodine rarely help in the workup of asymptomatic thyroid nodules. They can aid in the determination of which nodules should be biopsied

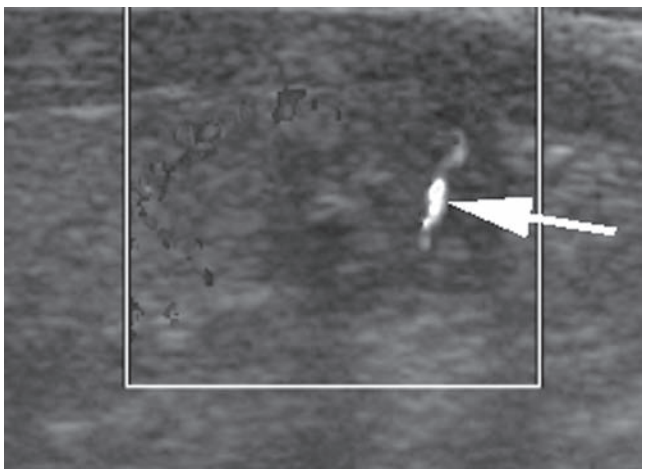


**FIGURE 28-16.** Ultrasound image of a thyroid nodule being biopsied with fine-needle aspiration. The needle is seen in the nodule as an echogenic line (*arrow*).

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in the patient with multiple nodules, as cold nodules are three times more likely than other nodules to be cancer. Radioactive iodine studies are used often for follow-up of papillary and follicular cancer, but not all cell lines are or remain iodine avid. Thallium-201 has been used as a general tumor marker for thyroid cancer. Octriotide nuclear scanning is useful for detecting and staging medullary thyroid cancer. FDG-PET is also used for evaluation of recurrent thyroid cancer, usually in the scenario where despite a rising thyroglobulin level, iodine-131 scan does not show activity. These iodine negative metastases are better detected with FDG-PET.[10] FDG-PET is also useful for more aggressive biologically active tumors such as medullary and anaplastic cancers and remains useful for the detection of distant metastases.

Once the diagnosis of thyroid cancer is established, CT or MRI can be used for staging. CT is limited as intravenous iodinated contrast hinders subsequent postoperative tumor ablation or scanning with radioactive iodine for several weeks. MRI is therefore the study of choice. Both modalities can assess extension of tumor outside of the thyroid capsule (Fig. 28-17). The amount of extraglandular extension is important for surgical planning. MRI is best for imaging invasion of the trachea and esophagus. Axial T2-weighted images are especially useful for demonstrating invasion of the esophageal wall (Fig. 28-18). CT may be better at demonstrating invasion of the laryngeal cartilages (Fig. 28-19). Both CT and MRI can document encasement of the carotid artery (Fig. 28-20) or invasion of the jugular vein (Fig. 28-21), as well as involvement of the recurrent laryngeal nerve resulting in hoarseness.

Regional lymph node assessment can be made with CT or MRI, with positive nodes most commonly seen in the low neck. Positive neck nodes are often calcified. In general, if calcified low neck lymph nodes are encountered on CT scan, thyroid cancer should be considered, even if a lesion is not seen within the thyroid gland. Imaging is critical for lymph node staging as level VI, mediastinal, and retropharyngeal lymph nodes cannot be palpated. The presence of positive retropharyngeal lymph nodes is not uncommon (Fig. 28-22).

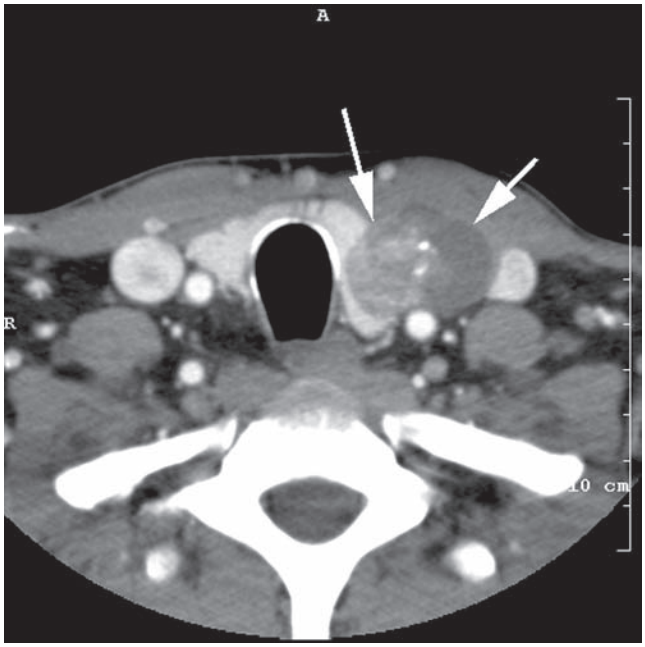



**FIGURE 28-17.** Axial contrast-enhanced CT scan shows a papillary thyroid cancer containing a solid enhancing portion, calcifications, and a more lateral cystic portion. The tumor (*arrows*) has clearly invaded through the thyroid capsule into the surrounding soft tissue.

Posttreatment surveillance imaging for local recurrence can be performed with CT or MRI, but MRI is preferred because it is superior for differentiating tumor from scar. Most follow-up imaging is performed with iodine-131 scans, thallium-201 scans, or

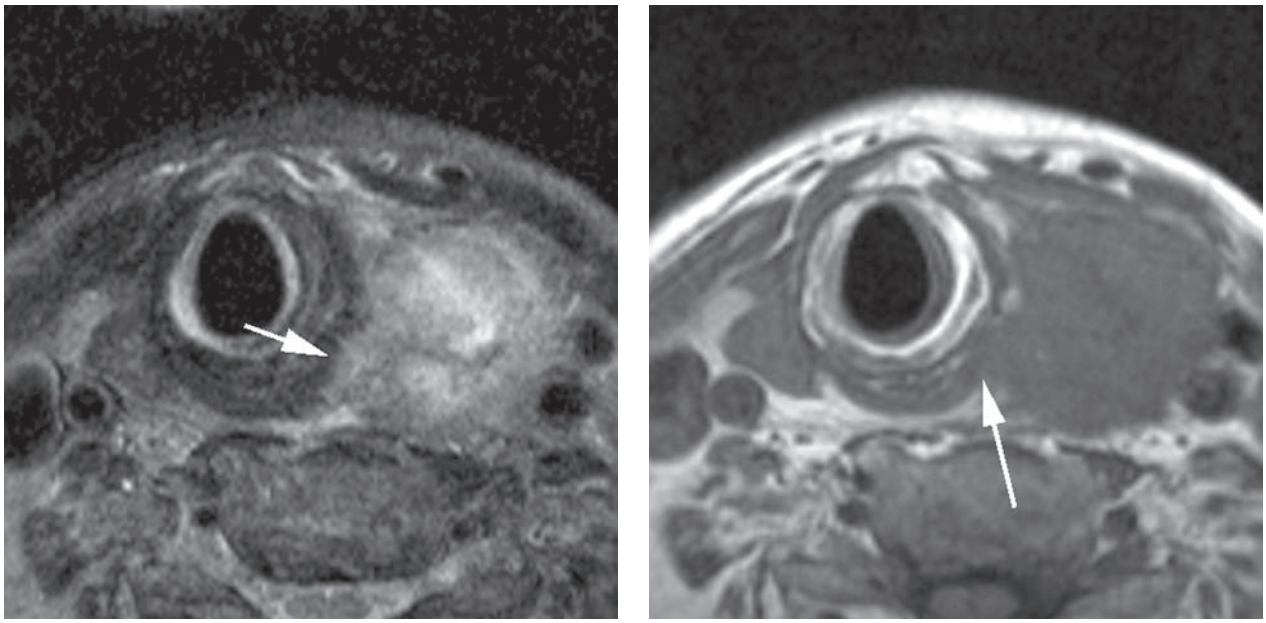
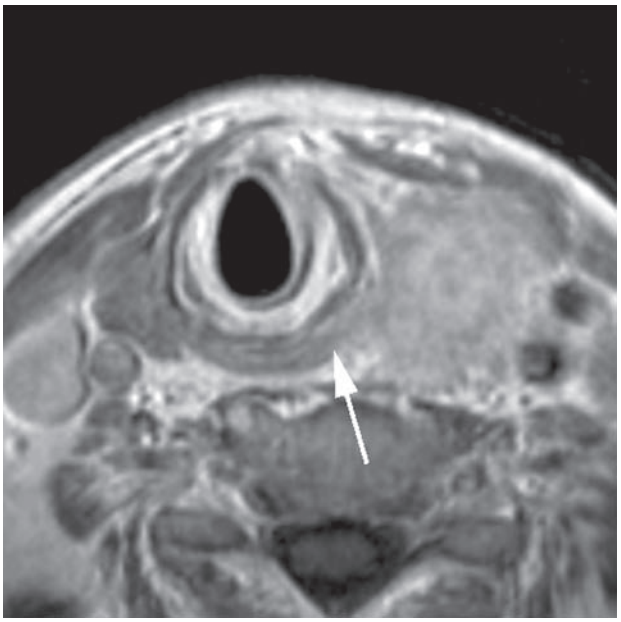



**FIGURE 28-18.** Axial T2-weighted MRI **(A)**, axial noncontrast T1-weighted MRI **(B)**, and axial postcontrast T1-weighted MRI **(C)** of a medullary thyroid cancer of the left lobe that has extended outside of the capsule and demonstrates early invasion of the esophageal verge (*arrows*).

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**FIGURE 28-18.** *Continued*



C

FDG-PET scans. Indium-111 octreotide scans are used to follow-up medullary thyroid cancer.

Parathyroid cancer (Fig. 28-23) is often suspected preoperatively by very high calcium or parathyroid hormone levels, a palpable neck mass, or relatively large or aggressive appearing lesions seen on ultrasound, CT, or MRI, usually in the region of the posterior thyroid. These lesions must be carefully staged with attention to tumor encroaching on the recurrent laryngeal nerve and tracheoesophageal margin.

Radiologists are frequently asked to localize abnormal parathyroid glands in patients with hyperparathyroidism. The recommended first test to locate a parathyroid adenoma is a Tc-99m Sestamibi nuclear medicine scan,[11] although ultrasound in experienced hands is a good alternative. Recent studies have investigated the use of dynamic contrast-enhanced CT scanning[12,13] utilizing the characteristic of early contrast enhancement of parathyroid adenomas for their identification. These studies are typically performed with a power injector

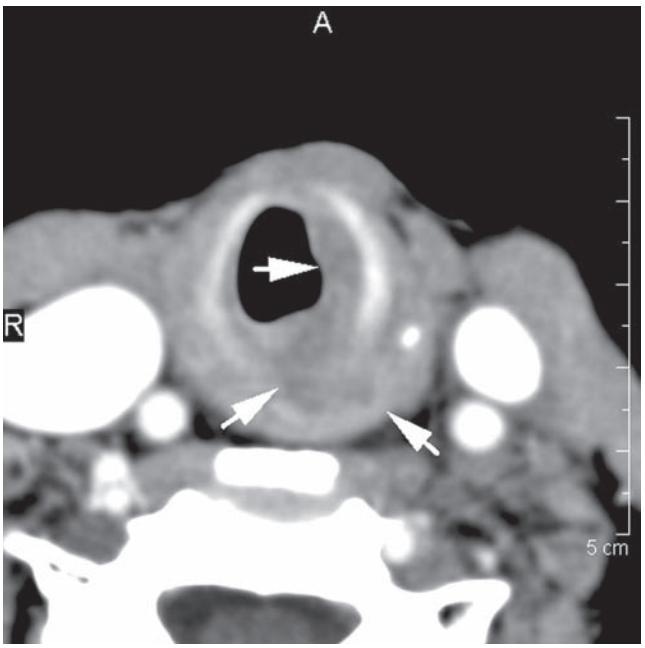



**FIGURE 28-19.** Axial postcontrast CT scan shows a recurrent medullary carcinoma of the thyroid, which has invaded through the cricoid cartilage into the subglottic larynx (*arrows*).

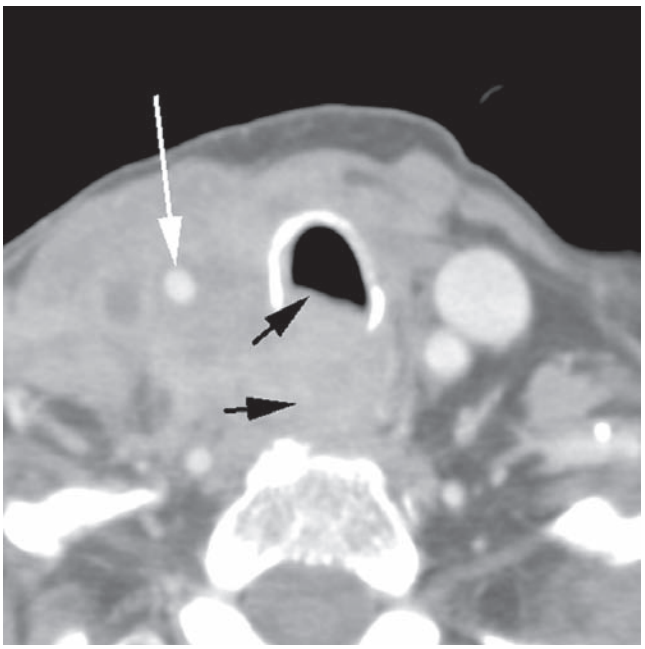
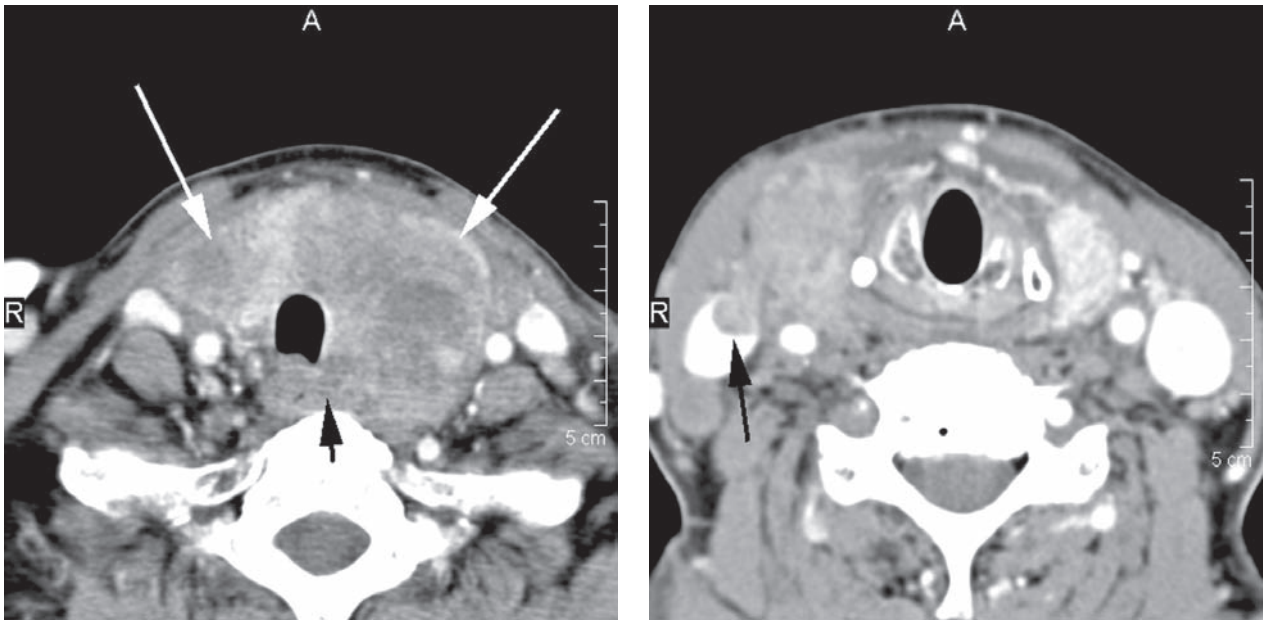


**FIGURE 28-20.** Axial postcontrast CT scan of a very aggressive thyroid cancer that has completely encased the right carotid artery (*white arrow*). The right jugular vein is occluded. The tumor has invaded the trachea and the esophagus (*black arrows*).

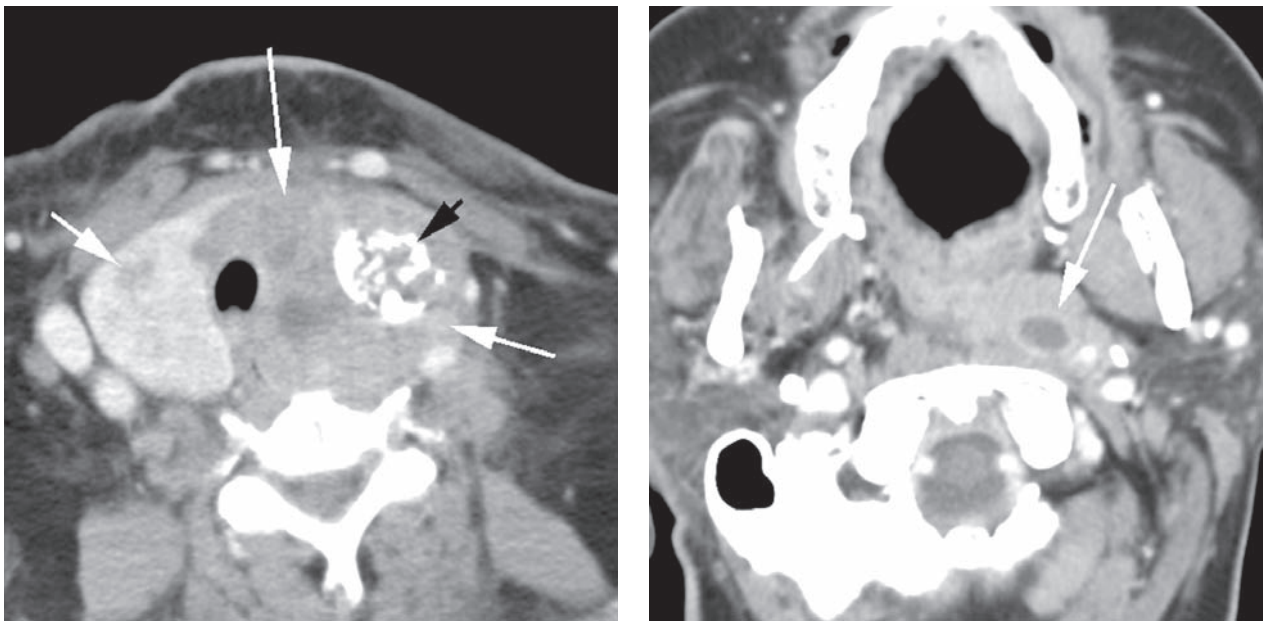
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A B

**FIGURE 28-21.** Axial contrast-enhanced CT scan of an anaplastic thyroid carcinoma. **A:** Tumor is seen to replace almost the entire thyroid gland (*white arrows*). The border between tumor and the esophagus is blurred (*black arrow*). MRI would be more definitive in showing invasion of the esophagus. **B:** There is direct extension of tumor into the jugular vein (*arrow*) and tumor abuts the carotid artery on the right.

to inject contrast at 3 mL/s, and scans are obtained at 30, 60, and 90 seconds following the initiation of the IV contrast injection. The sensitivity and specificity of CT localization has been reported at 82% and 92%, respectively.[13] A recent study investigated the effectiveness of C-11 methionine PET/CT for parathyroid adenomas.[14] This study reported a sensitivity of 83% for single gland adenomas and 67% for multiglandular disease. However, this technique is more expensive and less available than the alternatives. Suggested protocols are given in Figures 28-24 to 28-27.



A B

**FIGURE 28-22.** Axial contrast-enhanced CT scan of an anaplastic thyroid carcinoma. **A:** Heterogeneously enhancing tumor is seen in both lobes of the thyroid (*white arrows*) and dystrophic calcification is present in the left lobe (*black arrow*). **B:** A positive left lateral retropharyngeal node is present (*arrow*).

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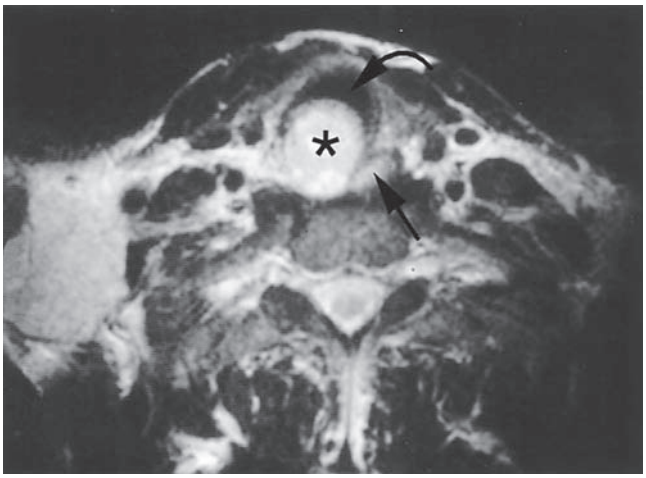
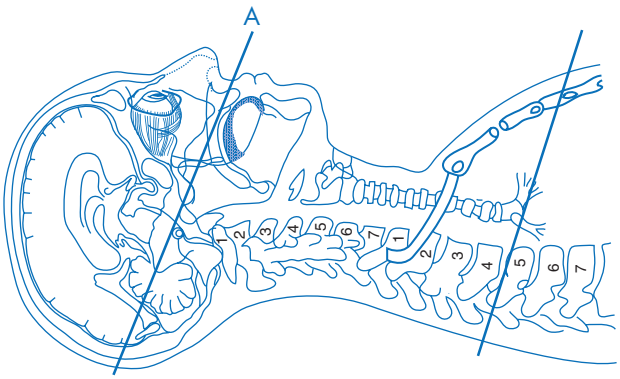


**FIGURE 28-23.** Parathyroid carcinoma. Axial T2-weighted magnetic resonance imaging shows a large submucosal lesion bulging from the tracheoesophageal groove into the tracheal lumen (*asterisk*), compromising the airway (*curved arrow*), and invading the esophagus (*arrow*).

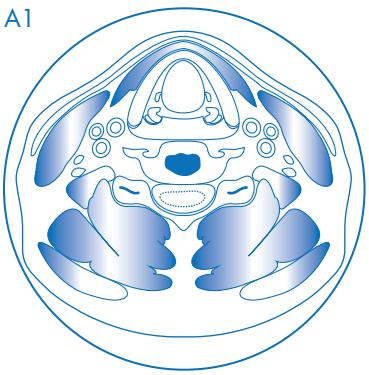
ACQUISITION




| | | |
|---|---|---|
| | Patient position | Supine<br>Chin slightly extended |
| | Contrast | 100 mL adult |
| | Injection rate | 1 mL/sec, 60 sec delay |
| | Respiration | Quiet, NO Swallowing |
| | Volume acquisition Specs | Appropriate to achieve images as specified in following reconstruction tables.<br>Head FOV. |
| A | Begin | Hard palate |
| | End | Carina |

RECONSTRUCTION

A1



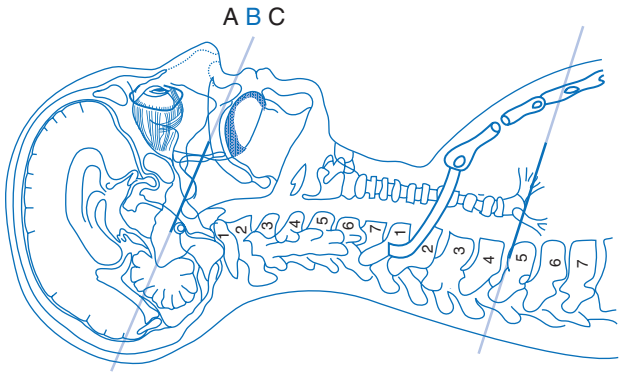
| | | |
|---|---|---|
| A1 | Algorithm | Soft |
| | Thickness | 2.5 mm |
| | Spacing | 2.5 mm |
| | F.O.V. | Approx. 160–190 |

**FIGURE 28-24.** Protocol for CT scan of the neck with intravenous contrast.

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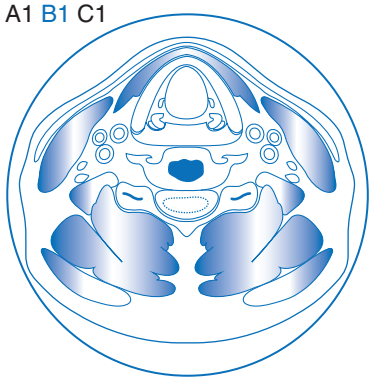
ACQUISITION




| | | |
|---|---|---|
| | Patient position | Supine<br>Chin slightly extended |
| | Contrast | 100 mL adult |
| | Injection rate | 3 mL/sec, visual trigger at hyoid |
| | Respiration | Quiet, NO Swallowing |
| | Volume acquisition Specs | Appropriate to achieve images as specified in following reconstruction tables.<br>Head FOV. |
| A | Begin | C-2, arterial visual trigger |
| | End | Carina |
| B | Begin | Scan begins 25 sec from visual trigger |
| | End | |
| C | Begin | Scan begins 50 sec from visual trigger |
| | End | |

RECONSTRUCTION

A1 B1 C1



| | | |
|---|---|---|
| A1 | Algorithm | Soft |
| | Thickness | 2.5 mm |
| | Spacing | 2.5 mm |
| | F.O.V. | Approx. 160–190 |

| | | |
|---|---|---|
| B1 | Algorithm | Soft |
| | Thickness | 2.5 mm |
| | Spacing | 2.5 mm |
| | F.O.V. | Approx. 160–190 |

| | | |
|---|---|---|
| C1 | Algorithm | Soft |
| | Thickness | 2.5 mm |
| | Spacing | 2.5 mm |
| | F.O.V. | Approx. 160–190 |

**FIGURE 28-25.** Protocol for three-phase CT scan of the neck for parathyroids with intravenous contrast.

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| Acquisition | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Plane | Sagittal | Axial | Axial | Axial | Coronal (angled) | Sagittal |
| Sequence | T1 | T1 | T2-FSE | T1 | T1 | T1 |
| Contrast | None | None | Gd | post-Gd | post-Gd | post-Gd |
| SLT/SP | 3/0 mm | 3/0 mm | 3/0 mm | 3/0 mm | 3/0 mm | 3/0 mm |
| FOV | 16 cm | 16 cm | 16 cm | 16 cm | 16 cm | 16 cm |

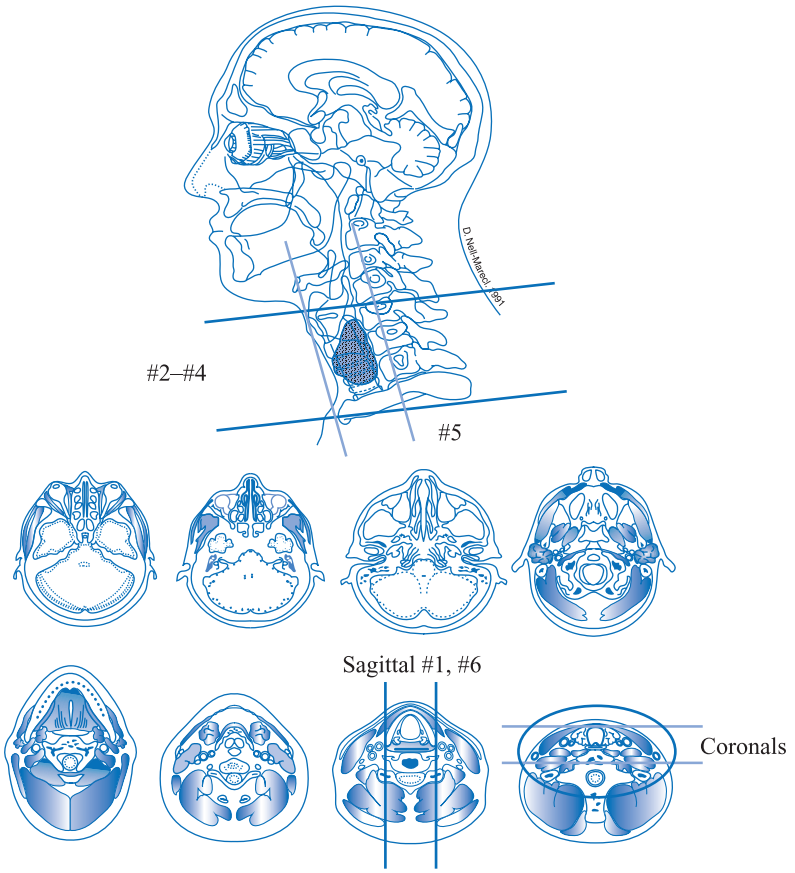



**FIGURE 28-26.** Protocol for MRI of the thyroid with intravenous contrast.

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| Acquisition | Localizer | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| Plane | 3-plane | Sagittal | Axial | Axial | Axial | Axial |
| Sequence | — | T1 | T1 | T2-FSE | T1 | T2-FSE |
| Contrast | — | None | None | None | None | None |
| SLT/SP | — | 4/0 mm | 4/0 mm | 4/0 mm | 8–10/0 mm | 8–10/0 mm |
| FOV | — | 16 cm | 16 cm | 16 cm | 25 cm | 25 cm |

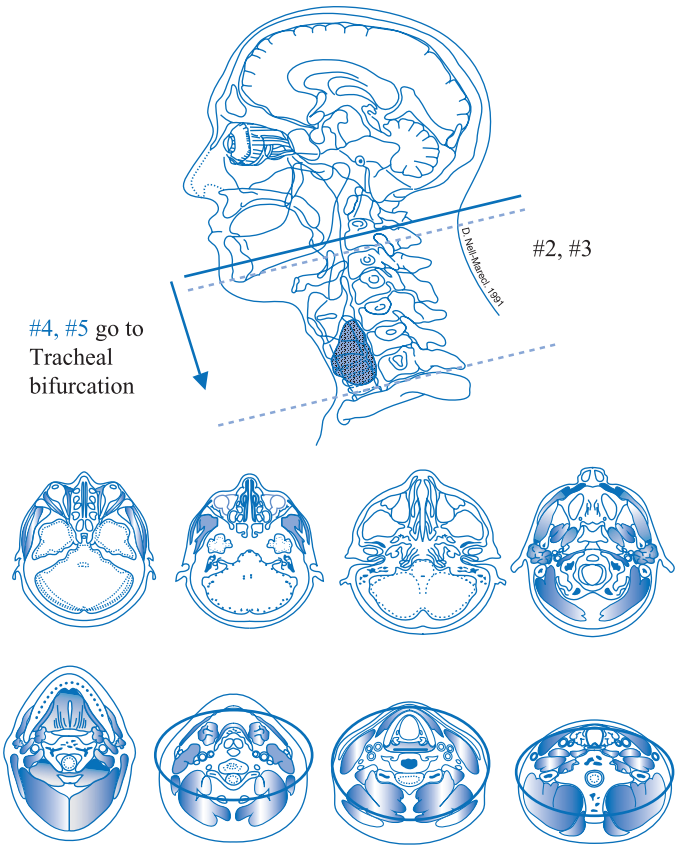



**FIGURE 28-27.** Protocol for MRI of the parathyroids with intravenous contrast.

*Source:* Reprinted from Mancuso AA, Hanafee WN. *Head and Neck Radiology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2011:2239, with permission.


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# PART C:
# Surgical Technique

James Kenneth Byrd, Samuel L. Oyer, and Eric J. Lentsch

Historically, little change has occurred in thyroid surgery since Theodore Kocher developed the classic techniques of thyroid surgery described below. However, in the last few decades there has been a period of innovation with the advent of "minimally invasive" surgical techniques. Over this time, multiple minimally invasive techniques (including $CO_2$ insufflation, endoscopic without $CO_2$, and video assisted) have been described, and for each technique multiple approaches (including cervical, axillary, postauricular, sublingual, and chest wall) have been followed. Of the many procedures, two techniques have become popular and well-studied—minimally invasive video-assisted thyroidectomy (MIVAT) and transaxillary endoscopic thyroidectomy, with or without robotic assistance.

MIVAT was developed for thyroid nodules, but soon the technique was expanded for use in early thyroid cancer and even central compartment dissections.[1] Multiple groups have reported on the safety and efficacy of the procedure for thyroid nodules,[1,2,3] and the data continue to be compelling for its use in early differentiated thyroid cancer.[4,5] However, the studies on the use of MIVAT for cancer have very short follow-up, and more time is necessary to fully evaluate its efficacy in the cancer setting.

Transaxillary endoscopic thyroidectomy, with or without robotic assistance, is the latest progression in the evolution of thyroid surgery and has taken the "minimally invasive" concept to its extreme by providing for "scarless" thyroid surgery. The best studied example of this is transaxillary endoscopic/robotic thyroidectomy. This technique can be done with standard endoscopic instruments or with the use of the daVinci robot; it has become popular in the past decade in Korea and Japan because it completely avoids a neck incision. When compared with open thyroidectomy, preliminary experiences have shown a comparable rate of complications and surgical completeness with superior cosmesis.[6] However, few studies are available to document the efficacy of this technique for thyroid cancer,[7] and as with MIVAT, they are limited in terms of follow-up.

Therefore, at this time "classical" open thyroid surgery, as described by Kocher, remains the "gold standard" for thyroid cancer. Thyroid lobectomy (or hemi-thyroidectomy) may be an option for early cancers, as has been well demonstrated in the literature. However, at this time most thyroid cancers are treated with total thyroidectomy. Recent evidence has shown that MIVAT appears to provide as complete a removal of diseased tissue as open techniques,[4] however, the follow-up data on patients undergoing this procedure are not mature, and definitive recommendations for its use are difficult to make with certainty. In our opinion, it is a reasonable technique for early-stage differentiated cancers, but the surgeon should be willing to convert to an open technique if complete tumor removal is in any way compromised. Transaxillary endoscopic/robotic thyroidectomy has not been well studied in cancer patients and no recommendations for its use can be made. The following technique descriptions represent the distillation of these techniques and represent the current mainstays in our surgical armamentarium of thyroid surgery.

## CLASSIC THYROIDECTOMY

The classic procedure for thyroidectomy has changed little since Kocher's time. Paramount to the surgery is identification of critical structures in the neck, including the superior and recurrent laryngeal nerves, common carotid artery, superior and inferior thyroid arteries, middle thyroid vein, and parathyroid glands.

The classic thyroidectomy begins with the patient under general anesthesia, positioned supine, with a shoulder roll in place. A horizontal skin incision, preferably placed in a skin crease, is made between the cricoid cartilage and sternal notch. Dissection is taken to the strap muscles, which are separated in the midline to expose the gland (Fig. 28-28A).

The middle thyroid vein is usually encountered first and ligated to provide better exposure (see Fig. 28-28B and C). Next the gland is dissected superiorly, remaining on the thyroid capsule, and the superior thyroid vessels are identified. When taking

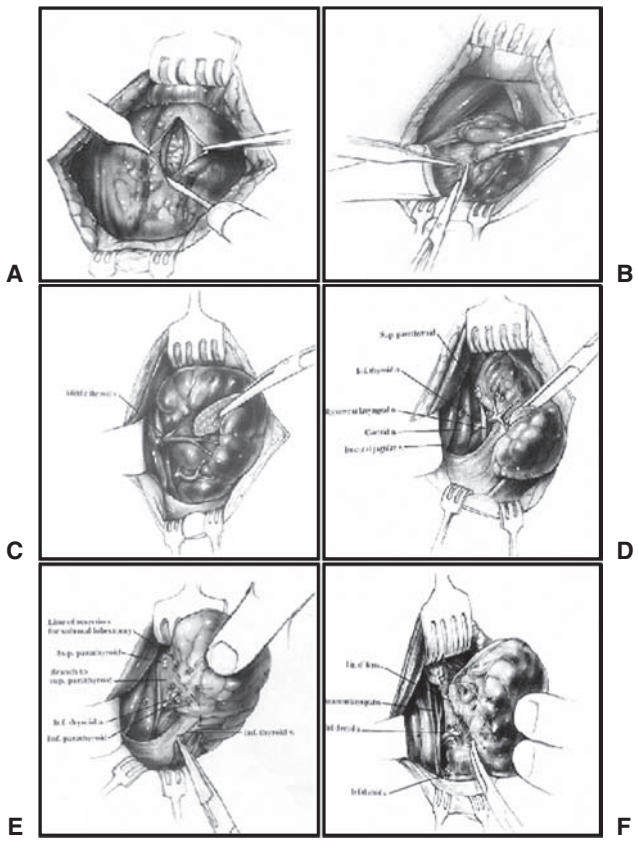



**FIGURE 28-28.** Classical thyroidectomy. **A:** Exposure via the midline raphe; **B:** Initial dissection; **C:** Middle thyroid vein ligation; **D:** Superior pedicle dissection; **E:** Inferior pedicle dissection; **F:** Dissection off of trachea.

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down the superior pedicle, individual branches of the artery should be divided on the gland with the superior laryngeal nerve visualized, as the nerve may cross the superior pole of the gland (see Fig. 28-28D). As the gland is dissected inferiorly, a careful observation should reveal the parathyroid glands and the recurrent laryngeal nerve. The inferior thyroid artery is a relatively reliable landmark for the recurrent laryngeal nerve, which crosses deep to the artery in most, but not all, cases. At this point, the inferior thyroid vessels are identified and ligated (see Fig. 28-28E). As the gland is further rotated medially, the gland is dissected free from the recurrent laryngeal nerve. By tracing the nerve to its point of entry into the larynx, the gland can be dissected off Berry ligament, and subsequently off the trachea (see Fig. 28-28F). The pyramidal lobe, if present, is removed at this time. If a lobectomy is to be performed, the isthmus is divided and the procedure ended. If a total thyroidectomy is to be performed, the identical procedure is performed on the opposite side. The wound is closed in multiple layers, with or without a drain.

## LARGE GOITER AND SUBSTERNAL GOITER

Large goiter can be a cause of concern for both the anesthesiologist and the surgeon. Goiter size and bilateral goiter appear to be predictors of difficult intubation[8]; therefore, careful preoperative planning with the anesthesiologist may be required in these cases.

In cases of substernal goiter, standard techniques and gentle upward traction on the gland is usually all that is needed to "deliver" the gland into the neck. Identification and tracing the RLN inferiorly is often necessary to free the gland from surrounding tissues and safely pull the substernal portion superiorly. The need for sternotomy or thoracotomy in substernal goiter is rare. A recent review of the literature, found that extracervical approach was required only 2% of the time.[9] To date, there are no clear-cut indications for sternotomy, and much of the time it is dependent on the surgeon's experience, skill, and comfort level.

## MINIMALLY INVASIVE TECHNIQUES

### Video-assisted Thyroidectomy

In this technique, the room is set up as shown in Figure 28-29. The surgeon may stand on either side of the neck based on preference, with one to two assistants standing on the opposite side. The patient is positioned as for a classical thyroidectomy, except the neck is only slightly extended without the use of a shoulder roll. A 15-to-25-mm horizontal cervical incision is placed in the midline conforming to a preexisting skin crease if possible (Fig. 28-30A). The incision is made and carried down through the skin, dermis, and subcutaneous tissues. Notably, the platysma muscle is typically not encountered because the location and short length of the incision results in a dissection plane between the medial heads of this muscle. The midline raphe is exposed and opened and the thyroid gland is identified (see Fig. 28-30B). The thyroid gland is then mobilized away from the strap muscles, and the middle thyroid vein branches are ligated with the ultrasonic shears. At this point, retractors are placed laterally around the strap muscles, and medially around the thyroid gland itself, to retract the gland up and over the trachea.

At this point, the endoscope is brought into the field. Usually a 5-mm 30-degree laparoscopic telescope is placed just inside the wound, and both the surgeon and the assistant work off the appropriately positioned monitors. The dissection is then carried out, as described above, for a classical thyroidectomy (see Fig. 28-30C–D) until the gland is mobilized and freed from all surrounding structures. The main difference in this portion of the operation is the use of special endoscopic instruments, and the ultrasonic shears are used throughout.

Once the gland has been mobilized, the final removal of the gland is achieved using an open approach. The thyroid isthmus is divided at this point, or alternately it can be done as a last step before retrieving the specimen. The thyroid gland is delivered through the wound and remains attached primarily by the ligament of Berry. At this point, the recurrent laryngeal nerve is traced to its entry in the region of the cricothyroid joint (see Fig. 28-30E). The connective tissue attachments between the gland and the trachea are divided and the specimen is removed (see Fig. 28-30F). If a total thyroidectomy is to be performed, the contralateral gland is removed in similar fashion.

### Transaxillary Endoscopic/Robotic Thyroidectomy

The differences in technique for robotic thyroidectomy are many and are beyond the scope of this chapter. However, of note, the surgeon sits at the robotic control console across the room, with an assistant next to the surgical field to use the suction and apply clips if necessary. Patient positioning is different since the approach is from the axilla and over the chest wall. In addition, the surgeon must get used to approaching the gland from

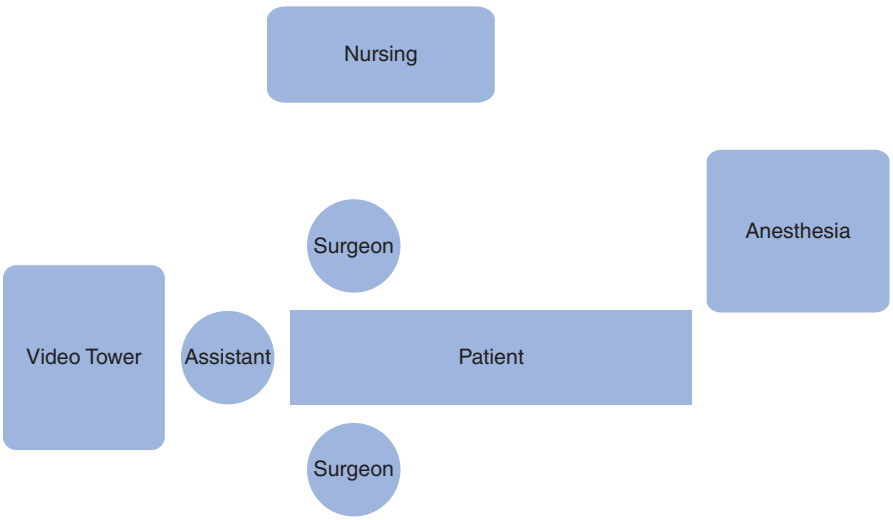



**FIGURE 28-29.** Positioning for minimally invasive thyroidectomy.

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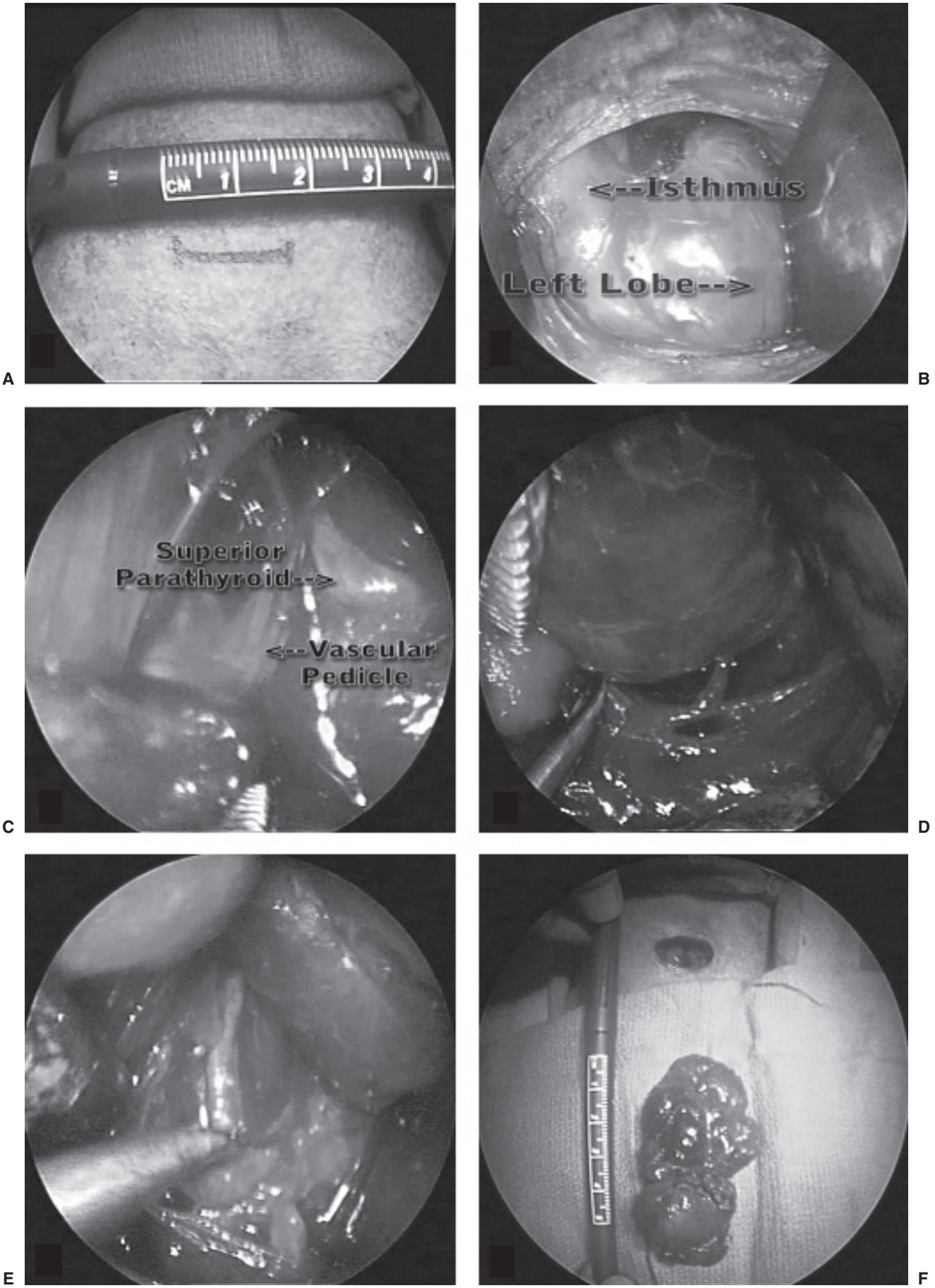



**FIGURE 28-30.** Minimally invasive thyroidectomy (MIVAT). **A:** Incision; **B:** Exposure via the midline raphe; **C:** Superior pedicle dissection; **D:** Inferior pedicle dissection; **E:** Recurrent laryngeal nerve dissection; **F:** Removed specimen. (See color insert.)

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lateral to the strap muscles, rather than from the midline of the neck. As noted above, the procedure can be done with standard endoscopic instruments or the daVinci Surgical System.

## Surgery for Locally Invasive Disease

Extension of cancer beyond the thyroid gland is associated with a poorer prognosis, higher rates of recurrence, and distant metastases and necessitates extension of surgical resection beyond total thyroidectomy. When extrathyroidal extension occurs, the strap muscles are most commonly involved (53%), followed by the RLN (47%), trachea (37%), esophagus (21%), and larynx (12%).[10] Local invasion is the norm for anaplastic carcinoma, and the role of surgery in this disease is generally limited to confirming a diagnosis with biopsy or establishing a secure airway; therefore, the focus of this section will be on management of local invasion of differentiated and medullary carcinoma. Surgery remains the primary treatment modality for local invasion of these tumors with the goal of complete tumor removal with negative margins. Resection of many of these structures, however, is associated with significant morbidity, and there has been much debate regarding the appropriate extent of resection, particularly for patients with airway invasion.

***Strap Muscle Invasion.*** Local invasion of the strap muscles is the most commonly encountered pattern of invasion, and the surgical management is the most straightforward. The involved muscle including a cuff of normal muscle should be resected along with the primary tumor when possible. There is relatively little morbidity associated with strap muscle resection.

***Recurrent Laryngeal Nerve Invasion.*** Invasion of the RLN is often suspected preoperatively when a patient describes hoarseness or has an immobile vocal cord on exam. The most likely locations of RLN invasion include the entry point into the larynx at the cricothyroid joint and along the course of the inferior thyroid artery,[11] but any portion of the nerve can be involved. In general, RLN preservation should be the goal for any nerve that is functional preoperatively, as long as all grossly visible tumor can be removed. Even when tumor is found to encase or compress the RLN, if a plane of dissection can be established between the tumor and the epineurium, the nerve can be preserved without negatively impacting survival.[12] This is done by identifying the nerve both proximal and distal to the site of involvement and painstakingly dissecting parallel to the course of the nerve until the tumor is freed. RLN function can be affected by either compression or direct neural invasion. In patients with abnormal preoperative vocal cord movement without frank tumor invasion of the RLN, the nerve can be safely preserved with some patients demonstrating return of RLN function once the compression is relieved.[13]

Alternatively, if there is a known vocal cord paralysis with tumor clearly invading the nerve at the time of surgery, there is no benefit to attempting nerve preservation, and the involved segment should be resected. When resection is necessary, it is important to know the functional status of the contralateral RLN, and if the tumor is extensive, it may be wise to explore both nerves before sacrifice to determine if one RLN can be spared to prevent the patient the morbidity of bilateral vocal cord paralysis and tracheostomy-dependent airway. If RLN sacrifice is necessary, the nerve should be resected *en bloc* with the rest of the specimen, including proximal and distal margins to determine the completeness of resection. It is possible to perform vocal rehabilitation procedures at the time of nerve sacrifice, and authors have reported improved outcomes with simultaneous type I thyroplasty and arytenoid adduction procedures compared with delayed intervention.[14] Alternatively, others advocate for concomitant neurorrhaphy at the time of RLN sacrifice. Generally, there is not sufficient length of the remaining nerve to accomplish a tension-free primary neurorrhaphy, but return of neural function measured by voice analysis, laryngoscopy, and EMG has been demonstrated following RLN repair with nerve grafting in conjunction with nimodipine therapy.[15] Nerve grafting is accomplished first by harvesting an appropriate donor nerve (e.g., great auricular, sural, etc.) of adequate length to bridge the resulting defect without tension. Next, under loupe or microscopic magnification, neurroraphy is carried out on both ends of nerve graft with three to four interrupted 9-0 or 10-0 permanent sutures placed in the epineurium.

***Pharyngoesophageal Invasion.*** Fortunately, the mucosa of the pharynx and esophagus represents a relatively resistant barrier to cancer spread, and true intraluminal invasion is rare. When pharyngoesophageal involvement is evident, the invaded muscle should be resected along with the primary tumor. Often it is possible to separate the tumor from the pharyngeal submucosa without violation of the mucosa, and in such cases, no further repair is required. Small mucosal tears that occur during dissection should be repaired primarily. When mucosal invasion is present, the involved mucosa and surrounding muscular layers require resection, and repair should be carried out in a layered fashion with reinforcement from a vascularized muscular flap like a portion of the sternocleidomastoid. Larger defects that cannot be closed primarily may require reconstruction with larger regional flaps or free tissue transfer in a manner similar to management of pharyngeal defects created for squamous cell carcinoma of the pharynx.

***Laryngotracheal Invasion.*** Much debate surrounds the appropriate extent of resection for tumors that invade the airway, and this is largely related to varying definitions of tumor invasion and surgical technique. McCaffrey has developed a useful staging system for extent of thyroid cancer invasion where stage I disease represents an intrathyroidal tumor, stage II describes a tumor that invades the perichondrium without cartilage invasion, stage III represents a tumor that has invaded into cartilage without submucosal extension, stage IV is for submucosal involvement, and stage V describes transmucosal spread.[16] Stage I disease is treated with total thyroidectomy alone, whereas stages II and III require partial thickness resection of the involved airway segment, and stages IV and V necessitate complete through-and-through resection of the airway.

Partial thickness airway resection is commonly known as a "shave resection" in which all grossly visible tumor is removed without violating the luminal mucosal surface. Studies have demonstrated that both shave excisions and complete resection offer superior survival to incomplete resection, and the removal of all grossly apparent tumor is paramount.[17] For these cases, a thyroidectomy is carried out as described with mobilization of the gland off the airway, wherever there is a clear plane of dissection. The site and extent of airway invasion is identified and the depth of invasion determined. Bronchoscopy may be necessary to evaluate for intraluminal or submucosal involvement, and in cases where circumferential resection is planned, rigid bronchoscopy is required to delineate the superior and inferior margins of extent. If superficial invasion only is present, the perichondrium may be gently freed off the underlying cartilage. When the tumor has invaded beyond the perichondrium, however, at least a partial thickness resection of the underlying cartilage is necessary. For stages II and III disease, the involved portion of cartilage can gently be dissected off the underlying submucosal layer leaving the airway mucosa and submucosa intact. A defect of one or more tracheal rings involving <30% the airway circumference with intact mucosa is known as "window resection," and reconstruction can involve primary repair if sufficient laxity exists, or

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reinforcement with a rotational flap such as a myoperiostial sternocleidomastoid flap.[18] An anterior window defect can occasionally be used for a tracheostomy with eventual decannulation and spontaneous healing.

The most common location for tracheal invasion is along small perforating tracheal vessels that pass between tracheal rings providing a direct route for tumor spread into the airway.[19] Airway invasion can also occur through the cricothyroid membrane, thyroid, or cricoid cartilage, or posterolateral to the thyroid cartilage into the paraglottic space and pyriform sinus. Stages IV and V lesions or those that involve >30% to 50% of the circumference of the trachea or cricoid cartilage require circumferential airway resection. This is carried out in the standard fashion limiting circumferential dissection only to the portion of the airway that will be resected to avoid devascularizing surrounding segments of airway. At least one RLN should be preserved if possible, and primary anastomosis is generally achievable following adequate mobilization of the remaining airway segments. The importance of negative margins cannot be overemphasized as tumor recurrence can lead to anastomotic breakdown. Generally, patients remain intubated for a few days following the procedure with the tube cuff distal to the anastomosis, or a temporary tracheostomy may be required.

Direct laryngeal invasion through the thyroid cartilage or paraglottic space may require a partial laryngectomy, and a vertical hemilaryngectomy is generally sufficient. Rarely, a total laryngectomy may be needed for bilateral involvement with a dysfunctional larynx or extensive subglottic extension. This is most frequently encountered in recurrent disease or extension from metastatic paratracheal lymph nodes.

Symptoms such as hoarseness and hemoptysis are clues to advanced local invasion of thyroid cancer, and ideally the extent of tumor invasion is identified preoperatively so both the surgeon and patient can prepare for the appropriate aggressiveness of resection and related operative morbidities. Occasionally, local tumor invasion is only identified intraoperatively at which point the surgeon must be prepared to perform the necessary resection or abort the procedure. Adjuvant therapy such as radioactive iodine or external beam radiation may play a role in control of microscopic disease, but should not be expected to treat grossly residual tumor. Therefore, the surgeon undertaking an operation on advanced thyroid cancer should be knowledgeable and trained in various surgical techniques required to adequately resect and reconstruct invasion of the surrounding structures to provide optimal patient outcomes.

## Neck Dissection

Lymphatic metastases are common in thyroid cancer, particularly among the papillary and medullary subtypes. Although nodal spread has been shown to decrease survival in medullary carcinoma, the impact in papillary carcinoma is less clear cut, especially among younger patients. Therefore, indications for lymph node dissection in thyroid cancer are controversial with much debate in the literature. Current guidelines for differentiated thyroid cancer from the American Thyroid Association recommend therapeutic central-compartment lymph node dissection when clinically involved central or lateral neck nodes are present and consideration of a prophylactic central-compartment dissection for patients with advanced primary tumors.[20] However, a recent meta-analysis[21] including 16 studies and >3,500 patients found no difference in locoregional recurrence between patients treated with thyroidectomy plus central neck dissection versus thyroidectomy alone; this trend persisted even for the subgroup of patients who underwent a central neck dissection for therapeutic removal of positive nodes. A prophylactic central neck dissection is recommended for patients with medullary thyroid cancer, regardless of nodal involvement.[22]

The first echelon of lymphatic drainage for the thyroid gland is the central compartment or level VI. This consists of the lymphatic structures bounded by the carotid arteries laterally, the innominate artery inferiorly, and the hyoid bone superiorly. Generally, this accounts for 5 to 10 lymph nodes, including the prelaryngeal (Delphian) and pretracheal nodes, as well as paratracheal nodes bilaterally along the tracheoesophageal groove. When performing a thyroidectomy for cancer, the central compartment lymph nodes should be inspected intraoperatively, and a central neck dissection performed if the nodes appear involved. A unilateral central neck dissection consists of removing the prelaryngeal and pretracheal nodes along with the paratracheal nodes on the same side of the tumor, while a bilateral dissection involves removing all lymph nodes from the central compartment.

Dissection begins by skeletonizing the boundaries of the central compartment described above. If the nodes are matted with tumor and contiguous with the primary cancer, they should be removed along with the thyroid gland; otherwise, the neck dissection can be performed once the thyroid is removed to improve visualization. The pretracheal and prelaryngeal nodes with any intervening lymphatic vessels are dissected off the airway leaving the perichondrium intact, unless there is evidence of direct invasion. Next, the RLN is identified and isolated atraumatically throughout its course to allow for thorough dissection of the entire paratracheal gutter from the level of the cricoid cartilage to the plane of the innominate artery intersection with the trachea. Care should be taken to preserve the parathyroid glands along with their vascular supply by separating the feeding vessels as distally as possible and retracting the parathyroids laterally on their respective vascular pedicle. Often the inferior parathyroid glands are more difficult to dissect freely during a level VI dissection, and any glands that appear devascularized should be autotransplanted and marked with a clip to minimize potential hypocalcemia. Rates of hypocalcemia and RLN injury are higher following central neck dissection compared with standard thyroidectomy due to the more extensive dissection of the tracheoesophageal groove.

Occasionally, retropharyngeal nodes are a site of tumor metastasis or direction extension and require dissection. This is accomplished by following the visceral facial layer that invests the thyroid gland and airway posteriorly and reflecting the aerodigestive tract laterally. Dissection is continued bluntly around the posterior aspect of the pharynx until the retropharyngeal space is exposed between the buccopharyngeal fascia overlying the pharynx and the alar fascia. The involved lymph nodes are then removed. The prevertebral tissues should be inspected for involvement when retropharyngeal dissection is necessary, but fortunately prevertebral spread is rare in thyroid cancer.

Following spread to the central compartment, tumor metastases tend to reach the lateral neck in predictable patterns based on the course of the thyroid vasculature. Tumors of the superior lobe often metastasize to the upper jugular lymph nodes of levels II and III along the course of the superior thyroid artery. The inferior thyroid artery courses posterior to the carotid after it branches off the thyrocervical trunk and can be a route of spread to the inferior neck levels IV and V. Spread to level I is exceedingly rare, and level V involvement is uncommon in isolation, but skip metastases to the lateral neck can occur without obvious central neck involvement.[23] The type of neck dissection performed is dictated by the extent of disease as most are therapeutic dissections to eradicate clinically positive nodes. Generally, at least a selective dissection of all involved levels is preferred to a “berry plucking” procedure, but level I dissections are almost never required, and the jugular vein, sternocleidomastoid, and accessory nerve can usually be preserved. The dissection can be performed through an extension of the thryoidectomy incision using standard techniques described elsewhere in this

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text. If disease is present in the lower neck levels IV to Vb, it is important to evaluate for tumor located posterior to the carotid artery along the course of the inferior thyroid artery. Dissection in this area should proceed cautiously to avoid damage to the sympathetic chain, thoracic duct, and brachial plexus.

## Parathyroid Surgery

Unlike thyroid cancer, parathyroid cancer is often not suspected prior to definitive surgery. Therefore, surgery for parathyroid cancer is often done without preparation, when the diagnosis is made intraoperatively during a parathyroidectomy. A high level of suspicion, as well as good pathological analysis, is necessary to make the diagnosis. Intraoperatively, parathyroid cancers may be distinguished from adenomas by their firm, stony-hard consistency and lobulation. They also tend to be a grayish-white color and infiltrate adjacent tissues. Parathyroid adenomas, on the other hand, tend to be soft, round, or oval in shape, and of a reddish-brown color. Parathyroid cancers also tend to be larger, mostly >3 cm, whereas most benign adenomas are 1 to 2 cm in size. Histopathologically, capsular and vascular invasions appear to be the most significant markers of malignancy.[24]

Surgery is the only known curative therapy for parathyroid carcinoma. Due to the rarity of the disease, few data exist to guide our surgical decision making; however, it is clear that standard parathyroidectomy is not sufficient treatment for most parathyroid cancers, as local recurrences are approximately 50%.[25] Instead, definitive surgery involves *en bloc* resection of the tumor with all potential areas of invasion. This usually includes the strap muscles and the ipsilateral thyroid (sometimes total) and may involve resection of the recurrent laryngeal, thyroid cartilage, constrictor muscles, trachea, or esophagus. Cervical lymph node dissection should be reserved for those patients with enlarged or firm nodes, particularly those found in level VI and levels III and IV.

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CHAPTER 29

# Soft Tissue and Bone Sarcomas of the Head and Neck

## PART A:
## General Principles and Management

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### INTRODUCTION

Sarcomas are rare malignancies of mesodermal origin. The annual incidence is <10,000 per year in North America. Fifteen percent of cases occur in the head and neck region comprising <1% of all head and neck cancers. Not only are they rare, but also an excess of 40 histopathologic subtypes may affect numerous anatomic sites within the head and neck. Unique challenges present themselves in the head and neck demanding special expertise in nutritional support, dental and voice rehabilitation, ophthalmology, and social support.[1] The rarity and complex nature of these tumors warrant referral to specialized centers for multidisciplinary evaluation, including expert imaging and pathology assessment.[2] All such consultations and evaluations should take place prior to therapy. A recent report evaluated outcome in 4,205 operative cases of soft tissue sarcomas (STS) and showed that high volume centers (those in the upper one-third of case volume in a geographic region) had better survival outcomes in numerous sites, including the head and neck, which comprised 12% of the cases studied.[3] Smaller centers may have more difficulty formulating a multidisciplinary team with all necessary components of care, including access to an effective multidisciplinary cancer conference that meets frequently and regularly. This is especially so for head and neck sarcoma management where the case volume is low. It may be preferable to have linkage with the main sarcoma team at the center so that treatment protocols and pathology expertise are maintained as consistently as possible. We have found the latter approach to be essential in our practice even though both the overall sarcoma referral and the head and neck program are of substantial size.

The management of head and neck sarcoma follows principles extrapolated from other anatomic sites where the disease is more common.[4,5] Although primary data about the head and neck would be desirable, evidence that the biologic behavior differs by anatomic site is not apparent. What sets these lesions apart from tumors elsewhere are the unique functional and cosmetic imperatives of the treatment.[1] Thus, both surgery and radiotherapy must be applied more precisely and with greater complexity than elsewhere in the body because of the presence of critical anatomy. In particular, juxtaposed neurologic tissues (especially optic apparatus, spinal cord, and brain stem), nonexpendable vascular anatomy, organs necessary for speech and swallowing, and cosmetically sensitive tissues provide substantial challenges.

The chapter provides general information for both soft tissue tumors and their osseous counterparts relying on individual center experience, outcome reports from several registries, and reports of meta-analyses and clinical trials where these are available. Management focuses on the principles of curative approach initially for the more common STS, followed by bone tumors. The discussion of adjuvant systemic treatments will rely for the most part on published meta-analyses for soft tissue sarcoma and the meta-analysis (overviews) that have been undertaken in head and neck osteosarcoma. Special features in the head and neck including treatment or behavior of unique histologic subtypes are also acknowledged. The general problem of salvage for recurrence and the treatment of metastases (soft tissue and bone) will conclude the discussion.

### PATHOLOGY AND GRADING

Soft tissue and bone sarcoma may present in a nondescript manner related to the presence of a mass, since the full range of histologic subtypes seen in other body sites can present in the head and neck. However, there are also several rare clinical entities that are disproportionately represented in the head and neck but space limitations prevents a comprehensive discussion. A summary of some of the main issues to be considered in evaluating and classifying these lesions is presented. A brief description of particular clinical features different histologic subtypes is also presented later.



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## Classification of STS Subtypes

The most common classification scheme for soft tissue sarcoma is based on histogenesis, as outlined in the World Health Organization (WHO) classification (Table 29.1).[6] The classification is reproducible for the better differentiated tumors. However, as the degree of histologic differentiation declines, the determination of cellular origin becomes increasingly difficult. In the head and neck, as elsewhere in the body, the prototypical STS has been the malignant fibrous histiocytoma (MFH) but additional unique predispositions include nonpleomorphic rhabdomyosarcoma, angiosarcoma of the scalp and facial regions, hemangiopericytoma of the sinonasal region (Fig. 29-1), and dermatofibrosarcoma protuberans of the dermal regions of the low neck and supraclavicular regions. Recently, advances in molecular genetic pathology are influencing the classification, diagnosis, and treatment of soft tissue tumors of the head and neck.[7–9] Molecular biologic techniques are becoming the preferred means of understanding the pathogenesis and behavior of sarcomas, and the specific chromosomal aberrations found in certain types of sarcoma can be exploited for diagnosis. Already a number of cytogenetic findings and corresponding genetic abnormalities characterize a number of the histologic subtypes (Table 29.2). For example, in synovial sarcoma, the t(X;18) translocation can almost invariably be detected with the demonstration of a fusion between the *SSX* and *SYT* genes providing a very useful diagnostic tool that is also associated with the two morphologic forms of this disease (the *SSX1* associated with monophasic histology and the *SSX2* gene with biphasic histology) (Fig. 29-2). The specific molecular subtypes of the SYT-SSX fusion transcripts have also been associated with prognostic discrimination,[10] although this evidence has recently been overshadowed by observations that morphologically determined tumor grade may override this.[11]

Nonpleomorphic rhabdomyosarcoma, most often of alveolar histology, can be defined by the presence of PAX3 or PAX7 translocation, partnered with FOXO1, which is much more sensitive at defining the biologic behavior than histology alone.

Since the late 1970s, MFH has borne the mantle of most common STS of middle and late adulthood and is therefore mentioned specifically though it has no particular predilection for head and neck and there is now doubt about its status as a specific entity. Originally described in the 1960s, the term MFH was used to describe a group of sarcomas considered to have a mixed histiocytic and fibroblastic lineage. However, it is now regarded as a heterogeneous group of tumors without a specific line of differentiation. Reclassification of many tumors in this group seems to afford better prognostication and the old term "MFH" is generally considered obsolete today.[12] Current nomenclature recognizes the entities undifferentiated high-grade pleomorphic sarcoma (previously storiform-pleomorphic "MFH") and myxofibrosarcoma (formerly myxoid "MFH").

**TABLE 29.1 Principal Histologic Types of Soft Tissue Sarcoma in the World Health Organization (WHO) Classification of Bone Tumors with International Classification of Diseases for Oncology (ICD-O) Morphology Rubrics Listed in Alphabetic Order**

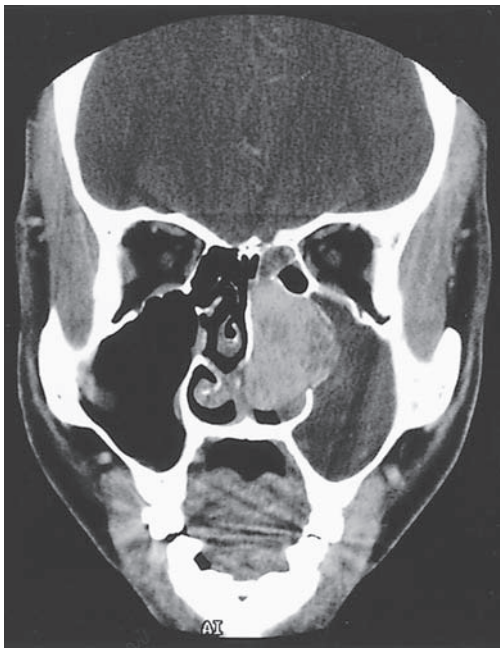
| Histologic Type | ICD-O Morphology |
|---|---|
| Alveolar soft part sarcoma | 9,581/3 |
| Angiosarcoma | 9,120/3 |
| Clear cell sarcoma | 9,044/3 |
| Dermatofibrosarcoma protuberans | 8,832/3 |
| Epithelioid sarcoma | 8,804/3 |
| Extraskeletal chondrosarcoma | 9,220/3 |
| Extraskeletal osteosarcoma | 9,180/3 |
| Fibrosarcoma | 8,810/3 |
| Leiomyosarcoma | 8,890/3 |
| Liposarcoma | 8,850/3 |
| Malignant fibrous histiocytoma | 8,830/3 |
| Malignant hemangiopericytoma | 9,150/3 |
| Malignant mesenchymoma | 8,990/3 |
| Malignant peripheral nerve sheath tumor | 9,540/3 |
| Malignant Schwannoma, melanotic | 9,560/3 |
| Rhabdomyosarcoma | 8,900/3 |
| Synovial sarcoma | 9,040/3 |
| Sarcoma NOS (not otherwise specified) | 8,800/3 |

*Source:* From Weiss SW, Sobin LH. *Histologic Typing of Soft Tissue Tumors.* 2nd ed. Berlin, Germany: Springer-Verlag; 1994, with permission.

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A




B



C

**FIGURE 29-1.** Hemangiopericytoma of the left nasal fossa in a 40-year-old. This patient underwent resection with positive margins for well circumscribed lesion in 1994 (**A** and **B**). Postoperative radiotherapy to a dose of 60 Gy achieved durable local control. After 8 years, he relapsed with two bone lesions one in the left chest wall and the second in the right pelvis without other lesions shown on nuclide bone scan **(C)**. Both lesions were successfully treated with combined radiotherapy and surgery but diffuse metastases resulted several years later. The original primary site also shows nucleotide uptake but cross-sectional anatomic imaging and clinical examination failed to reveal recurrent tumor.

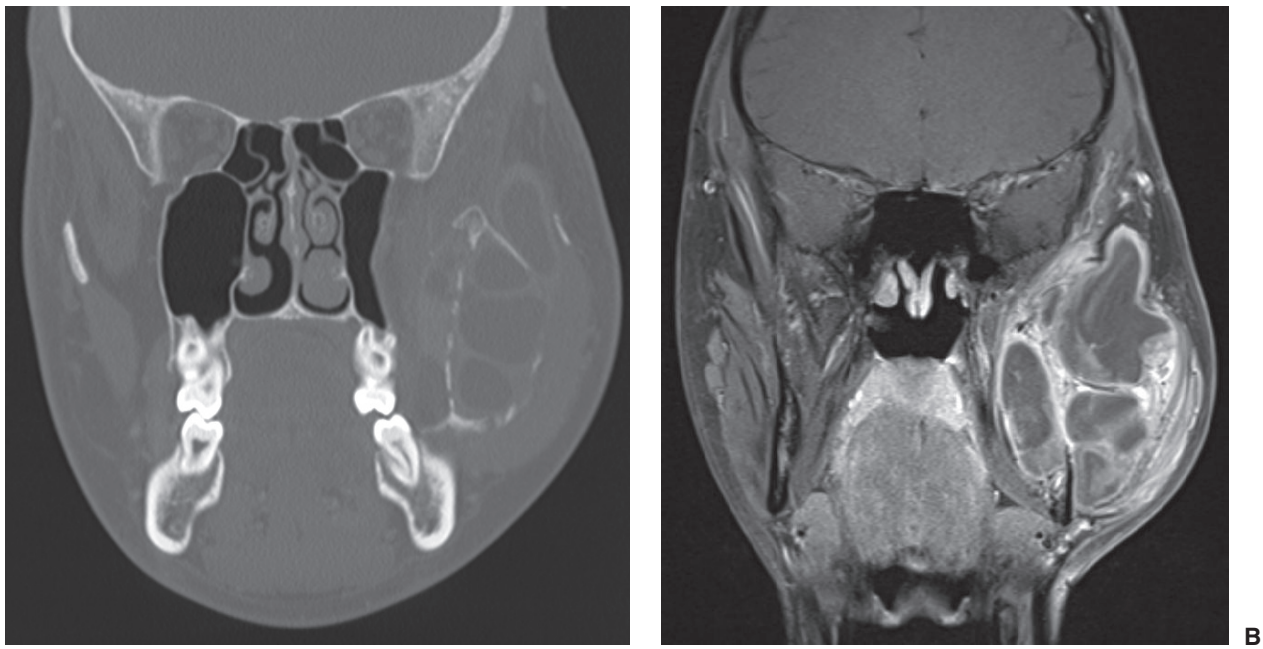
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**TABLE 29.2 Cytogenetic Abnormalities in Soft Tissue Sarcoma**

| Histologic Subtype | Usual Translocations | Genes Involved |
|---|---|---|
| Alveolar sarcoma of soft parts | t(X;17) | — |
| Chondrosarcomas extraskeletal myxoid | t(9;22), (q22;q12.2) | *EWS/CHN* |
| Clear cell sarcoma | t(12;22)(q13;q12) | *EWS/ATF1* |
| Congenital infantile fibrosarcoma | t(15;15)(p13;q25) | *ETV6, NTRK3* |
| Dermatofibrosarcoma protuberans | t(17;22)(q22;q13) | *Collagen type 1 α1; PDGF-B* |
| Desmoplastic small round-cell tumor | t(11;22)(p13;q12) | *EWS/WT1* |
| Lipoma (minimal atypia) | 12q abnormalities | Amplified *12q 13-15* |
| Liposarcoma (myxoid) | t(12;16)(q13;p11) | *TLS/CHOP* |
| | (12;22)(q13;p12) | *CHOP/EWS* |
| Liposarcoma well differentiated | Rings and giant markers | Amplified *12q13-15; HMG1-C CDK4; MDM2* |
| Rhabdomyosarcoma (alveolar) | t(2;13)(q35;q14) t(1;13)(p36;q14) | *PAX3 (or 7)/FKHR* |
| Rhabdomyosarcoma (embryonal) | Loss of heterozygosity at 11p15 | — |
| Synovial sarcoma | t(X;18)(p11.2;q11.2) | *SYT/SSX1 or SSX2* |

## Grading STS

One of the most durable prognostic factors for the risk of distant metastasis and tumor-specific mortality in STS is histologic grade whose effect is so pronounced that it is included in the staging classification. Although a number of grading systems have been used in the management of soft tissue sarcoma, the three-tier system proposed by the French Federation of Cancer Centres is precisely defined, easy to use, and most widely employed. The French system relies on a relatively balanced evaluation of



**A** **B**

**FIGURE 29-2.** **A:** Coronal projection of computed tomography (CT) of an 18-year-old patient with synovial sarcoma arising from the left temporomandibular joint region. There is a large heterogeneously enhancing soft tissue mass causing distortion of the facial contour. Remodeling of bone is apparent as well as spiculated periosteal reaction and calcification. The diagnosis was established by the characteristic molecular gene fusion and translocation seen in synovial sarcoma (see text). **B:** T1 sequence postgadolinium magnetic resonance image (MRI) in coronal plane of the patient in **A**. The expansile mass is again apparent with heterogeneous features centered along the mandibular ramus and involving the temporalis muscle into the suprazygomatic masticator space.

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parameters (differentiation score, mitoses, necrosis), but its greatest limitation lies in the assignment of a differentiation score.[13] Roughly defined as the extent to which a lesion resembles normal tissue, differentiation score has little applicability for tumors which ostensibly have no normal tissue counterpart.

It is also recognized that no system performs perfectly in all sarcomas. In a recent review, Deyrup and Weiss highlighted problems including the fact that some STS do not lend themselves well to grading. These include (a) those in which grade provides no additional information (e.g., well-differentiated liposarcoma/atypical lipomatous neoplasm); (b) "ungradable" histologic subtypes (e.g., epithelioid sarcoma, clear cell sarcoma, angiosarcoma); and (c) sarcomas that have traditionally been graded but where this characteristic does not appear to differentiate these lesions prognostically (e.g., malignant peripheral nerve sheath tumor [MPNST]).[13]

## CLASSIFICATION OF SELECTED BONE SUBTYPES

In contrast to STS, primary malignant tumors of bone are predominantly confined to two histologic types: osteosarcoma and chondrosarcoma. Other histologies including primitive neuroectodermal tumor/Ewing sarcoma are much less frequent in the head and neck although a wide variety of histologic subtypes may be found[14] (Table 29.3).

### Osteosarcoma

Osteosarcoma is a primary malignancy of osteoblastic tissue and is discriminated from all other tumors, including chondrosarcoma, by the direct formation of bone or osteoid tissue by its tumor cells. It covers a wide spectrum of lesions with distinct clinical and pathologic features. The malignant component comprises an undifferentiated stroma characterized by dense cellularity, pleomorphism, and cytologically atypical osteoblasts. Although the tumor is derived from osteoblasts and the malignant cells can be shown to contain intracytoplasmic alkaline phosphatase, it usually exhibits a mixed picture containing fibroblastic, osteoblastic, and chondroblastic areas, based on the predominant characteristic of the stroma. Tumor osteoid may be seen copiously with numerous pleomorphic tumor osteoblasts.

Smith et al. reported the largest series, that of the National Cancer Data Base (NCDB), for patients diagnosed with osteosarcoma of the head and neck from 1985 to 1996.[15] Accounting for about 5% to 10% of all osteosarcomas, they most usually affect individuals in the fourth decade of life of equal gender. The mandible (40%) and maxilla are the most frequent bones involved, although other skull bones may be affected.[15] In general, it is perceived that they often comprise low-grade lesions, different from their high-grade counterparts found in the long bones, have a lower potential for metastatic spread compared with other sites, and thus patients with these tumor may not necessarily benefit from neoadjuvant or adjuvant chemotherapy.

### Chondrosarcoma

Chondrosarcoma constitutes approximately 10% of malignancies of bone and is the second most common sarcoma of bone after osteosarcoma. Like osteosarcoma, the largest series ($n = 400$) of chondrosarcoma of the head and neck was also reported from the National Cancer Data Base (NCDB) for the years 1985 to 1995.[16] This comprised 0.1% of head and neck cancers during the same period and makes up 1% to 12% of chondrosarcoma in various reports.[16] The hallmark of chondrosarcoma is its origin from tumor cells that form chondroid (cartilage) as opposed to osteoid. In addition, most (60%) arose from osseous tissue grouped as "head and neck bones" and "sinonasal," the latter including 8% originating in the mandible. Almost one-quarter

**TABLE 29.3 Principal Histologic Types of Bone Sarcoma Selected from the Second Edition (1993) World Health Organization (WHO) Classification of Bone Tumors**

| Histologic Type | ICD-O Morphology |
|---|---|
| **Bone-forming tumors** | |
| Conventional central osteosarcoma | 9,180/3 |
| Telangiectatic osteosarcoma | 9,183/3 |
| Intraosseous well-differentiated (low-grade) osteosarcoma | 9,180/31 |
| Round-cell osteosarcoma | 9,185/3 |
| Parosteal (juxtacortical) osteosarcoma | 9,190/31 |
| Periosteal osteosarcoma | 9,190/32 |
| High-grade surface osteosarcoma | 9,190/33 |
| **Cartilage-forming tumors** | **9,220/3** |
| Chondrosarcoma | 9,220/3 |
| Juxtacortical (periosteal) chondrosarcoma | 9,211/3 |
| Mesenchymal chondrosarcoma | 9,240/3 |
| Dedifferentiated chondrosarcoma | |
| Clear cell chondrosarcoma | |
| Malignant chondroblastoma | |
| **Marrow tumors (round-cell tumors)** | **9,150/3** |
| Ewing sarcoma | 9,260/3 |
| Primitive neuroectodermal tumor of bone | 9,473/3 |
| Malignant lymphoma of bone | 9,590/3 |
| Myeloma | 9,732/3 |
| **Vascular tumors** | |
| Angiosarcoma of bone | 9,120/3 |
| Malignant hemangiopericytoma | 9,150/3 |
| **Other connective tumors** | **9,040/3** |
| Fibrosarcoma | 8,810/3 |
| Leiomyosarcoma | 8,890/3 |
| Liposarcoma | 8,850/3 |
| Malignant fibrous histiocytoma | 8,830/3 |
| Malignant mesenchymoma | 8,990/3 |
| Undifferentiated sarcoma | 8,800/3 |

ICD-O, International Classification of Diseases for Oncology.

*Source:* From Schajowicz F, Sissons HA, Sobin. The World Health Organization's histologic classification of bone tumors. A commentary on the second edition. *Cancer.* 1995;75:1208–1214, with permission.

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arose from the laryngotracheal cartilages.[16] While a rare site for chondrosarcoma, the cricoid lamina of the larynx is a unique tumor of generally indolent behavior.

Mesenchymal chondrosarcoma is seen in the skull as well as the bones of the trunk. This highly malignant tumor is composed of primitive mesenchymal cells focally differentiating in cartilage. The lesion is usually osteolytic with poorly defined limits and permeates cortex into soft tissues. A biphasic appearance is usual with two histologic patterns comprising sheets of dense small round or oval undifferentiated cells resembling Ewing sarcoma or lymphoma, alternating with a second pattern of easily identified cartilaginous tissue. Chondroid islands may appear quite abruptly among the undifferentiated cells that mimic early chondrogenesis, although more gradual transitions are also seen. Mitoses are frequent.

## Ewing Sarcoma

Ewing sarcoma also amounts to about 10% of bone tumors but is exceptionally rare in the head and neck comprising 1% to 9% of all Ewing sarcoma.[17] A cooperative Ewing sarcoma study of 301 cases recruited only 6 lesions affecting skull bones (2%) and 3 (1%) in the clavicles.[18] The true cell of origin remains elusive, although it appears to arise from pluripotent mesenchymal tissue although a neuroectodermal origin is suspected.[19,20] The histologic features are characterized by a structureless array of small hyperchromatic cells as one of the group of "small round blue cell" tumors. The diagnosis is established by additional measures beyond conventional light microscopy. For example, the majority of Ewing sarcomas (at least 80%) exhibit the specific translocation t(11;22)(q24;q12) between the *EWS* gene on chromosome 22 and the *FLI1* gene on chromosome 11. Alternate partners within the E-twenty-six (ETS) family are also present. Regardless of site, the treatment of all Ewing sarcoma mandates multiagent chemotherapy, in addition to local therapy, to reduce the likelihood of distant recurrent disease.

## Grading Bone Sarcomas

As with STS, the grading of bone tumors provides an important prognostic measure and has been incorporated in the tumor, lymph node, metastasis (TNM) staging system discussed below.[21]

Osteosarcomas are graded according to the cell type and relative anaplasia of the stromal component of the tumor. Low-grade lesions (grade 1) may resemble parosteal osteosarcoma or fibrous dysplasia. Increasingly anaplastic tumors are given higher grades with the least well-differentiated tumors representing the highest grade. High-grade tumors (grade 3 or 4) generally comprise conventional (osteoblastic), telangiectatic, and dedifferentiated tumors. Chondroblastic and fibroblastic tumors are usually lower grade (grade 1 or 2).

The gross and microscopic appearance of chondrosarcoma varies according to the grade and anatomical site, which itself is often associated with grade. For chondrosarcoma, well-differentiated appearance (grade 1) is associated with longevity and favorable prognosis. For example, as mentioned earlier, tumors of the cricoid cartilage are invariably low grade as determined by cellularity, nuclear features, and mitotic activity. Metastasis is almost never seen and dedifferentiation to high-grade sarcoma is quite exceptional. In the NCDB report, progression to distant metastases was three times more likely to occur among higher-grade cases than the lower-grade cases. Overall, most cases in the NCDB series were grade 1 (50%) and grade 2 (37%) whereas only a minority were grades 3 and 4.[16] Low-grade (well-differentiated) chondrosarcomas may also be difficult to discriminate histologically from benign cartilaginous lesions because they have the consistency of hyaline cartilage. Although most chondrosarcomas have a clearly dominant grade, multiple foci of different grade may be present and there is controversy about whether grading should only consider the highest grade identified within a tumor or be the predominant grade.[16] Myxomatous changes with cystic degeneration in the tumor correlates well with a low or medium histologic grade though it is important not to confuse myxoid change in common chondrosarcoma with the myxoid chondrosarcoma variant.[16] An absence of cartilaginous lobulation and the presence of spindle cell forms is characteristic of high-grade (grade 3) malignancy and heralds an unfavorable prognosis.

Of importance, Ewing sarcoma is always classified as high grade (and grade IV in the AJCC TNM classification).

# ETIOLOGY AND SCREENING

## Etiology

Apart from the diagnostic dilemma in distinguishing additional neurofibromata from metastatic lesions in patients with neurofibromatosis, the precise etiology of an individual sarcoma is of little clinical significance because it does not affect therapeutic decision making beyond the obvious fact that patients who have sarcomas arising in a previously irradiated field usually cannot receive further external-beam radiotherapy (EBRT). In fact, most sarcomas of the head and neck or elsewhere are without obvious cause. Of known factors, an induced STS and osteosarcoma is a long-term hazard of either iatrogenic or accidental exposure to radiation. Frequently, such tumors arise in the low-dose areas at the edge of prior radiation target volumes. Sarcomas have also been reported after chemotherapy, especially for pediatric cancers, such as acute lymphatic leukemia. The relative risk appears to increase with cumulative exposure to alkylating agents. Chemical exposure (usually occupational) is also linked to sarcoma causation being most recognized with thorotrast (x-ray technicians), vinyl chloride gas (plastics industry), phenoxy acetic acids (agricultural and forestry workers), chlorophenols (sawmill workers), and arsenic (vineyard work).

Association of rhabdomyosarcoma with genitourinary or central nervous system anomalies have been noted, as well as links to a variety of genetic conditions.[22] Multiple factors are implicated in the etiology of angiosarcoma. Although the usual patient with a head and neck angiosarcoma will not manifest these, the disease is typically seen in the scalp and face of an elderly white male. In addition to prior radiation exposure, chronic infection or solar exposure have been implicated, as well as vinyl chloride, thorotrast, insecticides, and steroid exposure. There is up to a 10% cumulative lifetime risk of developing sarcoma (usually malignant peripheral nerve sheath tumor) in patients with type 1 neurofibromatosis, an autosomal dominant disease with dysfunction of the *NF1* gene on chromosome 17q11.2.[23] The *NF1* gene product (neurofibromin) appears to be a tumor suppressor gene acting through GTPase activity with mutations leading to dysfunction and uncontrolled signaling via *ras* pathways. This may facilitate the development of malignant peripheral nerve sheath tumor.

Osteosarcoma (OS) has a number of risk factors. Exposure to radiation was noted earlier, but trauma and thorotrast exposure have also been described. OS may develop secondarily to underlying Paget disease, fibrous dysplasia, multiple osteochondromatosis, chronic osteomyelitis, and myositis ossificans. Retinoblastoma survivors provide a specific example of a dysfunctional or deleted tumor suppressor genetic element (in this case, the product of the *Rb* gene on chromosome 13q14) rendering these patients and their families at risk of soft tissue sarcoma, osteosarcoma (with or without radiotherapy) and several other malignancies including breast cancer. Alterations in *p53* germlines are also associated with the high predisposition of families

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with Li-Fraumeni syndrome for the development of osteosarcoma, again with or without radiotherapy.[24]

The etiology of chondrosarcoma remains obscure although various physical and chemical agents may be implicated. Speculation concerning undetermined dietary or environmental factors was prompted by the observation of a disproportionate incidence in low-income patients, although the mesenchymal subtype was more common among higher income groups.[16] Chondrosarcoma (especially in the skull base) may complicate Maffucci syndrome, a congenital nonhereditary condition associating multiple cutaneous hemangiomas, dyschondroplasia, and often enchondromas (see Fig. 29-12B).[25]

## Screening for Sarcomas

Predisposing genetic tendencies and environmental exposures associated with sarcoma development should be borne in mind when assessing patients. Genetic counseling would be appropriate to discuss issues relating to the genetic predispositions. However, no general screening is indicated beyond routine health care surveillance because of the rarity of sarcoma, with the rare exception of families suspected of carrying germline *p53* abnormalities associated with Li-Fraumeni syndrome.[26] A more detailed clinical evaluation in certain subjects is reasonable and with a lower threshold of intervention than one might use for general health care. For example, rapidly growing and/or symptomatic masses in patients with neurofibromatosis merit resection because of potential malignant transformation within a neurofibroma. Similarly painful and dramatic deformity in Paget disease should be viewed with concern about underlying osteosarcoma. Superficial or deep abnormalities of skin or soft tissues in patients with a history of prior radiation therapy should also be regarded with suspicion, given the known increased risk of sarcoma.

# CLINICAL PRESENTATION, EVALUATION, STAGE CLASSIFICATIONS

## Local Presentation

Sarcomas of the head and neck present in multiple ways depending on the numerous potential anatomic sites where disruption of function and contour may result. Local management starts with imaging and physical examination to determine whether soft tissue lesions originate superficial or deep to the investing fascia at the local site and whether bone tumors are intramedullary or have invaded into the extraosseous compartment. Evidence of bone, vascular, or neural invasion (uncommon) should be excluded.

Lesions may originate in the upper aerodigestive tract, paranasal sinus, and skull base with symptoms referable to these areas (e.g., nasal symptoms including obstruction or discharge and ocular proptosis from direct invasion in paranasal sinus tumors; cranial nerve abnormalities in lesions arising in the skull base or masticator space; alteration of voice or airway compromise for laryngeal and hypopharyngeal lesion lesions). Tumors originating in the subcutaneous tissues of the face, neck, or scalp can initially present with a superficial mass.

Both bone and cartilage tumors often present with pain in addition to symptoms of mass and compression. Pain generally relates to infiltration and expansion of bone. In lower-grade lesions, pain can be of long duration and characterized as a prolonged aching sensation, sometimes present for several years. Most often, they present as a slow growing mass or with looseness of dentition. Because of the potential to also arise in the skull base and paranasal sinuses, a wide variety of symptoms are also possible, depending on tumor site. These include cranial neuropathy and visual disturbance (including ophthalmoplegia and proptosis) in addition to pain, the latter being evident in about half the cases.

## Metastatic Manifestations

Most sarcomas present with localized disease and metastases are present in only 10% of cases at the time of diagnosis. Generally, the patient is asymptomatic and staging investigations (computed tomography [CT] chest) are needed to demonstrate the metastatic process as the predominant risk is to the lungs. Regional lymph node involvement is unusual but is represented most frequently in certain histologic subtypes, most notably rhabdomyosarcoma, epithelioid, alveolar soft part, clear cell, and synovial sarcomas. Rarely, remote bone marrow metastases are apparent but are seen almost exclusively in rhabdomyosarcoma with associated lymphadenopathy. In osteosarcoma, bone metastases may be present in the absence of lung involvement but this is exceptional.

## Evaluation

***Initial Assessment.*** Successful outcome starts with reliance on basic principles and understanding the behavior of the disease and the necessary steps to be undertaken. The overall management of head and neck soft tissue sarcoma is summarized in the treatment algorithm (Fig. 29-3). Before embarking on treatment, histologic confirmation of the diagnosis is necessary. All soft tissue masses deep to the investing fascia should be considered to be sarcoma until proven otherwise. The same vigilance is needed for bone lesions but here the opinion of an experienced diagnostic radiologist is required. Both bone and soft tissue lesions should be staged with cross-sectional imaging before the biopsy to avoid compromising the planning of appropriate management.

***Establishing the Diagnosis.*** Fine-needle aspiration biopsy (FNAB) is useful for establishing the presence of recurrence (both local and metastatic). However, its use as a primary diagnostic tool is controversial and should only be used where a cytopathologist with extensive experience in sarcoma is available. Core-needle biopsy under local anesthesia provides a more consistent tissue specimen and cell preparation compared with fine-needle aspiration. In our experience, open biopsy of soft tissue sarcoma is rarely indicated but yields a diagnosis when needle biopsy is unsuccessful (about 10% of cases).

Interventional radiologists are often requested to biopsy deep-seated lesions using ultrasound or CT guidance. An atraumatic biopsy close to critical structures or where the lesion is difficult to palpate can be accomplished. The radiologist should collaborate with the oncologists who will resect or irradiate the lesion. Needle tracts are potential sites of tumor contamination and the surgeon and radiation oncologist should be involved in planning the optimal biopsy route and be aware of potential contamination.

***Imaging Local Disease.*** Both CT scan and magnetic resonance imaging (MRI) are used widely. CT provides better bony detail than MRI, but MRI provides multiplanar images without losing specificity and is likely the best instrument for tumor definition with optimal tissue contrast. Therefore, in those situation where it is important to visualize the matrix of a lesion, CT is preferred. This usually occurs in flat bones including the calvarium. Plain radiography is also useful for bony lesions but has largely been replaced by CT. Both have the advantage of exhibiting calcification in tumor which may be characteristic of certain histologies (e.g., chondrosarcoma and synovial sarcoma). Malignant bone lesions will frequently present with marked permeative bone destruction, ill-defined transition to normal bone, aggressive periosteal reaction,

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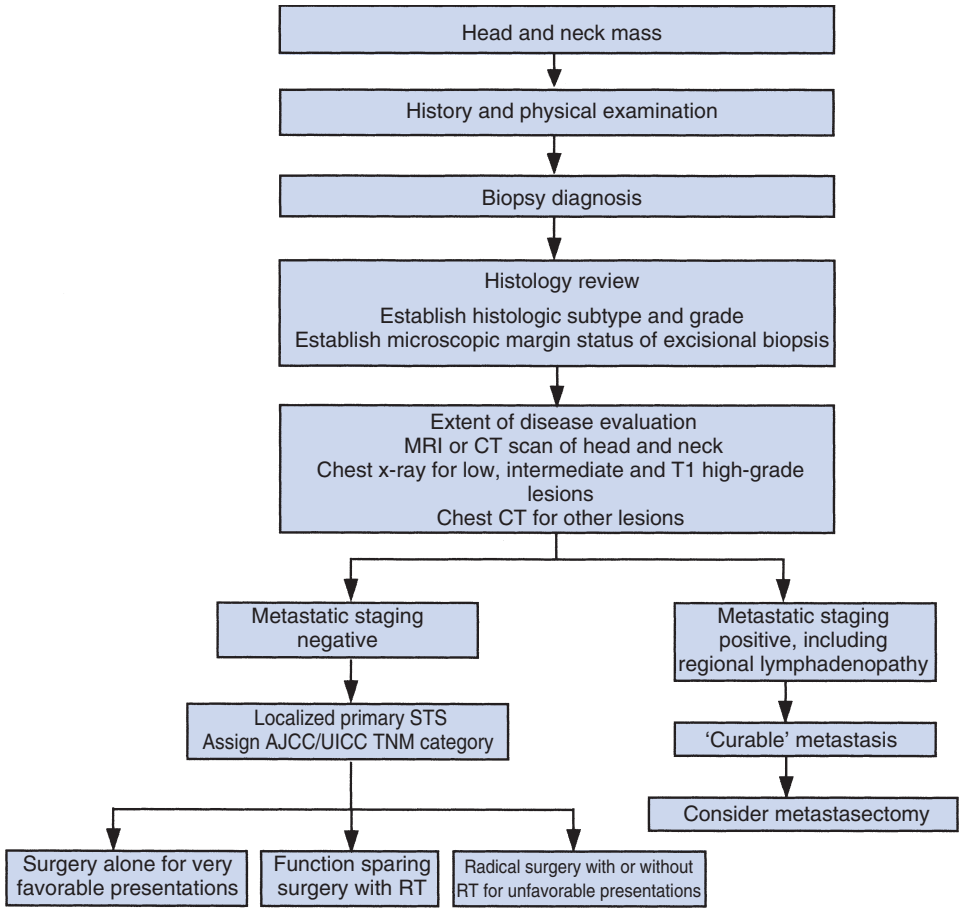



**FIGURE 29-3.** Flow schema for the assessment and management of soft tissue sarcoma (STS) of the head and neck. Because of the heterogeneity of tumor and anatomical sites, individualization is also needed. Thus some diseases, such as rhabdomyosarcoma, may need additional investigations (e.g., bone marrow examination)—see text for details of management. MRI, magnetic resonance imaging; CT, computed tomography; AJCC, American Joint Committee for Cancer; UICC, International Union Against Cancer; TNM, tumor, node, metastasis; RT, radiation therapy.

and an accompanying soft tissue mass. In the end, it is our impression that MRI generally provides superior depiction of intra- and extraosseous tumor in most malignant tumors of bone. Axial imaging complemented by either coronal or sagittal imaging planes using T1- and T2-weighted SPIN echo sequences most often provides accurate depiction of intra- and extraosseous tumor. To improve conspicuity, these sequences could be augmented by fat-suppressed pulse sequences. The maximum dimension of the tumor must be measured prior to any treatment.

In soft tissue sarcoma, low signal intensity on T1-weighted images and a high signal on T2-weighted images are the usual appearances and can be readily separated from normal soft tissue structures. Again lesion size should be recorded.

Although the diagnostic evaluation may be equally served by CT or MRI, the treatment-planning requirements (e.g., for both surgery and radiotherapy) frequently require additional information provided by the multiplanar capability of MRI and provides additional advantages through MRI/CT image-fusion techniques for radiotherapy treatment planning (Fig. 29-4).

Radionuclide bone scanning is a sensitive indicator of osteoblastic activity but lacks specificity. It can demonstrate multiple lesions but may also overestimate the extent of intramedullary infiltration when compared with MRI scanning.

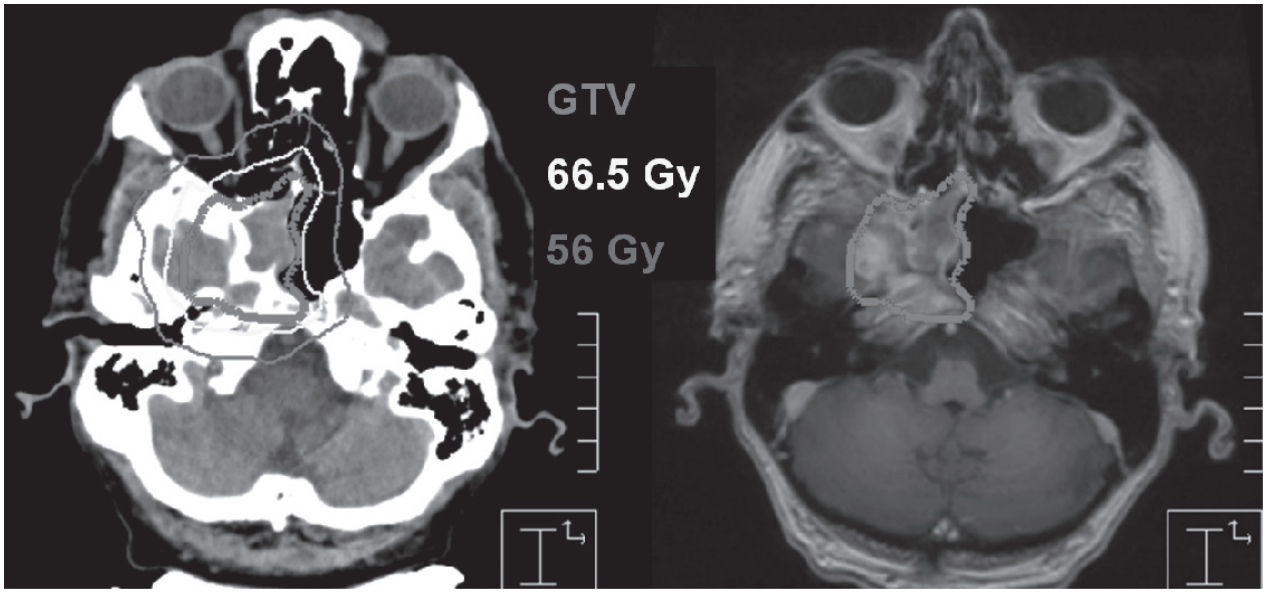
Positron emission tomography (PET) uses radiotracers specific to biologic processes to produce images of regional tissue metabolism with fluorodeoxyglucose, the most commonly employed radiotracer for this purpose. However, the contribution of PET imaging to routine management is currently uncertain. New tracers are being evaluated that may refine the differing roles for PET imaging that include evaluation of (a) the grade and extent of local disease including the potential for "skip" lesions in adjacent bone and (b) the response to initial (i.e., neoadjuvant) treatment as a surrogate to prognosticate on future outcome. It does seem that high- versus low-grade lesions may be distinguished and may even provide an imaging technique for biopsy guidance; in addition, response prediction to induction treatments seems to be possible.[27–30]

***Evaluation of Metastasis.*** For metastatic staging, CT of the chest is required, excepting very low-grade lesions where a plain chest radiograph is sufficient. If the underlying diagnosis is rhabdomyosarcoma, a bone scan and bone marrow biopsy is also necessary. Angiography is only rarely required in the evaluation of sarcomas. PET scan is also not widely used but may have applicability in identifying unusual sites of metastases in high-risk subsets (e.g., recurrent high-grade tumors).[31] Technetium scintigraphy is the examination of choice for evaluating the entire skeleton to determine whether there are multiple lesions and is particularly important for diseases with high propensity for bone metastasis such as Ewing sarcoma. Occasionally, intrapulmonary osteoblastic metastases may be demonstrated.

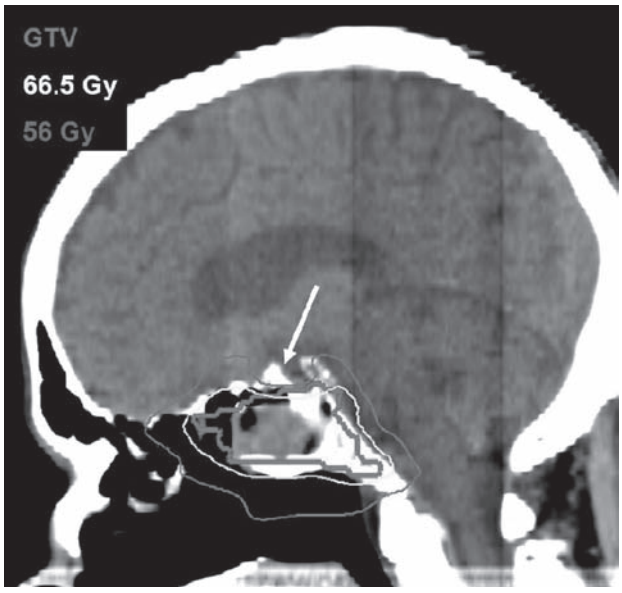
## Staging Classifications

Both soft tissue and bone sarcomas are classified according to the TNM stage classification (7th edition).[21] The classification has provided the possibility of combining a number of relevant factors including those addressing behavior (by means of inclusion

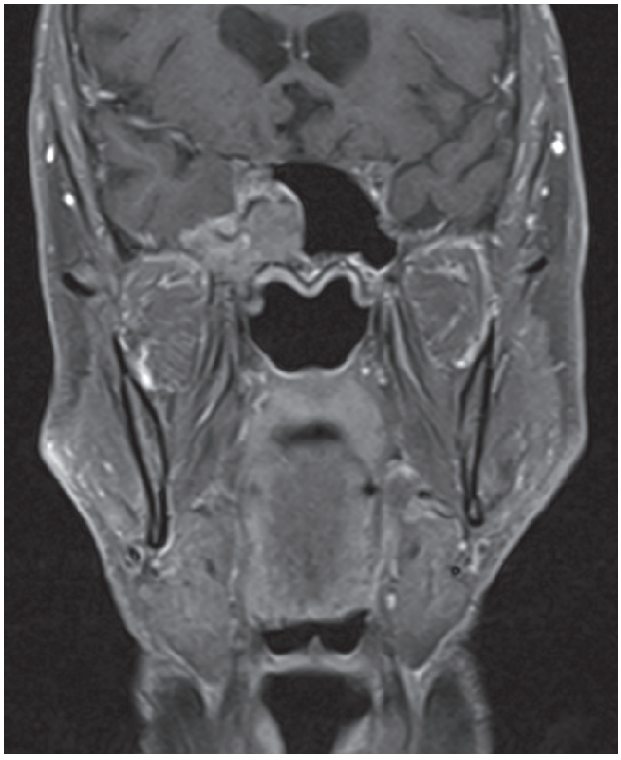
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A



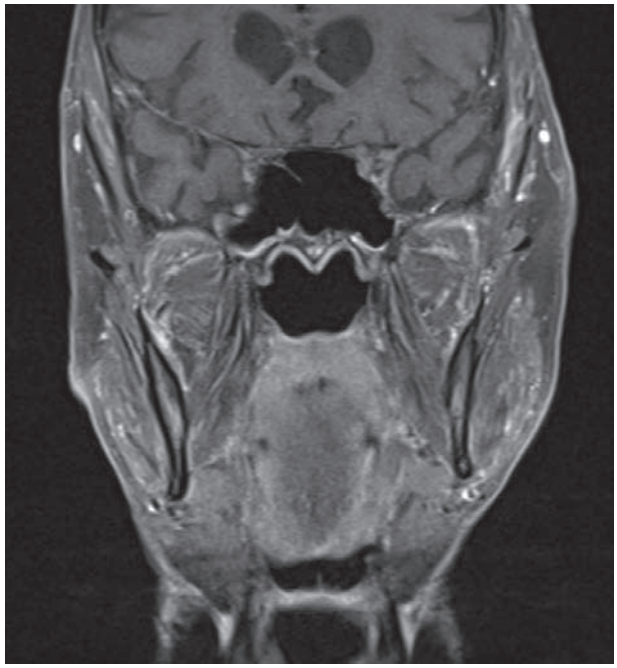

B



C

**FIGURE 29-4.** **A:** Magnetic resonance image (MRI) used for fusion in the axial plane for computed tomography (CT) intensity-modulated radiotherapy (IMRT) planning of an unresectable malignant fibrous histiocytoma of the right base of skull. Shown are the 66.5 Gy isodose (95% of the prescribed dose of 70 Gy in 35 fractions) and the 56 Gy peripheral isodose line for radical IMRT for this lesion. MRI imaging shown on the right side is far superior to the CT planning data set on the left in delineating the lesion depicted as the gross tumor volume (GTV) in red in both images. **B:** The sagittal view of the radiotherapy plan shows the 66.5 Gy isodose (95% of the prescribed dose of 70 Gy in 35 fractions) and the 56 Gy peripheral isodose line for a course of radical radiotherapy alone in this patient. There is dose reduction to protect the optic chiasm using IMRT (*arrow*). **C:** The initial coronal MRI is shown with an enhancing mass centered along the right lateral wall of the sphenoid sinus and projecting medially into the sphenoid sinus and laterally into the middle cranial fossa. The lesion was considered unresectable because of involvement of the cavernous sinus with encasement of the right internal carotid artery. **D:** The patient experienced a complete response to fractionated photon irradiation using IMRT delivered stereotactically with 3-year follow-up and is currently asymptomatic without evidence of disease.

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D

**FIGURE 29-4.** *Continued*

of grade) and anatomic factors.[32] However, a major limitation of the staging system is that it does not take into account the anatomic and histologic heterogeneity of these lesions. The system is also optimally designed to stage extremity tumors and is also applicable to the head and neck although lacks subtlety since the T-category size criterion dwarfs the anatomic sites of origin in the head and neck, which tend to be much smaller. An additional issue concerns rhabdomyosarcoma, where two separate descriptions of disease extent exist.

### *Soft Tissue Sarcoma*

*"Ordinary" Soft Tissue Sarcoma.* The relative rarity of STS, the anatomic heterogeneity of these lesions, and the presence of >30 recognized histologic subtypes of variable grade have made it difficult to establish a functional system that can accurately stage all forms of this disease. The American Joint Committee on Cancer (AJCC) TNM (7th edition) staging system[21] is the most widely employed staging system for STS and is unusual within the overall TNM classification system in that, like the bone classification, it incorporates histologic grade with anatomical disease characteristics. The soft tissue classification employs a three-tiered grading system based largely on the wish to incorporate the French system.[21] In general, the classification is based on an ascending hierarchy of risk depending on whether a lesion is deemed to have no adverse features for relapse or one, two, or three factors present represented by size partitioned at the 5-cm break point, grade (three-tiered system), and lesion depth as "a" (superficial tumor arising outside the investing fascia) or "b" (a deep tumor that arises beneath the fascia or invades the fascia) (Table 29.4).

*Rhabdomyosarcoma.* For nonpleomorphic rhabdomyosarcoma (RMS), the description of disease extent has traditionally been by a postoperative surgical classification developed by the North American Intergroup Rhabdomyosarcoma Study Group (IRSG) more than two decades ago (Table 29.5). This is not always relevant in the head and neck as such lesions will frequently be treated with aggressive chemoradiotherapy protocols (Fig. 29-5). Indeed, most lesions would be unresectable and thus classified as group III at diagnosis. They are most often parameningeal in location, considered an "unfavorable" site by the IRSG system, and thus labeled as stage 3. The International Society of Pediatric Oncology (SIOP) has suggested a TNM presurgical staging system more in keeping with contemporary TNM staging for soft tissue sarcoma including a T-category breakpoint at 5 cm (Table 29.6).[33] This process of staging prior to treatment is also being introduced in North America.[22] Regardless

**TABLE 29.4 American Joint Committee on Cancer (AJCC) TNM Classification (7th Edition) of Soft Tissue Sarcomas**

**Primary tumor (T)**

| | |
|---|---|
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| T1 | Tumor 5 cm or less in greatest dimension |
| | T1a, superficial tumor |
| | T2b, deep tumor |
| T2 | Tumor >5 cm in greatest dimension |
| | T2a, superficial tumor |
| | T2b, deep tumor |

*Note:* Superficial tumor is located exclusively above the superficial fascia without invasion of the fascia; deep tumor is located either exclusively beneath the superficial fascia, superficial to the fascia with invasion of or through the fascia, or both superficial yet beneath the fascia.

**Regional lymph nodes (N)**

| | |
|---|---|
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Regional lymph node metastasis |

*Note:* Presence of positive nodes (N1) in M0 tumors is considered Stage III.

**Distant metastasis (M)**

| | |
|---|---|
| MX | Distant metastasis cannot be assessed |
| M0 | No distant metastasis |
| MI | Distant metastasis |

**Stage grouping**

| | | | | |
|---|---|---|---|---|
| Stage IA | G1 | T1a, 1b | N0 | M0 |
| Stage IB | G1 | T2a, 2b | N0 | M0 |
| Stage IIA | G2-3 | T1a, 1b | N0 | M0 |
| Stage IIB | G2 | T2a, 2b | N0 | M0 |
| Stage III | G3 | T2a, T2b | N0 | M0 |
| | Any G | Any T | N1 | M0 |
| Stage IV | Any G | Any T | Any N | M1 |

G, Grade.

*Source:* From Edge SB, Byrd DR, Compton CC, et al. *AJCC Cancer Staging Manual.* 7th ed. New York, NY: Springer; 2010, with permission.

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**TABLE 29.5 Intergroup Rhabdomyosarcoma Study Group Postsurgical Grouping Classification**

**Group 1:** Localized disease, completely excised and no residual microscopic disease

A. Confined to the site of origin, completely resected
B. Infiltrating beyond site of origin, completely resected

**Group 2:** Total gross resection

A. Gross resection with evidence of microscopic local residual disease
B. Regional disease with involved lymph nodes, completely resected with no microscopic residual disease
C. Microscopic local and/or nodal residual disease

**Group 3:** Incomplete resection or biopsy with gross residual disease

**Group 4:** Distant metastases

of the classification used, adequate imaging of regional lymph nodes is imperative in patients in RMS.

***Bone Sarcoma.*** The AJCC TNM classification of bone tumors (Table 29.7) considers maximum lesion size (with a break point at 8 cm) and the presence discontinuous tumors in the same bone without other distant metastasis. Of interest, metastasis to nonpulmonary sits are distinguished from M1 disease based on lung involvement alone. The staging system is applicable to all primary malignant tumors of bone except multiple myeloma, malignant lymphoma (both having different natural history), and juxtacortical osteosarcoma and chondrosarcoma (both with much more favorable prognosis).[21]

## TREATMENT OF SOFT TISSUE SARCOMA

The benchmark for local control rates for extremity sarcomas rests at approximately 90% in modern series, and the overall 5-year survival of patients with STS can be expected to be in the range of 60%,[34] although this will vary as a function of prognostic factors from case to case. Unfortunately, series of head and neck sarcoma have usually not achieved these high local control rates. Mendenhall et al.[35] recently performed a systematic literature review and showed that the local control rate after surgery alone or combined with radiotherapy is approximately 60% to 70%. The probability of local control is influenced by histologic grade, tumor size, and surgical margins. Patients with high-grade tumors and/or positive margins have improved local control if adjuvant radiotherapy is used. Distant metastases manifest in about 10% to 30% of patients, figures that are somewhat lower than extremity lesions and is probably explained by the smaller size of lesion in the head and neck that presents earlier due to proximity to critical functional and cosmetic anatomy. The 5-year overall and cause-specific survival rates ranges from 60% to 70% and seems to be influenced by age, histologic grade, previous treatment of tumor, invasion of deep structures, and adequacy of surgery. The disappointing results in head and neck STS has been attributed to the traditional

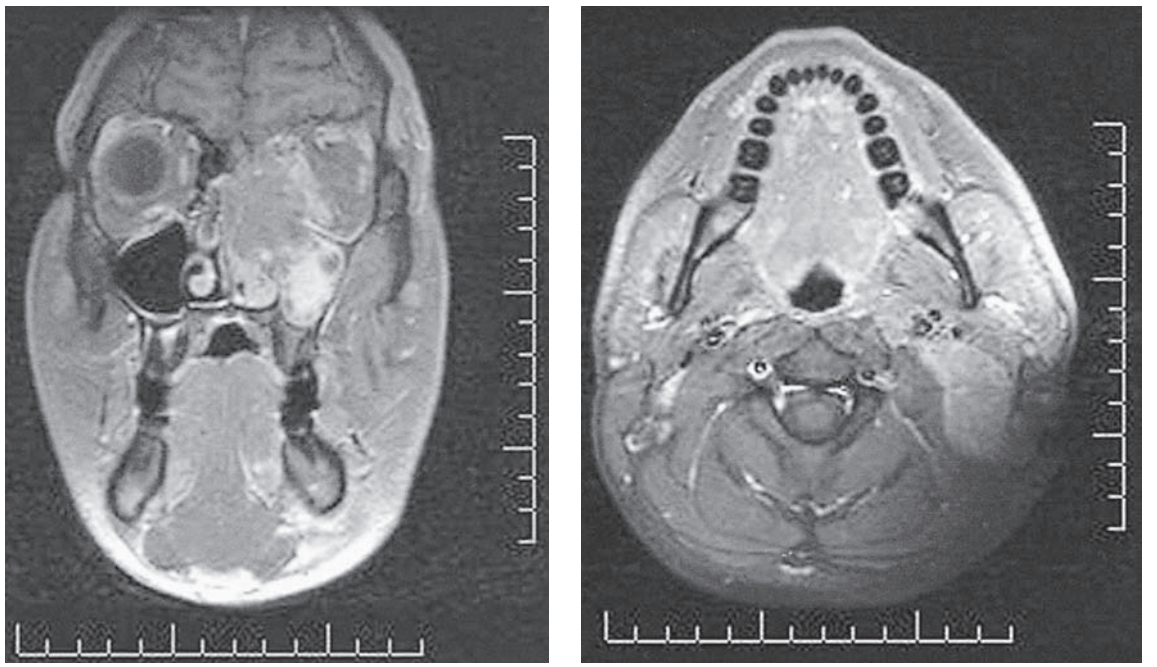



**FIGURE 29-5.** Magnetic resonance image of an alveolar rhabdomyosarcoma of the ethmoid sinus in a young adult. **A:** coronal view showing extensive orbital invasion; **B:** axial view showing concurrent extensive regional lymphadenopathy; **C:** complete response following combination chemotherapy with cyclophosphamide, actinomycin-D, vincristine (CAV), and etoposide with ifosfamide. Although consolidation radiotherapy commonly achieves local-regional control in these responsive tumors, such patients are at extremely high risk of failure in bone marrow, lung, and leptomeningeal sites.

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C

**FIGURE 29-5.** *Continued*

inability to deliver aggressive treatments because of their location in the critical anatomy of the head and neck. It may also relate to problems in delivering care for these rare diseases, if undertaken in the absence of a full multidisciplinary team. However, properly deployed principles and approaches should be able to achieve results in the head and neck that are comparable to similar lesions in extremity sites. Several randomized controlled trials have collectively established important milestones in the evolution of the local management of STS. With one exception, these trials have focused on extremity lesions and around the themes of surgery and adjuvant radiotherapy. These results are also highly relevant to the head and neck because of the similarity of biologic behavior of STS across body sites, even if the different histologic subtypes are not equally distributed by site.

**TABLE 29.6 International Society of Pediatric Oncology (SIOP) Presurgical Staging Classification (Clinical and Radiologic Staging)**

| Stage | Tumor | Node | Metastases |
|---|---|---|---|
| I | T1a or T1b | N0, Nx | $M_0$ |
| II | T2a or T2b | N0, Nx | $M_0$ |
| III | Ant T | N1 | $M_0$ |
| IV | Any T | Any N | $M_1$ |

T1, Confined to the anatomic site of origin; T2, Extension and/or fixation to surrounding tissue; (a), ≤5 centimeters in diameter; (b), >5 centimeters in diameter; Nx, Unknown nodal status; N0, No nodes present clinically; N1, Regional nodes present; Mo, No distal metastasis; Mo, Metastasis present.

*Source:* From Stevens MCG. Malignant mesenchymal tumours of childhood. In: Souhami RL, Tannock I, Hohenberger P, et al., eds. *Oxford Textbook of Oncology*. 2nd ed. Oxford, UK: Oxford University Press; 2002:2525–2538, with permission.

**TABLE 29.7 American Joint Committee on Cancer (AJCC) TNM Classification (7th Edition) of Bone Sarcomas**

**Primary tumor (T)**

| | |
|---|---|
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| T1 | Tumor (maximum dimension) ≤8 cm at time of diagnosis |
| T2 | Tumor (maximum dimension) >8 cm at time of diagnosis |
| T3 | Skip metastases-two discontinuous tumors in the same bone with no other distant metastases |

**Regional lymph nodes (N)**

| | |
|---|---|
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Regional lymph node metastasis to be considered equivalent to distant metastatic disease (see $M_{1b}$ below) |

*Note:* Because of the rarity of lymph node involvement in sarcomas, the designation NX may not be appropriate and could be considered N0 if no clinical involvement is evident.

**Distant Metastasis (M)**

MX = Distant metastasis cannot be assessed

M0 = No distant metastasis

M1 = Distant metastasis

M1a = Lung-only metastases

M1b = All other distant metastases including lymph nodes

**Stage Grouping**

| | | | | |
|---|---|---|---|---|
| Stage IA | G1,2 | T1 | N0 | M0 |
| Stage IB | G1,2 | T2 | N0 | M0 |
| | G1,2 | T3 | N0 | M0 |
| Stage IIA | G3,4 | T1 | N0 | M0 |
| Stage IIB | G3,4 | T2 | N0 | M0 |
| Stage III | G3,4 | T3 | N0 | M0 |
| Stage IVA | Any G | Any T | N0 | M1a |
| Stage IVB | Any G | Any T | N0/N1 | M1b |

G, Grade.

*Source:* From Edge SB, Byrd DR, Compton CC, et al. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010, with permission.

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## Surgery

***Major Ablation Versus Conservation Management.*** In the 1970s, it became apparent that RT in combination with surgery could achieve equivalent results to more ablative surgery in STS. This observation was confirmed in a trial that randomized high-grade sarcoma of the extremities to receive amputation versus a limb-sparing operation followed by adjuvant RT.[36] The result of this trial, combined with numerous institutional reports, heralded a new era in STS management.

***Extent of Surgery and Characterization of Margins.*** An important component of contemporary management is the value of imaging in demonstrating the radial extent of sarcoma within the compartment or site of origin and, together with radiotherapy, permits conservation of much of the surrounding soft tissue without increased local failure. Of more importance than the description of the type of surgery is the actual extent of viable residual disease remaining after surgery. This variable (the amount of residual viable disease remaining in the wound following resection) can never be known exactly, but is probably best represented by expert pathologic assessment of the surgical margin. Characterization of the margin guides the need for adjuvant RT for those tumors with insufficient normal tissue at the surface to reliably prevent local recurrence. Patients with positive margins of resection have inferior local control in STS and this prevails in the head and neck to the same degree as in other sites.[37]

The cause of positive margins is rarely discussed. The policy in STS surgery should be to achieve negative surgical margins, and this is best achieved by performing surgery at an experienced referral center. More recently, we have also shown, in a blinded study using a prospective data base, that a small isolated positive resection margin, planned from the outset by the multidisciplinary team with the intention of sparing a critical anatomic structure (e.g., at a major nerve, vessel, or bone), has a favorable outcome provided radiotherapy is administered (local recurrence 3.6%, 95% CI, 0–10.4) compared with an "unplanned excision" margin-positive situation (local recurrence 31.6%, 95% CI, 10.7–52.5).[38] Substantial contamination with tumor seeding in a hypoxic environment may mean that subsequent radiotherapy is less capable of eliminating tumor seeding in the "unplanned excision" circumstance.

***Evidence for Using Surgery Alone.*** Although the evidence is compelling that major ablation is avoidable in most cases, it is also helpful to consider whether adjuvant radiotherapy is needed to achieve conservation management, in comparison with surgery alone. This issue is complicated by case heterogeneity but a subgroup of patients undoubtedly do not need RT based on several sources of evidence, although none reported in the head and neck specifically. These rely on single-institutional experience with practices involving degrees of selection including subcutaneous or intramuscular presentation, or extramuscular lesions with favorable resection margin status. However, most deep sarcomas in all sites are referred with lesions significantly expanding out of a single muscle unit or have undergone biopsy prior to referral and therefore need radiotherapy combined with surgery. The approach is less applicable in the head and neck because the proximity to critical anatomy makes it less likely to achieve sufficient clearance to have confidence that surgery alone would eradicate disease, and there remains the added concern that local failure in head and neck STS confers extremely adverse outcome. The latter includes mortality directly from progressive local disease,[39] a phenomenon not relevant to extremity lesions.

## Radiotherapy

***Adjuvant Radiotherapy.*** Adjuvant RT with conservative surgical resection has been evaluated in two randomized clinical trials.[40,41] Yang et al. at the National Cancer Institute (NCI) randomized high-grade extremity lesions following limb-sparing surgery to receive adjuvant RT or no further treatment following the surgery. Chemotherapy was also used depending on grade. The local control for those receiving RT was 99% compared with 70% in the control group ($p = 0.0001$).[41] The results were similar for high- and low-grade tumors. Adjuvant RT, using brachytherapy (BRT), was also evaluated in a second randomized trial at Memorial Sloan-Kettering Cancer Center with a similar effect in high-grade lesions.[40] Of interest, no improvement in local control was evident in the low-grade tumors, potentially related to slowly cycling cells not entering the radiosensitive phases of the cycle during the short BRT-dwell time.[40]

For head and neck STS, relatively high rates of local relapse in different treatment settings have historically been reported by numerous institutions, as compared with extremity STS and surgical excision is often constrained by anatomical considerations. The probability of local control is influenced by histologic grade, tumor size, and surgical margins and appears to be improved by adjuvant radiotherapy.[35] However, if the principles used in other sites are applied in the head and neck, where tissue preservation is paramount, the results should be similar. Advantages to a combined modality approach are evident in a series where local control was 52% in those treated with surgery alone versus 90% in those treated with combined radiotherapy and surgery.[42] Additional evidence from our institution indicates that head and neck STS patients with clear surgical margins or microscopic residuum had similar local control rates (26% and 30% failure, respectively), provided radiotherapy was administered (Fig. 29-6).[39]

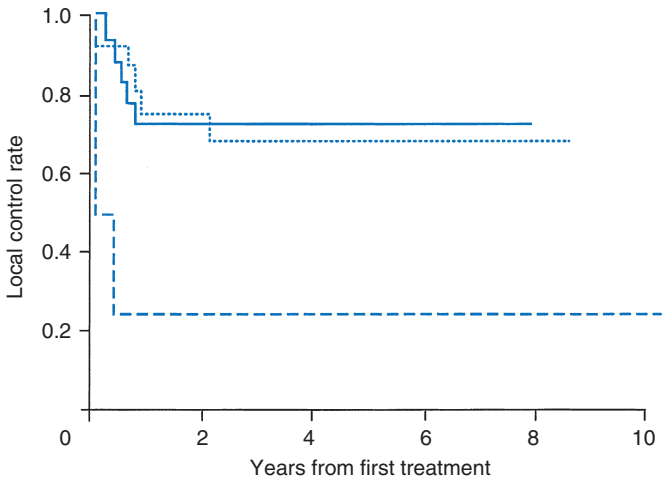



**FIGURE 29-6.** Actuarial estimate of local control rate in soft tissue sarcoma of the head and neck by surgical margins. Histopathologically clear (*solid line*), microscopically positive (*dotted line*), and gross disease (*dashed*) line are shown for patients treated with curative intent following surgical resection.

*Source:* Data reproduced with permission from Le Vay J, O'Sullivan B, Catton C, et al. An assessment of prognostic factors in soft-tissue sarcoma of the head and neck. *Arch Otolaryngol Head Neck Surg.* 1994;120:981–986.

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Indeed these outcomes for radiotherapy following R0/R1 resections approach those achieved in extremity sarcoma. Finally, a prospective series of high-risk cases has been treated on a consistent combined modality protocol with preoperative radiotherapy.[43] The results are comparable to extremity sarcoma of similar histology and are certainly superior to our historical series.[39,43]

***Timing of Radiotherapy (Preoperative vs. Postoperative Radiotherapy).*** Preoperative RT promotes collaboration between the surgical and radiation oncologist and facilitates a complete management plan to be fashioned prior to any surgical intervention. Preoperative RT is also delivered to an undisturbed and potentially better oxygenated tumor site and permits administration of lower dosages and smaller fields of radiation without compromising local control. These observations were confirmed in our randomized trial comparing preoperative and postoperative radiotherapy in extremity soft tissue sarcoma. Local control was equivalent in both groups (93%).[44] Others have suggested that preoperative RT has advantages in certain situations especially for gross disease at referral and large tumors. However, preoperative RT is often delivered on a partially representative biopsy and may interfere with future histopathologic analysis. Additional concerns about pre-op RT include the increased risk of wound complications in some anatomic sites, but not at all in others.[44] Flaps are also commonly used in the reconstruction, and wound-healing problems do not occur with the frequency evident with preoperative radiotherapy in extremity lesion.[43] In fact, in the combined modality approach to head and neck STS, preoperative radiotherapy is particularly suited because of the smaller RT volumes and lower doses to critical anatomy in difficult surgical access locations, especially in the base of skull (Fig. 29-7). At present, our guidelines for using preoperative radiotherapy are (a) the need to maximally restrict RT volumes in some anatomic sites (e.g., head and neck), (b) the desire to minimize RT dose in some situations (e.g., where critical neurologic tissues are in close proximity), and (c) the desire to not irradiate new tissues, especially vascular reconstructions vulnerable to the effects of high-dose postoperative RT.

***Radiotherapy Alone in Soft Tissue Sarcoma.*** Historically, patients treated with radiotherapy alone for gross disease do not achieve the same outcome although approximately 25% are controlled (see Fig. 29-6),[39] with similar observations by Tran et al.[42] At the same time, this may be the only option of management in selected adverse presentations in the head and neck where surgical management is not feasible (see Fig. 29-4). Recently, Kepka et al. updated a historical series of patients with tumors in any anatomic site at the Massachusetts General Hospital ($n$ = 112) who underwent radiotherapy for gross disease. Local control at 5 years was 51%, 45%, and 9% for tumors <5 cm, 5 to 10 cm, and >10 cm, respectively. Patients who received doses of <63 Gy had inferior 5-year outcomes compared with those receiving higher doses including local control: 22% versus 60%; disease-free survival: 10% versus 36%; and overall survival rates: 14% versus 52%.[45] Kepka et al. also noted a rise in complications at doses of 68 Gy or more, which appears to provide a therapeutic window. It is possible that the outcomes of these problematic cases may be improved by more precise delivery methods, such as intensity-modulated radiation therapy (IMRT) (see Fig. 29-4) or particle beam with protons or carbon ion, thereby permitting higher doses without the same danger to normal tissue.[45,46] Chemotherapy may further enhance local control based on evidence from some of the randomized trials (see "Influence of chemotherapy on local control" below). A recent report also appeared to suggest a better outcome following radiochemotherapy with ifosfamide compared with radiotherapy alone or radiotherapy combined with other radiosensitizers in localized unresectable soft tissue sarcoma.[47]



**FIGURE 29-7.** Leiomyosarcoma of the skull base with optic nerve compression. Such patients are preferentially managed at the authors' center with preoperative radiotherapy to limit not only the volume of radiotherapy but also the dose that is administered because of the constraints imposed by the presence of critical adjacent anatomy (i.e., the optic chiasm). In addition, chemotherapy may be added in an additional attempt to enhance local control.[53] This patient was managed in this fashion although the orbit required exenteration primarily but the optic chiasm and opposite optic nerve and eye were protected and the patient remains disease free with 7-year follow-up.

One exception to the almost universal need for combined surgery and radiotherapy in STS is in the treatment of rhabdomyosarcoma, where control with radiotherapy alone with chemotherapy is an expected result because of the unusual radioresponsive nature of these lesions. The use of a conservative tissue conserving approach may be preferable in such patients if surgery is very problematic, given the very high risk of distant metastasis in these patients.

***Radiotherapy Modality.*** Two methods of RT delivery are commonly employed: EBRT in the ambulatory setting and brachytherapy (BRT). No randomized data compare these modalities directly, and it is unclear how similar the selection criteria are for both approaches. As noted earlier, both have been compared with surgery alone. BRT has several advantages over EBRT including a shorter overall treatment time (e.g., classically 4–6 days vs. 5–6.5 weeks), and treatment can be initiated sooner following surgery when clonogen numbers are at a minimum. In the head and neck, additional potential advantages include the ability to treat close to critical anatomy such as the spinal cord. The concerns about lack of effect for low-grade tumors was noted earlier, a feature not apparent with EBRT.

EBRT may include photons or particle beam (electrons, protons, neutrons, or carbon ions). Protons have similar radiobiologic effects to photons. Their main advantage is when tumors lie in direct proximity to critical structures due to the ability to achieve more accurate targeting. High linear energy transfer radiation such as neutrons confer radiobiologic advantages over photons, which include reduced repair of radiation damage in tumor

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cells, sensitivity of cancer cells to RT throughout the cell cycle, and less protection offered to hypoxic cancer cells. However, any such advantages are tempered by late damage because the usual repair processes in action with fractionated radiotherapy do not occur and they have not become widely available due to lack of spatial targeting. More recently carbon-ion radiotherapy has emerged as an option due to the associated high linear transfer excellent dose localizing properties in comparison with other ion species and seem especially promising in the management of unresectable disease.[46] A more traditional alternative is the use of intraoperative RT (IORT). The major interest for IORT has been in retroperitoneal sarcoma, but experience in other sites, especially the head and neck, is minimal.

***Radiotherapy Dose Fractionation.*** EBRT prescriptions for postoperative RT depend on the tumor grade and involvement of the surgical margin but typically use 60 and 66 Gy for low- and high-grade tumors, respectively, with a "shrinking field" techniques following 50 Gy at 1.8 to 2 Gy per fraction. In the head and neck, critical structures in the target volume frequently require doses to be curtailed to 45 to 50 Gy in components of the target volume to minimize the occurrence of catastrophic sequelae (e.g., blindness or paralysis). At most institutions the preoperative dose is 50 Gy in daily fractions over approximately 5 weeks (Fig. 29-8) as used in our recent randomized trial.[44] Sparing of late effects may be expected with smaller fraction size in altered fractionation protocols and may be important when critical structures are irradiated. However, an improvement in therapeutic gain remains unproven from this strategy in STS.

Unresected disease being treated with the goal of long-term control should receive at least 70 Gy in 35 fractions or equivalent (see Fig. 29-4).

***Radiation Target Volume.*** STS generally respect barriers to tumor spread in the site of origin, such as bone, interosseous membrane, major fascial planes, and so forth. Thus, the margins of radiation therapy must be wide, especially along the direction of the involved musculature but care must be taken to ensure that the fascial planes are appropriately recognized and encompassed in the radiation target volume. In the preoperative setting, the gross tumor volume (GTV) is typically represented by the radiologically defined tumor. Some sarcomas have extensive peri-tumor edema which extends along fascial planes and may lie at some distance from the primary tumor. A recent study correlating radiologic imaging features to pathologic examination showed that the edema often contains viable tumor cells.[48] A zone of potential microscopic disease beyond the GTV comprises the clinical target volume (CTV) and should include the edema although this can influence the size of the treatment volume considerably. For postoperative RT planning, the high-risk target area includes the surgical field containing all the tissues handled during the surgical procedure, including scars and drain sites. Again, an additional zone

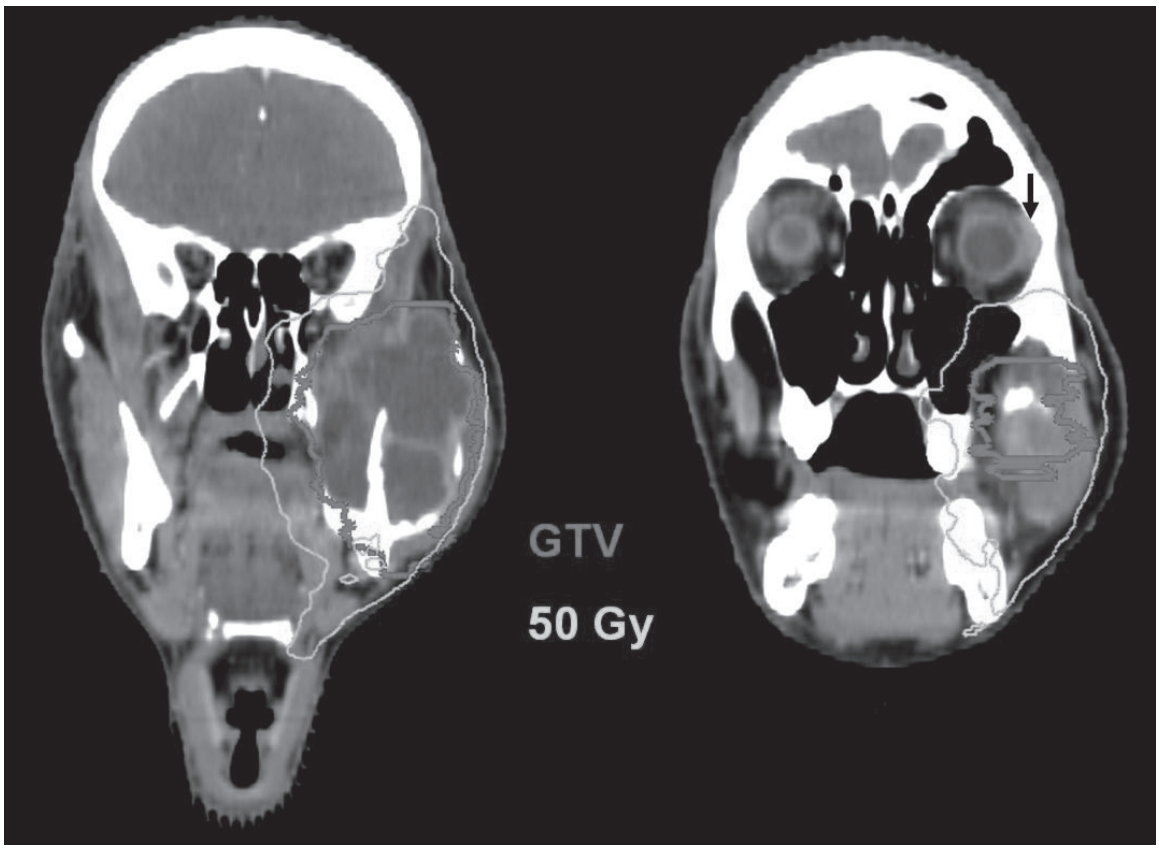



**FIGURE 29-8.** Coronal projections of an intensity-modulated radiation therapy (IMRT) plan to delivery preoperative radiotherapy (50 Gy in 25 fractions). This patient was initially treated with neoadjuvant chemotherapy for this large synovial sarcoma. Outlined in red is the coronal projection of gross target volume (GTV) for the two illustrative coronal slices and the 50 Gy isodose line (*green*) that encompasses a target that includes the superior extension into the temporalis region **(left)**. The right side of the figure shows a plan that illustrates the conformality achieved in treating this complex target in order to avoid overdose to critical anatomy within the adjacent orbit, including the lacrimal gland (*arrow*).

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beyond this comprises the CTV. Typically, in STS RT planning, the recommended CTV margins beyond high-risk areas are approximately 5 cm[44] although it is recognized this is often not feasible in the complex anatomy of the head and neck. Bone, interosseus membranes, and fascial planes are considered barriers to tumor spread and permit RT margins to be narrower. In contrast, the BRT protocol at Memorial Sloan Kettering Cancer Center (MSKCC) uses margins of only 2 cm around the surgical bed[40] although cases may not always be selected similarly for EBRT and BRT protocols.

Other than for the individual histologic subtypes at risk of regional lymph node involvement, elective irradiation of the neck is not ordinarily recommended in STS.

## Adjuvant Chemotherapy

***Rationale.*** Various rationales underpin the use of adjuvant chemotherapy in STS. Firstly, the efficacy of cytotoxic agents can be expected to be greater in the setting of a low tumor burden (e.g., microscopic potential disease) compared to the high (visible) tumor burden associated with overt metastatic disease. Secondly, chemotherapy might be better tolerated in association with a low tumor burden. Thirdly, the growth fraction is postulated to be high in tumors with a low tumor burden and decreases with increasing tumor size. This is relevant because tumors with a high growth fraction are believed to be more sensitive to chemotherapy. Finally, although generally considered a strategy to enhance metastatic outcome, there is also the potential to improve local control in circumstances where optimal local control strategies cannot be used because of constraints resulting from sensitive anatomical locations.

***Meta-analysis of Randomized Trials.*** The individual data from the 1,568 patients randomized in all 14 trials that addressed the role of doxorubicin-based adjuvant chemotherapy in STS were combined in a landmark individual patient data (IPD) meta-analysis.[49] Problems related to the meta-analysis have been discussed,[50] and there is some disagreement about whether the results should be interpreted with respect to whether adjuvant chemotherapy should be used routinely in STS.[50,51] In the meta-analysis, the figures for distant relapse-free interval and overall recurrence-free survival were significantly in favor of the use of adjuvant chemotherapy. However, and most importantly, the difference in overall survival, the ultimate aim of adjuvant chemotherapy, was not significantly different between the chemotherapy and the control groups ($p = 0.12$) (Table 29.8). The suggested potential absolute benefit was 4% at 10 years representing a possible survival improvement from 50% to 54% ($p = 0.12$). Thus, based on these results, routine use of chemotherapy would result in 96% of patients receiving chemotherapy with its intrinsic side effects, but with only a modest benefit accrued to the population.[50]

Only 3 trials in the meta-analysis were of a relatively large sample size, that of the European Organization for the Research and Treatment of Cancer (EORTC), the Scandinavian Sarcoma Group (SSG), and the Gynecological Oncology Group (GOG).[52–54] However, given the heterogeneity of STS, even these three studies may be too small to render definitive conclusions. In part, this may arise from inclusion of cases with minimal or only small risk of metastatic failure thereby diluting the power of the studies to detect an effect which may exist only for those patients at substantial risk of metastasis. Most trials addressed other body sites, although head and neck STS were included to varying degrees in half of the studies, including those examining doxorubicin alone versus controls[52,55–57] or doxorubicin combination chemotherapy versus controls.[53,58,59]

More recently, a literature based meta-analysis, and consequently less statistically robust than its IPD counterpart, was performed including the 14 trials mentioned above with an additional 4 randomized trials included, for a total of 1,953 patients.[60] A combination of doxorubicin and ifosfamide was used in five trials. The mean follow-up was 4.9 years and the absolute improvement for OS was 6% in favor of the chemotherapy (40% vs. 46%, $p = 0.003$). Chemotherapy also reduced local recurrence by 4% (19% vs. 15%) and distant recurrence by 9% (37% vs. 28%). These results need to be verified in a further individual patient data meta-analysis. Again, clinicians must balance the short- and long-term toxicity of combination chemotherapy with doxorubicin and ifosfamide with the absolute advantage to survival. However, notable exceptions are that all patients with nonpleomorphic rhabdomyosarcoma, and Ewing sarcoma in the case of bone tumors, deserve multiagent chemotherapy. Both diseases are discussed later in the chapter.

**TABLE 29.8 Hazard Ratios for Individual Patient Data Meta-analysis in 1,568 Patients for 14 Trials of Doxorubicin-based Chemotherapy in Adult Soft Tissue Sarcoma**

| Outcome | Hazard Ratio | 95% Confidence Intervals | *p* Value |
|---|---|---|---|
| Local RFI | 0.73 | 0.56–0.94 | 0.016 |
| Distant RFI | 0.70 | 0.57–0.85 | 0.0003 |
| Overall recurrence-free survival | 0.75 | 0.64–0.87 | 0.0001 |
| Overall survival | 0.89 | 0.76–1.03 | 0.12 |

RFI, Recurrence-free interval.

*Source:* Data from reference Sarcoma Meta-analysis Collaboration. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. *Lancet.* 1997;350:1647–1654, with permission.

***Influence of Chemotherapy on Local Control.*** Of interest, the largest trial in the meta-analysis (that of the EORTC) compared the outcome of adjuvant CYVADIC chemotherapy with control in 468 patients. The relapse-free survival was significantly better after CYVADIC (56% vs. 43% for controls; $p = 0.007$) and local recurrence was significantly reduced by CYVADIC (17% vs. 31%; $p = 0.01$).[53] This favorable result in this subset analysis appeared to be confined to head, neck, and trunk tumors. In contrast, distant metastases rates were similar in both arms as were overall survival rates (63% vs. 56%; $p = 0.64$). Thus, there is the potential for adjuvant chemotherapy to improve local control in this high-risk group of STS, where local control has traditionally not been as satisfactory as with STS overall and surgery and radiotherapy cannot be administered with the same freedom as other anatomical sites.

***Additional Data.*** Since the publication of the original individual patient data meta-analysis in 1997, another important study was reported from Bologna, Italy, and is included in the literature based meta-analysis reported by Pervaiz and colleagues.[60] The inclusion criteria for this trial were appropriately restricted to very adverse tumors (confined to large high-grade lesions) and a very intensive cytotoxic regimen (5 cycles of 4'-epidoxorubicin 60 mg/m$^2$ days 1 and 2 and ifosfamide 1.8 g/m$^2$ days 1 through 5, with hydration, mesna, and granulocyte colony-stimulating factor) compared with no systemic treatment.[61] The disease-free

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and overall survival rates were statistically improved at preliminary analysis, and at the time of reporting.[61,62] However, by the time of publication, the metastatic rate in both arms of the randomized trial was virtually identical (44% and 45%).[61,63] Unfortunately, this raises the question whether the potential value of aggressive chemotherapy may largely be in delaying the manifestation of distant metastasis, but not in their prevention. This study is of particular interest because a dose-intensive chemotherapy regimen was administered to a high-risk group patients.

***Recommendation for Individual Patients.*** At this time, given the overall results of the individual patient data meta-analysis, and the uncertain nature of this recent positive trial of the Bologna trial, postoperative chemotherapy cannot be considered standard therapy for patients with localized soft tissue sarcoma. We have not adopted systemic chemotherapy for routine use and have preferred to intensify local control strategies by maximizing the completeness of resection and delivering accurate and intensive adjuvant radiotherapy. On the other hand, we feel that chemotherapy should continue to be evaluated in randomized controlled trials in head and neck and other body sites wherever possible. Additional comments about individual selected histologic types should also be considered especially for synovial sarcoma which some believe may readily respond objectively to chemotherapy. Evidence of a true benefit is lacking; nonetheless, many centers may employ chemotherapy for the larger synovial sarcomas given the adverse risk of distant metastases in these patients with responding tumors.[64]

## Clinical Management of Selected STS Subtypes

***Undifferentiated Pleomorphic STS (Formerly MFH).*** As noted earlier, this entity has held a historical position in the management of STS. Nevertheless, despite its relegation to a diagnosis by exclusion, many tumors still fall into this category and clinicians are still faced with the challenge of treating this group of patients which probably still forms one of the largest group of malignant soft tissue tumors. Like most sarcomas, the head and neck is one of the rarer locations for the tumor. One of the larger series was described by Clark and colleagues from the M.D. Anderson Cancer Center (MDACC) and addressed 95 patients managed between 1973 and 2005. The median age at diagnosis in their report was 53 years (range, 3–90 years); 69% of the patients were men. The parotid or neck was the most common subsite (35%), and 23% of the cases were associated with prior radiation exposure. With a median follow-up of 34 months, 32 (39%) of the 83 patients treated at MDACC with curative intent had a recurrence (isolated local recurrence in 18, isolated distant recurrence in 8, both local and distant recurrence in 5, and regional recurrence in 1). For patients treated with curative intent, 5-year overall, disease-free, and disease-specific survival rates were 55%, 44%, and 69%, respectively. Management should follow the principles described generally for STS with a strong emphasis on multidisciplinary assessment and treatment.[65]

***Angiosarcoma.*** Angiosarcoma, a rare soft tissue sarcoma, is unusually well represented in the head and neck (approximately half of all angiosarcomas), and most often as a lesion in the scalp or malar skin with the lower face only rarely involved.[66] Patients typically present in their seventh to eighth decade and males outnumber females by a factor of 3:1. The clinical manifestation of the disease is a mixture of macular, nodular, and ulcerative lesion some of which present as "blood blisters."[67] The most frequent presentation therefore is with diffuse purple maculae on the scalp with edema and bleeding. Lesions often seem multifocal with considerable distance between apparent separate nodules of ulceration or patchy macularity of purplish hue. Involvement of the eyelid and periorbital tissues is particularly problematic.

Local control is an overwhelming problem because of the difficulty deciding the optimal extent of surgical and radiotherapy margins from gross tumor and local recurrence beyond the treatment areas seems to be invariable. Regional node metastasis is more frequent than in most other sarcoma subtypes in the head and neck. Distant metastasis is also frequent, especially to lung, but bone and liver are also affected more often than expected. As with other soft tissue sarcoma, treatment has often comprised radiation therapy and surgery. All too frequently, these tumors fail beyond surgical and/or radiotherapy fields and it becomes debatable if wide surgical excision is benefiting many of these patients given the inexorable out-field recurrences in those cases with multifocal disease. Indeed, the sinister behavior of these lesions warrants evaluation of new approaches of a technical, biologic, or combined modality nature.

Historically, the 5-year survival ranges between 10% and 30%[68] and the median survival remains at approximately 8 months.[67] A recent report from the MDACC suggested that primary local management with combined modality therapies is associated with improved local control including disease-specific survival of 46% and overall survival of 43% at 5 years.[69] The authors also provide useful comments concerning radiotherapy target margins encompassing the gross disease and techniques that may be employed with emphasis on wide field margins to encompass established and potential sites of disease. Paclitaxel and doxorubicin remain important choices in the treatment of advanced disease.[69–73] Bevacizumab, a humanized monoclonal antibody to vascular endothelial growth factor (VEGF), is an attractive agent to consider in this aggressive vascular tumor given its ability to inhibit tumor growth. Koontz et al. recently reported promising results in two patients using neoadjuvant bevacizumab combined with radiation therapy.[74] Similarly, multityrosine kinases targeting similar pathways are continued to be explored.[75,76]

***Hemangiopericytoma.*** Hemangiopericytoma, with origin from the pericytes, is a rare soft tissue neoplasms but a disproportionate number (about 20%) is located in the head and neck. Often unpredictable, a true diagnosis of malignant hemangiopericytoma remains a diagnosis of exclusion, and pathologists are reluctant to predict behavior, in contrast to most sarcomas where prognostic factors are relatively reliable. Sinonasal hemangiopericytomas are reputed to be biologically less aggressive tumors than those in other anatomic sites. However, we have seen adverse outcome and metastasis in such lesions and would advise against undercautious approaches to management (see Fig. 29-1). Fletcher has indicated that unlike most so-called hemangiopericytomas elsewhere, these head and neck lesions, typically originating in the nasal cavity or paranasal sinuses, are of true pericytic origin[77] and that perhaps this provides a distinction from apparently similar lesions in other anatomic sites. Potentially, this may explain the more favorable behavior of the head lesions compared with others; alternatively, the putative, less detrimental behavior may merely be a reflection of the fact that these tumors likely present earlier within the confines of the nasoethmoid region due to earlier resulting symptoms and are therefore smaller than their counterparts elsewhere. Histologically, tumor cells are arranged around relatively prominent, small, thin-walled blood vessels. The vessels form a "staghorn pattern" and contain perivascular hyalinization (Fig. 29-9).

Sinonasal hemangiopericytoma often presents with nasal obstruction and epistaxis and appears as a grey polypoid mass that bleeds briskly on manipulation. Wide local excision is the treatment of choice. In contemporary management, this may be accomplished endoscopically, though supplementary radiotherapy may be needed if an oncologic resection is not possible.

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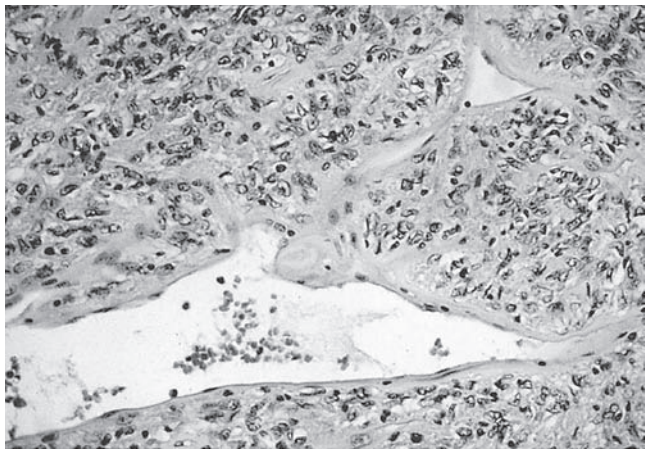


**FIGURE 29-9.** Photomicrograph of hemangiopericytoma. Dilated sinusoidal vascular channels, surrounded by tumor cells with indistinct cellular outlines ("staghorn" or "antler" configuration) is a hallmark of this tumor of "unpredictable" behavior (also see Fig. 29-1).

*Source:* Provided by Dr David Howarth, Staff Pathologist, Sarcoma Site Program, Princess Margaret Hospital and Mount Sinai Hospital, University of Toronto.

Preoperative treatments with radiotherapy or embolization may also be considered. Although a low-grade malignancy, metastases have been reported in 3% of cases with a similar incidence of death. Metastases usually occur in lung, bone, and rarely in locoregional lymph nodes.

***Synovial Sarcoma.*** Synovial sarcomas are of interest for several reasons. The name is a misnomer because such lesions virtually never originate from intra-articular or synovial tissue but have origin from undifferentiated or pluripotent mesenchymal cells. Specific translocations have assisted in their classification and may have prognostic significance (see "Classification of STS Subtypes" earlier). Location in the prevertebral, parapharyngeal, and retropharyngeal spaces is most typical and may explain the common presenting complaint of neck pain reported in a series from the MDACC, the largest single-institution cohort.[64] These tumors can also be seen elsewhere in the head and neck, including neck and tongue, and rarely may originate from the temporomandibular joint which is distinctive as synovial sarcoma almost never arises from an actual synovial joint despite the suggestive name. An enhanced incidence of lymph node involvement has been reported. Calcification in the tumor is common (evident in about half of cases and often seen radiologically; therefore, care must be taken to exclude papillary thyroid carcinoma because of the epithelial appearance of biphasic tumors and the presence of calcification) (see Fig. 29-2). Treatment approaches should follow the generic principles for the management of STS described earlier. In addition, as observed above, synovial sarcoma is notably sensitive to chemotherapy,[64] occasionally manifesting complete responses to ifosfamide and doxorubicin, and multicenter trials of adjuvant therapy are therefore warranted.

***Dermatofibrosarcoma Protuberans.*** Dermatofibrosarcoma protuberans (DFSP), as the name suggests, is an elevated nodular ("protuberant") lesion arising from the dermis with characteristic slow but persistent growth over many years. An analysis of the Surveillance, Epidemiology, and End Results (SEER) database from 1992 to 2004 showed that DFSP comprises 18.4% of all cutaneous sarcomas with an equal gender predisposition.[78] Although borderline to low grade in histologic appearance, it has a propensity for local recurrence after simple excision. Typical manifestations are of a red- to purple-colored lesion on the upper trunk, especially in proximity to the clavicular regions where it is frequent on the shoulder and supraclavicular regions of the head and neck. Not infrequently, small satellite lesions are evident at the site or bordering a skin graft following an unsuccessful previous excision. Management is best with wide surgical margins or more conservative cosmesis facilitating surgery with adjuvant EBRT following which the recurrence rate is extremely low.[79] Adjuvant radiotherapy should certainly be considered in cases of recurrence especially when disease is escaping control by traditional surgical approaches to prevent escalation to more adverse histology. Controversy exists regarding surgical margin width and excision techniques. Recent data indicate that relatively narrow surgical margins (median 2 cm) permits primary closure in 69% of patients and is associated with a very low recurrence rate (1%).[80] Mohs surgery is also advocated by some investigators. The recent observations of response to imatinib (STI 571, Gleevec) in DFSP predicted by the presence of the t(17;22) translocation which fuses the *COL1A1* collagen gene to platelet-derived growth factor receptor (*PDGFR*)[81] provides possibilities for molecular target therapies. In general, however, the typical cases fare extremely well with surgery alone or supplemented with adjuvant radiotherapy and these should remain the conventional management approaches at this time for curable disease.[79]

***Liposarcoma.*** While liposarcoma represents one of the most common STS, like the previous or current entity recognized by the term MFH, it has no particular significance in the head and neck and the principles of management for STS outlined later should be applied. As in other body sites, the most favorable outcome is associated with the well-differentiated subtype. The myxoid variant is present in 40% to 50% of all cases. Round-cell admixture and pleomorphic histology are associated with a poor prognosis. Of interest, myxoid liposarcoma may demonstrate unusual natural history with metastasis to extrapulmonary soft tissue sites (e.g., the retroperitoneum, chest wall, pleura, and pericardium being typical).[82] Such remote metastasis to unusual sites may masquerade as isolated "second sarcomas" but share identical lineage to the original primary by virtue of monoclonality confirmed by analysis of TLS-CHOP or EWS-CHOP rearrangements.[83] Another unique feature of this tumor is an unusually high response to radiotherapy compared with other STS.[84]

A detailed report of head and neck liposarcoma from the MDACC showed that both disease-specific and overall survival rates were higher in patients with well-differentiated or myxoid tumors compared with patients with round-cell or pleomorphic tumors. In fact, crude disease-specific survival was 100% for well-differentiated liposarcomas and myxoid liposarcomas versus 60% for round-cell tumors and only 45% for pleomorphic liposarcomas. This finding highlights the importance of grading and subtyping these tumors to accurately prognosticate and select appropriate treatment.[85]

### Rhabdomyosarcoma

*Clinical Issues.* A recent report examined head and neck rhabdomyosarcoma diagnosed between 1973 and 2007 in the SEER program and found an increasing annual incidence of 1.16%.[86] The authors also indicate that, despite reported advantages in overall and disease-free survival, population-based analyses seem not to have demonstrated substantial improvement over the past three decades. Prognosis is largely dependent on disease extent at diagnosis although multivariate analysis has consistently shown that young age (e.g., <10 years at diagnosis) and lack of *FOXO1* translocation t(1;13) or t(2;13) is associated with improved survival.[86] Although most tumors are diagnosed in children (age 0–9 years: 46%; 10–19 years: 23%) almost one-third

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**TABLE 29.9 Definition of Sites of Origin of Rhabdomyosarcoma of the Head and Neck**

| Site | Relative Proportions | Definition, Where Appropriate |
|---|---|---|
| Orbit | 25% | |
| Parameningeal | 50% | Nasopharynx, nasal cavity, paranasal sinuses, middle ear, mastoid, pterygoid fossa, and any parameningeal site with extension into a parameningeal location |
| Nonparameningeal site | 25% | |

*Source:* Data from Stevens MCG. Malignant mesenchymal tumours of childhood. In: Souhami RL, Tannock I, Hohenberger P, et al., eds. *Oxford Textbook of Oncology.* 2nd ed. Oxford, UK: Oxford University Press; 2002:2525–2538, with permission.

of head and neck rhabdomyosarcomas are identified in adults (age 20–55 years: 23%; >55 years: 8%) This tumor is the fifth most common cancer in children.[22] The most common sites of origin are the head and neck (about 40%) and the genitourinary tract (about 20%).[33] Among head and neck lesions, one-quarter affect the orbit, one-half are parameningeal (Table 29.9), and the remainder are in other sites.[33] The site of origin is important because it provides information concerning patterns of spread and relapse. Thus, orbital lesions, although presenting with dramatic early orbital content displacement, rarely manifest regional node metastasis or distant disease and are associated with an excellent outcome. In contrast, parameningeal sites provide significant risk of intracranial extension and leptomeningeal metastasis as well as distant disease. The initial evaluation of rhabdomyosarcoma is similar to regular STS but should include bone scan and bone marrow examination as the risk is moderate and the prognosis unfavorable. Increasingly, $F^{18}$-FDG-PET is being used to stage and assess response in RMS.[87] Treatment of these children and young adults is arduous and associated not only with a considerable burden of toxicity experienced by the individual at the time, but also with late sequelae.[33] Because most of these patients are young children, the principal dilemma concerns the use of disfiguring local treatments. On the one hand, surgery, an immediate and potentially major intrusion, usually results in cosmetic and function loss and is hardly ever advisable. On the other hand, radiotherapy has a high probability for growth and tissue maldevelopment, secondary malignancy, cataracts, and hypopituitarism later. Philosophically, only one local treatment should be employed where feasible and with the minimum possible intensity. In many ways the role of chemotherapy has been to facilitate this, in addition to treating micrometastatic disease.

*Surgery.* The role of surgery is very limited given the great sensitivity of these lesions to chemotherapy and radiotherapy and may only be reasonable in select nonorbital and nonparameningeal sites. It should only be performed at diagnosis in the absence of metastasis to lymph nodes or distant sites as prompt chemotherapy is the most critical intervention required to realize a favorable outcome. "Secondary surgery" to achieve local control following initial chemotherapy is reasonable but should be conservative. In general, radiotherapy is used most often in the head and neck sites.[33] In the young adult, where growth arrest and structural abnormalities from radiotherapy are not an issue, we only recommend surgery for the smallest lesions in favorable sites in the primary nonsalvage situation. Frequently, radiotherapy would also be added to sterilize the field and treat potential lymph node regions since this risk is high in our experience of treating young adults (see Fig. 29-5).

*Chemotherapy.* Over several decades, a complex and impressive series of trials addressing the role of chemotherapy predominantly have been completed through cooperative group mechanisms in North America and Europe and chemotherapy has improved the outcome of this disease. Its purpose is to both ameliorate the risk of distant metastasis manifestation and reduce the extent of subsequent surgery or radiotherapy (or even eliminate them).

The classic drugs have been vincristine (V), actinomycin-D (A), and cyclophosphamide (C). In addition, doxorubicin (adr) has been used in some schedules, or alone, though its role in initial therapy is uncertain.[33] Combinations have included VA, VAC (the most established), and VACadr. Recent approaches, especially in Europe, have involved substitution of ifosfamide for cyclophosphamide although the superiority of one over the other remains unproven. Ifosfamide is frequently used in combination with etoposide. These strategies are often intended to overcome drug resistance especially in advanced disease protocols. The standard of care in North America for young patients with nonmetastatic head and neck RMS would include VAC; however, we often use the combination of ifosfamide and etoposide while radiotherapy is being administered following initial induction with VACadr because of prohibitive normal tissue sensitization doxorubicin. Whenever possible, young adults with RMS should be offered enrolment onto clinical trials, most often sponsored by pediatric cooperative groups to ensure standardization of therapy.

*Radiotherapy.* Radiotherapy alone (meaning with chemotherapy) is a very effective strategy to effect local control, achieving rates in the order of 90% with doses of approximately 45 to 60 Gy at conventional daily fractionation of 2 Gy per day. In children, it is highly desirable to maintain doses at a minimum. In consequence, research is exploring the lower dose limits that can be used safely. The potential to use doses $< 40$ Gy is being considered in very select situations for lesions outside of the head and neck, although there is also concern that this may be insufficient, especially for adverse situations such as the alveolar subtype or in the face of overt clinic disease. Other strategies have included altered fractionation employing lower dose per fraction with the potential to exploit radiobiology strategies for additional normal tissue protection. The current standard is to provide doses in the order of 45 to 54 Gy and where possible use doses in the 45-Gy range. In the full-grown patient, our usual approach is to prescribe 60 Gy to sites of gross disease, while administering 50 Gy to potential areas of involvement, including the nodal regions at risk.

Radiotherapy target volumes are problematic especially in parameningeal sites where local failure and leptomeningeal relapse is possible. Thus, wide margins intracranially are considered but are associated with major potential sequelae.[33] Radiotherapy volumes should also consider coverage of the lymph nodes at risk or involved in these adverse parameningeal sites.

*Results.* Since the introduction of combination chemotherapy, survival outcome has improved dramatically from approximately 25% to 5-year survival rates of approximately 70%. The rates exceed 80% for embryonal and are somewhat lower (~65%) for alveolar (translocation-positive) and lower again for undifferentiated lesions. Good prognostic factors include favorable sites, such as nonparameningeal or orbit in the head and neck, and lack of intracranial extension or bone erosion.[88] As yet unexplained is the observation that the different histologic subtypes have an intrinsically worse prognosis in adults compared with children.[86,89] Adults may manifest extremely unfavorable behavior including

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sanctuary site metastasis and bone marrow replacement not long following initial combined modality treatment including aggressive adjuvant chemotherapy.

## TREATMENT OF BONE SARCOMAS OF THE HEAD AND NECK

The management of bone sarcomas in the head and neck suffers even more than STS from the paucity of data since they are even rarer. Approaches are again extrapolated from the more usual body sites, predominantly the limbs. Local treatment is again compromised by the proximity to important anatomic structures making resection and radiotherapy more challenging than elsewhere. The situation differs from STS in that radiotherapy is much less established as a component of treatment in bone tumors, and chemotherapy is more established in osteosarcoma and the very rarely seen Ewing tumors.

### Osteosarcoma

***Background.*** Few centers see more than one case of head and neck osteogenic sarcoma annually and differences in reported outcome appear to relate to the rarity of the disease, case selection, and variable practice patterns. Moreover, histologic grade strongly influences outcome and comparison and prediction of outcome and behavior appear to be particularly vulnerable to treatment selection bias.[90,91] Although generally considered more favorable than other osteosarcomas, possibly because of lower histologic grade, agreement is not uniform about whether the risk of metastasis is less than in long-bone tumors. The pertinent data concerning this tumor were thoroughly reviewed recently and showed that overall reported survival rates are approximately 60% to 70%.[92] At the same time, local relapse in head and neck lesions remains a grave sequel. The recent NCDB report showed a year disease-specific survival rate of 60%.[15] Factors associated with a poor prognosis were age older than 60 years; nonmandibular tumor location; tumor size >6 cm; histologic type of tumor; advanced disease stage; nonsurgical initial therapy; and positive margins of resection. The 5-year survival figures for some of these factors are shown in Table 29.10.

***Surgery.*** The foundation of local treatment is surgery and, like osteosarcoma elsewhere, should be accomplished with clear resection margins. Most usually, this follows neoadjuvant chemotherapy (see subsequent text). The principles of resection and reconstruction should be observed including anticipation of the routes of spread into difficult areas in the head and neck and skull base (Fig. 29-10). The local resection should be planned with a very clear definition of tumor extent, particularly the intramedullary component. MRI is particularly useful to delineate both intramedullary extent and any extraosseous component. Intraoperatively, tumor clearance is confirmed by pathologic examination of marrow biopsy at the resection site; similarly, verification of completeness of resection is recommended in doubtful areas such as tissues adjacent to neurovascular structures in proximity to the tumor. Any biopsy scars or other access routes for disease to "track" from the primary site should also be excised.

#### Radiotherapy

*Adjuvant Radiotherapy.* At times, only marginal resection is feasible and other options for local management must be considered. Revision surgery where feasible is advisable because the outlook for these patients is bleak. Although radiotherapy is intuitively attractive, the reality is that adjuvant radiotherapy for high-risk osteogenic sarcoma does not appear to confer the high rates of local control seen in oncology in general. Nevertheless, we feel it should be considered in these adverse situations even though it was not found to be of benefit in two systematic reviews of the

**TABLE 29.10 Disease-specific Survival Rates by Grade, Anatomical Site, Age, Size, and Margin Status from the National Cancer Database Report on Osteosarcoma of the Head and Neck**

| | | 1 Yr | 2 Yr | 3 Yr | 4 Yr | 5 Yr |
|---|---|---|---|---|---|---|
| Grade | Low 1–2 | 93.8 | 90.4 | 78.6 | 74.3 | 74.3 |
| | High 3–4 | 75.3 | 60.0 | 45.9 | 42.3 | 42.3 |
| Anatomical site | Skull/facial bones | 79.9 | 67.0 | 58.1 | 56.7 | 56.7 |
| | Mandible | 94.4 | 83.4 | 78.0 | 70.1 | 65.3 |
| Age | <30 yr | 93.0 | 83.6 | 74.8 | 71.0 | 68.7 |
| | 30–60 yr | 86.6 | 79.8 | 71.0 | 67.2 | 64.8 |
| | >60 yr | 63.4 | 44.5 | 38.2 | 34.4 | 34.4 |
| Tumor size | <3 cm | 83.6 | 83.6 | 74.0 | 69.1 | 69.1 |
| | 3–6 cm | 95.4 | 88.0 | 77.4 | 74.4 | 66.5 |
| | >6 cm | 64.7 | 38.8 | 38.8 | 25.9 | 25.9 |
| Histologic type | Osteoblastic | 84.5 | 72.3 | 63.7 | 60.8 | 58.5 |
| | Chondroblastic | 96.6 | 88.5 | 83.4 | 78.1 | 78.1 |
| Surgical margins | Clear | 95.3 | 87.9 | 81.2 | 78.7 | 75.4 |
| | Residual disease | 60.8 | 50.6 | 31.7 | 31.7 | 31.7 |

*Source:* Data from Smith RB, Apostolakis LW, Karnell LH, et al. National Cancer Data Base report on osteosarcoma of the head and neck. *Cancer.* 2003;98:1670–1680, with permission.

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**FIGURE 29-10.** Chondroblastic osteosarcoma of the vertical mandibular ramus with temporomandibular joint destruction and invasion of masticator apparatus and infratemporal fossa in a 25-year-old male. The soft tissue component has virtually "exploded" the bone. This patient did not experience local control following postinduction chemotherapy surgery and later failed combined surgery with proton beam radiotherapy. Progressive pulmonary metastases developed that were refractory to all chemotherapy until gemcitabine achieved complete and sustained remission of local and metastatic disease for some years.

literature.[90,91] As noted earlier, a significant problem affecting the literature of this disease is selection bias in the choice of adjuvant treatments and it remains possible that radiotherapy may provide valuable delay in progression. Indeed, the results of evaluation of radiotherapy indicate that it either confers no significant value[91] or is associated with worse outcome[90] because of selection of cases due to unresectability or residual disease after surgery.

Guadagnolo et al. described a series at the MDACC treated with gross total resection alone (92 patients) or combined with adjuvant radiotherapy (27 patients) from 1960 to 2007. Fourteen patients (12%) had recurrent lesions. Adjuvant radiotherapy to a median dose of 60 Gy (range, 50–66 Gy) was given to 27 patients (preoperative in 5 and postoperative in 22). Multivariate analysis revealed that only margin status predicted overall survival. Thirty-eight patients had positive or uncertain margins; 27 were treated with surgery alone, and 11 patients received adjuvant radiotherapy. The use of adjuvant radiotherapy did not improve local control in patients with negative margins ($p = 0.48$) but did improve local control for those with positive or uncertain margins ($p = 0.006$).[93] Furthermore, the use of radiotherapy for patients with positive resection margins resulted in improved overall survival in this report.

DeLaney et al.[94] described an overall local control rate at 5 years of 68% (±8.3%) in 41 patients in whom surgical resection with widely negative margins is not possible. Seventeen of these patients also had their tumor arising in the head and neck and 8 were of spinal origin. They concluded that RT can help provide local control of osteosarcoma for patients and appears most effective in situations in which microscopic or minimal residual disease is being treated.[94]

Another unusual approach that originated in extremity osteosarcoma offers prospect for combining systemic treatment with radiotherapy. Machak et al.[95] described an experience of neoadjuvant chemotherapy administered with EBRT in a consecutive series of 31 of 187 patients with nonmetastatic osteosarcoma who had refused surgery. In the subgroup with a pronounced response to chemotherapy, the 5-year survival after chemoradiotherapy was 90%. These results suggest that the disappointing effect of standard doses of radiotherapy on osteosarcoma may not apply in the setting of effective response to chemotherapy. Notwithstanding these selected results, they must still be balanced against the potential of late adverse outcomes, including local and metastatic recurrence, as well as deleterious normal tissue effects, even if the theoretical promise of this nonsurgical approach is to enhance function and quality of life.

It would seem from these retrospective results that the role of radiotherapy has not been explored adequately, as the actual contribution is only modest in some series and more robust in others and the studies themselves seem to be confounded by selection bias. What are needed are controlled trials, but it would be most improbable that this will ever be explored in a randomized prospective fashion, even through a multicenter mechanism, because of disease rarity. At the same time, the role of radiotherapy is not likely to be considered in osteogenic sarcoma of the limbs where the local control rate is at least 90% following neoadjuvant chemotherapy and limb salvage surgery, and wide application of adjuvant radiotherapy is unnecessary.

Finally, if radiotherapy is employed it should follow identical principles described earlier for STS. In essence, routes of spread and location of tumor including potential tissues contaminated by surgery, biopsy, or tumor invasion/incursion should be considered in the planning volumes. Adequate doses are also necessary and should probably exceed 60 Gy in the postoperative setting, even when only microscopic disease is present because of the known reputation for relative radioresistance.

*Radiotherapy Alone.* At the present time, the literature does not provide any convincing evidence that radiation as a sole modality is useful for the local management of osteosarcoma. It should therefore be confined to the experimental approach or may need to be reserved for palliation. Unfortunately, in our experience it has not been successful for the latter. One promising strategy is the use of carbon-ion radiation therapy that is only available at a few highly specialized facilities worldwide. Jingu and colleagues described a small series that achieved a 3-year local control rate of 85.7% for unresectable osteosarcoma treated with 70.4 GyE, but the result was much inferior with lower doses.[46]

### Adjuvant Chemotherapy

*Adjuvant Chemotherapy for Osteosarcoma in General.* A number of trials have established the routine use of chemotherapy in extremity osteosarcoma, although initially controversy existed about whether the apparent survival benefits could relate to improvements in other aspects of the illness and not to the use of systemic treatment. Specifically, a change in natural history was posited as contributing combined with more aggressive staging and surgical intervention for metastases, as well as better local surgery. The discordant views were addressed by the completion of the Multi-institution Osteosarcoma Study[96] in which patients were randomized to observation only (instead of systemic therapy) or multiagent chemotherapy (Rosen T10 protocol). In Rosen protocols, a variety of drugs were used (methotrexate, doxorubicin, bleomycin, actinomycin-D, and cyclophosphamide

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given repeatedly for up to 1 year) including cisplatin for "poor responders" (see below). A significant improvement in disease-free survival was observed in favor of the chemotherapy arm of the trial although overall survival was not apparently different in the initial report of the trial. A putative influence of salvage treatment may have explained the early observation, but with later follow-up a survival advantage in favor of early chemotherapy was apparent.[97]

Recently, however, Allison et al. comprehensively reviewed all significant published data regarding osteosarcoma and outcome in the modern medical era in an attempt to evaluate treatment progress over time. The study specifically excluded head and neck osteosarcoma and low-grade lesions in general. In total, 5-year overall survival was reported in 47,227 nonmetastatic, high-grade osteosarcoma patients aggregated from 264 series. Published survival improved dramatically from 1960s to 1980s and then leveled, or in some measures decreased. Recurrence rates decreased in the 1970s and then leveled. Though significant gains have been made in the past, no improvement in published osteosarcoma survival has been seen since 1980, highlighting the importance of a new strategy in the systemic management of this still very lethal condition.[98] To what degree these results apply to the general management of head and neck osteosarcoma remains unclear, given the more favorable biology of this tumor compared with the more common presentations of the disease.

As noted, a variety of agents have been used have been used in the chemotherapy of osteosarcoma. Currently, high-dose methotrexate-based chemotherapy with leucovorin rescue, doxorubicin, and cisplatin are accepted active agents, though the ideal combination remains to be defined.[99] Because of toxicity of prolonged chemotherapy, the European Osteosarcoma Intergroup performed a multicenter randomized study comparing 12 months of multiagent methotrexate-based chemotherapy versus 6 courses of doxorubicin/cisplatin. Survival appeared comparable for both groups.[100] More recently, ifosfamide has emerged as an active agent but questions remain about optimal scheduling and dosage. Ongoing trials are in progress evaluating these questions and include the use of hematopoietic growth factors such as granulocyte-stimulating factor (G-CSF) in intensification protocols.

An additional approach has involved the combination of the immunomodulator liposomal muramyl tripeptide phosphatidylethanolamine (MTP-PE) with postoperative chemotherapy. A statistically significant overall survival advantage and a non-significant trend in event-free survival have been reported in a randomized trial employing this strategy.[101] Despite this, reservations remain concerning the exact role of this novel immunomodulator approach.[99]

There still remains uncertainty about whether neoadjuvant chemotherapy is superior to prompt postoperative chemotherapy in terms of survival benefit. Neoadjuvant chemotherapy permits the potential for early eradication of micrometastatic disease, delivery of chemotherapy to an intact blood supply, and assessment of the effectiveness of the preoperative chemotherapy regimen used. The latter has become an important principle in the management of osteogenic sarcoma through assessment of histologic response after systemic chemotherapy. It also appears to facilitate surgery and was pivotal in the introduction of limb preservation for osteosarcoma of limb bones. In osteosarcoma of the extremities, completeness of histologic response to neoadjuvant chemotherapy (e.g., <5%–10% tumor viability at surgical resection) has been correlated with improved survival. Whether modulating chemotherapy in poor responders offers benefit remains unknown and was the subject of a recently completed international randomized controlled trial (EURAMOS I). The results of this trial will not be available for a few years.

*Adjuvant Chemotherapy in Head and Neck Osteosarcoma.* Although important trials have been completed in extremity osteosarcoma, prospective studies in the head and neck are lacking and treatment has been inconsistent. As a result, there is disagreement about its role in the seemingly more favorable osteosarcomas of the mandible and maxilla compared with extremity lesions. Remarkably, in this rare condition, two independent "quasi" meta-analyses of the retrospective data regarding the role of adjuvant chemotherapy were reported simultaneously.[90,91] In both studies, the authors described their methodology in detail, which were similar in restricting cases to those where individual patient data were available in the reports chosen for analysis. In this way, actuarial estimates of outcome could be calculated and proportional hazards techniques applied to estimate risk and to attempt to control for prognostic variables. Of importance, both studies report the conclusion that radiotherapy seemed to be unhelpful, bearing in mind the caveats mentioned earlier and that the inherent biases of retrospective studies that cannot be completely controlled for.

In addition, however, the authors reached different conclusions regarding the efficacy of systemic chemotherapy. On the one hand, Kassir and colleagues concluded that the role of chemotherapy in head and neck osteosarcoma remains unproven.[90] In contrast, Smeeles and colleagues maintained that chemotherapy does improve survival and advocated for the adoption of the same chemotherapy protocols as used for long-bone primary sites.[91] It turns out that an important distinction separates the two studies. Kassir et al. accepted all nonmetastatic patients whereas Smeeles et al. restricted entry to those studies that reported on surgical margins. Both the variables "involved margins" and "chemotherapy," when adjusted for each other turned out to be significant.[102] Although it is of interest to observe the findings by Smeeles et al., we would also caution that neither the "margin status" nor the "response to chemotherapy" are known at baseline when a patient first presents at diagnosis, and the patients who performed well in their study following chemotherapy are already selected by virtue of favorable responses to surgery (i.e., clear margins). Moreover, the margin status could itself be complicated by whether there was a favorable response to preoperative chemotherapy. In other words, we still do not have strong evidence about what to recommend for a given patient presenting for the first time until after surgery has been performed, and in most cases after induction chemotherapy as well. In the NCDB report, no substantial difference in the 5-year survival rate was noted between treatment with surgery alone (74.7%) and surgery with adjuvant chemotherapy (71.3%).[15]

***Recommendation for Individual Patients.*** Notwithstanding the discussion concerning the evidence about the role of adjuvant chemotherapy in osteogenic sarcoma and the possible more favorable behavior compared with long-bone lesions, it is our view that certain of these lesions can manifest sinister behavior (see Fig. 29-10) and we would routinely advise systemic chemotherapy in fit patients. This is administered using a neoadjuvant/induction approach. Of interest, despite their results suggesting a lack of benefit, Kassir et al., influenced by their observation of relatively poor prognosis for these lesions, provide similar recommendations to ours.[90] Our general approach to management of head and neck osteosarcoma is summarized in the algorithm (Fig. 29-11).

## Chondrosarcoma

***General Comments.*** Chondrosarcomas make up 10% of malignant bone tumors and is the second most common sarcoma arising in bone (after osteosarcoma). Chondrosarcoma also comprises <10% of these primary bone malignancies in the

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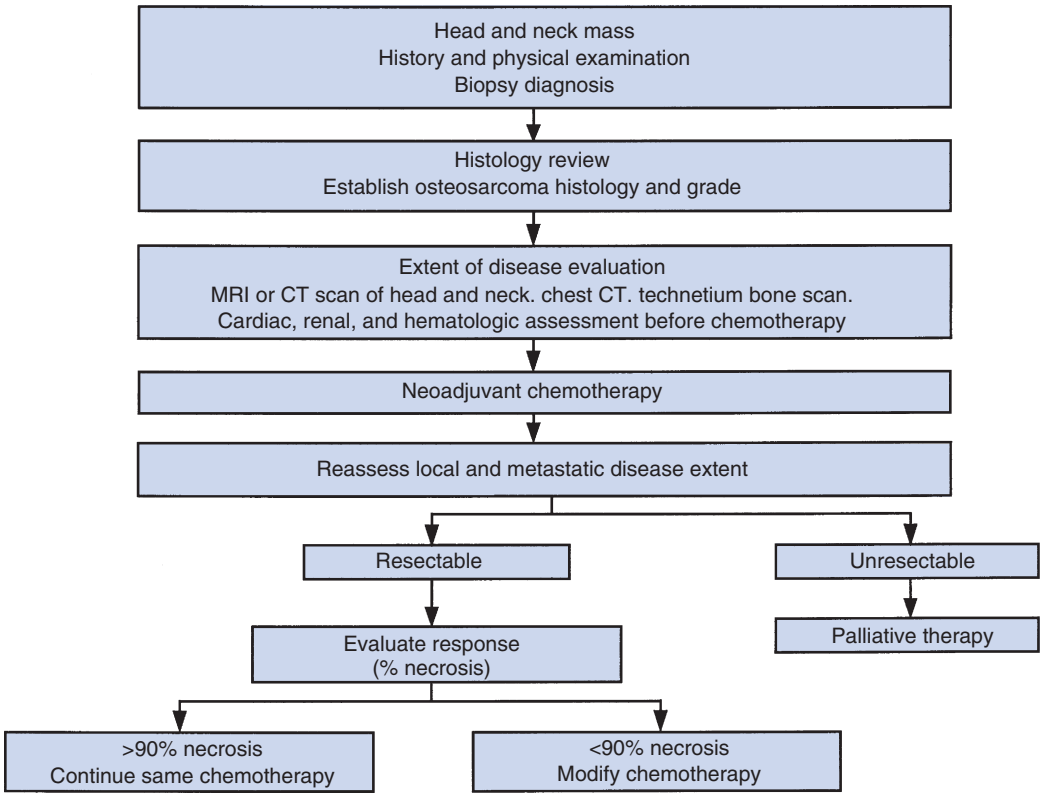



**FIGURE 29-11.** Flow diagram for the management of osteosarcoma of the head and neck using usual approach of induction chemotherapy with pathologic response assessment.

head and neck. In this location, it presents a broad spectrum of tumors of similar histology but widely dissimilar behavior and demographic character. For example, age and gender distribution vary by histologic subtype and site. In the National Cancer Data Base Report, older age (>50 years) was most prevalent among laryngotracheal cases (90%) and among men.[16] In contrast, women and patients younger than 50 years were more likely to be associated with lesions of the osseous head and neck skeleton including the sinonasal region. These demographic differences in a large contemporary database indicate that head and neck chondrosarcoma encompasses subgroups of dissimilar cancers and the great heterogeneity of presentation and biology, as well as potential management strategies, makes it difficult to summarize outcome succinctly. The NCDB analysis also demonstrated that decreased survival was statistically associated with advanced-stage, higher-grade, and the histologic subtypes myxoid or mesenchymal.

***Surgery.*** All evidence about the management of chondrosarcoma of the head and neck would support the use of surgical excision as the primary treatment when possible. In addition, the surgery should concentrate on the primary tumor following the principles outlined for osteosarcoma, including adequacy and verification of complete excision and meticulous staging prior to excision. These principles will not be repeated other than to emphasize that wide excision beyond the pseudocapsule is required since chondrosarcomas tend to have microscopic fingerlike extensions and have a notorious propensity to seed the wound with later nodular recurrence if the tumor is violated. In addition, neck dissection is not indicated because of the overall low incidence of regional metastases (~5%).[16]

### *Adjuvant Treatment*

*Adjuvant Chemotherapy.* The management of osteosarcoma and chondrosarcoma differ in two significant ways, both relating to the use of adjuvant treatments. Firstly and for reasons of efficacy, chemotherapy is not ordinarily a component of management of chondrosarcoma, in contrast with osteosarcoma. The exception is in the mesenchymal subtype where chemotherapy was used in the majority of mesenchymal chondrosarcoma cases (57.5%) in the NCDB series and has been our policy at Princess Margaret Hospital.[103] By extrapolation, chemotherapy would be used as for osteosarcoma or Ewing.

*Adjuvant Radiotherapy.* Radiotherapy, usually a doubtful addition to the treatment of osteosarcoma, can be a very effective adjunct to the treatment of chondrosarcoma where there is concern about the adequacy of resection, although it is acknowledged opinions vary as to its value. At our center, we have always regarded positive resection margins as an indication for adjuvant radiotherapy[104] and would expect similar outcome to high-risk positive-margin STS following combined surgery and radiotherapy. Goda et al. reported the outcome of 60 patients with extracranial high-risk chondrosarcoma who underwent surgery and RT between 1986 and 2006. Sites included pelvis/lower extremity (48%), chest wall (22%), spine/paraspinal (17%), and head and neck (13%). Overall, median tumor size was 7 cm (range, 1–22 cm) and at least 40% had positive resection margins with a reasonable number with overt gross tumor remaining following resection. Preoperative radiotherapy (median, 50 Gy) and postoperative radiotherapy (median, 60 Gy) were used in 40% and 60% patients, respectively. The crude local control rate was 90%. Patients with R0, R1, and R2 resections had local control of

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100%, 94%, and 42%, respectively. The 10-year overall survival, progression-free survival, and cause-specific survival were 86%, 80.5%, and 89.4%, respectively.[104]

Both adjuvant radiotherapy and radiotherapy as a sole modality (see below) should follow similar principles regarding planning, dose-fractionation parameters, and target volumes as outlined for STS and osteosarcoma. Of interest, the use of radiotherapy is not altogether unusual having been used as a component of management in >20% of cases in the large NCDB report,[16] which would follow our general recommendations.

***Radiotherapy Alone.*** Radiotherapy as sole modality is also capable of long-term control of chondrosarcomas in difficult locations, such as the clival regions, although here opinions may vary about whether this is best accomplished with proton beam radiotherapy, heavy ions, or IMRT. Ten-year control rates in the order of 70% to 80% have been reported from excellent centers using proton beam radiotherapy. Our approach is to use radiotherapy as the sole modality in cases where the lesion is not resectable without great risk to the patient. Examples would include the need to sacrifice the critical vascular supply in clival lesions and especially where the lesion is of small volume (Fig. 29-12).

***Results of Management of Chondrosarcoma.*** As noted earlier, the grade of the lesion and the accessibility for treatment are important determinants of outcome. In the NCDB, survival rates appeared similar regardless of the site of disease and are profoundly influenced by the grade of the lesion. The 5-year disease-specific rates generally exceed 80%. The beneficial outcomes are clearly related to the fact that grade 1 (50%) and grade 2 (37%) were the predominant subtypes with grades 3 and 4 representing only 8% and 4%, respectively, since superior outcome for patients with lower-grade tumors (93.2%) compared with higher-grade tumors (67.3%) ($p = 0.0265$) (Table 29.11).[16] Individual series have not reported as favorable outcomes for the higher-grade lesions.

### *Special Situations in Head and Neck Chondrosarcoma*

*Chondrosarcoma of the Larynx.* Chondrosarcoma is the most common sarcoma of the larynx. Usually, it presents as a mass originating on the posterior cricoid lamina eventually resulting in airway compromise and voice dysfunction (Fig. 29-13). This neoplasm is particularly indolent in behavior, carrying an extraordinarily favorable outcome in terms of survival. Generally, in the older age group (>50 years), >90% of cases are low-grade lesions, and males are most frequently affected. Complete laryngectomy is virtually always curable but more conservative approach as suggested by the Mayo Clinic report appears more appropriate given the excellent survival rates.[105,106] In their series, only 14% received total laryngectomy. Despite a high recurrence rate among patients treated without total laryngectomy by either "complete external removal" (27% recurrence rate) or by "subtotal external removal" (67% recurrence rate), acceptable 5-year survival (90.1%) and 10-year survival (80.9%) resulted from salvage surgery. The results when compared with expected survival for a controlled population appear to show no detriment to survival

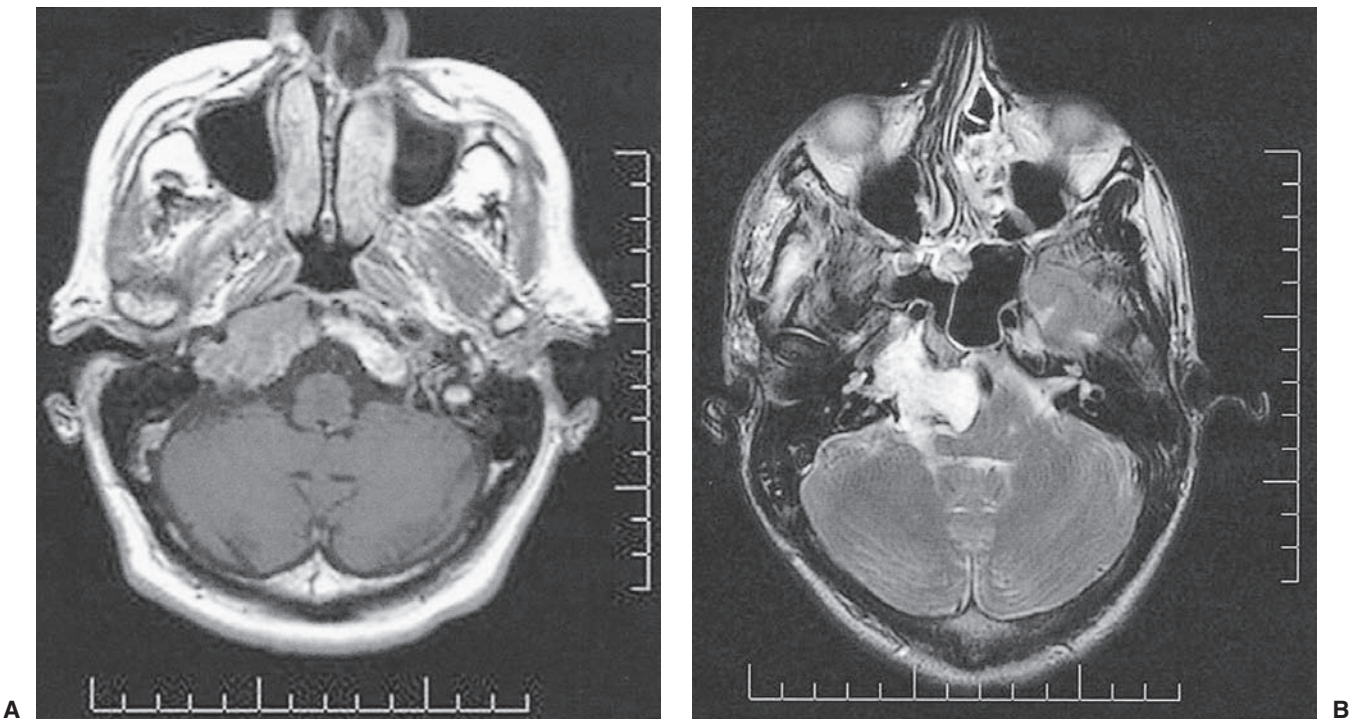


**FIGURE 29-12.** Magnetic resonance imaging (MRI) of two cases of chondrosarcoma of the petroclival region. In one, an enhancing mass is seen destroying the right side of the clivus. The right internal carotid artery is incorporated within the mass at the skull base and through the petrous portion. The patient was treated with stereotactic intensity-modulated radiation therapy (IMRT) to a high-fractionated dose and remains asymptomatic with 12 years of follow-up **(A)**. The second case **(B)** exhibits a chondrosarcoma of the petroclivus complicating Maffucci syndrome (see text for details). This 21-year-old male was managed with surgery followed by postoperative stereotactic IMRT to minimize the dose as much as possible to the juxtaposed brain stem (limit of 55 Gy fractionated to a small portion of the brain stem was achieved with this technique). He is also well with >10 years of follow-up.

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**TABLE 29.11 Disease-specific Survival Rates (%) by Grade and Anatomical Site from the National Cancer Database Report on Chondrosarcoma of the Head and Neck**

| | 1 Yr | 2 Yr | 3 Yr | 4 Yr | 5 Yr |
|---|---|---|---|---|---|
| **Grade** | | | | | |
| 1–2 | 97.6 | 97.6 | 96.2 | 93.2 | 93.2 |
| 3–4 | 90.9 | 90.9 | 79.6 | 67.3 | 67.3 |
| **Anatomical site** | | | | | |
| Head and neck bones | 96.7 | 96.7 | 94.6 | 92.4 | 92.4 |
| Laryngotracheal | 95.8 | 95.8 | 93.3 | 88.0 | 88.0 |
| Sinonasal | 93.9 | 93.9 | 93.9 | 87.5 | 87.5 |
| Head and neck soft tissue | 100 | 93.6 | 93.6 | 80.2 | 80.2 |

*Source:* Data from Koch BB, Karnell LH, Hoffman HT, et al. National cancer database report on chondrosarcoma of the head and neck. *Head Neck.* 2000;22:408–425, with permission.

because of the chondrosarcoma (Fig. 29-14). We normally explain to patients that postoperatively radiotherapy following conservation laryngeal surgery should improve the ultimate likelihood of larynx retention even though an improvement in survival cannot be realized by this approach.

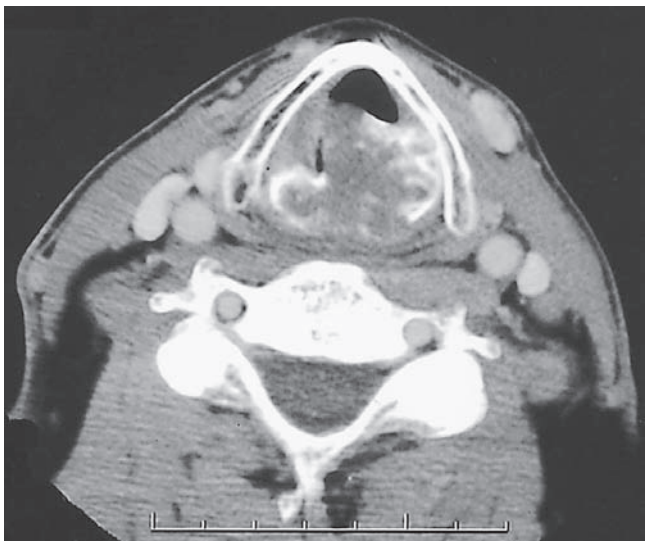


**FIGURE 29-13.** Contrast-enhanced computed tomography axial view of a typical low-grade chondrosarcoma of the posterior cricoid lamina in a middle-aged male. Note airway reduction by the calcified and well-demarcated lesion. Although recommended intralesional resection with likely prospect of future and repeated reexcisions, he received postoperative radiotherapy by one of the authors (BO'S), at patient's request to minimize risk of local failure. He remains well without recurrence with good voice 11 years later.

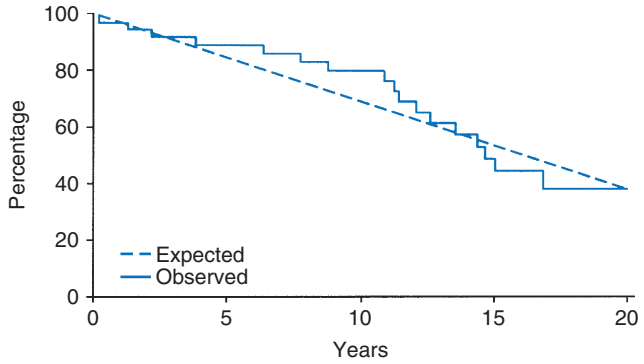



**FIGURE 29-14.** Survival curve for chondrosarcoma of the larynx treated at the Mayo clinic compared with normal population survival.

*Source:* Reproduced with permission from Lewis JE, Olsen KD, Inwards CY. Cartilaginous tumors of the larynx: clinicopathologic review of 47 cases. *Ann Otol Rhinol Laryngol.* 1997;106:94–100.

*Skull Base Chondrosarcomas.* Although rare, chondrosarcomas often arise in the skull base including clivus and petrous temporal bone. Such lesions pose particularly severe problems including pain or gradually progressive features of brain stem compression from intracranial intrusion (e.g., cranial nerve dysfunctions especially sixth nerve at the outset). The only favorable aspect is that they are, like the majority of chondrosarcomas, usually of low-grade histology.

Given the grave significance of chondrosarcomas in these locations, and the inability to perform a complete excision in the majority of cases (see Fig. 29-12), suitable patients with skull base primaries should be referred to specialized centers for consideration of expert skull base surgery in conjunction with specialized radiotherapy approaches including particle beam therapy, or stereotactic photons treatments with or without IMRT. A number of small series have shown that a combination of surgical debulking and high-dose precision radiotherapy results in durable local control in a large proportion of skull base chondrosarcomas (in excess of 80%) with modest late toxicity. The outcome of lesions <25 mL in volume is particularly impressive especially if adequate doses are administered with a combination of photons and protons to approximately 70 Cobalt Gray Equivalent (CGE).[107] Others have reported similar impressive results[108] and are also apparent in smaller series with either protons or fractionated stereotactic radiotherapy,[109,110] and more recently carbon ions.[111] Such series generally also combine radiotherapy with surgery. Evaluation of this literature is problematic as it is frequent to that outcome of skull base and cervical spine chordoma is reported together with that of chondrosarcoma. The literature is also changing in this regard as technology involves including the use of carbon ion that is only available at a very few centers worldwide.[46,111] Schulz-Ertner et al. recently described their experience of treating 54 patients with low-grade and intermediate-grade chondrosarcomas of the skull base using carbon-ion radiation therapy (RT) between 1998 and 2005. All patients had gross residual disease following surgery. The actuarial local control rates were 96.2% and 89.8% at 3 and 4 years; overall survival was 98.2% at 5 years. Only one patient had grade 3 toxicity.[111]

*Mesenchymal Chondrosarcoma.* This subtype tends to be more aggressive locally and has a higher rate of metastasis. Survival tends to be lower as a consequence, and it is most commonly managed with multimodality approaches. As noted earlier, this would ordinarily include a similar chemotherapy approach as used for osteosarcoma in addition to surgery and radiotherapy.[103]

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## Ewing Sarcoma

***General Comments.*** Earlier, we mentioned that this tumor is exceptionally rare in the head and neck. The disease afflicts children predominately but is rarely seen below the age of 5 and in patients older than 30 years. About 25% of patient present with distant metastasis, most often to bone.

Multimodality treatment is strongly recommended consisting of external-beam radiation, and/or surgery, and multiagent chemotherapy. We cannot emphasize too strongly the need for multidisciplinary assessments in such patients from the start, especially to make sure that the disease is adequately documented with CT and MRI before treatment is initiated. Chemotherapy is usually the first intervention, and it is usually several months before radiotherapy or surgery is performed. By that time the situation will have changed and the true areas of risk may long since have been disguised in the chemotherapy response.

Although radiotherapy is highly effective, recent evidence has drawn attention to the problem of local failure in bulky disease, effects on bone growth, and second malignancies following radiotherapy.[112] Surgery should therefore also be considered in the management of different situations. We would emphasize that, with the current state of knowledge, chemotherapy alone should not be regarded as a standard to control gross tumor.

A recent report of a small series from the University of Florida has emphasized a strong role for radiotherapy in combination with multidrug chemotherapy instead of tumor debulking surgery when oncologic excision is not possible.[17] These authors also advocate strongly for achieving local control irrespective of treatment modality and local management philosophy. In essence, they suggest that local control may have a role in reducing distant metastasis which was exceptionally uncommon in their series of head and neck Ewing sarcoma.[17]

***Radiotherapy.*** Appropriate radiotherapy target volumes should include the entire bone that was involved as well as any extraosseous soft tissue component of the tumor. Treatment planning should be based on the original tumor volume before chemotherapy. Classically, an initial 5-cm margin beyond disease and bone has been recommended for Ewing sarcoma.[113] However, as in STS and chondrosarcoma head and neck planning, this needs to be tailored to the suitability of the anatomic region. Care must be taken to protect critical organs in the head and neck and the "classic" approach will rarely be used. Additional boost to the original area of visualized gross disease is also highly recommended.

Whenever a partial bone resection is undertaken, radiotherapy is indicated to the microscopic areas and a boost applied to any gross residual disease as noted above.

Doses of radiotherapy should exceed 50 Gy in 1.8 to 2 Gy per fraction for gross disease and need to be tailored to the critical organs at risk, the bulk of disease at the start of chemotherapy, the response to chemotherapy, and how complete any contemplated resection may be. Generally conventional daily fractionated radiotherapy is used, but studies of smaller dose per fraction altered fractionation are being tested to assess ability to minimized late-responding tissue damage.

***Surgery.*** Surgery should allow radiotherapy to be avoided entirely in low-volume disease. Concern about resection margins is an indication that radiotherapy is needed, which hopefully can be administered with lower dose as the gross disease will have been resected. This may be particularly helpful in the vicinity of critical anatomy and, in that circumstance, a preoperative radiotherapy approach may have advantages for the reasons described earlier for other tumors. We feel that very large disease is an indication for combined treatment (surgery and radiotherapy), but small volume disease is best managed with radiotherapy as the sole local modality unless disease is limited and surgery can be accomplished with wide margins obviating the need for radiotherapy. Alternatively, where radiotherapy is compromised with respect to dose and/or volume considerations, surgery should also be considered.

***Chemotherapy.*** Chemotherapy is critical to the improvements that have been seen in the management of Ewing sarcoma in recent decades. The classical approach is a five-drug regimen of vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide.[114] Most recently, interval compression of chemotherapy delivered every 2 weeks has demonstrated improvement in 5-year event-free survival from 65% to 73%.[115] The treatment of head and neck Ewing tumors would follow the same principles as tumors located at other sites with local control being offered prior to completing the first half of chemotherapy.

# MANAGEMENT OF LOCAL RECURRENCE AND METASTASIS

This important area is discussed in the context of local recurrence following definitive local management. In some situations, this may be associated with regional lymph node (rarely) or with distant metastasis. More commonly, distant metastasis will manifest as disease confined to the lungs as the first manifestation of recurrence. In general, distant metastasis at presentation should be approached using similar principles.

## Local Recurrence

***General Approach.*** Appropriate treatment of an isolated local sarcoma recurrence can result in cure, or prolonged disease-free survival, and the approach to management should be similar to that taken with a primary tumor. However, effective management is often complex and influenced by tumor location and extent, and any prior local therapy. We have outlined an approach to the evaluation and management of locally recurrent soft tissue sarcoma (Table 29.12).[116] Assessment must include a knowledge of all prior surgery, including resection margins achieved as well as previous radiotherapy and chemotherapy. A biopsy is necessary both to confirm the diagnosis and to determine change in tumor character from the original lesion.

***Adjuvant "Naïve" Recurrence.*** In patients with STS not previously treated with radiotherapy or chemotherapy, combined modality therapy should be used especially because these can generally be administered safely. In STS, the potential for adjuvant chemotherapy to enhance local control may mean it could have a role in local salvage as it is improbable that it was used initially. In osteogenic sarcoma, this should include consideration of induction chemotherapy as described earlier for primary tumors and additional radiotherapy considered if resection margins remain a concern. In the case of soft tissue sarcoma and chondrosarcoma, we would generally recommend preoperative radiotherapy because of the better opportunity to spare critical structures since there is limited opportunity for tissue sparing due to prior resection of tissues in addition to contamination by previous surgery. Adequate postoperative radiotherapy following further surgery would also be appropriate but more problematic.

***Recurrence with Prior Adjuvant Therapy.*** For previously treated lesions, individualization is needed. Prior irradiated STS and chondrosarcomas would generally undergo tumor bed implantation with brachytherapy catheters in conjunction with a wide local excision. If resection margins are closer than 1 cm, brachytherapy is administered 5 to 7 days postoperatively. Osteosarcomas

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**TABLE 29.12 Schema for the Management of Locally Recurrent Sarcoma**

| Context of Local Recurrence | Recommended Approach |
|---|---|
| No prior chemotherapy and/or radiotherapy | Consider combined approach with external-beam radiotherapy. In osteogenic sarcoma, consider induction chemotherapy with pathologic response assessment |
| Prior radiotherapy | Combined approach with brachytherapy |
| Critical structure involvement | Consider preoperative radiotherapy |
| | Ablative approach may need to be considered |
| In the presence of metastases | Multiple metastases—palliative treatment possibly including aggressive local treatment |
| | Few resectable metastases—local management as for nonmetastatic context with metastasectomy |

*Source:* Modified from Catton C, Swallow CJ, O'Sullivan B. Approaches to local salvage of soft tissue sarcoma after primary site failure. *Semin Radiat Oncol.* 1999;9:378–388, with permission.

should undergo chemotherapy if this is still possible bearing in mind prior treatment. This is followed by resection and potentially additional radiotherapy considered if resection margins remain a concern as radiotherapy is unlikely to have been used at initial management.

***Local Recurrence with Metastasis.*** Concurrent metastases are occasionally identified with local relapse. Patients who recur with multiple symptomatic metastases after a short disease-free interval are best managed with palliative approaches. Aggressive surgical palliation is rarely indicated in this situation, but local excision of a small or superficial recurrence may delay or prevent the development of local complications. The occasional patient presenting with local recurrence and limited systemic disease may benefit from aggressive treatment, especially after a long disease-free interval. This should include local salvage according to the principles outlined above, in addition to consideration of metastasectomy as described below.

## Metastatic Disease

***Surgery for Metastases.*** Sarcomas of both bone and soft tissue show an unusual predilection for metastasis to the lung, including disease isolated to the chest at presentation or recurrence. In selected cases, pulmonary metastasectomy has the potential to be a curative although distant disease at other sites is unlikely to be cured, excepting soft tissue metastasis in liposarcoma. However, treatment of metastatic bone disease is unfortunately palliative.

***Chemotherapy for Metastases.*** Systemic therapy is available in the metastatic setting though the choice of drug and timing of treatment initiation in incurable, locally advanced or metastatic STS remains debatable. Bramwell et al. performed a meta-analysis on data on 2,281 participants from eight Randomized Clinical Trials (RCTs) from reports of single-agent doxorubicin versus doxorubicin-based combination chemotherapy and concluded that single-agent doxorubicin was the optimal therapy. Median survival ranged from 7.7 to 12.0 months with single-agent doxorubicin ranged and 7.3 to 12.7 months with combination chemotherapy.[117] Recently, a randomized trial confirmed that a novel tyrosine kinase inhibitor, pazopanib, improved the disease-free and overall survival of patients with metastatic STS.[118] Pazopanib is now approved for use in patients with advanced sarcoma in the United States.

Advanced osteosarcoma remains difficult to treat, and chemotherapy alone does not appear to be curative for inoperable metastatic disease. There have been no controlled studies designed to demonstrate the benefit of chemotherapy at recurrence in terms of adding to salvage rates. Also, unlike the case for many STS cases, many osteosarcoma patients will already have been treated with active agents.

***Recommendation for Individual Patients with Metastases.*** In the absence of additional data, and in view of the potential to salvage a modest number of patients, pulmonary metastasectomy may also be considered in appropriate patients. Generally, we choose patients with a long disease-free interval (preferably at least 2 years from initial treatment), relatively few lesions (>4 lesions is less likely to be successful), and where clear margins are likely to be obtained. Occasionally, postoperative radiotherapy is administered for microscopic residual disease in an accessible site using similar principles to those described for radiotherapy of primary lesions. Appropriate cases should be identifiable through regular surveillance chest imaging following prior treatment of the primary tumor. We also advise resection for bilateral as well as unilateral disease recognizing that the latter is more likely to be favorable. Systemic therapy may also be used to control disease progression especially if symptomatic in otherwise fit and usually young patients. Resection may be considered subsequently.

In practice, it is often beneficial to allow a period of observation once metastases have been detected prior to any intervention to appreciate the biology of the disease. This is because additional initial subclinical metastases may manifest subsequently, thereby permitting selection of the more favorable cases that may benefit from resection. The thoracic surgeon must also determine whether a lateral thoracotomy approach should be chosen versus a median sternotomy as the latter provides the opportunity to examine both lungs for additional palpable lesions that may not have been detected by imaging.

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# PART B:
# Radiologic Imaging Concerns

Jeffrey A. Bennett

Almost all varieties of sarcoma occur in the head and neck, and virtually all warrant imaging prior to treatment. When the tumor is small, the site of origin can often be determined, such as bone or muscle, which can help predict the pathology, but biopsy will nevertheless be required. Fine-needle aspiration is often inadequate for diagnosis, thus a core biopsy or open biopsy may be required. When an image-guided core biopsy is performed, the needle tract should be documented, as well as the skin entry site, as there is the potential for seeding of tumor and the surgeon may elect to resect the tract.

As with all tumors of the head and neck, the goal of imaging is to reveal the full extent of local disease, the presence of cervical lymphadenopathy, and the presence of distant metastases, so that an optimal treatment plan can be made. For certain sarcomas, complete resection of the tumor is a primary goal for improved prognosis when there are no distant metastases,[1,2,3] and imaging is used to guide the surgeon. Often CT and MRI are complementary. CT is superior for visualizing bony destruction as well as the tumor matrix. MRI is better at visualizing the soft tissue boundaries of the lesion, although often this can be difficult when there is peritumoral edema.

Rhabdomyosarcoma is the most common malignancy of striated muscle cell origin in the head and neck[4] and certainly the most common in children.[5] About one-third arise in the orbit and the rest elsewhere in the head and neck. They are typically not surgical lesions, but are treated with combined chemotherapy and radiation therapy. Defining the full local extent of the tumor on imaging studies is thus essential for setting up the radiation fields. These tumors are most often very bright on T2-weighted images, are isointense to muscle on T1-weighted images, and enhance with contrast (Fig. 29-15). Necrosis is commonly seen in larger tumors (Fig. 29-16). Other malignant mesenchymal sarcomas are rare. One such tumor is the synovial cell sarcoma, which despite its name does not arise from joints (Fig. 29-17).

Osteosarcomas have a very characteristic imaging appearance on CT where the bone is destroyed and replaced by tumor which grows an osteoid matrix (Fig. 29-18). A sunburst periosteal reaction can often be seen. Adjacent soft tissue invasion is common. On MRI, the calcified osteoid matrix is dark on T1- and T2-weighted images (Fig. 29-19).

Chondrosarcomas have a different matrix as seen on noncontrast CT. This matrix typically consists of thin arcs and rings of calcium (Fig. 29-20), although not infrequently no matrix will be seen in the lesion. On MRI, the characteristic feature is the very high signal seen on T2-weighted images. These lesions are more commonly seen at the skull base, usually laterally at the petroclival fissure (Fig. 29-21).

Postradiation sarcomas can be seen in the head and neck, typically 10 to 20 years following treatment. These lesions usually have a different appearance from the original tumor, raising suspicion for a radiation-induced sarcoma (Fig. 29-22). Debnam et al.[6] published a useful paper about the spectrum of imaging findings seen in radiation-induced sarcomas.

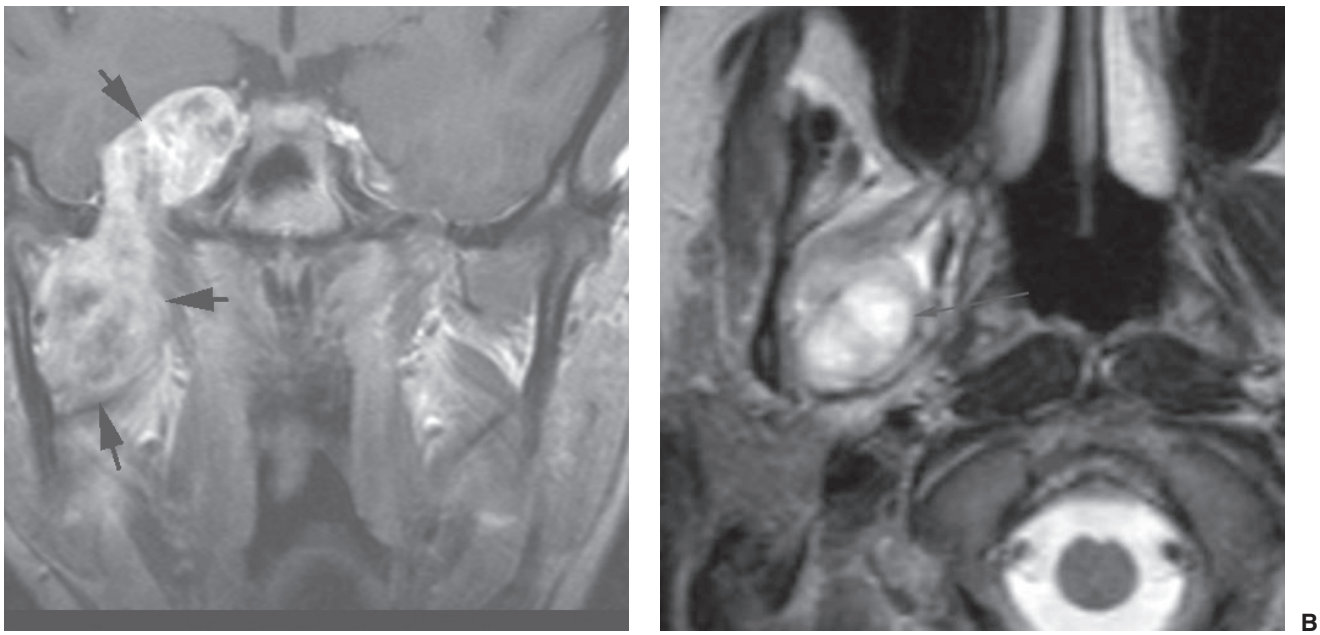


**FIGURE 29-15. A:** Coronal postcontrast MRI shows an avidly enhancing rhabdomyosarcoma (*arrows*) that spread along V3 through foramen ovale. **B:** Axial T2-weighted MRI shows the typical very high signal (*arrow*) seen in rhabdomyosarcomas.

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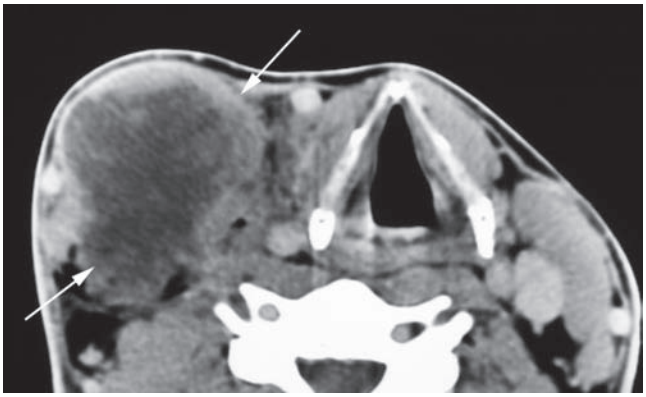


**FIGURE 29-16.** Axial contrast-enhanced CT scan shows a large rhabdomyosarcoma (*arrows*) arising from the sternocleidomastoid muscle with central necrosis.

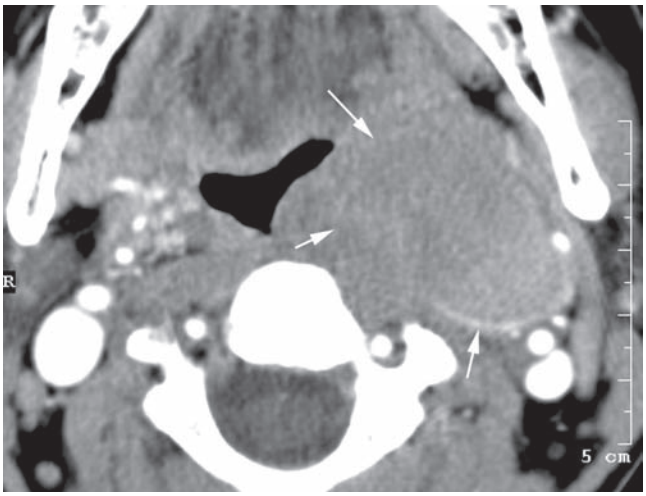



**FIGURE 29-17.** Axial contrast-enhanced CT scan of a synovial cell sarcoma that presented as a submucosal oropharyngeal mass. The posterolateral margin shows relatively defined contrast enhancement, but the anteromedial edge of the tumor is indistinct.

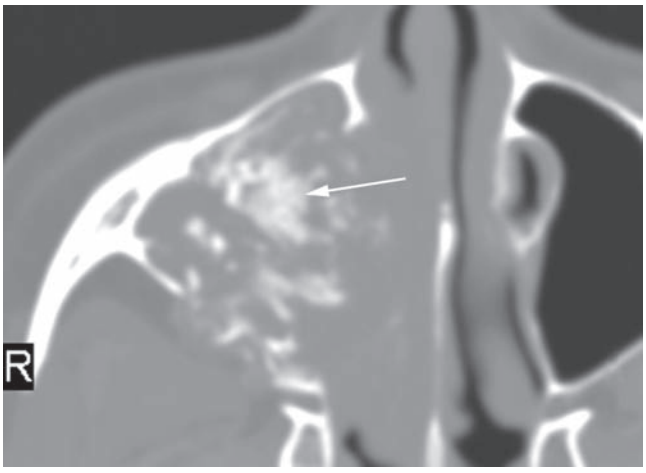



**FIGURE 29-18.** Axial noncontrast CT scan shows the typical solid osteoid matrix (*arrow*) of this osteosarcoma of the maxilla.



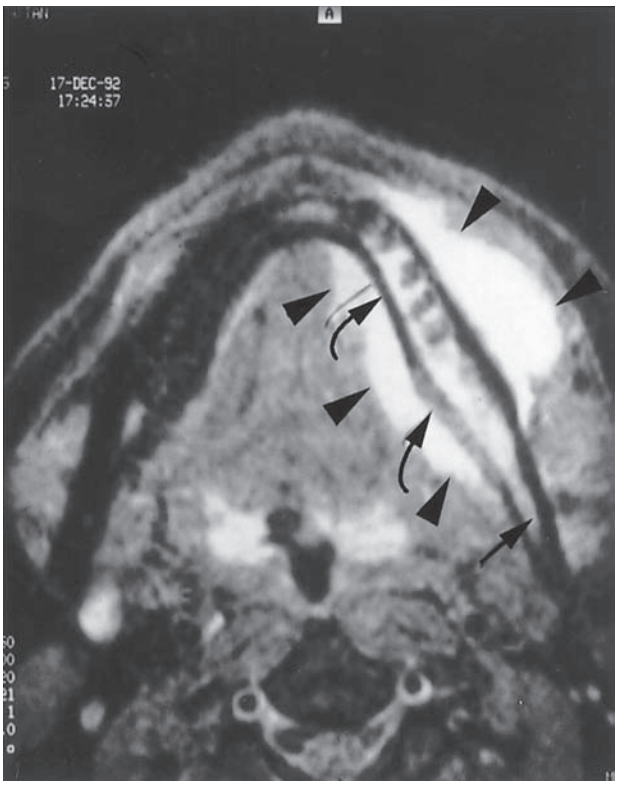




**FIGURE 29-19.** Osteosarcoma of the mandible. Direct coronal T1 **(A)** and axial fat-suppressed T2-type **(B)** magnetic resonance images show a permeative lesion expanding in all directions from body of left mandible (*arrowheads*). Note signal abnormality tracking proximally along angle of jaw (*arrow*) and apparent integrity of bone cortex (*curved arrows*).

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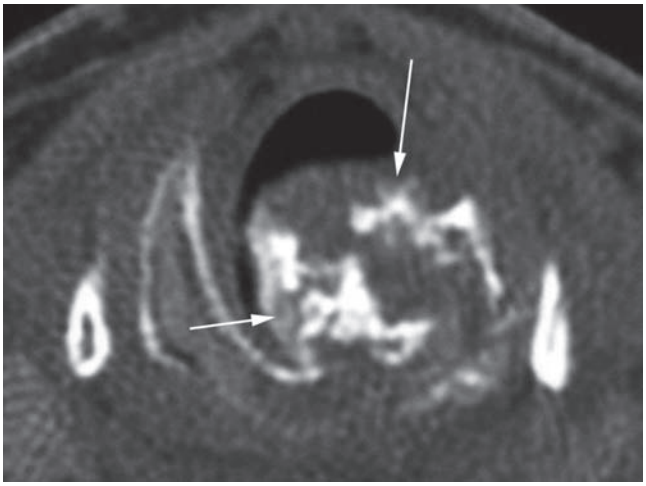


**FIGURE 29-20.** Axial noncontrast CT scan shows a chondrosarcoma of the cricoid cartilage which demonstrates rings and arcs (*arrows*) of calcified matrix.

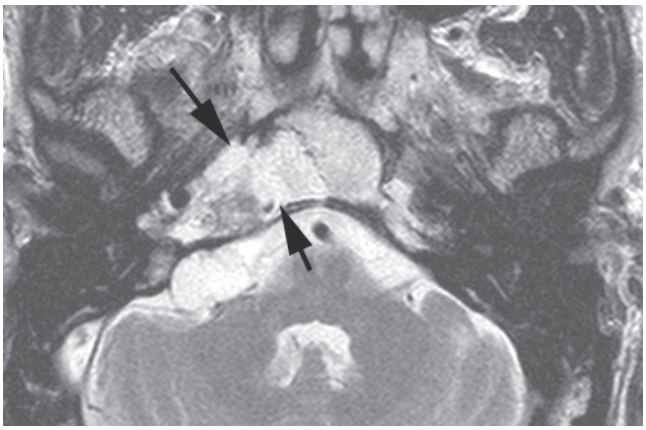


**FIGURE 29-21.** Axial T2-weighted MRI of a chondrosarcoma centered at the petroclival fissure. This lesion is very bright on T2-weighted images.

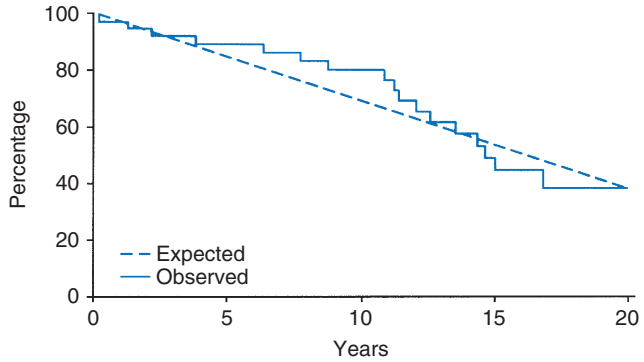



**FIGURE 29-22.** Treatment-related sarcoma. Enhanced axial computed tomography of the mid neck shows a heterogeneously enhancing mass (*arrows*) that developed within the irradiated field several years after nasopharynx cancer. Neck dissection yielded malignant fibrous histiocytoma.

Soft tissue sarcomas of the head and neck have variable radiotracer uptake on FDG-PET, which limits its use for surveillance imaging posttreatment for certain sarcomas. Metabolic activity correlates with the grade of malignancy.[7]

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CHAPTER 30

Matthew G. Fury and David G. Pfister

# Systemic Targeted Therapy for Recurrent and Metastatic Head and Neck Squamous Cell Cancer

This chapter reviews chemotherapy options for patients with recurrent and metastatic (R/M) head and neck squamous cell cancer (HNSCC) and discusses several avenues of clinical research for this patient population.

For locoregional recurrence of disease, surgical resection or ablative procedures may provide long-term disease control in a minority of patients.[1] In select patients, reirradiation may be applied, although most patients do not experience durable disease control.[2] Further details regarding resection and reirradiation are noted elsewhere in other chapters. Selected patients with limited metastatic lesions may also be considered for surgical resection if their performance status allows, or ablative procedures if surgery is not planned.[3–4]

For patients with R/M disease that is not deemed suitable for local therapy, systemic therapy given with palliative, not curative, intent is appropriately considered. In patients with lung-only metastasis(es), it may be difficult to clearly distinguish metastatic disease from a new lung primary. Clinical factors may help differentiate these two possibilities. For patients in whom the primary was an oropharynx tumor associated with the human papillomavirus (HPV), detection of HPV in the lung lesion can be used to help establish the diagnosis of metastatic disease.[5]

As reviewed later in this chapter, several drugs have activity in HNSCC. However, no single chemotherapeutic agent has consistently or conclusively demonstrated superiority in terms of overall survival when compared with another drug in randomized clinical trials. It should be noted that the interpretability of some randomized trials, particularly the older ones, is compromised by modest sample sizes that increase the risk of false negative results. The selection of systemic therapy for patients with R/M HNSCC takes into account many variables, including patient's performance status, medical comorbidities, and prior treatment history.[6] For example, single-agent palliative therapy may be appropriate for minimally symptomatic patients with low-volume disease or frail patients with a decreased performance status, whereas doublet or triplet chemotherapy regimens may be appropriate for fit patients with more symptomatic or higher-volume disease. Table 30.1 lists clinical factors that appear to predict outcomes among patients with R/M HNSCC.[7–10] Tumor status with regard to the presence or absence of the HPV has robust associations with response to therapy, and prognosis in patients with locally/regionally advanced disease,[11] but the potential impact of HPV status on outcomes in the R/M disease setting has not been clearly established.

## CONVENTIONAL CYTOTOXIC AGENTS

### Platinum Agents and Antimetabolic Agents

Cisplatin was among the first agents to demonstrate significant activity against HNSCC.[11] A randomized phase III trial with a $2 \times 2$ factorial design ($n = 116$ subjects) compared (a) cisplatin, (b) bleomycin, (c) cisplatin + bleomycin, and (d) no chemotherapy.[13] Among all patients treated with chemotherapy, the response rate was 25%. Treatment with cisplatin versus "no chemotherapy" was associated with a 10-week improvement in median overall survival.[12] Subsequent studies generally have not included a "no chemotherapy" group, due to both logistical and ethical concerns about such designs after this initial proof-of-principle.

Cisplatin and methotrexate have antitumor efficacy as single agents for patients with advanced HNSCC. In a randomized comparison ($n = 44$ patients) of cisplatin versus methotrexate in patients with recurrent HNSCC, response rates (P, 29%; M, 24%) and median survivals (~ 6 months) were similar in both arms.[14] Cisplatin and methotrexate yielded comparable median survival times (18 and 20 weeks, respectively) in a randomized study for patients ($n = 100$) with advanced head and neck cancer.[15]

The PF (cisplatin, 5-fluorouracil) regimen achieved a response rate of 70% in a single-institution study,[16] although response rates were lower in subsequent studies. A three-arm randomized comparison of (PF vs. P vs. F, $n = 249$ subjects) demonstrated superior response rate in the PF group (PF, 32%; P, 17%; F, 13%), but hematologic toxicity was also higher for PF, and median survival was approximately 5.7 months for all study arms.[17]

Cytotoxic chemotherapy combination regimens historically have yielded higher objective response rates compared with monotherapy, but generally do not improve overall survival for patients with R/M HNSCC. The combination regimens, generally, are associated with increased treatment-related toxicities compared with monotherapy, which is a major concern in the palliative setting. For example, the EORTC randomized 382 subjects patients with R/M HNSCC to either PF versus CABO (cisplatin, methotrexate, bleomycin, and vincristine) versus cisplatin monotherapy.[18] PF and CABO yielded the higher response rates (PF, 31%; CABO, 34%; P, 15%) at the expense of greater hematologic and nonhematologic toxicity, but there was no significant difference in overall survival among the three arms.

Carboplatin is generally well tolerated and may be preferable to cisplatin due to favorable adverse event profile as palliative



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**TABLE 30.1 Factors Associated with Inferior Overall Survival in R/M HNSCC Patients**

| |
|---|
| Low performance status |
| Lack of response to prior chemotherapy |
| Prior radiation therapy |
| Hypopharynx or oral cavity primary site |
| Weight loss >5% |
| Malignant hypercalcemia (end-stage disease) |

*Source:* From Deleyiannis FW-B, Thomas DB, Vaughan TL, et al. Alcoholism: independent predictor of survival in patients with head and neck cancer. *J Natl Cancer Inst.* 1996;88:542–549; Lee J-J, Jeng J-H, Wang H-M, et al. Univariate and multivariate analysis of prognostic significance of betel quid chewing in squamous cell carcinoma of the buccal mucosa in Taiwan. *J Surg Oncol.* 2005;91:41–47; Argiris A, Li Y, Forastiere A. Prognostic factors and long-term survivorship in patients with recurrent or metastatic carcinoma of the head and neck: an analysis of two Eastern Cooperative Oncology Group randomized trials. *Cancer.* 2004;101:2222–2229; Penel N, Berthon C, Everard F, et al. Prognosis of hypercalcemia in aerodigestive tract cancers: a study of 136 recent cases. *Oral Oncol.* 2005;41:884–889, with permission.

therapy for some patients with advanced head and neck cancer. In a phase II study for patients ($N = 31$) with R/M HNSCC, carboplatin monotherapy was associated with a response rate of 26%.[19] In a subsequent study, carboplatin achieved a response rate of 24% among 29 subjects with recurrent HNSCC.[20]

A three-arm randomized trial ($n = 261$ subjects) compared PF versus carboplatin plus 5-fluorouracil (CbF) versus methotrexate (M).[21] The starting Cb dose was 300 mg/m$^2$, with guidelines for carboplatin dose escalation to achieve grade 2 myelosuppression. Response rates by group were PF 32%, CbF 21%, and M 10%. Adverse events were also more common in the PF group, and there was no significant difference in median overall surival between the three groups. Limitations of this study include (a) it was not statistically powered to provide a definitive comparison of PF versus CbF, (b) it used a dosing strategy Cb that is not used widely in clinical practice, and (c) the PF schedule was every 3 weeks and the CbF schedule was every 4 weeks.[21]

Table 30.2 summarizes results from selected clinical trials involving platinum-based regimens for patients with R/M HNSCC.

## Paclitaxel and Docetaxel

Early nonrandomized studies of taxane monotherapy demonstrated impressive objective response rates (paclitaxel, 40%; docetaxel 42%) among patients who had not received prior chemotherapy for R/M HNSCC.[22,23] The combination of cisplatin

**TABLE 30.2 Results of Selected Chemotherapy Trials in Recurrent and Metastatic Head and Neck Squamous Cell Cancer**

| First Author | Year | Number of Subjects | Treatment Groups | Response Rate (%) | Median Overall Survival (Months) |
|---|---|---|---|---|---|
| Hong[14] | 1983 | 44 | Cisplatin | 29 | 6.3 |
| | | | Methotrexate | 24 | 6.1 |
| Grose[15] | 1985 | 100 | Cisplatin | 8 | 4.1 |
| | | | Methotrexate | 16 | 4.6 |
| Jacobs[17] | 1992 | 249 | Cisplatin + 5FU | 32* | 5.5 |
| | | | Cisplatin | 17 | 5.0 |
| | | | 5FU | 13 | 6.1 |
| Forastiere[21] | 1992 | 227 | Cisplatin + 5FU | 32* | 6.6 |
| | | | Carboplatin + 5FU | 21 | 5.0 |
| | | | Cisplatin | 10 | 5.6 |
| Clavel[18] | 1994 | 382 | CABO[a] | 34* | 6.7[b] |
| | | | Cisplatin + 5FU | 31* | |
| | | | Cisplatin | 15 | |
| Gibson[24] | 2005 | 218 | Cisplatin + 5FU | 27 | 8.7 |
| | | | Cisplatin + Paclitaxel | 26 | 8.1 |
| Vermorken[54] | 2008 | 442 | Platinum (Cis or Carbo) + 5FU + Cetuximab[c] | 36[d] | 10.1[d] |
| | | | Platinum (Cis or Carbo) + 5FU | 20 | 7.4 |

[a]CABO = cisplatin, methotrexate, bleomycin, and vincristine.

[b]Overall survival was 29 weeks (6.7 months) for the entire study, with no significant differences between groups.

[c]In the experimental arm, maintenance cetuximab monotherapy was allowed after 6 cycles of triplet therapy.

[d]Statistically significant difference compared with control arm.

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plus paclitaxel (PT) was compared with PF in a randomized study ($n$ = 218 subjects). No significant difference in response rate (PF, 27%; PT, 26%) or overall survival (PF, 8.7 months; PT group, 8.1 months) was observed between the two groups. Gastrointestinal and hematologic toxicities were less common with PT.[24] PT and PF both became accepted as palliative regimens for patients with R/M HNSCC. In the context of concerns about the tolerability of cisplatin-based chemotherapy among some patients with R/M HNSCC, carboplatin plus paclitaxel has been evaluated in phase II studies, both in every 3 week[25,26] and weekly[27] dosing schedules. However, there has not been a rigorous prospective comparison versus cisplatin-based doublets in this patient population.

Another attempt to improve chemotherapy results has been the utilization of three-drug combinations utilizing a third drug in addition to a platinum compound and a taxane. TIP (paclitaxel, ifosfamide, cisplatin),[28] TIC (paclitaxel, ifosfamide, carboplatin),[29] and modified TPF (docetaxel, cisplatin, 5-fluorouracil)[30] were associated with encouraging response rates in (44%–59%) in phase II studies, but median survival times (8.8–11 months) were not clearly superior to those achieved with doublet chemotherapy with R/M disease.[24]

## Other Cytotoxic Agents that Have Been Evaluated for R/M HNSCC

Weekly vinorelbine achieved response rates of 7.5% and 16% in two phase II studies and was generally well tolerated.[31,32] Ifosfamide monotherapy also demonstrated palliative activity (response rates 4%–26%) in R/M HNSCC patients who had received prior chemotherapy.[33]

Pemetrexed is a multitargeted antifolate, which inhibits multiple enzymes involved in both pyrimidine and purine synthesis, including thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyl transferase (GARFT). Gemcitabine is a pyrimidine antimetabolite, which is anabolized into a diphosphate form, which inhibits ribonucleotide reductase and a triphosphate form which is incorporated into the DNA, thereby blocking DNA replication.

A phase II study evaluated pemetrexed (500 mg/m$^2$ IV q21 days) in 35 patients with locally advanced or metastatic HNSCC not amenable to curative surgery or radiotherapy. Patients did not receive supplementation with vitamin B12 or folate. The objective response rate was 27% and median overall survival was 7.3 months.[34] The activity of pemetrexed against HNSCC might be viewed as somewhat surprising, in view of the apparent low efficacy of this agent against squamous cell cancer (SCC) of the lung.[35] This discordance underscores the risks of assuming that the activities of chemotherapeutic agents against R/M HNSCC and against SCC of lung will always be similar.

In R/M HNSCC, gemcitabine monotherapy was evaluated in two phase II trials. In a study of 47 patients with R/M HNSCC, the overall response rate was 13%.[36] In a more recent trial, no objective responses were seen among 26 patients with R/M HNSCC.[37] The results of these two small studies indicate that the activity of single-agent gemcitabine is low in R/M HNSCC, and gemcitabine monotherapy is rarely used in the management of these patients. It should be noted, however, that gemcitabine is an active drug in patients with R/M nasopharynx cancer and is regularly used in this disease setting.[38,39]

Based on preclinical evidence of synergy and encouraging phase I results[40] the combination of gemcitabine and pemetrexed was evaluated in phase II studies in this patient population. In a study for 25 patients with R/M HNSCC, pemetrexed plus gemcitabine was administered every 2 weeks with vitamin support. Treatment was generally well tolerated, but the objective response rate was only 16%, indicating no evidence of additive or synergistic effects with these two drugs.[41] Similarly, in another study of pemetrexed plus gemcitabine q2W, only two responses (one confirmed) were seen among 17 patients with R/M HNSCC.[42]

Pemetrexed has shown encouraging efficacy when combined with bevacizumab[43] and remains of significant interest for further study. Pemetrexed plus cisplatin has been compared with cisplatin alone in a large, double-blind randomized trial in 795 patients with R/M HNSCC. There was no significant difference between the arms with regard to overall and progression-free survival, although on subset analyses, the combination arm had superior survival outcomes in performance status 0 and 1 patients and those with oropharynx primary tumors.[44] However, in the absence of randomized data to demonstrate superiority to other agents commonly used in the management of R/M HNSCC or a clear advantage when used in combination therapy, use of pemetrexed outside of a clinical trial in this patient population is not currently recommended.

Irinotecan resulted in objective responses in approximately 20% of subjects as first-line therapy for R/M HNSCC, but was not active as second-line therapy.[45] Neither vinorelbine, ifosfamide, nor irinotecan has been evaluated in a randomized phase III study for R/M HNSCC. Older cytotoxic agents such as bleomycin, vinblastine, cyclophosphamide, and adriamycin also have activity,[46] but these agents have largely been supplanted in the contemporary era by the platinum agents, taxanes, 5-fluorouracil, methotrexate, and cetuximab (Table 30.3).

## Antiepidermal Growth Factor Receptor Agents

The epidermal growth factor receptor (EGFR) is a transmembrane receptor tyrosine kinase that is expressed by most HNSCC tumors, and high levels of EGFR expression are associated with inferior clinical outcomes.[47,48] The receptor can be activated by a variety of ligands, including EGF, transforming growth factor alpha (TGF-α), and amphiregulin. The activated receptor forms homodimers or heterodimers with other ErbB family members, resulting in activation of the tyrosine kinase domain, stimulation of cell DNA synthesis, and cell proliferation through stimulation of multiple pathways. Two strategies of EGFR inhibition have been studied in clinical trials: monoclonal antibodies directed against the outer domain of the EGFR and small molecule inhibitors of the intracellular tyrosine kinase domain. Cetuximab is the only EGFR-targeting agent with approval from the United States Food and Drug Administration for the treatment of HNSCC.

Cetuximab, a human-murine chimeric immunoglobulin G (IgG1) monoclonal antibody, binds to the extracellular domain of EGFR.[49] As weekly monotherapy (400 mg/m$^2$ loading

**TABLE 30.3 Chemotherapeutic Agents Commonly Used in the Management of R/M HNSCC**

| Class | Agent |
|---|---|
| Platinum | Cisplatin, carboplatin |
| Taxane | Paclitaxel, docetaxel |
| Antimetabolite | 5-Fluorouracil, methotrexate |
| EGFR inhibitor | Cetuximab |

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dose, followed by 250 mg/m$^2$ weekly) for patients with advanced platinum-refractory HNSCC, cetuximab achieves objective radiographic response rates of 10% to 13% in phase II studies.[50,51] Similar efficacy and tolerability has been observed with single-agent cetuximab 500 mg/m$^2$ every 2 weeks for patients with R/M HNSCC.[52]

A randomized phase III study compared cetuximab plus cisplatin versus placebo plus cisplatin among 123 patients who had not received any prior chemotherapy for R/M HNSCC. Objective response rate favored the cetuximab arm (26% vs. 10%, $p = 0.03$), but progression-free survival and overall survival did not differ significantly between the groups.[53]

However, in a larger randomized trial, cetuximab improved the efficacy of standard platinum-based chemotherapy for patients with R/M HNSCC. The EXTREME trial randomized R/M HNSCC patients ($N = 442$) with either cisplatin or carboplatin plus 5-fluorouacil compared with the same chemotherapy options with the addition of weekly cetuximab, including 6 months of maintenance cetuximab among responding patients tolerating therapy in the latter arm. Choice of cisplatin or carboplatin was per investigator discretion. Patients had not received any prior therapy for R/M. The cetuximab plus platinum doublet, compared with the platinum doublet alone, was associated with a significantly improved response rate (36% vs. 20%), progression-free survival (5.6 vs. 3.3 months), and overall survival (10.1 vs. 7.4 months).[54]

Panitumumab is a fully humanized IgG2 monoclonal antibody directed against the extracellular domain of EGFR. A large (657 patients) randomized phase III study of the addition of panitumumab to the PF doublet was deemed negative because there was no significant improvement in overall survival associated with the addition of this antibody to the doublet.[55] Of interest, and discussed later in this chapter, on subsequent subset analysis, survival benefit was demonstrated in the HPV-negative subgroup as assessed by p16 status.

Zalutumumab, a fully humanized IgG1 anti-EGFR monoclonal antibody, was evaluated in a randomized phase III study for patients with noncurable HNSCC. Patients ($n = 286$) were randomly assigned to either weekly zalutumumab + best supportive care or best supportive care with optional methotrexate. Zalutumumab, versus the control group, did not result in a significant increase in overall survival (6.7 vs. 5.2 months, $p = 0.06$), which was the primary endpoint of the study.[56] As such, cetuximab remains the only monoclonal against EGFR that is commercially available for HNSCC patients in the United States.

Several inhibitors of the EGFR tyrosine kinase domain have been evaluated for patients with advanced HNSCC. In a phase II trial of gefitinib 500 mg/day ($n = 47$ subjects), the objective response rate was 10.6% and median survival was 8.1 months.[57] In a randomized phase III comparison with methotrexate, gefitinib (at either 500 or 250 mg/day) did not improve overall survival compared with methotrexate,[58] but the risk of tumor-hemorrhage events was greater on the gefitinib arms (11.4% and 8.5%, respectively) than with methotrexate (1.9%).

Erlotinib is an orally available, reversible, and selective inhibitor of the EGFR tyrosine kinase that is currently approved for the treatment of refractory non-small cell lung cancer (NSCLC). In a phase II study ($n = 115$ subjects), erlotinib yielded a major response rate of 4% among patients with R/M HNSCC.[59]

Preclinical studies have suggested that resistance to EGFR inhibitors may be related to activity of other ErbB family members.[60] Strategies to broadly inhibit ErbB signaling are being explored clinically. Lapatinib, a dual inhibitor of EGFR and ErbB2 tyrosine kinases, is commercially available for the treatment of some women with advanced breast cancer. In a phase II study for patients with R/M HNSCC (27 subjects with prior exposure to EGFR inhibitor and 15 subjects with no prior exposure to EGFR inhibitor), no objective responses were seen.[61] Afatinib, a potent inhibitor of the tyrosine kinase domains of EGFR, ErbB2, and ErbB4, is an investigational agent that is being studied for several tumor types. Afatinib was compared with cetuximab in a randomized phase II study for patients with R/M HNSCC ($n = 124$ subjects). The confirmed partial response rate was higher in the afatinib group versus the cetuximab group, but progression-free survival did not differ between the two arms.[62]

## CLINICAL RESEARCH REGARDING NOVEL MOLECULAR TARGETS

### PI3 Kinase/Akt/mTOR Pathway

EGFR and other transmembrane receptors converge to control a variety of intracellular signaling pathways, such as the phosphoinositide-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway. Activation of the pathway may be due to somatic mutation in the gene encoding the catalytic subunit of PI3K (*PIK3CA*), activation of receptor tyrosine kinases upstream of PI3K, loss or inactivation of the PTEN suppressor gene, or genetic lesions in Akt or other downstream signaling molecules.[63–65] The mTOR, a serine/threonine kinase, is a major downstream effector that resides in two multiprotein complexes (mTORC1 and mTORC2) that regulate transcription, protein translation, metabolism, cell growth, and survival.[66]

The importance of the PI3K/Akt/mTOR pathway in HNSCC was demonstrated in a study by the Head and Neck Cancer Tissue Array Initiative.[67] The tissue microarray ($n = 547$ cores) was interrogated with antibodies directed against key signaling molecules in head and neck cancer, including p53, the EGFR, and components of the Akt-mTOR pathway. Alterations of the PI3K/Akt/mTOR pathway were found in most cases. Expression levels of phosphorylated AKT and pS6 were significantly higher in HNSCC tumors, compared with normal mucosa, across all degrees of differentiation. An unsupervised clustering approach demonstrated that the pathway often appeared to be activated in the setting of negative staining for phosphoryated EGFR.[67] This suggests that activation of the PI3K/Akt/mTOR pathway may occur independently of EGFR activation in many HNSCC patients, although the inherent technical limitations of immunohistochemistry prevent any definitive conclusions. These findings may provide insight into the relatively low-to-modest clinical efficacy of EGFR inhibition strategies in this disease[68] and suggest that downstream inhibition of mTOR merits further study as a potential therapeutic strategy in HNSCC.

Rapamycin, the prototypic mTORC1 inhibitor, demonstrates modest antiproliferative effects against HNSCC cell lines, with IC50s in the range of 5 to 20 $\mu$M.[69] In HNSCC xenografts, dramatic tumor growth inhibition was achieved with temsirolimus[70] or rapamycin.[71] Because it is probable that mTOR inhibitors will have no better than modest clinical activity against HNSCC when given as single agents, the true utility of these agents may derive from their ability to potentiate the antitumor effects of other cytotoxic chemotherapeutic agents.

In 1995, Mills and coworkers reported that rapamycin enhanced the cytotoxic effects of cisplatin against a human leukemia cell line (HL-60) and an ovarian cancer cell line (SKOV3).[72] Subsequent preclinical studies demonstrated additive or synergistic effects when mTOR inhibitors were combined with platinum or taxane chemotherapy agents in studies of NSCLC, breast cancer, and HNSCC cell lines.[69,73,74] mTORC1 inhibition appears

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to reverse resistance to paclitaxel in a cervical cancer cell line (CaSki)[75] and cisplatin in a lung cancer cell line (SCLCSR2).[76]

Temsirolimus and everolimus are two mTORC1 inhibitors that are commercially available for the treatment of patients with advanced renal cell carcinoma (everolimus also has an indication for progressive neuroendocrine tumors of pancreatic origin) and are under investigation for patients with head and neck cancer and other malignancies. In a phase I study of everolimus + low-dose weekly cisplatin, partial response was observed in one patient with sinus carcinoma metastatic to lung, and prolonged stable disease was observed in a patient with metastatic oropharyngeal squamous cell carcinoma.[77] Weekly everolimus was well tolerated when combined with weekly paclitaxel in a phase I study, and no significant pharmacokinetic interaction between the mTOR inhibitor and paclitaxel was identified.[78] In a pharmacodynamic study, the ability of temsirolimus to inhibit mTOR activity was demonstrated in posttreatment tumor biopsies with reduced expression of two key signaling molecules downstream of mTORC1, pS6, and p4E-BP1.[79] A phase I/II study of temsirolimus, plus weekly carboplatin and paclitaxel, recently completed the dose-escalation portion of the study and is enrolling patients on the phase II portion of the study (ClinicalTrials.gov identifier: NCT01016769).

One potential mechanism of resistance to mTOR inhibitors such as temsirolimus appears to involve enhanced phosphorylation of Akt due to loss of negative feedback of S6 kinase on growth factor receptors.[80,81] Enhanced phosphorylation of Akt during treatment with mTOR inhibitors has been demonstrated in cancer cell lines and in patients with glioblastoma, breast cancer, and colorectal cancer.[80,82]

Enhancement of Akt phosphorylation inhibits apoptosis by at least two mechanisms, both of which involve stabilization of members of the Bcl-2 antiapoptotic family of proteins (Bcl-2, Bcl-xL, Mcl-1). First, there is indirect evidence that Akt stabilizes Mcl-1. Stabilization of Mcl-1 during treatment of cells with rapamycin appears to coincide with feedback activation of Akt.[83,84] Second, a downstream effect of enhancement of phosphorylation of Akt is enhancement of phosphorylation of eIF4E, which regulates cap-dependent translation of Bcl-2 family members.[81] Preclinical evidence demonstrates that eIF4E promotes cell survival by enhancing translation of Bcl-2, Bcl-xL, and/or Mcl-1 in cancer cell lines.[85,86]

To overcome resistance to mTOR inhibitors, preclinical models have explored combined inhibition of mTOR and the Bcl-2 family of proteins. In small cell lung cancer cell lines that are resistant to rapamycin, reduction of Bcl-2 expression (either with an antisense construct or a Bcl-2 specific inhibitor) rendered the cells sensitive to apoptosis with rapamycin treatment.[87] In a murine xenograft model of NSCLC, combined treatment with rapamycin and ABT-737 (an inhibitor of Bcl-2 and Bcl-xL) in the setting of radiation therapy (RT) achieved significantly greater tumor growth delay, compared with radiation therapy plus either drug alone.[88]

In summary, resistance to mTOR inhibition may be associated with paradoxical activation of Akt and eIF4E due to loss of negative feedback, resulting in increased translation and/or stabilization of antiapoptotic Bcl-2 family members. In preclinical models, downregulation or inhibition of Bcl-2 family members sensitizes cancer cell lines and xenograft tumor models to rapamycin-induced apoptosis.[87–91] As such, one research strategy to overcome resistance to mTOR inhibition would be to combine with inhibitors of Bcl-2 family of proteins.

The foregoing considerations have focused on mTOR and downstream components of the pathway. More recently, direct inhibitors of the upstream portion of the PI3K/Akt/mTOR pathway have entered early clinical studies. These include pure PI3K inhibitors such as BKM120 and GDC-0941,[92–94] dual PI3K/mTOR inhibitors such as BEZ235 and PKI-587,[95–97] and Akt inhibitors such as MK-2206.[98] All of these compounds are of significant interest for further study in HNSCC. Figure 30-1 is a simplified representation of the PI3K/Akt/mTOR pathway that includes pharmacologic inhibitors of key signaling proteins in the cascade.

## Angiogenesis

Increased tumor expression of vascular endothelial growth factor A (VEGF-A) is associated with a poor prognosis in HNSCC. In a meta-analysis of 12 studies which evaluated VEGF-A expression in HNSCC ($n$ = 1,002 patients), VEGF-positivity was associated with a 1.88-fold higher risk of death at 2 years.[99] Preclinical and

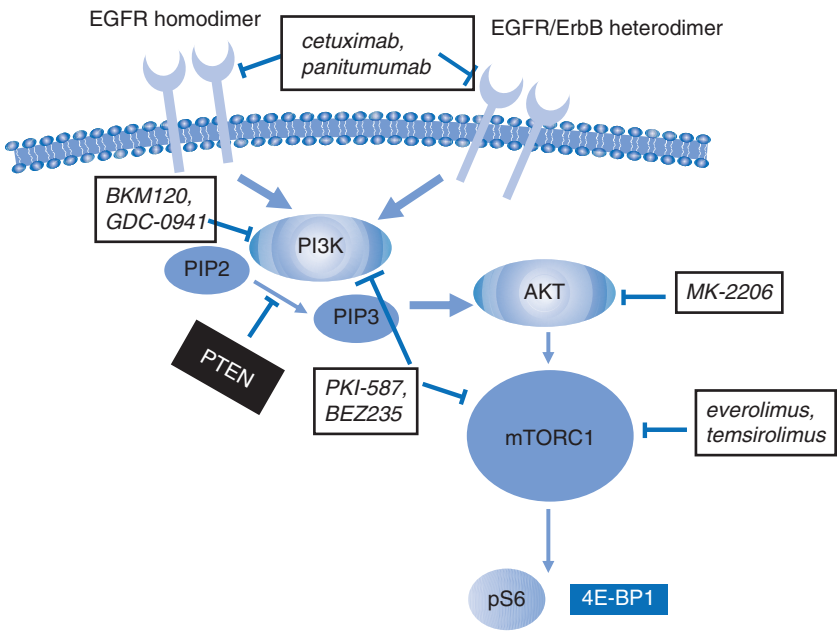



**FIGURE 30-1.** Simplified schematic illustration. EGFR homodimers and EGFR/ErbB heterodimers activate PI3 kinase, which favors the conversion of phosphatidylinositol bisphosphate (PIP2) to phosphatidylinositol triphosphate (PIP3), with subsequent activation of Akt and mTORC1. Two well-characterized phosphorylation targets of mTORC1 are eIF4E-binding protein (4E-BP1) and p70 S6 kinase 1 (S6K1), which regulate translation of proteins required for G1-S phase progression in the cell cycle. Monoclonal antibodies directed against the extracellular domain of EGFR (e.g., cetuximab, panitumumab) represent the most clinically advanced strategy to inhibit this pathway in HNSCC at present. Small molecules to inhibit intracellular processes in this cascade are under investigation, including PI3 kinase inhibitors (e.g., BKM120, GDC-0941), Akt inhibitors (e.g., MK-2206), mTORC1 inhibitors (everolimus, temsirolimus), and dual PI3 kinase/mTOR inhibitors (PKI 587, BEZ235), among others. (See color insert.)

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early clinical studies support a model in which cross-talk between EGFR and VEGF pathways enhances tumor growth and angiogenesis in HNSCC. In studies with the A431 squamous carcinoma cell line, treatment with cetuximab resulted in dose-dependent reduction of VEGF expression *in vitro*.[100] In pilot data from a clinical study for patients with R/M HNSCC, the combination of cetuximab and bevacizumab yielded objective tumor responses in 4 of 15 (27%) evaluable patients.[101] Although preliminary, these data suggest that the combination of cetuximab and bevacizumab may yield additive efficacy in HNSCC.

The combination of cetuximab plus bevacizumab with chemotherapy has been associated with decreased efficacy in colorectal cancers harboring K-RAS mutations,[102] but K-RAS mutations are uncommon in HNSCC. In an analysis of 197 HNSCC specimens, K-RAS exon 12 mutations were encountered in 3.5% of cases.[103] These results are consistent with other smaller studies, which found that K-RAS mutation is uncommon in HNSCC.[104–106] These results argue against extrapolation of the clinical trial experience regarding cetuximab plus bevacizumab in colorectal cancer to HNSCC.

The combination of bevacizumab with EGFR inhibitors provides a research strategy to potentially improve efficacy. In a phase I/II study of bevacizumab + erlotinib for patients with R/M HNSCC, seven partial responses were observed among 48 evaluable patients in the phase II portion of the study. Three patients had serious bleeding events of grade III or higher. Among 11 patients with available tissue for research studies, higher baseline expression of phosphorylated VEGF receptor-2 in tumors and phosphorylated EGFR in endothelial cells appeared to be associated with efficacy.[107] In a phase II study for patients with R/M HNSCC, the combination of cetuximab + bevacizumab yielded a partial response rate of 18% (8 responses among 45 patients). Grade III hemorrhage occurred in 2 patients.[108] The Eastern Cooperative Oncology Group (ECOG) is currently conducting a randomized phase III study to evaluate the efficacy of bevacizumab added to standard chemotherapy for patients with R/M HNSCC (ClinicalTrials.gov identifier: NCT00588770).

Several small molecule inhibitors directed against the kinase domain of VEGF receptor 2 have been evaluated. Semaxanib (SU5416) yielded only one partial response among 31 patients with advanced head and neck cancer, and the median survival was 6.25 months.[109] Sunitinib is a potent inhibitor of the kinase domains of VEGF receptors 1, 2, and 3, PDGFR $\alpha$ and $\beta$, and KIT. It has been evaluated in three phase II studies for patients with R/M HNSCC, but two of these studies failed to provide any suggestion of clinically significant efficacy.[110,111] In the third study of sunitinib in advanced head and neck cancer ($n = 38$ subjects), there was one partial response and there were five unconfirmed partial responses, but there were four fatal hemorrhage events.[112] Sorafenib has a broad target profile, including potent inhibition of B-Raf and VEGF receptors 1, 2, and 3. Combining the results of two separate phase II studies of sorafenib for patients with advanced head and neck cancers,[113,114] there were only two partial responses among 67 patients evaluable for response, but treatment was generally well tolerated and there was evidence that this agent might merit further study due to the potential to achieve disease stabilization in some patients.

## Other Targeted Agents under Investigation in R/M HNSCC

Met is the transmembrane cell surface receptor for hepatocyte growth factor (HGF).[115] Hepatocyte growth factor appears to be secreted by stromal cells, leading to paracrine activation of HN tumors expressing Met.[116] Upon ligand binding, the receptor dimerizes and the intracellular tyrosine kinase domain is activated. Downstream effects can include activation of the PI3K/Akt pathway and the MAPK pathway, among others.[117] Met is expressed in most HNSCC tumors, and *MET* gene amplification was detectable in 13% (3 of 23) tumor tissues in one report.[118] Activating mutations in the tyrosine kinase domain have been described in approximately 10% to 12% of HNSCC tumors,[118,119] but the incidence of these mutations may be lower in primary tumors than in metastatic lesions.[120,121] Recent whole exome sequencing indicates that the incidence of *MET* mutations in primary HNSCC tumors is very low.[122,123]

Foretinib (formerly XL880) is an orally available multikinase inhibitor targeting inhibitor of Met, VEGF receptor 2, and others. Foretinib has been evaluated in a phase I study[124] and in a phase II study for patients with R/M HNSCC that recently completed accrual (NCT00725764). Preclinical studies suggest that the efficacy Met inhibition may be enhanced in the context of concurrent inhibition of EGFR, Src, or cytotoxic chemotherapy.[118,125,126] These combinations have not yet been tested in the clinic for patients with R/M HNSCC. Study of combined Met and EGFR inhibition in HNSCC may be particularly compelling, in view of the demonstration in NSCLC that *MET* amplification leads to resistance to EGFR tyrosine kinase inhibition.[127]

Src is a nonreceptor tyrosine kinase that regulates a wide variety of cellular processes including proliferation, survival, adhesion, motility, and invasion.[128,129] Increased Src activity has been detected in a variety of head and neck cancers and other tumor types.[129,130] Inhibition of Src activity in a human HNSCC cell line reduced cell proliferation and invasion in comparison with control cells.[131,132] In studies with dasatinib, a small molecule inhibitor of Src family kinases, HNSCC cell lines were markedly more sensitive to growth inhibition than were NSCLC cell lines.[133] Single-agent phase II trials of orally available Src kinase inhibitors saracatinib[134] and dasatinib[135] failed to demonstrate single-agent activity for either of these agents. However, based on preclinical data that Src may mediate resistance to cetuximab,[136,137] the combination of dasatinib and cetuximab is being evaluated in a phase II study for patients with advanced HNSCC (NCT01488318).

# PREDICTING RESPONSE TO TARGETED THERAPY

The development of rash during treatment with cetuximab appears to be associated with antitumor efficacy, but there are no clinical or molecular factors that can reliably predict which patients will benefit from cetuximab prior to the initiation of therapy. An association between the development of rash and favorable clinical outcome with EGFR inhibitor treatment has been described in many,[50,53,57,59] but not all,[54] studies of these agents in R/M HNSCC. Prophylactic treatment of rash has been associated with decreased incidence and intensity of dermatologic toxicity among colorectal cancer patients treated with panitumumab.[138] As such prophylactic management of skin toxicity becomes more widespread in clinical practice for patients with head and neck cancer, the clinical associations between rash and tumor response may become less evident.

Molecular markers to predict sensitivity or resistance to cetuximab are needed in R/M HNSCC. Mutations in *EGFR* are clinically useful predictors of response to EGFR tyrosine kinase inhibitors in lung cancer adenocarcinoma,[139] but *EGFR* mutations are uncommon in HNSCC in the Western world.[140] Other candidate biomarkers are being explored in this disease. *EGFR* gene amplification was not associated with outcomes in patients treated with a platinum doublet plus cetuximab in the EXTREME study.[141] It is possible that the contribution of cytotoxic

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chemotherapy may have confounded any association between gene amplification and response to cetuximab. It would be interesting to explore if *EGFR* gene amplification might be associated with efficacy in study of R/M HNSCC patients treated with cetuximab monotherapy.

EGFR variant III (EGFRvIII) contains an truncated extracellular EGF-binding domain and is under active study as a potential biomarker for response to EGFR inhibitors. The incidence of EGFRvIII in HNSCC tumors was 42% (14 of 33 specimens) in a single-institution retrospective study.[142] A recent study of R/M HNSCC tumors also detected EGFRvIII in 42% specimens and suggested that the presence of EGFRvIII may be associated with better disease control, independent of whether patients received erlotinib-based treatment or not.[143] The association between EGFRvIII and response to EGFR inhibitors in R/M HNSCC merits further study.

It is not known if HPV status might be associated with efficacy of anti-EGFR therapy in patients with R/M HNSCC. In subgroup analysis of SPECTRUM (the previously reviewed phase III study of platinum/5-fluorouracil [PF] with or without panitumumab for R/M HNSCC),[55] HPV status was indirectly assessed by immunohistochemical detection of p16, a biomarker for HPV status. Tissue was available for p16 testing in 377 subjects. Among patients with p16-negative tumors, the addition of panitumumab to the platinum doublet was associated with a significant improvement in overall survival (11.8 vs. 8.6 months, panitumumab plus PF vs. PF, respectively; $p = 0.02$).[144] Among patients with p16-positive tumors, there was no significant difference in survival associated with the addition of panitumumab.[144] These data have only been presented in abstract form. The observation that patients with p16-negative tumors, but not p16-positive tumors, may benefit from panitumumab should be viewed as hypothesis-generating only at this time.

Other potential biomarkers for resistance or sensitivity to EGFR inhibitors in HNSCC have been described. Heparin binding EGF-like growth factor (HB-EGF) is an EGFR ligand that is expressed at higher levels in the plasma of patients with R/M HNSCC than in patients with newly diagnosed disease and may be associated with resistance to EGFR inhibitors.[145] The potential role of genetic polymorphisms in response to EGFR inhibitors is currently not well understood. A study of HNSCC cell lines evaluated a specific genetic polymorphism, the number of CA nucleotide repeats in intron one of *EGFR*. The number of CA dinucleotide repeats was associated with levels of EGFR mRNA and protein and response to erlotinib.[146] While the foregoing considerations have focused on the impact of EGFR inhibition on signaling pathways in tumor cells, the role of cell-mediated cytotoxicity in patients treated with cetuximab is also under investigation.[147] A specific polymorphism of Fc gamma receptor IIIa on effector cells appears to be associated with the cytotoxicity of cetuximab against HNSCC cell lines and merits further study in clinical trials.[148]

## CONCLUSION

The main classes of drugs for the management of patients with R/M HNSCC are platinum agents, taxanes, antimetabolites, and the EGFR inhibitor cetuximab. The selection of therapy takes into consideration numerous variables, including prior treatment, extent of disease, medical comorbidities, and goals of care. The EXTREME study highlights the potential of targeted agents to improve the efficacy of standard chemotherapy for patients with R/M HNSCC,[54] but there remains a clear need for the development of improved treatments. Many targeted agents are under clinical investigation, and a central challenge of these efforts is to develop clinical and molecular markers to identify patients most likely to benefit from a given therapy.

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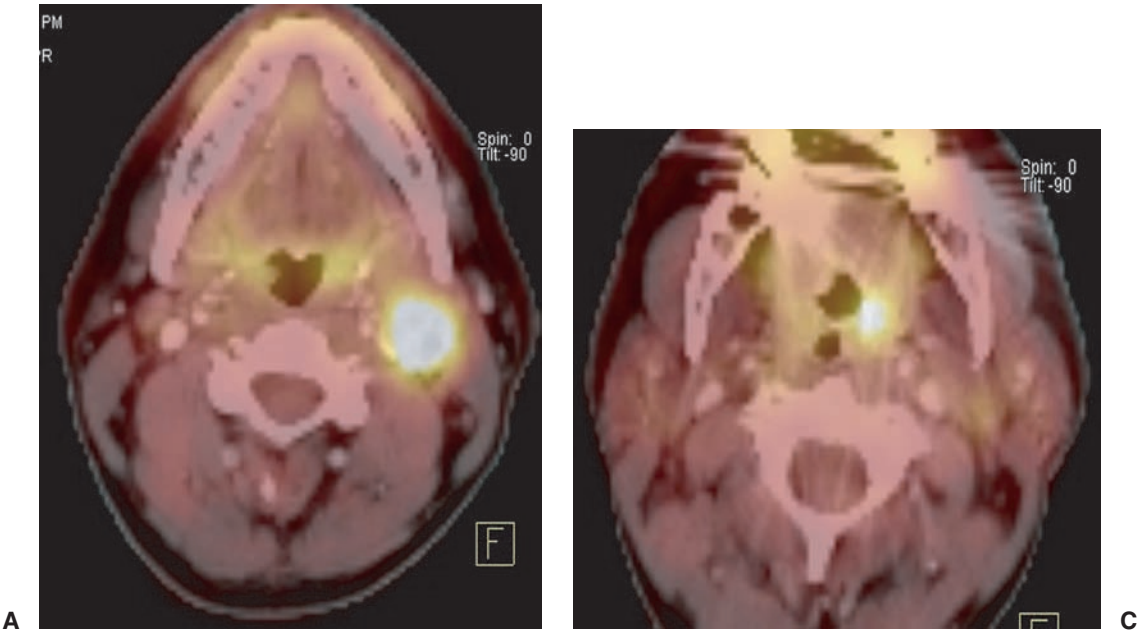



**FIGURE 4-17.** Axial PET-CT (**A**) performed in patient with a biopsy-proved nodal metastases shows uptake in the left level II lymph node. PET-CT (**C**) shows focal uptake in the left tonsil that was suspicious for a primary site. The patient underwent a left tonsillectomy, and pathology revealed squamous cell carcinoma. PET, positron emission tomography; CT, computed tomography.

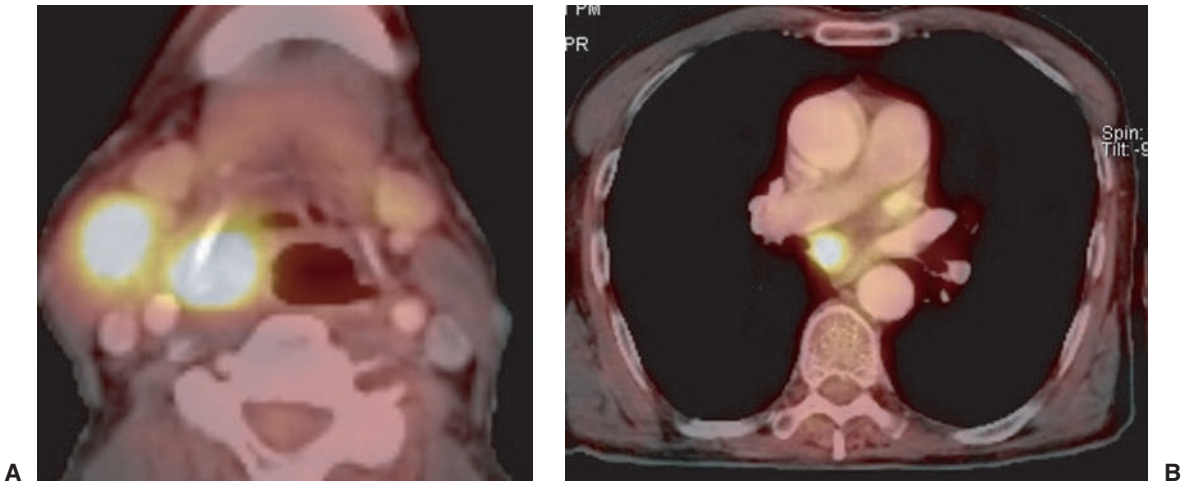



**FIGURE 4-18.** **A:** PET-CT performed in a patient with a known right pyriform simus carcinoma and level II nodal disease shows uptake at the primary site and lymph node. **B:** There is also abnormal uptake in a mediastinal lymph node, which is not detected in standard cross-sectional imaging. PET, positron emission tomography; CT, computed tomography.

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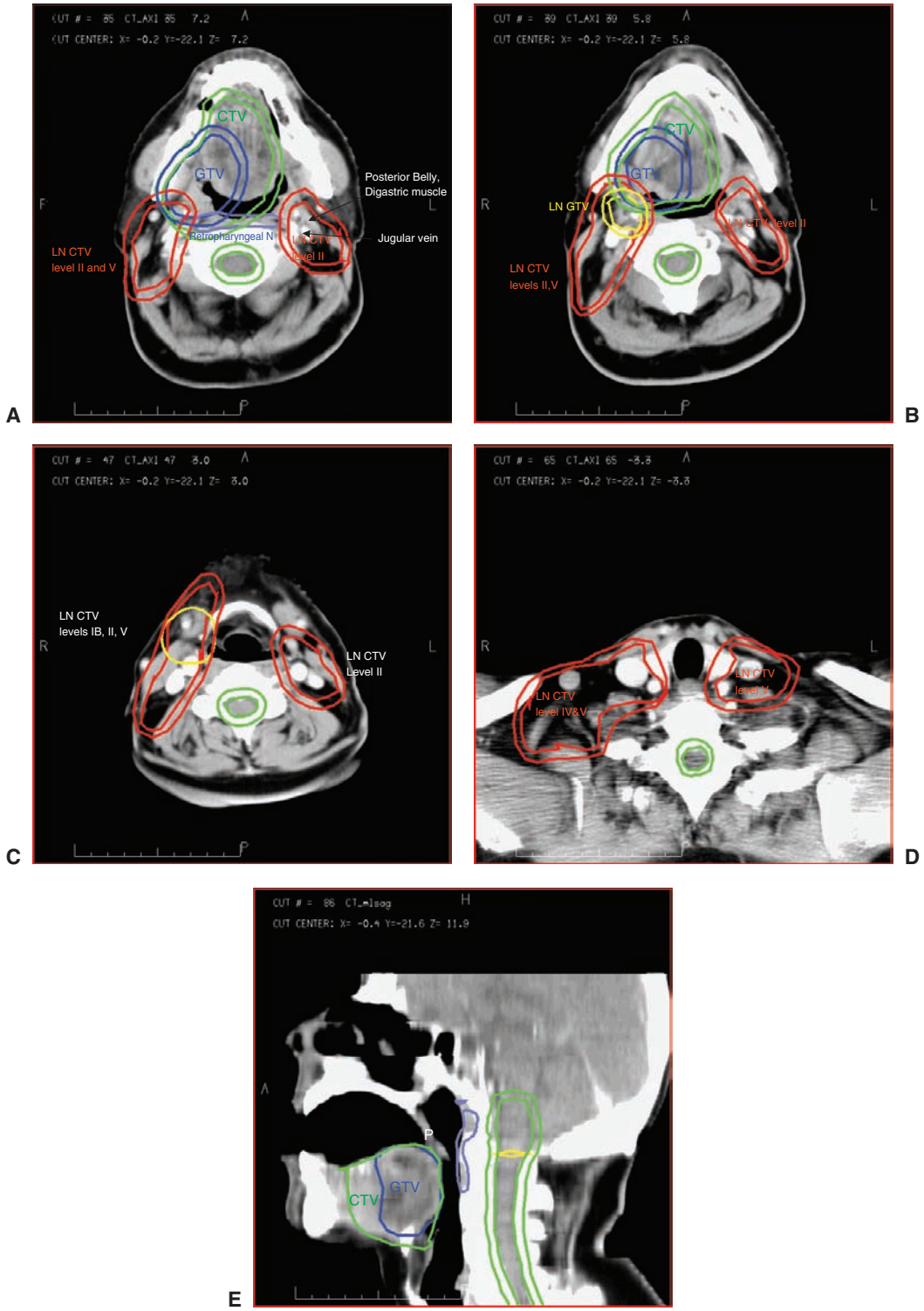
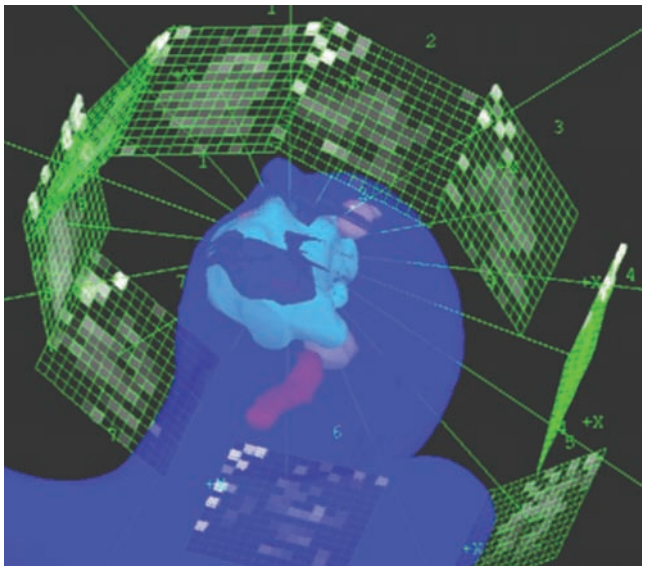
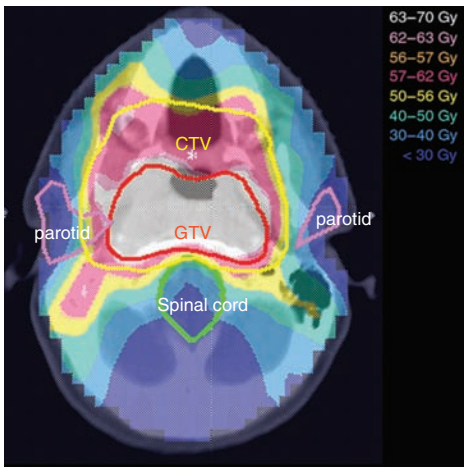



**FIGURE 5-1.** The targets outlined on planning CT in a case of stage T2, N1 carcinoma of the right tonsil, involving the lateral base of the tongue. The GTV, primary tumor CTV, and lymphatic GTV and CTVs are each expanded uniformly by 0.5 cm to yield the corresponding PTV. **A:** Level II nodal targets in the ipsilateral neck, and the retropharyngeal nodes bilaterally, are outlined through the base of the skull. Level II nodes in the contralateral neck are outlined up to the level in which the posterior belly of the digastric muscle crosses the jugular vein. Cephalad to this level, only the ipsilateral (LT) level II nodal CTVs and the retropharyngeal nodes are outlined. In cases where the contralateral neck contains clinical or radiologic evidence of metastasis, or in the case of nasopharyngeal cancer, level II is outlined through the base of the skull bilaterally. **B:** Nodal metastasis in the LT neck is outlined as a nodal GTV, expanded to yield its PTV. **C** and **D:** In the ipsilateral lower neck, nodal levels IV and V are included in the CTV. Only level IV is outlined in the contralateral lower neck (the contralateral neck did not have clinical evidence of metastasis). **E:** A sagittal reconstruction of the CT may help in the assessment of the extent of disease. On axial images, it is difficult to distinguish the soft palate from the base of tongue that contains the targets. The sagittal view facilitates the exclusion of the soft palate (*P*) from the targets. CT, computed tomography; GTV, gross tumor volume; CTV, clinical target volume; PTV, planning tumor volumes.

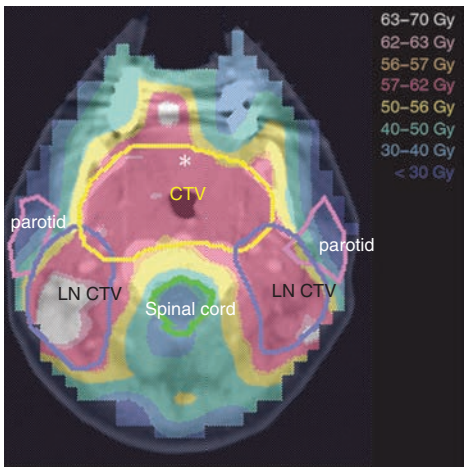
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**FIGURE 5-2.** Beam arrangement for IMRT using an MLC. Nine coplanar, equidistant beams are used, each containing 1 × 1 cm or 0.5 × 0.5 cm pencil "beamlets." IMRT, intensity-modulated radiotherapy.

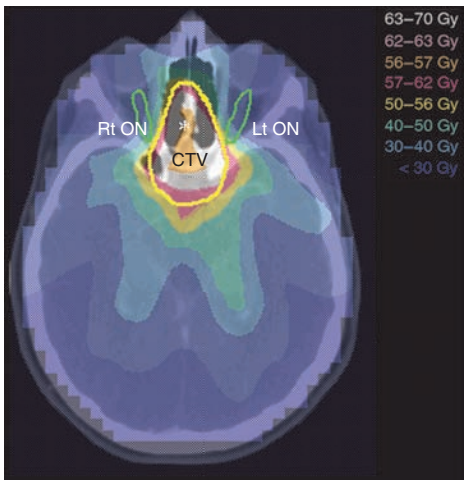





A




B




C

**FIGURE 5-3.** Targets and doses in IMRT of nasopharyngeal cancer. **A:** The GTV was outlined following registration of the planning CT with diagnostic MRI. The CTV includes the base of the skull, the posterior paranasal sinuses, the clivus, and the parapharyngeal space. **B:** Caudal to the GTV, the CTV contains the parapharyngeal and posterior pharyngeal space through midtonsils. Level II nodal CTV is outlined through the base of the skull bilaterally. **C:** The CTV encompasses the sphenoid and cavernous sinuses in locally advanced cases. Limiting the dose to the optic pathways is an important objective of planning. IMRT, intensity-modulated radiotherapy; GTV, gross targe volume; CT, computed tomography; CTV, clinical target volume.

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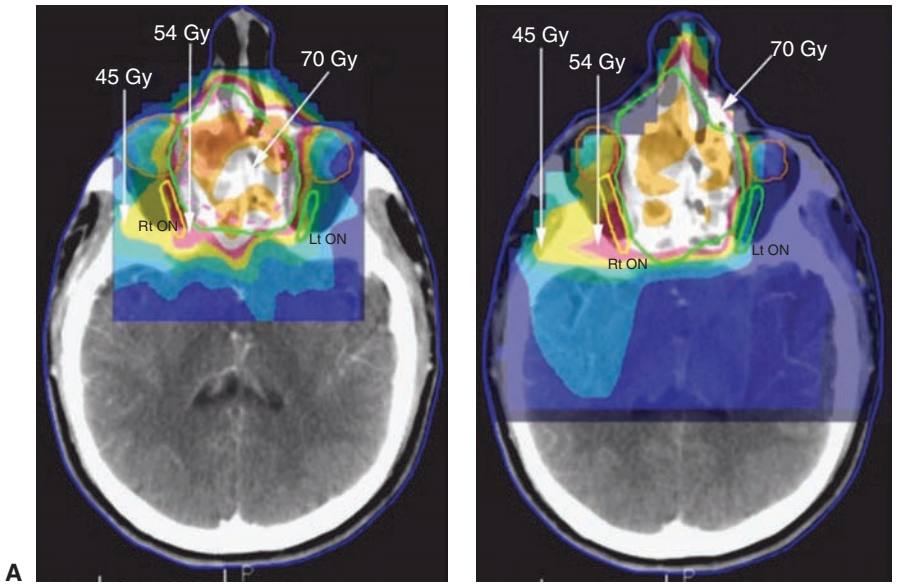



**FIGURE 5-4.** **A** and **B:** Isodoses of IMRT for advanced paranasal sinus cancer. Sparing the optic pathways was a major planning objective. IMRT, intensity-modulated radiotherapy.

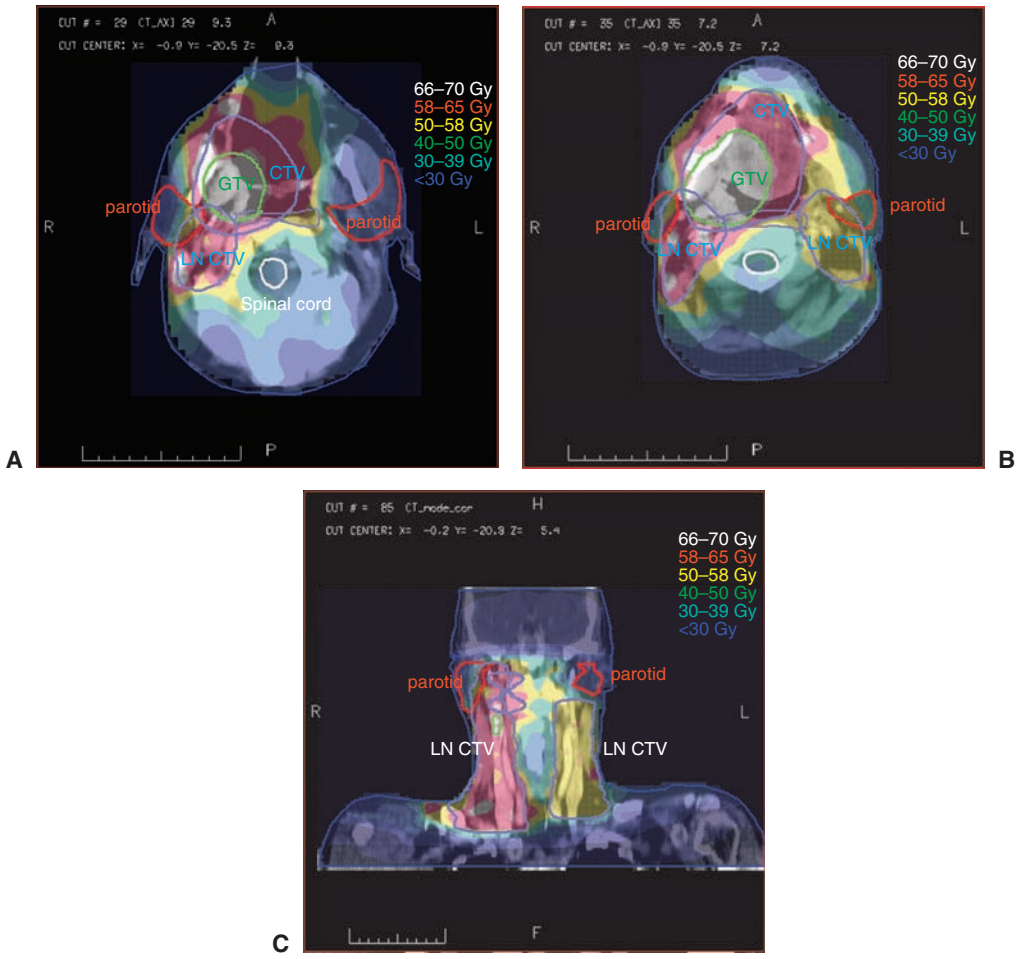



**FIGURE 5-5.** **A** to **C:** Isodoses of IMRT for the patient described in Figure 5.1. The contralateral parotid gland received a low dose (mean 17 Gy) and the ipsilateral gland a moderate dose (mean 32 Gy). IMRT, intensity-modulated radiotherapy.

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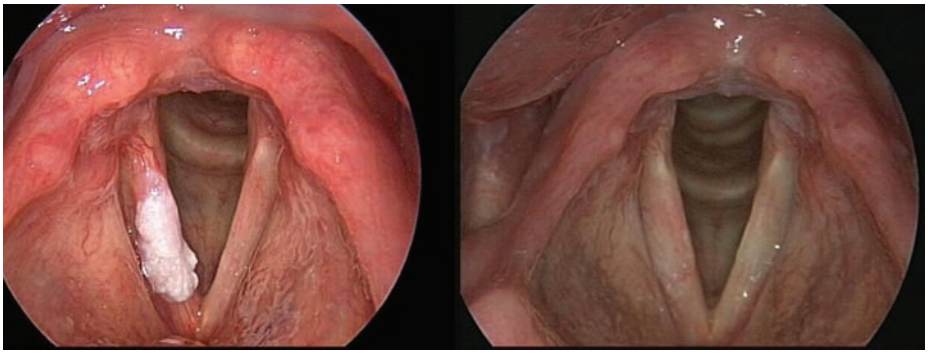


**FIGURE 6-3.** Preoperative **(left)** and postoperative **(right)** views of a T1 verrucous carcinoma resected via transoral laser microsurgery. The surgical defect is not evident, despite submucosal resection down to the vocal ligament. Adaptive remodeling of the larynx after transoral laser microsurgery may provide better functional outcomes that expected, when the proper lesion is choice. No radiation therapy was given.

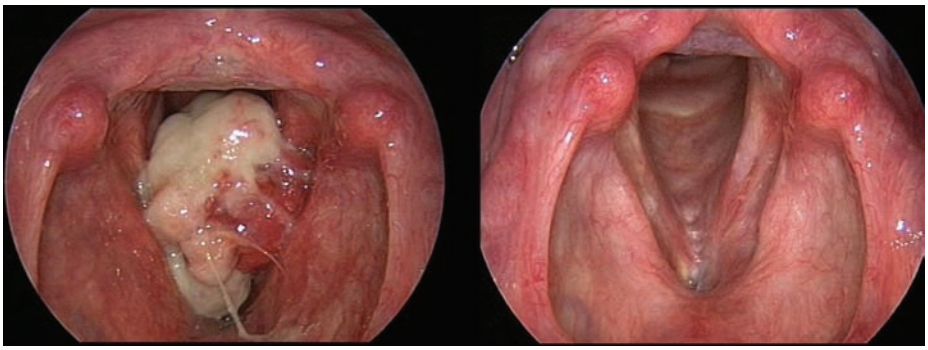


**FIGURE 6-4.** Preoperative **(left)** and 3-year postoperative **(right)** views of a squamous carcinoma of the larynx. CT imaging staged this as a T3 lesion, though the tumor was pedunculated from the undersurface of the left false cord. The tumor was resected via transoral laser microsurgery and no postoperative radiation therapy was given.

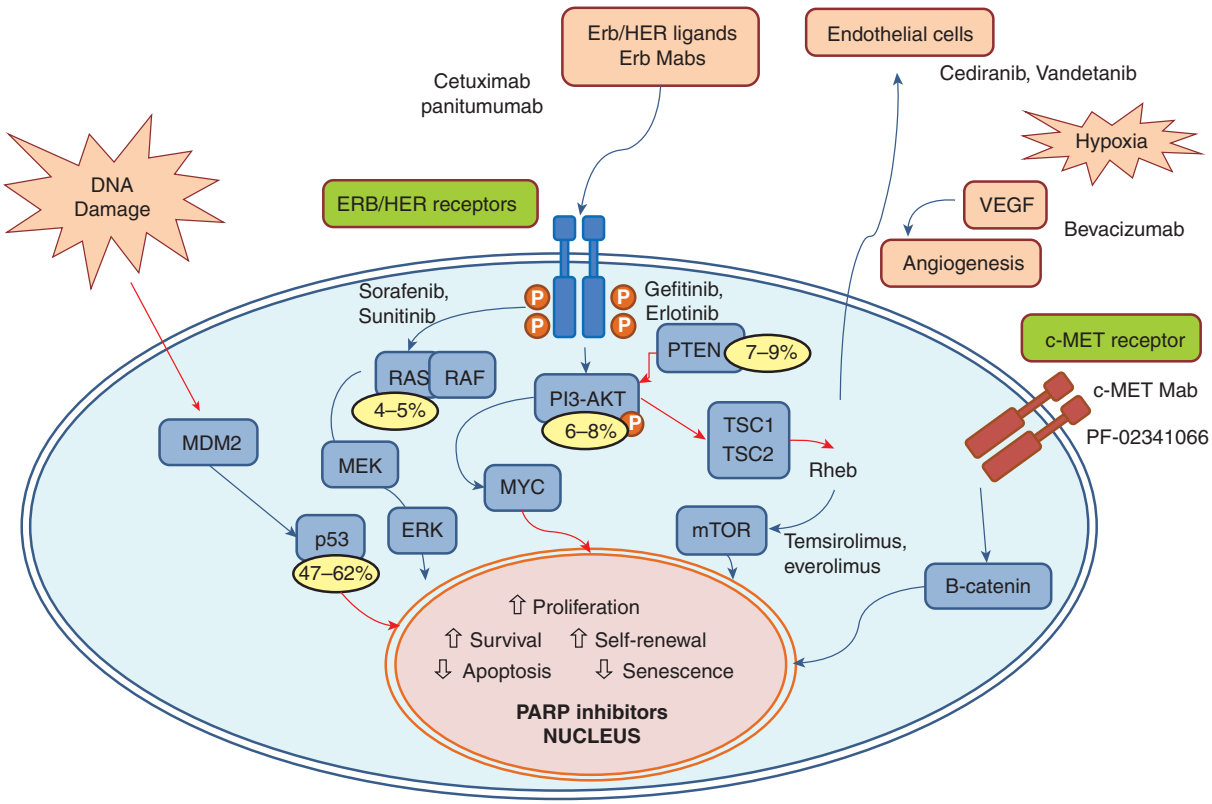
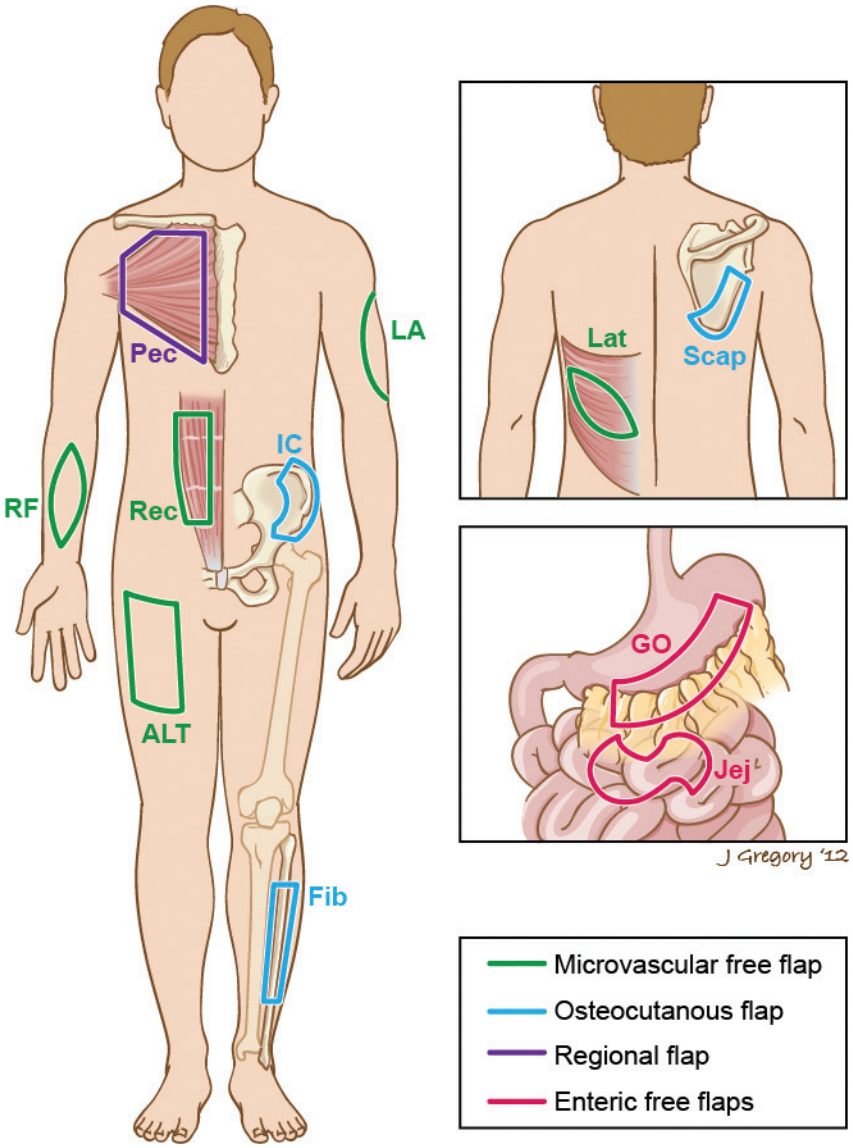



**FIGURE 7-1.** Selected pathways, targeted agents, and mutations important in squamous cell carcinoma of the head and neck. Red arrow, inhibitory activity; blue arrow, stimulatory activity; yellow circles; frequency of mutated genes; bold names, targeted drugs; PARP, poly(ADP-ribose)polymerases.

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**FIGURE 8-1**. Types of regional and free microvascular, osteocutaneous, and enteric flaps.



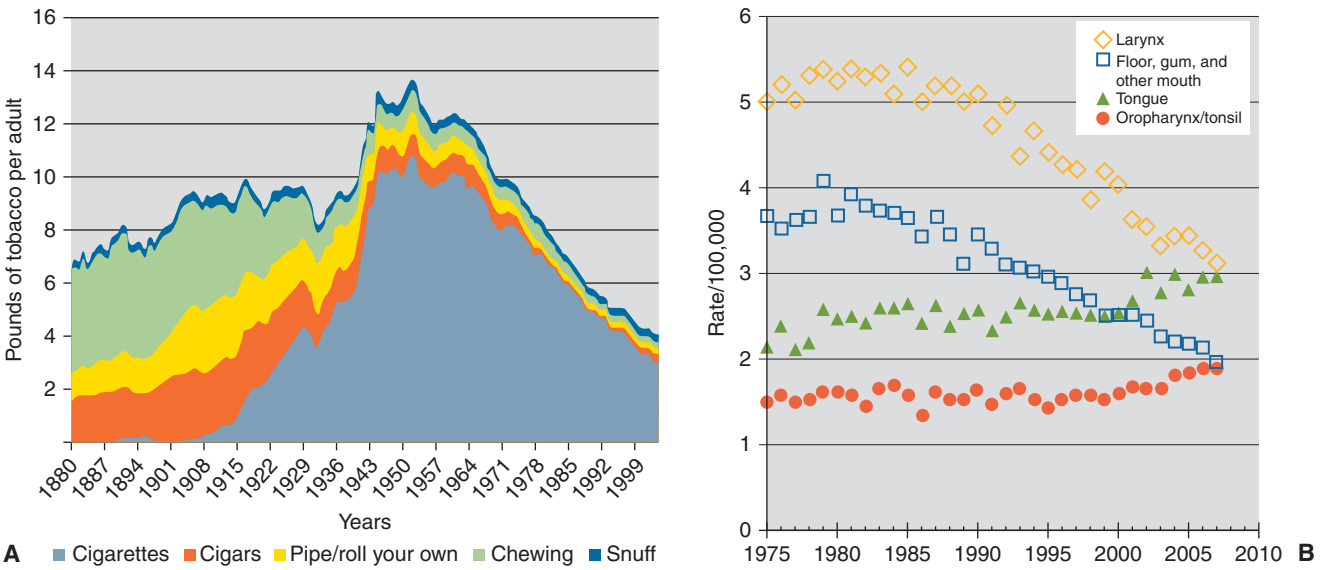




**FIGURE 12-1. A:** Trends in per capita consumption of various tobacco products in the United States, 1880 to 2004[4]; reproduced with permission. **B:** Age-adjusted SEER incidence rates for laryngeal cancers, floor of mouth/gingival/other mouth cancer, tongue cancers, and oropharyngeal cancers in the United States.

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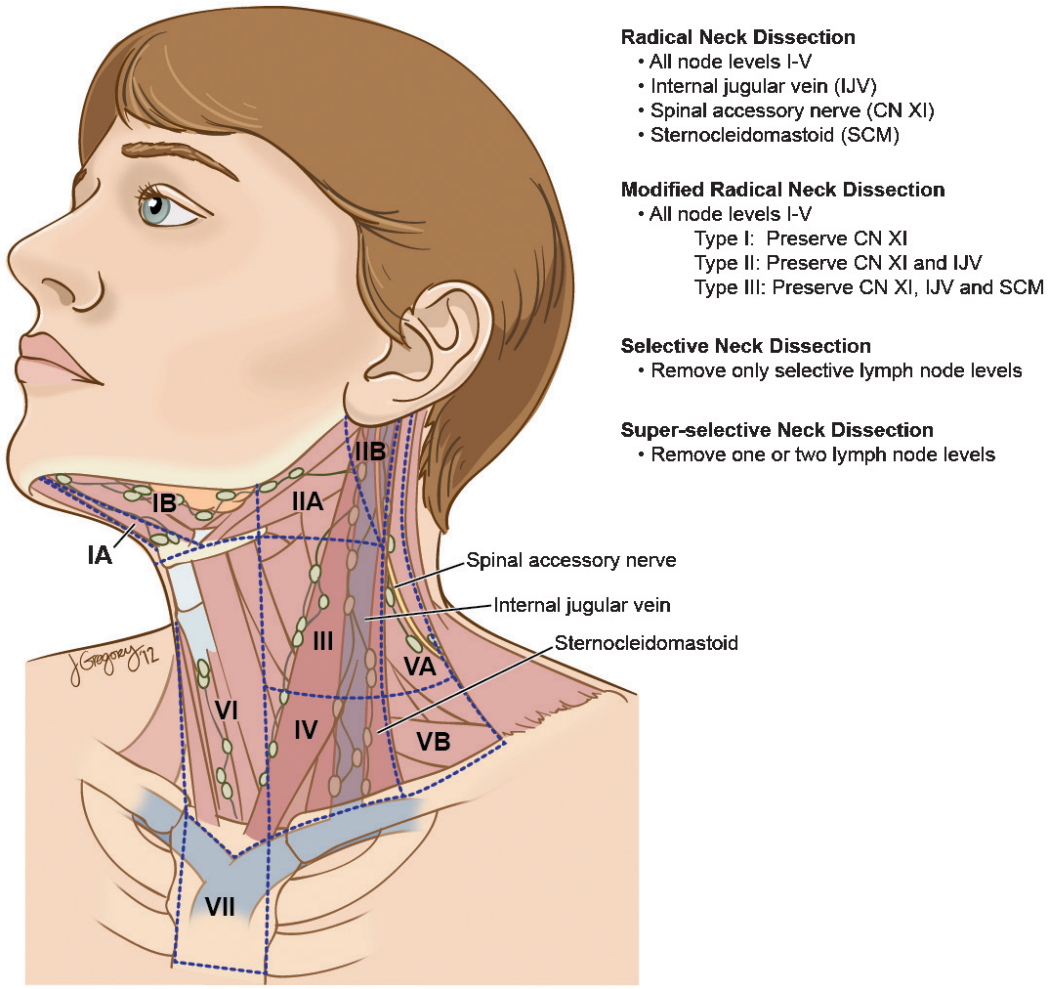
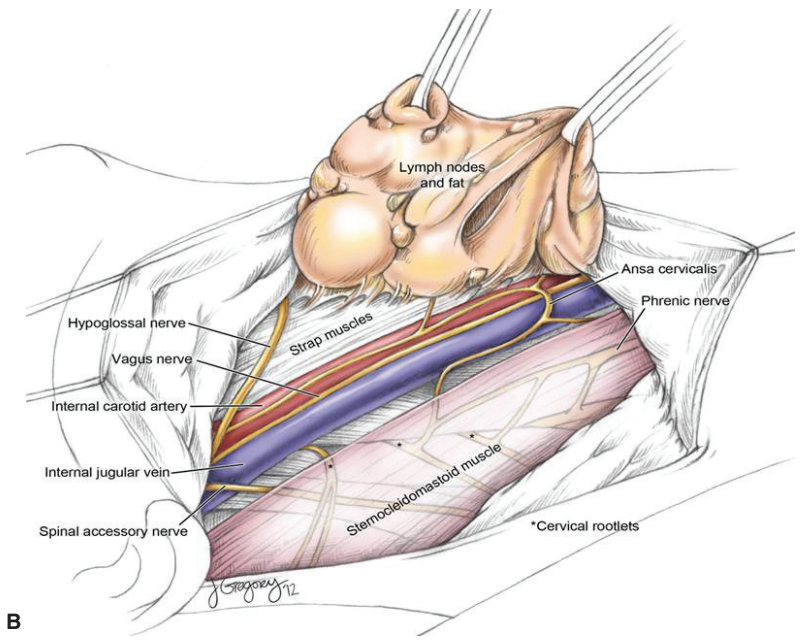



**FIGURE 14-1.** Nodal delineation for the electively treated node-negative and node-positive neck. On the left, are nodal stations delineated in a node-negative neck. On the right, are target delineation of level II nodal level up to the skull base in a node-positive neck. On the left, is shown the target delineation of level II in an electively treated neck. Note the differences in the superior margin allows substantial sparing of the parotid gland. RP, retropharygeal node; ICA, internal carotid artery; JV, jugular vein; PG, parotid gland; PB of JGD, posterior belly of the jugulodigastric muscle; BP, brachial plexus. See Table 14.10 for boundaries of nodal stations.

**FIGURE 14-3.** Selective neck dissection. **B:** Illustration of selective removal of lymph node levels II, II, and IV.




B

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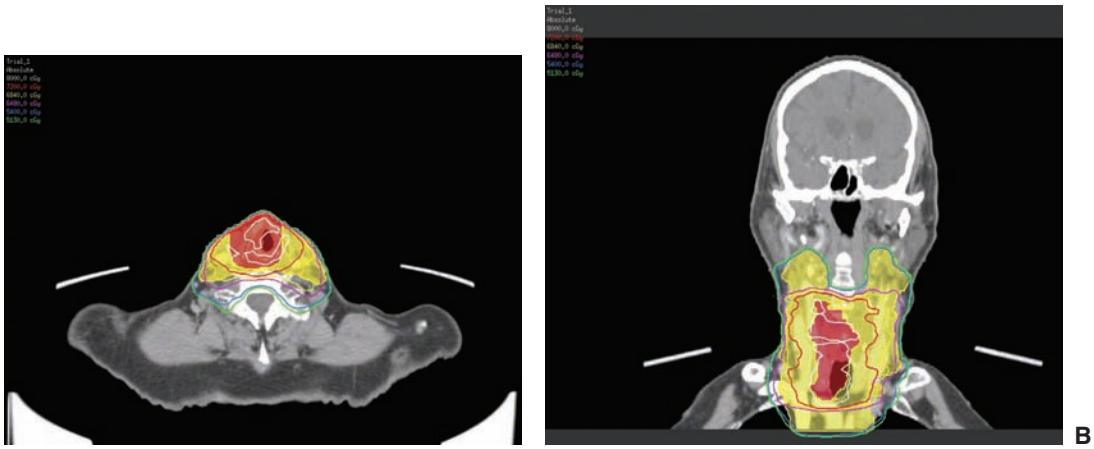



**FIGURE 15-10.** **A & B:** Patient with a T0N2B squamous cell carcinoma from an unknown primary site with left neck adenopathy. The patient is treated with IMRT with 6-MV X-rays. The oropharnyx and positive nodes receive 64.8 Gy at 1.8 Gy per once-daily fraction. The gross disease is boosted to 70 Gy. The standard-risk clinical target volume (SR-CTV) receives 50 Gy. **A)** Axial contour; **B)** Sapittal contour. A PET-CT is obtained after radiotherapy and a left dissection is performed if the response is incomplete.

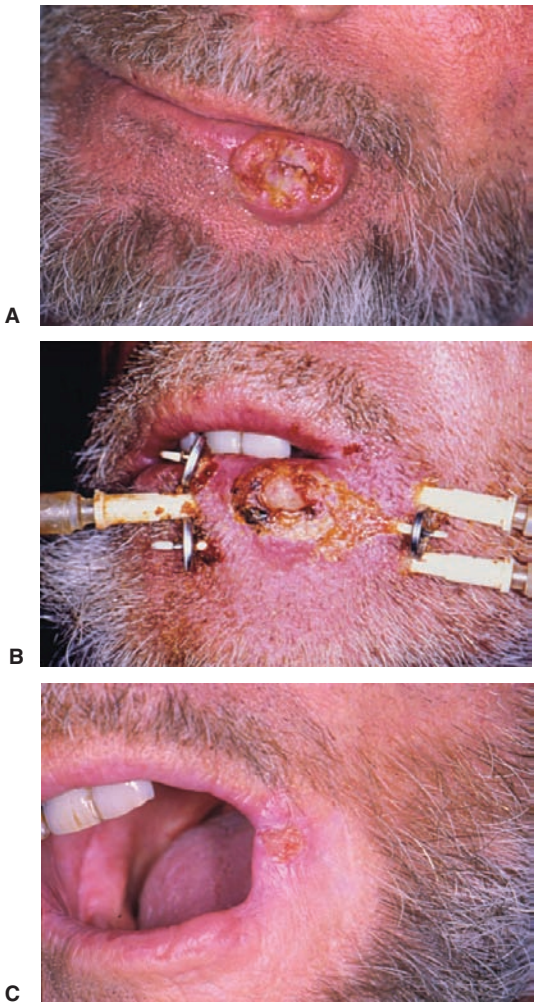



**FIGURE 16-33.** Patient had a 2.5-cm squamous cell cancer of the left side of the lower lip, near the lip commissure. Radiation was selected as the primary treatment due to the enhanced functional and cosmetic result in this particular case, given location near commissure. **A:** The lesion is seen. **B:** Patient had implantation of $^{192}$Ir via afterloading angiocatheters. A single plane implant was used and the catheters were 1 cm apart. A total of 6,000 cGy in 6 days was delivered. This photograph was taken on Day 6, just after source removal. The lesion has already regressed. **C:** Six months after implant. Patient has no evidence of disease.

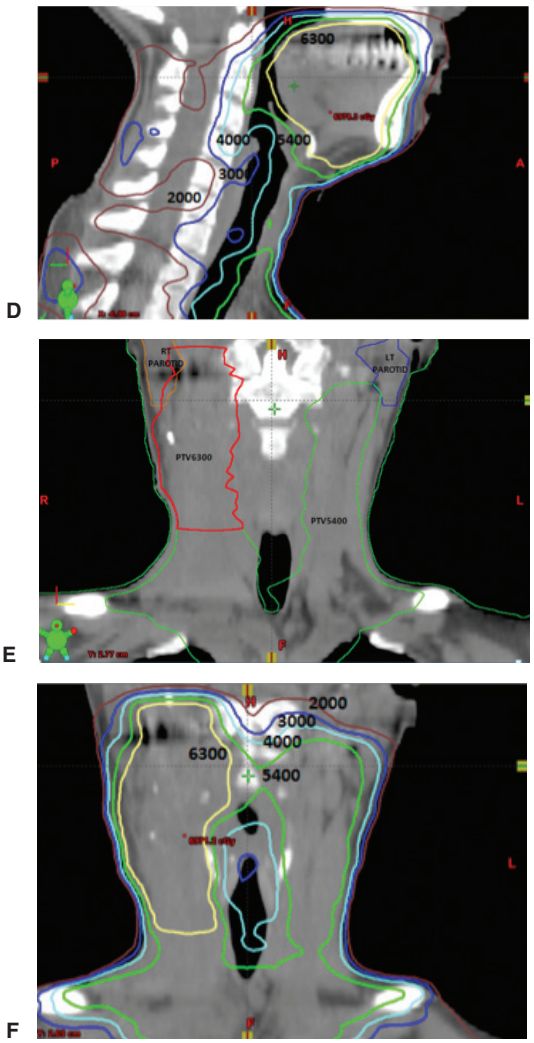



**FIGURE 16-36.** **D:** Same midsagittal CT slice as **C.** For ease in visual display, the contours have been removed, but the isodose curves for 6,300, 5,400, 4,000, 3,000, and 2,000 cGy are shown. Note the relative protection of the posterior pharyngeal wall. **E:** Coronal CT display showing PTV 63 and PTV 54. PTV 63 encompasses the right upper neck levels 2 and 3 in this display. The PTV 54 encompasses the right lower neck as well as the entire left neck. Note the sparing of the left (contralateral parotid gland). **F:** Same coronal CT display as **E**. As in prior figures, the contours are removed and the isodose lines are shown.

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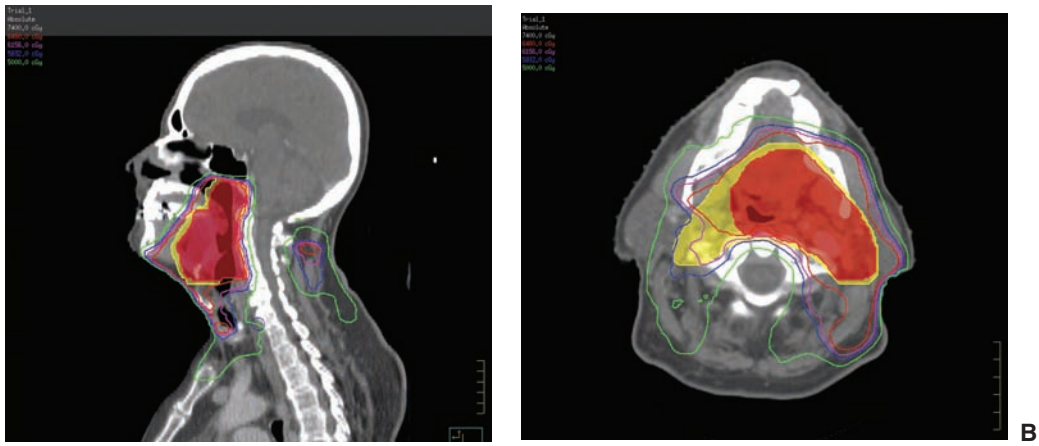
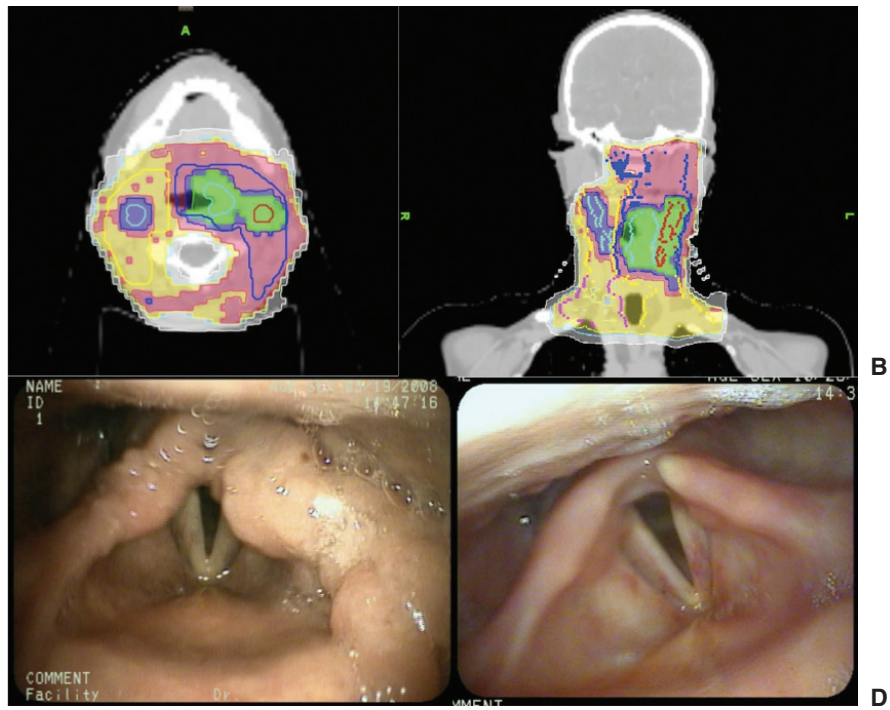


**FIGURE 18-25.** **A & B:** Patient with a T3N0 squamous cell carcinoma of the glottic larynx. The patient is treated with 6-MV X-rays with IMRT. The high-risk clinical target volume (HR-CTV) receives 70 Gy at 2 Gy per once-daily fraction or its equivalent using altered fractionation. The standard-risk CTV (SR-CTV) receives 54 Gy. **A)** Axilla contour; **B)** Control contour.

**FIGURE 19-9.** Axial (**A**) and coronal (**B**) dose distributions of a patient with a T3N2b SCC of the left pyriform sinus and aryepiglottic fold, treated with helical tomotherapy on protocol RTOG 0522. Turquoise contour represents the primary GTV, with involved left node contoured in red, both encompassed by a 70 Gy dose-cloud. Elective nodal areas received doses of 66 Gy (purple), 60 Gy (pink), and 56 Gy (yellow). Sparing of the right parotid is demonstrated on the coronal image. Panel (**C**) demonstrates the primary tumor prior to treatment via endoscopic examination, with complete response demonstrated at 3 years follow-up in panel (**D**).



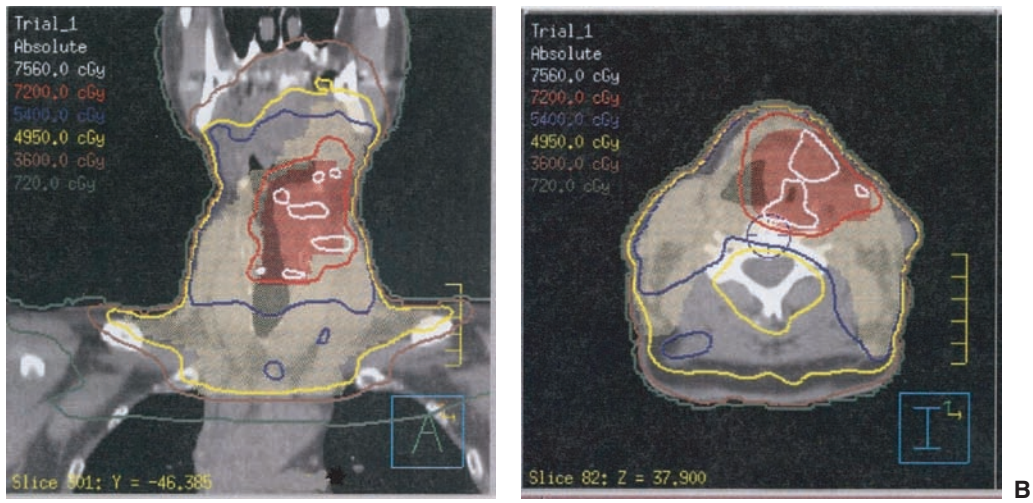




**FIGURE 19-28.** A seventy-nine-year-old man with a T3N2B squamous cell carcinoma of the left pyriform sinus. The gross tumor received 72.0 Gy in 42 fractions using the concomitant boost technique. The moderate risk volumes received 54.0 Gy. The patient received seven cycles of concomitant weekly cisplatin. The mean dose to the right parotid was 25.1 Gy.

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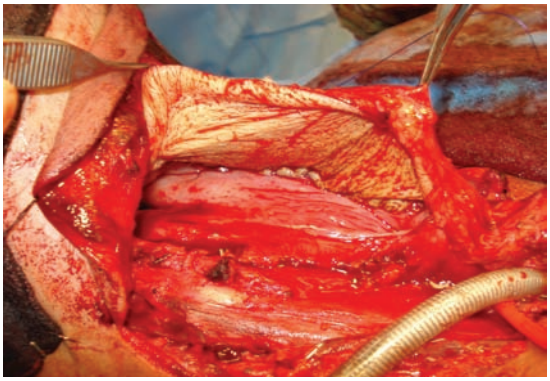


**FIGURE 19-30.** Pharyngeal reconstruction after total laryngectomy and partial pharyngectomy.

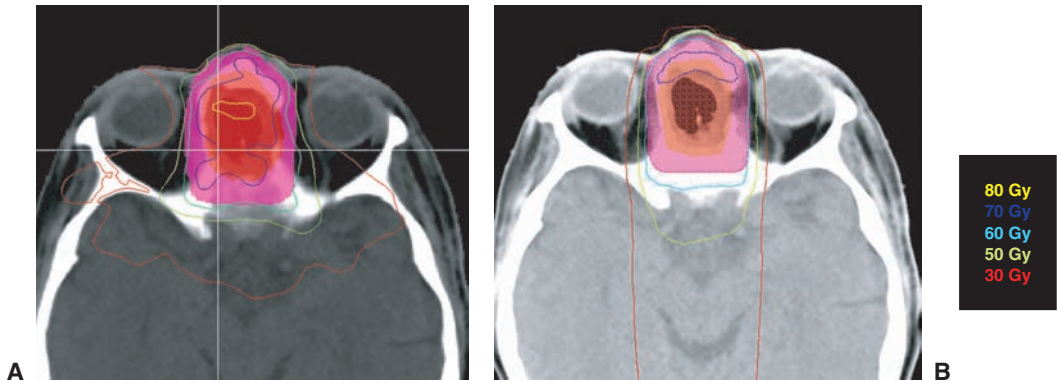



**FIGURE 21-1.** An example of an ethmoid sinus tumor being planned using **(A)** IMRT and **(B)** 3D-CRT. Notice that the 70-Gy isodose line (dark blue) coverage is superior in the IMRT versus the 3D-CRT plan. In addition, there is superior sparing of the optic chiasm when compared with the 3D-CRT plan. IMRT, intensity modulated radiation therapy; 3D-CRT, three-dimensional conformal radiotherapy.

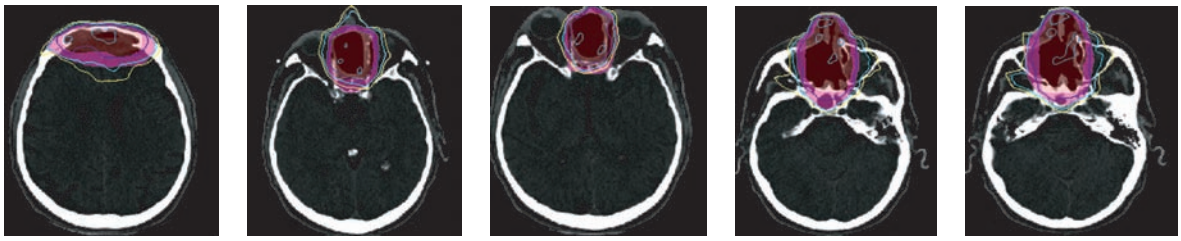


**FIGURE 21-9.** An example of different axial slices showing contours of a patient with ethmoid sinus tumor who underwent craniofacial resection. Red is the clinical target volume, which encompassed the preoperative GTV plus postoperative bed, whereas magenta is the PTV. Light blue is the 60-Gy prescription isodose line. GTV, gross tumor volume; PTV, planning target volume.

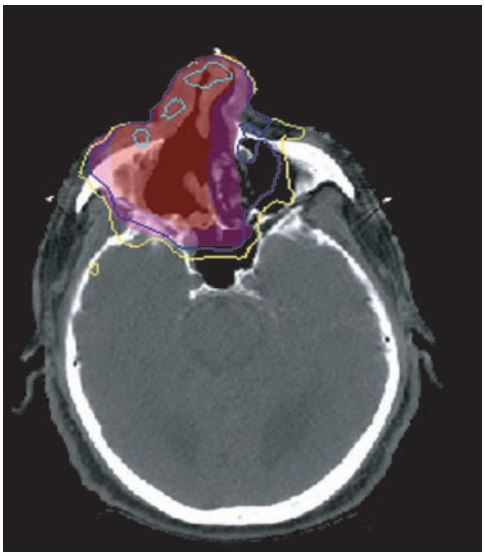
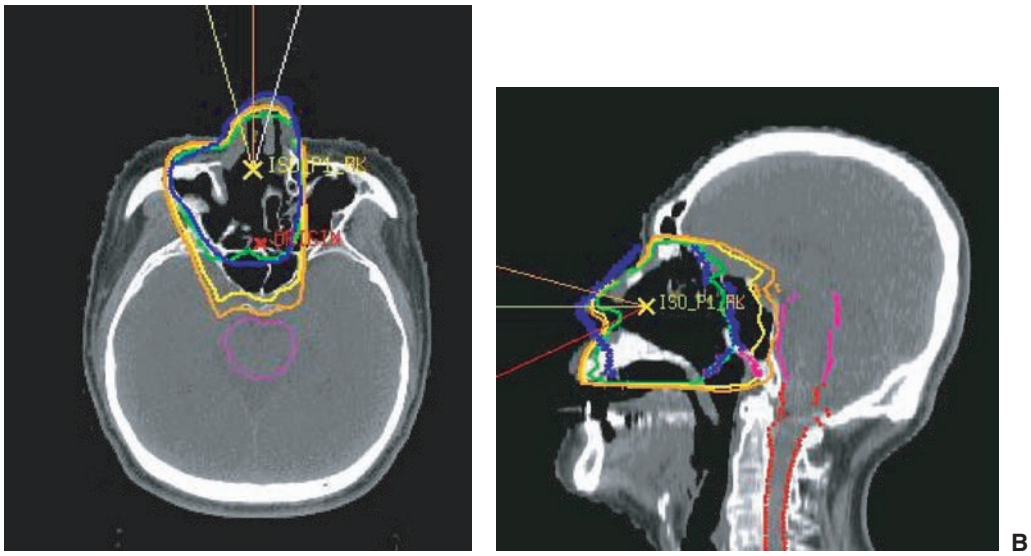


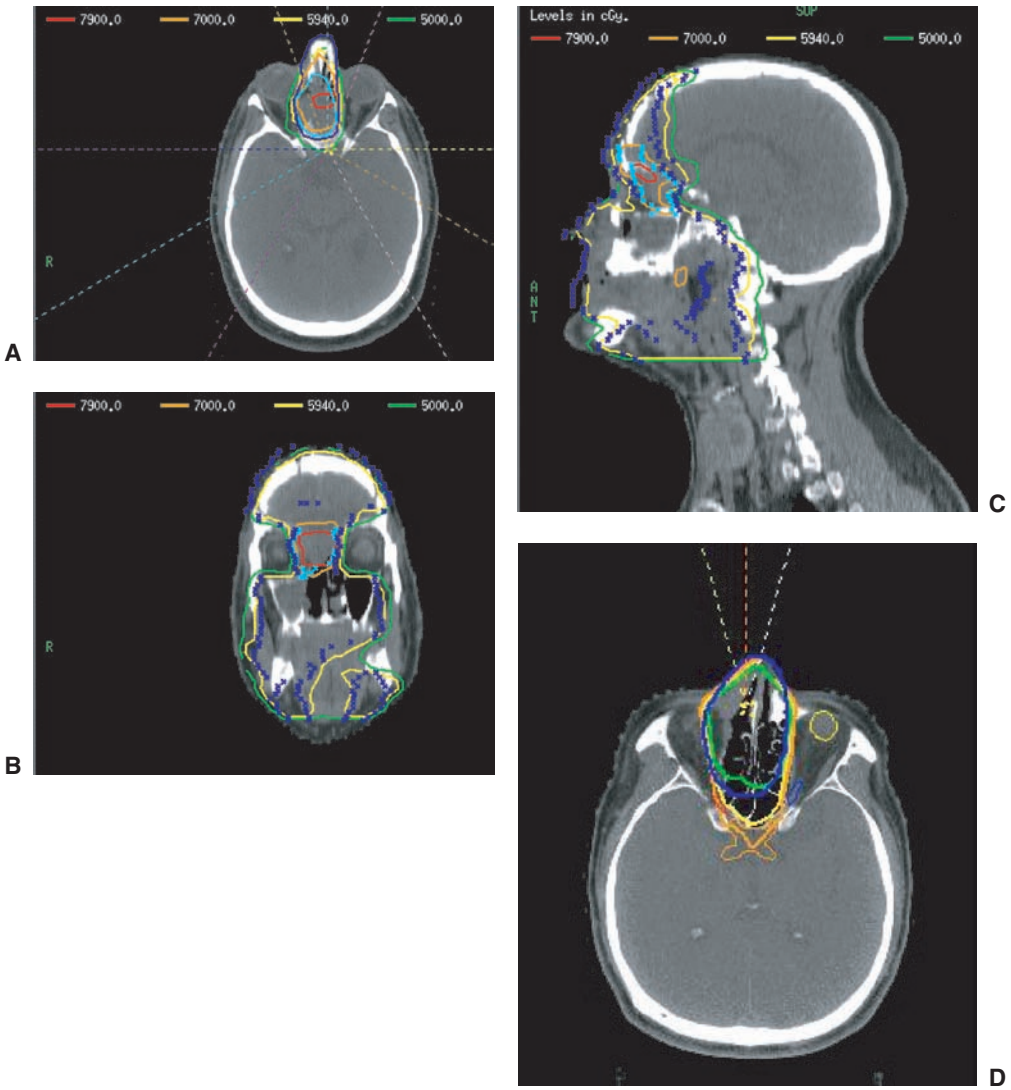
**FIGURE 21-10.** An example of a patient with maxillary sinus tumor who underwent craniofacial resection. Red is the clinical target volume which encompassed the preoperative GTV plus postoperative bed, whereas magenta is the PTV. Dark blue is the 60-Gy isodose line, whereas yellow is the 54-Gy isodose line. GTV, gross tumor volume; PTV, planning target volume.

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A B

**FIGURE 21-11.** An example of a patient with squamous cell carcinoma and the nasal septum and the right maxillary sinus. The patient underwent surgery with a close margin. Notice the nice conformality of the 60-Gy isodose line encompassing the nasal cavity and the right maxillary sinus while keeping the optic structures and the brainstem below tolerance. **A:** Axial view. **B:** Sagittal view. Four noncoplanar beams were used in this IMRT plan. IMRT, intensity modulated radiation therapy.




A B C D

**FIGURE 21-12.** An example of a patient with sinonasal undifferentiated carcinoma where the tumor extended through the cribriform plate into the anterior cranial fossa. Despite two attempts at surgery, there was still gross residual disease. **A:** Notice the conformal dose distribution surrounding the gross tumor while sparing the optic structures. **B:** Axial view. **C:** Coronal view. **D:** Sagittal view.

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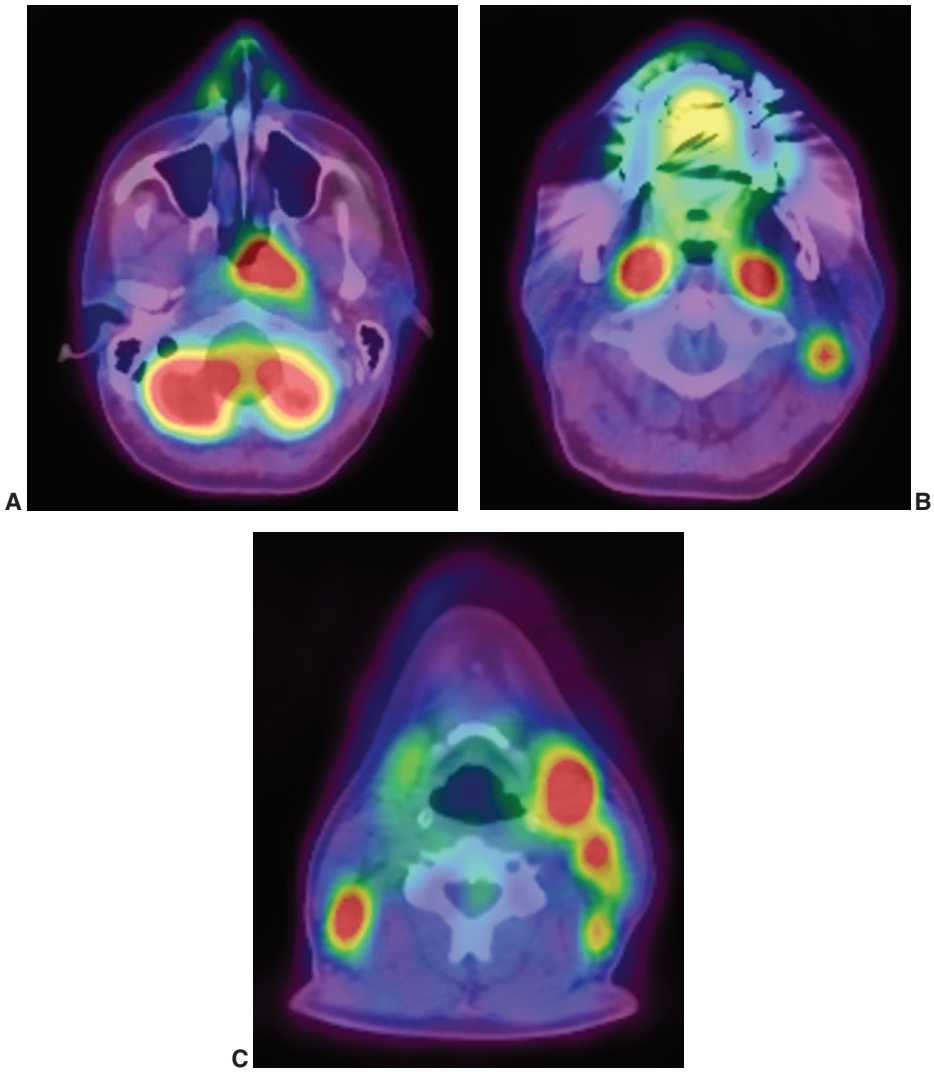



**FIGURE 22-17.** Axial composite images from a PET-CT show FDG uptake in the left nasopharynx **(A)** from the primary tumor. Bilateral retropharyngeal lymph nodes **(B)** and bilateral cervical nodes **(C)** are also positive for tumor.

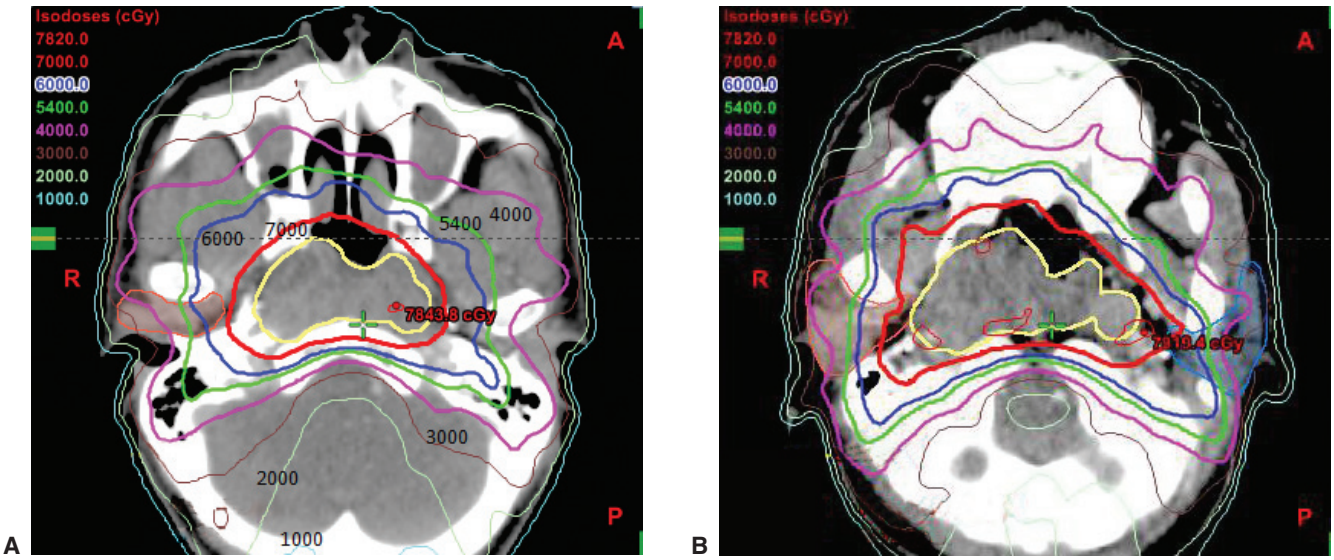
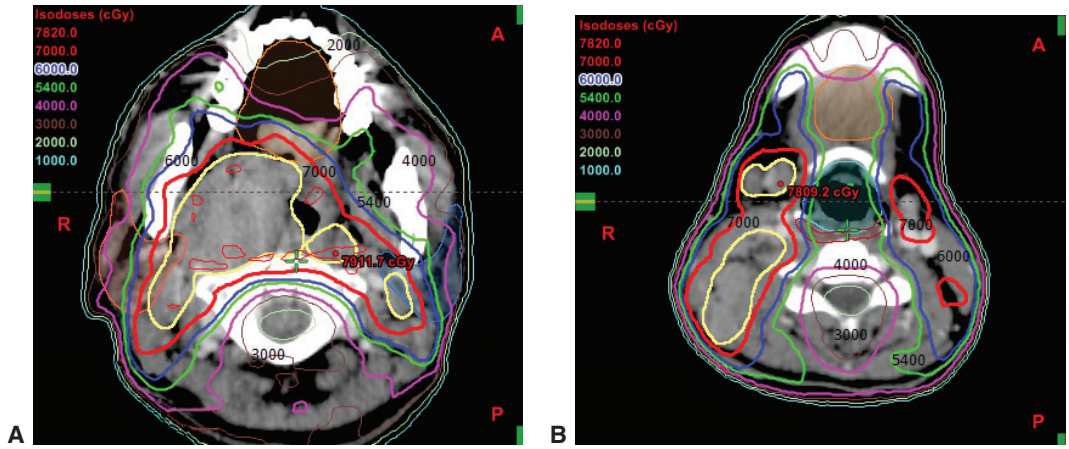


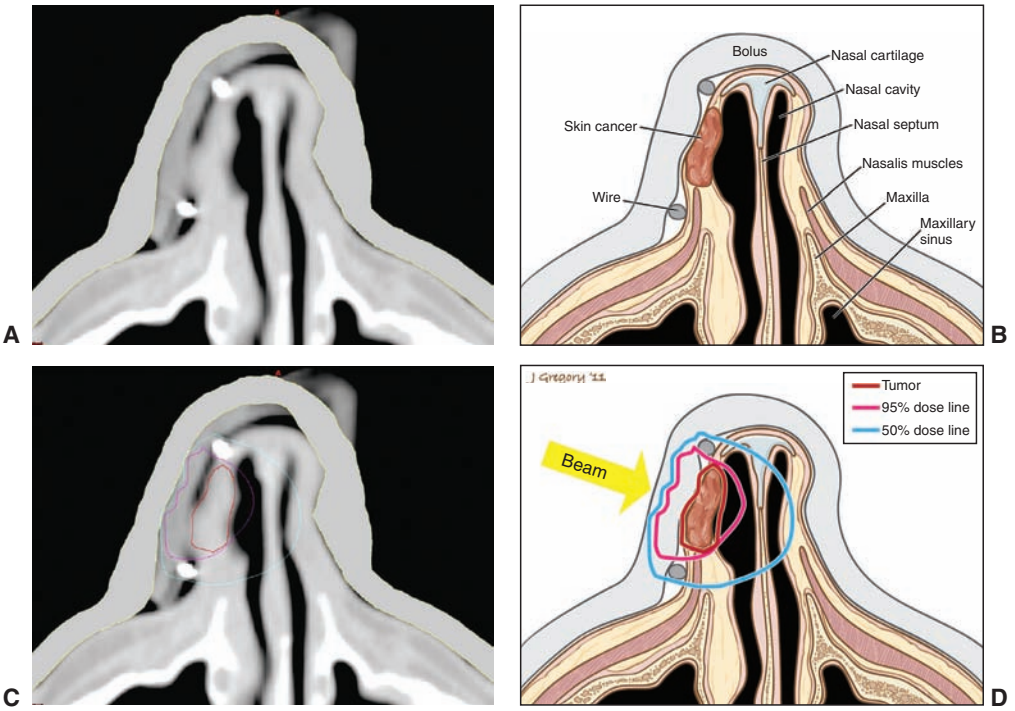

**FIGURE 22-22.** Isodose display through the nasopharynx **(A)** and through the superior aspect of the oropharynx **(B)**. The inner contour is the gross tumor volume covering the primary tumor and adjacent retropharyngeal nodes. The next contours, from inside out, are isodose levels 7,000, 6,000, 5,400, 4,000, 3,000, 2,000, and 1,000 cGy.

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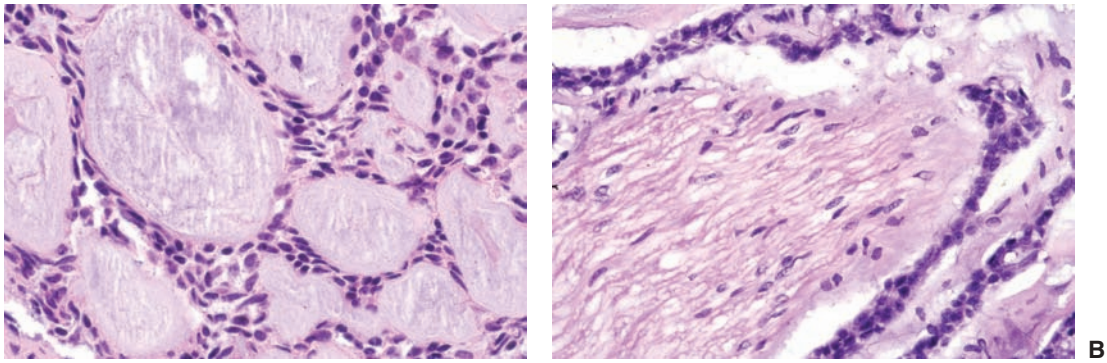

A B

**FIGURE 22-23.** Isodose display through oropharynx **(A)** and neck **(B)**. The gross tumor volume covers the primary tumor extension and the involved lymph nodes. The isodose contours, from inside out, are 7,000, 6,000, 5,400, 4,000, 3,000, 2,000, and 1,000 cGy. The oral cavity is outlined on **(B)** so it can be relatively spared, in an effort to protect the minor salivary glands.




A B C D

**FIGURE 23-33.** These are the images and drawing corresponding to the patient in Figure 23.32. **A:** CT planning image with custom bolus and wire around lesion visualized. **B:** Anatomical drawing corresponding to **A**. **C:** CT planning image with isodose distribution. **D:** Anatomical drawing corresponding to **C**.



A B

**FIGURE 25-5.** **A:** Cribriform type of adenoid cystic carcinoma with basaloid cells surrounding a myxoid matrix. **B:** Adenoid cystic carcinoma with extensive perineural spread.

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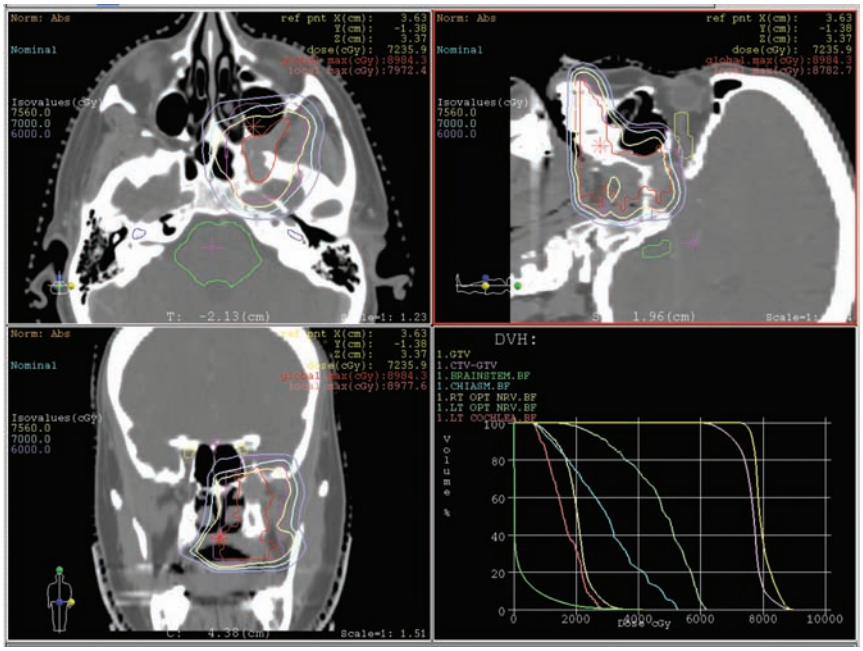



**FIGURE 25-14.** Definitive proton therapy for an unresectable adenoid cystic carcinoma of the hard palate with gross involvement of V2. Note the restriction of the irradiated volume to the defined CTV and relative sparing of the optic structures and the brain stem. There is no fall off or compromise of dose in the deepest part of the skull base. This patient is NED 6 years after 75.6 GyE to the GTV.

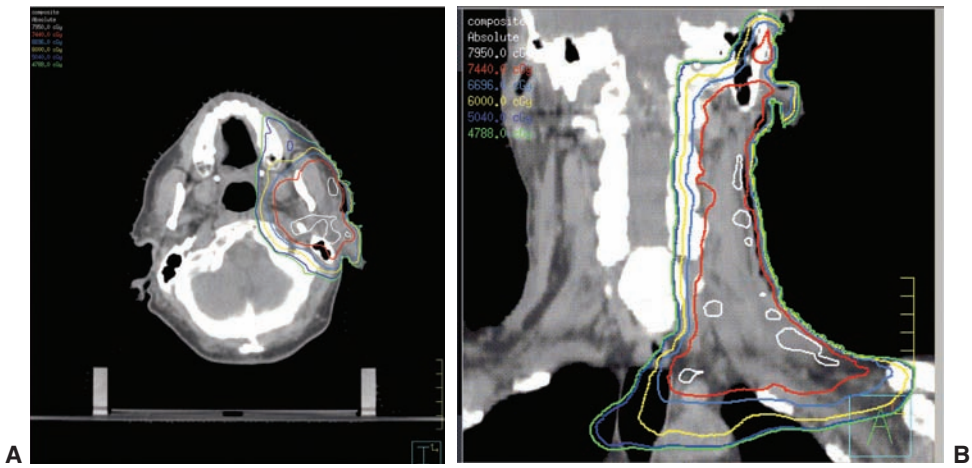



**FIGURE 25-26.** The patient underwent a left parotidectomy and neck dissection for a $T_3N_{2B}$ high-grade mucoepidermoid carcinoma of the left parotid gland. Although a gross total dissection was achieved, margins were microscopically positive. Postoperative IMRT was used to treat the left parotid bed and neck to 74.4 Gy in 62 twice-daily fractions. **A:** Axial dose distribution. **B:** Coronal dose distribution.

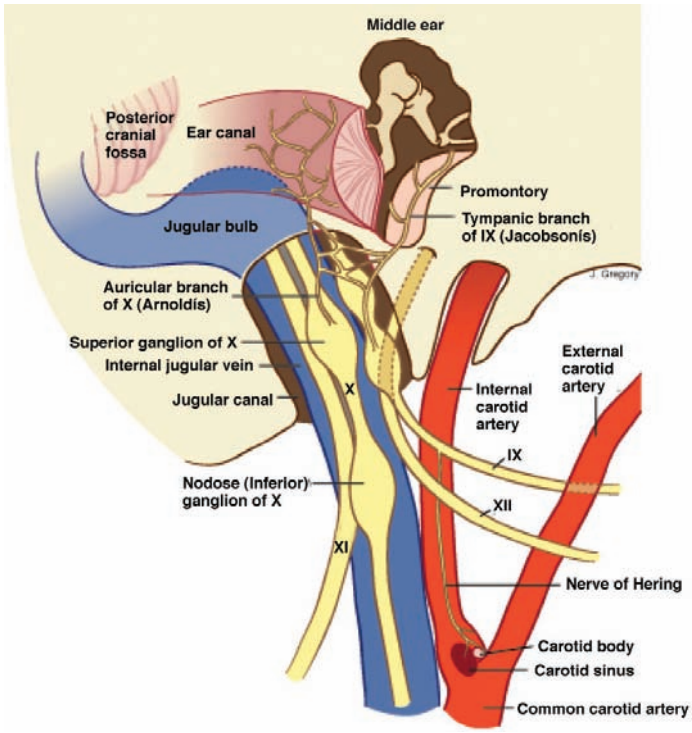



**FIGURE 27-2.** Schematic representation of lower cranial nerves at the level of jugular foramen.

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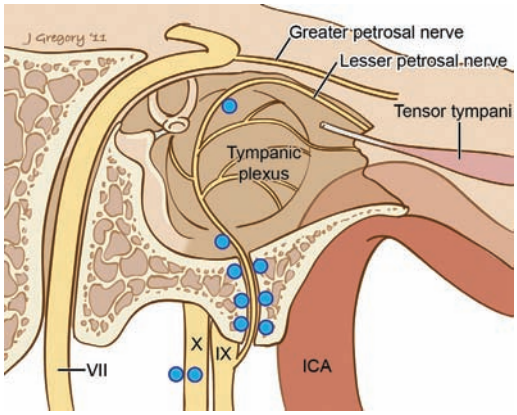
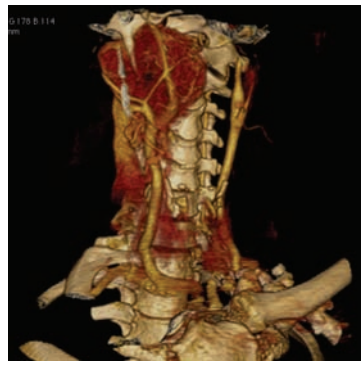
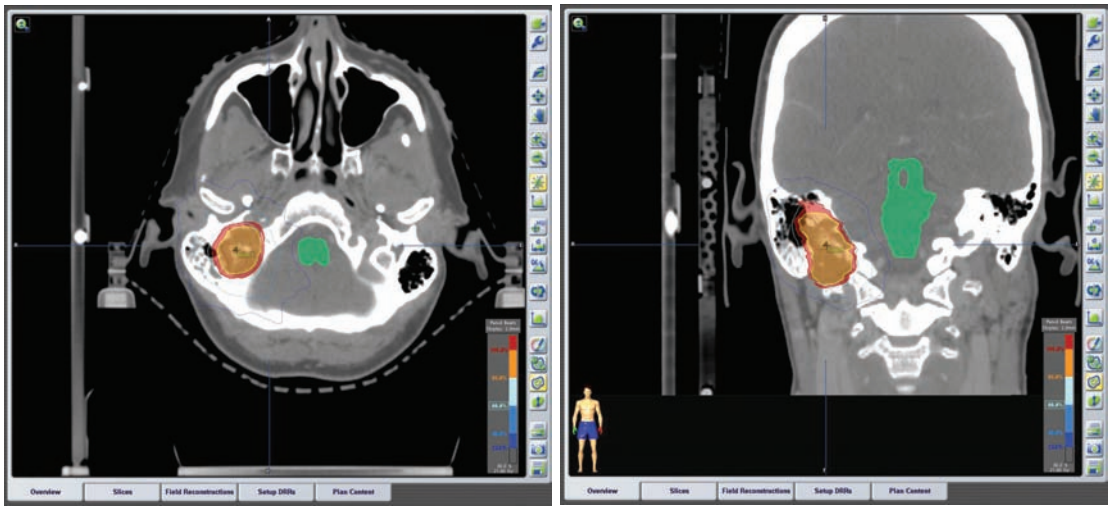



**FIGURE 27-3.** Distribution of frequent locations for glomus bodies in the temporal bone.



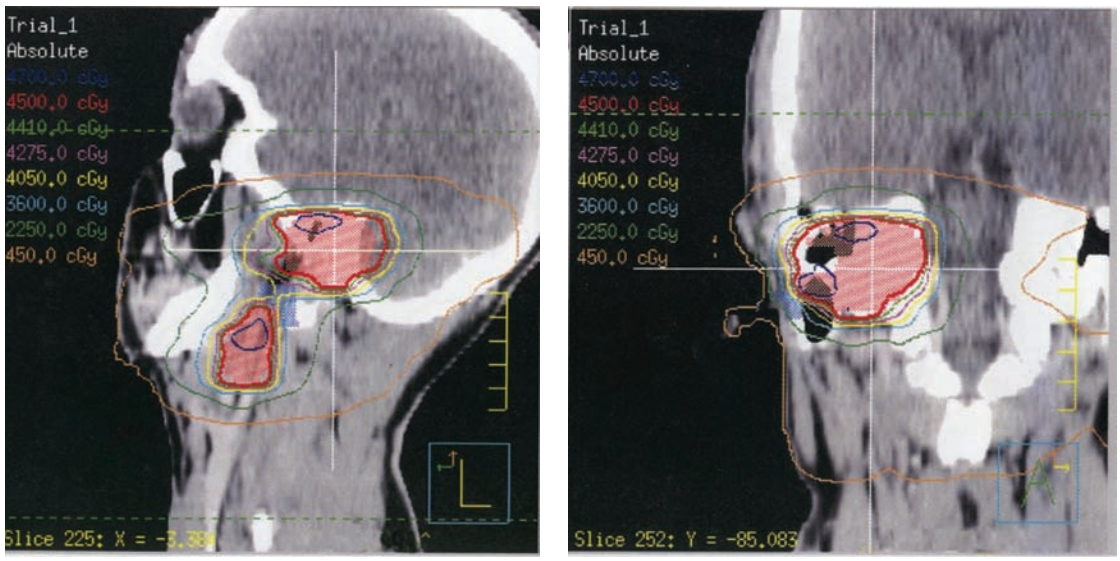
A

**FIGURE 27-9.** Computed tomography angiogram of a patient with a large paraganglioma. **A:** Volumetric surface rendering shows anterolateral displacement of the internal carotid artery and narrowing of its lumen. Note the filling of the internal jugular vein with contrast posterior to the common carotid artery, demonstrating the high flow within this tumor.



C D

**FIGURE 27-20.** Fifty-year-old female with an incapacitating jugulotympanic paraganglioma causing tinnitus and dizziness causing gait instability and nausea. Due to the size of the lesion and proximity to the seventh and eighth cranial nerve, a stereotactic fractionated radiation therapy approach was recommended to minimize risk of iatrogenic neuropathy. Dosimetry is seen in axial **(C)** and coronal views **(D)**.




A B

**FIGURE 27-24.** Intensity-modulated radiation therapy (IMRT) for ipsilateral tumor. The patient is a 34-year-old man found to have a right glomus vagale and a right glomus tympanicum. The patient was treated with IMRT and received 45.0 Gy in 25 fractions. The mean right parotid dose was 21.5 Gy and the mean left parotid dose was 3.0 Gy. Follow-up with magnetic resonance imaging (MRI) revealed the paragangliomas to be stable 1 year after IMRT (**A:** sagittal; **B:** coronal).

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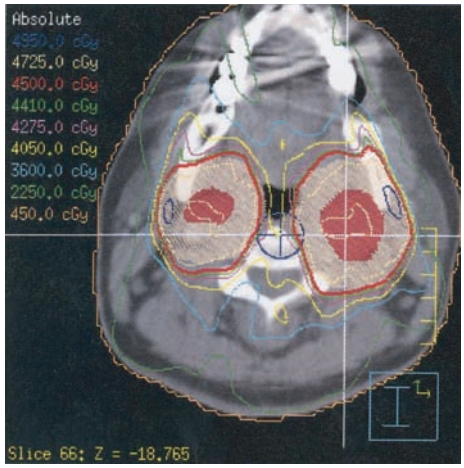



**FIGURE 27-25.** The patient is a 33-year-old woman with bilateral glomus vagale paragangliomas. She received 45 Gy in 25 fractions with 6-mV x-rays using intensity-modulated radiation therapy (IMRT). The mean parotid doses were 18.4 Gy and 20.2 Gy, respectively. Follow-up computed tomography (CT) at 1 year revealed no evidence of progression.

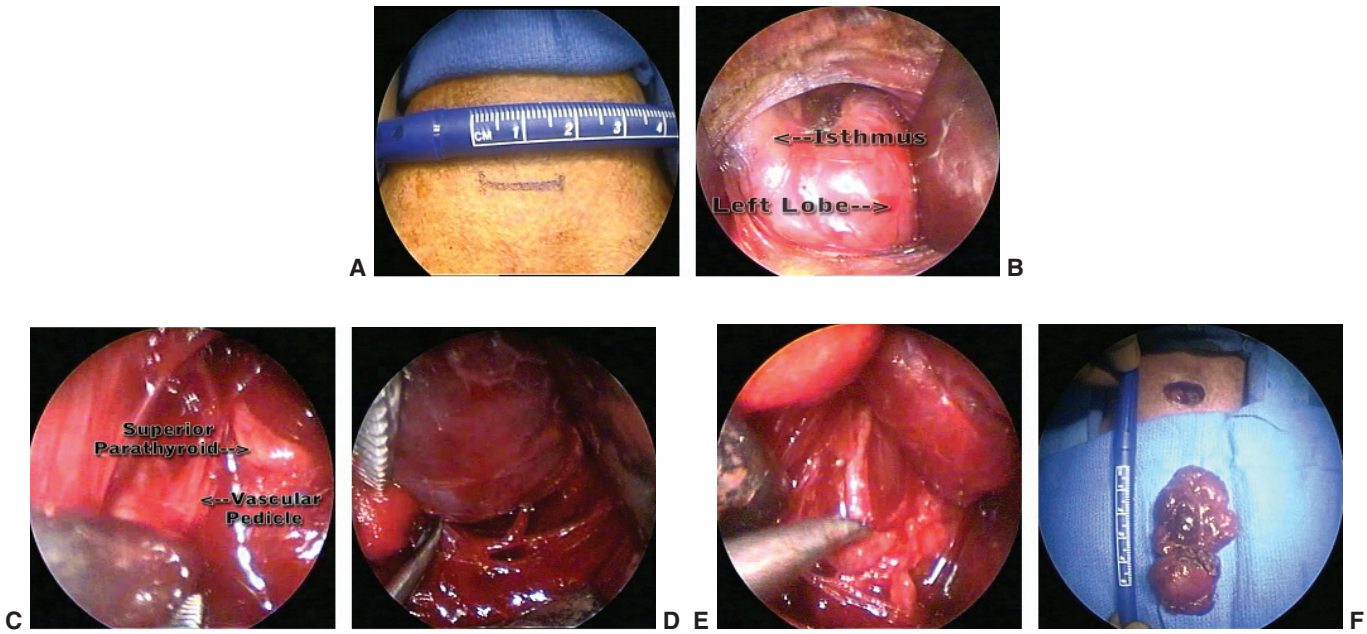



**FIGURE 28-30.** Minimally invasive thyroidectomy (MIVAT). **A:** Incision; **B:** Exposure via the midline raphe; **C:** Superior pedicle dissection; **D:** Inferior pedicle dissection; **E:** Recurrent laryngeal nerve dissection; **F:** Removed specimen.

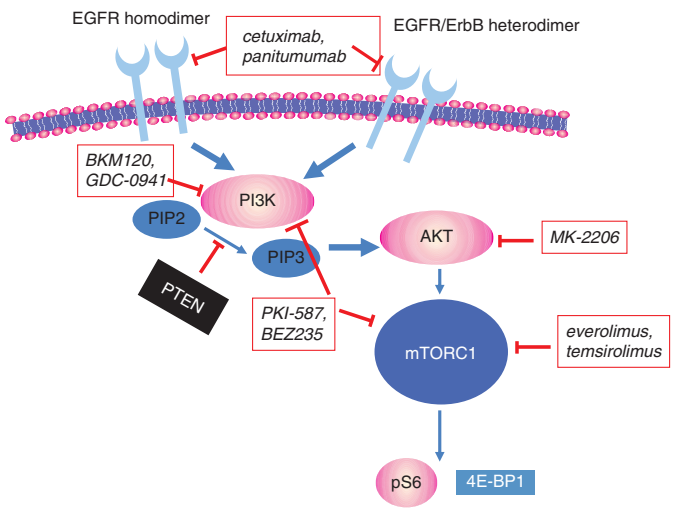



**FIGURE 30-1.** Simplified schematic illustration. EGFR homodimers and EGFR/ErbB heterodimers activate PI3 kinase, which favors the conversion of phosphatidylinositol bisphosphate (PIP2) to phosphatidylinositol triphosphate (PIP3), with subsequent activation of Akt and mTORC1. Two well-characterized phosphorylation targets of mTORC1 are eIF4E-binding protein (4E-BP1) and p70 S6 kinase 1 (S6K1), which regulate translation of proteins required for G1-S phase progression in the cell cycle. Monoclonal antibodies directed against the extracellular domain of EGFR (e.g., cetuximab, panitumumab) represent the most clinically advanced strategy to inhibit this pathway in HNSCC at present. Small molecules to inhibit intracellular processes in this cascade are under investigation, including PI3 kinase inhibitors (e.g., BKM120, GDC-0941), Akt inhibitors (e.g., MK-2206), mTORC1 inhibitors (everolimus, temsirolimus), and dual PI3 kinase/mTOR inhibitors (PKI 587, BEZ235), among others.

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