Contemporary Oral Oncology

Diagnosis and Management

Moni Abraham Kuriakose
Editor

Springer

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To my parents for igniting the fire for gaining and sharing knowledge
To my teachers and colleagues for keeping that fire burning
To my students for keeping me on my toes
To Rohan and Mili for keeping me grounded
To my patients for enduring our quest for cure
To Maria for being a patient partner in this quest

MAK

Foreword

Writing and editing a comprehensive multivolume text and a reference source on a focused topic is a dream of a life time for scores of academicians, but only a handful are capable of and committed to realize that dream. Dr. Moni Abraham Kuriakose is to be commended to bring that dream to a reality in the field of oral cancer. He has successfully gathered an assembly of world-class leaders from all corners of the globe to contribute to this exhaustive four-volume treatise on the current state of the art and science of oral oncology. The organization and planning of such an in-depth reference source takes deep understanding of the biology of the disease, and mastery in clinical management of the patient. The editor in chief has very carefully selected scholars from the Roswell Park Memorial Institute, coupled with others from North America, Europe, and Australasia, in the specialty of oro-maxillo-facial surgery and oncology, to have a global perspective of the disease. This provides a global perspective from different geographic regions of the world, with diverse patient populations and varied socioeconomic and cultural differences.

Although, the commonly identified etiologic agents for oral cancer are prevalent throughout the world, the biological behavior and natural history of these tumors are different in various regions of the world. For example, the presentation and behavior of oral cancer seen in South Asia is quite different than that in the western world. The authors have very elegantly delved into the biology of these differences and have highlighted the frontiers in research in this area. Similarly, practical issues in the clinical management of patients in diverse socioeconomic regions are discussed to make this a valuable resource for clinicians throughout the world.

This four-volume, in-depth, and exhaustive text presents frontiers in current research in basic sciences and the biological basis of carcinogenesis, tumor progression, metastases, and recurrence. The breadth and depth of the biology of squamous carcinoma covered in the text by global experts is impressive. Equally well covered are the chapters on diagnosis, treatment, operative technical details, and outcomes: both functional and oncologic. Each chapter is well illustrated with photographs, and superb artwork, to convey to the reader the intricate details from biological processes, to surgical techniques. Each and every chapter is accompanied by an endless list of references, to make this a "go to" resource and a reference text on the topic. This opus of oral oncology from molecular signatures to CAD-CAM technology in reconstructive surgery is a one of a kind publication on this subject published in a long time.

The four-volume set in *Contemporary Oral Oncology*, will have a solid place in the libraries of medical schools, postgraduate institutions, Cancer centers, and specialty departments in Universities. It is a wonderful state-of-the-art resource for the trainee as well as the practitioners of oral oncology, to remain current with the topic, and as a ready reference in basic and clinical research as well as day today management of patients. This exhaustive work stands alone in the presentation of biology, diagnosis, clinical care, prevention, and outcomes in oral cancer.

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Preface

Oral oncology is emerging as a distinct discipline. Comprehensive management of oral cancer requires multidisciplinary input of interconnected specialties. Every aspect of the management from diagnosis, treatment, reconstruction, and rehabilitation has biological basis. The biologic understanding of oral cancer and the treatment is changing with time. Understanding and updating developments in each of the related fields are essential to offer the patients the best possible treatment.

This book, in four volumes, is an in-depth reference guide that covers all aspects of the management of oral cancer from a multidisciplinary perspective and on the basis of a strong scientific foundation. Individual volumes are devoted to tumor biology, epidemiology, etiology, and prevention; diagnosis and treatment options; reconstructive surgical techniques; and rehabilitation and supportive care. By integrating current scientific knowledge into a manual for comprehensive care of the oral cavity cancer patient, this book is expected to fill a substantial void in the literature. Further key features are attention to the practical significance of emerging technology and the inclusion of contributions from authors in diverse geographic locations and practice settings in order to ensure that the guidance is of global relevance. The text is supported by ample illustrations and by case studies highlighting important practical issues.

There is lack of a single multidisciplinary comprehensive reference guide in oral oncology. This book is envisioned to fill this substantial void in literature. This book is intended for both trainees and practicing specialists in oral oncology. During my training, clinical practice, and research, I had the opportunity to gain knowledge and skills from different disciplines that includes dentistry, medicine, oral and maxillofacial surgery, general surgery, otolaryngology, plastic surgery, and basic science research spanning three continents. This unique opportunity provided me an insight into the importance of cross-fertilization of ideas from different disciplines and geographic regions. This book is an attempt to impart that principle to the field of oral oncology.

The first volume is dedicated to tumor biology, epidemiology, etiology, emerging role of cancer stem cells, and the prevention of oral cancer. It opens by discussing oral carcinogenesis in general and the role of different carcinogens and human papillomavirus, in particular. Global epidemiology and changes in disease prevalence are then addressed. Up-to-date information is provided on emerging cancer biomarkers, and the biologic basis of personalized therapy is explained.

Histopathological features of malignant and premalignant neoplasms and their relevance to management are described. Further chapters focus on the current status of chemoprevention, the management of oral submucous fibrosis, and the value of various diagnostic adjuncts. This volume concludes by critically evaluating the efficacy of oral screening methods.

The second volume deals with diagnosis and management of oral cancer. This volume addresses a range of management issues in oral cancer, from imaging and staging through to the roles of radiation therapy and chemotherapy. Principles of ablative surgery are explained, and neck dissection and sentinel lymph node biopsy techniques are described. Detailed consideration is also given to the management of complications, salvage surgery and re-radiation, the biologic basis of treatment failure, and emerging approaches to overcome treatment resistance. The inclusion of resource-stratified guidelines will meet the needs of practitioners in different geographic regions with varying resources.

The third volume is devoted to the reconstructive surgical techniques used in patients with oral cancer. Following introductory chapters outlining the general principles of reconstructive surgery in the oral cavity and the planning of maxillofacial reconstruction, detailed descriptions of the options and techniques employed in reconstruction of each of the functional subunits are provided. Important technologic advances are also discussed, including image-guided surgery, robotic surgery, and tissue-engineered and prefabricated approaches. Finally, the current status of face transplantation for maxillofacial reconstruction is reviewed.

The last of this four-volume book deals with the most important and often neglected aspect of rehabilitation and supportive care. This volume focuses on the topic of comprehensive rehabilitation and supportive care in oral cancer. The coverage includes the role of maxillofacial prosthodontics, advances in anaplastology techniques, and management of oral mucositis during radiation and chemotherapy. Holistic and supportive care approaches are discussed, and advice is provided on post-therapy surveillance and the use of different measures to assess quality of life. Nutritional evaluation and management and issues relating to healthcare economics are also considered. This volume will be of interest both to practicing specialists and to ancillary service staff involved in the care of oral cancer patients.

This book was authored by leaders in the field from diverse medical disciples and geographic regions. I thank the authors whose expertise and hard work that has distilled a vast body of information into a clear and detailed discussion of various aspects of oral oncology. I would like to express my thanks to the Springer Nature for supporting me in developing this book, to Wilma McHugh for project management and constant support, and to Abha Krishnan and Eswaran Kayalvizhi for the editorial assistance.

I have personally benefitted immensely by the tutelage of many mentors notably Sripathy Rao, Paul Salins, K. Kamalamma, Adrian Sugar, Anwar Perriman, Montague Barker, Paddy Smith, Brian Awry, John Hawksford, Keith Postlethwaite, Leo Stassen, Ian Martin, Andrew Ryan, Collin Edge, Mark DeLacure, Wesley Hicks Jr., Thom Loree, Richard Bankert, and my colleagues at New York University: Mark DeLacure, Richard Cohen, Robert Glickman, Fang-An Chen; Roswell Park

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Clinical Evaluation and Staging of Oral Cancer

1

Christina Mimikos, Sudhir Nair, and David Cohan

1.1 Introduction

The identification and evaluation of the patient with oral cavity cancer is an inherently multidisciplinary proposition. For most patients, the initial identification and evaluation of an oral lesion is undertaken by a primary healthcare giver—dentists, primary care physicians, oral surgeons, and general practitioners—before referal to a tertiary care center. Accurate diagnosis and staging at the initial visit is vital to appropriate decision-making and treatment planning. It is critical that the first examination of the oral cancer patient be comprehensive. Equally important is that the history taken is complete and elicits pertinent details that will give the oncologic care providers information relevant to the care of the patient. Initial evaluation of the oral cavity cancer patient will not only result in tumor staging but also determine most appropriate interventions and identify comorbidities that may influence treatment choices. Attempts should be made to identify the social support network of the patient has to facilitate consistent treatment and surveillance.

1.2 History

All patient encounters should begin with a complete and detailed history, with particular emphasis on oncologic risk factors. Medical conditions, past surgical history, medications, allergies, and social as well as family history should be addressed during the consultation. Medical and cardiac clearance may be required for patients with underlying or uncontrolled pathology, and medical status should ideally be

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optimized prior to beginning treatment. Past surgical history can dictate or limit the extent of resection or reconstruction. Medications, including all supplements, should be reviewed so that the surgeon can anticipate possible related complications.

An accurate social history is particularly important to the workup and treatment of oral cavity cancer. Smoking status and history, smokeless tobacco, betel nut use, alcohol use, illicit drug use, and occupational exposures should all be explored. Relevant information includes the duration and quantity of the patient's substance use and current status. Patients should be counseled to discontinue any substance use prior to treatment and assisted with medications or support programs. Continued smoking or alcohol use, particularly during adjuvant radiation, is associated with poor overall and disease-free survival and predisposes to second primary malignancies [1–3]. Social history is also a valuable source of information regarding a patient's ability and willingness to comply with and complete treatment. Many oral cancer patients require adjuvant radiotherapy for advanced disease, and treatment interruption or prolongation directly impacts overall survival [4]. Pretreatment evaluation can identify those individuals who are at risk for treatment interruption so that they may be assisted by social work prior to any intervention.

The history of the present illness should always include the presence or absence of oral and dental pain, bleeding, trismus, odynophagia, dysphagia, otalgia, weight loss, dysarthria, facial pain or numbness, change in the fit of a preexisting denture, and halitosis. This information will help to clarify the clinical picture should gross examination or imaging render equivocal findings regarding nerve or muscle involvement. Trismus suggests involvement of the masseter or pterygoid musculature or the presence of submucosal fibrosis. It may be present with or without pain. Adequate symptomatic pain control should be a goal from initial patient contact through the entirety of treatment. When trismus and pain are present, they may preclude adequate examination in the awake patient and necessitate examination under anesthesia.

Relevant signs and symptoms	
Ulcer	Any ulcer in the oral cavity persisting for more than 3 weeks requires evaluation and biopsy
Pain	Pain is not an initial symptom, but occurs when the mucosa is breached and the submucosal nerve endings are involved
Trismus	A recent onset trismus in an oral cancer patient can be due to severe pain or due to involvement of pterygoid muscles. Longstanding trismus can be due to oral submucous fibrosis
Otalgia	Referred pain to the ear is usually from a lesion in the oral or the base of the tongue or pyriform sinus (requires endoscopic evaluation)
Dental Pain, bleeding gums, loose teeth, ill-fitting dentures	May indicate an early primary lesion of the alveolus
Numbness	Numbness around the lower lip indicates involvement of the mental nerve, inferior alveolar nerve, or mandibular nerve
	Numbness in the cheek indicates involvement of the maxillary nerve

1.3 Risk Factors

Tobacco and alcohol are the leading risk factors for the development of OCC. Smoking tobacco confers a two- to fourfold increase in the risk of developing HNSCC and has a dose-response relationship for frequency and duration. Alcohol alone confers a twofold risk in heavy drinkers. Combined use of tobacco and alcohol by the same individual multiply the risk for HNSCC. Furthermore, 40 % of patients who continue to smoke after definitive treatment of an oral cavity lesion will have a recurrence [5].

Patient distribution is different between smokers and nonsmokers. Nonsmokers are represented by a higher percentage of women, more likely to be at the extremes of age (30 < or >80), and tumors are more likely to present in the oral tongue, buccal mucosa, and alveolar ridge. Smokers are more likely to be male, present with tumors of the larynx, hypopharynx, and floor of mouth, with a markedly higher rate of p53 transformation [6].

Smokeless tobacco and snuff are also associated with oral cancer, and they can produce visible changes in the oral mucosa with prolonged use. Similarly, the use of betel or areca nut has been associated with submucosal fibrosis and an increased risk of oral malignancy. The use of these products is more frequently seen in Southeast Asia and India than in western countries [7].

Human papillomavirus (HPV) is not as highly associated with malignant tumors of the oral cavity as in oropharynx, but HPV oncoproteins E6 and E7 have the ability to bind and degrade tumor suppressor gene products of p53 and pRb[8]. This can impair the ability of the cell cycle to arrest for the repair of DNA damage and result in accumulating genetic changes.

Additional factors, which can predispose to carcinoma of the oral cavity, include Plummer-Vinson syndrome, syphilis, ill-fitting dentures, long-term immunosuppression (up to a 30-fold increase with renal transplant) [5], pipe smoking, and UV exposure. Pipe smoking and UV exposure are particularly associated with carcinoma of the lip.

Risk factors associated with oral squamous cell cancer
Smoked tobacco
Smokeless tobacco
Alcohol
Betel nut chewing
Human papillomavirus
Plummer-Vinson syndrome
Long-term immunosuppression
Ill-fitting dentures
Repeated trauma
Pipe smoking (carcinoma of the lip)
Chronic exposure to UV light (for carcinoma of the lip)

1.4 Examination

Thorough evaluation of the oral cavity should yield the practitioner enough information to accurately stage the tumor, exclude a synchronous upper aerodigestive tract lesion, assess the patient's current functional status from the standpoint of airway and nutrition, and plan for treatment and reconstruction. This evaluation begins with careful inspection of the head and neck and cranial nerves, with emphasis on the oral cavity, pharynx, and larynx. Mirror or video pharyngoscopy may be required to assess lesions extending into the oropharynx. The lesion should be palpated to assess for fixation to the maxillary or mandibular periosteum, underlying musculature, and overlying the skin. The neck should be palpated for the assessment of lymphatic involvement. Prior surgery or radiation treatment effect should be identified and assessed as the reconstruction plan is formulated. A tissue diagnosis should be obtained by either biopsy or fine-needle aspiration. If biopsy was performed at an outside institution, the slides should be obtained and reviewed by a head and neck pathologist in order to confirm the diagnosis. Patients with severe pain or trismus may require examination under anesthesia for both staging and diagnostic purposes (Fig. 1.1).

Evaluation of oral cavity subsite:

(a) Tongue
(b) Floor of the mouth
(c) Alveolus
(d) Buccal mucosa
(e) Palate
(f) Retromolar trigone
(g) Lip and commissure

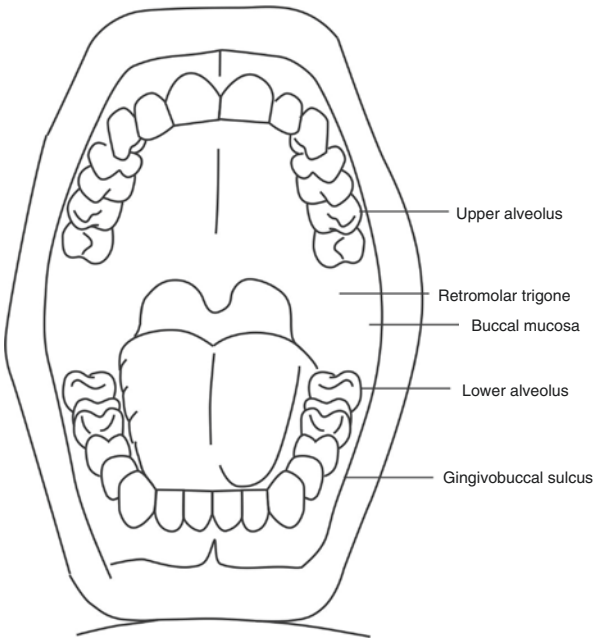

Fig. 1.1 Oral cavity subsites

1.5 Anatomy

The oral cavity extends from the vermillion border of the lip to the hard palate-soft palate junction posterosuperiorly, inferiorly to the circumvallate papillae, and laterally to the anterior tonsillar pillars. The oral cavity is divided into the following subsites: lip, oral tongue, floor of the mouth, hard palate, dentoalveolar ridges, retromolar trigone, and buccal mucosa.

The lips are the transition from the facial skin to the mucous membranes of the oral cavity. The transition begins at the vermillion border and extends proximally to the mucosa of the labiogingival sulcus. Innervation is via the infraorbital nerve (V2) to the upper lip and the mental nerve (V3) to the lower lip. The vascular supply to the lips is derived from branches of the external carotid system, namely, the superior and inferior labial arteries from the facial artery, superficial and deep branches of the submental artery, and the mental branch of the inferior alveolar artery. Lymphatic drainage corresponds to level IB, primarily the submandibular lymph nodes. Midline lower lip lesions may present with submental (IA) spread, and upper lip lesions have the potential to spread to the preauricular, infraparotid, and perifacial lymph nodes.

The dentoalveolar ridge is composed of the mucosa overlying the alveolus, from the transition of buccal mucosa laterally to the floor of the mouth and hard palate medially. Inferiorly, the ascending ramus of the mandible marks the posterior limit of the alveolar ridge. Superiorly the posterior limit is demarcated by the superior aspect of the pterygopalatine arch. The blood supply to the lower alveolus is primarily from the inferior alveolar artery, with supplemental flow from the mandibular periosteum. The blood supply of the hard palate is derived from the greater palatine and the anterior, middle, and posterior superior alveolar arteries. The lymphatic drainage of the buccal sides of the alveolar ridges is to levels IA–B. The lingual surfaces drain to level II and the lateral retropharyngeal nodes.

The hard palate spans from the maxillary alveolar ridges anteriorly and laterally to the soft palate posteriorly and forms the bony boundary between the nasal and maxillary sinus cavities and the oral cavity. Sensation is supplied by the nasopalatine nerve (V2). Lymphatic drainage is to the upper cervical lymphatics and the lateral retropharyngeal nodes. The blood supply to the hard palate is from the greater palatine artery and superior alveolar artery.

The oral tongue is defined as the portion of the tongue anterior to the linea terminalis. It is composed of four intrinsic and four extrinsic muscles and contains a fibrous midline septum. The extrinsic muscles originate outside the body of the tongue. The genioglossus functions to depress and protrude the tongue and provides the majority of the bulk. The hyoglossus depresses the tongue, while styloglossus elevates and retracts. Palatoglossus functions to depress the soft palate and elevate the back of the tongue. The intrinsic muscles of the tongue lie superficial to the genioglossus and function to alter the shape of the tongue. The intrinsic muscles are oriented superoinferiorly longitudinal, transverse, and vertical. There is no distinct plane between these muscles, which can allow a diffuse, infiltrating tumor pattern. Motor innervation is provided by the hypoglossal nerve except for the palatoglossus, which is innervated by a pharyngeal branch of the vagus nerve. General sensory innervation is provided to the anterior two thirds of the tongue by the lingual nerve, which also carries the chorda tympani, providing special sensory innervation. Both

functions in the base of the tongue are served by the glossopharyngeal nerve. The lymphatics of the oral tongue can be divided by region. The tip of the tongue drains to the submental nodes and the lateral tongue to levels I–II primarily. There is evidence, however, for a direct drainage pathway from the lateral tongue to levels III/IV. There is little crossover of lymphatics within the oral tongue, and tumors tend to drain to the ipsilateral nodal basins. This is in sharp contrast to the base of the tongue, where tumors frequently metastasize bilaterally.

The retromolar trigone is composed of the mucosa overlying the ascending ramus of the mandible and coronoid process. It is bounded by the buccal mucosa laterally and the anterior tonsillar pillar medially. Superiorly, it is bounded by the maxillary tuberosity, and the anterior margin is the posterior aspect of the mandibular second molar. Periosteal involvement is common given the close proximity of this site to the mandibular ramus, and lower lip paresthesias are common when the inferior alveolar nerve is involved at the mandibular foramen. Sensory innervation is provided by the lesser palatine nerve and branches of the glossopharyngeal nerve. Involvement of CN IX causes referred otalgia by tumors in this subsite. Lymphatic drainage is to levels II and III.

The floor of the mouth is bounded anteriorly and laterally by the mandibular alveolar ridge. The anterior tonsillar pillar is the posterior boundary. The lingual frenulum separates the space into right and left sides. The mylohyoid and hyoglossus muscle provide support for the floor of the mouth and an inferior boundary. The hypoglossal and lingual nerves run within this compartment, and involvement of these nerves may be the presenting complaint for patients with lesions in this subsite, resulting in dysphagia, dysarthria, dysgeusia, paresthesias, or pain. The blood supply to the floor of the mouth is derived from the branches of the submental artery and ascending pharyngeal and lesser palatine arteries. Sensory innervation is derived from branches of the lingual nerve, and lymphatic drainage is to bilateral levels IA–II.

The buccal mucosa extends from the posterior aspect of the lip to the alveolar ridges medially and the pterygomandibular raphe posteriorly. It is pierced by the parotid duct lateral to the second maxillary molar. Sensation is provided by V2 and V3. Lymphatics drain to ipsilateral IA–B.

1.6 Imaging

Appropriate imaging should be obtained to assess the extent of disease, which may either confirm or alter the clinical stage of the patient. Computed tomography is most frequently obtained and is the primary imaging modality for identifying cortical bone erosion and lymph node metastasis. MRI is a useful adjunct for the evaluation of soft tissue extension, nerve, and bone marrow involvement.

Radiograpic assesment of tumor boundaries can be invalueable in treatment planning. Involvement of masticator space is considered advanced local disease (T4b). However, tumors below the mandibular notch (infranotch lesions) or amenable for resection with favorable outcome. In case of tongue cancers, MRI can be helpful to identify features such as tumor extension across the midline, tumor thickness, and

involvement of extrinsic muscles. These findings have implications in staging as well as in the management of the primary and neck.

Preoperative chest imaging should be obtained with either plain film or computed tomography. Positron emission tomography (PET) scanning is becoming more frequently employed as a modality to image and assist in staging patients with oral cavity cancer; however, the use of PET and PET-CT varies from institution to institution. Evaluation of distant metastases is one frequently employed use for PET, and suspicious lesions may be confirmed by CT-guided biopsy. While the NCCN recommends routine PET-CT for stage III and IV disease, it may be reserved for patients with recurrent or second primary disease in a resource-constrained setting (Figs. 1.2 and 1.3) [9].

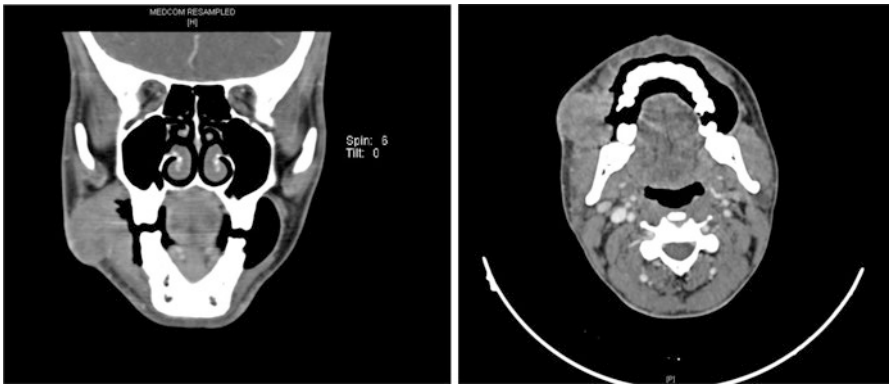

Fig. 1.2 Right BM with skin involvement

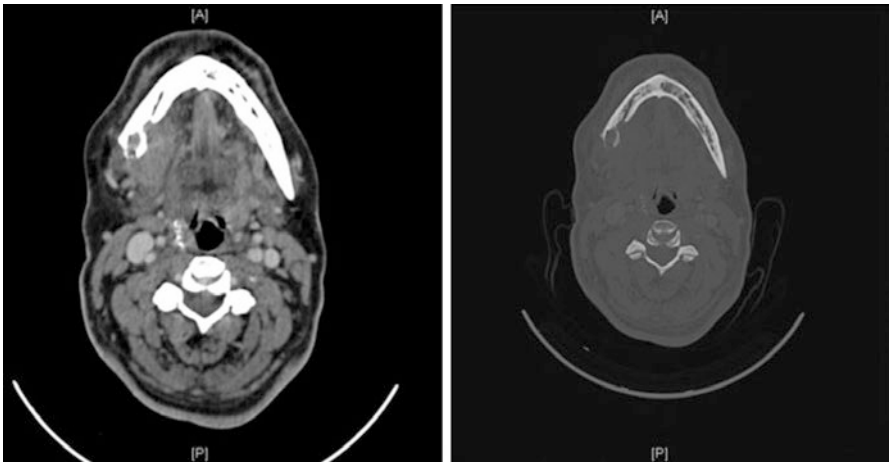

Fig. 1.3 Gross mandible erosion

1.7 Ancillary Services

Patients scheduled for definitive chemoradiation or major operative head and neck interventions must be carefully screened for factors that have the potential to impact or interrupt treatment. In the oral cavity in particular, the dentition must be evaluated and carefully addressed prior to treatment. In the event that the patient will require dental rehabilitation, skilled dentists and prosthodontists are invaluable additions to the treatment team. Nutritional assessment and appropriate intervention should be completed on every oral cancer patient in the pretreatment period. Malnutrition can predispose the patient to wound complications, failure to complete treatment, and overall higher rates of treatment failure. Early consultation for PEG tube placement is encouraged in all but the most limited tumors, if deglutition is suspected to be or to become a problem. Physical therapy can help to minimize debility in postoperative patients and may avert further trismus in patients with submucosal fibrosis.

1.8 Oral Cavity Lesions

There are several premalignant and malignant entities of the oral cavity, which are discussed in depth elsewhere in this work. Briefly, the premalignant lesions that are often encountered consist of leukoplakia (which can undergo a 2–3 % rate of malignant transformation), erythroplakia (5–10 % rate of transformation), lichen planus (transformation varies by subtype), and submucosal fibrosis (highly associated with transformation to SCCA). Leukoplakia and erythroplakia are characterized as white or red patches of the oral mucosa. They may also be present together as mixed lesion, designated erythroleukoplakia. Biopsy of these lesions is warranted to rule out microinvasive carcinoma. Lichen planus is a cell-mediated immune response which presents as whitish-gray linear or reticular streaking over a violaceous background of the oral mucosa. Lesions may persist for years. Submucosal fibrosis is a chronic fibrotic change of the upper aerodigestive mucosa. Early stages may present with oral burning sensation, vesicle formation, blanching, and leathery changes of the mucosa. Late submucosal fibrosis can result in fibrous bands within the mucosa leading to trismus, oropharyngeal stenosis, uvular distortion, and woody changes to the oral mucosa and tongue. It is most commonly seen in areas where habitual areca nut use is present, and the rates of transformation have been reported as high as 7.6 % [10]. Oral dysplasia is graded from mild to severe and is acknowledged to be part of the premalignant continuum. It can present a treatment challenge in the oral cavity, where wide-field exposure to carcinogens may have been present for years, resulting in field cancerization and dysplasia of a large area of oral mucosa. Verrucous hyperplasia is diagnosed on histology and clinically appears similar to verrucous carcinoma. It does not, however, invade the basement membrane. Necrotizing sialometaplasia is a benign process associated with trauma

to the minor salivary glands resulting in an ulcerated area, most commonly at the hard-soft palate junction. This can be seen in the context of an ill-fitting denture. Potentially malignant lesions may be self-limited or progressive and are potentiated by the continuing use of tobacco, alcohol, and betel nut products. The extent of these lesions may not be clear under white light examination in the office or operating theater; therefore, adjuvant examination techniques have been developed. Toluidine blue is an acidophilic metachromatic nuclear stain that will stain carcinoma and some premalignant lesions blue, while normal mucosa is left unstained. Sensitivity and specificity have been reported as high as 95 % and 71 %, respectively [11]. Chemiluminescence has also been investigated as an aid to determine the extent of premalignant lesions. It works by comparing the reflective properties of normal tissues with those of preneoplastic or malignant cells, which have a higher reflective index. Sensitivity and specificity have been reported up to 95 % and 84 %, respectively [12]. These techniques may be helpful in determining the extent of poorly defined premalignant lesions or early carcinomas.

Oral potentially malignant lesions	
Leukoplakia (Fig. 1.4)	"A white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer"
	Annual malignant transformation rate 1 %
	More common in smokers than in nonsmokers
	Clinically classified into homogeneous and nonhomogeneous leukoplakia
	Nonhomogeneous leukoplakia is further classified into erythroleukoplakia, verrucous leukoplakia, and proliferative verrucous leukoplakia
	Full-thickness biopsy is warranted to rule out microinvasive carcinoma
Lichen planus	Whitish-gray linear or reticular streaking over a violaceous background
	Annual malignant transformation rate is <1 %
	Reticular, ulcerative, and atrophic are the common morphologies seen in oral cavity
	Usually bilateral with more or less symmetrical pattern
Erythroplakia	"A fiery red patch that cannot be characterized clinically or pathologically as any other definable disease"
	Associated with tobacco and alcohol consumption
	High malignant potential (17 times that of leukoplakia)
Submucous fibrosis	Mostly restricted to Southeast Asia
	Most common etiology is areca nut chewing
	Characterized by burning sensation, blanching, and stiffness of oral mucosa followed by formation of vertical bands and trismus
	Annual malignant transformation rate is approximately 0.5 %

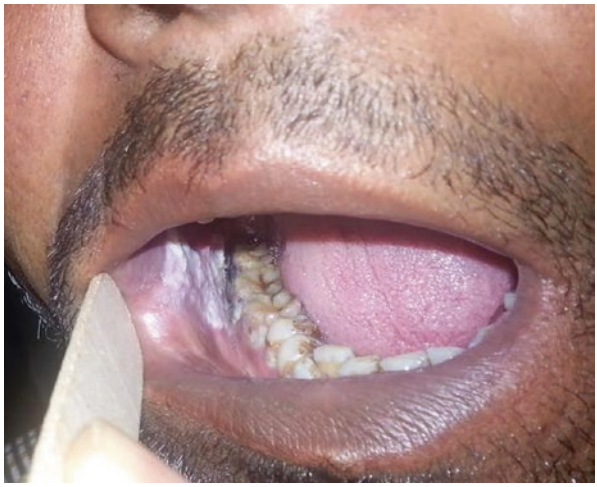

Fig. 1.4 Extensive leukoplakia

The discussion of oral cavity carcinoma is nearly synonymous with a discussion of squamous cell carcinoma. Variants include sarcomatoid, basaloid, and verrucous carcinoma. Other epithelial malignancies of the oral cavity include mucoepidermoid carcinoma, adenoid cystic carcinoma, and adenocarcinoma orginations in the salivary glands. Sarcomas include osteosarcoma, chondrosarcoma, malignant fibrous histiocytoma, rhabdomyosarcoma, and liposarcoma. They are generally seen overlying the mandible or hard palate. Kaposi sarcoma should be considered in mucosal lesions in HIV-positive patients. Melanoma may present on the lip or in the mucosa. In almost all cases, treatment for these lesions is surgical excision, with adjuvant therapy on an individual bases depending on the pathology and stage of disease.

Malignant lesions of the oral cavity	
Squamous cell carcinoma (most common) (Figs. 1.5, 1.6, 1.7, and 1.8)	Verrucous
	Basaloid
	Papillary
	Spindle cell
Minor salivary gland tumor	Mucoepidermoid carcinoma
	Adenoid cystic carcinoma
	Adenocarcinoma
Sarcoma	Osteosarcoma
	Chondrosarcoma
	Malignant fibrous histiocytoma
	Liposarcoma
	Rhabdomyosarcoma
	Kaposi sarcoma (in HIV-positive patients)
Mucosal melanoma	

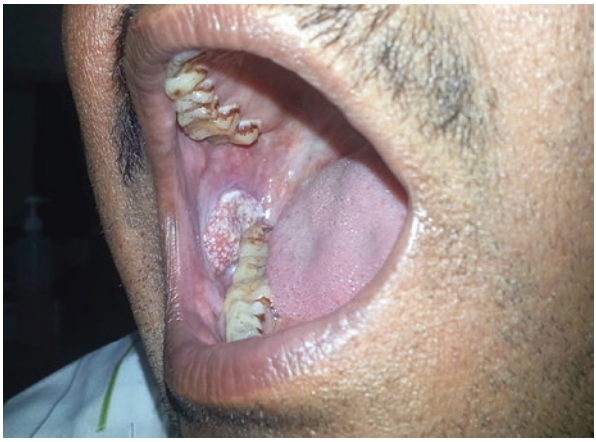

Fig. 1.5 Carcinoma of buccal mucosa with extension to retromolar trigone area

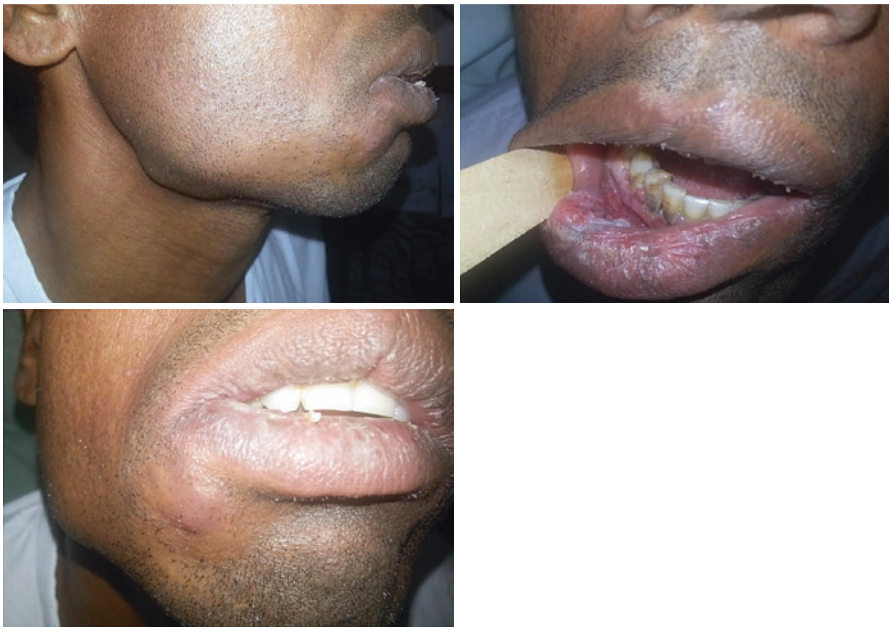

Fig. 1.6 Carcinoma of GB sulcus with infiltration of skin and enlarged level IB lymph node

1.9 Current Staging

The current staging paradigm for the oral cavity is based on the American Joint Committee on Cancer (AJCC) Tumor, Nodes, Metastasis (TNM) system. The goal of staging is to provide a relevant system for classification and outcome prediction

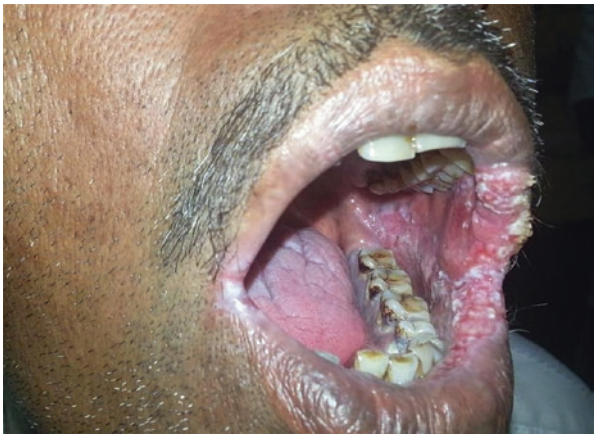

Fig. 1.7 Carcinoma of buccal mucosa with a preexisting leukoplakia

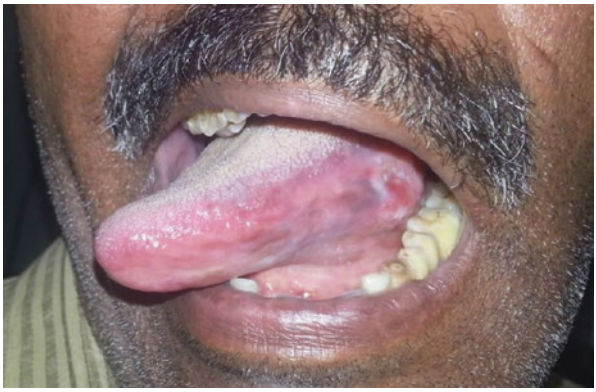

Fig. 1.8 Early stage carcinoma of tongue

of cancer that is compatible with systems of cancer population surveillance [13]. In an ideal staging system, tumors of the same stage would behave in a homogenous fashion, and outcomes could be easily predicted based on staging information (Fig. 1.9 and Table 1.1).

1.10 Pitfalls

Cancer is staged in order to provide guidance for treatment and information about prognosis. It then follows that staging guidelines attempt to consolidate disease stages into groups, which behave as homogeneously as possible. Recently, Belcher et al. reported 5-year survival rates for oral cavity carcinoma: stage I 72 %, stage II 54 %, stage III 37 %, and stage IV 29 % [14]. These numbers, however, do not take into account individual variations in either tumor or patient. The AJCC TNM staging system is the same for all subsites of the oral cavity, despite the wide variations in local tumor behavior and propensity for nodal metastasis [28]. There are a variety of

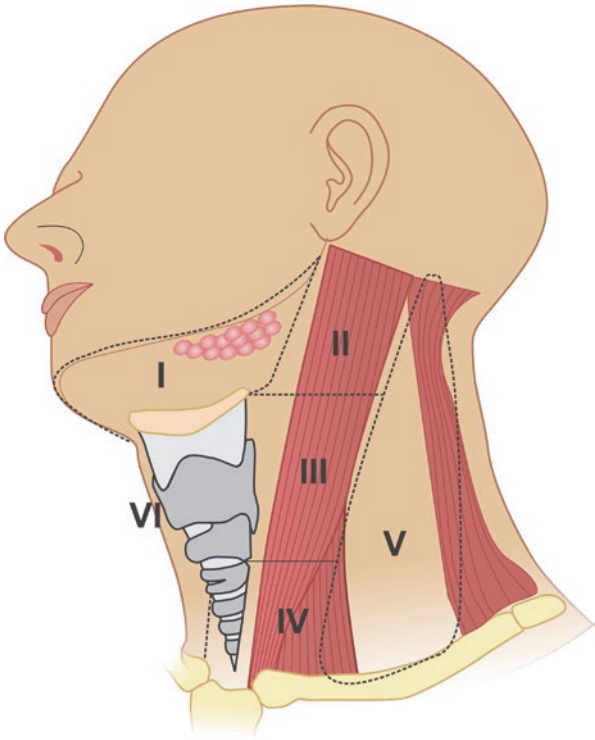

Fig. 1.9 Lymph node levels of neck

Table 1.1 TNM staging system for cancers of the lips and oral cavity

Primary tumor (T)	
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 ≤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, or skin of face, i.e., chin or nose[a]
T4a	Moderately advanced local disease[a]
	(Lip) Tumor invades through the cortical bone, mouth, or skin of the face (i.e., chin or nose)
	(Oral cavity) Tumor invades adjacent structures (e.g., through cortical bone [mandible or maxilla] into the deep [extrinsic] muscle of the tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, or skin of the face)
T4b	Very advanced local disease
	Tumor involves masticator space, pterygoid plates, or skull base and/or encases internal carotid artery

(continued)

Table 1.1 (continued)

Regional lymph nodes (N)			
NX	Regional 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 ≤6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none >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, 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		
[a]Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumor as T4			
Distant metastases (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Stage grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	Any T	N3	M9
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

From Edge et al. [41]

reasons for not incorporating each emerging factor into the staging system. Ideally, any variable included in a staging system should have individual statistically significant effect on overall survival on multivariant analysis and be user-friendly when staging in the clinical setting. Many of the factors affecting both the outcomes and management of oral cavity cancers either do not have sufficient statistical power, cannot be preoperatively assessed, or require advanced statistical analysis to implement, which would encumber the current staging system beyond clinical usefulness. Nonetheless, efforts to truly understand and predict cancer behavior rest on the continuing evolution of our understanding of cancer biology and the incorporation of new

findings into staging and treatment algorithms. Nodal metastasis is widely acknowledged as the most important prognostic factor in head and neck cancer, as survival falls below 40 % in its presence [15]. Because of this, much of the investigation into prognostic factors in the oral cavity is aimed at determining which tumor, histopathologic, and patient characteristics influence the risk of nodal metastasis, especially in early-stage disease with a clinically negative neck. As more work is done to identify these risk factors, it is incumbent that managing physicians take these factors into account and acknowledge what the staging system does not. Subsite, tumor thickness, depth of invasion, perineural invasion, number rather than laterality or size of nodes, and HPV status have all been investigated as significant prognostic factors that are not addressed by the current staging system, but may still have repercussions on treatment out comes.

1.11 Depth of Invasion, Tumor Thickness, and Tumor Volume

The idea of tumor thickness and depth of invasion influencing prognosis is not a new one; in 1986 Moore et al. suggested that the TNM system be amended to accommodate tumor thickness in both oral and oropharyngeal carcinomas [16]. There is abundant evidence to support tumor thickness as a significant prognostic factor, with Gupta et al. reporting that tumors less than 2 mm demonstrated a 5–13 % rate of occult metastasis and a 95 % 5-year survival. For tumors >5 mm thick, the rate of occult metastasis increased to 64 % and 85 % 5-year survival. A depth of invasion greater than 9 mm was associated with a 65 % rate of regional metastasis and a 5-year survival of 65 % [17]. These findings were reiterated by Thiagarajan et al. in a recent retrospective study of 586 patients with oral tongue carcinoma. His group also found that tumor thickness of more than 11 mm significantly affected overall survival [15]. Similarly, a meta-analysis by Huang et al. found that a thickness of more than 4 mm was statistically significant for pathologically positive occult nodal disease [18]. Tumor thickness goes hand in hand with tumor volume, which has also been shown to correlate more closely with local control than surface diameter [19]. Computed tomography calculations of tumor volume can be used preoperatively for surgical planning. Low et al. demonstrated that in early-stage oral carcinoma, there was no prognostic significance between T1 and T2 designation when evaluating overall survival and disease-specific survival. Interestingly, they proposed a new classification for early-stage oral cavity carcinoma, wherein T1 lesions are classified as those ≤4 cm in diameter and less than 5 mm thick, while T2 lesions are those measuring ≤4 cm in diameter but 5 mm in thickness or greater. This restratification provided statistically significant differences between T1 and T2 lesions in both disease-specific survival (DSS) and overall survival (OS), when controlled for nodal status [20]. The difference between tumor thickness which is defined as overall height of the tumor mass and depth of invasion, defined as the penetration of the tumor mass through the basement membrane, is worth noting. The proximity of the tumor to vasculature and lymphatics is thought to increase the risk of nodal metastasis. This would suggest that depth of invasion would be a more accurate determinate of risk. However, there are technical difficulties involved in

measuring the deepest extent of the tumor to the level of the basement membrane, which may be eroded or absent in ulcerative tumors. Because of this technical difficulty, other investigator name looked into tumor thickness as a prognostic factor. Pentenero et al. undertook a review of the literature to determine which of these methods correlated more accurately with prognosis in the oral cavity and determined that there has not been a standard method for measuring and that various studies have reported full tumor thickness, thickness from the "normal mucosal line," thickness from a basement membrane line, and thickness from the tumor ulcer base. Cutoff values also remain widely reported, ranging from 1.5 to 10 mm. The most commonly reported thickness at which nodal metastasis changed statistically significantly is >4 mm [21]. Interestingly, the only consensus is that tumor thickness is a significant prognostic factor for occult nodal disease as well as an independent factor for disease-free survival and overall survival, regardless of nodal status. Some of the discrepancy regarding what constituted appropriate cutoff values was reconciled by a meta-analysis performed by the International Consortium for Outcome Research, which developed a model in which T1 lesions were upstaged if they demonstrated a depth of invasion 5 mm or greater, and T2–T3 lesions were upstaged if they demonstrated a depth of invasion of 10 mm or greater. T4 lesions with a depth of invasion less than 10 mm were downstaged. This provided greatly improved stratification of patients into distinct prognostic categories based on integrating depth of invasion with the current staging parameter of surface dimension [22]. A prospective study which compared tumor thickness to depth of invasion would shed further light on prognostic fidelity if inconsistencies in measurement techniques could be controlled, but for now the consensus remains that tumor thickness and/or depth of invasion significantly impacts survival and should therefore impact staging and treatment (Fig. 1.10).

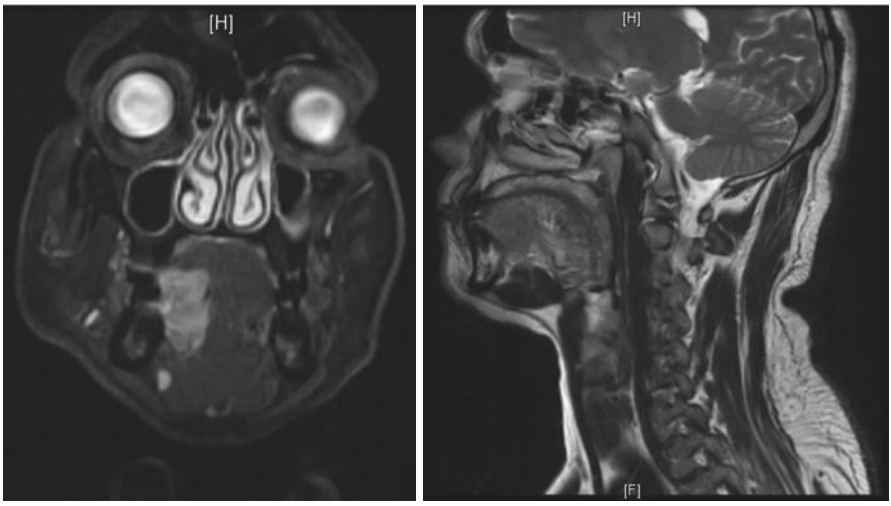

Fig. 1.10 MRI of carcinoma of tongue

1.12 Histologic Characteristics

There has been much investigation into the various histopathologic risk factors that contribute to tumor behavior, recurrence, and patient mortality. Anneroth's classification is a commonly used diagnostic tool for predicting lymph node metastasis. It is comprised of keratinization, nuclear pleomorphism, and mitosis evaluated throughout the tumor thickness and scored from 1 to 4. In the most invasive margins of the specimen, the pattern of invasion (pushing vs. infiltrative), stage of invasion, and lymphoplasmacytic infiltration were also graded from 1 to 4. The sum of the scores is grouped from 6 to 12 (grade I), 13–18 (grade II), and 19–24 (grade III). Pattern of invasion has been found to be an independent risk factor for prognosis, with an infiltrating pattern associated with a worse outcome [23, 24]. Conversely, the presence of intratumoral and peritumoral lymphoplasmacytic infiltration decreased the incidence of cervical nodal metastasis [23, 25, 26]. Vascular and neural invasion have also been implicated as independent risk factors for cervical metastasis as well as distant metastasis, locoregional recurrence, and overall survival [25, 27], respectively.

1.13 The Neck

Extracapsular extension (ECE) is a significant determinant of prognosis due to its association with an increased risk of recurrence in the neck and distantly. The presence of gross (macroscopic) ECE triples the risk of neck recurrence [29]. In addition to the characteristics of the nodes, number of nodes also appears to be directly related to the rate of regional or distant metastasis and survival. Further, the presence of positive nodal disease outside the primary lymphatic drainage pathways was found by Mamelle et al. to significantly reduce 5-year survival and increase the rate of distant metastasis by up to 30 %. The size of positive nodes is part of the current TNM system; however, nodal size correlates more closely with regional recurrence than with survival [17, 30]. There have been multiple propositions to revise the node portion of the TNM staging, the most recent of which suggest that N2b and N2c disease is determined by number of nodes rather than laterality and that N2a and N1 have similar prognostic outcomes and could thus be combined for the purposes of staging [30].

1.14 Biomarkers

The body of work on serum, salivary, and tumor biomarkers has expanded rapidly over the last two decades. Currently there is no single, widely accepted tumor marker for SCCA of the head and neck; however, factors, cell surface markers, enzymes, and signaling pathways are all under investigation.

Elevated levels of squamous cell carcinoma antigen (SCC-Ag) and C-reactive protein (CRP) have been found to be associated with higher tumor stage,

thickness, and cervical nodal status [31]. Increased CD44 expression is associated with an increased cancer stem cell population, which has been linked to a more aggressive tumor phenotype [32]. Metalloproteinase 9 has been associated with and upregulation of epithelial mesenchymal transition pathway, resulting in a potentially more invasive tumor [33]. Inhibitor of apoptosis-stimulating protein of p53 (iASPP) is overexpressed in several solid tumors, and increased expression may correlate with decreased locoregional control, disease-free survival, and overall survival in OSCC [34]. Cyclin D1 is the rate limiting proto-oncogene controlling progression through G1. Primary tumor positivity for cyclin D1 increases the risk of occult metastasis [17]. Finally, the expression of cytokeratin 8/18 has been found to be associated with increased cellular motility and was reported as an independent prognostic marker for decreased overall survival and progression-free survival [35].

Tumor growth is dependent upon angiogenesis, mediated in part by vascular endothelial growth factor (VEGF). The effects of VEGF can be indirectly measured by assessing tumor microvessel density (MVD). Increased MVD is associated with an increased risk of cervical nodal metastasis and locoregional recurrence [36]. Angiogenic activity can be assessed by IHC proteins such as factor VIII, CD31, CD34, and CD105 [37]. Epidermal growth factor receptor (EGFR) and ligand transforming growth factor alpha (TGFR-α) are frequently overexpressed in HNSCC. They may be markers of radioresistance and poor prognosis [17].

The association and prognostic significance of HPV in OCSCC is not as strong or as clear as in oropharyngeal SCCA. Ritchie et al. reported a 35 % incidence of HPV + tumors of the oral cavity, as opposed to 65 % of the oropharynx [38]. They reported improved overall survival with HPV + tumors. This is well established for oropharyngeal tumors, but has not been previously reported for the oral cavity alone. According to their report, the interaction between HPV detection and tumor location on survival was nonsignificant. This distribution was similar to that reported by Khode et al, who cite the prevalence of HPV at 36–71 % in the oropharynx and 23–40 % in the oral cavity [8]. The question is relevant because of the dramatically improved overall survival in oropharyngeal SCCA that is HPV +, with risk of disease-specific death reduced by 60–80 % [39]. There are series with data reported for both oral cavity and oropharynx together and series which compare HPV + OP to HPV- OC; however, there are no large series that directly compare HPV+ OP to HPV + OC. Therefore, the impact of HPV infection on oral cavity tumors has yet to be clearly defined.

1.15 Discussion

The purpose of staging is to enable clinicians to prognosticate accurately regarding patient disease and to choose therapies most appropriately. Based on the wide variety of factors influencing tumor behavior, changes to the staging system will likely not be enough on their own to canvas the full spectrum of risk factors that make up an individual patient's risk and prognostic pictures. The TNM system of staging

does, however, provide a universal language between providers and is a widely accepted way of classifying disease. To abandon it entirely would require a unified method of classifying head and neck cancers, a method which would face the same challenges as the TNM system. Rather, the existing system could be refined through the addition of rigorously studied factors such as depth of invasion in order to better stratify patients according to prognosis.

In addition to changing the staging system, there are other tools which may be utilized in order to provide a more personalized outlook for patients with oral cavity cancer. Memorial Sloan Kettering recently published a nomogram to predict 5-year patient overall survival, risk of cancer-related mortality, and risk of locoregional recurrence using gender, age, race, comorbidity, alcohol use, tobacco use, year of diagnosis, subsite, clinical tumor stage, and clinical neck stage. The factors significantly impacting OS were age, race, presence of severe comorbidity, tobacco use, and clinical nodal status. Cancer-specific mortality was most heavily influenced by primary tumor dimension, subsite, clinical nodal status, and bone invasion. These same factors also negatively impacted locoregional recurrence-free survival [40]. Tools such as the nomogram may provide additional information, which can inform treatment planning.

There is increasingly complex and compelling evidence for clinical, pathologic, and molecular findings which significantly impact prognosis for our patients. A discriminating hand is necessary to determine which of these, if any, should be incorporated into a new staging system for the oral cavity or impact treatment planning.

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Imaging in Malignancy of the Oral Cavity and Role of PET CT in Squamous Cell Carcinoma of Head and Neck Region

2

Venkatraman Bhat and H.V. Sunil

2.1 Imaging in Malignancy of the Oral Cavity

2.1.1 Introduction

Imaging plays a vital role in obtaining accurate, reproducible information about a lesion in an anatomically complex body region like the oral cavity. Precise imaging information built on the requirements of clinical management strategies are needed for optimal patient management and subsequent follow-up. The choice of appropriate imaging method is equally important for obtaining the required information and optimizing resource utilization. This review provides the basis and essential pathway for interpreting normal and pathological imaging observations of oral cavity lesions

2.1.2 Anatomy of Neck and Facial Compartments

Interpretation of images of the head and neck region demands a thorough understanding of the anatomical intricacies of neck viscera, muscles, vascular and neural structures, locations and boundaries of complex facial planes, knowledge regarding the spectrum of pathological conditions, and manifestations of disease spread within the anatomical spaces [1]. The general layout of the neck anatomy and locations of various pathological conditions is practically understood by going through the excellent review of compartments detailed by Hansberger and Osborn [2], which help in the radiological analysis [2]. The imaging study should be tailored to individual

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sub-sites, thus maximizing information for intended specific management. A detailed anatomy of the individual sub-sites is presented in the following discussion.

2.1.3 Imaging the Oral Cavity

2.1.3.1 Anatomy

For descriptive and analytical purposes, this region is sub-categorized as the oral cavity proper and the oropharynx. The oral cavity includes the floor of the mouth, the anterior two-thirds of the tongue, the lips, and the oral vestibule. A plane of circumvallate papillae forms the posterior boundary of the oral cavity, separating it from the oropharynx. The alveolar ridge of the upper and lower alveolus separates the oral cavity from the vestibule. Mucosal layer is reflected from the alveolar ridge to the outer wall of the vestibule at the superior and inferior gingivo-buccal sulcus. The external boundary of the vestibule is formed by buccal mucosa, closely applied to the buccinator muscle, facial vein, and adjacent fat. The posterior extent of the vestibule continues over the alveolar ridge, behind the third molar, as the retromolar trigone (RMT), an extremely important site for malignancy. This region has close proximity with the pterygomandibular raphe and thus to the interface between the superior pharyngeal constrictor and buccinator. Superiorly, the RMT is closely related to the maxillary tuberosity. The lower RMT, also an important location of squamous cell carcinoma, is located between the third molar and the mandibular ramus. The pterygomandibular raphe is a fascial band extending from the hamulus of the medial pterygoid plate to the mylohyoid ridge of the mandible, which provides an origin for the buccinator and superior pharyngeal constrictor muscles. The pterygomandibular raphe serves as an important pathway for the spread of malignancy from the maxillary retro-molar region to the maxillary tuberosity via the pterygomandibular ligament, further extending posteriorly to the retro-antral masticator space and inferiorly to reach the floor of the mouth. Mandibular retromolar malignancies can spread along this raphe to the maxillary tuberosity. The buccomasseteric region comprises the buccal space, traversed by the parotid duct, the buccinator and masseter muscles, and the body of the mandible [3].

The tongue comprises the intrinsic musculature (superior and inferior; longitudinal, transverse, and vertical muscle fibers) and extrinsic muscles (genioglossus, styloglossus, hyoglossus, and palatoglossus muscles). The floor of the mouth is formed of the mylohyoid muscles, united by a median raphe, and supplemented in the midline by geniohyoid muscles, located below the genioglossus muscles. It is supported by the anterior bellies of the digastric muscles, which border the triangular submental space containing fat and lymph nodes (nodal level IA). At the posterior margin of the mylohyoid muscle, the submandibular gland extends through a gap between the hyoglossus and mylohyoid muscles. Its deep portion is contained in the sublingual space together with the sublingual gland, the lingual nerves laterally, and the lingual artery and vein medially. The term "root of the tongue" refers to the junctional region of the lingual septum and extrinsic tongue muscles [1] (Fig. 2.1). The root of the tongue is bounded inferiorly by the mylohyoid muscle, anteriorly by the mandibular symphysis, and, along with the laterally positioned sublingual space,

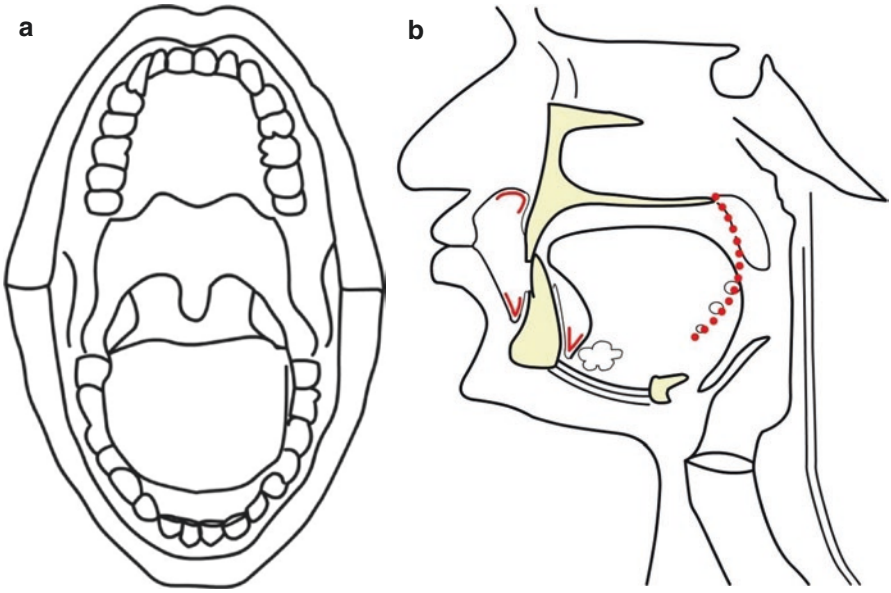

Fig. 2.1 (**a** and **b**): Diagram demonstrating anatomical landmarks and important structures in the oral cavity (**a**) Contents of the oral cavity viewed from an anterior aspect, demonstrating the alveolar ridges, hard and soft palate, palatoglossal fold, tongue, and tonsils. (**b**) Diaphragmatic representation of the lateral view in the midline, showing superior and inferior recesses of the anterior vestibule, mucosa of the floor of the mouth, the tongue with the mylohyoid diaphragm at the base, the hyoid bone, and the vallecula. The plane passing through the circumvallate papillae and the hard–soft palate junction (*curved red dotted line*) separates the anterior oral cavity with the posterior oro-pharynx

forms the floor of the mouth. Spread of malignancy to the root of the tongue upstages oral cavity tumors to T4 according to the TNM staging system [1]

Posteriorly, the sublingual space freely communicates with the submandibular space, as no fascial boundary separates them. The submandibular space contains lymph nodes (level IB) and the submandibular gland, with the facial artery medially and the facial vein laterally.

The oral vestibule separates the lips and cheeks to form the teeth and the alveolar process by a reflection of the buccal mucosa onto the maxilla and mandible. Adjacent to the alveolar process, the gingivobuccal and the glosso-alveolar sulci are common locations for squamous cell carcinoma of the vestibule and floor of the mouth respectively.

Apart from the identification of the standard anatomy of the structures of the oropharyngeal region, appreciation of the tissue planes, compartments, and their content as displayed using imaging methods is necessary [3].

The submandibular space is of importance in evaluating the extent of nodal disease [submandibular (level 1b) and submental space (level 1a) lymph nodes]. Other components of the space are the facial vein and artery, fat, and the inferior loop of the hypoglossal nerve [1].

The sublingual space, which contains the anterior parts of the hyoglossus muscle; the lingual nerve, artery, and vein; the glossopharyngeal and hypoglossal cranial

nerves; the sublingual glands and ducts; the deep component of the submandibular gland; and the submandibular (Wharton's) duct [1, 4], is not encapsulated by fascia and is often involved in lesions of the floor of the mouth.

Posteriorly, the masticator space and the infratemporal fossa are areas of special attention in the evaluation of disease spread. The masticator space contains the ramus of the mandible with the inferior alveolar nerve within the canal, the masseter, the medial pterygoid, temporalis muscles, the mandibular nerve, and the internal maxillary artery. Although it is a closely confined place, it is open anteriorly toward the buccal space. Posteriorly, it is separated from the parotid space by the fascia and medially related to the parapharyngeal space. The masticator space has a close border with the skull base. The foramina ovale and the spinosum with its contents belong to the space.

There is a slight difference in the terminology of the spaces in the radiological and surgical literature. However, the unambiguous demonstration of an important landmark, the sigmoid notch and demonstration of tumor extension in relation to this landmark, should be a common goal in the evaluation. The spread of malignancy above the level of the sigmoid notch is considered unsuitable for surgical management (T4 b). Important structures in the suprasigmoid notch region are the temporalis muscle and the lateral head of the lateral pterygoid.

The term 'infratemporal fossa', sometimes interchangeably used with the masticator space, which is a much broader space consisting of part of the masticator space, but excluding the masseter, the retro-antral buccal space, and part of the parapharyngeal space. Thus, it contains the medial and lateral pterygoid muscles, distal branches of the internal maxillary artery, and branches of mandibular nerve divisions and the rich network of the pterygoid venous plexus. Description of lesions with reference to the infratemporal fossa is invariable in radiology reports in view of its intimate relationship between lesion and the anatomical space and clinical significance of spread of disease to the tissue planes, Identification of nerves and foramina through which nerve passes are important in determining the extent of perineural disease spread.

Anatomical reference to the pterygopalatine fossa is of paramount importance for understanding disease spread from anteriorly located oral, palatal, maxillary, and nasal malignancy to posterior tissue spaces through eight bony canals [5, 6]. The pterygopalatine fossa is bounded anteriorly by the posterior maxilla and posteriorly by the base of the pterygoid plates. The pterygopalatine fissure is the potential space communicating freely with the infratemporal fossa laterally and connecting medially with the nasal cavity through the nasopalatine foramen. There is a free communication of the pterygopalatine fossa with the orbit through the inferior orbital fissure. The foramen rotundum, containing the maxillary nerve, is on the posterior wall of the pterygopalatine fossa, allows communication with the Gasserian ganglion of the trigeminal nerve. Important contents of the pterygopalatine fissure include fat, the sphenopalatine (pterygopalatine) ganglion, the maxillary nerve and its divisions, the para-sympathetic plexus and the distal branches of the internal maxillary artery. The pterygopalatine fossa constitutes one of the major links for disease spread from the oral cavity, the RMT to the infratemporal fossa, and also an important pathway for neural tumor spread [6].

A thorough understanding of sectional anatomy is essential for the interpretation of CT and MR images. Anatomical information is obtained from data sets of CT and MRI are quite comparable for most practical purposes. However, the relative strength and weakness of the individual techniques dictates how each can be used to the best advantage in a given situation. The multidetector computed tomography (MDCT) imaging technique is based on the principle of gray-scale display of the volumetric images obtained from the X-ray attenuation profile of tissues. The range of tissue gray-scale values depends upon the tissue density and the atomic number of the tissues. CT imaging is highly suited to evaluation of the bony structures, for possible erosion or for the 3D reconstruction of bony components. In view of the fact that many tissue planes are defined by fat component, CT examination allows optimal evaluation of soft tissues and fascial boundaries of the subsites. Volumetric CT data sets allow reconstruction of images in the conventional three orthogonal planes and provide a choice of reconstruction in areas of interest, as defined by the imaging specialist. Teeth and metal implants in the bony skeleton and dental fillings lead to streak artifacts, degrading the quality of the images in the adjacent vicinity. On the other hand, MRI techniques display tissues based on hydrogen content. MR images have an intrinsic ability for high tissue contrast, and the ability to evaluate bone marrow. Newer MR techniques provide options for a wide variety of information in the form of angiography, spectroscopy, and perfusion characteristics of the tissues. Relatively high contrast between normal and pathological tissues allows the detection of smaller lesions. Hence, MR techniques are ideal for visualization of small soft-tissue lesions. Gadolinium-enhanced MR images are an essential part of the tumor assessment. Ferromagnetic materials in the form of dental implants or a metal prosthesis cause degradation in the image quality owing to blooming artifacts, which are seen as black (dark) areas without structural details.

Structural details of the oral cavity, tongue, oral cavity, and various compartments are optimally studied in the axial and coronal planes (Fig. 2.2). Sagittal planes add to the information on midline structures such as the anterior part of the oral vestibule, the floor of the mouth, the palate, the dorsum of the tongue, the epiglottis, and the prevertebral spaces. The following CT and MR images illustrate the anatomical structures of subsites, important landmarks such as neuro-vascular bundles (Fig. 2.3) and relationships with muscles and adjacent spaces (Figs. 2.3, 2.4, and 2.5).

2.1.3.2 Pathways of Tumor Spread

Focused systematic gathering of image information is improved by understanding the behavior of the pathology and expected pattern of spread. Some typical patterns at subsites are illustrated herewith. Lesions of the tongue located along the lateral border, spread to sublingual space, extrinsic muscles of the floor of the mouth inferiorly and to the neurovascular bundle medially. Hyoid bone may be involved through the extension via the mylohyoid diaphragm. Occasionally, lesions in the anterior floor of the mouth involve the sublingual/submandibular duct leading to dilated saliva ducts. Posterior tongue lesions can spread along the lateral wall to the tonsillar pillars; in the midline they can involve the vallecula and epiglottis. Lesions

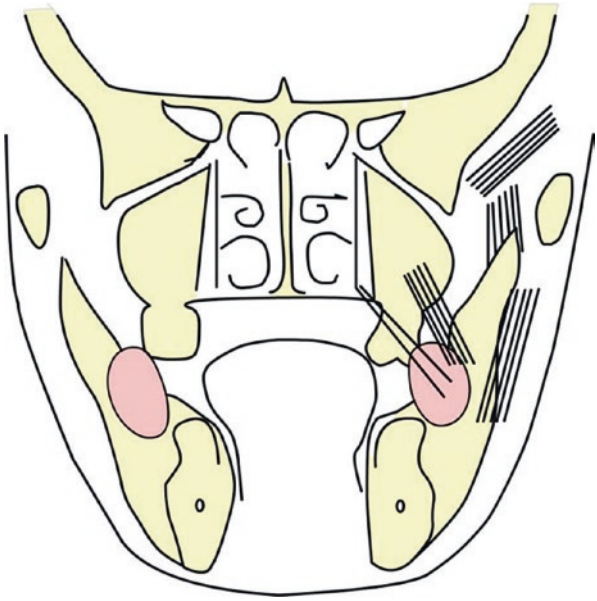

Fig. 2.2 Diaphragmatic coronal image, illustrating the location of the retromolar trigone (RMT) (*pink*) and its relation to the mandible, pterygomandibular raphe, medial pterygoid, and masseter muscles

of the buccal mucosa can spread laterally to the buccal fat and the subcutaneous tissues, posteriorly to the masseter and infratemporal fossa, and extend medially to involve the gingival mucosa. The gingival lesions can invade into the adjacent bony structures. Subtle involvement of the marrow is well illustrated using contrast-enhanced MR techniques that show high T2 values and contrast enhancement when there is tumor invasion. Perineural extension of the tumor is one of the underestimated aspects of tumor spread. The regional nerves of each space may be involved, showing the caudal and cranial extension of the tumor through perineural spread. The tumor size, extent and the precise estimation of the extent of intended surgical excision can be predicted by image analysis. As a general principle, if more than 30 % of the tissue needs to be removed, a reconstructive procedure is needed [7].

Mandibular invasion requires special reference, as the regional involvement directly translates to mandibular resection of varying degrees. The surgical technique varies from marginal mandibulotomy to mandibular resection [8–10]. Imaging plays a crucial role in the assessment of bone involvement, as clinical examination has it's limitations. When the lesion abuts the mandible or involves the superficial cortex, marginal mandibulectomy is performed. Deep bony erosions and involvement of the cancellous bone require a segmental mandibulectomy. Hemimandibulectomy is required and there is involvement of the inferior alveolar canal [8, 10]. In an edentulous mandible, if the tumor components are in the vicinity, a segmental mandibulectomy is a preferred. Mandibular thickness of at least a centimeter is required to maintain stability in the region; this can be confidently estimated using image reconstruction and analysis. Imaging also provides information regarding the remaining uninvolved mandible.

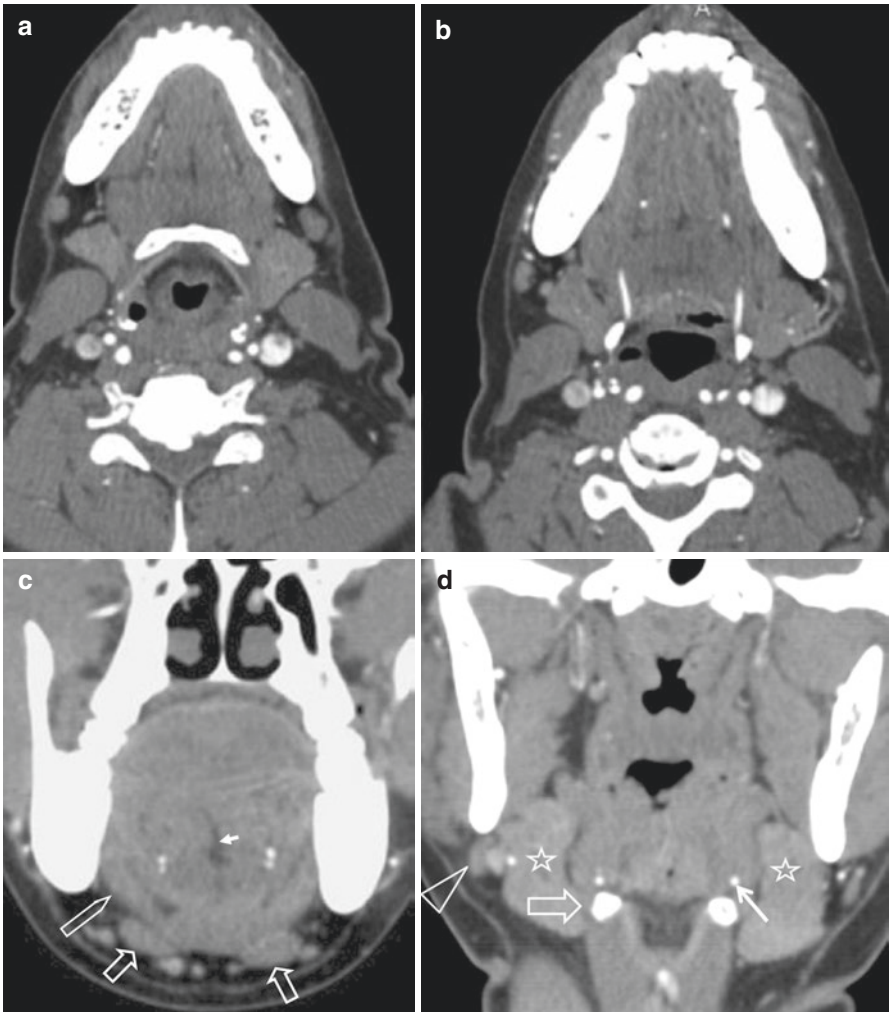

Fig. 2.3 Axial (**a** and **b**) and coronal (**c** and **d**) contrast-enhanced CT images showing the lingual artery and neurovascular bundle within the tongue. In the coronal image (**c**) midline septum of the tongue is visible as a hypodense strip (*arrow*). Myelohyoid muscle (*pointer*) and anterior belly of diagastic muscle (*open arrows*) are also seen. Coronal CT image at posterior part of oral cavity (**d**), show lingual artery (*white arrow*), Hyoid bone (*open arrow*), submandibular gland (*star*) and level I B node (*triangle*)

2.1.3.3 Imaging Assessment

After clinical evaluation has been carried out and malignancy is suspected, imaging is essential to determine the morphology of the lesion, the stage of the tumor, and the presence of metastasis. There are number of prognostic factors that determine the survival of patients and affect treatment decisions. The basic prognostic factors are tumor size (T-stage), regional nodal involvement (N-stage), and the presence or

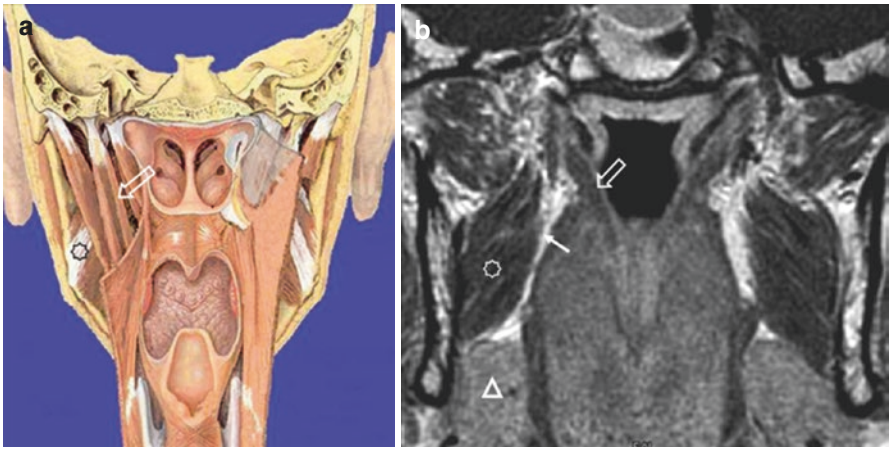

Fig. 2.4 Important relationships of the posterior tongue. (**a**) The styloglossus muscle (*open arrow*) and the medial pterygoid (*star*) are shown in anatomical illustration and on coronal T2-weighted MRI. (**b**) In the coronal MR image (**b**) fat planes (*solid arrow*) are clearly visible between the tongue and medial pterygoid. More anteriorly, the submandibular gland is visible (*triangle*)

absence of distant metastasis (M-stage). The modified TNM classification used today is recommended by the American Joint Society of Cancer Control (AJCC; Table 2.1). Thorough understanding of the biological behavior of the lesion is essential for the radiologist for strategizing imaging requirements. Although uncommon on initial presentation, the presence of distant metastasis and second primary cancers of the upper aerodigestive tract should be evaluated. Imaging plays a definitive role in detecting second primary and evaluating distant metastasis. Imaging methods must be utilized in combination to maximize the strength of each modality [10].

Tumor thickness has been associated with local recurrence and survival of cancer of the oral tongue. The exact depth of invasion and correlation with survival is not clear; however, several studies have suggested that tumor thickness greater than 4.0 mm significantly increases the risk for regional metastases and, therefore, has a negative impact on survival [11]; thus, treatment is recommended in clinically N0 neck, even in the absence of other high-risk histopathological features. Recently, Patel et al. [12] demonstrated that patients with increased tumor thickness are at a high risk of nodal metastases, supporting the liberal use of elective neck dissection in these patients, despite being clinically negative. In this direction, there is a strong recommendation for sentinel lymph node biopsy (SLNB) for squamous cell carcinoma of the oral cavity to detect early nodal involvement irrespective of the tumor depth or thickness measured.

High-risk histopathological features that influence the risk of local regional recurrence include angio-invasion, lymphatic emboli, and perineural invasion. One of the most significant prognosticators on imaging studies of oral cancer is the presence of the extra-capsular spread (ECS) of lymph node metastases [10, 13]. ECS has been identified as an indicator of poor prognosis; therefore, patients with ECS are commonly treated with adjuvant therapy, including radiotherapy and chemo-radiotherapy.

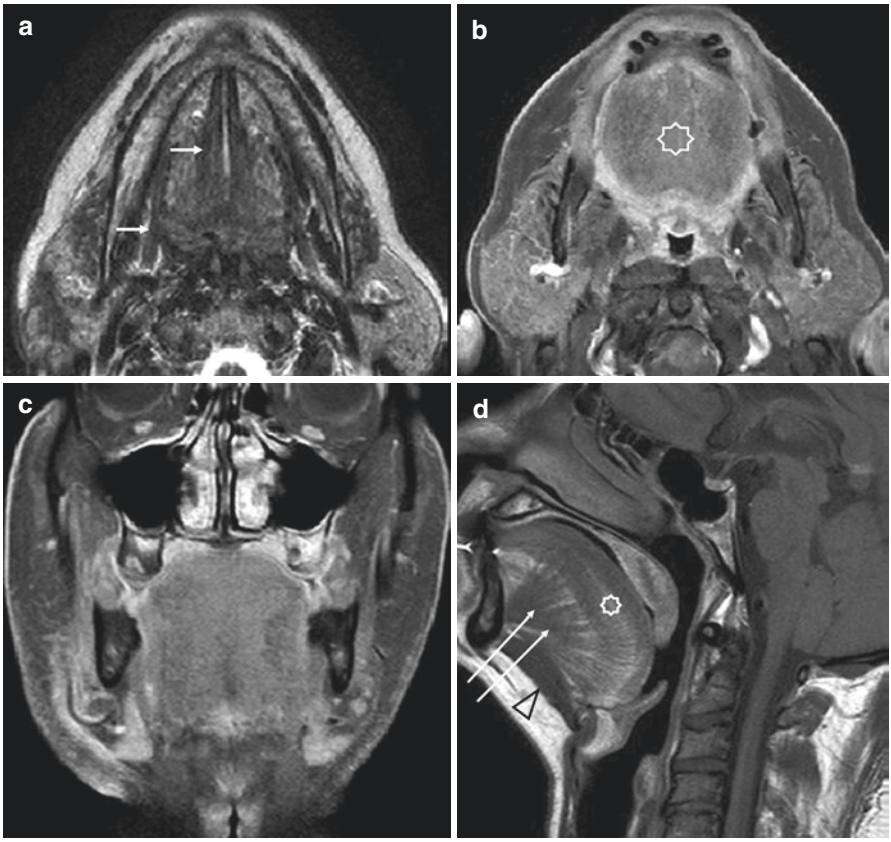

Fig. 2.5 (**a**, **b**) axial T2-weighted and STIR images showing the extrinsic (*arrows*) and intrinsic (*star*) musculature of the tongue. (**c**, **d**) Coronal and sagittal images showing the intrinsic musculature (*star*) of the tongue, supported inferiorly by the genioglossus and geniohyoid (*long arrows* and *triangle*). Cortical outline of the hard palate is clearly visible. More posteriorly, there is a clear fat plane between the dorsum of the tongue and the epiglottis

Imaging provides essential information regarding the respectability of a neoplastic lesion. On one hand imaging methods provide information regarding the detection and extent of the lesion; on the other hand, it also demonstrates the status of vital surrounding structures (arteries, nerves, airway), an information much needed for planning surgery. In special situations, such as in T4a and T4b category lesions, a critical decision has to be made, classifying lesions as resectable or unresectable. Even within the T4a (advanced resectable group), there are critical determinants that define the expected extent of major surgical morbidity and mortality. Ouyang and Branstetter [14] analyzed in an extensive review the literature on imaging to determine the parameters (diagnostic criteria) and accuracy of different modalities for evaluating these critical T4a and T4b factors. The following important information obtained by imaging is evaluated for the prognostication of outcome: arterial

Table 2.1 TNM classification for lesions of the oral cavity and lips

American Joint Committee on Cancer (7th edition) TNM staging for SCC of oral cavity and lips
Tumor
TX – primary tumor cannot be assessed
T0 – no e/o primary tumor
Tis – carcinoma *in situ*
T1 – ≤2 cm
T2 – >2 cm but ≤4 cm
T3 – >4 cm
T4a – moderately advanced local disease
(Oral cavity) Tumor invades cortical bone, deep (extrinsic) muscles of tongue, maxillary sinus, or skin of face (Lip) Tumor invades cortical bone, inferior alveolar nerve, floor of mouth, or skin of face
T4b – very advanced local disease
Tumor involves masticator space, pterygoid plates, skull base, or encases internal carotid artery
Node
NX – cannot be assessed
N0 – no regional lymph node metastasis
N1 – single ipsilateral lymph node, ≤3 cm in greatest dimension
N2
N2a – single ipsilateral lymph node, >3 cm and ≤6 cm in greatest dimension
N2b – multiple ipsilateral lymph nodes, ≤6 cm in greatest dimension
N2c – bilateral or contralateral lymph nodes, ≤6 cm in greatest dimension
N3 – lymph node(s) >6 cm in greatest dimension
Metastasis
M0 – none
Ml – yes

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encasement, prevertebral fascia involvement, mediastinal infiltration, tracheal and esophageal extension, laryngeal cartilage penetration, pre-epiglottic fat involvement, dural spread, bone (mandible/maxilla and skull base) infiltration, perineural spread, orbital involvement, and brachial plexus invasion [14].

For the oral cavity lesions, bone involvement, perineural spread and the resectability of large lymph nodes in the vicinity of the carotid sheath are most important. For the most part, the studies find MR imaging with higher sensitivity but lower specificity than CT. An ever-increasing role for PET/CT is suggested, especially for distant spread, in view of the unique mechanism of lesion detection based on glucose uptake, using the PET technique.

2.1.3.4 Imaging Modalities

Radiological interpretation and reporting format must conform to the latest classification system and portray meaningful information for clinical colleagues [7]. The essential role of imaging modalities in the head and neck region is to provide

accurate staging of malignancy. Plain radiography no longer plays a role in the evaluation of soft-tissue lesions. It may be useful in demonstrating calcifications and gross bone destruction involving the bony structures. Pan tomography plays a role in the initial assessment of mandibular erosions, although MDCT and dentascan have similar, more precise abilities in the detection of bone erosion. MDCT with administration of intravenous contrast medium offers an initial assessment of soft tissue, bone, and mucosal involvement. Clearly, CT is extremely useful when there are clinical limitations such as trismus or pain, limiting satisfactory clinical examination. The diagnostic quality of CT is adversely affected by artifacts caused by dental metals, but a slight modification of the imaging technique sometimes overcomes artifacts related to dental amalgam. MDCT is complemented by the puffed cheek technique (PCT), when a lesion in the oral cavity is suspected. PCT involves voluntary blowing of the oral cavity with air during the CT examination (Figs. 2.6, 2.7, and 2.8). Compliance with the technique is variable, depending on the extent and location of the disease. Good-quality examination is usually possible in small lesions, where the contribution of the technique is maximal. Lesions of buccal mucosa at typical anatomical sites, a diagrammatic illustration of the location of lesions in parts of the oral cavity, and patterns of likely spread are illustrated in Fig. 2.9.

This technique is very useful when clinical evaluation is limited or the lesion is posterior or in hidden areas (Fig. 2.10). Asymptomatic, self-limiting pneumoparotid is seen in 17 % of patients using the puffed cheek technique [15]. Other dynamic

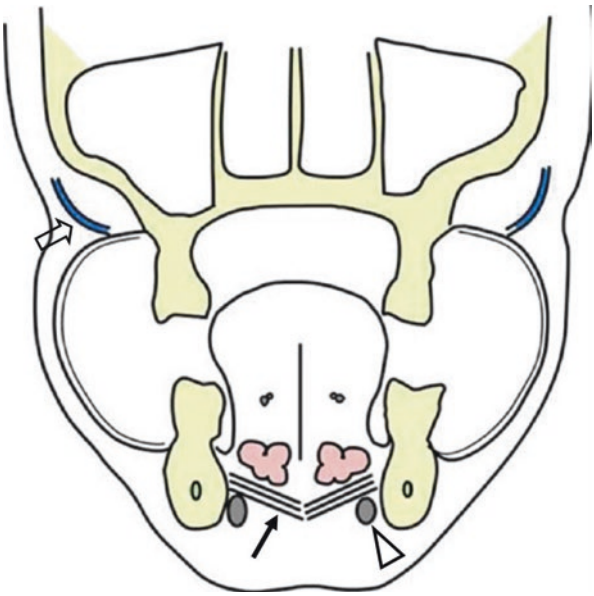


Fig. 2.6 Diaphragmatic anatomy of the oral cavity at the mid-cavity level, as illustrated by the puffed cheek technique. Parotid ducts open at upper part of vestibule, opening at the level of the second molar (*open arrow*). Inferiorly and superiorly, the mucosa reflects and merges with the gingiva. The relationship among the myelo-hyoid diaphragm (*black arrow*), the salivary glands (*pink*), and the 1A lymph node is illustrated (*Triangle*)

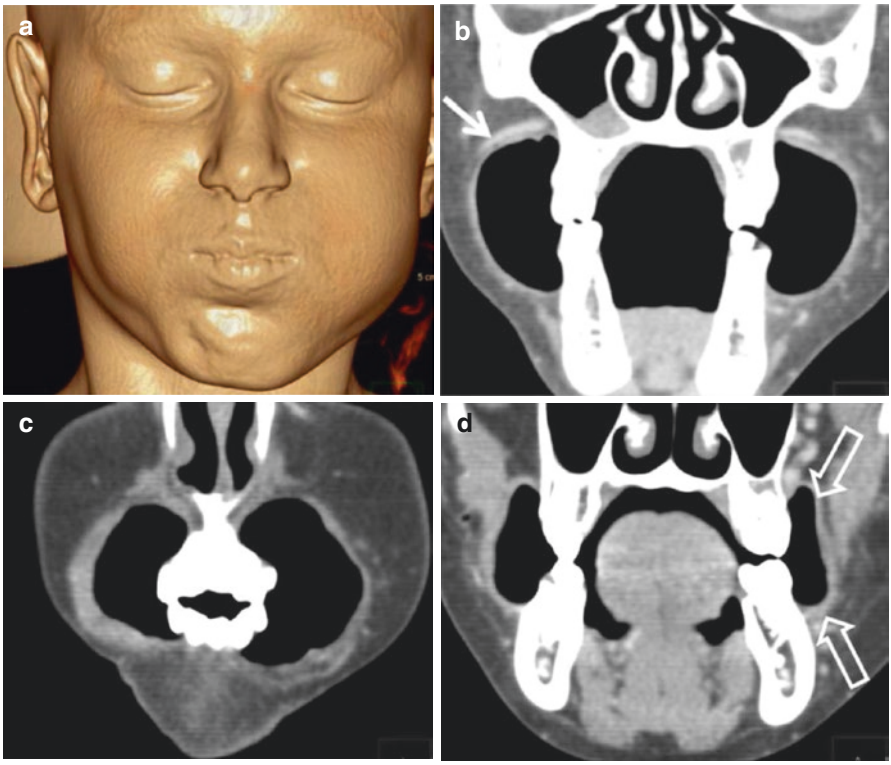


Fig. 2.7 Anatomy of the oral cavity with the puffed cheek CT (PCT) technique. (**a**) 3 D rendered image showing distended cheek. Coronal images demonstrating anatomy at the mid (**b**), anterior (**c**), and posterior cavity (**d**). *Arrow* in Fig. **b** points to facial vein. *Open arrows* in Fig. **d** show superior and inferior gingivo-buccal sulci

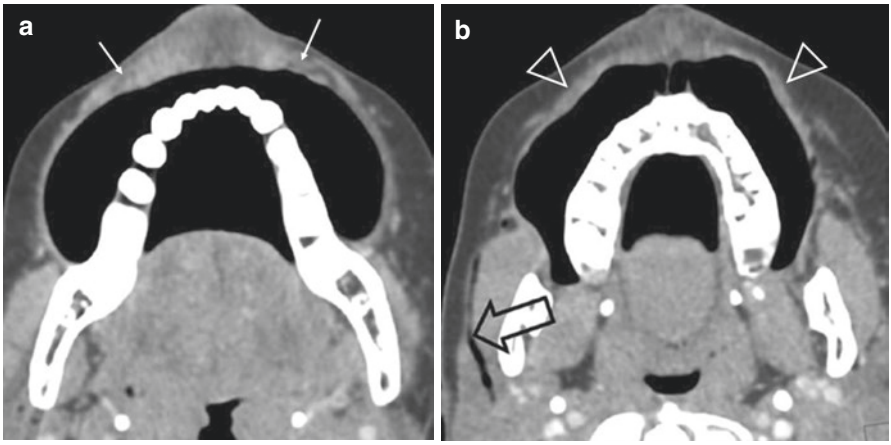


Fig. 2.8 Anatomy of the oral cavity with the puffed cheek CT technique. Axial images of the lower vestibule (**a**) and the upper vestibule (**b**) . There is an incidental right pneumoparotid (*open arrow*). *Arrow* in Fig. **a** point to orbicularis oris; *Tringle* is Fig. **b** show focal densities due to zygomaticus major

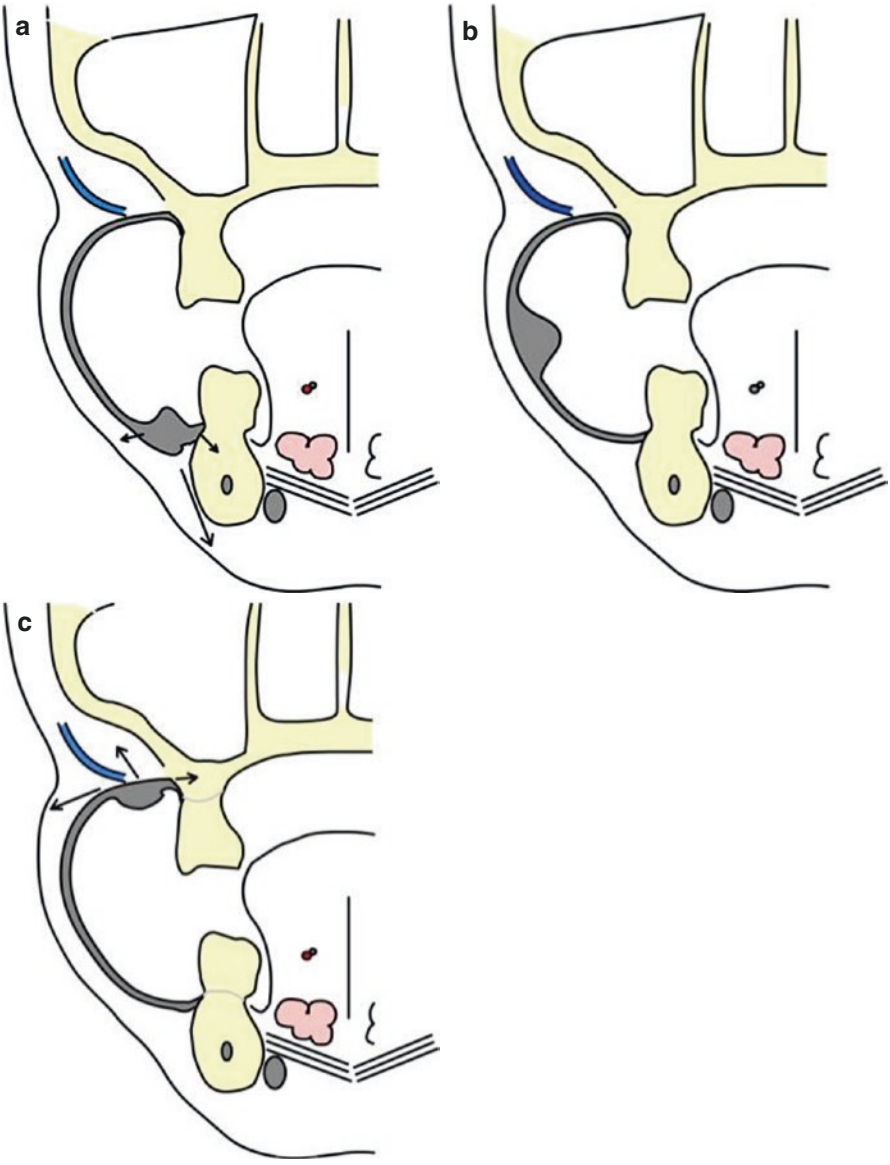


Fig. 2.9 Coronal diaphragmatic illustrations showing the location of the lesion in the buccal mucosa. (**a**) Lesion at the inferior gingivo-buccal sulcus (GBS) showing the pattern of spread. (**b**) Lesion at the mid-buccal mucosa at the level of the occlusal plane. (**c**) Lesion at the superior GBS, showing the pattern of spread

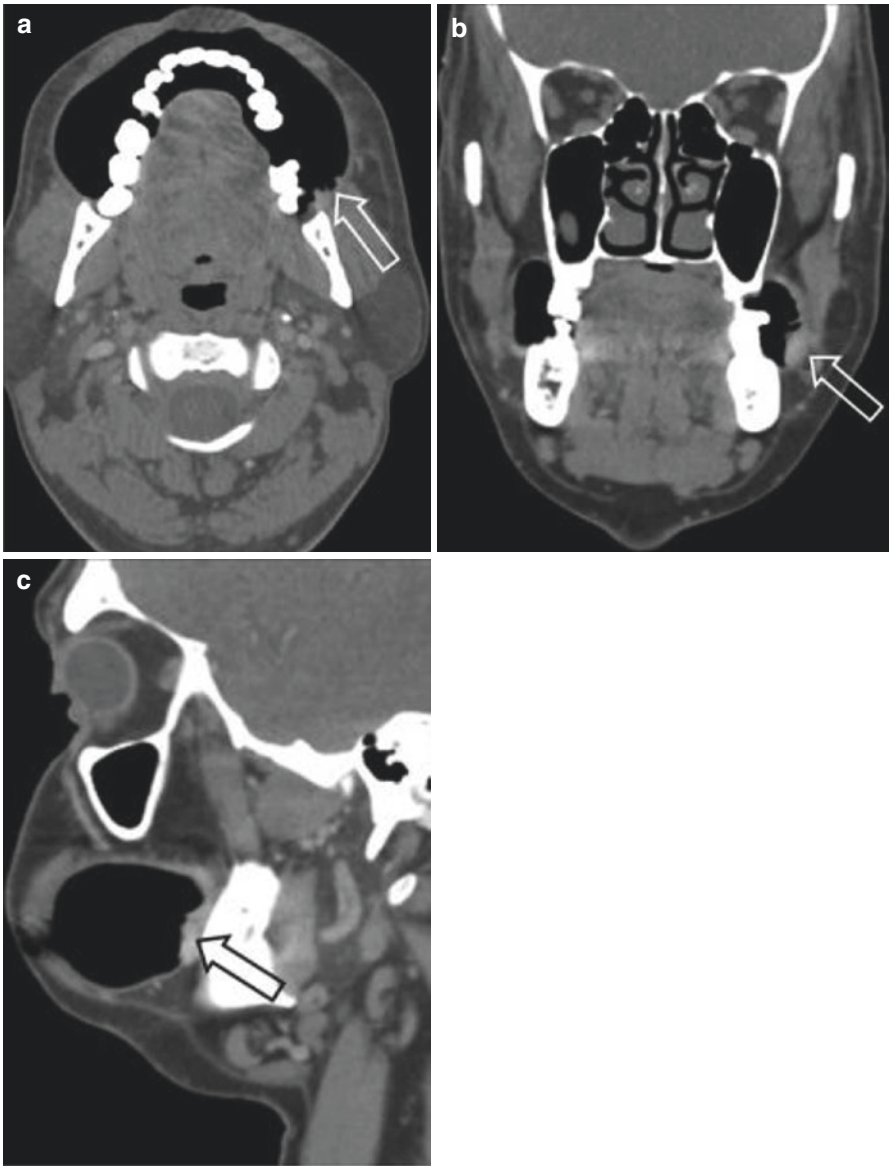


Fig. 2.10 Lesions located relatively posteriorly in the oral cavity are difficult to examine clinically. However, a well-performed PCT examination clearly reveals the lesion. Axial (**a**), coronal (**b**) and sagittal (**c**) CT images demonstrate the lesion (*open arrow*) and provide added information regarding relation to bone

maneuvers, including the modified Valsalva, open-mouth, and phonation maneuvers, are not particularly useful in the assessment of the oral cavity. The extent and depth of the lesion can be easily be demonstrated (Figs. 2.11, 2.12, and 2.13) on CT and MRI. We find spiral the CT technique with multiplanar reconstruction a

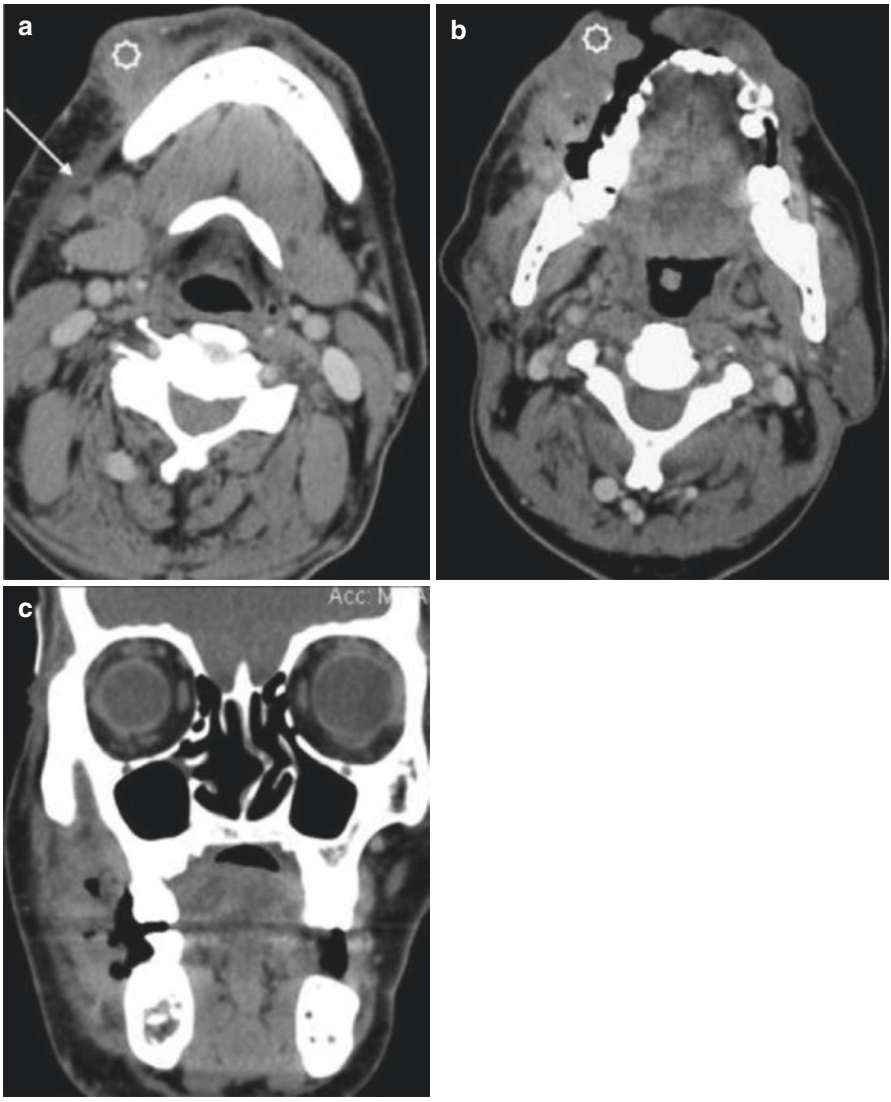


Fig. 2.11 (**a**, **b**, **c**) CT images of a patient with an extensive malignant lesion of the right cheek, the lip demonstrating transmural spread and dermal involvement (*star*). There is fistulation anteriorly and thickening and infiltration of the platysma (*solid arrow*). Coronal projection shows the extent of the lesion, involving the superior and inferior GBS

practical option, with diagnostic quality images for evaluating regional and distant spread. One of the underused option in MDCT evaluation is the curved reconstruction option, which can facilitate demonstration of subtle bone erosions, provide global view of extent of bone destruction and show relation of bone erosion in relation mandibular canal canal. It had special value in erosions around mid-line (Fig. 2.14) and RMT region (Fig. 2.15). In the RMT region, it also shows

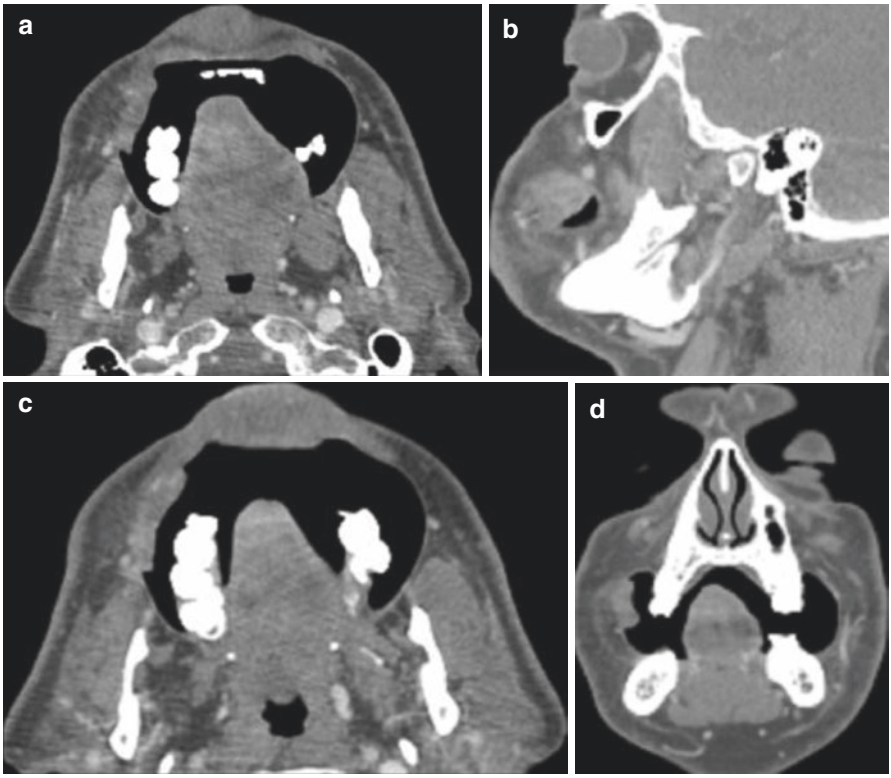


Fig. 2.12 Axial (**a** and **c**) sagittal (**b**) and coronal (**d**) CT images showing a well-circumscribed elevated lesion at the buccal aspect of the right cheek. CT examination allows demonstration of the precise depth of the lesion (**c**) (*arrows*)

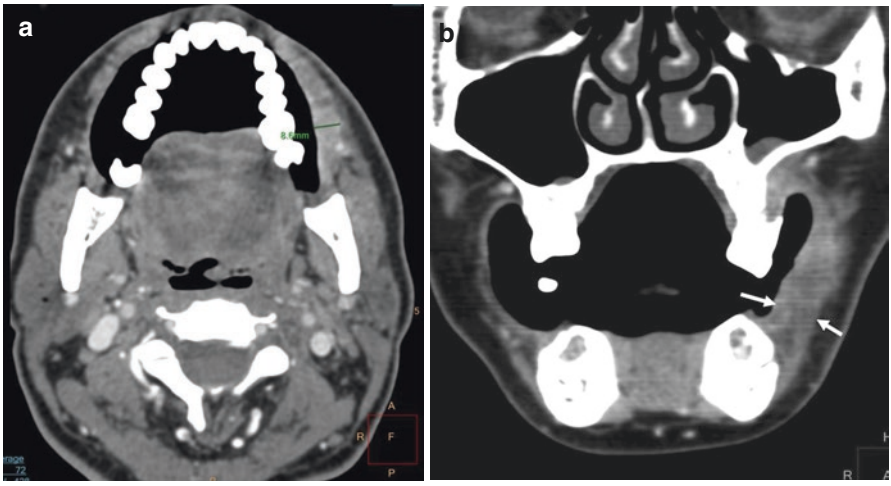


Fig. 2.13 A submucosal lesion may appear normal clinically. CT examination with PCT in Axial (**a**) and coronal plane (**b**), however, demonstrates diffuse thickening of the left buccal mucosa (*arrows*) in addition to limited relative distension of left side of the buccal cavity

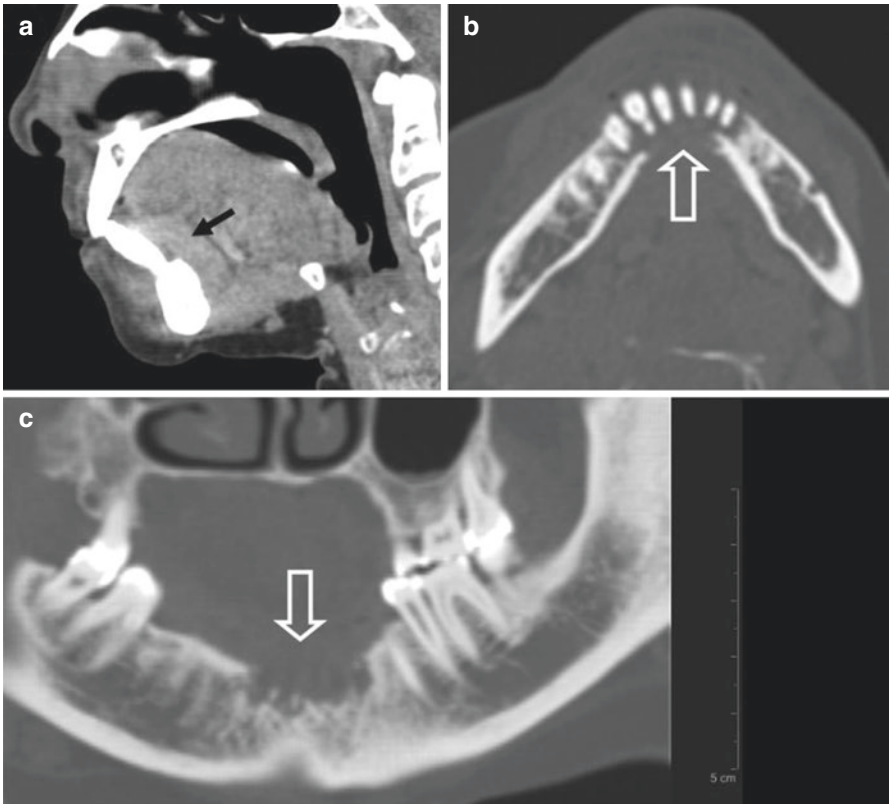


Fig. 2.14 Sagittal image of CT (**a**) demonstrates enhancing lesion at floor of mouth (*black arrow*) adjacent to mandible. Axial bone window (**b**) shows inner cortical erosion (*open arrow*) Extent and depth of lesion is best demonstrated by curved reformation (**c**)

involvement of anterior fibers of temporalis (Fig. 2.15b). Another unexplored option of image processing is 3-D rendered images of the oral vestibule, which can show proliferate lesions, lesions in posterior part of oral vestibule, sometimes clinically invisible. Examples of normal appearances in selected part of oral vestibule is shown in Fig. 2.16. MDCT is a comprehensive solution for assessment of soft tissue and bone.

Our examinations are performed using 64-slice MDCT scanners for the detection of alveolar, buccal, lip, and RMT carcinoma. We routinely use the PCT technique for suspected lesions in the oral cavity and oropharynx. Our protocol also involves imaging of the thoracic cavity up to the level of the diaphragmatic domes. We reconstruct chest data for lungs and mediastinum in axial, sagittal, and coronal planes.

The MDCT protocol involves the acquisition of 5-mm spiral data with and without intravenous contrast medium with the PCT for lesions of the oral cavity. Subsequent reconstruction is performed at 0.625-mm intervals. We display image data in the axial, sagittal, and coronal planes. Dedicated additional curved planes are utilized when there is a requirement for the resolution of specific issues.

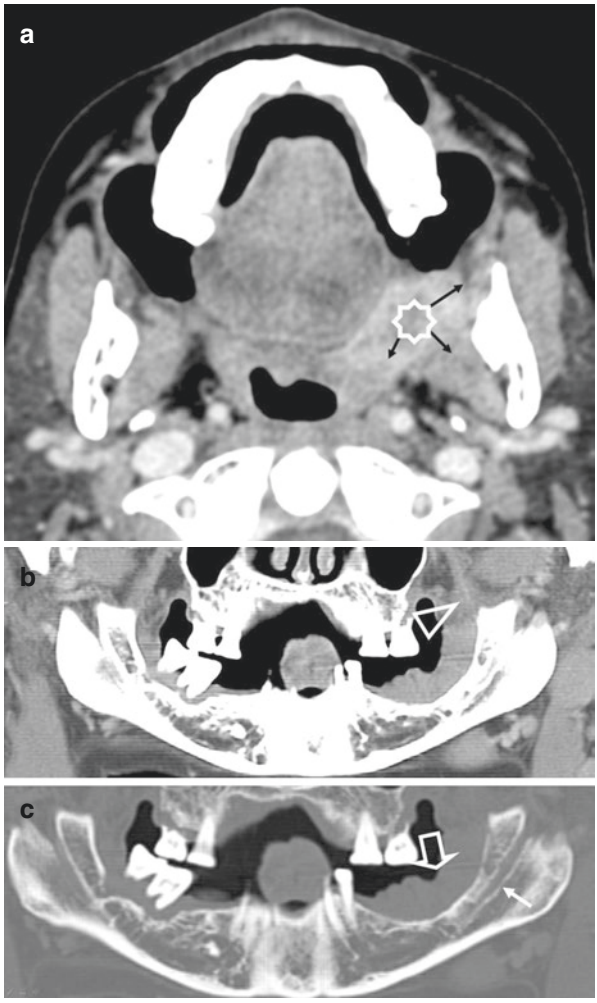


Fig. 2.15 Axial CT image (**a**) shows a left oropharyngeal lesion (*star*) extending to RMT and anterior infratemporal fossa (*black arrow*). Curved soft tissue reconstruction (**b**) revels involvement of anterior fibers of temporalis (*triangle*) and considerable extension along alveolar margin. Curved bone window image (**c**) shows extent f bone destruction and relation of bone erosion (*open arrow*) in relation to mandibular canal (*arrow*)

Occasionally, evaluation of volume rendered images of the PCT technique offer valuable information for better definition of the lesion.

A slightly different technique, cone-beam CT, uses a cone-shaped beam, rather than the fan-shaped beam of X-rays. The X-ray source and detector make one full rotation around the patient's head and generate "projection data," similar to MDCT. These data are then processed to generate 3D volumetric data, from which reconstructed images in all three planes can be obtained. Cone-beam CT also has MPR and curved planar capabilities. Its chief advantages are a lower radiation dose compared with MDCT [14], a rapid scan time (comparable with that of MDCT systems), the availability of display modes unique to maxillofacial imaging, and a smaller size and cost than conventional CT units, making it more suitable for use in clinical dental practices [14].

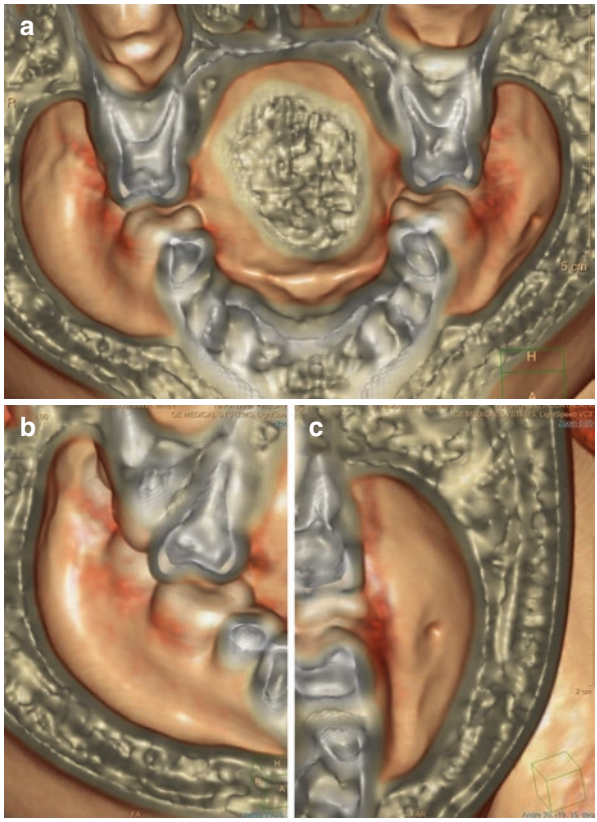


Fig. 2.16 3D surface rendered image (**a**) of interior of the oral cavity showing normal mucosal interface. Image (**b**) demonstrates detailed view of posterior part of vestibule. Image (**c**) shows inferior gingivo-buccal region

Currently, cone-beam CT is best suited to evaluating osseous structures in the craniofacial area, but MDCT remains preferable for the evaluation of soft-tissue lesions, including tumors [16].

Imaging methods, along with clinical information, provides the basis for the staging of the lesion and further patient management strategy. Although in most instances lesion definition is simple and straightforward, there are special situations where the ability of imaging methods are put to the test.

In view of the multiple management options/decisions with mandibular involvement, many imaging techniques have been evaluated in this context. Apart from conventional techniques, coned beam CT, PET CT, and SPECT imaging have been considered [17–21]. SPECT radionuclide imaging has shown higher sensitivity at the cost of very low specificity [22]. Thin-section CT with bone reconstruction appears to be the best choice given the relatively higher sensitivity and specificity for the exclusion of bone involvement [7, 23, 24]. Some surgeons referred to performing periosteal stripping in the context of negative CT/imaging studies. A combination of imaging methods has been proposed to implement the strategy to increase the sensitivity and high negative predictive value [21, 25–27].

When the prime concern is the invasion of the deep soft tissue, muscle or nerve or lesions located in organs such as the tongue and soft palate, MRI is more accurate [28]. MRI is inherently well suited to the early detection of soft tissue lesion and demonstration of perineural invasion. The features of perineural spread is to be specially scrutinized in patients with adenoid cystic carcinoma. Thus, enhancing a lingual, alveolar or trigeminal nerve may suggest perineural involvement. Although MRI is less definitive in demonstrating cortical bone involvement, it is very sensitive in assessing bone marrow involvement. Invasion of the mandibular marrow, the hard palate or the skull base are potential areas where MRI provides maximum value. A technical limitation of MRI in the neck is the involuntary motion, especially related to swallowing, limiting utility in evaluation of the larynx. The advancement of technology has partially compensated for this limitation. The overall accuracy of CT and MRI for T-staging is comparable [29]. CT is more accurate in nodal assessment [9] Our MRI examination are performed on a 1.5-T scanner with an eight channel dedicated head–neck coil. Standard T1 (TSE,TR 600-900ms; TE 8-15ms)- and T2 (TSE TR 8000-9600ms; TE 90-120ms)-weighted images, STIR TR 6000-7000ms; TE 70ms, diffusion-weighted imaging (DWI), and contrast-enhanced fat-saturated images are performed. A section thickness of 3–5 mm is optimal in most situations. We use matrix size of 512x512 and FOV of 18-24cm. For gross nodal assessment a section thickness of 5 mm is adequate. The PCT can also be utilized along with MRI. Additional MR techniques for improving the quality of images of the oral cavity involve using spacers within the vestibule of the mouth to separate it from the teeth and the alveolar ridges. MRI is the preferred technique for lesions of the oral tongue, the floor of the mouth, and lesions involving the hard palate or bone marrow. MRI also shows great strength in the early detection of perineural extension and the detection of intracranial structures. Magnetic resonance angiography, perfusion magnetic resonance imaging, and spectroscopy offer additional information. MRI is particularly useful in evaluating the encasement of the carotid arteries. Perfusion-weighted MR imaging is finding increasing utility in evaluating tumor response to therapy.

The role of ultrasound is well established in the evaluation of thyroid disease and the assessment of lymph nodes. It can be used for assessment of depth of tumor invasion in anterior tongue and problem solving tool in the lesion involving cheek. Ease of use, availability, and the non-invasive technique without ionizing radiation makes it an excellent choice. The main limiting factor is the inter-observer variability and lack of clear imaging format, which can be perceived as a limitation by the referring surgeon. Part of the limitation can be addressed with a clear understanding of the requirements and proper communication. Nowadays, there is renewed interest in the ultrasound technique, with the microbubble contrast agents for the examination of target lymph nodes. High-resolution ultrasound with dynamic contrast-enhanced examination of lymph nodes may emerge as a preferred technique in the assessment of early nodal involvement by malignancy and response to chemotherapy. The importance of high-resolution ultrasound imaging in the demonstration of superficial tumor invasion and salivary gland/duct involvement is highlighted by some studies [1]

2.1.3.5 TNM Classification of Oral Cavity Lesions

The TNM classification provides the goal and basis for image interpretation and documentation. Management of oral cancer needs precise nodal staging to delineate the complete extent of the disease. The combination of clinical evaluation, biopsy

confirmation, and imaging plays a critical role. As an objective, reproducible modality, CT imaging is the preferred technique for nodal assessment. Equally sensitive input can be obtained with MRI; however, it has low specificity. Ultrasound fails to provide a global view of the extent of lymph node disease. Often, MDCT is the modality that is used for the assessment of primary lesion as well as for nodal assessment. Tongue cancers and floor of the mouth tumors are preferentially evaluated by MRI for staging [30–35]. The rest of the oral cavity can be imaged using MDCT puffed cheek evaluation with contrast medium.

2.1.3.6 Neck Node Evaluation

Regional nodal spread is closely linked to the location of the lesion, the vicinity with the midline and histological behavior of the lesion. Tongue cancers usually spread to ipsilateral nodes with the possibility of skip metastasis and contralateral spread. SCC of the oral cavity and gingiva occurs in regional 1A, IB, and 2 nodes. Lesions of the hard palate are not often associated with nodal spread. CT and MR techniques are equally as efficient for nodal assessment. Signs of nodal involvement are increases in size, obliteration of the fatty hilum, increased vascularity, an ill-defined outline, and intranodal necrosis. Ten millimeters or more in an axial section are considered positive for nodal involvement. However, false-positive or false-negative results of 15–20 % are noted in the literature [36]. Ultrasound with fine needle aspiration under ultrasound guidance, contrast-enhanced ultrasound, contrast analysis curves of dynamic CT and MRI have been used for nodal assessment [37–39]. Recent meta analyses [37] utilizing ultrasound-guided FNA, contrast-enhanced MRI and CT has shown slight superiority of ultrasound-guided FNA over other techniques. However, in the study patient with clinically negative nodes, the sensitivity of ultrasound FNA was around 48 % [7]. In the evaluation of nodal neck assessment by MRI, the inclusion of DWI increases the sensitivity and specificity to 76 and 86 % respectively [38], an outcome nearly comparable with CT and PET. DWI images provide additional value to improve the confidence level for predicting nodal involvement. PET imaging appears to play a limited role in the neck −ve malignancy, in view of the high number of false-positive examinations [39].

In the T staging of the lips and oral cavity, interpretation of TX, T0, T1, T2, and T3 are unambiguous. (Table 2.1). T4 staging, however, needs subtle imaging input for further categorization and requires more specific elaboration. *T4a* consists of lesions of the lip in which the tumor invades through the cortical bone, inferior alveolar nerve, floor of the mouth, or skin of the face (i.e., the chin or nose). For lesions of the oral cavity, the tumor invades through the cortical bone, into the deep extrinsic muscle of the tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of the face. In *T4b* lesions, the tumor involves the masticator space, the pterygoid plates, or the skull base and/or encases the internal carotid artery.[1] Subcategories a and b were introduced based on involvement of vital structures and thus their suitability for surgical resection. T4a implies locally advanced but resectable tumor, while T4b implies a tumor that is not technically resectable, but that is suitable for nonsurgical options such as chemo- or radiotherapy [40, 41].

[1] Superficial erosion of the bone/tooth socket alone by a gingival primary tumor is not sufficient to be classified as T4.

Most experts consider CT to be superior to MRI at detecting extracapsular nodal extension, and there are reports that imaging criteria such as involvement of intranodal fat or spiculated margins of metastatic disease are reliable indicators [41, 42]. Most studies that have compared the accuracy of CT and MRI for the assessment of the neck have found no significant difference between these two modalities [43]. In studies reporting on the important issue of the accuracy of CT or MRI for the assessment of the N0 neck, specificities and sensitivities of CT and MRI vary considerably [9], but as a general rule, between 40 and 60 % of all occult metastases are found using either CT or MRI.

2.1.3.7 Important Imaging Considerations in Individual Subsite: Mandibular/Maxillary Invasion

In the evaluation of the lesions of oral cavity, certain areas deserve special attention. When the lesion is in close proximity with bone, imaging becomes more challenging. The following locations are considered individually.

2.1.3.8 Mandibular/Maxillary Invasion

The presence of bone involvement and assessment of the extent is the most important input for planning the extent of surgical resection and the demand for reconstructive procedures.

The mandibular cortex may be involved by adherence or direct extension of the tumor. The medullary cavity may be involved in a more extensive manner by a deeply penetrating tumor, in which case there may be far more bone involvement than is apparent on the surface. Generally, bone involvement is underestimated by CT, whereas with MRI and bone scintigraphy with SPECT, the extent of bone involvement is often overestimated [2, 44]. A negative MRI or bone scan in all likelihood excludes mandibular invasion. For bone involvement of the RMT, the sensitivity of CT is approximately 50 % with a negative predictive value of 60 %. However, the positive-predictive value is approximately 90 %. Thus, although the CT scan is accurate when bone erosion is clearly identified, when it is negative, the predictive value is unacceptably low. Therefore, it is an inaccurate indicator of bone invasion at the RMT [45]. CT provides an excellent view of both the soft tissue and the bone of the mandible (Figs. 2.17 and 2.18); however, it has several technical limitations, the most significant being artifact caused by dental metals, which can obscure demonstration of the invasion of the mandibular cortex. In addition, CT may misleadingly detect defects in the cortex resulting from irregularly shaped alveoli or peri-apical disease

The diagnostic accuracy of dentascan for mandibular invasion is high, yielding a sensitivity of 95 %, and a specificity of 79 % with a positive predictive value of 87 % and a negative-predictive value of 92 % [46]. Dentascan is, therefore, an accurate method for the preoperative evaluation of mandibular invasion in patients with squamous cell carcinoma of the oral cavity.

It has been conclusively demonstrated that MRI is superior for evaluating the medullary space of the mandible (Fig. 2.19), but inadequate for assessing cortical mandibular invasion. Unless there is frank invasion of the bony cortex, periosteal stripping followed by frozen section examination at the time of surgery is often the most reliable measure for managing borderline cases with suspected bone invasion. Recent studies have shown that technetium Tc 99 m bone scintigraphy in the form of planar views or

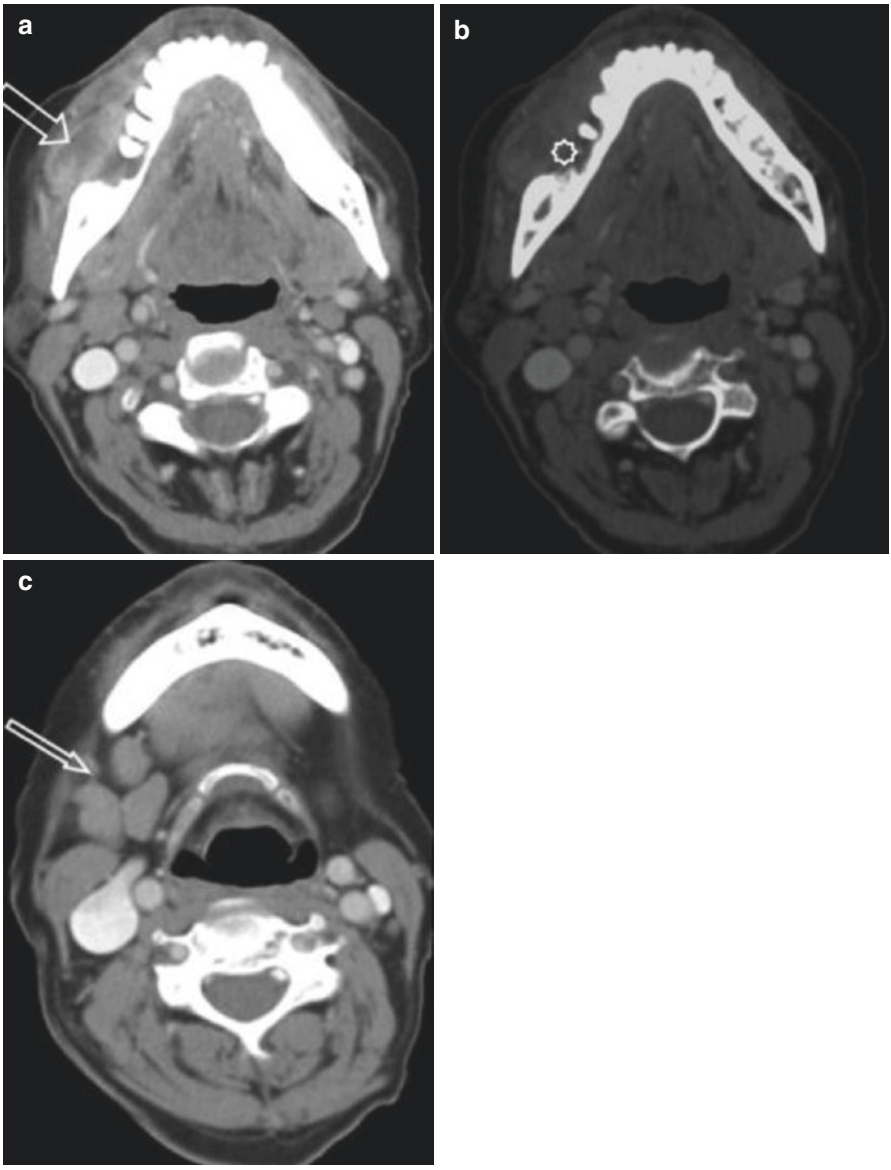


Fig. 2.17 Axial contrast CT images of the oral cavity (**a**) showing a full-thickness soft-tissue mass (*open arrow*) with associated cortical bone destruction (**b**) and Fig. (**c**) demonstrated multiple, enlarged IB lymph nodes (*thin arrow*)

as SPECT provide a high degree of diagnostic accuracy for mandibular invasion by oral squamous cell carcinoma of the alveolus, in both edentulous and dentate patients.

Demonstration of bony erosion involving the maxilla is quite similar in principle. MDCT evaluation with multiplanar bone reconstruction is the optimal method for the demonstration of bone erosion. The dentascan is technically superior in showing subtle bony details. However, MRI examination has limited value.

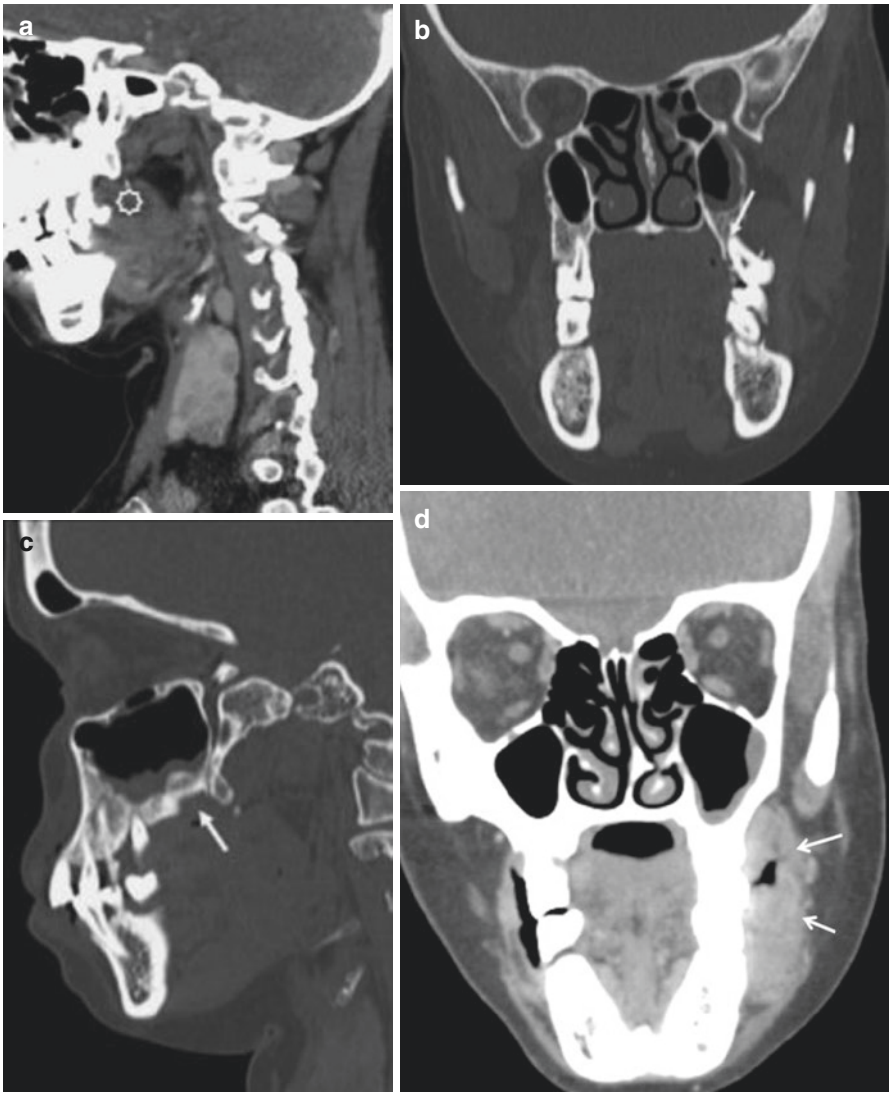


Fig. 2.18 Subtle bone destruction, especially of the maxilla requires more extensive scrutiny. Parasagittal CT reconstruction (**a**) shows a soft-tissue mass (*star*) with focal bone destruction. Compete extent of the lesion is seen at the posterolateral aspect of the maxilla in coronal (**b**) parasagittal (**c**) bone window reconstruction (*solid arrow*). Coronal image in soft tissue window (**d**) demonstrate thickened buccal mucosa (*arrows*) due to SCC

2.1.3.9 Palate

Preoperative imaging of this area is important to assess the invasion of the maxillary sinus, palatal bone, and nasal vault. MDCT is optimal for evaluating this region because it offers a high-resolution image of the palatal and nasal bones, optimally displayed in orthogonal planes. Lateral tumors may present signs of invasion and

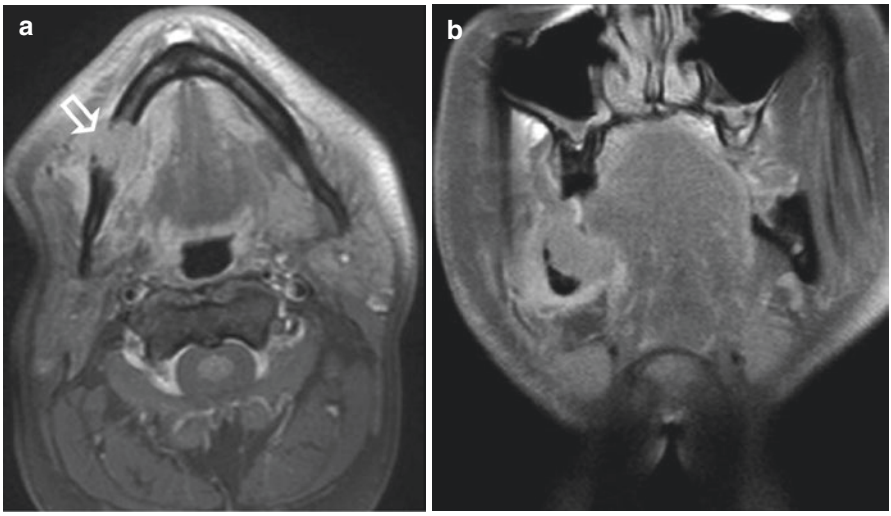


Fig. 2.19 Axial (**a**) and coronal (**b**) MR examination showing cortical and marrow involvement of the posterior body of the right side of the mandible (*open arrow*)

perineural spread via the palatine or trigeminal neurovascular bundle. Pain or anesthesia may suggest nerve invasion and MRI with gadolinium is recommended to demonstrate enhancement or edema of the nerve. DWI with optimized technical parameters enhances the early detection of perineural spread. The depth of invasion dictates the extent of the surgical resection. Superficial lesions of the palatal mucosa are best managed with a wide surgical resection, including the underlying palatal periosteum. The MRI is ideal for imaging the floor of the mouth because it is accurate in identifying soft tissue extent of the lesion and perineural invasion.

2.1.3.10 Infratemporal Fossa

Extension of the lesion to the infratemporal fossa (ITF) and the masticator space up-stages the lesion to the T4a category. Diagrammatic representation of the pathways of spread to the ITF is shown in Fig. 2.20. The pterygomandibular raphe connects the hamulus of the medial pterygoid to the mandible, and serves as a pathway for the spread of the lesion to the ITF, including bony extension to the maxillary tuberosity. RMT lesions also extend along this anatomical pathway by extending through the pterygomandibular ligament. CT and MRI are equally suited for demonstrating lesion spread. However, CT may be preferred in situations where bone involvement is suspected. T1-weighted, fat-suppressed, contrast-enhanced MRI is the best available modality for demonstrating perineural spread.

2.1.3.11 Tongue

Magnetic resonance imaging is the preferred method for assessing tongue lesions. There is a difference between the behavior of squamous cell carcinoma of the oral tongue and dorsum of tongue. Extent of the regional involvement, dictates treatment options and extent of surgery in case of surgical management. Important factors to

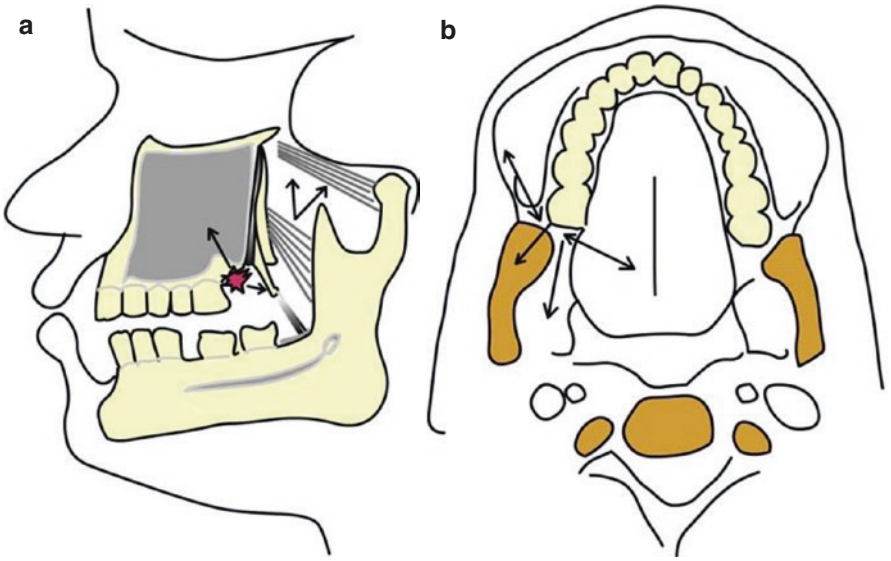


Fig. 2.20 (**a**) diaphragmatic Illustration showing the location of the lesion at the posterior upper RMT, depicting the pattern of disease spread to the maxilla, pterygopalatine fossa, and infratemporal fossa. (**b**) axial diaphragmatic illustration showing the location of the lesion in the mandible. The RMT and the pattern of disease spread, as illustrated by the *arrows*

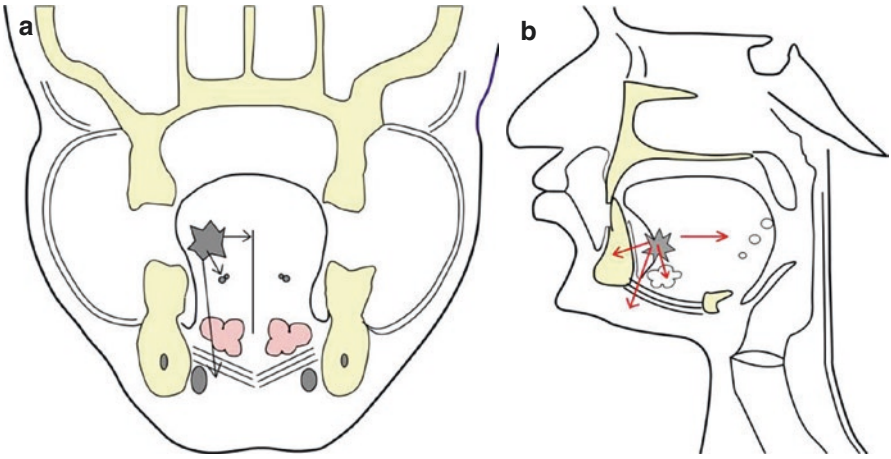


Fig. 2.21 (**a**) Coronal diaphragmatic illustration showing the lesion in the mid-tongue and the patterns of spread, across the midline, to the salivary gland and floor of the mouth. (**b**) Diaphragmatic illustration in the sagittal plane showing the lesion in the anterior floor of the tongue and the likely pattern of malignancy illustrated by the *red arrows*

scrutinize in anterior tongue lesion are the involvement of the neurovascular bundle, invasion of the submandibular duct, the spread of lesions across the midline septum and mandible bone erosion (Figs. 2.21 and 2.22). The posterior tongue has different avenues of extension. Areas to look for are extension to the dorsum of tongue,

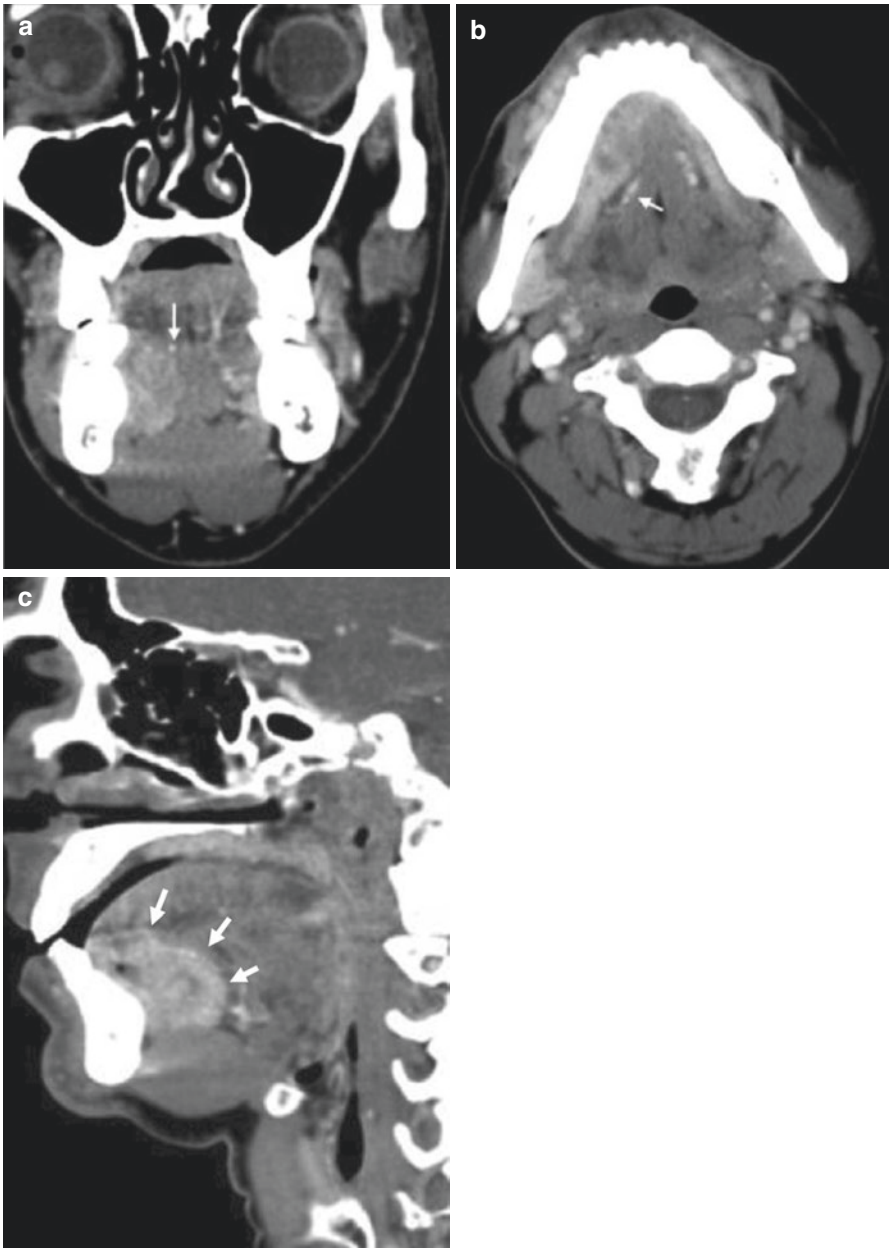


Fig. 2.22 Enhancing sublingual lesion with involvement of the ipsilateral half of the tongue is seen on the right side, as demonstrated by coronal (**a**), axial (**b**) and sagital (**c**) images of contrast-enhanced CT. multidetector computed tomography (MDCT). *Arrows* in Fig. **a** and **b** demonstrate the location of lingual artery. Multiple arrows in Fig. **c** show the margins of the lesion.

vallecula, and epiglottis in the midline. Laterally, extension of the lesion to the palatoglossal fold, tonsils, RMT, and ITF are to be sought (Figs. 2.23, 2.24, and 2.25). MR imaging has a special role in demonstrating the depth of tumour invasion. Capability of the multiplanar evaluation makes it easy to obtain optimal imaging planes for optimal assessment. Contrast-enhanced MR provide a more precise

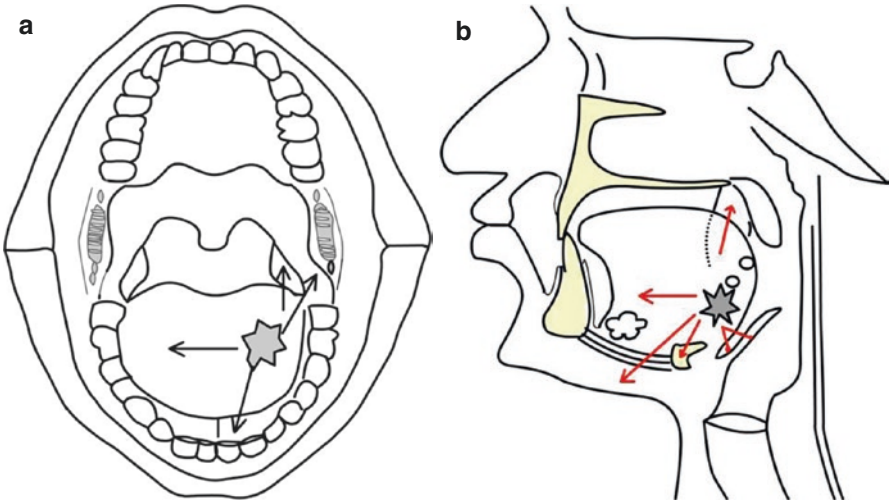


Fig. 2.23 (**a**) Diaphragmatic illustration of the posterior tongue lesion from the frontal perspective. *Arrows* demonstrate spread of the disease contralaterally, posterior to the palatoglossal fold and tonsil. (**b**) Sagittal diaphragm for malignancy in the posterior tongue, showing extension of the disease to the anterior tongue, floor of the mouth, the hyoid bone, the vallecula, and the lateral wall of the oropharynx

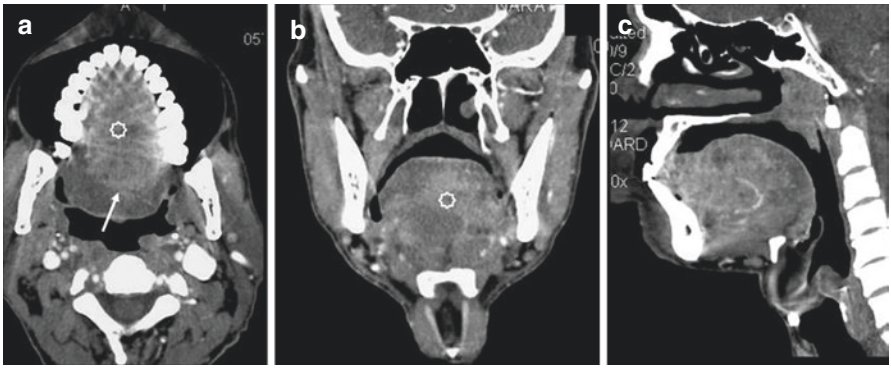


Fig. 2.24 CT reconsrtuction in axial (**a**), coronal (**b**) and sagittal plane (**c**) demonstrating an extensive lingual lesion crossing the midline (*star*). However, the dorsum of the tongue is spared. Arrow in Fig. (**a**) points to the posterior margin of the lesion

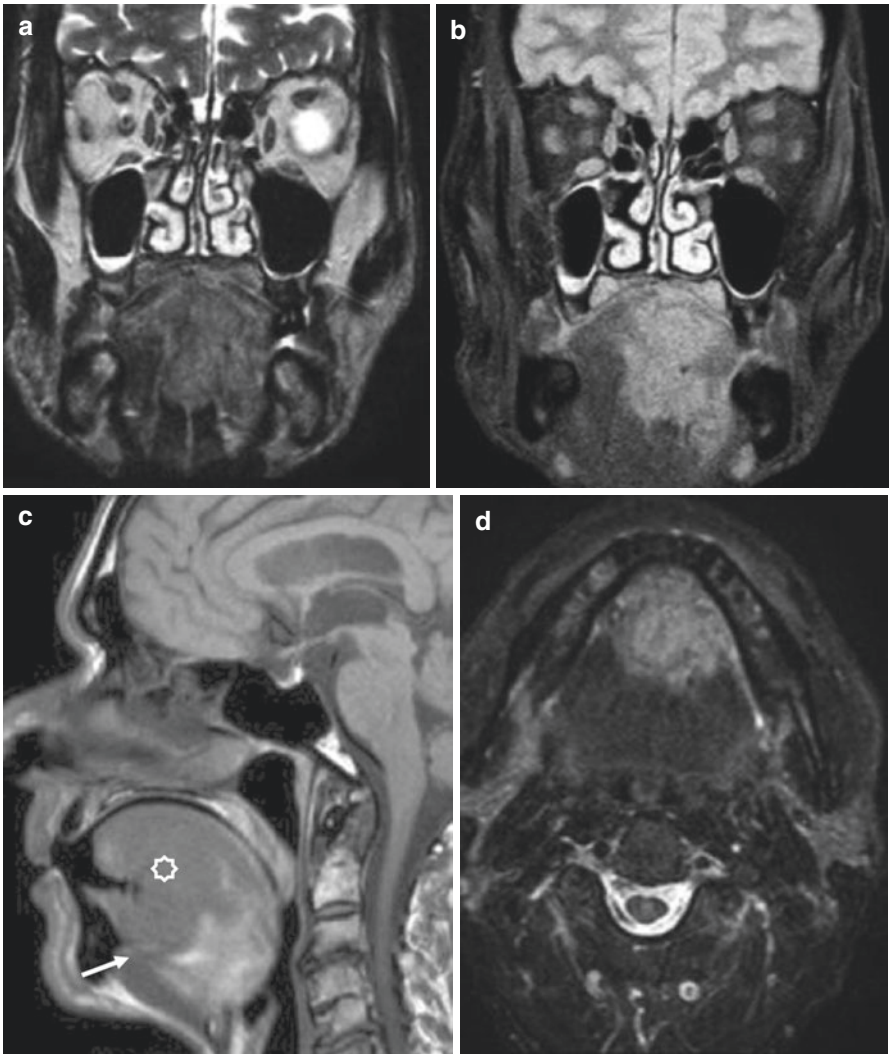


Fig. 2.25 (**a**, **d**) T2 images showing mildly T2 hyperintense lesions in an anterior tongue. Contrast-enhanced T1-weighted fat-saturated images (**b**, **c**, **e**, **f**) clearly show an ulcerative anterior tongue lesion (*star*), crossing the midline, reaching up to the mylohyoid diaphragm. (*white arrow*) The dorsum of the tongue, however, is spared

information regarding deeper extension, compared to non-contrast T2 images. Depth beyond 9.7 mm is closely associated with the increased regional metastasis, hence unfavorable prognosis [47, 48]. Extension of lesions due to extrinsic tongue muscle has poor prognosis, often requires multiple modality treatment.

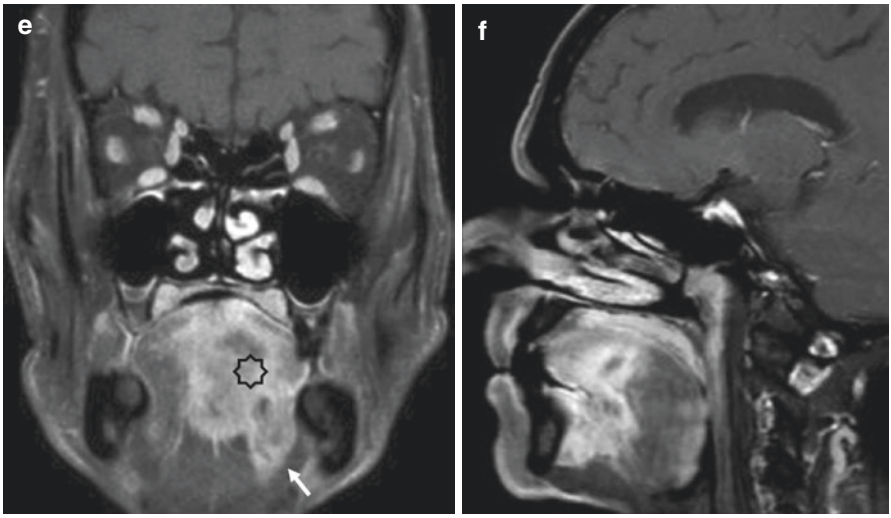


Fig. 2.25 (continued)

2.1.3.12 Retromolar Trigone

Primary and secondary involvement of the RMT is a crucial stage in the spread of oral malignancy (Figs. 2.26, 2.27, and 2.28). An essential imaging requirement is to establish the possibility of bone erosion and look for subtle evidence of the spread of the lesion along the pterygomandibular raphe. Imaging plays a greater role than clinical assessment in this region owing to limited direct clinical access. MDCT is preferred as bone erosion is often present. It is also important to establish whether bony involvement involves only the cortical bone or also involves the mandibular marrow. Erosion of the alveolar margin is often non-specific, and does not need extensive surgery, whereas erosion of the lateral cortex or mandibular marrow calls for resection of the bone involved.

2.1.3.13 Neck Nodes

Nodal assessment can be established using multiple imaging methods. MDCT scores over the others by being a one-stop shop for oral malignancy (Fig. 2.29). In specific situations in which single draining nodes need to be studied, ultrasound study combined with fine-needle aspiration biopsy (FNAB) can be performed. Ultrasound-guided fine-needle aspiration biopsy (UGFNAB) has a specificity of 100 %. This combined technique is demonstrated to be accurate for the evaluation of regional recurrent or residual metastatic disease [2, 49, 50]. Although the technique is not difficult, considerable training is required to successfully aspirate lymph nodes as small as 5 mm and to select the most suspicious lymph nodes that can be aspirated. In patients with a clinically negative neck, the results of UGFNAB are less impressive, as detection of lymph node metastasis with the use of imaging techniques requires a minimum size. UGFNAB identifies clinically occult metastases with a sensitivity of no more than 48–73 % [50, 51]. Sentinel node scintigraphy is a per-operative procedure that may help the surgeon to make a specific decision during surgery.

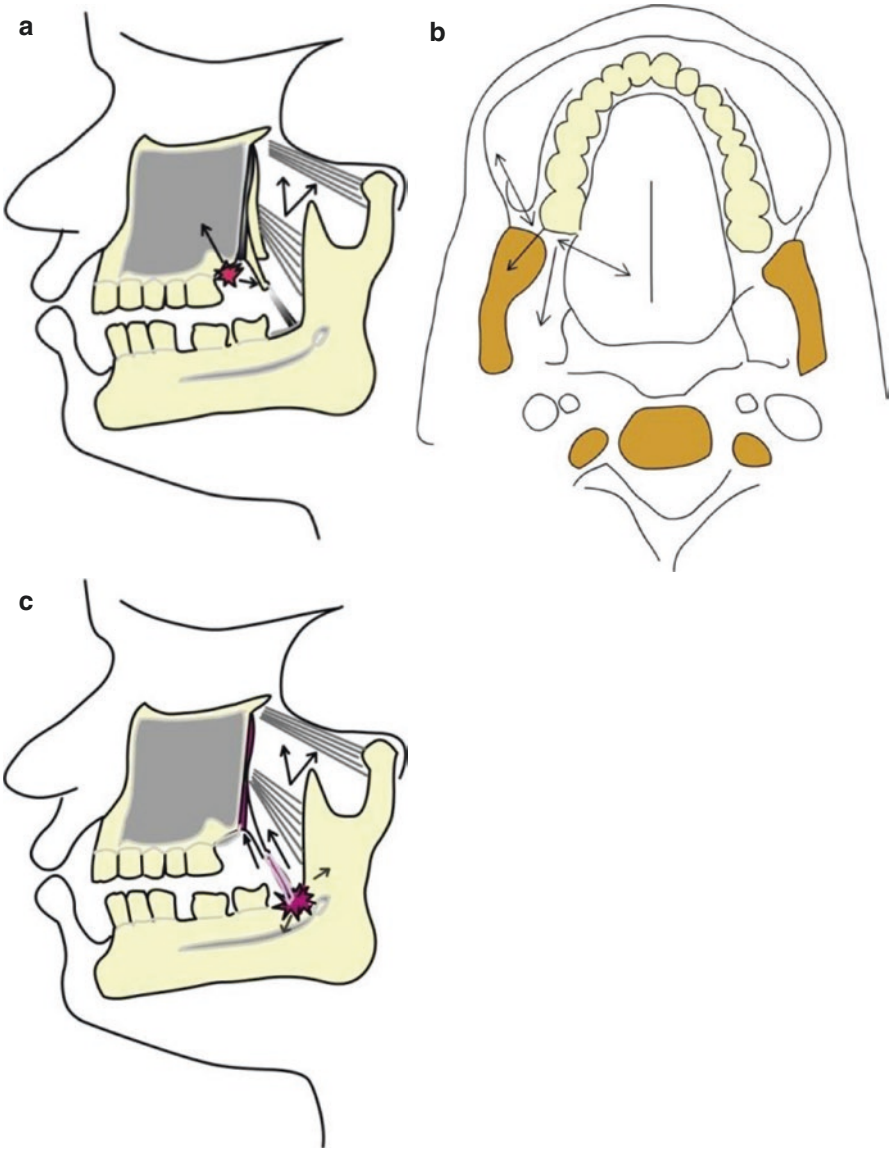


Fig. 2.26 (**a**) Lesion in the maxillary RMT showing a pathway of the disease spread to the pterygopalatine fossa and infratemporal fossa. (**b, c**) Lesion in the mandibular RMT: illustrating the disease spread along the pterygomandibular raphae, medial pterygoid, and lateral pterygoid. Inferiorly and posteriorly, the lesion extends to the mandibular ramus and mylohyoid canal respectively. *Arrows* point to pathway of disease spread

The nodal mass can be large at level II a, IIb regions almost encircling the carotid vessels. The internal jugular vein can be sacrificed without much morbidity. On the other hand, carotid arterial encasement results in increased morbidity. The diagnostic value of CT in detecting vascular invasion by head and neck malignancies has been assessed by different groups.

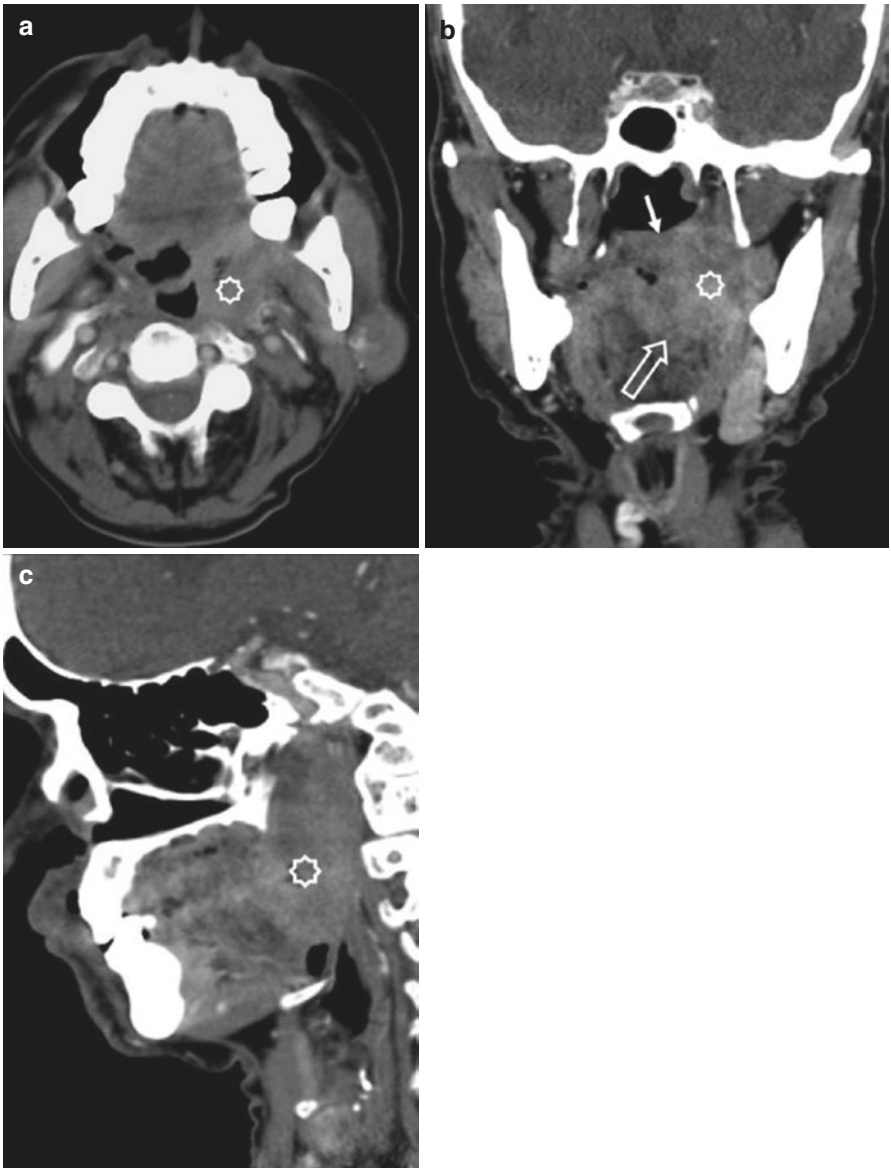


Fig. 2.27 Axial (**a**) CT image show a lesion located in the left wall of the oropharynx (*star*). (**b**) Coronal examination showing extension of the lesion to the posterior tongue (*open arrow*), and to the soft palate. (**c**) Sagittal reconstruction centered on the oropharynx showing the epicenter of the disease

Ouyang and Branstetter [14] described six types of vascular involvement of the carotid artery and jugular vein on CT in 43 patients with malignant head and neck tumors. The highest accuracy (84.1 %) was recorded in two types: compression and deformation of the common carotid artery (CCA) or internal carotid artery (ICA),

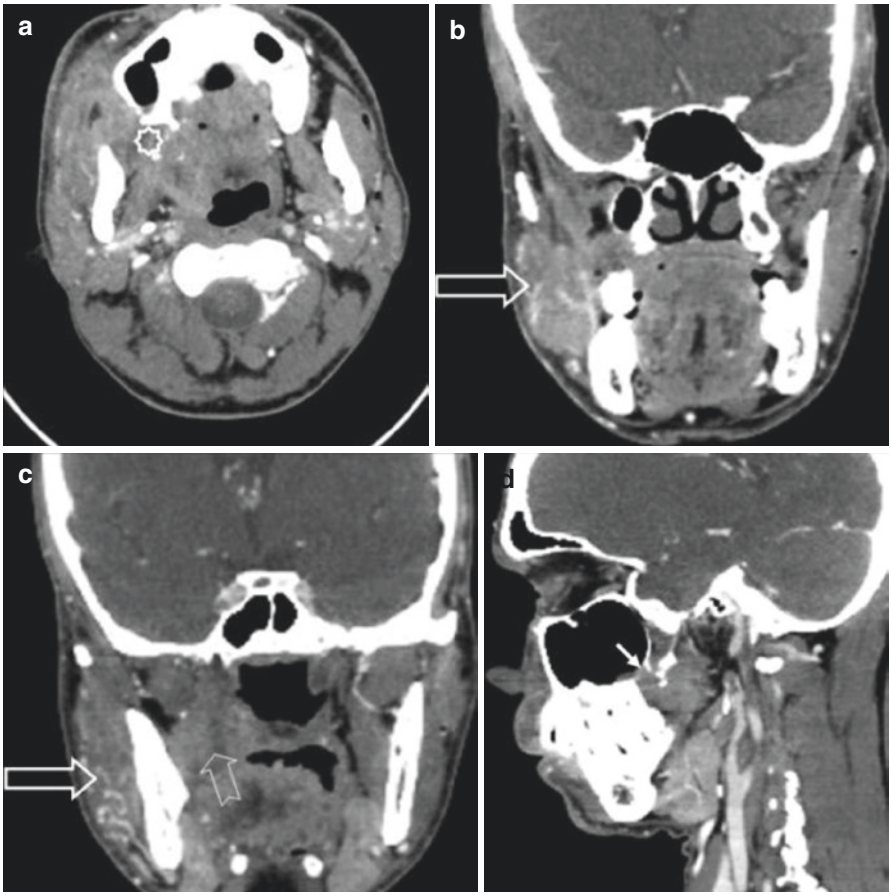


Fig. 2.28 Axial contrast enhanced CT (**a**) demonstrates a retromolar region lesion showing the extension of the disease posteriorly to the medial pterygoid and pterygopalatine fossa (*arrows*). Coronal reformats (**b** and **c**) show extension of the disease laterally to involve the masseter (*open arrow*) and obliteration of the fat plane behind the maxilla (*triangle*). (**d**) Sagittal reconstruction shows bony erosion at posterior wall of maxilla

and partial loss of fat or facial plane between the tumor and the CCA or ICA. Circumferential vessel-wall involvement of greater than 180° on CT had a sensitivity as low as 18.5 %. The authors concluded that the accurate diagnosis of carotid artery involvement by CT was difficult

Mann et al. [52] developed a helpful ultrasound staging system for carotid artery involvement based on findings from 41 patients with extensive metastatic neck disease.

Five patients with stages III and IV underwent transcranial Doppler (TCD)ultrasound to determine crossflow in the middle cerebral artery (MCA) with compression testing of the CCA. They concluded that a crossflow circulation of the MCA by using TCD ultrasound, demonstrating greater than 90 % of the flow velocity obtained under normal conditions within 20 s after external compression of the carotid artery allows safe resectability of this vessel [52].

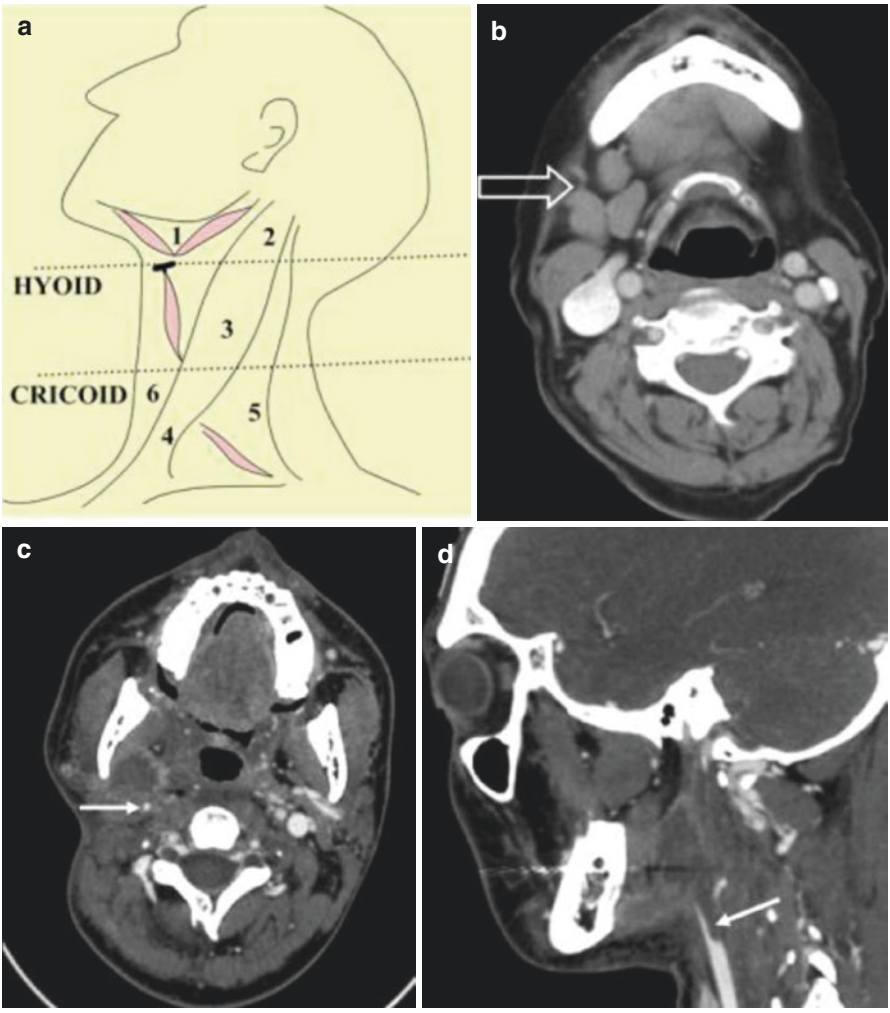


Fig. 2.29 Diagram shows levels of cervical lymph nodes for staging description. (**a**) Axial contrast-enhanced images shows right level I B lymph node enlargement. (**b**) Axial and sagittal (**d**) images in a different patient show level II lymphadenopathy with occlusion of the carotid artery (*arrow*)

The authors (Ouyang and Branstetter) found that the single criterion of involvement of 270° or more of the circumference of the carotid artery was accurate in predicting the surgeon's inability to peel the tumor off the carotid artery in 100% of cases [14]. Table 2.2 summarizes the relative merits and limitations of available imaging modalities and its usefulness in various sub-sites of oral cavity [48]. This analysis does not include the role of PET imaging ,which is discussed subsequently in the chapter.

Post-operative imaging follow up is often required to exclude recurrence or residual disease. MDCT is most practical tool for post-operative assessment. Imaging

Table 2.2 Choice of imaging methods for T staging at various subsites of oral cavity squamous cell carcinomas (OCSCC)

Site of SCC	Imaging method of choice	Advantages	Disadvantages
Oral tongue and floor of mouth	CE-MRI	A. Superior soft-tissue characterization for ✓ Extrinsic muscle invasion ✓ Posterior and inferior soft tissue extent B. Highly sensitive for bone erosion (that occurs in <10 % cases in tongue cancers)	A. MRI* can overestimate inferior alveolar canal involvement and mandibular cortical erosion (due to chemical shift artifacts) B. Swallowing artifacts Problem solving for bone erosion – May add: (a) CT (has better specificity OR (b) SPECT has increased sensitivity)
Gingival and buccal cancers	CE-MDCT with puffed-cheek technique[a]	A. Bone erosion (high positive predictive value) B. Speed of scanning C. Adequate for posterior soft tissue extent to decide resectability (can display infra and supra-notch T4b disease)	A. Dental amalgam artifacts B. May miss early perineural spread
RMT *comparable	CE-MRI*	Accurate T staging and relations	A. Overestimation of mandibular invasion B. Swallowing artifacts
	CE-MDCT*with puffed cheek technique[a]	High accuracy for bone erosion adequate for soft-tissue extent	May miss early perineural spread
Hard palate	CE-MRI	A. High accuracy for marrow and perineural invasion B. Complete soft-tissue extent depicted	Cortical erosion less well depicted (CE-MDCT is therefore complementary)
Lip	CE-MDCT with puffed-cheek technique[a]	High accuracy for bone erosion adequate for soft-tissue extent	CT may miss early perineural spread, but MRI could overestimate perineural spread

Reproduced with kind permission of Arya et al. [7]
CE-MRI contrast-enhanced magnetic resonance imaging, *CE-MDCT* contrast-enhanced multidetector computed tomography, *CT* computed tomography, *SPECT* single photon emission computed tomography
[a]Preferred in the authors' institute
*Refers to the clinical practice of the reference author

specialist should be familiar with tissue changes following surgery or radiotherapy (RT). Post RT changes are generally diffuse in neck,corresponding to the field, include non specific thickening of tissue planes and edema or fibrosis,depending on the duration following treatment. Also familiarity with range of bony and soft reconstruction methods, greatly facilitate interpretation (Fig. 2.30a and b).

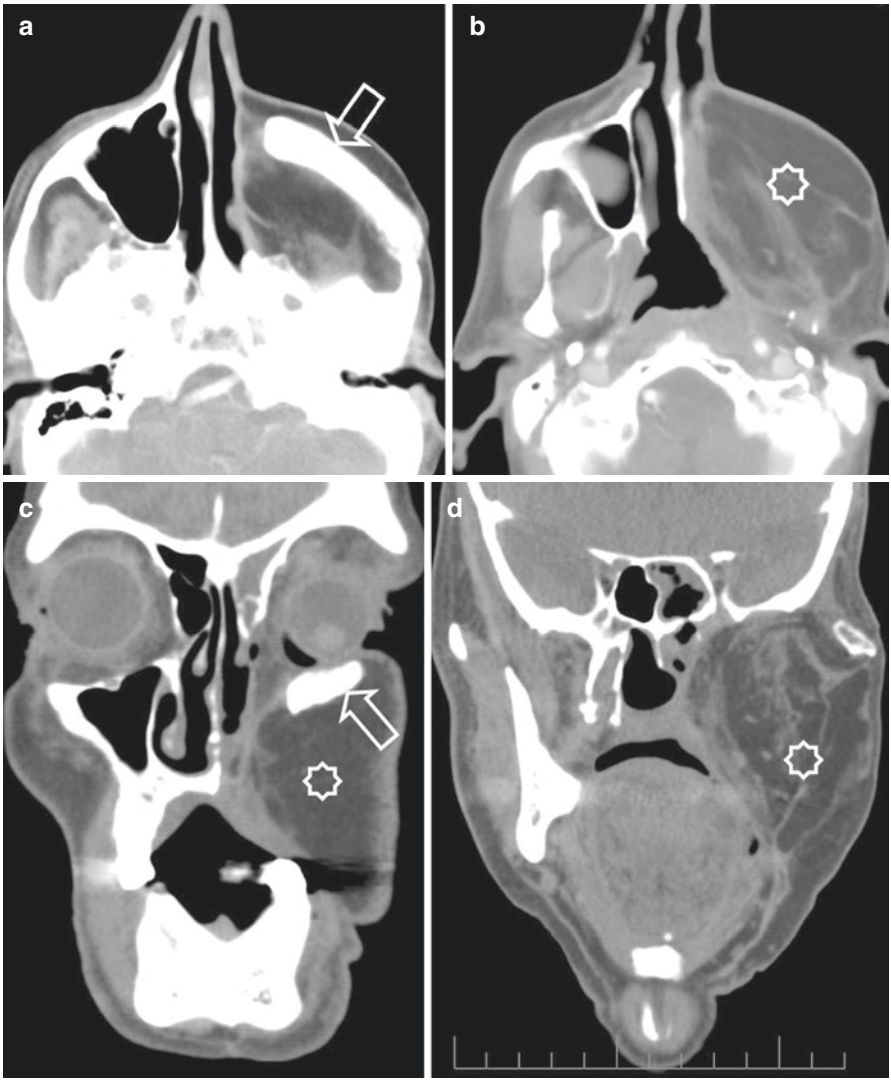


Fig. 2.30 Axial CT images (**a** and **b**) following maxillectomy, segemntal mandibulectomy and ITF clearance for advanced oral malignancy. Reconstruction done with rib graft (*open arrow*) and pectrolis major flap (*star*). Coronal CT reconstruction (**c** and **d**) show the extent of the reconstred region. There is no residual disease or recurrence

2.2 PET CT in Squamous Cell Carcinoma of the Head and Neck Region: A Pictorial Review

Head and neck squamous cell carcinoma (HNC) is the most common malignancy in India. This is due to the prevalence of risk factors such as smoking and tobacco and betel nut chewing. FDG PET CT is the work horse of oncological imaging in nuclear medicine [53]. There are specific clinical indications in head and neck cancer in which FDG PET CT plays a prominent role.

Table 2.3 Studies evaluating performance of 18F-FDG PET or PET/CT for the detection of carcinoma of unknown primary in patients with negative workup

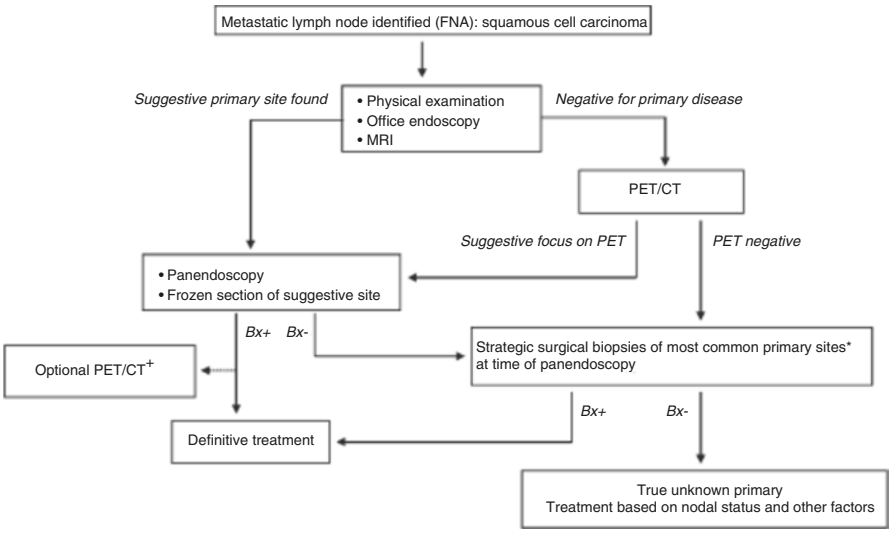
Authors, year	Number of patients	All positive	True positive	False positive	Percent detected by PET
Padovani et al. 2009	13	9	7	2	54 %
Silva et al. 2007	25	9	3	6	12 %
Fakhry et al. 2006	20	10	7	3	35 %
Wong and Saunders 2003	17	8	5	3	29 %
Fogarty et al. 2003	21	6	1	5	5 %
Johansen et al. 2002	42	20	10	10	24 %
Kresnik et al. 2001	15	12	11	1	73 %
Jungehulsing et al. 2000	27	7	7	0	26 %
Total	180	81	51	30	28 %

Review Article: Al-Ibraheem et al. [54]

2.2.1 Diagnosis of an Unknown Primary Tumor

This modality (PET CT) detects the primary tumor in approximately 30 % of cases. It can guide the site of the biopsy and it is recommended for use before panendoscopy and blind biopsy. PET may miss small submucosal lesions situated in physiological sites of FDG uptake in the head and neck region (Fig. 2.31; Table 2.3) [54].

A suggested algorithm for the use of PET in detecting an unknown primary in head and neck cancer is: [55]



Quon et al. [55]

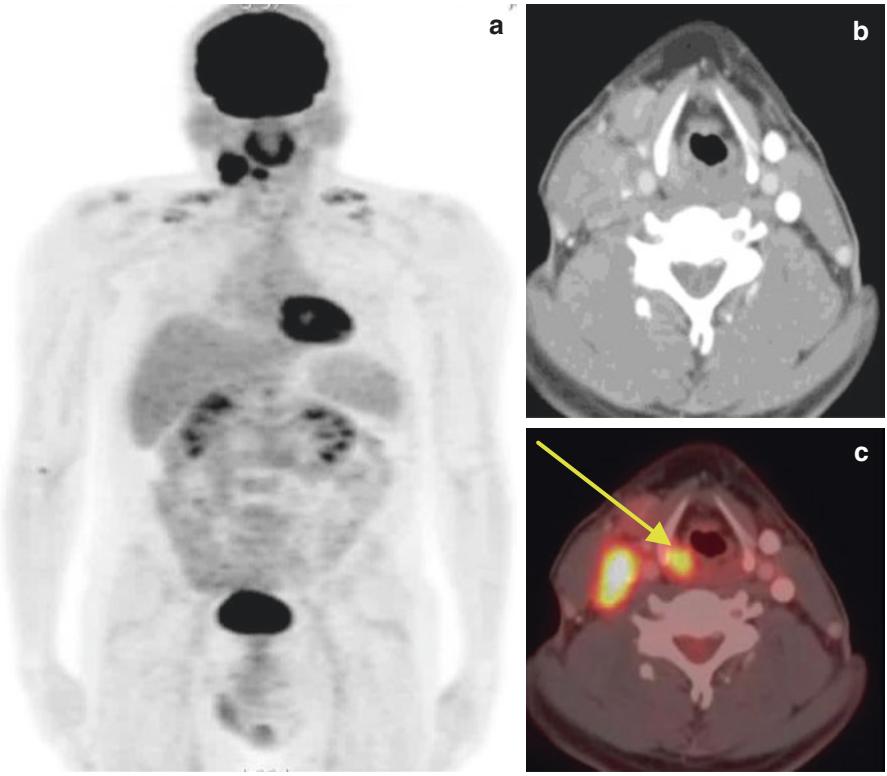


Fig. 2.31 The use of FDG PET CT in a patient with metastatic squamous cell carcinoma in head and neck cancer with an unknown primary. Primary tumor detected in the right pyriform sinus (*arrows*). (**a**) PET image showing right level II cervical lymph node and primary tumour in right hypo pharynx. (**b**) Transaxial CT Images showing the right level II cervical lymph node. Primary tumour is no obvious. (**c**) Transaxial PET CT images highlight right level II cervical lymph node and primary tumour in right pyriform sinus (Indicated by *yellow arrow*)

2.2.2 FDG PET CT at Initial Staging

The role of 18F-FDG PET for the staging of distant metastases in HNC is acknowledged as being one of the most powerful indications in head and neck cancer. There is general agreement that 18F-FDG PET is indicated for the initial staging of HNC when there are suspected distant metastases and a synchronous second tumor. The incidence of distant metastasis increases with locally advanced disease (T3–T4), N2, or N3 disease, extracapsular extension of lymph node involvement, and perineural invasion. PET CT at initial diagnosis is indicated in locally advanced tumors (T3/T4) and they have an approximately 20–25 % chance of having distant metastasis and approximately 8 % chances of having synchronous second primaries. For T staging we primarily depend on the simultaneously

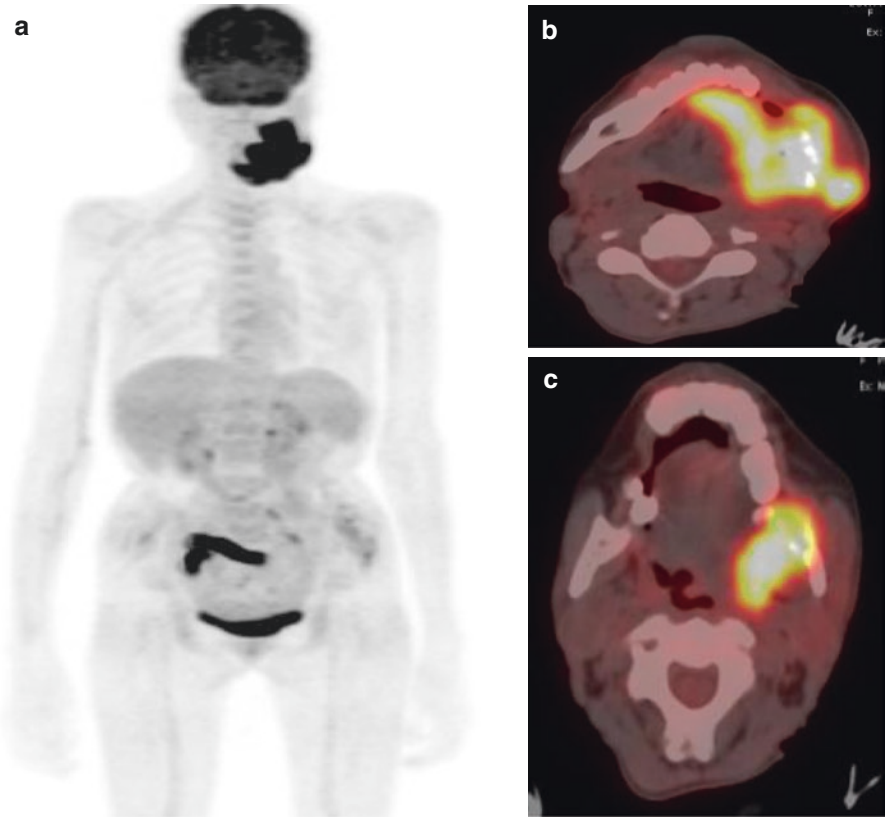


Fig. 2.32 The use of FDG PET CT for initial staging in a patient with a T4 squamous cell carcinoma of the left buccal mucosa with infratemporal extension. FDG PET CT ruled out distant metastasis, thereby enabling curative resection of the primary. (**a**) PET Image showing FDG avid recurrent mass in left floor of mouth and left cheek. (**b**) Transaxial PET CT image showing recurrent tumour in the left floor of mouth with extension to left lateral cheek (**c**) Transaxial PET CT Image showing extension of the tumour to left retromolar trigone with erosion of ramus of left hemi mandible

performed diagnostic contrast-enhanced PET CT. The semiquantitative measurement of glucose uptake in a tumor is SUVmax (standardized uptake value corrected to the whole body weight or lean body mass). SUVmax >10 at initial diagnosis on FDG PET CT predicts a poor prognosis (Figs. 2.32, 2.33, and 2.34).

In a review by Schöder and Yeung, an average sensitivity of 87–90 % and a specificity of 80–93 % were reported for 18 F-FDG PET/CT; a sensitivity of 61–97 % and specificity of 21–100 % were reported for morphological imaging modalities, including MRI and CT. Clearly, for the detection of metastasis in cervical lymph nodes, sentinel lymph node lymphoscintigraphy is superior to PET. However, PET has higher sensitivity than CT/MRI for detecting metastasis in sub-centimeter lymph nodes (Fig. 2.35; Table 2.4).

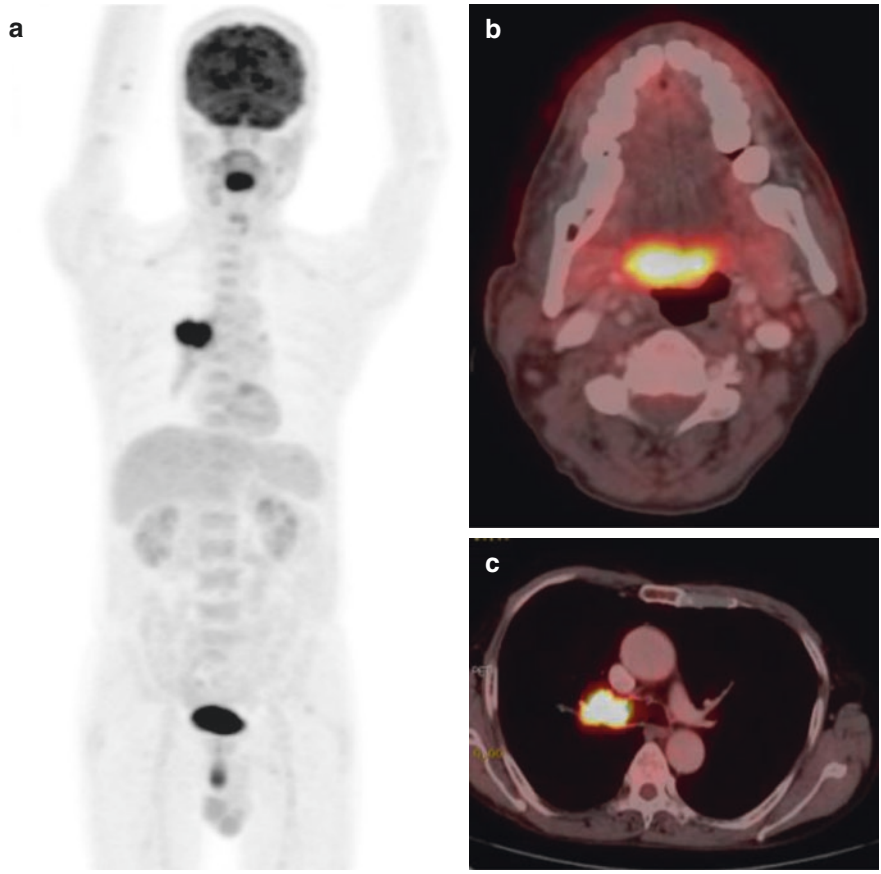


Fig. 2.33 The use of FDG PET CT for initial staging in a patient with squamous cell carcinoma of the base of the tongue. FDG PET CT revealed a synchronous second primary tumor in the right main stem bronchus. (**a**) PET Image showing synchronous primary tumours in base of tongue ans right hilar region. (**b**) Transaxial PET CT Image showing hypermetabolic primary tumour in the base of tongue. (**c**) Transaxial PET CT Image showing synchronous second primary tumour in the right main stem bronchus

When used appropriately at initial staging, PET alters the management plan in approximately 30 % of the patients (Tables 2.5 and 2.6) [56].

2.2.3 Assessment of Response to Therapy

The PET CT technique is recommended at 12–16 weeks after chemo-radiotherapy. It has a high negative predictive value of >97 %. Positive predictive value is about 64 % (owing to therapy-associated inflammatory changes); thus, a biopsy is recommended before further therapeutic decisions [57]. PET is better

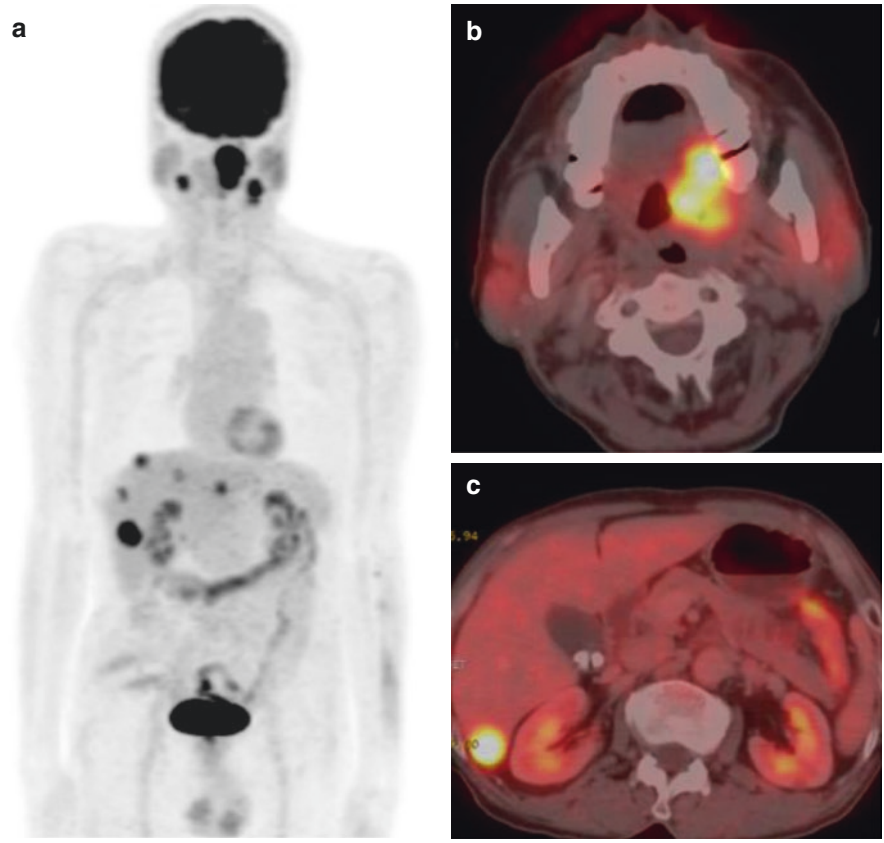


Fig. 2.34 The use of FDG PET CT for initial staging in a patient with a T4 squamous cell carcinoma of the left oropharynx. FDG PET CT revealed metastasis to the bilateral cervical lymph nodes and liver, thereby triaging the patient toward palliative chemotherapy. (**a**) PET Image showing primary tumour in left posterior tongue and retromolar trigone with metastasis to bilateral cervical lymph nodes and liver. (**b**) Transaxial PET CT image showing primary tumour in left posterior tongue and retromolar trigone. (**c**) Transaxial PET CT Image showing hypermetabolic metastatic nodule in segment VI of the liver

than CT/MRI at accurately detecting the response to therapy, especially with the use of newer cytostatic agents such as cetuximab, which does not lead to a significant decrease in tumor size (Fig. 2.36; Tables 2.7 and 2.8).

2.2.4 Surveillance/Detection of Recurrence

There are currently no evidence based, well-established guidelines for the frequency of surveillance. However, when clinical recurrence is suspected, PET CT is better than CT/MRI at detecting the site of recurrence and for restaging (Table 2.9).

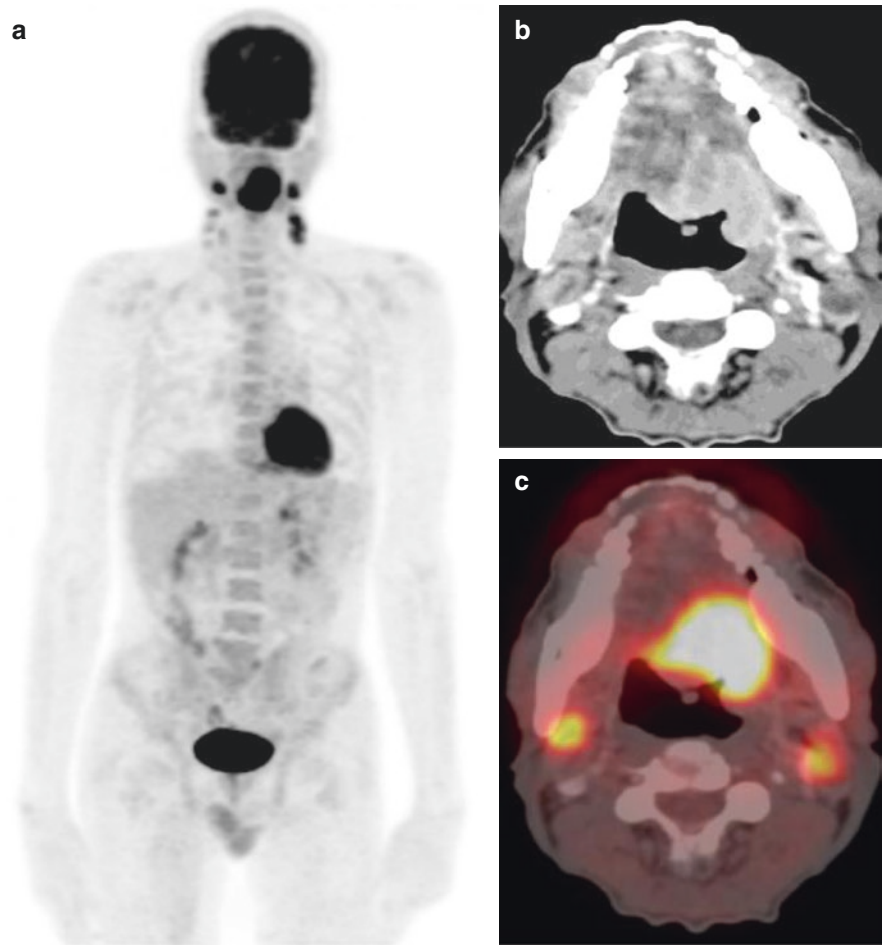


Fig. 2.35 The use of FDG PET CT for the initial staging in a patient with a T4 squamous cell carcinoma of the left oropharynx. FDG PET CT revealed metastasis to the bilateral cervical lymph nodes. The radiotherapy field was modified to deliver a therapeutic dose to the bilateral neck nodes. (**a**) PET Image showing primary tumour in the oropharynx with metastasis to bilateral cervical lymph nodes. (**b**) Transaxial CT image showing enhancing primary tumour in the left posterior 1/3rd and base of tongue and left vallecula. Necrotic left level II cervical lymph node. (**c**). Transaxial PET CT Image showing hypermetabolic primary tumour in the left posterior 1/3rd and base of tongue and left vallecula with metastasis to bilateral cervical lymph nodes

Table 2.4 Studies evaluating the performance of FDG PET for the detection of distant metastases and synchronous second tumor in HNC

Authors, year	Number of patients	Positive PET	True positive (distant mets + 2nd primary)	False positive	Notes
Ng et al., 2009	111	16	13/16	3/16	CT/MR detect 4/16
Chua et al., 2009	68	6	5/6	1/6	CT + BS detect 4/6
Liu et al., 2007	300	61	50/61	11/61	
Yen et al., 2005	118	32	24/32	8/32	
Goerres et al., 2003	34	8	7/8	1/8	PET modified treatment in 15 %
Sigg et al., 2003	58	8	7/8	1/8	PET modified treatment in 5 %
Schwartz et al., 2003	33	7	7/7	0/7	
Total	722	138	113/138	25/138	

Review Article: Al-Ibraheem et al. [54]

Table 2.5 Pre-PET and post-PET management plans

			Post-PET plan			
	Pre-PET plan		Management unchanged		Management changed	
	All patients					
Management plan	*n*	%	*n*	%	*n*	%
Radiotherapy	15	21.1	10	14.1	6	8.5
Radiotherapy, then other (CT of chest and likely CT-guided biopsy of lung)	–	–	0	0.0	1	1.4
Surgery	9	12.7	5	7.0	1	1.4
Surgery, then other (core biopsy)	–	–	0	0.0	1	1.4
Surgery, then radiotherapy	10	14.1	7	9.9	4	5.6
Surgery, then chemotherapy, then radiotherapy, or	3	4.2	2	2.8	1	1.4
Radiotherapy, then chemotherapy						
Chemotherapy/radiotherapy (consecutive or concurrent)	32	45.1	22	31.0	10	14.1
Other (observation × 1, bronchoscopy × 1)	2	2.8	1*	1.4	0	0.0
Total	71	100.0	47	66.2	24	33.8

Scott et al. [56]
*Observation

Table 2.6 Impact of PET on detailed patient management plans

Pre-PET plan	n	Post-PET plan	Impact	n
Radiotherapy	15	Radiotherapy	Treatment unchanged	10
		Radiotherapy, then chemotherapy	Chemotherapy added as second modality	1
		Radiotherapy, then chemotherapy	Chemotherapy added as second modality; change of intent from curative to palliative	1
		Radiotherapy	Radiotherapy course changed	1
		Radiotherapy	Radiotherapy course changed; change of intent from curative to palliative	1
		Radiotherapy, then other (CT of chest and likely CT-guided biopsy of lung)	Other added as second modality	1
Surgery	9	Surgery	Treatment unchanged	
		Surgery, then radiotherapy	Radiotherapy added as second modality	1
		Radiotherapy	Radiotherapy instead of surgery; change of intent from curative to palliative	1
		Surgery, then radiotherapy, then chemotherapy	Radiotherapy + chemotherapy added	1
		Surgery, then other (core biopsy)	Other added as second modality	1
Surgery, then radiotherapy	10	Surgery, then radiotherapy	Treatment unchanged	
		Surgery, then radiotherapy	Course of treatment changed	
		Radiotherapy and chemotherapy	Chemotherapy added as a primary modality	1
Surgery, then chemotherapy and radiotherapy	2	Surgery, then chemotherapy and radiotherapy	Treatment unchanged	1
		Radiotherapy and chemotherapy	Surgery not performed	1
Surgery, then chemotherapy, then radiotherapy	1	Surgery, then chemotherapy, then radiotherapy	Treatment unchanged	1
Chemotherapy, then radiotherapy	3	Chemotherapy, then radiotherapy	Treatment unchanged	
		Chemotherapy, then radiotherapy	Course of treatment changed	1
Radiotherapy and chemotherapy and other (±tirapazamine)	1	Radiotherapy and chemotherapy and other (± tirapazamine)	Course of treatment changed	1

(continued)

Table 2.6 (continued)

Pre-PET plan	n	Post-PET plan	Impact	n
Chemotherapy and radiotherapy	28	Chemotherapy and radiotherapy	Treatment unchanged	20
		Chemotherapy and radiotherapy	Course of treatment changed	4
		Radiotherapy	Chemotherapy abandoned; change of intent from curative to palliative	3
		Surgery, then radiotherapy	Chemotherapy abandoned, surgery added; change of intent from palliative to curative	1
Other (observation)	1	Other (observation)	Treatment unchanged	1
Other (bronchoscopy)	1	Surgery	Surgery instead of other	1
Total	71			71

Scott et al. [56]

2.2.5 Radiotherapy Planning

An emerging indication for the use of PET CT is in radiotherapy planning in head and neck cancers (Tables 2.10 and 2.11).

Overall, in 56 % cases, gross tumor volume (GTV) delineation was changed significantly if information from PET/CT was used in the planning process. This modification in GTV translated into altered PTV (>20 %) in 46 % of cases. In 16 % of the cases, PET/CT revealed distant metastases, changing the treatment strategy from curative to palliative [58].

Table 2.7 Summary of published data: patients

Study	No. of patients	Primary site	Study purpose	Patient characteristics	Hemi necks	P/R	Mode of treatment	Stage	Median age (y)
Yao	85	79 % OP. OC. La	Res dz after defin or postop RT?	Defin or postop RT	NA	R	58 defin (C)RT (70–74 Gy); 27 postop RT (60–66 Gy); all IMRT	No data	No data
Me Column	40	88 % OP. OC. La	Assess primary after induction chemo; assess neck after defin CRT	Induction chemo, followed by CRT	NA	R	CRT (70 Gy)	3–4	54
Ware	53	74 % OC. OP. La	Any res dz?	Res structural abnormality (9 % postop; 15 % op + RT; 15 % RT only; 55 % CRT; 6 % induction chemo)	NA	R	Mixed; see patient characteristics	1–4	No data
Yao	53	81 % GP. La	Res neck dz?	Defin (C)RT; cpl response at primary	70	R	Defin (C)RT; 45 with IMRT	2–4	53
Porceddu	39	92 % OP. La	Res neck dz?	Res neck mass 8 week after (C)RT	50	R	Defin (C)RT, chemo in 35/29	3–4	55
Brkovich	19	No data	Res neck dz?	Cpl response at primary site	21	P	(C)RT, no details	3–4	58
Andrade [a]	28	85 % OC, OC. La	Any persistent locoregional dz?	28 consecutive pts after defin (C)RT	NA	R	CRT (58–80 Gy), all IMRT	2–4	58
Gourin [a]	17	All OP or La	Res neck dz?	Cpl response at primary site; planned ND	NA	R	CRT (68–72 Gy)	4	53

(continued)

Table 2.7 (continued)

Study	No. of patients	Primary site	Study purpose	Patient characteristics	Hemi necks	P/R	Mode of treatment	Stage	Median age (y)
Nayak [a]	43	95 % OC, OP. La	Res neck dz?	N2-3 dz after CRT (details unknown in 5; some pts also had brachy- or molecular therapy)	Not reported	R	CRT (64 ± 11 Gy; median, 68); 14 had IMRT	4	No details
Tan	48	90 % OP, La	Res neck dz?	Defin CRT	72	R	CRT (66–72 Gy)	4	No data
Yao	188	85 % OC. OP. La	Res dz primary or neck?	PET within 12 months after RT (128 defin (C)RT; 60 postop)	NA	R	128 defin (96 CRT, 32 RT only); 60 postop (4 CRT; 56 RT only)	1–4	57
Ong [a]	65	89 % OP, La	Res neck dz?	Defin CRT	84	R	CRT (66–72 Gy)	3–4	57

C chemo, *chemo* chemotherapy, *cpl* complete, *CRT* chemoradiotherapy, *defin* definitive, *dz* disease, *IMRT* intensity-modulated radiotherapy, *La* larynx, *NA* not applicable, *ND* neck dissection, *OC* oral cavity, *op* operation, *OP* oropharynx, *P* prospective, *postop* postoperative, *pts* patents, *R* retrospective, *res* residual, *RT* radiotherapy

[a] All patients underwent PET/CT

Table 2.8 Summary of published data: results

Study	PET or PET/CT	PET criteria	Gold standard	Median F/U after PET (months: range)	Index (%) [a]								Fraction of pts with pos primary site or heminecks (prevalence)	Δt from RT to PET (weeks: median or range)	Dedicated NM reader?
					Primary site				Necks						
					Sen	Spec	PPV	NPV	Spec	Sen	PPV	NPV			
Yao	Some PET/CT	Focal uptake	Bx. ND. clin F/U	No data	86	90	54	97	100	96	77	100	Primary: 19%; neck: 15%	No details ("most scans 3–6 month RT")	Yes
McCohmn	PET	2 NM physicians read scans as pos or neg; no details	Bx. ND. overt clin recurence	20 (16–31) [b]	100	65	27	100	67	53	46	73	3/26 (11%) after ICT; 9/37 (24%) after CRT	4–12	Yes
									67 [c]	57 [c]	33 [c]	84 [c]			
Ware	PET	Focal uptake > background: nonphysiologic	Bx, clin F/U	55									Locoregional 19/46 (51%)	>6 week alter op; >2 months after RT	Yes
Yao	Either	Focal uptake	Bx, clin F/U	26 (12–57)	– [d]	– [d]	– [d]	– [d]	100	94	43	100	Neck: 3/70(4%)	15 (5–29; 41% 12–20 weeks)	Yes
Porceddu	PET	Not specified	Bx, clin F/U	34	– [d]	– [d]	– [d]	– [d]	83	93	71	97	Neck: 6/39(15%)	12 (8–32; 39% 8–12 weeks)	Yes
Brkovich	PET	NM physician read scans as pos or neg	All had ND		– [d]	– [d]	– [d]	– [d]	76	65	33	92	Neck: 4/21 (19%)	9(7–12)	No
Andrade	PET/CT	Focal: moderate or intense	Bx, ND, clin F/U	17 (4.5–34)									Locoregional: 13/28(46%)	8 (4–16)	Yes

(continued)

Table 2.8 (continued)

Study	PET or PET/CT	PET criteria	Gold standard	Median F/U after PET (months: range)	Index (%) [a]								Fraction of pts with pos primary site or heminecks (prevalence)	Δt from RT to PET (weeks: median or range)	Dedicated NM reader?
					Primary site				Necks						
					Sen	Spec	PPV	NPV	Spec	Sen	PPV	NPV			
Gourin	PET/CT	Uptake "significantly higher than muscle or blood pool, fusing to lymph node on CT"	All had planned ND	NA	– [d]	– [d]	– [d]	– [d]	40	25	18	50	Neck: 5/17(29 %)	8–10	Yes
Nayak	PET/CT	"Radiologist impression"	ND. clin F/U	18 (5 minimum)	– [d]	– [d]	– [d]	– [d]	87	91	70	97	Neck: 10/43 (23 %)	8–26	Yes
Tan	PET	"Residual hypermetabolic uptake"	ND or clin F/U	20 (10–55)	– [d]	– [d]	– [d]	– [d]	25	83	15	90	Neck: 8/72(11 %)	10(5–22)	No (unclear)
Yao	Either	Focal uptake	ND. Bx. overt clin progression	29	86	86	32	99	86	97	70	98	Primary: 37/188 (20 %): neck: 14/188 (7.5 %)	15(5.1–44:74 % m 10–20 weeks)	Yes
Ong	PET/CT	Abnormal (nonphysiologic) focal uptake, fusing to nodes on CT	ND or clin F/U	37 (excluding DOD or RD: 43 months)	NA	95	NA	97	71	89	38	97	Neck: 7/84 (8 %)	12 (8–27)	Yes
									80 [e]	74 [e]	40 [e]	94 [e]			

Schöder et al. [57]

Bx biopsy, *clin* clinical, *CRT* chemoradiotherapy, *DOD* death of disease, *RD* recurrent disease, *Δt* time interval, *F/U* follow-up, *ICT* induction chemotherapy, *NA* not applicable, *ND* neck dissection, *neg* negative, *NM* nuclear medicine, *pos* positive, *pts* patients, *RT* radiotherapy, *sen* sensitivity, *spec* specificity

[a] Only locoregional index values were reported by Ware (PPV, 95 %; NPV. 83 %) and Andrade (sensitivity. 76 %: specificity. 93 %; PPV, 90 %; NPV, 82 %)

[b] Follow-up time for patients who had no neck dissection

[c] When considering ND and clinical follow-up

[d] Not reported or not primary objective

[e] Residual enlarged lymph node only

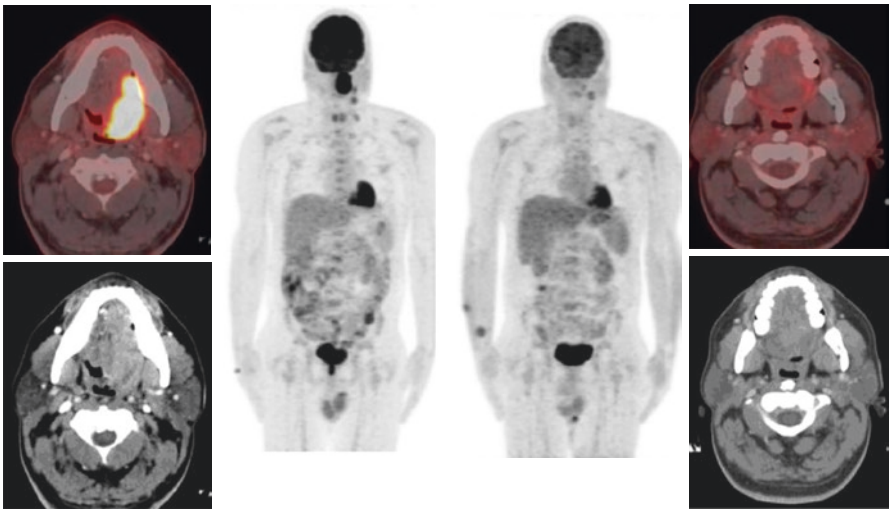


Fig. 2.36 The use of FDG PET CT at initial staging in a patient with a squamous cell carcinoma on the left base of the tongue. Twelve weeks after curative intent chemo-radiotherapy a second PET CT shows a complete metabolic response to therapy

Table 2.9 Studies evaluating the performance of 18 F-FDG PET and PET/CT for the detection of recurrent disease in head and neck cancers

Authors, year	Number of patients	Sensitivity	Specificity	Accuracy	Notes
Abgral et al. 2009	91	100 %	85 %	90 %	FDG PET/CT
					Prospective
Wang et al. 2009	44	100 %	98 %	98 %	PET performance > CT
Cermik et al. 2007	50	83 %	93 %		
Álvarez Pérez et al. 2007	60	98 %	90 %		Prospective
Salaun et al. 2007	30	100 %	95 %	97 %	
Goerres et al. 2004	26	91 %	93 %		Prospective
					Prospective
Kubota et al. 2004	36	90 %	78 %	81 %	Accuracy significantly higher than CT/MR

Review Article: Al-Ibraheem et al. [54]

Table 2.10 Studies evaluating the role of FDG PET and PET/CT in radiation planning

Authors, year	Number of patients	Study type	Results	Notes
Soto et al., 2008	61 (9 LRF)	Retrospective	8/9 LRF within BTV-PET	
Rothschild et al., 2007	45	Case-control analysis	PET/CT with IMRT improved cure rates	Advanced pharyngeal carcinoma
Wang et al., 2006	28	Prospective	PET/CT-based GTV significantly different from CT scans alone in 50 % of cases	PET/CT upgraded T and N stage in 18 p.
Breen et al., 2007	10		No significant differences in the GTVs between PET/CT and CT alone	CT volumes were larger than PET-CT
El-Bassiouni et al., 2007	25		PET/CT-based volume significantly smaller than CT.	
Koshy et al., 2005	36	Retrospective	TNM changed in 36 %, RT volume and dose changed in 14 %	
Heron et al., 2004	21	Prospective	PET/CT improves delineation of normal tissues from tumor areas	PET/CT improves staging
Ciernik et al., 2003	12HNC of 39	Retrospective	PET/CT changed GTV in 50 % compared to CT	
Nishioka et al., 2002	21		PET improves GTV, normal tissue sparing	PET alone

Review Article: Al-Ibraheem et al. [54]
IMRT intensity-modulated radiation therapy, *GTV* gross target volume, *BTV* biological target volume, *LRF* locoregional failure

Table 2.11 Change in gross tumor volume (GTV; >25 %): PET/CT vs CT

	Increased GTV (%)	Decreased GTV (%)
Head and neck	17	33
Lung	17	67
Pelvis	33	19

2.3 Conclusion (Table 2.12)

Table 2.12 Key benefits of 18F-FDG PET/CT for HNSCC

Clinical scenario	Benefit
Initial staging	Delineate extent of regional nodal metastases (radiotherapy target volumes and neck dissection choices may be significantly altered)
	Detect distant metastases
	Identify synchronous primary tumors
	Detect unknown primary tumor in patients with a squamous cell carcinoma neck metastasis
Monitoring therapy Surveillance	Accurately differentiate responders from nonresponders for salvage surgery
	Detect recurrence
	Detect metastatic disease
	Detect a second primary tumor

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General Principles and Management Guidelines in Oral Cancer

3

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3.1 Introduction

Clinicians have multiple options at every step in the comprehensive care of oral cancer from diagnosis, treatment, reconstruction, and rehabilitation and surveillance. To guide the clinicians to choose a specific management option, there exist several well-defined guidelines. As with any guidelines, the management options change constantly with improved understanding of cancer and varies with individual patient needs. Therefore, these guidelines though can give a generalized recommendation; it needs to be constantly updated and tailored to an individual patient. This individualized treatment plan is best through a multidisciplinary tumor board or clinic, which is the cornerstone of optimal oncology practice. Though individual clinicians have to take responsibility in the care of a specific aspect treatment, the overall care plan is best developed by the multidisciplinary team. This should be made before initiation of treatment.

This document outlines management options that are available for patients with different stage of tumor and at different time point during the overall care of the patients – diagnosis, primary treatment, adjuvant treatment, and surveillance. Each of these components of treatment is elaborated in detail during the subsequent chapters.

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3.2 Existing Guidelines for the Management of Oral Cancers

Evidence-based guidelines outlining optimal approaches to treatment of head and neck cancer have been established. National Comprehensive Cancer Network (NCCN) Practice Guidelines for Head and Neck [35], SIGN guidelines [13, 29], and EHNS-ESMO-ESTRO guidelines [21] are among the few. Tata Memorial Hospital in Mumbai [23] has developed an evidence-based management guideline for the management of head and neck cancers. ICMR has published guideline for the management of buccal mucosa cancers, and they are in process of developing guidelines for other subsites too [39].

NCCN clinical practice guidelines in oncology Head and Neck cancers The latest version is 2.2014 [35]. It has a section on cancers of the oral cavity. It is a consensus document of the authors regarding their views of the currently accepted approaches to the treatment. The authors have followed an algorithmic approach, which is comprehensive but at times complex and intricate. The section for oral cavity is divided into five branches; T1-2N0, T3N0,T1-3N1-3,T4A any N, and the very advanced group including T4B any N and unresectable nodal disease. Also there are further branches for follow-up strategy and recurrent disease. In oral cavity algorithm, there is category 1 recommendation (based upon high level of evidence, there is uniform NCCN consensus that the intervention is appropriate) only for adjuvant chemoradiotherapy in patients with extracapsular nodal spread or positive margins after surgery. All the other recommendations are category 2A (based upon lower level evidence, there is uniform consensus that the intervention is appropriate). This shows the lack of high-quality evidence especially in a surgically treated disease like oral cavity.

The latest version of the NCCN guidelines have recommended sentinel node biopsy (SNB) for T1T2 oral cancers in centers where expertise is available. There is no direct comparison of SNB with the practice of elective neck dissection. Hence, sufficient caution has to be exercised when offering it as an alternative to the elective neck procedure.

Tata Memorial Center, Mumbai, India [23], has published a very comprehensive document as guidelines in the management of head and neck cancers. It has sections giving the general principles as well as separate sections for each site and subsites. A descriptive approach is adopted. Though each recommendation is not specifically supported by cited references, important references are given as suggested reading.

EHNS-ESMO-ESTRO guidelines [21] provide a concise three-page guideline summarizing the diagnosis treatment and follow-up for head and neck cancers, but it is not specific for oral cavity.

Indian Council of Medical Research (ICMR) [39] has published a guideline for buccal mucosal cancer. Buccal mucosal cancer being more common in the Indian subcontinent, the document, gives an Indian perspective to the management of the cancer.

3.3 Diagnosis and Evaluation

Accurate mapping of the extend of involvement of surrounding structures such as the bone, deep musculature of the tongue, floor of the mouth, surrounding skin and soft tissue has to be done. Presence of regional lymph nodes and any synchronous second primary also has to be seen.

Pathological diagnosis should be confirmed with tissue biopsy. A fine-needle aspiration (FNA) should be done (ultrasound-guided FNA improves the accuracy and specificity) of suspected regional cervical metastases [26].

The clinical evaluation needs to be supplemented with imaging studies. The investigations for bony involvement can be orthopantomogram (OPG), computed tomographic scan (CT scan), or magnetic resonance imaging (MRI) scan. OPG is not preferred because a minimum of 30 % bone erosion is required to be detected. Moreover, it may not be the best for assessing the midline lesions of the mandible due to the overlap by the spine.

CT scan is better in demonstrating mandibular cortical involvement and the status of cervical lymph nodes [4, 19, 27]. MRI is preferred to assess the extent of involvement of soft tissue, skull base, and infratemporal fossa. It is also useful in radiotherapy planning and medullary bone involvement. Hence, CT scan is preferred in buccal mucosa cancer, while MRI is favored for tongue cancer. In early-stage lesions amenable to transoral excision with a clinically node-negative (confirmed by imaging) neck, ultrasound with or without FNA is the initial investigation of choice for the neck [12]. Ultrasound is also preferred for close observation and follow-up of the neck in patients who are lymph node negative [26].

The role of PET-CT scan in pretreatment assessment is limited. However, it is useful in assessing posttreatment residual/recurrent disease [14, 18, 26].

3.4 Staging of Cancer

Cancer treatment rarely needs to be initiated without confirming histologic diagnosis and staging. Well-established AJCC/UICC staging criteria can be used to categorize the patients into different groups that will dictate the treatment options (please see Vol. II, Chap. 1) [15]. However, on a practicing physician's perspective, the patients can be grouped into following categories:

Curative intent treatment group

1. T1, N0, M0
2. T2-T4a, N0, M0
3. T2-T4a, N1, M0
4. T2-T4a, N2,3, M0

Palliative intent treatment group

1. T4b, any N-stage, M0
2. Any T-stage, N3 with carotid or paraspinal muscle involvement
3. Any T-stage, any N-stage with M1
4. Any T-stage, any N-stage, any M-stage with poor performance status

3.5 Treatment Decision Algorithm

It is essential that a comprehensive treatment plan be made for every patient prior to initiating treatment. This however needs to be periodically reevaluated and modified during the course of treatment. This process requires formulation of several decision points based on the patient and tumor characteristics (Box 3.1).

The first treatment decision that needs to be made is to determine the intent of treatment – whether the treatment is directed with a curative or palliative intent. Though a large proportion of oral cavity cancers can be managed with curative intent, it may not be possible in patients presenting with either advanced state of disease or due to significant comorbidity. Within both the curative intent and the palliative intent group, there are multiple treatment options (Fig. 3.1), which will be discussed in the following section. The treatment decision has to be made for primary tumor, nodal disease, and adjuvant treatment.

3.5.1 Curative Intent Treatment

The treatment algorithm for oral cavity cancer is summarized in Fig. 3.2.

Box 3.1
Critical decisions to be made to formulate management strategy for oral cancer:

D1. What is the intent of treatment: curative or palliative?
D2. Should the primary treatment modality be surgery or radiation?
D3. Is it necessary to address the neck metastasis?
D4. What type of neck dissection in N0 neck?
D5. What type of neck dissection in N+ neck?
D6. Indications for adjuvant radiation
D7. Indications for adjuvant chemoradiation
D8. Is there any indication for induction chemotherapy?
D9. Is there indication for primary chemoradiotherapy?
D10. What is the best supportive care?

D: Decision

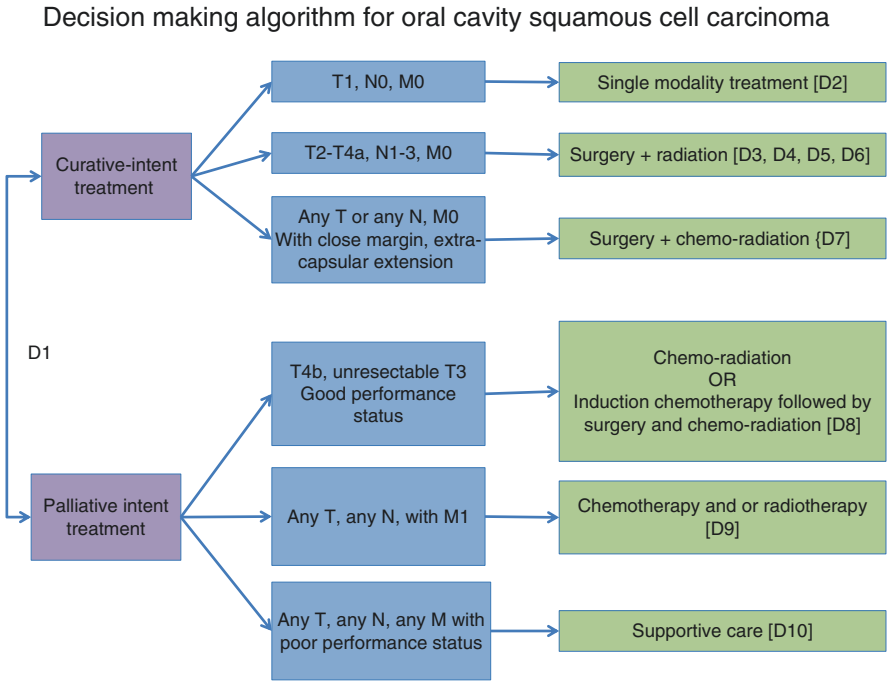

Fig. 3.1 General treatment decision-making algorithm in oral cancer [D-Decision]

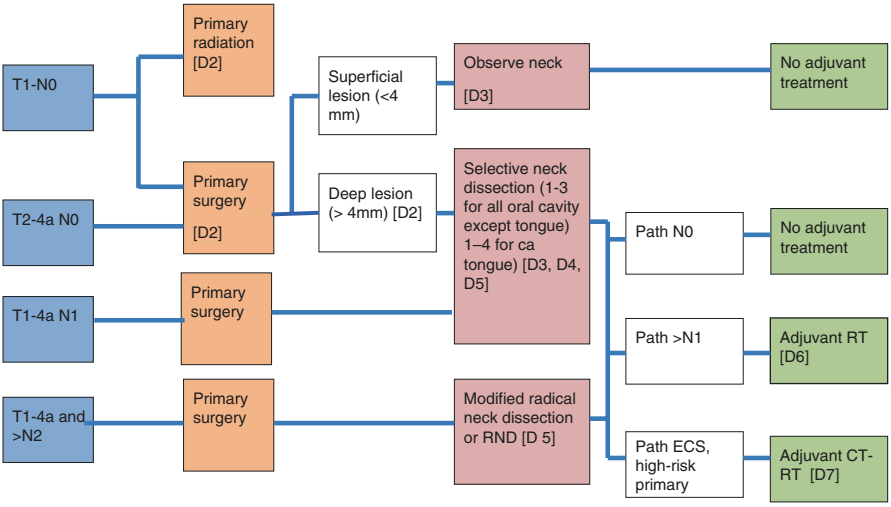

Fig. 3.2 Curative-intent treatment guidelines

3.5.1.1 Early-Stage Cancers with No Cervical Nodal Metastasis (T1, N0, M0)

Primary tumor: These cancers can be managed with a single modality treatment, either surgery or radiotherapy. The logic for this principle is that both the modalities can result in similar cure rates and more or less similar morbidity results. Surgery is preferred over radiotherapy as a single modality in sites where surgery is not morbid (cosmetically and functionally), lesions involving or close to bone; to prevent radionecrosis, young patients – possibility of a subsequent second primary and presence of submucous fibrosis (SMF). Radiotherapy is preferred over surgery as a single modality, where a severe impairment of function or cosmesis is likely with surgery, patient refuses surgery, or there is high risk for surgery [11]. The preferred modality may also vary according to the patient preferences and across the treatment centers. However, general surgery is the preferred choice of treatment of oral cavity with the exception of commissure of mouth and selected buccal mucosal cancers [9].

Management of node-negative neck: Management of clinically and radiologically node neck is controversial. In general, the neck needs to be addressed if the chances of occult metastasis are more than 20 % [41]. T1 buccal mucosa and T1T2 upper alveolus (gingiva) and T1T2 hard palate may qualify as having the chance of occult metastasis below 20 %. In advanced stages of these subsites and all stages of the remaining subsites, the neck needs to be addressed. However, there is a lack of good evidence defining the most appropriate treatment threshold. If primary is treated with surgery, the choice will be an elective neck dissection (END), and in cases where the primary is treated with radiotherapy, elective neck irradiation (ENI) is the choice. Also a cutoff tumor thickness of 4 mm [22] is also suggested as a threshold for addressing the neck. Perhaps the greatest limitation to use the 4 mm tumor thickness cutoff is the difficulty to obtain this information preoperatively, reliably, and in a cost-effective manner.

In a surgically treated case, the management options for dealing the clinically and radiologically negative neck include observation or elective neck dissection. Sentinel node biopsy is an upcoming strategy in between, but considering the evidence available, it may still have to be considered as an investigational tool.

The criteria for the levels of neck nodes that need to be cleared is well defined (ref). Elective selective neck dissection levels I–III are recommended for oral cavity primary. Level IV may be included in oral tongue tumors considering the possibility of isolated "skip metastasis" in level IV [6]. But this is controversial [2, 17]. Advanced tumors of tongue, floor of mouth, and lip, especially those crossing the midline, will require contralateral selective neck dissection in addition.

In summary, since oral cancer has a high propensity for nodal metastasis, the neck needs to be addressed in majority of patients. Using a decision-tree algorithm, balancing morbidity and benefits, Weiss MH et al. [41] have determined that in cancer of oral cavity, if surgery is chosen as treatment option, elective neck dissection should be performed if the risk of occult metastasis is over 20 %. Though

several clinic-pathologic factors have been evaluated to determine the tumors with high propensity for occult metastasis [8], depth of invasion of over 4 mm is determined as the single most important factor that correlates with occult nodal metastasis [32]. However, it has been shown in a large prospective randomized trial that in patients with T1, T2 oral cavity cancers, elective neck dissection has significant survival advantage over wait-and-watch policy [10]. Therefore, all but superficial tumors should be managed by elective neck dissection.

Based on the pattern of node metastasis, the type of neck dissection can be planned. In patients with all tumors other than tongue, they should be managed by selective neck dissection levels 1 to 3. For carcinoma of tongue, additional level 4 needs to be removed [2, 38, 43]. There were discussion about avoiding level 2b (supraspinal) group of nodes to minimize the risk of accessory nerve injury [16]. The current status of sentinel node dissection is discussed in other chapter. As of now, there is no strong evidence for or against sentinel node biopsy in oral cancer with potential occult metastasis [20, 36, 42].

3.5.1.2 Oral Cancer with Clinically Positive Neck Disease (T2-T4a, N1/N >2, M0)

These tumors are managed with a combined modality approach. In oral cavity cancers, the preferred option would be surgery followed by adjuvant therapy, which can be either radiotherapy or chemoradiotherapy depending on the risk factors identified on the surgical specimen [30].

3.5.2 Treatment of Primary Tumor

Surgery involves the excision of the tumor with adequate three-dimensional margins, management of the neck, and appropriate reconstruction. Adequate resection is generally defined as the one that is done to obtain adequate clearance of the tumor all around. In oral cavity, at least 1 cm of the normal and palpable mucosa and 1 cm of the soft tissue in the third dimension is taken. This can be confirmed on frozen section and on specimen pathology. A clear margin is when there is 5 mm or more measurable distance between the tumor and the resection edge. A close margin is when there is between 1 and 5 mm, and a positive margin is when there is tumor at the cut edge or less than 5 mm distance between the tumor and the resection edge [44]. But this may not be applicable universally across the oral subsites due to anatomical reasons [40]. Oral tongue, being a muscular organ, this three-dimensional concept of margins beyond the tumor is easily applicable, but in other subsites, being closer to bone, a concept based on the anatomical layers [31] have to be applied. A normal tissue layer beyond the involved anatomical layer may be considered as adequate. This may involve the resection of a margin or segment of the mandible or maxillary bone as appropriate.

Management of mandible [5]*:* When the tumor is close to or involving the mandible, a margin or a segment of the mandible needs to be resected.

Indications for marginal mandibulectomy:

1. Whenever tumor is close or abutting, the mandible has to achieve adequate margin.
2. Limited superficial bony erosion.
3. Limited periosteal invasion.

A minimum of 1 cm of inferior rim of the mandible needs to be retained.
Contraindications of marginal mandibulectomy:

1. Edentulous mandible in an elderly individual
2. Post-radiotherapy cases
3. Gross cortical and medullary involvement of the mandible
4. Gross paramandibular involvement of the tumor

Indications for segmental mandibulectomy:

1. Gross tumor invading the mandible
2. Prior radiotherapy
3. Edentulous mandible
4. Gross paramandibular disease

Management of the skin: Skin involvement classifies as T4a disease. In situations where the tumor is either invading toward or involving the skin, resection of 1–2 cm of normal skin abutting the tumor is required [25].

3.5.2.1 Management of N-Positive Neck

The clinical and radiologic criteria of cervical nodes are well defined. These include the following.

1. Size criteria:
   (a) >10 mm in short axis
   (b) Level I nodes >15 mm in short axis
   (c) Retropharyngeal nodes: >8 mm in short axis
   Size criteria alone
2. Size-independent criteria
   (a) Loss of fatty hilum
   (b) Central necrosis
   (c) Cystic nodes
   It has been shown that size criteria alone can result in an error rate of 10–20 %. As more spherical nodes are likely to be metastatic, long-to-short axis ratio has been proposed. When the nodes have a ratio of >2 (elongated nodes), majority of the nodes will be benign. If the ratio is <2 (spherical nodes), it is likely to be metastatic [39].

3.5.2.2 Management of Node-Positive Neck

A node-positive neck requires a comprehensive neck dissection including levels I–V (MRND). The non-lymphatic structures (spinal accessory nerve, internal jugular vein, and sternomastoid muscle) have to be preserved if not involved [35].

With the improved understanding of the pattern of cervical node metastasis, it has been even in cervical node positive patients, the tumor rarely metastasize to level 5. Moreover, level 5 metastasis is even rarer without tumor metastasis to level 4. Based on these findings in patients with N1 neck state, selective levels 1–3 for all oral cavity cancer is proven to be effective, with the exception that oral tongue cancer needs levels 1–4 dissection.

3.5.2.3 Management of the Contralateral Neck

Contralateral node-positive neck will require a comprehensive neck dissection. Contralateral node-negative neck needs to be addressed prophylactically with a selective neck dissection in large midline lesions or lesions crossing over the midline to involve the opposite side [7].

The conventional recommendation for any patients with clinically and radiologically node-positive disease is to undertake modified radical neck dissection clearing levels 1–5.

Principles of reconstruction are dealt separately in subsequent chapters.

3.5.2.4 Principles of Radiotherapy

Primary radiotherapy [24, 28, 33, 45]: Early-stage cancers of the oral cavity [lip, floor of the mouth, and retromandibular triangle] are curable by surgery or radiation therapy. Radical radiotherapy is used in treating T1 or T2 tumors with proliferative component, where the functional or cosmetic result is likely to be better, with similar chances of local control and survival.

Radiation therapy can be administered by external-beam radiation therapy (EBRT) or interstitial implantation alone. Small superficial tumors away from bone may be treated with interstitial brachytherapy alone, while for tumors more than 2 cm, usually both the modalities are combined. The addition of brachytherapy to EBRT has shown to improve the results compared to EBRT alone, but the time interval between them has to be as short as possible. Increasing the overall treatment time has shown to affect the treatment outcome adversely. When brachytherapy is used alone, the recommended dose is 66–70 Gy with LDR brachytherapy and 45–60 Gy with 3–6 Gy per fraction with HDR brachytherapy. When EBRT is used alone, the dose is 66–70 Gy in conventional fractionation over 6–7 weeks, or hypofractionated RT 5250 cGy in 15 fractions over 3 weeks. When the modalities are combined, 45–50 Gy is given initially with conventional fractionation to the primary site and nodal stations with EBRT. This is followed by brachytherapy boost to the primary tumor site with margins with a dose of 25–30 Gy with LDR or 21 Gy in 3 fractions with HDR brachytherapy.

3.5.3 Adjuvant Treatment

Postsurgical adjuvant treatment options depend on whether adverse features are present on pathology.

Indications of adjuvant radiotherapy [1, 34]:

1. Advanced T-stage (T3/T4)
2. Presence of lymphovascular invasion
3. Presence of perineural invasion
4. Positive surgical margins
5. Multiple lymph node involvement
6. Extracapsular nodal extension

Indications of adjuvant chemoradiotherapy [3]:

1. Positive tumor margins
2. Extracapsular nodal extension

For patients with positive surgical margins, management options include (1) re-resection or (2) chemoradiotherapy.

In adjuvant setting, postoperative adjuvant EBRT is given in conventional fractionation, with a dose of 60Gy in 30 fractions to the surgical bed and first echelon nodal stations, while the low-risk nodal stations are treated with 50–54 Gy in conventional fractionation. In case of high-risk features like perinodal spread or positive or close margins, patients are treated with concurrent chemoradiation, and the high-risk regions are treated to a total dose of 66Gy.

3.5.4 Palliative Intent Treatment

Two factors that are critical in triaging a patient from curative intent treatment to palliative intent treatment are resectability of tumor and performance status of the patient.

3.5.4.1 Assessment of Resectability [46]

The criteria for resectability of a tumor may vary according to the surgical expertise and reconstructive backup. But in general, tumor involvement of the following structures is considered technically unresectable in a squamous cell carcinoma of the oral cavity.

(a) Erosion of skull base, sphenoid bone, and widening of foramen ovale
(b) Encasement of internal carotid artery, defined radiologically as tumor surrounding the carotids >270° [47].
(c) Involvement of mediastinal structures
(d) Involvement of prevertebral fascia or cervical vertebrae

3.5.4.2 Assessment of Performance Status

Performance status is an independent predictor of disease outcome in oral cavity cancers [37]. It can be determined by standardized clinical criteria (Box 3.2). It must be noted that though these scoring system was developed primarily to determine tolerability of patients to chemotherapy, it is effective in assessing general health status of a patient.

Unlike curative intent treatment, in patients with very advanced locoregional disease, clinicians do not have strong evidence-based treatment recommendation. Figure 3.3 outlines a proposed practical management guideline, which is not based on strong evidence from literature.

Box 3.2: Performance Score

Karnofsky score

100 – Normal, no evidence of disease
90 – Able to carry out normal activity, minor signs or symptoms of disease
80 – Can undertake normal activity with effort, some signs or symptoms of disease
70 – Unable to carryout normal activity or to do active work, but cares for self
60 – Able to care for personal needs, but require occasional assistance
50 – Require considerable assistance and frequent medical care
40 – Disabled, requires special care and assistance
30 – Severely disabled, hospital admission is indicated, but death not imminent
20 – Very sick, hospital admission is necessary, active supportive treatment necessary
10 – Moribund, fatal processes progressing rapidly
0 – Death

ECOG/WHO/Zubrod score

0 – Asymptomatic
1 – Symptomatic but completely ambulatory
2 – Symptomatic, less than 50 % in bed during the day
3 – Symptomatic, but more than 50 % in bed, but not bedbound
4 – Bedbound
5 – Death

Comparison of Karnofsky and Zubrod scores

Zubrod 0–1 equals Karnofsky 80–100.
Zubrod 2 equals Karnofsky 60–70.
Zubrod 3–4 equals Karnofsky 10–50.

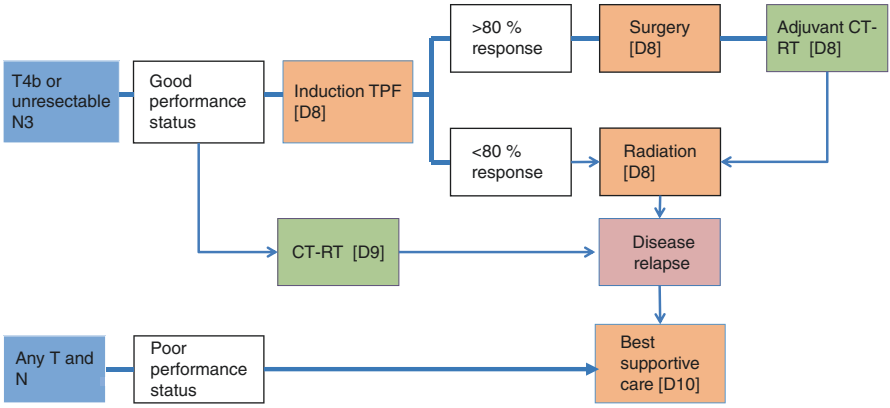

Fig. 3.3 Palliative-intent treatment guideline

3.6 Surveillance

All patients should have regular follow-up visits to assess the symptoms and tumor recurrence. Dental evaluation, speech and swallowing evaluation, and rehabilitation should be a part of the follow-up.

3.7 Management of the Recurrences

Surgically resectable primary recurrences should be re-resected with a curative intent. Neck recurrences in an untreated neck should be treated with neck dissection. Recurrence in an already treated area of the primary and neck has to be resected if possible. If no prior radiotherapy has been given, adjuvant radiotherapy has to be considered. Re-irradiation should be considered only in very selected cases after concurrence from a multidisciplinary tumor board.

Conclusions

There is a wide geographical variation in the incidence of oral cancer. The most important risk factor is the tobacco consumption. Ultrasonography, preferably with guided FNAC, is the preferred imaging modality in early stage tumors. Advanced stages will require contrast-enhanced CT scan or MRI scan. PET-CT scan is helpful in detecting recurrences and distant metastases. Though early-stage cancers can be treated with single modality, either surgery or radiotherapy, surgery is preferred. Advanced stages will require surgery followed by radiotherapy or chemoradiotherapy depending on the risk status. Elective neck dissection is warranted in clinically negative cervical lymph nodes with thick tumors.

A comprehensive neck dissection removing I–V neck nodal levels is preferred in node-positive neck. There is no direct comparison between sentinel node biopsy and elective neck dissection strategies, and hence its application should be guarded. Well-established guidelines exist to help make individualized treatment decisions for a particular patient in a multidisciplinary tumor board.

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Radiotherapy in the Management of Carcinoma of the Oral Cavity

4

Michael Mix and Anurag K. Singh

4.1 Introduction

Treatment of advanced head and neck malignancies is generally a combined modality approach, often requiring surgery, radiotherapy, and chemotherapy to obtain the best control rates. Oral cavity cancers follow this paradigm. While certain head and neck sites (e.g., oropharynx, larynx) have experienced drastic shifts toward non-operative management, the oral cavity largely remains a surgical disease. Radiotherapy is frequently used in the adjuvant setting, to improve both local-regional control and survival. The overarching paradigm is for surgical resection followed by adjuvant therapy based on the presence of adverse pathologic features. Not all patients, however, are able or willing to undergo surgery; consequently, certain cases may be managed with (chemo- and/or) radiotherapy alone. This chapter will briefly review the use of radiation therapy in the treatment of oral cavity cancers.

4.2 History and Evolution of Radiotherapy in the Oral Cavity

4.2.1 Origins of Radiotherapy in the Oral Cavity

Historically, surgery has been the mainstay of oral cavity cancer treatment. However, surgery alone is often unable to obtain complete local control making the combination of surgery followed by radiation an attractive approach. Fletcher et al. showed that those managed with surgery alone exhibited failure rates between 38 and 73 %, while those managed with combined modality treatment failed at a rate of 18 % [1].

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Also, reports were published detailing the results of treatment with radiotherapy (RT) alone. Delclos et al. reported a series of 46 patients with cancers of the floor of mouth (FOM) or oral tongue (OT) treated with either interstitial brachytherapy (BT) alone, or with the addition of external beam radiation therapy (EBRT) [2]. Low-dose rate (LDR) needles were used, with either iridium or radium isotopes. A few patients received gold grain implants. Perhaps most importantly, the results of this experience detail the decreased rates of necrosis (soft tissue or bone) relative to historical controls. The authors attributed this decrease to the advent of computer dosimetry in 1961. This allowed a more complex and precise evaluation of dose distribution among tissues. This ability to more closely model and sculpt radiation dose heralded an important era in radiation oncology, one where an emphasis on treatment planning, accurate dosimetry, and plan evaluation was recognized to be vital to improving outcomes and decreasing morbidity.

4.2.2 External Beam Radiation Therapy (EBRT) and Brachytherapy (BT)

Radiotherapy is broadly categorized into two categories: teletherapy, or external beam radiotherapy (EBRT), and brachytherapy (BT). EBRT involves directing a beam of radiation (photons or particles) from an external source toward and through the patient. The beam is generally shaped to conform to the target outline, while sparing adjacent normal tissues as much as possible. This technique has seen dramatic evolution over the years. The original teletherapy units contained a radioactive source (e.g., Cobalt-60) in a state of constant decay, which was only opened once the patient and the gantry were in position. This predated the linear accelerator, which does not contain an active source. Linear accelerators generate a high energy beam of electrons which strike a metallic target (e.g., tungsten); the energy lost as the electron slows in the metal causes the production of x-ray photons (a process called bremsstrahlung) which can be shaped to create the desired beam. Alternatively, the target can be removed from the beam path to use the electrons themselves for therapy. Compared to cobalt machines, linear accelerators have the advantages of not requiring source changes, and the ability to vary the energy of the beam which has implications for depth of treatment. This comes at the cost, however, of a more complicated mechanism more prone to breakdown. Other forms of teletherapy do exist, including low-energy units (kilovoltage range) designed to treat superficial tumors. Finally, more advanced cobalt-based devices are available for cranial radiosurgery and for MRI-based treatments. These will not be discussed further, as they are beyond the scope of the chapter.

Brachytherapy, from the Greek word *brachys* meaning short distance, refers to the treatment with radiotherapy from within the patient, generally with small radioactive sources. Brachytherapy is further divided into interstitial and intracavitary types. Interstitial refers to the placement of sources directly into the tissue scheduled to be irradiated either directly, or via applicators (e.g., catheters), which is known as afterloading. Intracavitary BT refers to the utilization of natural anatomical cavities for treatment (e.g., cervix, bronchus, etc). This chapter will contain no further discussion of the latter.

LDR devices can generally be handled by clinicians during the brief period of implantation, but often require as long as 72 h to deliver the prescribed dose. High dose rate (HDR) sources are not considered safe to be handled; thus, they have to be delivered with an afterloading system. This has the advantage of much quicker treatment times, but generally requires multiple fractions of therapy, with the implants/catheters remaining in place during the intervening time. Medium-dose rate BT is not widely favored, because it tends to introduce the disadvantages of both of the prior groups, rendering it unsafe to manual manipulation and inconvenient for fractionated dosing.

For many years, interstitial BT utilized primarily LDR radium needles. The shape and rigidity of the needle-shaped radium sources impeded safety as the size and the complexity of the target increased. As noted above, the advent of computerized dosimetry helped provide a greater understanding of the true dose being delivered, but could not mitigate the physical limitations of the sources themselves. Proposed in the late 1950s and starting in the early 1970s, iridium-192 HDR sources began to gain popularity. A report from Wang et al. details the early use of modern catheter-based Ir-192 HDR BT in the oral cavity, as well other sites [3]. They utilized vascular catheters, which were placed directly into the tissue using the needles contained within the catheters for penetration.

4.2.3 Commonly Used Tools in Radiation Therapy of the Oral Cavity

Delivery of radiotherapy is a complex process that goes beyond the technical aspects involved in generating the treatment beam itself. Patient positioning, immobilization, and the ability to recreate the treatment environment accurately over a prolonged course (up to 7 weeks) are vital factors for safe and effective treatment. During simulation, a thermoplastic mask (Fig. 4.1) is created, which serves to both immobilize

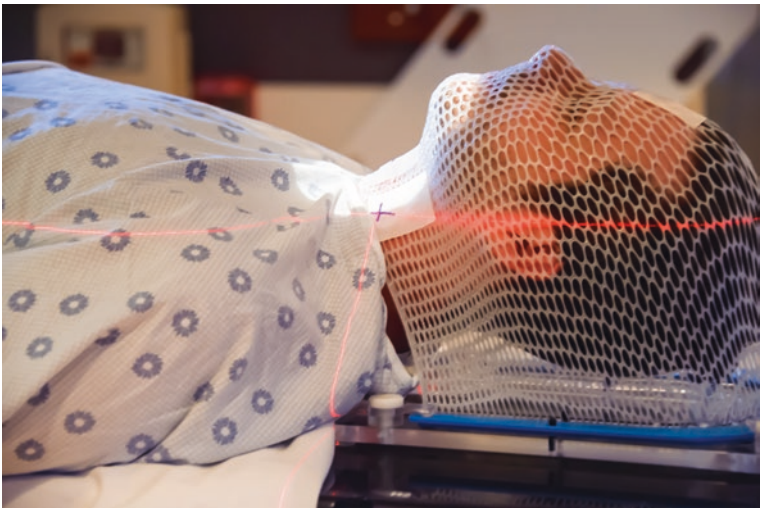

Fig. 4.1 Patient in position with thermoplastic mask used for immobilization. Multiple lasers are used for verification of proper isocenter and patient alignment

the patient during treatment and ensure the patient's position on the treatment couch is consistent from fraction to fraction. The mask also obviates the need for skin marks or tattoos, which are the typical landmarks used for alignment with the lasers in the treatment vault. "Vault" and other common terms are shown in (Table 4.1).

Table 4.1 Glossary of commonly used terms in radiation oncology

Dosimetry	Measurement and calculation of absorbed dose delivered during delivery of ionized radiation; also a professional field dedicated to the task of radiation planning
Interstitial brachytherapy	Treatment where radioactive sources, or catheters, which will serve as passageway for sources, are implanted directly into tumor and/or surrounding tissue – treatment is from within
Teletherapy	Treatment from outside the body, a beam of radiation is directed at the target (a.k.a. external beam radiation)
Gantry	Mobile head of a teletherapy unit, rotates into position prior to delivering radiation toward target
Linear accelerator	Modern teletherapy unit, uses large-voltage potential to create beam of electrons or x-rays
Collimation	The process of modifying a beam of radiation to achieve a desired shape, generally conformal to the target
Gray	Unit of absorbed dose, with which radiation is typically prescribed. 1 Gy = 1 joule absorbed by 1 kg of matter
Low-dose rate (LDR)	Refers to brachytherapy in which the dose delivered does not exceed a rate of 2 cGy/min
High-dose rate (HDR)	Refers to brachytherapy in which the dose delivered exceeds a rate of 20 cGy/min
Fractionation	The process of splitting a dose of radiation into multiple smaller treatments, generally with the goal of allowing adequate healing time for irradiated normal tissue
Simulation	Pretreatment procedure where the patient is aligned and positioned akin to treatment, so images and measurements can be obtained necessary for the planning process
Couch	Flat surface on which the patient lies, under the treatment unit. Capable of moving in all directions, brings patient into position under the treatment beam
Vault	Treatment room specifically engineered to contain the high-energy radiation used in modern radiation treatments. Often contains several feet of cement, lead, and other materials to achieve appropriate shielding
Wedge	A tool placed in the gantry, in the beam path, meant to create an uneven beam to compensate for irregular thickness. The goal is to create a homogenous dose distribution within the patient
Multi-leaf collimator (MLC)	An apparatus within the gantry capable of producing customized beam shapes through the movement of multiple small "leaves"
Three-dimensional conformal radiation therapy	Type of planning using CT images obtained during simulation. Allows for delineation of targets and organs in three dimensions, leading to volume-based planning
Intensity-modulated radiotherapy	An advanced technique designed to minimize dose to normal structures surrounding the target. This is accomplished by modulating the position of the MLC leaves during treatment delivery, creating a nonuniform dose distribution

Table 4.1 (continued)

Isocenter	Point in patient around which the treatment gantry rotates. Generally corresponds to alignment marks placed on patient during simulation
Portal images	Images taken by treatment unit, used to verify patient's position prior to radiation delivery
On-board Imaging (OBI)	Modern addition to linear accelerator, capable of producing high-quality images of patient on the treatment couch
Image-guided radiation therapy (IGRT)	Refers to the use of OBI to more precisely verify patient's position on treatment couch, prior to complex treatment delivery
Radiation therapist	Medical professional with expertise in patient setup and delivery of daily radiation treatments prescribed by physician
Stereotactic body radiation therapy (SBRT)	Highly conformal radiation treatment given in no more than 1–5 fractions, referring to non-cranial targets
Altered fractionation	Radiation regimen that deviates from conventional/standard fractionation (i.e., 1.8–2.0 Gy per fraction, per day). Common examples include accelerated, hyper-, hypo-, and concomitant boost fractionation
Boost	A term used to denote additional dose beyond that already given, usually implying a smaller field as well

Fig. 4.2 Examples of intraoral devices used for positioning, shielding, or immobilization of the oral cavity. Devices are made prior to simulation and remain in place during every fraction, ensuring reproducibility

Intraoral devices are often used for treatment of certain head and neck malignancies, especially those of the oral cavity (Fig. 4.2). They can accomplish one of two goals with regard to enhancing normal tissue sparing. Shielding and positional devices serve to attenuate radiation and displace normal tissue from the field, respectively [4]. These are typically designed as a collaborative effort between the radiation oncologist and dentist. A common example of a positioning device is an intraoral stent used to depress the tongue and mandible. This is particularly useful for treatment of the hard palate, where the tongue and lower oral cavity is not meant to be targeted. Without said device, the thermoplastic mask would be created for the patient with a closed jaw, leaving the oral tongue in close juxtaposition with the hard palate. Shielding devices are made from photon-attenuating materials (e.g., Cerrobend), which will serve to shield normal tissues from high doses of radiation, if not desired to be included as target tissue.

4.2.4 Three-Dimensional Radiation Therapy and Intensity-Modulated Radiation Therapy

The ability to use tools to modulate the beam to better cover the tumor (e.g., wedges, blocking) allowed for patient- and plan-specific beam design. The mechanical feature that was perhaps the biggest leap forward in beam shaping was the multi-leaf collimator (MLC). This is a device that allowed automated, custom beam shaping. It consists of multiple leaves that travel parallel to one another and meet on a central perpendicular axis (Fig. 4.3). This obviated the need for creating custom blocks for the corners of fields, which was very time and labor intensive. A parallel development was that of three-dimensional radiation therapy (3DRT). This is a process of simulation, planning, and treatment based on 3D images (i.e., stacked CT slices). The ability to devise and create radiation plans on a 3D image set allowed for delineation of volumes and evaluation of dose to a volume. Combining the 3D planning and the aforementioned MLC leads to one of our modern standards, three-dimensional conformal radiation therapy, or 3DCRT. By prescribing dose to a volume, it is possible to ensure adequate coverage to the entire target volume (i.e., tumor), as opposed to calculating dose to a point within the center of the tumor, which was the norm with two-dimensional radiation therapy.

With the above technique, a dose is prescribed to a volume, and the resulting radiation plan is evaluated in terms of target coverage, and dose to adjacent critical structures. This is known as forward planning. Since the advent of computer dosimetry in the 1960s, we have developed increasingly complex uses for computation in the treatment planning process. Intensity-modulated radiation therapy (IMRT)

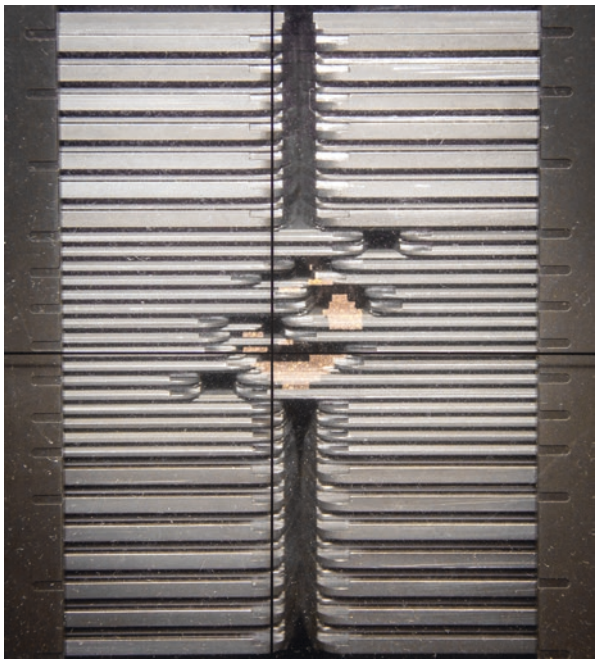

Fig. 4.3 Multi-leaf collimator. Multiple small leaves conform to desired shape, or move during treatment delivery to create a modulated field

represents a dramatic advance. IMRT is a marriage of two distinct processes. The first is inverse planning. Contrary to forward planning, inverse planning specifies the desired dose for a treatment volume and identifies dose limits to adjacent critical structures. A computer-based optimization algorithm subsequently modulates the intensity of the delivered beams in an effort to achieve the prescribed dose constraints (both target and organ). The modulation is affected by dynamic action from the MLC. In other words, the conformation of the MLC during the delivery of radiation for a given field is not steady. This allows different areas of the same radiation field to receive more or less dose (i.e., dose modulation). The end result of these processes is the ability to create bends in the delivered dose distribution (Fig. 4.4).

IMRT has been widely adopted for treatment in head and neck cancers due to this ability to dose escalate while achieving improved normal tissue sparing. Using IMRT postoperatively for oral cavity squamous cell carcinoma (OCSCC), Gomez et al. reported 3-year estimates of 77 %, 85 %, 64 %, and 74 % for locoregional progression-free survival (PFS), distant metastasis-free survival (DMFS), disease-free survival (DFS), and overall survival (OS), respectively. Trismus and osteoradionecrosis (ORN) were noted in 17 % and 5 %, respectively [5]. Similarly, Chen et al. compared outcomes of 49 stage III and IV OCSCC patients treated with either postoperative IMRT or conventional radiotherapy. At 3 years, the OS was comparable, and acute toxicities did not differ. Late toxicity appeared to be significantly reduced by the use of IMRT, 36 % vs. 82 % for xerostomia and 21 % vs. 59 % for dysphagia [6]. Chen et al. published a second report looking at IMRT use in their postoperative oral cavity patients from 2005 to 2008 and reported increased 3-year locoregional control (76 % vs. 54 %) and disease-free survival rate (70 % vs. 48 %) for IMRT and conventional RT, respectively [7]. Daly et al. reported on 37 patients undergoing IMRT for OCSCC (30 postoperative, 7 definitive). They reported 3-year actuarial estimates of local control (67 %), locoregional control (53 %), freedom from distant metastasis (81 %), and OS (60 %) among postoperative patients. The

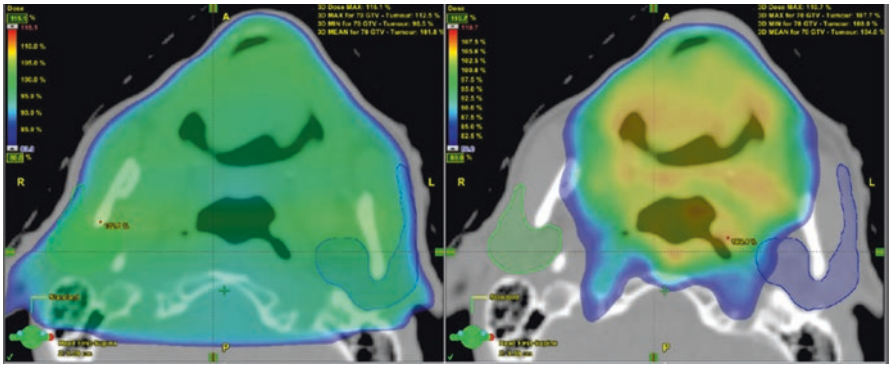

Fig. 4.4 *Left*: dose distribution typical of 3DCRT plan. Note the posterior edge of the radiation field is roughly linear, correlating with the designed field blocking. The parotid tissue (outlined in *green*/*blue*) is receiving full dose. *Right*: dose distribution typical of IMRT plan. The dose is sculpted to conform to the target tissues, while sparing the parotid glands

authors highlighted the balance required between target delineation and organ sparing. Their cohort experienced a few marginal misses, which led them to emphasize the importance of target delineation and perhaps dose intensification [8].

A multicenter randomized phase III trial performed in the United Kingdom was published in 2011. This study included only patients with SCC of the pharynx, but was effective in showing xerostomia could be effectively reduced. At 24 months, grade 2 or worse xerostomia was seen in 83 % of patients receiving conventional radiation vs. 29 % in those receiving parotid-sparing IMRT. The authors concluded that the results were likely generalizable to all head and neck cancer sites [9]. Another multicenter prospective trial from Europe allowed multiple head and neck subsites, including 24 patients with oral cancer. Two-year locoregional control and overall survival were 86 % and 86.7 %, respectively. Reduced rates of xerostomia relative to historical controls were seen as well. The authors concluded that IMRT was capable of reducing late side effects without compromising local control or survival [10].

Studer et al. retrospectively analyzed the outcomes of 160 oral cavity patients treated with IMRT between 2002 and 2011. One hundred twenty-two were treated primarily with radiation, while 38 were referred for recurrence, at least 3 months after surgery alone. Seventy-two percent of patients received concomitant chemotherapy. Patients who received IMRT as primary treatment or postoperative IMRT with macroscopic residual disease had significantly poorer outcomes compared with those receiving IMRT after a R0–1 resection. Three-year local control rates and overall survival rates were 35–37 % vs. 80 % and 30–37 % vs. 80 %, respectively. Patients with T1 tumor status post resection exhibited 100 % 4-year locoregional control (LRC), and T2-T4 had LRC rates of 70–80 %. In stark contrast, all T-stages of patients treated with primary radiation had 4-year LRC rates of 30–40 % [11]. This suggests IMRT is not a substitute for resection.

In one of the largest pure OCSCC populations reported, Chan et al. published outcomes on postoperative patients who received IMRT with or without concurrent chemotherapy. Two-year OS and LRC were 65 % and 78 %, respectively. Thirty-eight patients experienced locoregional failures. Of these, 26 were in-field, 7 were marginal, and 5 were out of field. Locoregional failures occurred in six patients receiving ipsilateral neck irradiation, one patient receiving primary site irradiation only, and five patients receiving bilateral neck irradiation [12]. These results again emphasize the importance of careful target delineation and thorough consideration of chosen elective neck volumes. Having the power to spare normal tissue must be carefully weighed with the risk of marginal/out-of-field failures. Additional small series have demonstrated comparable rates of locoregional failure, further supporting routine use of IMRT in the postoperative setting [13].

4.2.5 Image-Guided Radiation Therapy

The ability to tailor dose delivery to irregularly shaped targets while achieving rapid dose falloff carries with it the responsibility of delivering the planned treatment accurately. Advances in dose delivery have paralleled advances in real-time imaging during radiation therapy.

A significant advance was made with the introduction of on-board imaging (Fig. 4.5). The acquired images can be compared side by side or overlaid with simulation planning images. The physician is capable of making real-time shifts of the patient's position on the treatment table, immediately prior to the therapy being delivered (Fig. 4.6). This on-the-spot, physician-approved, verification process is known as image-guided radiation therapy (IGRT). More complex on-board imaging modalities are now available as well,

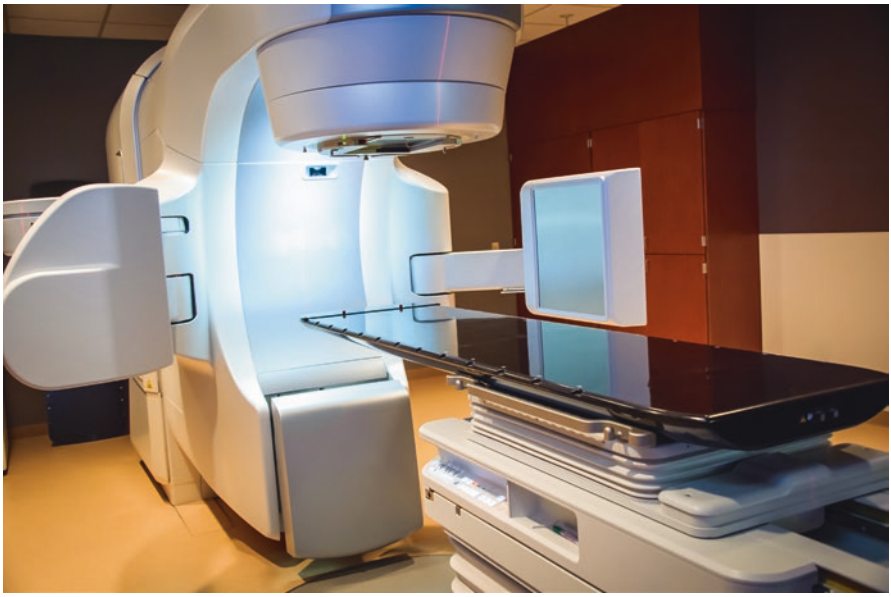

Fig. 4.5 Modern linear accelerator with imaging arms extended (OBI). They are capable of obtaining X-rays vital for patient setup. By rotating 360°, the imaging arms are capable of producing a CT image set

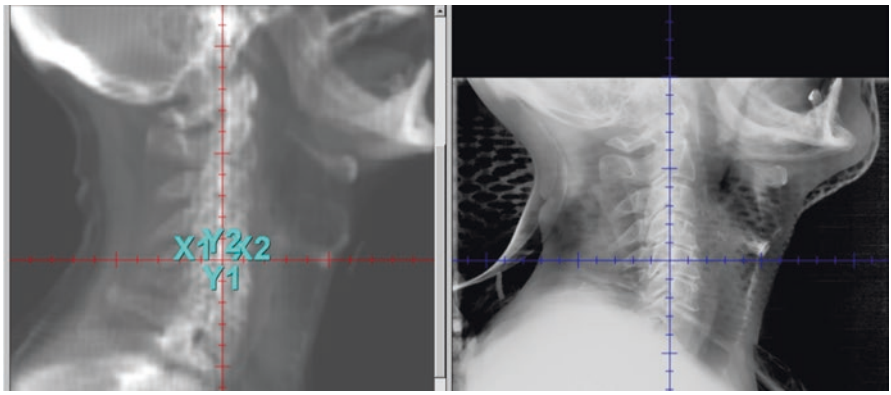

Fig. 4.6 *Left*: digitally reconstructed radiograph generated from the simulation CT images. *Right*: X-ray film taken by the linear accelerator, with the patient in the treatment position. The two images are compared to ensure positional accuracy, and shifts are made in real time if necessary

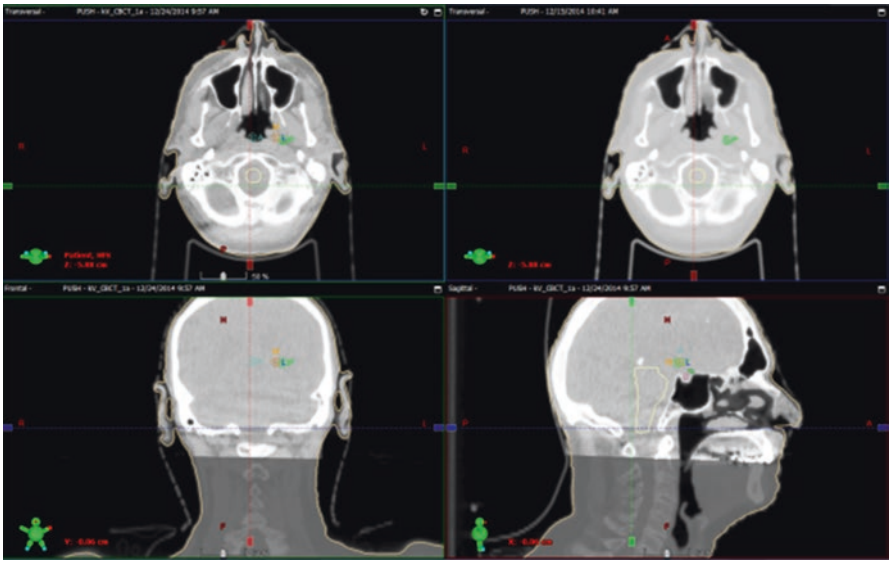

Fig. 4.7 Functional comparison of CT scan acquired by linear accelerator and simulation-acquired CT scan. This process allows for three-dimensional shifts prior to treatment, a process known as IGRT

including CT scans (Fig. 4.7), fluoroscopy, and fiducial-guided tumor/target tracking. These processes have become vital to the delivery of more complex, and higher dose-per-fraction treatments. A study looking at daily patient realignment data for head and neck treatment analyzed different IGRT protocols. When IGRT is used only 15–30 % of the time during treatment, errors of 3 mm or greater, and 5 mm or greater, are seen 50–60 % of the time and 26–31 % of the time, respectively [14]. While 3–5 mm may seem like a small and acceptable margin of error, these discrepancies are certainly of great clinical importance when high-dose regions are immediately adjacent to vital structures being spared (e.g., parotid glands, spinal cord) or targeted (e.g., tumors, elective nodal volumes). For this reason, it has become standard to use IGRT prior to treatment (with images verified by radiation therapists and intermittently approved by the treating physician), to allow planning margins to approach 3 mm. The delivery of complex treatments (e.g., IMRT) without accounting for daily setup errors has been suggested to have significant implications for accuracy [15].

4.2.6 Stereotactic Body Radiation Therapy (SBRT)

With the ability to deliver radiation dose in an extremely conformal manner, and the capability to confidently verify patient positioning in real time, there has been interest in delivering larger doses per fraction, while reducing the total number of fractions. Much of this work has focused on tumor types that have suboptimal outcomes with fractionated therapy such as brain and lung cancers. Compared to brain and

lung tumors, the outcomes of head and neck cancer treated by fractionated radiation therapy are quite high. Consequently, the head and neck SBRT literature is largely limited to patients with recurrent disease.

In a retrospective-matched cohort study, Heron et al. reported outcomes of 70 patients receiving SBRT for locally recurrent HNSCC (including nasopharynx, larynx, oral cavity, and oropharynx), with or without cetuximab. Patients received a median of 40 Gy in 5 fractions. Response rates were 63–77 %, and median duration of LC was 13–24 months. Local failure occurred in 50–60 % of cases. There were no grade 4–5 toxicities, and grade 3 toxicity was seen in only three patients [16]. A multi-intuitional, European phase II SBRT trial included inoperable recurrent HNSCC, or new primary HNSCC in a previously irradiated area. SBRT consisted of 36 Gy in 6 fractions, with concurrent cetuximab. Results demonstrated a 58 % response rate, 92 % disease control rate, and a 1-year OS rate of 48 %. One treatment-related death was attributed to hemorrhage and malnutrition [17].

As the technique thus far seems safe and relatively effective, its use as primary treatment has been attempted in certain populations. The largest series of this type comes from Kawaguchi et al., where 14 patients with HNSCC (5 oral cavity) were treated with SBRT. Dosing was 35–42 Gy, in 3 or 5 fractions. After a mean follow-up of 36 months, local control and overall survival rates were 71 % and 79 %, respectively [18]. Two smaller case series have reported similar results and also seem to suggest reasonable toxicity profiles [19, 20].

4.2.7 Experience Matters and Outcomes Are Improving

Evidence exists across all disciplines of medicine for improved patient outcomes in centers of excellence and for those who care for large volumes of patients. A matched pair analysis was performed seeking to determine if patients receiving adjuvant radiation therapy at an academic center fared better than their counterparts who received it in the community, all following curative resection at an academic center. The analysis revealed improved OS, DSS, and LRC for those who received their RT at the academic center. However, there were notable discrepancies between the groups. There was a higher percentage of never smokers in the group treated at academic centers, and those treated at non-academic centers received a lower total and fractional dose. On multivariate analysis accounting for these imbalances, the difference in OS remained significant [21]. Besides treatment location, prognoses have changed over time as well. A large retrospective study from seven international cancer centers revealed improved outcomes in OCSCC during the first decade of the new millennium, compared to the prior decade. Five-year OS improved from 59 to 70 %, despite the latter cohort having more advanced tumors, higher rate of distant metastases, and older age. This group also underwent selective neck dissection more often and, most notably, received adjuvant RT more often, reflecting the evolving treatment programs for OCSCC [22].

4.3 General Management Options with Radiotherapy in the Oral Cavity

4.3.1 Definitive Radiotherapy

A report from Sher et al. published in 2011 details the results of 42 patients treated with IMRT, either in the postoperative or definitive setting. Patients were treated between 2004 and 2009 and consisted of 12 % stage I, 24 % stage II, 33 % stage III, and 31 % stage IV. Thirty of 42 patients received surgery prior to radiotherapy. The remaining 12 received concurrent chemoradiotherapy (CRT), with or without induction chemotherapy. In this population, results from definitive RT were significantly inferior. Two-year OS was 85 % and 63 %, and LRC was 91 % and 64 %, for surgical vs. nonsurgical management, respectively [23]. A larger series assessing the impact of location of primary site within the oral cavity utilized definitive CRT alone. One hundred fifteen patients, staged IIIA, IVA, and IVB (6 %, 47 %, 47 %), received a median RT dose of 72 Gy. Response rate was 96.5 % (76.5 partial, 20 % complete). Overall, 3-year OS and PFS rates were 22 and 25 %. Interestingly, the 3-year PFS rates varied notably between subsites. Tumors of the buccal mucosa, FOM, and gingiva had a 3-year PFS of 51 %. Tumors of the retromolar trigone/hard palate and tongue/lip had significantly worse PFS, at 18 % and 6 %, respectively [24]. Cohen et al. retrospectively reviewed T4 OC tumors treated with definitive CRT on prospective protocols. Thirty-nine patients were reviewed and treated with a median 74 Gy. Results at 5 years of OS, PFS, and LC were 56 %, 51 %, and 75 %, respectively. The authors concluded that these were comparable results to historical controls and that primary CRT should be considered in this population [25]. Gore et al. retrospectively reported on 104 patients with advanced OCSCC treated with curative surgery or chemoradiation and found significantly improved survival in those treated with surgery [26].

4.3.2 Management of the Neck

Management of the elective nodal volumes in HNSCC is an important issue. Generally, structures of the oral cavity drain to bilateral lymphatics, with preferential involvement of certain levels [27]. There are exceptions, however, leading to instances in which unilateral neck radiation may be considered if the suspected contralateral failure rate is sufficiently low. This paradigm is well studied in the setting of the palatine tonsil [28, 29]. A small study assessing well-lateralized, early-stage OC tumors and tonsillar tumors following surgery revealed a 5 yr LRC of 100 % [30]. The best example of a well-lateralized structure within the oral cavity is the buccal mucosa. In a retrospective review of 145 patients receiving surgery and adjuvant RT, 83 % received unilateral neck RT. For all patients, the 5-year disease-specific survival (DSS) for stage I–IV was 87 %, 83 %, 61 %, and 60 %, respectively. There was no difference in LRC between patients who received unilateral vs.

bilateral treatment ($p=0.95$). The rate of failure within the contralateral neck was only 2.1 % [31]. Another retrospective review from Vergeer et al. assessed well-lateralized tumors of the oral cavity (oral tongue, FOM, alveolar process, buccal mucosa) and oropharynx. Sixty-one percent of those included had tumors of the gingiva or buccal mucosa. Eighty-three percent of patients had ipsilateral-only neck dissection. Contralateral neck failure occurred in 6 % of patients, and the only significant prognostic factor affecting contralateral neck failure was number of positive lymph nodes. Five-year rates of contralateral neck control were 99 %, 88 %, and 73 % in N0, N1 or N2a, and N2b cases, respectively. There was no significant difference in tumor subsite related to rate of contralateral neck failure [32].

4.3.3 Role of Altered Fractionation

Historically, radiotherapy has been fractionated in doses of 1.8–2.0 Gy/day, for a period of several weeks. This schema allowed dose escalation to the point of adequate tumor control, while taking advantage of normal tissue's ability to self-repair in between fractions. This pattern of treatment is generally referred to as conventional fractionation. Various alternate regimens have been attempted.

The seminal American trial for altered fractionation in squamous cell carcinoma of the head and neck (HNSCC) was Radiation Therapy Oncology Group (RTOG) 90–03. This trial enrolled about 1100 locally advanced patients (stage II–IV) with tumors of the oral cavity, oropharynx, hypopharynx, and supraglottic larynx. OC patients represented just over 10 % of the enrollees. Patients were randomized to one of four arms: (1) standard fractionation at 2 Gy/fraction/day, 5 days/week, to 70 Gy over 7 weeks; (2) hyperfractionation at 1.2 Gy, twice daily, 5 days/week to 81.6 Gy over 7 weeks; (3) accelerated fractionation with split at 1.6 Gy/fraction, twice daily, 5 days/week to 67.2 Gy over 6 weeks, including a 2-week break after 38.4 Gy; or (4) accelerated fractionation with concomitant boost at 1.8 Gy/fraction/day, 5 days/week and 1.5 Gy/fraction/day to a boost field as a second daily treatment during the last 12 days to a total of 72 Gy over 6 weeks. The trial was initially reported in 2000 [33] and revealed improved locoregional control compared with standard fractionation. While there was a trend toward improved PFS in these groups, neither it nor OS was significantly improved. All three altered fractionation groups had significantly worse acute toxicity. Final results from the trial were published in 2014 and revealed that only hyperfractionation improved LRC (HR 0.79, $p=0.05$) and OS (HR 0.81, $p=0.05$) without increasing delayed toxicity [34]. Another large, phase III trial was conducted in multiple continents to compare accelerated fractionation to standard fractionation. Nine hundred patients with HNSCC of the larynx, pharynx, or oral cavity were enrolled (24 % oral cavity). Standard fractionation consisted of 66–70 Gy in 33–35 fractions, while accelerated fractionation was the same total dose, while receiving 6 fractions/week. Five-year LRC was 42 % vs. 30 %, favoring the accelerated group ($p=0.004$) at the cost of significantly worse mucositis and skin reaction [35].

Regarding definitive management, concurrent chemotherapy and radiation have taken the forefront in advanced-stage disease of non-oral cavity subsites. Data suggests that modifying the fractionation style of radiation cannot compensate for the benefit that concurrent chemotherapy provides when it is required [36]. Currently, with chemotherapy, the usual radiotherapy fractionation is 5–6 fractions per week to a total dose between 66 and 72 Gy in 2–2.2 Gy daily fractions.

As surgery tends be the primary option for OCSCC, not definitive RT, altered fractionation is not as frequently discussed. There have been attempts to shorten the treatment time in the postoperative setting, however. The long-term results of small pilot study from Trotti et al. suggested that locoregional control could be improved with accelerated RT, consisting of 1.8 Gy per day in just over 5 weeks, using a concomitant boost approach. The total dose was 63 Gy, and patients received a second daily fraction once a week for the first 4 weeks, then on the final four treatment days. As expected, this approach did result in increased acute mucosal reactions, but did not affect rates of long-term toxicity [37]. Another small prospective study of accelerated RT following curative resection for HNSCC has been performed [38]. While thought provoking, these deviations from conventional fractionation have not garnered great support, and standard fractionation remains standard of care in the adjuvant setting.

4.3.4 Preoperative (Chemo)-Radiotherapy

RTOG 73–03 evaluated preoperative versus postoperative radiotherapy. It included 277 patients, and with 10-year median follow-up, LRC was significantly better in the postoperative population; however, there was no difference in survival [39]. This study established the postoperative treatment paradigm for HNSCC. A more modern series from Germany evaluated 151 patients specifically with OCSCC and N2 disease, who underwent either pre- or postoperative chemo-RT. They found an increased 5-year survival in those who received the therapy prior to surgery (46 % vs. 27 %, $p = 0.035$). When broken down by T-stage, the benefit was found to be confined to patients with T4 disease [40]. This series suggests a potential subgroup of patients who may benefit from neoadjuvant CRT, perhaps due to its ability to assist in curative resection with negative margins. This hypothesis is further supported by a retrospective study assessing pathologic response rate and effect on prognosis after neoadjuvant CRT. In this series of 154 patients, a clinical response rate of nearly 93 % and a pathologic complete response rate of 60 % were observed after a preoperative RT dose of only 40 Gy, together with platinum-based chemotherapy. After a complete clinical response, residual disease was found on dissection in only 8 % of cases, and only in levels IB-IIA. The authors suggest that neoadjuvant CRT might allow for a more tailored surgical intervention, perhaps avoiding multilevel selective neck dissection [41]. In a large literature-based meta-analysis of 2015 patients (predominantly stage III–IV), complete histopathological response was found in 48 %. After a number of analyses, the mean survival rates at 3 and 5 years were 73 and 57 % [42]. These are numbers that compare favorably to cohorts treated with postoperative therapy. It remains an attractive treatment approach; however, prospective randomized trials are required to firmly establish efficacy.

4.3.5 Induction Chemotherapy

Chemotherapy prior to definitive surgery for HNSCC (a.k.a. induction) has been studied for many years. Induction has also been studied extensively prior to definitive CRT in other cancers of the head and neck. This approach has many supporters and is backed by a wealth of hypothetical advantages. These facts aside, there is a lack of high-level evidence supporting the use of this modality. Large phase III trials have concluded the optimal regimen to be TPF (docetaxel, cisplatinum, 5-fluorouracil) [43, 44]. Recently, a phase III trial comparing induction chemotherapy followed by surgery to up-front surgery was reported in the OCSCC population. This trial randomized patients to two cycles of TPF followed by curative resection and postoperative RT vs. surgery and postoperative RT alone. Two hundred fifty-six patients were enrolled, and 222 completed the full course of treatment. Clinical response was 81 %. After a median of 30 months, there was no difference in OS or DFS. Again, clinical response was found to be predictive [45]. Induction chemotherapy prior to definitive surgery for OCSCC is not a recommendation from the National Comprehensive Cancer Network (NCCN) [46].

4.3.6 Repeat Irradiation

Locoregional recurrence represents a significant proportion of failures, and these are often in patients who have had prior radiation. Lee et al. have published their data on the subject, looking at 105 patients with recurrent HNSCC. Median RT dose was 59.4 Gy, and 2-year locoregional PFS and OS rates were 42 % and 37 %, respectively. The use of IMRT was found to be significant for decreasing LRF. Severe late complications were observed in 12 patients (11 %), which developed after a median of 6 months [47]. The RTOG conducted a prospective trial to assess the toxicity of re-irradiation with chemotherapy. There was a 7.6 % rate of grade 5 toxicity and an 18 % rate of grade 4 toxicity. Improved survival was seen in those who had an inter-treatment interval of greater than 1 year [48]. Comorbidity is also known to be a prognostic factor, as demonstrated by Tanvetyanon et al. who produced a nomogram, to predict probability of 24-month survival [49]. Despite the mentioned data, re-irradiation remains a high-risk venture, best left for clinical trials and experienced hands in high-volume centers.

4.4 Adjuvant Radiotherapy in the Oral Cavity

4.4.1 Paradigm Development and Indications for Adjuvant Treatment

Several studies have sought to define the tumor factors that portend high risk of recurrence and merit adjuvant radiation or chemoradiation therapy. In a prospective dose-finding trial from Peters et al., poor prognostic factors were identified in an attempt to tailor adjuvant RT dosing. Three hundred two patients with SCC of the oral cavity, oropharynx, hypopharynx, or larynx were enrolled, and 92 % had stage III–IV disease. Patients were stratified by risk group based on certain factors and randomized to one of three doses:

52.2 Gy, 63 Gy, or 68.4 Gy. Low risk could not receive the high dose and vice versa. Presumed risk factors for locoregional recurrence were drawn from prior reports and included site of disease, surgical margins, perineural invasion (PNI), number and location of involved lymph nodes, and presence of extracapsular extension (ECE). Patients receiving less than 54 Gy had higher primary failure rates. Only patients with ECE benefitted from a dose greater than 57.6 Gy, and ECE was a significant predictor of LRR. Other factors were found to confer increased risk when grouped in two or more. These included oral cavity primary, close/positive mucosal margins, PNI, 2 or more involved nodes, largest node greater than 3 cm, treatment delay greater than 3 weeks after surgery, and Eastern Cooperative Oncology Group (ECOG) performance status ≥2 [50]. A subsequent multi-institutional prospective trial that accrued between 1991 and 1995 enrolled 213 post-operative HNSCC patients. This trial aimed to validate the previously identified risk factors, while comparing conventional and accelerated RT in the adjuvant setting. Low-risk, intermediate-risk, and high-risk patients received no adjuvant treatment, 57.6 Gy and 63 Gy in either 5 or 7 weeks, respectively. Using the previously identified risk factors, patients were considered low risk if they had no adverse features, or intermediate risk if they had only one feature (excluding ECE). Anyone with ECE, or 2 or more other factors was considered high risk. Low- and intermediate-risk patients had a significantly improved LRC compared to high-risk patients, thereby validating the risk stratification. Notably, a decreased LRC rate was seen in high-risk patients experiencing a delay between surgery and the initiation of RT in the 7-week arm. Both LRC and OS were significantly worse in those who had RT initiated >6 weeks after the surgical date. Total treatment time of less than 11 weeks led to significantly improved outcomes [51].

The potential benefit of adding chemotherapy to further improve outcomes has also been studied. Two large phase III trials on this topic were accrued and published contemporaneously. EORTC (European Organization of Research and Treatment of Cancer) 22931 was a randomized trial that accrued 334 patients with SCC of the oral cavity, oropharynx, hypopharynx, or larynx. Eligible patients included those with T3–4 disease with negative margins, or early-stage disease with certain features (ECE, positive margins [defined as within 5 mm], PNI, lymphovascular invasion (LVI)). Oral cavity patients with nodal involvement of levels IV or V were included as well. Patients were randomized to RT with or without concomitant chemotherapy (cisplatin 100 mg/m^2 every 21 days). At 5 years, LRC, PFS, and OS were all significantly improved with the addition of chemotherapy [52]. The second trial that ran in parallel was an American one, run by the RTOG. RTOG 95–01 randomized 416 patients with SCC of the oral cavity, oropharynx, larynx, or hypopharynx following gross total resection to RT alone, or RT with chemotherapy. Eligibility for this trial was slightly different and included patients with two or more lymph nodes, ECE, or positive surgical margins [defined at the inked margin]. The primary endpoint was LRC. At 2 years, LRC was significantly improved with chemotherapy (82 % vs. 72 %). DFS was also significantly improved; however, the improvement in OS did not reach statistical significance [53]. Given the substantial similarity between the two trials, a combined analysis was undertaken. This was published in 2005 and revealed that ECE and positive surgical margins were the only risk factors for which combined chemotherapy and RT provided benefit [54]. For this reason, these factors represent Category 1 indications from the NCCN (National Comprehensive Cancer Network) for the use of combined chemoradiotherapy [46]. The above data are summarized in Table 4.2.

Table 4.2 Important trials regarding adjuvant radiotherapy in HNSCC

Author	# pts	% OC	Risk factors and inclusion	Arms/tiers	Outcomes	Impact
Tupchong et al. [39]	277	15	T2–4, any N	Preop RT	LRC 58 %	Helped establish postoperative RT as the treatment paradigm
				Postop RT	LRC 70 % (SS)	
Peters et al. [50]	240	32	Low: no risk factors Int: 1 risk factor (non-ECE) High: 2+ risk factors, or ECE	57.6 Gy 63 Gy 68.4 Gy	No dose response above 57.6 without ECE. With ECE, ≥63 Gy had improved response	Confirms proposed risk stratification Factors include OC primary, close or positive margins, PNI, ≥2 LN, LN >3 cm, treatment delay >6 weeks, PS ≥ 2
Ang et al. [51]	213	38	Low risk Intermediate risk High risk	No PORT 57.6 Gy 63 Gy/5 weeks 63 Gy/7 weeks	Significantly improved LRC in low and intermediate risk groups. Decreased LRC with treatment <11 weeks	Validates risk stratification. Highlights importance of total treatment package time following surgery
Bernier et al. [52]	334	26	Margins <5 mm, ECE, pT3-T4, LVI, PNI, OC/OP tumors with level IV/V LN	PORT alone	5-year OS 40 % 5-year LRC 69 % (SS)	Positive study for chemotherapy in addition to PORT for high-risk factors listed
				PORT + cisplatin	5-year OS 53 % 5-year LRC 82 % (SS)	
Cooper et al. [53]	416	27	≥2 LN, ECE, + margins	PORT alone	2-year LRC 72 %	Positive study for improved LRC, but survival not significantly improved
				PORT + cisplatin	2-year LRC 82 % (SS) OS: HR 0.78 (NS)	
Bernier et al. [54]	748	27	Combination of 2 above	Combined analysis of Bernier (2004) and Cooper (2004)	ECE and Involved margins are only factors which derived significant benefit from both trials	Establishes the standard indications for PORT + chemotherapy in HNSCC patients

Abbreviations: *Preop* preoperative, *Postop* postoperative, *LRC* locoregional control, *RT* radiotherapy, *Int* intermediate, *ECE* extracapsular extension, *OC* oral cavity, *PNI* perineural invasion, *LN* lymph node, *PS* performance status, *PORT* postoperative radiotherapy, *LVI* lymphovascular invasion, *OP* oropharynx, *SS* statistically significant, *NS* not significant, *HNSCC* squamous cell carcinoma of the head and neck

The aforementioned seminal trials for adjuvant RT in the head and neck were not specific to OCSCC. Studies have been published looking at the OC population exclusively. A retrospective series of 193 patients with OCSCC treated with or without RT actually suggested a disadvantage to treating intermediate-risk patients with adjuvant RT [55]. A decline in both LRC and 5-year survival was reported. After adjusting for known prognostic factors, the difference in outcomes remained. Such data must be interpreted with caution, given the high potential for selection bias. Nevertheless, there may be a role for further defining indications for adjuvant RT in intermediate-risk patients. Some data suggests inferior outcomes with certain subsites, including the oral tongue and floor of mouth [56]. OC-specific series have also corroborated the larger HNSCC trials in terms of chemotherapeutic benefit and importance of ECE as an indication [57].

4.4.2 Timing of Adjuvant Radiotherapy

As previously mentioned, one prospective trial has shown a decline in outcomes following a surgery to RT time greater than 6 weeks [51]. A large retrospective series set out to further define the effects of timing and delays on treatment results [58]. These results suggest that there are significant declines in relapse-free survival associated with increased duration of treatment gaps, in addition to traditional prognostic factors (positive margins, nodal metastases, etc.). Another notable finding was that small gaps (<21 days) were not significantly worse than longer delays (>21 days), except for those with positive surgical margins. This further emphasizes the importance of timely and uninterrupted treatment in patients with the highest risk of recurrence. The literature, however, is not unanimous on the subject. A retrospective study from Leon et al. indicated that time between surgery and RT was not an independent factor predicting for LC or OS [59]. The opposite result was found, however, in a series from Langendijk et al., looking exclusively at OC patients [60]. Overall treatment time correlated inversely with LRC and OS, favoring those who completed their treatment in <6 weeks.

4.4.3 Risk Assessment and Prognostic Factors in the Oral Cavity

While there are accepted risk factors known to predict for poor outcomes in HNSCC in general, only smaller (generally retrospective) series are available to validate these within the oral cavity specifically. A risk stratum was proposed by Parsons et al. in 1997, identifying patients at increased risk of LRC to be those with positive margins, or 4 or more high-risk features: bone invasion, close margins, carcinoma in situ, PNI, LVI, extension to soft tissues, or multicentricity. Patients meeting these high-risk criteria were found to have worse outcomes, despite receiving higher doses of postoperative RT [61]. Fan et al. suggested an ability to scale prognosis based on number of minor risk factors (PNI, LVI, depth of invasion, close margin) [62]. With this approach, 3-year recurrence-free survival rates were 82 %, 76 %, and

45 % with the presence of no risk factors, one or two risk factors, or three or more risk factors, respectively. The number of risk factors remained prognostic after multivariate analysis. Pathologic tumor stage remains very important in determining the need for adjuvant RT. In the absence of other established risk factors, a T1–2 lesion may be treated with surgery alone, and a T3 lesion may be indication enough to require adjuvant radiotherapy. However, Liao et al. has published data suggesting that T-stage as it is currently defined may be insufficient, and depth of invasion may be a more important factor in predicting LRC [63, 64]. While some data suggests that RT does not improve LC in cases of involved margin in the oral cavity [65], most studies posit the opposite. Data from Zelefsky et al. reveal that an elevated dose (>60 Gy) is likely required in the setting of positive margins, but excellent LC rates can still be achieved [66]. Whether a close margin is enough to warrant adjuvant therapy is less clear. At least one series reports excellent local control rates with close (<5 mm) margins and no additional risk factors [67]. Nomograms have been created to predict benefit of adjuvant radiotherapy [68, 69].

4.5 Site-Specific Outcomes with Radiotherapy in the Oral Cavity

4.5.1 Mucosal Lip and Alveolar Ridge

Oncologic outcomes in the mucosal lip are generally quite good and comparable between modalities. For this reason, treatment is selected chosen based on expected aesthetic outcome. Early studies suggested comparable outcomes, but improved functional benefits after RT [70]. Historically, radiation therapy has played a role in treatment of larger lesions, or those that involve the commissure. Interstitial LDR brachytherapy yields 10-year OS, DFS, and CSS rates of 53 %, 81 %, and 84 %, respectively. In one series, local control at 5 years was 90 %, 94 % when allowing for salvage surgery [71]. For those patients who do undergo primary surgery, there may be a role for adjuvant radiotherapy [72]. In a retrospective review, adjuvant radiotherapy demonstrated the ability to improve recurrence-free survival by 28 % at 2 years. There was no impact on OS, however [73]. A series from Love et al. details results of patients treated with alveolar ridge carcinoma and conveys a change in treatment preference around the mid-1950s [74]. Prior to that time, radiotherapy was the preferred technique, using either radium molds or external beam radiotherapy (superficial or megavoltage Co-60 teletherapy). After this, surgery with or without adjuvant radiotherapy became the mainstay of their practice. From this 1977-published report, crude 10-year and 5-year survival was 44 and 24 %. Local control at 5 years was 56 %. The lower alveolus presents a challenge for rigid-needle interstitial brachytherapy. Other systems were used to solve this problem, such as plastic catheters containing flexible iridium-192 wires [75]. This allowed the creation of a more curvilinear dose distribution. This small publication represents the type of innovation that was needed to create safe and effective treatment plans with brachytherapy applicators.

4.5.2 Buccal Mucosa

The buccal mucosa raises unique questions when considering management, especially given its well-lateralized vascular and lymphatic connections. Surgery is typically employed, with postoperative RT to the primary site with or without coverage of the nodal volumes, depending on adverse features. In a series from Lin et al., the contralateral neck failure was only 2.1 %, and did not differ between those undergoing unilateral vs. bilateral elective neck radiation after definitive resection [31]. Rates of local recurrence are relatively high in this subsite. A retrospective review spanning 20 years from Lin et al. revealed LRC rates of 30 % and with 37 % cause-specific survival [76]. Of the 57 % who experienced a locoregional recurrence, 80 % were at the primary site. Among T1-2N0 patients, the LR rate was greater than 40 % in those who were treated with surgery alone. A significant improvement in CSS was noted with the addition of RT to surgery. The results of those treated with primary radiotherapy were poor. In another small modern retrospective series, local and regional control was 58 % and 84 %, respectively, at 5 years. Overall survival and disease-specific survival were 69 and 76 % [77]. A much larger retrospective series from Jan et al. analyzed prognostic factors of patients with SCC of the buccal mucosa [78]. In this 415 patient series, 137 received radiotherapy in addition to surgery. Factors that were significantly associated with survival included margin status, presence of nodal metastasis, extracapsular spread, and tumor stage. LRR occurred in 55 %, and 5-year survival was 71 %. There was no appreciable difference in outcome based on adjuvant therapy received, perhaps due to retrospective biases.

In a series of 176 patients, postoperative RT was found to be effective in decreasing LRF [79]. Adjuvant RT improved LRC to 48 % from 11 % at 3 years for patients with stage III–IV cancer. The benefit was not significant for early-stage patients. After multivariate analysis, radiation proved useful in reducing locoregional recurrence in patients with tumors thicker than 1 cm, tumors with bony invasion, and tumors of high grade [79]. Another retrospective study of patients treated with surgery and adjuvant RT quotes 3-year LRC and OS of 64 % and 55 %, respectively [80]. Tumor invasion through to the skin of the cheek was the only factor prognostic for locoregional recurrence after multivariate analysis.

In the lone prospective trial, Mishra et al. randomized 140 patients with T3-4N1-2b buccal mucosa tumors to surgery alone, or surgery followed by radiotherapy. The groups were not evenly balanced, in that there were more patients with N1-2b disease and fewer N0 patients in the adjuvant radiation group. Despite this, the 3-year DFS was significantly improved with the addition of RT (68 % vs. 38 %). There were also numerically fewer local failures and death from any cause in the RT group, but these results were not reported to be statistically significant [81].

4.5.3 Retromolar Trigone

Radiotherapy may be indicated for early lesions of the retromolar trigone (RMT), while more advanced lesions generally require a multimodality approach [73]. A large report of patients from Lo et al. details outcomes in patients with SCC of the

RMT or anterior faucial pillar [82]. Most patients received EBRT with some combination of Co-60, electrons, and high-energy photons. Elective nodal irradiation was ipsilateral only in N0 patients. Five-year survival was 83 %, and 92 % experienced recurrence within 2 years. After salvage surgery, final failure rates were 0 %, 6 %, 8 %, and 20 % for T1–4 tumors, respectively. Infiltrative/ulcerative lesions had significantly higher rates of recurrence than exophytic/superficial lesions. Only 10 % of the group experienced a nodal recurrence, and half of these achieved long-term control with salvage. While somewhat outdated, these data indicate that there is a reasonable chance of long-term control with radiation alone (and subsequent surgical salvage if necessary), especially in early-stage, superficial tumors. Nodal recurrences are infrequent, and ipsilateral elective RT may be sufficient. A smaller, but similar report of roughly contemporary patients reveals superior outcomes with the inclusion of surgery in the treatment algorithm [83]. The 5-year DFS rates varied significantly by treatment program: 90 %, 63 %, and 31 % for preoperative RT and surgery, surgery and postoperative RT, and RT alone, respectively. Lymph node status was also found to be a significant prognosticator. A series from Mendenhall et al. reported improved outcomes with multimodality therapy [84]. SCC of the RMT exhibited 5-year local control of 42 % for RT alone and 62 % for surgery plus RT and was slightly more pronounced in patients staged I–III. The authors concluded decisively that a combined modality approach leads to better outcome than RT alone. A more recent series of lesions treated definitively with RT revealed an LRC rate of 49 % and 67 % after salvage surgery [85]. For early-stage patients alone (I–II), local control rates approached 90 %, allowing for salvage surgery. Of the 23 patients that experienced LRR, 5 were regional. These data argue that for well-selected, early-stage patients for whom surgical intervention is not optimal up front, RT is a reasonable option, especially if salvage surgery is feasible. The most recent report detailing SCC of RMT treated with primary RT comes from the Bayman et al. and utilized a hypofractionated course [86]. A median dose of 50 Gy in 16 fractions over 21 days was delivered. Half of the patients were early stage, and a third had nodal involvement. They reported an LRC at 5 years of 47 %, comparable with other series. While the data at large speaks to the importance of combined modality therapy—especially in advanced stage patients and those with adverse risk features, it should be noted that a nonsurgical approach can be employed with reasonable results in well-selected cases.

4.5.4 Floor of Mouth

For the floor of mouth (FOM), surgery plays the dominant role, with radiation used as adjuvant therapy for high-risk patients. Historically, many centers favored BT as the sole radiation approach, or as an adjunct to EBRT. Contrary to the difficulty previously described with tumors of the alveolar ridge, the FOM is amenable to straight-needle placement, traversing the soft tissues below the mandible. A series of 207 patients who received radiation for predominantly T1–2 lesions utilized EBRT alone, BT alone, or a combination thereof [87]. They demonstrated LC that

was quite good for RT alone, 97 % and 72 % for T1 and T2 tumors, respectively. The corresponding disease-specific survival was also excellent, with 5-year rates of 88 % and 47 %. Both the aforementioned rates dropped significantly with T3/4 tumors. T-stage was significant in predicting local control. The use of BT alone proved beneficial in T2N0 tumors. The authors concluded that BT alone without EBRT is the preferable treatment strategy in T1–2 FOM SCC. Gold grains (Au-198) are another form of BT used in the oral cavity that were especially favored in FOM tumors, after the decline of Radium-222 seeds. Matsumoto et al. detailed their experience with RT alone for FOM using ERBT, BT, or some combination. BT consisted mostly of gold grains (although some patients were treated with radium or cobalt needles, or iridium hairpins) [88]. T1 and T2a lesions had LC rates of 89 and 76 %. Tumors with gingival involvement fared significantly worse. When looking at those treated with gold grains, LC was 93 % in T1 tumors and 79 % in T2 tumors. The practice of BT in OC was a heterogeneous one, with many series suggesting good results with different techniques and applicators. Beyond the variation of the apparatus used to proximate the radioactive source to the target tissue, there are a number of different isotopes that are utilized in BT. As described earlier in the chapter, different isotopes decay at different rates, meaning the dose is delivered to the tissues over different time intervals. The reasons to choose between HDR and LDR are many, and some studies have sought to evaluate the efficacy of one versus the other. Inoue et al. published a series of patients treated with either LDR BT (Au-198) or HDR BT (Ir-192) in FOM cancer [89]. Local control rates were numerically superior with HDR interstitial BT (94 % vs. 75 % at 5 years), although the difference was not statistically significant. The majority received BT in addition to EBRT (36/41). These are among the data that support the use of HDR BT in HNSCC, a modality that ultimately supplanted LDR BT, for reasons including patient convenience and staff exposure. The predominant belief is that both dose rates lead to comparable results in experienced hands, and the choice of dose rate relates to logistical factors.

The role of RT in general for FOM cancers has evolved, and surgery remains preferable when appropriate, especially in higher-stage tumors. A retrospective review of 194 patients revealed ultimate LC rates of 90–94 % for T1 lesions and 83–86 % for T2 lesions [90]. The differences were negligible between surgically managed patients and those receiving RT alone. Of 29 patients with T3 lesions, 9 received surgery and RT and had 100 % local control. Of the 20 who received RT alone, LC was 55 % up front and 65 % allowing for salvage. In a similar series comparing different treatment strategies in FOM patients, outcomes were more disparate [91]. Five-year OS rates were 68 %, 45 %, 43 %, and 41 %, for those treated with surgery alone, RT alone, preoperative RT, and postoperative RT, respectively. These data should be interpreted with caution, because as is often the case, the patients who received more intensive therapy (RT plus surgery) had more advanced disease. LRC was actually superior in those who received RT. Five-year LRC was 52 %, 69 %, 58 %, 74 %, and 89 %, in those who received surgery, RT only, preoperative RT, postoperative RT, and BT, respectively. Such results confound our ability to clearly define a population that is appropriate for one

regimen versus the other. A largely surgical series from Roswell Park Cancer Institute confirmed the benefit on LRC with the addition of adjuvant radiotherapy, despite the group having a more advanced stage [92]. There was also a trend toward improved survival in the 10 % who received RT in addition to surgery. A more recent analysis of FOM was reported by Smee et al. [93]. Surgery was performed in the majority, while about 20 % were treated with RT alone. Twenty-three of 30 patients (77 %) who received RT alone experienced local failure, while only 15 % managed surgically failed (inclusive of those treated with a combined modality approach).

4.5.5 Hard Palate

The hard palate may be the least studied of the oral cavity subsites, due in part to its relative rarity. While surgery most certainly dominates treatment, there are some data to support the use of RT alone in patients who are not operable. Yorozu et al. in a 31 patient series included 26 patients treated nonsurgically [94]. Including minor salivary gland carcinomas, estimated 5-year local control was 53 % or 69 % with salvage surgery. T-stage was a predictive factor for local control, as early stage (T1–2) exhibited local control of 80 %. The authors concluded that radiotherapy alone may be a safe and effective treatment modality for these patients.

4.5.6 Oral Tongue

The anterior two third of the tongue has a high incidence of SCC, and various therapies have been well studied. Brachytherapy has played a historical role in the treatment of oral tongue cancer, given the ease with which interstitial needles can be placed in/on the lesion. As such, brachytherapy has produced local control rates that are quite good, especially when comparing to other sites within the oral cavity. Yamakazi et al. in a series of 591 patients revealed a 3-year LC rate of 81 % [95]. The majority of the patients were treated with LDR (Ir-192 pin, Ra-226 needle), but there was no difference in outcomes compared to those treated with HDR. Many patients also received an external beam component. Increased age (≥65) was found to be a significant determinant of local control in this cohort. Overall, 33 % experienced a regional failure (26 % T1, 33 % T2). Regarding 5-year cause-specific survival, rates were 82 % and 70 % for the older and younger age groups, respectively. The question of HDR vs. LDR BT was also addressed in a randomized trial from Inoue et al. [96]. Fifty-nine patients were enrolled, and 51 were evaluable. Patients were treated with interstitial BT alone, without EBRT. LDR treatment was delivered with an Ir-192 hairpin to a dose of 70 Gy over 4–9 days, while HDR treatments were delivered with an Ir-192 micro-source and an afterloading unit to a dose of 60 Gy in 10 Gy fractions over 1 week. Local control was not significantly different at 5 years; 84 % and 87 % for LDR and HDR, respectively. Regional control was also comparable, with failure rates below 35 % for both. In a series of patients with T1-T2N0

SCC of the oral tongue treated with EBRT followed by interstitial BT, treatment time was shown to be prognostic [97]. Five-year LC was 93 % for T1 tumors and 63 % for T2 tumors. Treatment time of 43 days or more resulted in worse local control in the entire patient population and in the T2 subgroup. A regression analysis of this data revealed a 2 % loss of local control per day after 30 days.

4.6 Sequelae of Radiation Therapy

Radiation therapy to the head and neck has proven to be very effective at achieving locoregional control either alone or with surgery, but often produces complications. Xerostomia, radionecrosis, dental issues, taste changes, and swallowing difficulties are among the long-term toxicity associated with radiotherapy. The effect that these sequelae have on quality of life (QOL) is well documented and has even been suggested to be an independent predictor of survival [98].

QOL was assessed in intermediate-risk patients specifically, and physical subscale scores were the most affected between those who received RT and those that did not [99]. A QOL survey assessing OCSCC patients noted that domains most perturbed were appearance, mood, saliva, and shoulder function [100]. An association was also drawn between increasing T-stage and worse QOL. Ch'ng et al. performed a prospective QOL assessment of OCSCC patients receiving postoperative RT [101]. At the 6-month time point posttreatment, global health status and xerostomia were significantly worse, while fatigue levels were marginal.

4.6.1 Xerostomia

One of the most significant long-term effects of head and neck radiotherapy is xerostomia. With traditional opposed lateral fields, there was no ability to spare the parotid glands, leading to almost certain decreased salivary function. With a decrease in salivary production comes other consequences as well, including dysgeusia and dental abnormalities. All of these produce a significant decline in quality of life – a fact that is not debated. As discussed earlier, the advent of IMRT and parotid gland sparing has allowed us to greatly reduce the number of patients left with significant xerostomia [102]. Our understanding of IMRT's ability to preserve salivary function continues to evolve, especially as spare additional glandular tissue without significantly compromising failure rates. Sparing the contralateral submandibular gland has also been suggested to lead to better salivary flow rates following therapy [103]. In 2011, Nutting et al. published a randomized trial verifying previous reports that parotid-sparing IMRT can truly reduce xerostomia rates [9]. At 2 years, 83 % of patients had grade 2 or higher xerostomia with conventional RT, compared to 29 % of those receiving IMRT. Quality-of-life scores were in line with the objective results, and most importantly, there were no differences in LRC, or OS. These results were obtained in a population undergoing definitive radiotherapy, a scenario not too common in the oral cavity. A retrospective review of patients who

underwent postoperative IMRT or conventional radiation therapy also demonstrated the ability to spare salivary function with IMRT [104]. These results are readily applied to the typical OCSCC patient.

4.6.2 Osteoradionecrosis

Radionecrosis of the bone is a serious long-term effect of high-dose RT in the oral cavity. Surgical and/or dental intervention is often required to remove the necrotic tissue, as conservative measures may be insufficient. A series of conventionally treated patients reported by Glanzmann et al. were analyzed for rates of osteoradionecrosis (ORN) [105]. The study included patients treated between 1980 and 1994, with doses between 60 and 78.2 Gy. There were no observed cases of ORN below 65 Gy. Above 66 Gy, at a daily fraction rate of 2.0–2.22 Gy, the rate of ORN requiring resection was almost 25 %. Between daily doses of 1.8 and 1.9 Gy, and a total dose of 69–75.6 Gy, the rate was 19.6 %. Dose is thus considered to be a significant factor in determining likelihood of developing ORN. Other factors include tumor proximity to bone and the volume of mandibular ramus receiving high dose. Another study comparing conventional fractionation to twice-daily radiotherapy with a minimum 4 hour inter-fraction interval revealed an unacceptable rate of ORN (23 %) [106]. The rate of ORN in those treated conventionally was only 9 %, and this rate was seen to steadily rise with increasing total dose. This unfortunate late effect has also been seen in those receiving brachytherapy. A report of ORN in patients receiving LDR BT for oral cancer quoted a rate of 10 % and suggested threshold values for the outcome, including dose rate and reference volume [107]. As with other toxicities, IMRT has shown promise to reduce the risk further. A dosimetric analysis from Studer et al. revealed that they were able to substantially decrease high-dose overlap with bone. Their belief is that this dose reduction to the bone will translate into fewer cases of ORN [108]. The presence or absence of surgical intervention to the mandible itself has also been posited as a significant predictor of ORN [109]. Hyperbaric oxygen (HBO) has been studied as a potential therapy for overt mandibular osteoradionecrosis [110]. Sixty-eight patients were accrued to a multi-institutional, randomized, double-blind trial of HBO versus hyperbaric nitrogen. The study was stopped prematurely after there was no improvement seen with HBO. In fact, more patients recovered in the placebo arm, although the difference was not statistically significant. Modern understanding of dose limits, and the ability to limit dose to bone (when not near a target) with IMRT, holds the promise to make ORN a less common toxicity.

4.6.3 Secondary Malignancy

Radiotherapy always carries with it a small but nonzero risk of contributing to a second malignancy within the treatment field. Given the field cancerization often associated with mucosal head and neck cancers, differentiating radiation-induced

cancers from second primaries or recurrences is not always possible. Radiation-induced solid tumors often are sarcomatous and tend to occur many years after treatment, however. A SEER (Surveillance, Epidemiology, and End Results) study analyzed the outcomes of over 30,000 patients with oral cavity cancer treated between 1973 and 1999 [111]. Five thousand and forty-two patients developed a metachronous second primary cancer. The relative risk was 1.64 (95 % CI 1.18–2.29) for RT alone and 1.49 (95 % CI 1.07, 2.06) for surgery plus RT. The figure was not significant for those receiving surgery alone (RR 1.28; 95 % CI 0.93, 1.76). Radiation became a significant risk factor after 10 years for development of a solid tumor (consistent with aforementioned latency) and became a risk factor for hematological malignancies after 1–5 years. Others have presented contrary data, however. A group from Colorado suggested that EBRT was associated with decreased risk of secondary cancers and hypothesized that this was due to eradication of microscopic foci of already-present second cancers [112]. Others have contended that radiation neither increases nor decreases the risk [113].

4.6.4 Other Toxicity

Tongue function has been studied in patients after treatment for oral cancers. Deterioration of function tends to occur within the first year of surgery/radiotherapy, likely during the window when fibrosis is developing. Patients treated with combined modality therapy tended to have worse sensory function and mobility [114]. Another study suggested that tongue function may decrease slightly, but improve over time as healing occurs. Tongue function may not parallel that of swallowing/pharyngeal function [115]. In a small prospective study, patients were also noted to have decreased masticatory performance and bite force after surgery and/or radiotherapy [116]. A small preliminary study has hypothesized an increased likelihood of obstructive sleep apnea with patients treated surgically, as opposed to those managed nonsurgically [117]. This study included both oral cavity and oropharyngeal patients. Investigations on the effects of these therapies on speech are ongoing. There is a larger literature for laryngeal SCC, and these authors posit there is a void in understanding speech outcomes in patients being treated for oral and oropharyngeal primaries [118].

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Current and Emerging Role of Chemotherapy in Oral Cancer

5

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5.1 Introduction

The role of chemotherapy in oral cancer has been evolving [1]. In addition to palliation, it also has an established role in curative management [2]. It can be offered as a single modality treatment for palliation, in combination with concomitant radiation therapy (chemoradiation) as either adjuvant therapy following surgical resection or primary definitive treatment for locally advanced disease, or as induction therapy prior to definitive treatment. Unlike surgery, chemotherapy usually exerts its cytotoxic activity systemically; therefore it is often associated with side effects caused by toxicities to the normal tissues. The toxicities and cellular resistance to chemotherapy are two major obstacles to the clinical efficacy of chemotherapy [3]. Recent advances in understanding molecular biology of HNSCC have opened many new research directions. In addition to traditional cytotoxic chemotherapy, novel targeted therapy has demonstrated its efficacy in palliation [4]. Although most of the studies of chemotherapy in HNSCC were not site specific, many of the findings may be applicable to oral cancers.

5.2 Chemotherapy Agents in HNSCC

The most commonly used cytotoxic chemotherapeutic agents in HNSCC are platinum derivatives (cisplatin, carboplatin), taxanes (paclitaxel, docetaxel), and antimetabolic agents (methotrexate, 5-fluorouracil (5-FU)) (Table 5.1).

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Table 5.1 New cytotoxic chemotherapy agents in HNSCC

Study	Trial design	Sample size (HNSCC/oral cavity)	Regimen	RR/PFS/TTP/TTF/DOR	OS
Schornagel et al. (1995) [5]	Phase III randomized trial for first-line chemotherapy treatment	131/43 (33 %)	Edatrexate 70 mg/m^2 weekly (reduced from 80 mg/m^2 due to toxicity)	RR 21 %[a] DOR: 6.1 months[a]	No OS difference
		133/43 (32 %)	Methotrexate 40 mg/m^2 weekly	RR 16 %[a] DOR: 6.4 months[a]	
Degardin et al. (1998) [6]	Phase II single-arm trial for first-line chemotherapy treatment	63/12 (19 %)	Vinorelbine 30 mg/m^2 weekly	RR 16 % DOR: 19 weeks	32 weeks
Testolin et al. (1994) [7]	Phase II single-arm trial for pretreated patient	15/1 (6.6 %)	Vinorelbine 20 mg/m^2 weekly	RR 6 %	Unknown
Degardin. et al. (1996) [8]	Phase II single-arm trial for first-line chemotherapy treatment	Unknown/40	Oxaliplatin 130 mg/m^2 every 3 weeks	RR 6 % (previously treated) DOR: 3 months (previously treated) RR 13 % (untreated) DOR: 2 months (untreated)	5 months
Murphy et al. (2001) [9]	Phase II single-arm (two dose cohorts) trial for first-line chemotherapy treatment	33/7 (21.2 %)	Irinotecan 125 mg/m^2 weekly ×4 every 6 weeks (19 patients)	RR 26.3 % RR 14.2 %	30.2 % (1 year)
			Irinotecan 75 mg/m^2 weekly ×2 every 3 weeks (14 patients)		
Pivot et al. (2001) [10]	Phase II single-arm trial for first-line chemotherapy treatment	34/Unknown	Pemetrexed 500 mg/m^2 every 21 days	RR 26.5 % TTF: 3.9 months	6.4 months
Martinez-Trufero et al. (2010) [11]	Phase II single-arm trial for pretreated patient (no more than one previous systemic chemotherapy)	40/Unknown	Capecitabine 1250 mg/m^2 bid 1–14 every 21 days	RR 24.2 % TTP: 4.8 months	7.3 months
Catimel. et al. (1994) [12]	Phase II single-arm trial including both first-line and pretreated patient	54/Unknown	Gemcitabine 800 mg/m^2 (or 1250 mg/m^2) weekly, 3 weeks on 1 week off	RR 13 %	Unknown

RR response rate, *PFS* progression-free survival, *TTP* time to disease progression, *TTF* time to treatment failure, *DOR* duration of response, *OS* overall survival

[a]No statistically significant difference among arms

5.2.1 Platinum Agents

Both cisplatin (*cis*-diamminedichloroplatinum(II)) and carboplatin (*cis*-diammine(1,1-cyclobutanedicarboxylato)platinum(II)) are platinum(II) complexes with two ammonia groups in the *cis* position. While cisplatin has two chloride "leaving" groups, carboplatin possesses a cyclobutane moiety. Although surgery with positive margin is a strong predictor of local recurrence, negative margin does not confer lack of disease relapse. Over 50 % of oral cavity cancers despite negative margin develop disease recurrence either locoregionally or at distant sites. Disease recurrence is often an indicator of incurability (Table 5.2).

Siddik has described the mechansism of action and resistance for cisplatin [18]. Cisplatin is first activated through a series of spontaneous equation reactions through which the *cis*-chloro ligands of cisplatin are replaced with water molecules [19]. The activated cisplatin then binds DNA and forms primarily intrastrand DNA adducts between adjacent guanines or a guanine and an adenine [19–21], which subsequently activates several signal transduction pathways, including those involving ATR, p53, p73, and MAPK, and eventually results in the activation of apoptosis [21]. Cisplatin has been the cornerstone of treatment for head and neck cancer. Carboplatin shares a similar mechanism of action as cisplatin. Carboplatin is generally less emetogenic, nephrotoxic, and neurotoxic but more myelosuppression than cisplatin [22].

In vitro studies using cisplatin-resistant cell lines have suggested the mechanism of resistance is multifactorial [23]. Any intracellular changes that interrupt the complex process of the cytotoxic effect of cisplatin, starting from the initial drug entry into cells to the final stages of apoptosis, will lead to drug resistance. These could occur through the reduction in drug accumulation due to either impaired influx through the cell membrane or enhanced efflux, inactivation of cisplatin by thiol-containing compounds, notably glutathione and metallothioneins, increased DNA adduct repair, and finally the inhibition of apoptotic activation induced by DNA damages. In HNSCC, a copper efflux transporter involved in the uptake of cisplatin, ATP7B, was found to contribute to the acquisition of cisplatin resistance in human oral squamous cell lines [24], and amplification of glutathione S-transferase π (GST-π) was suggested to be associated with cisplatin resistance and poor clinical outcomes in head and neck cancer patients treated with cisplatin-based therapy [25]. Of note, cisplatin-resistant tumors are fully cross-resistant to the platinum analogue carboplatin [26].

5.2.2 Taxanes

The taxanes are important newer class of anticancer agents that have showed activities in HNSCC. Initially derived from the bark of the scarce Pacific yew, paclitaxel can now be produced by partial synthesis from a precursor, 10-deacetylbaccatin III, derived from the needles of more abundant yew species [27, 28]. Docetaxel, an analogue of paclitaxel, is also derived semisynthetically from 10-deacetylbaccatin III [29].

Table 5.2 Selected platinum agent-based chemotherapy studies

Study	Trial design	Sample size (HNSCC/oral cavity)	Regimen	RR/PFS	OS
Liverpool Head and Neck Oncology Group (1990) [13]	Phase III randomized trial for first-line chemotherapy treatment	200/48	Cisplatin (100 mg/m^2) every 28 days	RR 21.5 %[a]	Single-agent cisplatin superior to single MTX alone, no significant difference among arms of cisplatin single agent or combination
			Methotrexate (40 mg/m^2) every 14 days		
			Cisplatin (100 mg/m^2) and 5-FU (1 g/m^2×4) every 28 days		
			Cisplatin (100 mg/m^2) and methotrexate (40 mg/m^2) every 28 days		
Forastiere et al. (1992) [14]	Phase III randomized trial for first-line chemotherapy treatment	277/unknown	Cisplatin (100 mg/m^2) and 5-FU (1 g/m^2×4) every 21 days	RR 32 %[b] DOR 4.2 months	6.6 months[a]
			Carboplatin (300 mg/m^2) and 5-FU (1 g/m^2×4) every 28 days	RR 21 % PFS 5.1 months	5.0 months[a]
			Methotrexate (40 mg/m^2) every 7 days	RR 10 % PFS 4.1 months	5.6 months[a]
Jacobs et al. (1992) [15]	Phase III randomized trial for first-line chemotherapy treatment	249/104	Cisplatin (100 mg/m^2) and 5-FU (1 g/m^2×4) every 21 days	RR 32 %[a] TTP <2.5 months[a]	5.7 month (no difference among arms)
			Cisplatin (100 mg/m^2) every 21 days	RR 17 %	
			5-FU (1 g/m^2×4) every 21 days	RR 13 %	
	Phase III randomized trial for first-line chemotherapy treatment		CABO (methotrexate (40 mg/m^2) days 1 and 15, bleomycin (10 mg) and vincristine (2 mg) days 1, 8, and 15, cisplatin (50 mg/m^2) day 4, every 21 days)	RR 34 %[a] PFS 19 weeks	

Clavel et al. (1994) [16]		356/140	cisplatin (100 mg/m^2) and 5-FU (1 g/m^2×4) every 21 days	RR 31 % PFS 17 weeks	29 weeks for the entire group, no difference among arms
			cisplatin (50 mg/m^2) days 1 and 8, every 28 days	RR 15 % PFS 12 weeks	
Gibson et al. (2005) [17]	Phase III randomized trial including both first-line and pretreated patient	104/18	Cisplatin (100 mg/m^2) and 5-FU (1 g/m2×4) every 21 days	RR 27 %[a]	8.7 months[a]
			Cisplatin (75 mg/m^2) and paclitaxel (175 mg/m^2 over 3 h) every 21 days	RR 26 %[a]	8.1 months[a]

RR response rate, *PFS* progression-free survival, *OS* overall survival
[a]No statistically significant difference among arms
[b]Higher response rates were statistically significant

Classically they bind to β-tubulin in microtubules, causing the formation of unusually stable microtubules and results in mitotic arrest [30–42], which further triggers the mitotic spindle checkpoint and results in apoptosis [42]. The main shared toxicities of paclitaxel and docetaxel are neutropenia and peripheral neuropathy. Hypersensitivity reactions to the polyoxyethylated castor oil vehicle of paclitaxel may occur during infusion. Transient sinus bradycardia can occur in patients receiving paclitaxel. Docetaxel may induce fluid retention, palmar-plantar erythrodysesthesia, and onychodystrophy. Less neurotoxicity but more stomatitis is associated with docetaxel than paclitaxel [43].

The intrinsic or acquired resistance to taxanes is often a multifactorial process, with the most common mechanism being through multidrug resistance (MDR) conferred by the expression of P-glycoprotein (Pgp), which is responsible for extruding taxanes across plasma membrane and the blood–brain barrier and/or associated coexpressed resistance mechanisms [44]. Additionally, altered metabolism of the drug, alterations in tubulin, and aberrant signal transduction pathways and/or cell death pathways can all contribute to the resistance as demonstrated by in vitro studies [24]. The feasibility of combining various Pgp inhibitors and taxanes were investigated extensively in multiple phase I clinical studies [27]. Inhibition of Pgp by tariquidar (XR9576) was detected in circulating mononuclear cells in patients with lung, ovarian, and cervical cancer [28]. However, whether Pgp inhibition can actually increase concentrations of anticancer agents in tumor tissue in the clinical setting remains to be demonstrated.

5.2.3 5-FU

5-FU is an analogue of the naturally occurring pyrimidine uracil. Upon entering the cells, it is converted to several active metabolites including fluorodeoxyuridine monophosphate (FdUMP), fluorodeoxyuridine triphosphate (FdUTP), and fluorouridine triphosphate (FUTP). The 5-FU cytotoxicities are executed through misincorporation of fluoronucleotides into RNA and DNA and inhibition of the nucleotide synthetic enzyme thymidylate synthase (TS) [45]. 5-FU is often administered as continuous infusion in HNSCC regimens. The common toxicities associated with 5-FU are diarrhea, mucositis, myelosuppression, and hand-foot syndrome [43].

Resistance to fluoropyrimidines is also a multifactorial event. Increased expression of TS; mutations in TS protein associated with reduced binding affinity to FdUMP; decreased levels of substrate for thymidylate synthase reaction; decreased corporation of 5-FU into RNA and DNA; decreased expression of mismatch repair enzymes, such as hMLH1 and hMSH2; increased DNA repair enzymes, uracil glycosylase and dUTPase; increased salvage of physiologic nucleotides including thymidine; and increased expression of the catabolic enzyme dihydropyrimidine dehydrogenase (DPD) are all associated with fluoropyrimidine resistance. Arsenic trioxide (ATO), an agent that inhibits TS protein and gene expression in vitro, significantly decreased TS gene expression in PBMC of all treated patients and the tumor tissue of half of the patients who underwent biopsy in a phase I study in colorectal cancer patients [31].

5.2.4 MTX

MTX enters cells through an active carrier transport mechanism or endocytic pathway. Inside cells, MTX is polyglutamylated and retained in the cells. MTX or its polyglutamylated form binds tightly to dihydrofolate reductase (DHFR) and inhibits the formation of tetrahydrofolate (THF). THF is required for thymidine biosynthesis. Additionally, polyglutamylated MTX also inhibits purine synthesis [46]. The main toxicities of MTX are myelosuppression and gastrointestinal toxicity [43].

Decreased carrier-mediated transport of MTX, increased expression or decreased binding affinity for MTX of DHFR and/or TS, decreased antifolate polyglutamylation through either decreased FPGS expression or increased expression of catabolic enzyme γ-glutamyl hydrolase, and expansion of intracellular THF cofactor pools are all involved in inherent and acquired resistance to MTX [47].

5.2.5 Cetuximab

Cetuximab is a human–murine chimeric immunoglobulin G1 (IgG1) monoclonal antibody that is directed against the human EGF receptor (EGFR). It competitively binds to the extracellular domain of the human EGFR. Cetuximab blocks binding of endogenous EGFR ligands, resulting in inhibition of the function of the receptor. Additionally, it induces downregulation of EGFR via internalization of EGFR and targets cytotoxic immune effector cells to EGFR-expressing tumor cells through antibody-dependent cell-mediated cytotoxicity [35].

Despite the clinical benefits observed with EGFR-targeted therapies, there are no validated biomarkers of response to cetuximab in HNSCC. The very high frequency of EGFR expression and low incidence of K-RAS exon 12/13 and EGFR tyrosine kinase domain mutations in HNSCC limit their utility in predicting response to cetuximab [36]. However, as observed in colorectal, non-small cell lung cancer, and pancreatic cancer, the presence and/or intensity of acneiform skin rash have been consistently associated with overall survival improvement in HNSCC [37].

5.3 The Role of Chemotherapy in Definitive Management

5.3.1 Chemotherapy with Concomitant Radiation as Adjuvant Therapy

5.3.1.1 Evidence

Surgery is the main modality of treatment of oral cavity cancer [48]. However, when the disease is locally advanced, the risk of relapse after surgery alone is high and additional treatment is usually indicated. Radiation therapy can eradicate micrometastases, decrease recurrence, and improve survival when offered postoperatively in patients with high-risk disease [49, 50]. The addition of concurrent chemotherapy can augment the effect of radiation, but it is often associated with increased

toxicities. Therefore identifying the patients who will derive a significant survival benefit from this approach is crucial. The combined data from two randomized studies, EORTC 22931 and RTOG 9501, defined the risk factors associated with poor outcome that can be overcome by the addition of concomitant chemotherapy to radiation therapy and established the proper criteria for postoperative concurrent chemoradiation [51–53].

Hazard ratio for overall survival	Primary end point	Definition of high risk	Percentage of patients with primary in oral cavity (%)	Study
OS was better with combined treatment. $p=0.02$ by the log-rank test; hazard ratio for death, 0.70; 95 % confidence interval, 0.52–0.95	Progression-free survival	Presence of tumor at the surgical section margins (at 5 mm or less), extracapsular extension (ECE) of nodal disease, clinical involvement of lymph nodes at levels 4 or 5 from carcinomas arising in the oral cavity or oropharynx, stage of pT3 or pT4 with any N except T3N0 of the larynx, N 2 or N3, perineural disease, and vascular embolism	26	EORTC
Overall survival was not significant (hazard ratio for death, 0.84; 95 % confidence interval, 0.65–1.09; $p=0.19$)	Locoregional disease control	Presence of tumor at the surgical section margins, ECE, and involvement of two or more lymph nodes	27	RTOG

Both studies demonstrated a significant improvement in locoregional control and disease-free or progression-free survival with combined modality therapy. However, the EORTC study showed a significant overall survival improvement, while the RTOG did not. A combined analysis of these two studies identified only ECE or positive margin as the most significant poor prognostic factors, and the addition of cisplatin to radiation improve all aspects of outcome including locoregional control, disease-free/progression-free survival, or overall survival in patients with those two risk factors. These studies provided the base for the risk-adapted strategies in postoperative adjuvant therapy and established ECE and positive margin as the indications for adding concomitant systemic chemotherapy to adjuvant radiation [51].

5.3.1.2 Recommended Regimen

Both EORTC 22931 and RTOG 9501 studies compared the addition of three planned cycles of concomitant cisplatin at 100 mg/m^2 every 3 weeks to radiotherapy (60–66 Gy, over 6–6.5 weeks, standard fractionation) with the same radiotherapy alone

in patients with high-risk features of oral cavity, oropharynx, larynx, or hypopharynx cancers. Hence concomitant cisplatin at 100 mg/m^2 every 3 weeks to radiotherapy on D1, D22, and D43 is the regimen of choice [52, 53]. Other variants of cisplatin dose like weekly administration and daily administration have been studied. It seems that weekly administered cisplatin is better tolerated than 3 weekly cisplatin. In addition patients unfit for weekly cisplatin have shown to have better tolerance to weekly cisplatin [54, 55, 56, 57].

5.3.1.3 Applicability in Oral Cancers

As more than 1/4th of patients in both studies were having oral cavity primary. These results seem applicable at this site.

5.3.1.4 Future Studies

As there is lack of studies dealing with oral cancers alone in this situation, Tata Memorial Hospital, Mumbai, has recently concluded a study called OCAT (oral cancer adjuvant treatment). This study of nearly 900 odd patients will further clarify the adjuvant treatment in oral cancers.

5.3.2 Chemotherapy with Concomitant Radiation as Primary Curative Management in Unresectable Disease

5.3.2.1 Evidence

Although primary surgical management has been widely accepted as the standard approach in treating locally advanced oral cavity cancers, in patients with surgically unresectable disease or patients who are medically inoperable, definitive radiotherapy can be offered as an alternative. When compared with radiation therapy alone, the addition of concurrent chemotherapy to radiation has been shown to be consistently associated with improved survival in patients with locally advanced HNSCC in randomized studies, and meta-analyses, therefore, should be offered to patients with locally advanced disease who are able to tolerate this approach [2, 58–61].

In an intergroup trial reported by Adelstein et al., 271 (oral cavity: 36) patients with unresectable locally advanced head and neck cancer were randomized to one of three arms: radiotherapy alone (70 Gy), concurrent cisplatin (100 mg/m^2 days 1, 22, and 43) and radiotherapy (70 Gy), or concurrent cisplatin and 5-fluorouracil (every 4 weeks) with split-course radiotherapy (radiotherapy to 30 Gy, evaluation for surgical respectability, then 30–40 Gy additional radiotherapy if unresectable or complete response). With a median follow-up of 41 months, concurrent cisplatin and radiotherapy without a planned treatment break led to a statistically significant survival benefit comparing with radiation alone (37 % vs. 23 % $p = .014$) without changing the rate of distant metastases, although more treatment-related toxicities were observed in the concurrent chemotherapy and radiotherapy arms [56].

In the meta-analysis of chemotherapy in head and neck cancer (MACH-NC) of 87 trials, Pignon et al. compared locoregional treatment with or without chemotherapy. The study showed that the addition of chemotherapy to radiotherapy

yielded an improvement in survival, with an overall absolute benefit of 4 % at 5 years. There was no significant benefit of adjuvant or neoadjuvant chemotherapy observed; however, a significant benefit of concomitant chemotherapy (absolute benefit at 2 and 5 years of 8 %) was detected [60, 61]. The update of MACH-NC further demonstrated that the benefit of concomitant chemotherapy appears to be similar irrespective of whether the radiotherapy was given conventionally or using altered fractionation. The study also concluded that multi-agent chemotherapy did not provide a significant benefit over single-agent cisplatin in the concurrent setting, although the effect of chemotherapy was significantly higher ($p=0.006$) with platinum than other mono-chemotherapy agents, and the magnitude of the benefit of concomitant chemotherapy is less in older patients [2].

In another meta-analysis comparing radiotherapy versus chemoradiation, Budach et al. adopted more strict criteria to exclude the trials using outdated chemotherapy agents or suboptimal radiation schedules. The study also intended to compare different radiation dose and fractionation schedules and chemotherapy regimens used in the chemoradiation trials. A large survival benefit of 12.0 months was observed in favor of concomitant chemoradiation irrespective of whether the radiation was delivered by conventionally fractionated, hyperfractionated, or accelerated schedules [62].

5.3.2.2 Recommended Regimen

On the basis of MACH-NC, single-agent cisplatin seems to be the modality of choice. The dose of cisplatin commonly used is same as the adjuvant CTRT.

In addition to cytotoxic chemotherapy, cetuximab, a monoclonal antibody against the epidermal growth factor receptor, is also associated with improvement in the local regional control (24.4 months vs. 14.9 $p=0.005$) and median overall survival (49 months vs. 29.3 $p=0.03$) when given with radiation concomitantly as reported by Bonner et al.]. *Of note*, *oral cavity cancer patients were excluded from the study* [63].

5.3.2.3 Applicability in Oral Cancers

These results seem to be completely applicable in oral cancers. The trial of Adelstein et al. had only 13 % of patients with oral cancers but MACH-NC analysis had more than 2000 patients of oral cancers included. Further the comprehensive site-specific analysis clearly shows that 5-year absolute benefits associated with the concomitant chemotherapy were 8.9 % in oral cavity cancers.

5.3.3 Chemotherapy as Induction Therapy in Resectable Disease

5.3.3.1 Evidence

Adding induction chemotherapy to standard surgery has also been tested extensively, but has not been proven to be effective in improving survival. In a randomized prospective study focused on oral cavity cancer reported by Licitra et al.,

patients with a resectable, stage T2–T4 (>3 cm), N0–N2, M0 disease were randomized to surgery with or without induction chemotherapy. Although a high response rate (clinical complete response rate 27 %) was achieved after three cycles of cisplatin and fluorouracil induction treatment, no significant difference in overall survival was detected, and a 55 % 5-year overall survival was observed in both arms. Nevertheless, the patients in the chemotherapy arm needed less segmental mandibulectomy (31 % vs. 52 % in the control group) and postoperative radiotherapy (33 % v 46 %). Since both procedures are associated with poor quality of life, the observation raised the question whether this approach can facilitate organ and function preservation and improvement of posttreatment quality of life [64, 65]. Similar findings of inability of TPF (triple drug) induction chemotherapy to improve survival in resectable oral cancers were published by Zhong et al. In addition NACT would identify a subset of patients who had pathological CR who had very good outcomes. In Licitra et al. publication, patients with either a pathologic complete response or with minimal residual disease had a 5-year disease-free survival rate of 85 % versus 49 % of cases with evident persistent disease ($p = .001$) [64].

5.3.3.2 Applicability in Oral Cancers

Both studies by Licitra et al. and Zhong et al. were done exclusively in oral cancer patients. At present induction chemotherapy cannot be recommended in resectable oral cancers for improvement in survival.

5.3.3.3 Future Studies

The study done by Licitra et al. showed that after induction chemotherapy, less segmental mandibulectomy was required. Hence this hypothesis that induction chemotherapy in oral cancers may be able to preserve mandible in resectable oral cancers who would have required upfront mandibular resection has been tested in a study in Tata Memorial Hospital, Mumbai.

Neoadjuvant chemotherapy has failed to improve survival. However metronomic chemotherapy given as neoadjuvant and then as maintenance for 18 months has shown to improve survival in oral cancers in a small retrospective study by Pai et al. [66]. This finding has been now tested in a large randomized study.

5.3.4 Chemotherapy as Induction Therapy in Unresectable Disease

When induction chemotherapy is used in conjunction with concurrent chemoradiation in HNSCC, the treatment is referred as sequential chemoradiation. The rationale underlying the use of induction chemotherapy is based on the expectation that drug delivery is better in untreated well-vascularized tumor, and the eradication of micrometastatic disease may be achieved because of high response rate and better tolerance to induction chemotherapy in treatment-naive HNSCC patients. However, this approach has been examined in multiple clinical trials for more than two decades without consistent proof of benefit.

In the MACH-NC meta-analysis and its update, although an absolute benefit of 4.5 % at 5 years is associated with the addition of chemotherapy to locoregional therapy, data did not show clear evidence of a benefit for induction chemotherapies. Even though a significant benefit with platinum plus fluorouracil (hazard ratio 0.88, 95 % CI 0.79–0.97) was reported in the analysis, this has not been verified in a single large randomized study [2, 61].

In three phase III randomized studies, this approach of induction chemotherapy followed by CTRT versus CTRT alone was evaluated with regimens containing newer cytotoxic agents, paclitaxel or docetaxel. All three studies failed to meet its primary end point [67–69]. Induction chemotherapy failed to improve the locoregional control or the overall survival. However in all three studies (Haddad et al., Cohen et al. and Hitt et al.), the percentage of patients with oral cancers was below 15 %, and these studies were not planned only for unresectable disease (but also included patients with resectable locally advanced cancers and candidates of organ preservation). Two of these studies, DeCIDE and PARADIGM, had nonstandard chemoradiation schedule and failed to complete its accrual [67, 68].

In a phase III study by Paccagnella in patients with operable or inoperable disease the impact of PF induction chemotherapy before definitive locoregional treatment was studied. There was no significant difference in overall survival between the two treatment groups. However, when the analysis was restricted to patients with inoperable disease, there was a modest survival advantage associated with induction chemotherapy [70].

5.3.4.1 Applicability in Oral Cancers

Very few patients in recent studies of induction chemotherapy had unresectable oral cancers, so applicability of these results to unresectable oral cancers is questionable. Similarly in MACH-NC analysis, though it had 4000 odd oral cancer patients, the subgroup analysis was never done for unresectable patients; hence the applicability of its results too need to be taken with a pinch of salt.

The recommendation of giving chemoradiation in unresectable oral cancers is not without issues pertaining to oral cancers. In unresectable cancers the volume of treatment required to cover the CTV is large. The tolerance of chemotherapy with such large fields is not well studied. The clinical judgment is imperative here.

5.3.4.2 Future

Induction regimens incorporating targeted agents have also been investigated in multiple phase II studies. Cetuximab has been combined with cisplatin and docetaxel (TPE), paclitaxel and carboplatin, or 5-FU, docetaxel, and cisplatin as induction therapy. Radiographic response rate after induction chemotherapy ranged from 76 to 96 %. Two-year PFS and OS with the TPE regimen was 80 % and 88 %, while 3-year PFS and OS with the cetuximab, carboplatin, and paclitaxel induction regimen was 87 % and 91 %, respectively [71, 72].

5.3.5 Chemotherapy as Induction Therapy in Technically Unresectable Disease

5.3.5.1 Evidence

Resectability of oral cancers is a subjective decision. The extent of the disease and surgical expertise both come into question. There are certain sites when involved by oral cancer these tumors then are considered unresectable. These are prevertebral fascia, complete encasement of carotid artery, and invasion of skull base. However certain T4b oral cancers and certain T4a oral cancers satisfying certain criteria are termed as technically unresectable. These criteria are highlighted in publication by Patil et al. [73]. These are;

1. Buccal mucosa primary, with diffuse margins and peritumoral edema going up to or above the level of zygomatic arch and without any satellite nodules
2. Tongue primary {anterior two-thirds} with the tumor extending up to or below the level of the hyoid bone
3. Extension of tumor in anterior two-thirds of oral tongue in the vallecula
4. Extension of tumor into the high infratemporal fossa, as defined by the extension of tumor above an axial plane passing at the level of the sigmoid notch
5. Extensive skin infiltration impacting the achievement of negative margins

These cohorts of patients when attempting resection can lead to high rate of margin-positive resections. Recently a large experience of 721 patients with stage IV technically unresectable oral cavity cancers receiving NACT was published. Three hundred and ten patients (43 %) had sufficient reduction in tumor size and underwent surgical resection. The locoregional control rate at 24 months was 20.6 % for the overall cohort, 32 % in patients undergoing surgery, and 15 % in patients undergoing nonsurgical treatment ($p=0.0001$). The median estimated OS in patients undergoing surgery was 19.6 months (95 % CI, 9.59–25.21 months) and 8.16 months (95 %, CI 7.57–8.76) in patients treated with nonsurgical treatment ($p=0.0001$) [73].

5.3.5.2 Applicability in Oral Cancers

The experience quoted is applicable to oral cancers only.

5.3.6 The Role of Chemotherapy in Palliation

For patients with recurrent and/or metastatic HNSCC (R/M HNSCC) who are considered incurable with surgery or radiation, systemic chemotherapy represents the mainstay of treatment. Chemotherapeutic agents can be used either in combination or as single agent in the management of M/R HNSCC including oral cavity cancers.

5.3.6.1 Single-Agent Chemotherapy

Data on the survival benefit derived from single-agent chemotherapy in recurrent or advanced head and neck cancer is limited. In a small randomized study, 31 (oral cavity: eight) patients treated with single-agent cisplatin demonstrated a 10-week improvement in survival compared with 26 (oral cavity: six) patients who received best supportive care. In this study, age, performance status, nodal status, number of courses, and response of the tumor were found to be associated with survival [64]. No single chemotherapeutic agent has conclusively showed superiority in terms of overall survival over another drug in a randomized clinical trial in R/M HNSCC. The response rates with cisplatin, carboplatin, 5-FU, MTX, paclitaxel, and docetaxel are generally in the 14–42 % range [13–16, 24, 74–88], while response duration is generally between 3 and 5 months [4].

Patients with platinum-refractory R/M HNSCC have a much lower response rate to other cytotoxic agent and very poor survival. Single-agent cetuximab has achieved a response rate of 13 % and median time to progression of 70 days in this population in a multicenter phase II trial study reported by Vermorken et al. [89, 90]. Based on this data, cisplatin has become a standard therapy in patients with platinum-refractory disease [91, 92].

5.3.6.2 Combination Chemotherapy

The use of combination therapy in general yields a statistically significant increase in the response rate to a range of 30–60 % but is associated with increased treatment-related toxicities. In most randomized studies comparing combination cytotoxic chemotherapies, no superiority in overall survival has been demonstrated with one regimen over another [4].

5.3.6.3 Combination Chemotherapy + Targeted Agent

In a randomized study comparing cisplatin-based chemotherapy with or without cetuximab, an EFGR targeting agent, a statistically significant improvement in survival was achieved with the addition of cetuximab. In this study, 442 (oral cavity: 88) subjects with R/M HNSCC were randomized to receive cisplatin (or carboplatin) and 5-FU with or without cetuximab for six cycles. Subjects on the experimental arm then continued cetuximab monotherapy until disease progression or unacceptable side effects. No crossover occurred between groups. The addition of cetuximab to the platinum doublet significantly prolonged the median overall survival from 7.4 to 10.1 months, prolonged the median progression-free survival time from 3.3 to 5.6 months, and increased the response rate from 20 to 36 % ($P<0.001$). In the subgroup analysis, oral cavity cancer patients had an improvement in overall survival (11.0 vs. 4.4 months, HR of 0.42 (0.26–0.67)) and progression-free survival (6.1 vs. 2.8 months, HR of 0.34 (0.21–0.55)) associated with the addition of cetuximab. No significant association between the appearance of a rash and survival (hazard ratio for death, 0.77; 95 % CI, 0.55–1.09; $p=0.14$ by the score test) was detected in this study. Since no crossover occurred for patients in the control group of the study, whether a sequential approach with platinum doublet until progression, followed by cetuximab monotherapy will achieve a similar survival benefit remains unclear [93].

The combination of cetuximab and cisplatin has been examined in a randomized phase III study evaluating cetuximab in untreated R/M HNSCC. One hundred and seventeen (oral cavity: 24) analyzable patients were randomized to cisplatin with placebo or cetuximab. Despite improved response rate detected in the cetuximab and cisplatin combination arm (26 % vs. 10 %, $p=0.03$), no significant benefit in OS or PFS was achieved by adding cetuximab to cisplatin [90]. Nevertheless, there appeared to be a survival advantage for the development of rash in patients who were treated on the cetuximab and cisplatin combination arm. Although evaluated in multiple phase II studies in the induction setting, cetuximab and taxane combinations have not been evaluated in R/M HNSCC in randomized prospective studies.

5.3.6.4 Metronomic Chemotherapy

Metronomic chemotherapy has shown a promise in palliative setting in head and neck cancers. In a recently concluded randomized study, patients in the metronomic (MCT) arm had significantly longer PFS (median 101 days, 95 % CI: 58.2–143.7 days) compared to the cisplatin (IP) arm (median 66 days, 95 % CI; 55.8–76.1 days) ($p=0.014$). The overall survival (OS) was also increased significantly in the MCT arm (median 249 days, 95 % CI: 222.5–275.5 days) compared to the IP arm (median 152 days, 95 % CI: 104.2–199.8 days) ($p=0.02$). There were fewer grade 3/4 adverse effects with MCT, which was not significant (18.9 % vs. 31.4 %, $p=0.14$) [94].

Applicability of Results to Oral Cancers

EXTREME study had 19 % patients with oral cancers. In subgroup analysis the maximum benefit in survival was achieved in patients with oral cancers (HR-0.42 95 % CI 0.26–0.67) [93].

Conclusion

Chemotherapy plays an important role in the management of oral cavity cancer. Postoperative adjuvant concurrent chemoradiation is indicated in patients with high-risk diseases. Definitive concurrent chemoradiation can be used as primary treatment in patients with locally advanced oral cavity cancer who are not a candidate for surgical resection. The benefit of sequential approach (induction chemotherapy followed by concurrent chemoradiation) remains to be proven. Chemotherapy is associated with survival benefit in patients with metastatic disease. EGFR-targeted therapy has demonstrated its efficacy in both curative and palliative management.

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Surgical Management of Oral Squamous Cell Carcinoma

6

Moni Abraham Kuriakose and Nirav P. Trivedi

6.1 Introduction

Surgery remains one of the principal treatment modalities of oral squamous cell carcinoma. With improved understanding of biologic behavior, pattern of spread of tumors of different subsites, and instrumentation, several technical modifications have been adopted in the recent past to improve oncological, functional, and aesthetic outcome of ablative surgery for oral cancer.

Oral cavity consists of various subsites that include lip, alveolus, buccal mucosa, tongue, floor of mouth, and hard palate. Each of these subsites has unique anatomic features that determine the pattern of invasion of tumor and biologic behavior. In addition, each of these subunits plays varying vital functions such as speech, mastication, and swallowing. Ablative surgery of these subsites would result in different degree of functional and cosmetic morbidity with significant impact in quality of life of patients. It is essential to select the appropriate surgical approaches and extent of resection that offers the best oncologic and functional outcome.

For early stage (T1) oral cavity cancers, though both surgery and radiation therapy offered similar oncologic outcome, morbidity associated with radiation of oral cavity prevented its wider use. It is observed that functional outcome is poorer with

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primary radiotherapy compared to primary surgery due to associated xerostomia, mucositis, long-term food intolerance, "radiation-caries" affecting teeth and risk of osteoradionecrosis. In comparison, primary surgery is better tolerated, faster, and less morbid. For advanced cancers that require multimodality treatment, surgery followed by radiotherapy or chemoradiotherapy (CT-RT) has been the standard of care for many years and continues to be so.

6.2 Principles of Ablative Surgery

The goal of ablative surgery is to remove tumor with microscopically uninvolved margin with least aesthetic and functional impairments. Balancing these two contradicting objectives require precise understanding of the subsite anatomy and function, pattern of invasion of tumor, and tumor biology. To meet these goals, oncologic surgical principles pertaining to the oral cavity needs to be followed. These include:

1. Adequacy of surgical margins
2. Appropriate utilization of intraoperative pathologic consultation (frozen section)
3. Wide excision versus compartmental resection
4. Access to oral cavity

6.2.1 Adequacy of Surgical Margins

Surgical margin is one of the few critical prognostic factors that is within the control of the surgeons. It has been demonstrated decades ago that failure to achieve uninvolved surgical margin is the single most important factor that determines the patient's mortality [1]. Positive surgical margin correlates with poor prognosis both in terms of locoregional failure and overall survival [2]. Reported local control rate with positive margin range from 20 to 45 % and disease-specific survival rate from 7 to 10 % [58, 59]. In a discussion of 12 studies investigating incidence and impact of close or positive margin in oral squamous cell carcinoma, Ch'ng et al. reported the incidence range from 5 to 94 % (median 29.6 %) depending on the oral cavity subsite [9].

6.2.1.1 Definition of Surgical Margin

There have been different definitions for surgical margin used in the past making it difficult to compare and interpret results from different studies. There is a general consensus that more than 5 mm of normal mucosa is considered as negative margin. Cut-through or margin less than 1 mm is considered as positive margin. Between 5 and 1 mm is considered as close margin [11, 12, 18]. The major controversy is with respect to close margin, in particular the presence of dysplasia in the surgical margin.

Slootweg et al. [14] included dysplasia of any grade at the margin as positive margin. Weijers et al. [13] considered less than 5 mm normal mucosa or dysplastic lesions as close margin. According to Garzino-Demon et al. [15], severe dysplasia,

carcinoma in situ or cut-through is considered as positive margin. Chiou et al. [16] used 1, 2, 3, 4, and 5 mm of normal mucosa and observed that 3-year locoregional control was 71 % in patients less than 3 mm margin and 95 % for those with over 3 mm margin. Therefore, over 3 mm of normal tissue was considered as negative margin. Spiro et al. [17] considered less than 1 high-power field as close margin and cut-through tumor as positive margin.

Studies have carried out to evaluate the impact of locoregional recurrence and survival rate in relation to the presence of dysplasia in the margin [19]. It was demonstrated that the presence of dysplastic mucosa at the surgical margin increases local recurrence rate (80 %), however, does not have an impact on disease-specific survival rate (60 %). The presence of carcinoma in situ and invasive carcinoma at the surgical margin has equal local recurrence rate (84 % vs 64 %) and similar poor disease-specific survival rate (23 % vs 28 %).

According to the UK Royal College of Pathologists guidelines [12], the lack of invasive carcinoma 5 mm away from the surgical margin is considered as negative margin, 1–5 mm as close and less than 1 mm as involved margin. According to these criteria, histologic cut-through tumors and those with less than 1 mm normal mucosa are considered as positive margin. This guideline does not take into consideration the presence or absence of dysplasia at the surgical margin. The margins should be separately reported for the mucosal and deep surfaces, and the presence of dysplasia and its grade should be noted separately.

6.2.1.2 Factors Determining Surgical Margin Status

Various factors can contribute towards surgical margin status. This include method of fixation of specimen, tumor site, choice of surgical approach, pattern of invasion, perineural invasion, lymphovascular invasion, tumor size, grade of tumor, and skill of surgeon.

It is to be noted that "surgical margin" will be different from the "pathologic margin" because of the tissue shrinkage. The degree of tissue shrinkage depends on the fixation agent as well as tissue type. The shrinkage observed after fixation in tongue was 25 % and that of buccal mucosa 33 % [10]. Hard tissue shrinkage is expected to be much less. This is the rationale for choosing 1 cm surgical margin to secure more than 5 mm pathologic margin.

Sutton et al. [39] in a series of 200 consecutive patients who underwent primary surgical resection for oral cancer investigated various factors that can contribute to the close or positive margin. They used Batsakis classification of surgical margin in this series and observed 42 % close and 4.5 % positive margin. The close or positive margins were associated with large size tumor (>2 cm), perineural invasion, lymphovascular invasion, high-grade tumor, and invasive tumor front. However the surgical margin did not correlate with the surgical access and between surgeons. This implies that close or positive margin is a product of aggressive tumor rather than inadequate surgical technique.

Scholl et al. [28] in a series of 268 patients with oral tongue carcinoma observed positive margin in 54 patients (20.1 %). They have observed worse local recurrence rate in patients who were made to have negative margin following re-excision of an

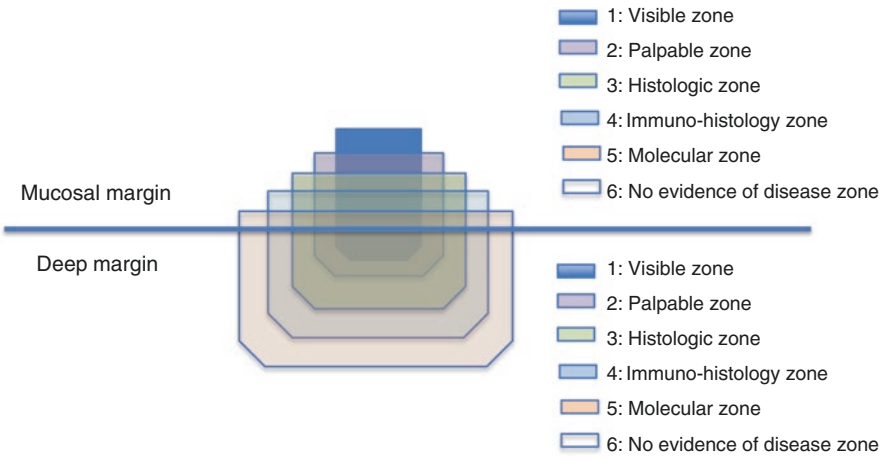


Fig. 6.1 Schematic representation of surgical margin, based on the method used to interpret the margins. Surgical margins need to be assessed at mucosal and soft tissue level

initial positive margin compared to those with negative margin at the first excision. This further underscores the fact that positive margin is a marker of aggressive tumor biology.

6.2.1.3 Biologic Basis of Surgical Margin

Upile et al. [20] have identified six zones denoting the extent of tumor on the mucosal surface based on the level of resolution of the detection method – visible zone, palpable zone, histologic zone, immunohistocytochemical zone, molecular zone, and tumor-negative zone. One can assume that the same phenomenon may be encountered for the deeper margins too (Fig. 6.1). However, the mechanism of tumor extension to the adjacent normal tissue is distinct for both these regions. While the extent of tumor spread on the mucosal surface is related to field cancerization, at the submucosal plane, it is determined by the pattern of invasive tumor front. The biologic basis of these two processes is quite distinct. The ideal goal of ablative surgery is to excise the tumor along tumor-negative zone.

Filed Cancerization

The biologic basis of field cancerization is described in detail in Chap. 1. Oral cancer develops as a multistep, multifocal process. Slaughter et al. [4] suggested the hypothesis of field cancerization based on their observation that serial sectioning of histologic examination of normal appearing mucosa revealed preneoplastic clones of cells away from the primary tumor. These lesions arising in a preconditioned epithelium can progress into new cancer. Based on the spatial and temporal relationship as well as the genetic similarity, Braakhuis et al. [40] proposed three distinct types of local tumor relapse: local recurrence, second primary tumor, and second field tumors (Fig. 6.2). Tumors that are developed less than 2 cm away from the primary tumor and in less than 3 years are considered as local recurrence. If they are

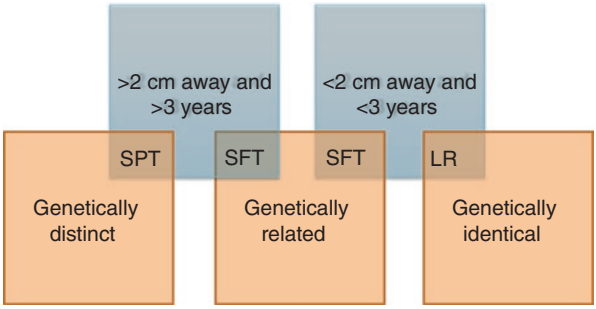


Fig. 6.2 Spatial, temporal, and genetic relationship of local disease relapse. *LR* local recurrence, *SFT* second field tumor, *SPT* second primary tumor (Adapted from Braakhuis et al. [40]

genetically identical, it can be considered as true local recurrence. If they are genetically related, it is considered as second field tumors. Those tumors that arise more than 2 cm away or over 3 years after the first tumor, it can be considered as second primary tumor. Based on the genetic similarity to the initial tumor, it can be considered as second field tumor if the tumor is genetically related or as true second primary tumor if they are genetically distinct. The genetic identity of the tumor in this study was carried out by analyzing the pattern of loss of heterozygosity at position 3p12, 3p14, 3p21, 3p24.3, 9p21, 17p11-12, and 17p13.1 [3]. It has been observed that these genetic changes can occur 5–7 cm away from the primary tumor.

Several molecular markers have been employed to identify conditioned mucosa. This includes p53 [6], eIF4E [7], methylation-specific polymerase chain reaction for promoter hypermethylation of O-6-methylguanine-DNA-methyltransferase (MGMT) gene, a DNA repair gene [5]. The clinical application of this technique is limited by the fact that these assays have high false-positive rates as well as it takes over 5 h to process the sample, limiting its intraoperative usage. It was also observed that adjuvant postoperative radiation therapy did not improve recurrence rate in subjects with molecular margin positive tumors [8].

Pattern of Invasion

It has been reported that deep positive margin carried a worse prognosis compared to mucosal positive margin. Pattern of invasion of tumor is considered as the primary determinant of probability of deep margin positivity. Brandwein-Gensler et al. [41] studied this relationship in a series of 168 patients with oral squamous cell carcinoma. They modified the existing pattern of invasion grading into five types: type 1, board tumor front; type 2, fingerlike tumor front; type 3, tumor islands of >15 cells; type 4, tumor islands with <15 cells; and type 5, tumor islands with <15 cells more than 1 mm apart. They have observed higher locoregional failure and overall survival in patients with more infiltrative tumor. They have also reported increased incidence of positive margin, perineural invasion, and low lymphocyte infiltration with more infiltrative tumor. Combining these prognostic factors (pattern of invasion, perineural invasion, and lymphocyte infiltration), the authors identified three risk groups. They have observed that while for high-risk group adjuvant postoperative radiotherapy was beneficial, in low-risk groups even with positive

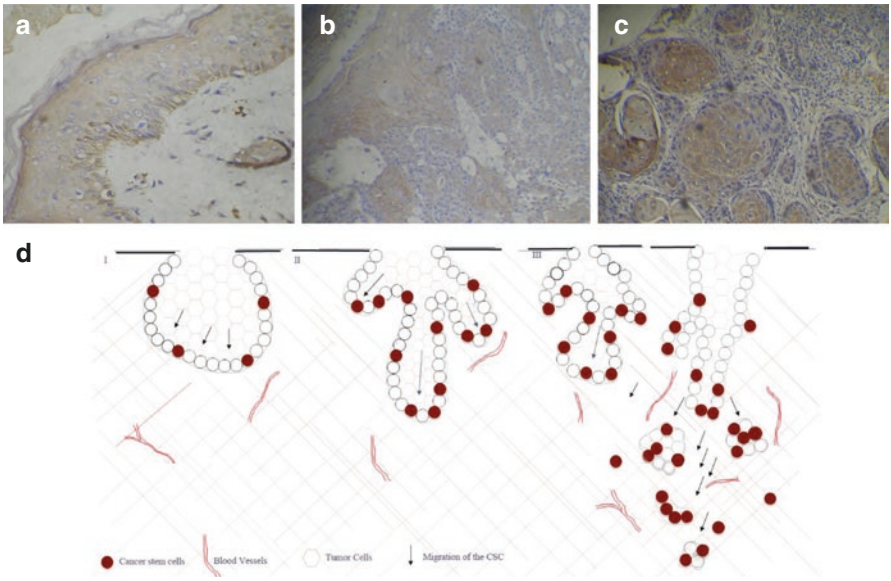


Fig. 6.3 Correlation of pattern of invasion and cancer stem cells. (**a**) Pushing boarder, (**b**) finger-like boarder, (**c**) infiltrative boarder. (**d**) Concept of cancer stem cells defining the pattern of invasion (Sindhu et al. [9])

margin, there was no additional benefit with adjuvant radiotherapy. This fact was further confirmed by Ch'ng et al. [7]. In a series of 144 patients with close but uninvolved margin (<5 mm), surgery alone obtained locoregional control rate of 91 % and disease-specific survival rate of 84 %. They have also observed stepwise reduction of the disease-specific surgical rate with each addition of high-risk factors of infiltrative pattern of invasion, perineural invasion, depth of invasion, and tumor subsite (buccal mucosa).

Sindhu et al. [9] further evaluate the factors that determine the pattern of invasion and which confer poor treatment outcome. They have hypothesized that the pattern of invasion of oral cancer is determined by the density of cancer stem cells (CSC); the higher the density of cancer stem cells the worse the pattern of invasion (Fig. 6.3). Furthermore, the CSCs have higher migration capacity as well as are resistant to both radiation and chemotherapy. They have observed a close correlation of pattern of invasion and putative cancer stem cell marker CD44 and poor treatment outcome. The CD44 expression also correlated with perineural invasion as well as lower lymphocyte infiltration.

6.2.1.4 Clinical Implications

Based on the above findings and randomized clinical trial of adjuvant therapy in head and neck cancer [42], one can formulate an algorithm for adjuvant treatment. This data is summarized in Table 6.1. It is to be noted that level 1 evidence is available only in determining when to give adjuvant chemoradiotherapy. All other recommendations are based on the interpretation of basic science and clinical research data, the art of clinical medicine practice.

Table 6.1 Clinical decision making based on the surgical margin status

Margin Status	Management strategy	Prognosis[a]	Reference
>5 mm histologically uninvolved margin, no dysplasia, or molecular markers of field cancerization[b]	Standard clinical follow-up[c]	Good local control rate (91.6 %) and good disease-specific survival (70.5 %)	Nason et al. (2009) [37]
>5 mm histologically uninvolved tissue, evidence dysplasia, or molecular markers of field cancerization in adjacent mucosa[b]	No adjuvant treatment, intense follow-up for early detection of second field cancer or second primary tumor, counseling for habit cessation and enroll in chemoprevention trials	High risk for second field cancer or second primary tumor (80 %) but has good disease-specific survival rate (60 %). Presence of carcinoma in situ has similar local recurrence rate (84 % vs 64 %) and similar poor disease specific survival rate (23 % vs 28 %).	Looser et al. (1978) [19] Tabore (2001) [3]
>5 mm histologically uninvolved tissue, with additional poor prognostic factors[d]	Consider adjuvant radiation	Moderate local disease control rate 74–91 %	Brendwein-Genslet et al. (2005)
<5 to >1 mm histologically uninvolved tissue with no additional poor prognostic factors[d]	No adjuvant treatment, standard follow-up	Good local control rate (87–91.4 %) and good disease-specific survival (84 %)	Ch'ng et al. (2013) [9] Weijers et al. [13] Brendwein-Genslet et al. (2005)
<5 to >1mm histologically uninvolved tissue with additional poor prognostic factors[d]	Adjuvant radiation	Moderate local control rate (86.4 %) and overall survival rate (69.6 %)	Nason et al. (2009) [37] Ch'ng et al. (2013) [9] Brendwein-Genslet et al. (2005)
<1 mm histologically uninvolved tissue or cut-through margin	Reresection if technically and clinically feasible[e] followed by CT-RT	Low local control rate (20–45 %) and disease-specific survival rate (7–10 %)	Byers (1978) [58] Chen (1987) [38]

[a]Prognosis in relation to surgical margin status. All other factors are considered equal

[b]Molecular markers of field cancerization: LOH markers, eIF4E,p53, p16, CD44

[c]Standard follow-up regimen: clinical review once every two months during the first year, 3 months during the second year and every six months during years 3 to five, and once a year since then

[d]Poor prognostic tumor features: infiltrative boarders, perineural invasion, lymphovascular invasion, high CD44 expression, and low lymphocyte reaction at the tumor borders Ch'ng et al. [9], Weijers et al. [13], Brendwein-Genslet et al. (2005)

[e]As positive surgical margin is often associated with poor prognostic features and not always due to technical error, CT-RT is recommended even after securing negative margin after reresection

6.2.2 Intraoperative Pathology Consultation (Frozen Section)

Intraoperative pathology consultation (frozen section) is often required for the successful execution of ablative surgery. It is essential for surgeons to know the capabilities and limitations of intraoperative pathologic consultation. The surgeons also should have a good working relationship and effective communication plan with the pathologists.

Common indications for intraoperative consultations are the following:

1. Frozen section of surgical margins to ensure completeness of resection.
2. Intraoperative assessment to plan the extent of surgical procedure (e.g., marginal vs segmental mandibulectomy).
3. Ensure that the diagnostic sample has representative tissue.
4. Evaluation of lymph nodes.

Frozen section of oral squamous cell carcinoma has a diagnostic accuracy rate (correlation of frozen section with that of permanent section) of about 97 % [22–26, 32]. About 3 % diagnostic error is attributed to improper sampling, technical error, interpretation inaccuracies, and error in communication. It is to be noted that the incidence of false-positive result is about 1 % [56]. Even with this high diagnostic accuracy rate, the frozen section needs to be used judiciously. Chathurvedi et al. [27] have questioned the value addition of frozen section over clinical examination, i.e., can frozen section detect lesions that could not have been detected clinically?

(a) *Frozen section of surgical margins*: The goal of this procedure is to ensure that surgery has removed the microscopic tumors from all the margins. Different institutions and surgeons have varying policies in handling the surgical specimens for frozen section to determine adequacy of surgical resection. (1) Send the entire specimen to the pathologist after insertion of orientation stitches. (2) Send additional circumferential margins from all around the resection bed and request frozen section of the re-excised tissue. (3) Margins from five to six regions of the surgical bed (medial, lateral, anterior, posterior, deep), or (4) margins from areas of close or suspicious margins. Considering the efforts required for the pathologists to process the tissue and to minimize interference with final pathology and normal tissue, option 4 or 5 is commonly practiced. It is essential that the tissue is appropriately labeled so that the frozen section result can be used effectively for further treatment decision making.

Although frozen section to permanent section concordance is over 97 %, there are areas of potential pitfalls in selected scenarios. Dysplastic lesions, which are difficult to interpret even by permanent sections, cannot be reliably evaluated by frozen section. Differentiation of pseudoepitheliomatous hyperplasia resulting from augmented tissue response to irritants can clinically mimic squamous cell carcinoma. The pathologic differentiation is based on cellular atypia and connective tissue invasion. These features are difficult to determine by frozen section. Another scenario is differentiating postradiation changes

from recurrent carcinoma. Although clinical and histologic features of acute radiation changes are nearly impossible to distingush from persistant carcinoma, it is rarely a practical issue as biopsy or surgical salvage are rarely carried out during the immediate post-radiation period. About 2 months after radiation, typical features of radiated oral mucosa can be appreciated. Recognizing these well-described features can help to distinguish persistent or recurrent tumors from radiation changes. These include atrophy of epithelium, cellular atypia, pseudoepitheliomatous hyperplasia of the minor salivary glands, squamous metaplasia of the salivary gland ducts, endothelial cell hypertrophy, and atypical fibroblasts.

(b) *Intraoperative decision making*: Frozen section is used in deciding what critical structures are to be sacrificed. This includes the margin from the carotid sheath and the tissue adjacent to the mandible or within the bone marrow to determine bone and perineural invasion along the nerves. Mandible of cranial nerves carries major morbidity frozen section is often employed to determine the tumor invasion status. It is to be noted that though the frozen section of the bone may not be feasible in many centers, imprint cytology or curettage from the marrow can help to determine adequacy of the bony margin. Other clinical scenarios include surgical margin around contralateral lingual artery during resection of advanced oral tongue carcinoma to determine whether the patient requires total glossectomy and margin status at the vallecula to determine the feasibility of larynx preservation with total glossectomy.

(c) *Lymph nodes*: Although macroscopic involvement of lymph nodes with squamous cell carcinoma can be determined with about 99 % accuracy, it cannot accurately detect lymphoma. Frozen section may be used to determine the extent of neck dissection. Intraoperative detection of metastatic node in level 4 may assist the decision to convert selective neck dissection to modified radical neck dissection [29, 30]. Frozen section has limited or no value in sentinel lymph node biopsy that attempt to identify small foci of metastatic disease. With macrometastasis (>0.2 mm), frozen section examination and imprint cytology of the lymph nodes were found to have similar diagnostic accuracy. The detection of micrometastasis (<0.2 mm) or isolated tumor cells requires serial step sectioning at every 2 mm and perhaps immunohistochemistry for cytokeratin [43].

6.2.3 Frozen Section Versus Clinical Examination

There is now considerable body of literature to substantiate that routine use of frozen section has very limited role in the management of oral squamous cell carcinoma. Chaturvedi et al. [27] in a prospective trial of 145 patients undergoing surgery for head and neck squamous cell carcinoma found that frozen section identified 83 % ($n=64$) of 565 mucosal and 104 soft tissue margins as positive of invasive carcinoma. This compromised surgical margin was associated with gross clinically close margin of less than 7 mm. They therefore recommend that there is no value in

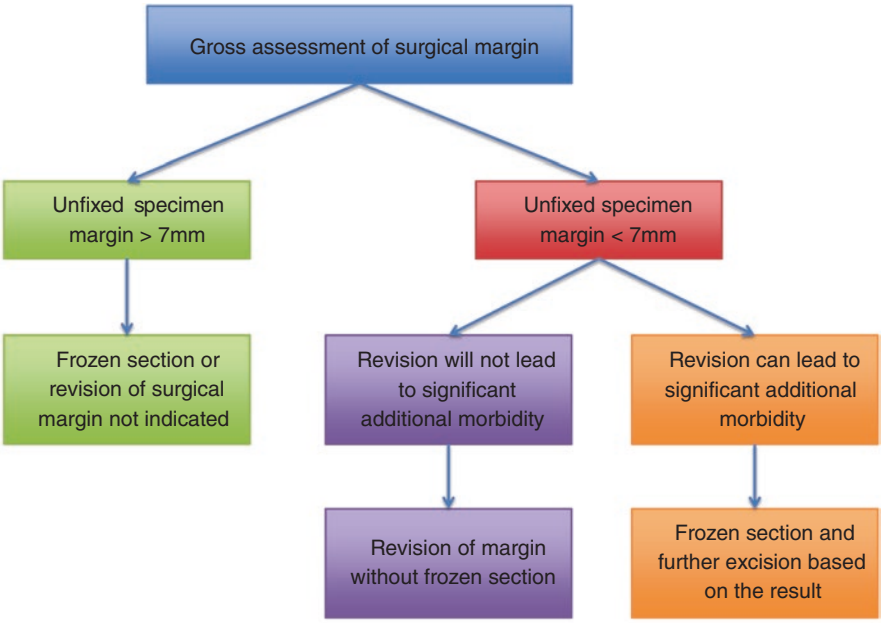


Fig. 6.4 Intraoperative treatment decision making based on gross clinical examination and frozen section examination (Chaturvedi et al. [27])

doing frozen section if the gross clinical margin is more than 7 mm. Similar findings has been reported by many authors demonstrating lack of clinical benefit for routine use of frozen section [23, 26, 32].

Based on the current evidence, Chaturvedi et al. [27] recommended a clinical decision making algorithm (Fig. 6.4). When frozen section is carried out, it is best to be performed from the surgical bed rather than the surgical specimen. The region of where the frozen section was taken should be accurately marked in relation to the primary resection specimen, so that appropriate and accurate intraoperative or postoperative decision can be made.

6.2.4 Circumferential Excision Versus Compartmental Resection

Traditional method of surgical excision of primary oral cavity squamous cell carcinoma is carried out using the principle of wide local excision with 1 cm normal tissue away from the visible and palpable tumor boarders. Even with apparent negative surgical margin, 30 % of oral cancer fails locally [9]. As stated above, although various biological factors such as pattern of invasion and perineural invasion may contribute to the development of local recurrence, surgical technique may be modified to improve the local disease control rate.

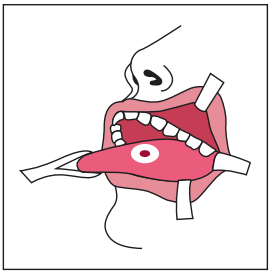
Compartment resection is based on the observation that tumor does not necessarily advance in a concentric fashion but follows pathways of least resistance. This is determined by anatomic structures that either facilitate invasion of tumors such as orientation of muscle fibers, nerve sheath, lymphatics and blood vessels, and structures that offers resistance to tumor invasion such as periosteum and fascia [33, 34]. It is to be noted that ablative surgery that cause discontinuation of a muscle, nerve or blood vessel will have similar functional consequences whether it is remove in part or complete. This formed the basis of compartmental resection that attempted to remove "anatomic compartments" that are involved by cancer. This concept is well established in soft tissue sarcoma surgery of extremities. It has been shown by Azzarelli et al. [35] in a series of 471 patients with extremity sarcoma that compartmental resection yielded significantly better local control rate of 76 % in comparison to 53 % with wide excision. Compartment resection needs to be distinguished from radical Halstedian principle that entails ultraradical excision of tumor and normal tissue of the affected organ disregard to the pattern of invasion of the tumor.

Technique of compartmental resection has been developed for advanced oral tongue [44] and gingivo-buccal carcinoma [31]. In a series of 193 patients with oral tongue carcinoma, Calabrese at al. [45] reported 88.4 % local control rate with compartmental resection in comparison to 71.6 % with conventional surgery. It is to be noted that the concept of compartment resection has application only in moderate to advanced tumors (T2–T4) of oral cavity that involve discernible anatomic units.

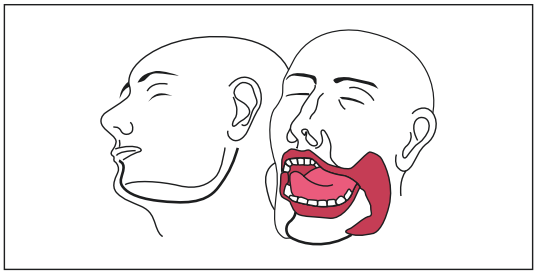
6.2.5 Surgical Access to Oral Cavity

Optimal exposure of the tumor is required for intraoperative examination, with maneuvering of instrumentations to achieve three-dimensional excision with uninvolved margins. In addition, the exposure should facilitate optimal reconstruction of the surgical defect. The commonly used methods to oral cavity tumors are peroral, lip split with mandibulotomy, lower cheek flap, visor flap, and upper cheek flap approaches and for advanced gingivo-buccal tumors with skin involvement, extension of the skin incision around the primary tumor excision to the neck (Fig. 6.5). The choice of approach depends on the site and extent of the tumor invasion, the need to remove a part or a segment of maxilla or mandible, dental status, and degree of mouth opening.

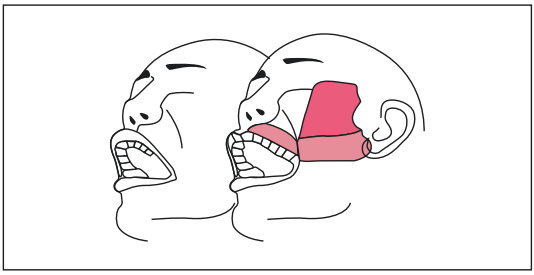
Many traditional approaches need to be reevaluated in the context of improved instrumentation, high-speed bone cutting instruments with varying geometry, and improved visualization with fiber optic lighting and endoscopes. These technologic advances have lead to the development of the field of minimally invasive surgery that has revolutionized many surgical fields, limiting morbidity of procedures. In the head and neck region, the impact of which is most apparent in skull base and laryngeal tumors. With the assistance of endoscopes, powered instruments, and lasers, one can safely resect tumors from these critical areas through a natural



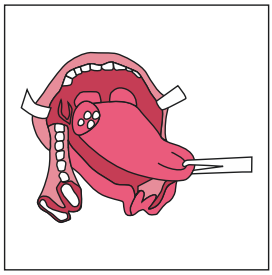
a Per Oral



b Lower Cheek Flap



c Upper Cheek Flap



d Mandibulotomy

e Visor Flap

Fig. 6.5 Choice of approaches to oral cavity (**a**) peroral, (**b**) lower lip split, (**c**) upper lip split, (**d**) lower lip split with mandibulotomy, (**e**) visor flap

opening of less than 2 cm in size. It is paradoxical that in the surgical management of oral cavity tumors with the availability of about 4×4 cm mouth opening, one often resorts to transcutaneous approaches. It is to be noted that almost all orthognathic surgeries that require osteotomy of maxillofacial skeleton from the mandibular condyle to the symphysis and from Lefort-1 to Lefort-3 are carried out almost exclusively through peroral approaches. Many instruments that are used for craniofacial surgery can be adapted for oral cavity cancer surgery.

6.2.5.1 Peroral Approach to Oral Cavity

Tumors of anterior tongue, buccal mucosa, floor of mouth, and alveolus that are either T1 or T2 stage with adequate mouth opening are considered ideal candidates for peroral excision [36]. However, there are recent studies attesting the feasibility of peroral excision for moderately advanced oral cancer (T2, T3) [46]. In a series of 79 consecutive patients with T2 and T3 oral cancer, they have demonstrated that peroral excision achieved comparable pathologic uninvolved margin status (81%) as transmandibular procedures. This was true for patients undergoing marginal or segmental mandibulectomy as well as posterior oral cavity tumors such as retromolar trigone cancers. Combining transcervical and peroral approach, without lip split, the incidence of deep soft tissue margins was also found to be comparable to that of open approaches. Sutton et al. [39] also have reported the lack of difference in surgical margin status based on the surgical approaches. In the series of Battoo et al. [46], 53 out of the 79 patients underwent suceesful free tissue transfer supporting the view that peroral excision does not limit exposure for appropropriate oral cavity reconstruction.

6.2.5.2 Mandibulectomy Approach

The primary indication for mandibulectomy approach is to resect tumors of the base of tongue or oropharynx. However, the technique also needs to be employed in situation where there is limited mouth opening. The need for marginal or segmental mandibulectomy is a contraindication of the technique. Though mandibulotomy can be performed as median (at the midline), paramedian (medial to mental foramen), or lateral (posterior to mental foramen), because of the least disruption to genioglossal muscle and mental nerve, paramedian mandibulotomy is preferred as the most optimal approach to posterior oral cavity and oropharynx. Step osteotomy was recommended in the past for improved stability of osteotomy in the era of less stable fixation techniques; however, with the availability of rigid fixation, it is rarely needed. Two 2.0 mm mini plates should be preadapted and screws inserted prior to mandibulotomy. The superior boarder plates should be fixed with mono-cortical screws and inferior boarder plates fixed with bicortical screws. Care should be taken to avoid injury to the mental nerve. During replating of preadapted plates, occlusion should be maintained either with manual pressure or with the aid of intermaxillary fixation (Fig. 6.6).

6.2.5.3 Lower Lip Split

The mandibulotomy needs to be combined with lower lip-split incision. Several modifications of the lower lip split have been introduced to improve aesthetic and functional results. These are (1) straight midline incision (Roux-Trotter), (2) straight midline with Z-plasty at labiomental crease (Kuriakose), (3) lateral lip split (Robson), (4) straight midline with chin contour (McGregor), and (5) straight midline with chin contour and vermilion and submental Z-plasty (Hayter) (Fig. 6.7) [60]. analyzed functional and aesthetic results of various incisions. They observed comparable aesthetic and functional results among the four groups except that the lateral lip split had worst outcome. The minor differences they observed were with respect to straight midline incision showing more vermilion notching compared to other incisions. The

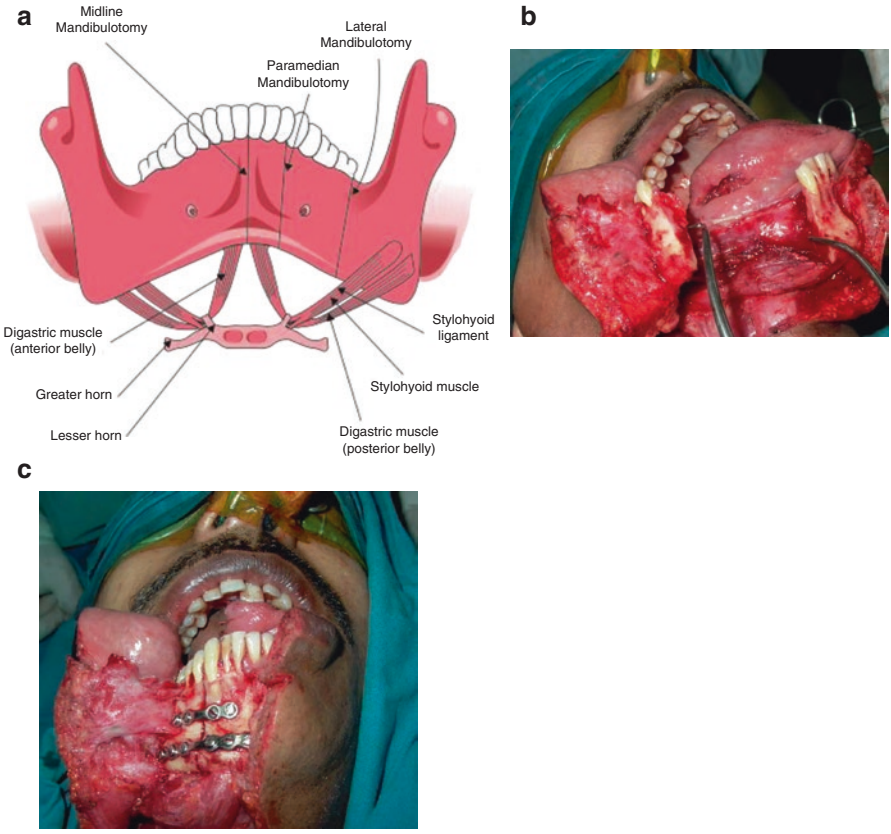


Fig. 6.6 Type of mandibulotomy and fixation technique. (**a**) Types of mandibulotomy, (**b**) clinical case of paramedian mandibulotomy performed between canine and first premolar teeth. Care was taken to preserve mental nerve and insertion of digastric muscle, (**c**) Technique of fixation of mandibulotomy with two mini-plates, The upper plate is fixed with mono-cortical screws and lower plate with bicortical screws

lip skin appearance was better with straight midline with chin-contour and vermilion and submental Z-plasty incision. Lip sensation was better with straight midline. However, the lip movements and oral incompetence was better with straight midline with chin-contour and vermilion and submental Z-plasty incision. To combine the advantages of all the incisions, a straight midline incision with Z-plasty at labiomental crease appears to give optimal result. As noted in Rapidis study, irrespective of type of incision, meticulous approximation of the vermilion boarder and muscles is essential to minimize aesthetic and functional impairments.

6.2.5.4 Lower Cheek Flap

The lip-split incisions described above without mandibulotomy is used for patients requiring either marginal mandibulectomy or segmental mandibulectomy. As this approach deinnervates the lower lip sensation, it is to be avoided in patients where

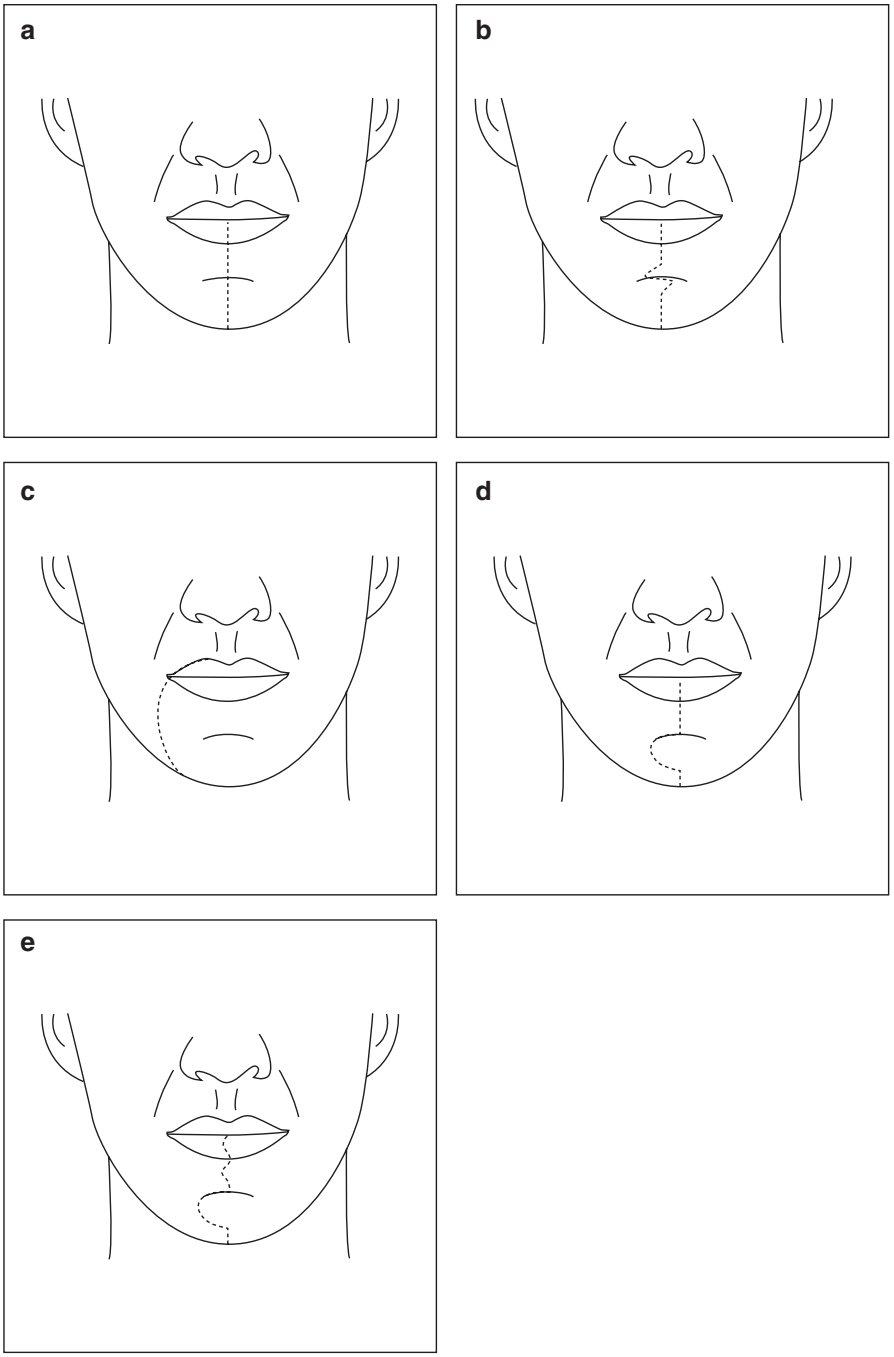


Fig. 6.7 Lower lip-split techniques: (**a**) straight midline, (**b**) midline with Z-plasty at labiomental crease, (**c**) lateral lip split, (**d**) straight midline with chin contour, (**e**) straight midline with chin contour and Z-plasty at vermilion and submental region

sacrifice of mental nerve or inferior alveolar nerve is not required as part of the ablative procedure. The only exception could be in patients with significant trismus often encountered in patients with associated oral submucous fibrosis.

6.2.5.5 Visor Flap

The visor flap involves elevation of bilateral upper cervical flap to the lower boarder of mandible and to drop tongue and floor of mouth to the neck after performing release incision along the mandibular alveolus or along with marginal mandibulectomy. This approach is used primarily to perform total or near-total glossectomy required for advanced oral tongue cancer. Whenever possible, attempts should be made to preserve or reattach anterior belly of the digastric muscle to the symphysis of mandible. It allows dynamic laryngeal suspension that is required to prevent aspiration following total laryngectomy.

Visor flap was also attempted to manage the floor of mouth cancer by releasing the flap over the mandible after placing releasing incision along the labial and buccal sulcus. This though avoids lower lip split, causing paresthesia of the lower lip, with major functional consequences. Therefore, this approach is no longer recommended.

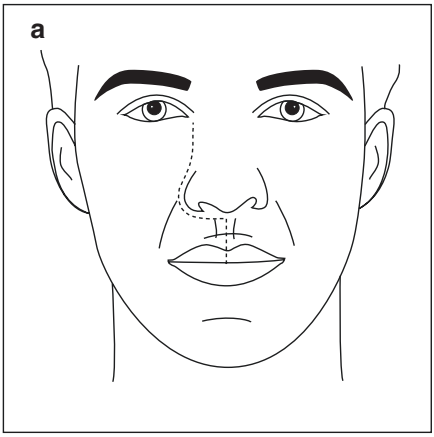
6.2.5.6 Upper Cheek Flap

Upper cheek flap is primarily used to expose carcinoma of posterior maxillary alveolus as well as tuberosity of the maxilla. Thankappan et al. [47] have described modification of the upper cheek flap designed to conform to aesthetic and functional subunits of face. This involves four critical modifications: (1) The midline upper lip incision is extended into the anterior nares. (2) From the anterior nares, the incision is extended superiorly along the alar cartilage to the junction dorsal and lateral nasal subunit. (3) The incision is further extended superiorly between the dorsal and lateral nasal subunits to the medial canthus region and (4) a Z-plasty at the medial canthus region, which is extended superiorly as Lynch extension or inferiorly as infraorbital incision (Fig. 6.8).

6.2.5.7 Exposure of Oral Cavity Tumor with Skin Involvement

Gingivo-buccal cancer has propensity to involve cheek skin, which needs to be removed in many advanced tumors. If this is required, the skin incision around the tumor can be extended to the neck incision, which will give adequate excision of the primary tumor as well as exposure of the neck to perform neck dissection (Fig. 6.9). For smaller skin defects, the incision can be modified to incorporate a large cervical rotation flap that can offer both exposure for surgical excision and neck dissection and provision of cover for the skin defect (Fig. 6.10).

Fig. 6.8 Upper lip-split technique: (**a**) midline upper lip, (**b**) midline along philtrum ridge, (**c**) lateral rhinotomy with lower eyelid extension, (**d**) aesthetic subunits of the face, (**e**) modification of incision based on aesthetic subunit principle. (**f**1) incision design of modified lateral rhinotomy, (**f**2) view after wound closure, (**f**3) wound appearance one week after surgery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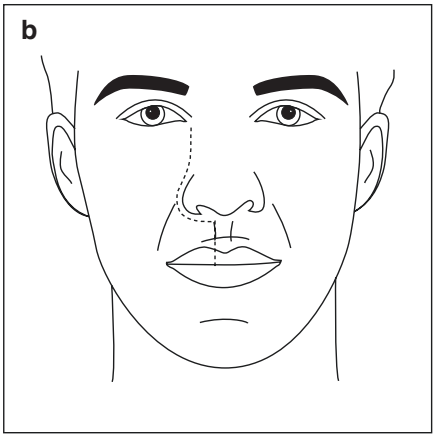
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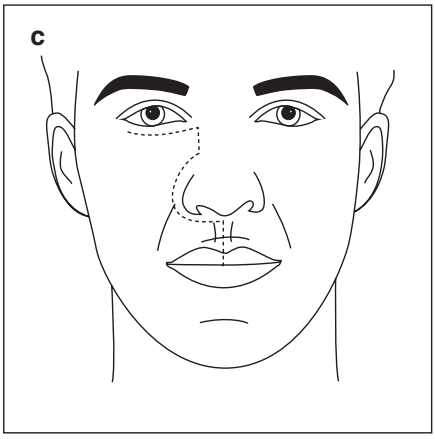
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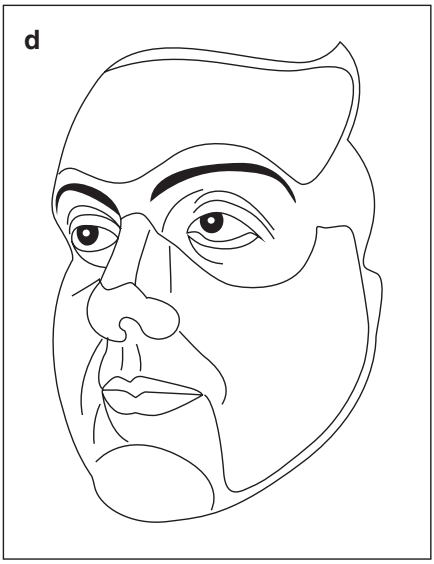
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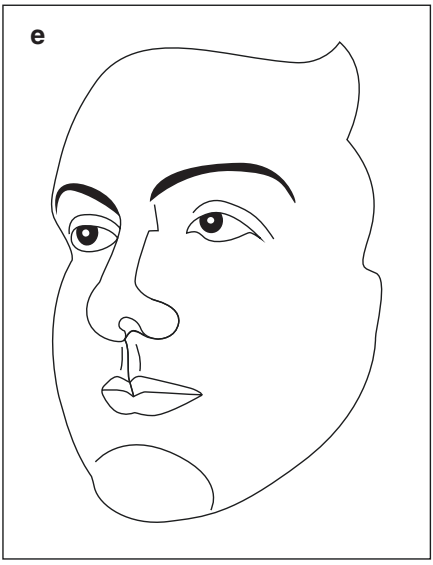
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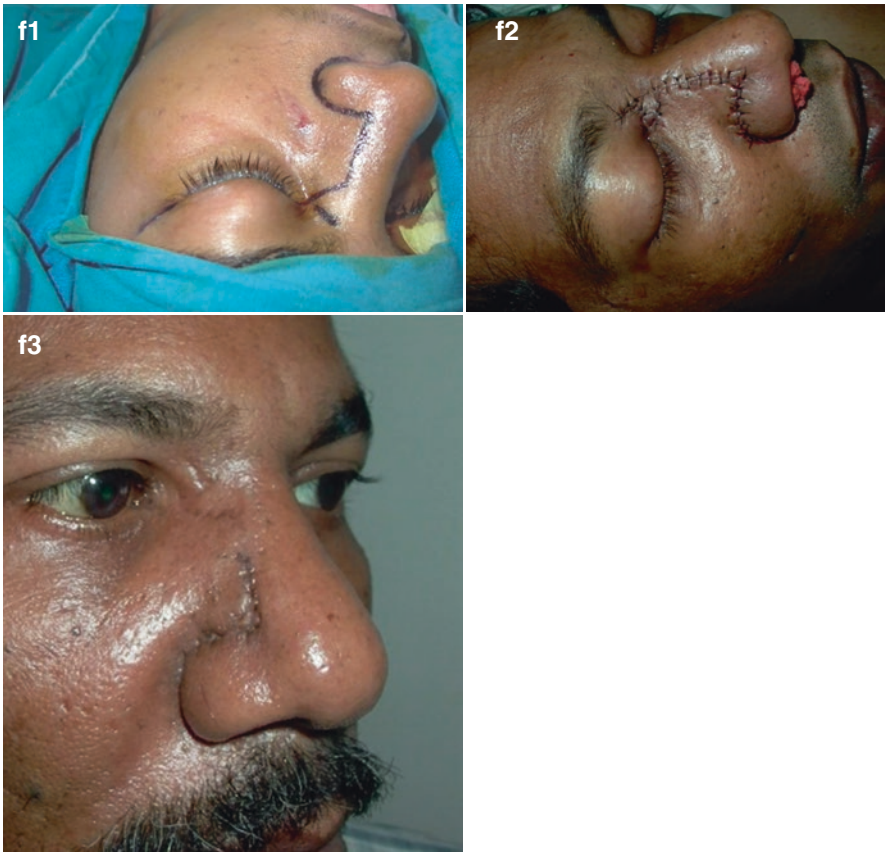


Fig. 6.8 continued

6.3 Surgery for Specific Oral Cavity Subsites

Oral cancer comprises of many subsites, namely, lip, tongue, and floor of mouth (FOM), buccal mucosa, alveolus, and hard palate. All these structures function in tandem regulating vital functions like speech, swallowing, and mastication. It is very important to understand their anatomy and pattern of disease spread to effectively remove cancer preserving function. Each of these subsites is discussed individually for relevant surgical anatomy, pattern of spread, and approach for surgical ablation.

6.3.1 Tongue and Floor of Mouth

6.3.1.1 Surgical Anatomy and Pattern of Spread

The tongue can be anatomically divided into the oral tongue and base of tongue (BOT). The oral tongue can be further divided into the anterior third and middle third. The tongue is a unique organ in the human body with viscoelastic property along with

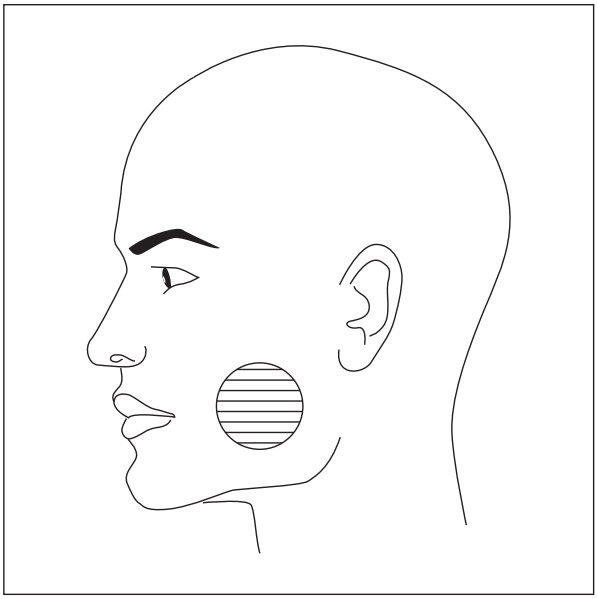


Fig. 6.9 Composite resection with overlying facial skin

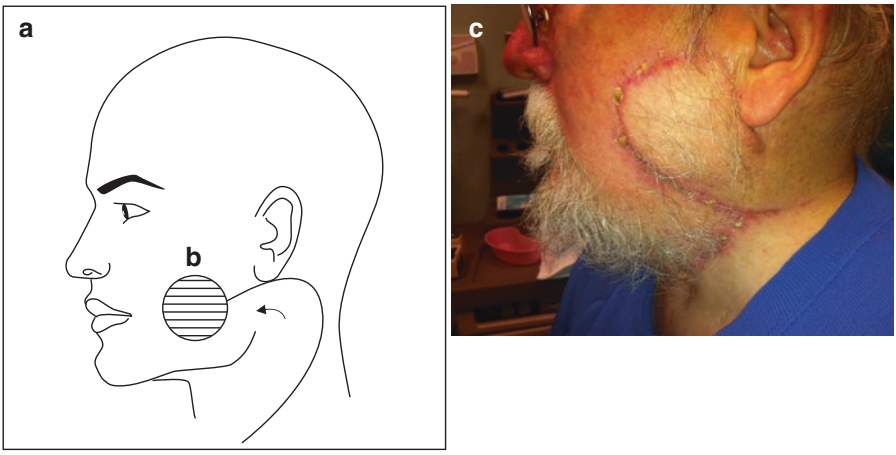


Fig. 6.10 (**a**) Composite resection with full thickness cheeck defect, (**b**) Anteriorly based cervical rotation flap to provide skin cover, and (**c**) posterioly based cervical rotation flap

multidirectional muscle activity which affords multidimensional movements and alters the shape to conform to the palatomaxillary complex during articulation and swallowing. Intrinsic muscle is responsible for shape alteration and the extrinsic muscle for multidirectional movements. The motor innervation of tongue is through the hypoglossal nerve and vascularity by lingual artery, which enters the organ posteriorly adjacent to the central raphe. Lingual artery is a branch of the external carotid artery and runs deep to the hyoglossus muscle just above the greater cornu of hyoid bone to pass through the BOT and supply the ipsilateral tongue. Both halves of tongue are

supplied by numerous cross-branches. Excision which extends beyond the midline can compromise this neurovascular pedicle and the tongue vitality and function. The ventral surface of the tongue extends from the lateral boarder of the tongue to the floor of the mouth (FOM). A clear demarcation is not always possible.

The sensory innervation of the anterior two-third of the tongue is provided by the lingual nerve, a branch of mandibular division of the trigeminal nerve. The nerve after dividing off the main trunk of the mandibular nerve runs anteroinferiorly between the tensor veli palatini and lateral pterygoid muscle and then medially to the medial pterygoid muscle. It exits the infratemporal fossa just medial to the retromolar trigon of the mandible close to the mandibular periosteum to enter the submandibular triangle. There it gives off two branches to the submandibular ganglion that provides parasympathetic innervation to the gland. It then runs between myelohyoid and the floor of the mouth mucosa. In this course, the lingual nerve is medial to the submandibular duct. It gives off several branches that supplies mucosa of the floor of the mouth and the anterior two-third of the tongue. The nerve can be identified both medial to the retromolar trigone, the submandibular triangle and at the floor of mouth. For the excision of squamous cell carcinoma located at the lateral boarder of the tongue, the lingual nerve trunk and its branches to the tip of tongue can be often preserved to retain the important sensory innervation to the tip of the tongue.

Oral tongue mucosa is contiguous with lingual alveolar mucosa which continues as gingival mucosa. Tumor from the lateral boarder of the tongue can spread to the floor of the mouth and then to the mandible. This lateral spread of the tumor to the mandible rarely spread inferior to the myelohyoid muscle and its insertion to the mandible at the internal oblique ridge. An oblique marginal mandibulectomy can be performed involving the alveolus and myelohyoid ridge to encompass the tumor at the same time conserve the mandibular continuity (Fig. 6.11).

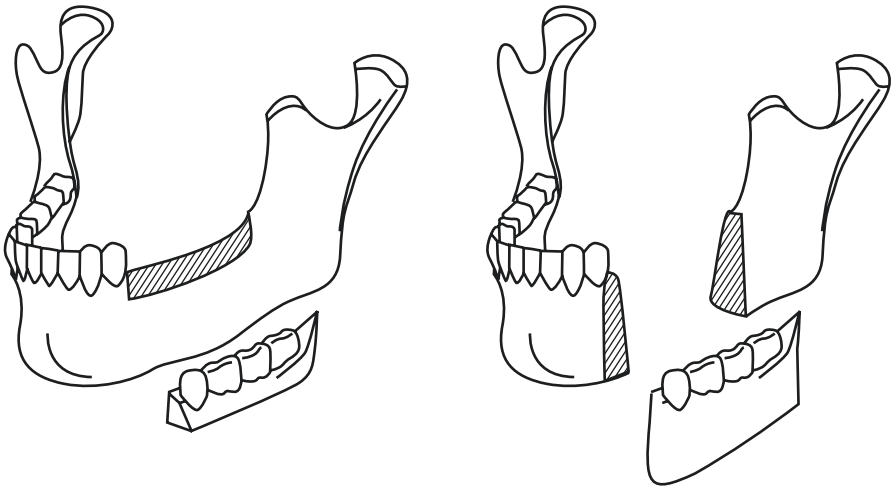


Fig. 6.11 Type of mandibulectomy: (**a**) marginal mandibulectomy, (**b**) segmental mandibulectomy

The concept of mandibular invasion was described initially by McGregor [48] and subsequently modified by Brown [49]. McGregor suggested that tumor spreads through occlusal surface of the mandible and has a preferential spread through bone marrow and inferior alveolar nerve. Brown et al. [49] in a subsequent study, however, have observed that tumor enters the mandible at the point of abutment and the extent of bone invasion is directly related to soft tissue involvement. This provided basis for performing marginal mandibulectomy for cancers that abut the mandible or cause superficial erosion (Fig. 6.12).

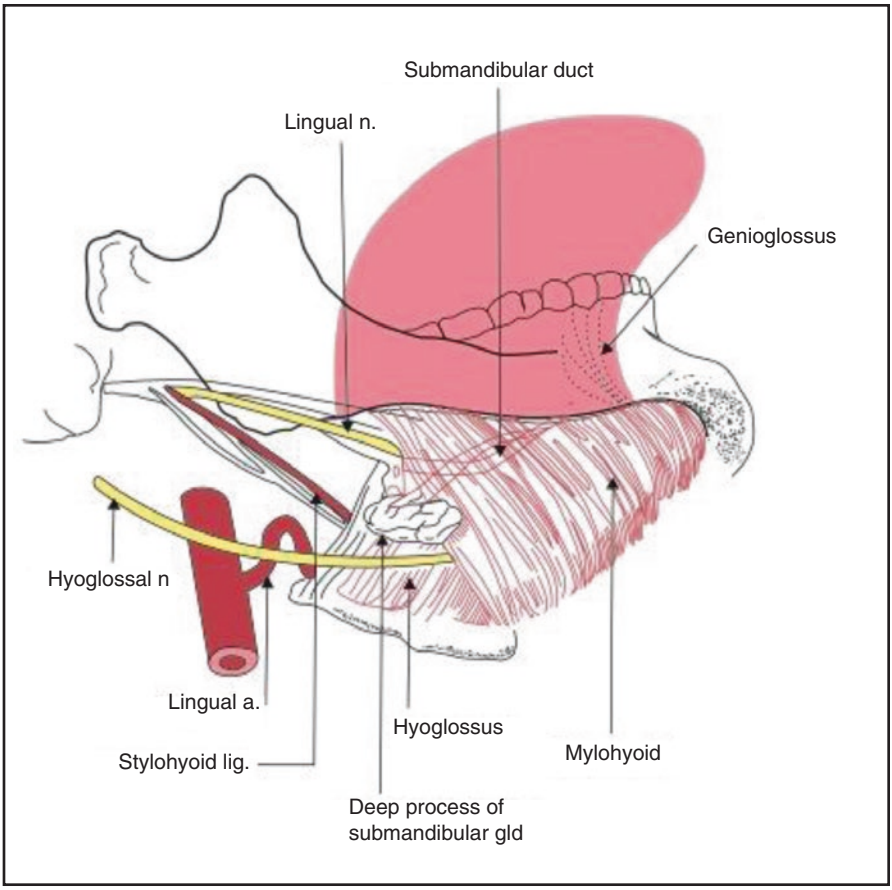
The hyoglossus muscle originates from the hyoid bone and courses superiorly, deep to the myelohyoid diaphragm to enter the lateral aspect of the tongue and decussates with the intrinsic muscles of the tongue (Fig. 6.13). As majority of the oral tongue carcinomas arise at the lateral boarder of the tongue, these tumors have the tendency to spread along the course of hyoglossus muscle towards the hyoid bone. For infiltrative tongue carcinomas to ensure resection with adequate margin, it is essential to remove this muscle from its origin from the hyoid bone and the involved part of the tongue. This forms the basis for the concept of compartmental resection of tongue carcinoma. It has shown that adopting compartmental resection principles in tongue carcinoma surgery has improved locoregional control rate compared to the conventional technique of oral tongue resection [45].

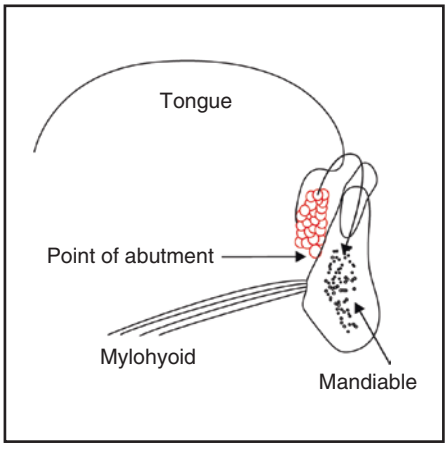
The tongue has rich lymphatic supply, and lymph node metastasis is seen quite early in this tumor subsite. The rate of occult metastasis is over 30 % for tongue cancer, and elective neck dissection is recommended for majority of tongue or FOM cancers. It has been noted that depth of invasion over 4 mm is an important predictive marker for occult metastasis of tongue and floor of mouth cancer [50]. Ipsilateral level I–III is commonly involved in lateral lesion of tongue, while skip metastasis at level IV is observed in about 10–15 % cases [51]. Bilateral lymph node involvement is common for cancers reaching or crossing midline.

6.4 Surgery

Planning of surgical resection depends upon tumor extent and the adjacent structures involved. It is important not only to remove gross tumor but also the areas which may contain microscopic cancer cells. The key to obtain improved locoregional control is to achieve negative margins in three dimensions (in depth). Hence, understanding the pattern of disease spread is critical for effective removal of cancer and minimizing the functional disability of excision of uninvolved anatomic structures. Imaging modalities help to understand the extent of tumor spread. Magnetic resonance imaging (MRI) has better soft tissue definition and is the preferred modality for the evaluation tongue cancer. Involvement of the mandible can be better evaluated by computed tomography (CT) scanning.

Superficial and early cancer of the tongue and floor of the mouth (T1) can be addressed by wide local excision (WLE) procedure (Figs. 6.14, 6.15, and 6.16). Majority of tongue cancers are infiltrative in nature and have more infiltration than


Submandibular duct
Lingual n.
Genioglossus
Hyoglossal n
Lingual a.
Stylohyoid lig.
Hyoglossus
Deep process of submandibular gld
Mylohyoid


Tongue
Point of abutment
Mylohyoid
Mandiable

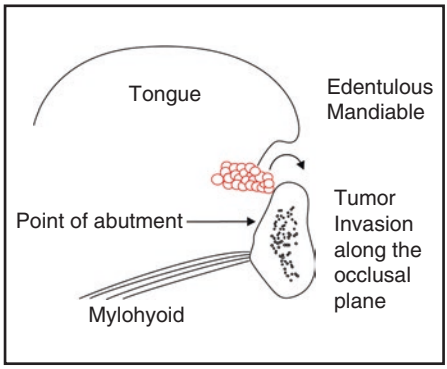
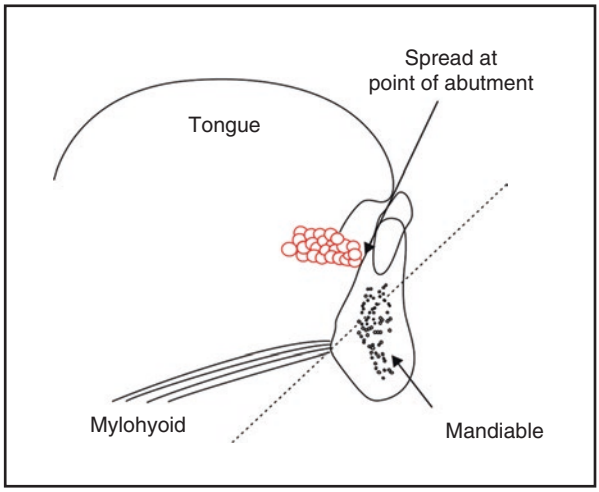

Tongue
Edentulous Mandiable
Point of abutment
Tumor Invasion along the occlusal plane
Mylohyoid

Fig. 6.12 Pattern of invasion of tongue and floor of the mouth cancer. (**a**) Normal anatomy of the tongue and the floor of the mouth showing relationship of mucosa, myelohyoid, and myelohyoid ridge, (**b**) carcinoma of the floor of the mouth abutting dentate mandible. The tumor preferentially invades the point of contact at the lingual cortex. (**c**) In edentulous mandible due to the loss of alveolar process the alveolar mucosa can come to the same level as that of the floor of the mouth mucosa. Tumor in this situation can gain access to the mandible through the alveolar crest. (**d**) Diagrammatic representation of marginal mandibulectomy for floor of the mouth cancer that abut the mandible. The oblique osteotomy can incorporate the mandibular alveolus, the myelohyoid ridge, and the overlying mucosa

Fig. 6.12 (continued)



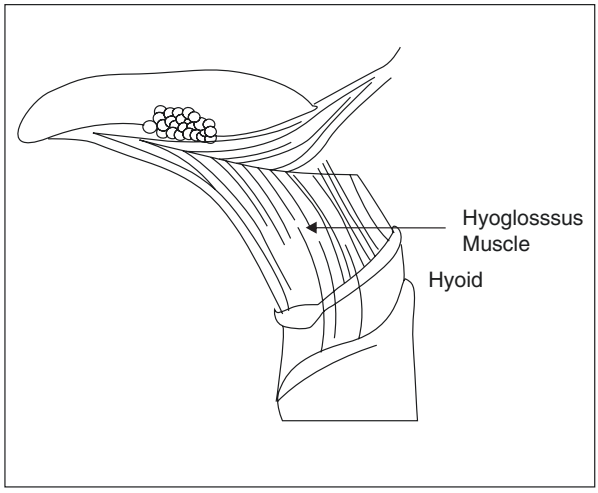


Fig. 6.13 Tumors of the lateral boarder of the tongue can invade the hyoglossus and depending on the location can invade other extrinsic muscles of the tongue – genioglossus, styloglossus, and pharyngoglossus

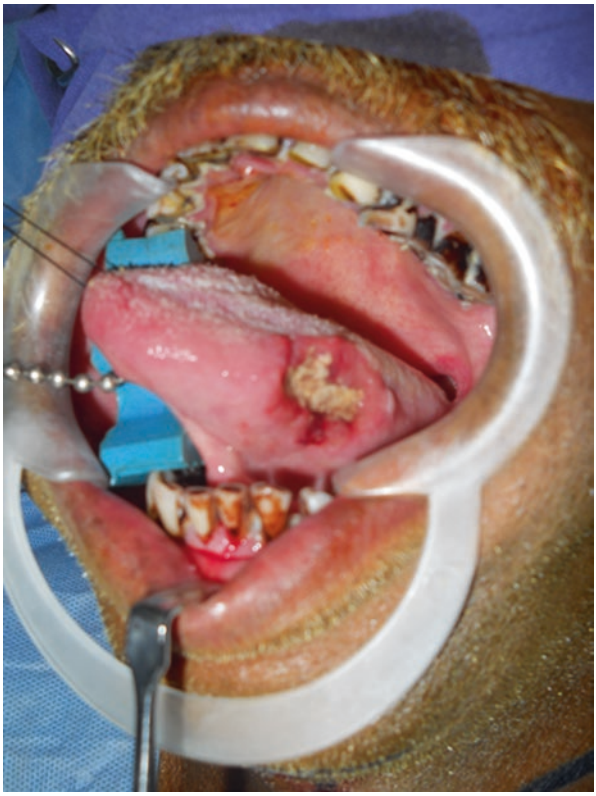


Fig. 6.14 Carcinoma of the oral cavity excised by peroral approach

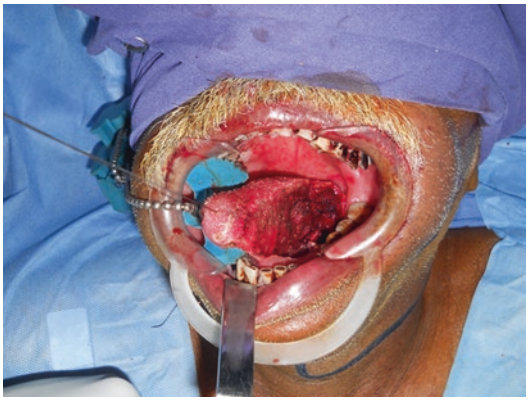


Fig. 6.15 Carcinoma of the oral cavity excised by peroral approach

that can be appreciated by clinical evaluation. Palpation of induration is an important guide for planning resection. Optimum margin for resection of tongue is 1–1.5 cm all around including depth. It is preferable to achieve 1.5 cm margins at the depth because of the preferential pattern of spread of tumor cells along the muscle fibers as well as higher contraction of muscles both by cautery and by

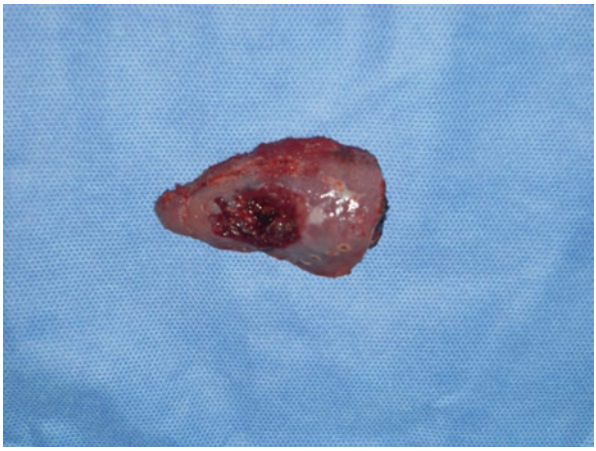


Fig. 6.16 Carcinoma of the oral cavity excised by peroral approach

Fig. 6.17 Compartmental resection of invasive tongue cancer

formalin fixation. For posteriorly located and infiltrative tumors, it is a useful practice to ligate lingual artery in neck before performing WLE. The resulting defects can be closed primarily in majority of patients with T1 tumors.

Moderately advance tongue and FOM cancers (T2–T3) pose a surgical challenge. Majority of these cancers are infiltrative in nature and either involve or lie in close proximity of adjoining structures. Appropriate evaluation of disease extent and careful planning of surgical approach is mandatory. These cancers warrant classical hemiglossectomy, except preserving the tip and base of tongue. This will involve removing one half of tongue from midline septum to mandible and inferiorly up to the hyoid bone (Figs. 6.17, 6.18, and 6.19). The common site of positive margin is at the depth in the hyoglossus muscle, which is also the typical site for local recurrence. Hence, it is advisable to remove the hyoglossus muscle from hyoid

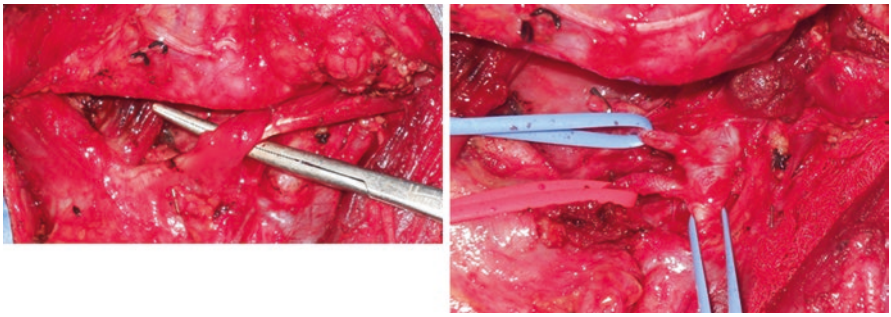


Fig. 6.18 Compartmental resection of invasive tongue cancer

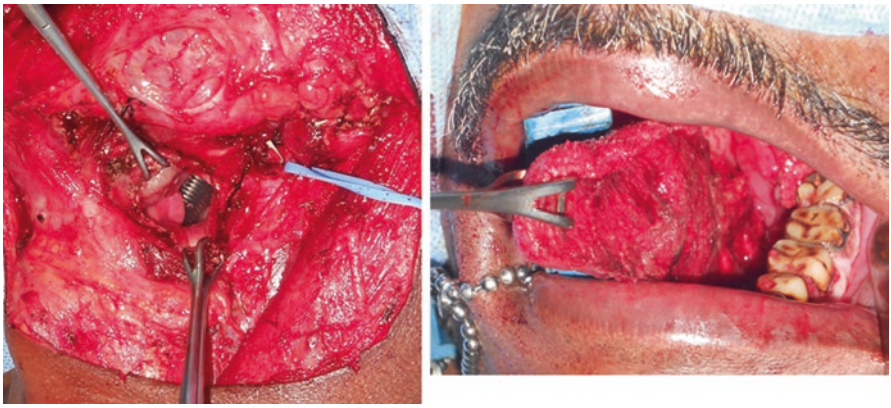


Fig. 6.19 Compartmental resection of invasive tongue cancer

bone. Since this muscle at the insertion in the tongue will be included in the primary tumor excision, detaching it from its origin will not have significant additional functional impairments. Ligating lingual artery in the neck before resecting the primary tumor improves haemostatic control. Majority of these tumors can be excised by a combination of peroral and trans-hyoid/pharyngeal approach, without the need for lip-spit or mandibulotomy. Rarely for large and bulky posterior lesions with extension to base of tongue and restricted mouth opening, mandibulotomy may be utilized to improve access. This should be considered as an exception. All these patients require reconstructive surgery. Free-flap reconstruction has become standard of care for tongue reconstruction.

Locally advanced (T4a) cancers (restricted mobility and hypoglossal palsy) of tongue need total glossectomy or near-total glossectomy (Fig. 6.20). Complete anatomical removal of tongue from mandible to hyoid is a standard total glossectomy procedure (Fig. 6.21). In certain cases where lesion is not involving opposite BOT, it may be preserved by performing near-total glossectomy. There is a potential for improved functional outcome with this approach but should be done only if cancer clearance is not compromised. The extend of excision of the base of tongue

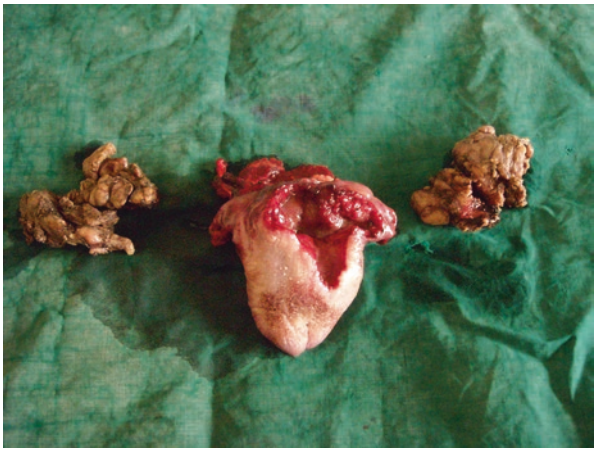


Fig. 6.20 Advanced tongue cancer requiring total glossectomy resected by visor flap approach

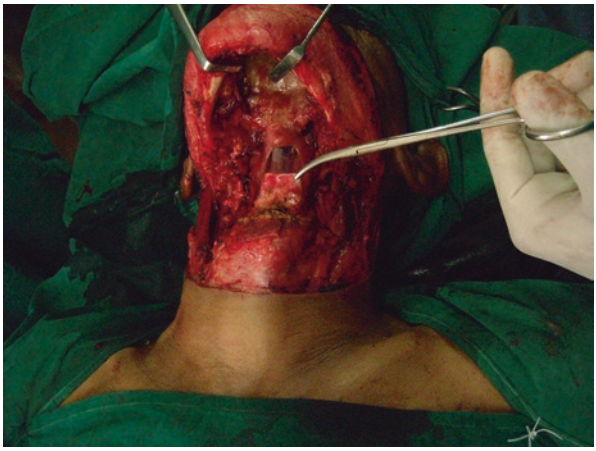


Fig. 6.21 Advanced tongue cancer requiring total glossectomy resected by visor flap approach

determines the postoperative swallowing function. Reconstruction requires a soft tissue flap with large volume to provide adequate bulk. Various flaps have been described for this procedure. Infra-hyoid release and larynx suspension technique are effective in preventing aspiration and improving post-operative swallowing function. The base of tongue lesions are part of oropharynx and are managed with non-surgical organ preservation in majority of patients. Advance base of tongue lesions can be approached with total glossectomy as described earlier. With the advent of trans-oral robotic assisted surgery, there is a resurgence of interest in surgical intervention of base of tongue tumors.

Tongue and FOM lesion involving or abutting mandible pose a unique challenge. Resecting segment of mandible increases morbidity and reconstructive challenge by many folds. Attempt should be made to preserve mandible whenever possible. Current approach is to perform marginal mandibulectomy when lesion is abutting mandible and mandible is either not involved or has minimal cortical erosion. Segmental

resection is preferred when either marrow is involved or there is gross cortical destruction present. Soft tissue extent of resection remains similar as described earlier.

Occult metastasis rate is over 30 % for tongue and FOM cancers and elective neck dissection is always recommended for clinically negative neck. It is an accepted practice to perform ipsilateral selective neck dissection of levels I–IV in majority of N0 and N+ patients. Removal of level V lymph node is reserved either when level IV or V is involved or in N3 nodal disease. Contralateral neck dissection is performed when lesion is approaching or crossing midline or imaging showing evidence of contralateral lymphadenopathy.

6.4.1 Gingivo-buccal Complex Cancer

6.4.1.1 Surgical Anatomy and Pattern of Spread

Gingivo-buccal sulcus complex (GBS) includes buccal mucosa, upper and lower gingivo-buccal sulcus, retromolar trigone (RMT), and lower and upper alveolus. Cancers affecting these subsites are different in their risk factor profile, clinical and biological behavior, and surgical approach in comparison to tongue and floor of mouth cancers. Buccal mucosa forms the central part of the GBS complex bounded above and below by upper and lower alveolus. Buccal mucosa consists of five layers from inside out, namely, the mucosa, buccinator muscle, submucous aponeurotic system (SMAS), subcutaneous tissue, and skin. The facial artery and branches of facial nerves run superficial to buccinator muscle and deep to SMAS. Distance between the mucosa and the skin is less in the anterior region compared to the posterior aspect, where there is the additional layer of buccal pad of fat. Overall the mucosa-to-skin distance is less than 1 cm, and infiltrative cancer of buccal mucosa can easily invade deeper layers and skin. Isolated buccal cancers in non-tobacco chewers have aggressive behavior with high tendency for regional and distant spread [52, 53]. However, GBS tumors developing as a result of chronic Gutka or tobacco chewing habits tend to be a more locally aggressive tumor rather than a metastatic disease [54].

Cancer affecting upper and lower GBS is quite unique to Indian subcontinent. It is seen mainly due to habit of chewing tobacco and Gutka. These are locally infiltrative cancers with the tendency to invade adjoining structures like the skin, alveolus, and infratemporal fossa (ITF). Histologic involvement of the mandible is seen only in half of cases, but it is associated with significant paramandibular spread in almost all cases [55]. Lymph node involvement is not very common and is generally of low volume and number. Distant metastasis rate is about 10 %. GBS cancer is essentially considered a locoregional disease.

Tumors arising from the mandibular alveolar mucosa can be broadly divided into early and advanced cancers. Early alveolar cancer show minimal or no cortical erosion and are staged according to their size (T1-3). Advanced cancers are one with marrow involvement and are staged as T4. Marginal mandibulectomy is an accepted surgical approach for early cancers, while segment resection needs to be performed for advanced T4 cancers. Preoperative imaging with CT scan is warranted for accurate assessment of bone invasion.

Retromolar trigone (RMT) is a narrow space posterior to the last molar tooth. Mucosa of the RMT is tightly attached to the mandible, and therefore, tumor involving this region shows early mandibular invasion. The pterygomandibular raphe, which provides anchorage for the buccinator muscle and superior constrictor, is attached to the RMT. The inferior limit of the temporalis muscle which is inserted to the coronoid process also extends to the RMT. Therefore, tumors of this region can extend superiorly along the temporalis muscle to the infratemporal fossa or along the pterygomandibular raphe to the pterygomaxillary fissure. Posterior spread of the tumor can invade the medial pterygoid muscle and gain access to the infratemporal fossa. More advanced tumor of this region can extend laterally to involve the masseter muscle and the skin.

Tumors of the upper GBS and the maxillary tuberosity are particularly aggressive tumors because of its ability to spread subclinically to the pterygomaxillary fissure and infratemporal fossa. These tumors can spread superiorly along the posterior boarder of maxilla, presumably along the posterior superior alveolar nerve to the pterygomaxillary fissure. From this point, it can get access to the inferior orbital fissure and the intracranial compartment, making the tumor unresectable. Liao et al. have classified the invasion of ITF as infrasigmoid and suprasigmoid notch regions [57]. Those with the former tumor extension had better local disease control rate compared to the latter. Lack of appreciation of this subclinical spread and deliberate attempt to resect the potentially affected tissue can cause significant risk of local failures.

6.4.2 Surgery

6.4.2.1 Buccal Mucosal Cancer

Buccal mucosa cancer can present with wide spectrum of disease ranging from oral potentially malignant lesions like leukoplakia to advance infiltrative and fungating cancers. Primary treatment for potentially malignant lesion is discontinuing their habit. However, surgical excision is recommended for leukoplakia showing moderate to severe dysplasia or for inhomogeneous leukoplakia (Fig. 6.22). Many clinicians prefer laser excision for improved healing and lower fibrosis. Similar results can be obtained by excision, by cautery and by reconstruction with buccal pad of fat. It is not always possible to remove all dysplastic lesions due to their diffuse nature. It is advisable to resect whatever is feasible and then do laser evaporation to remaining lesions. It is essential to send these specimens for pathology examination as there could be focus of invasive carcinoma in patients with dysplastic lesions.

Early buccal cancer is resected with an intraoral approach. Two features should be taken into account to ensure oncologic completeness of excision. (1) Irrespective of the size of the tumor (T-stage), it is important to appreciate the depth of invasion. In comparison to carcinoma of the tongue, majority of the early stage buccal mucosal carcinomas are exophytic and/or superficially spreading lesions and remain superficial to the buccinator muscle. Careful preoperative evaluation should be carried out to demonstrate absence of skin involvement. Preoperative clinical examination demonstrating subtle skin tethering and imaging studies showing stranding

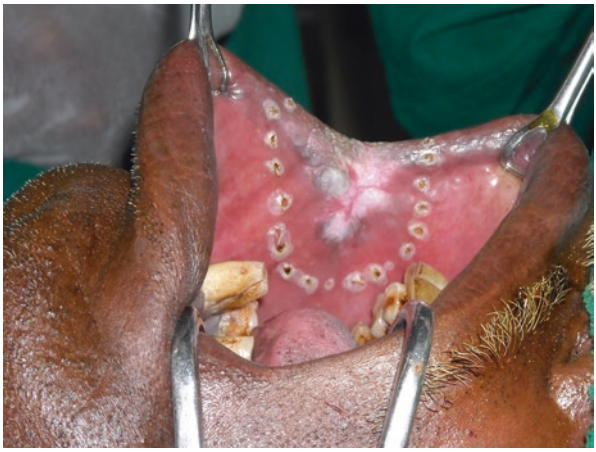


Fig. 6.22 Dysplastic lesion of the buccal mucosa being excised with CO2 laser

of subcutaneous fat are early signs of skin involvement. Careful intraoperative examination should be carried out to plan the extent of surgery. Because of the exophytic nature of these tumors, majority of early stage tumors can be removed per orally. The excision should include buccinator muscle. Care should be taken to preserve buccal braches of facial nerve, which would be traversing between buccinator and submucous aponeurotic system (SMAS). The facial artery and vein if found in the surgical bed should be ligated to avoid secondary hemorrhage. The parotid duct is likely to be encountered during the excision, which needs to be ligated to avoid salivary seal under the flap used for reconstruction. (2) As majority of buccal mucosal carcinoma is caused by local risk-babits, surrounding mucosa can have dysplastic lesions. Wide excision incorporating these dysplastic lesions should be carried out during ablative surgery. In patients with extensive field cancerization, all dysplastic mucosa cannot be removed during surgery. These should be managed postoperatively as other potentially malignant lesions with habit cessation and chemoprevention.

Advanced buccal mucosal cancers often will have skin involvement and, therefore, require full-thickness cheek resection (Fig. 6.26). Local failure is the major pattern of failure for advanced buccal cancer. It is mainly due to the inability to achieve negative surgical margins at depth. The skin should be resected when tumor infiltrates beyond buccinator muscle into subcutaneous tissue irrespective of actual involvement of the skin. In carcinoma of the posterior buccal mucosal where this is thick buccal pad of fat between buccinator and subcutaneous tissue, the skin could be preserved.

6.4.2.2 Gingivo-buccal Sulcus Cancer

Buccal mucosal carcinoma away from the buccal sulcus can be excised widely preserving the mandible (Fig. 6.23a, b). These smaller defects can be adequately reconstructed with buccal pad of fat (Fig. 6.24a, b). However, gingivo-buccal sulcus (GBS) tumors can abut the mandible and can have cortical erosion. Excision of tumor with marginal mandibulectomy offers resection with adequate surgical margin. This requires reverse marginal mandibulectomy, where the oblique bone cut is made on the buccal cortex rather than in the lingual cortex of the floor of the mouth carcinoma (Fig. 6.25a, b).

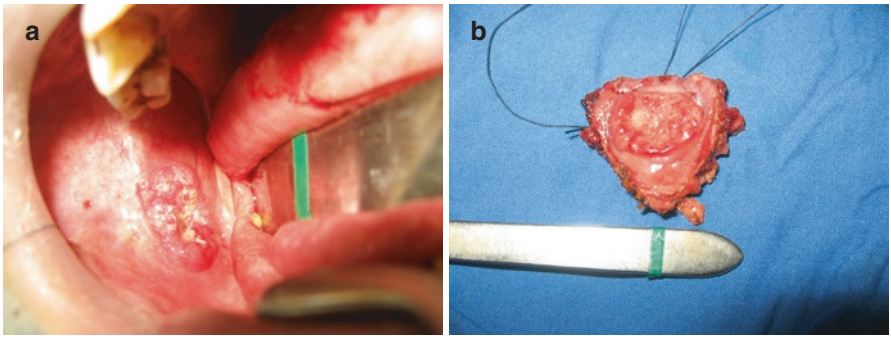


Fig. 6.23 (**a**) Early buccal mucosal carcinoma free of the mandible. (**b**) Peroral wide local excision

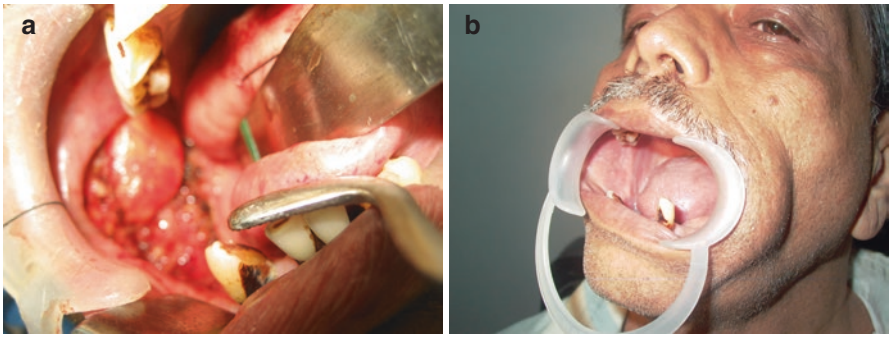


Fig. 6.24 (**a**) Repair of defect with buccal pad of fat. (**b**) Postoperative result

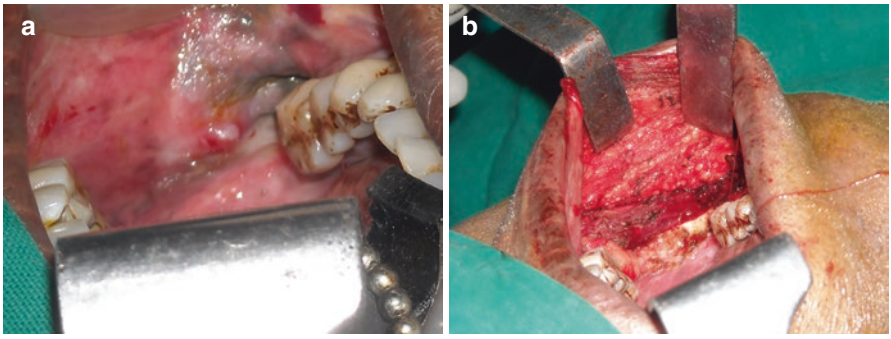


Fig. 6.25 (**a**, **b**) Buccal mucosal carcinoma abutting mandible requiring reverse marginal mandibulectomy and accessed per orally

Advanced GBS tumor will have either significant paramandibular spread and/or gross mandibular invasion. Overlying skin involvement is also often encountered. These patients often require segmental mandibulectomy and excision of overlying skin (Fig. 6.26a–c). Many cases with GBS cancer show no evidence of mandible

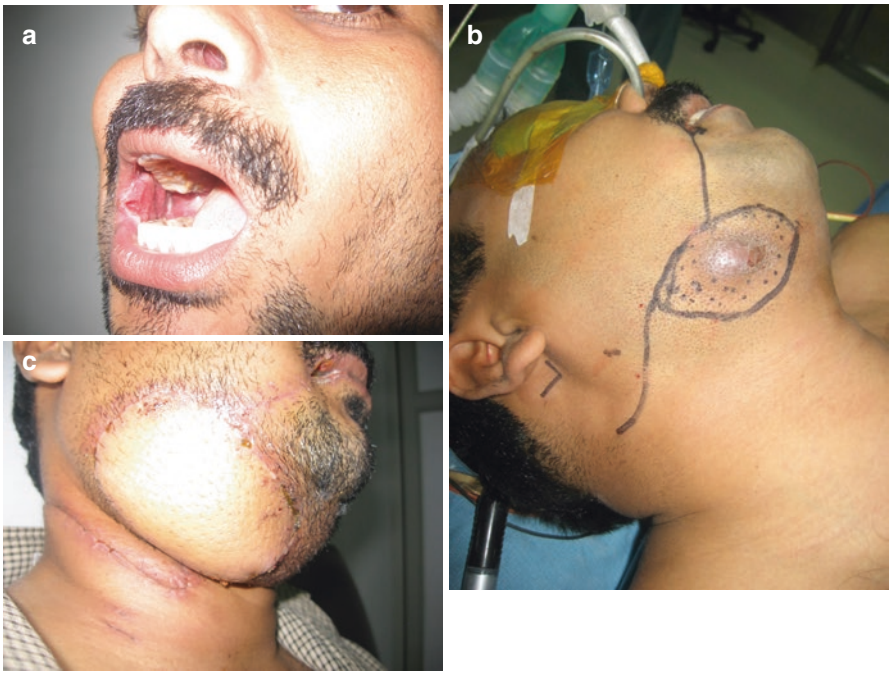


Fig. 6.26 (**a**–**c**) Advanced buccal mucosal carcinoma requiring composite resection including overlying skin

erosion but have significant paramandibular spread. Segmental mandibulectomy is an accepted approach for advanced lesion with paramandibular spread without mandible invasion. This is particularly necessary in patients who have associated trismus from preexisting oral submucous fibrosis. In selected cases on GBS carcinoma with paramandibular invasion and no trismus, excision of tumor with reverse marginal mandibulectomy may be considered.

6.4.2.3 Retromolar Trigone and Posterior Upper Gingivo-buccal Sulcus Carcinoma

Tumor involving the retromolar trigone (RMT) and posterior GBS carcinomas have higher incidence of local recurrence. This is not necessarily due to any intrinsic biologic aggressiveness of the tumor but due to the surgical inability to remove the tumor completely due to its higher propensity to involve infratemporal fossa (ITF) and pterygomandibular fissure. Majority of these patients present with trismus, and clinical evaluation may not be feasible. Trismus can be due to actual involvement of ITF or due to submucous fibrosis, which is a common predisposing lesion. Imaging modalities have their own limitations in predicting spread in ITF.

As retromolar trigone mucosa is tightly adherent to the mandibular alveolus, for tumors of this site, even without clinical or radiologic evidence of bone invasion, it is necessary to perform marginal mandibulectomy (Fig. 6.27a, b). In those tumors with mandibular cortical involvement, it is best managed by segmental mandibulectomy including coronoid process of the mandible (Fig. 6.28a–c). This is required both for

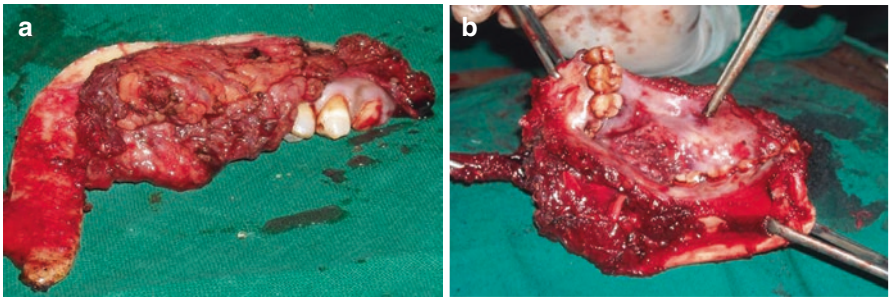


Fig. 6.27 (**a**, **b**) Early retromandibular carcinoma even without clinical or radiologic evidence of mandibular involvement would require marginal mandibulectomy

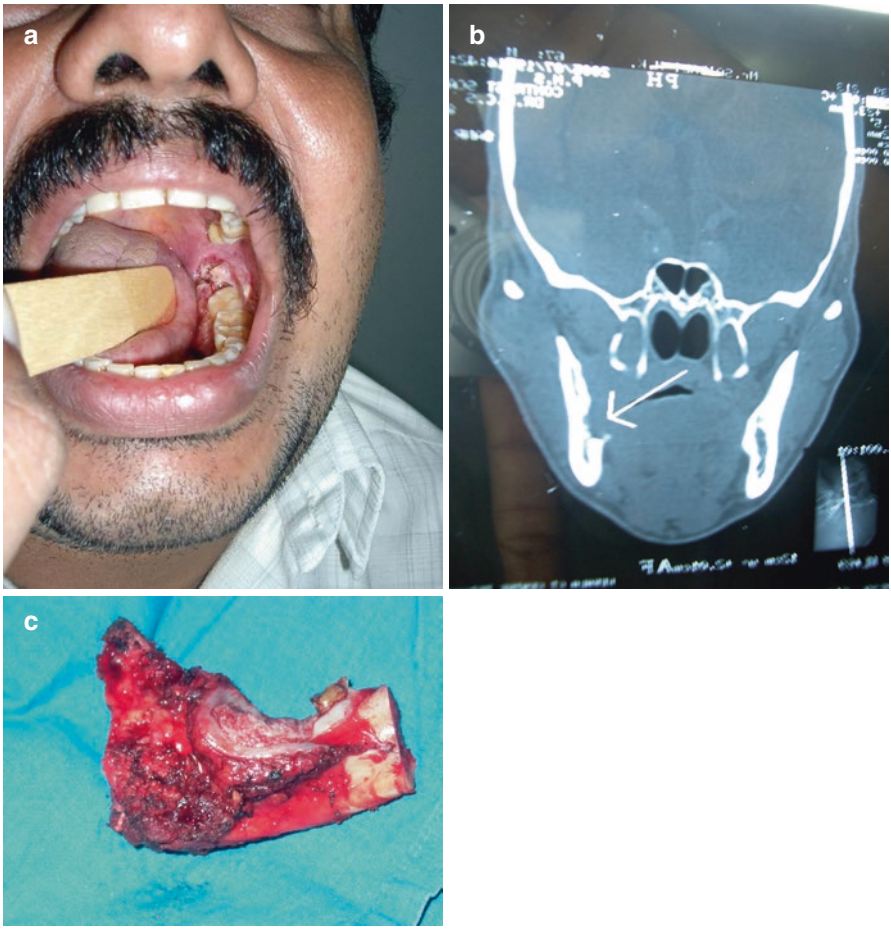


Fig. 6.28 (**a**–**c**) Retromolar trigone carcinoma with evidence of cortical involvement requires segmental mandibulectomy including coronoid process

oncologic and anatomic reason. A marginal mandibulectomy at this region can considerably weaken the mandible because of the presence of antigonial notch just anterior to the angle of the mandible. However, in selected patients with satisfactory mandibular bone height, it may be possible to perform marginal mandibulectomy. In those tumors involving infratemporal fossa, compartmental resection of the entire infratemproal fossa needs to be undertaken. The mandible may be managed by marginal mandibulectomy for those lesions without bone invasion and no evidence of trismus. In those with bone invasion and associated trismus, segmental resection of the mandible may be undertaken. The posterior upper alveolar lesions, without obvious pterygomandibular fissure involvement, may be excised by coronoidectomy, posterior maxillectomy, and excision of the pterygoid plates from its origin and the content of the ITF anterior to the foramen ovale. A large proportion of the RMT and posterior maxillary tumors do involve both the upper and lower jaw, requiring excision of ramus of mandible and posterior maxilla and contents of the ITF. This resection consists of distal segment of the mandible, partial upper alveolectomy, and complete removal of masseter and pterygoid muscles with pterygoid plates (Fig. 6.29a–d). This gives best possible chance to achieve negative margins in three dimensions. This approach aims to remove only additional nonfunctional tissue from the ITF and does not add functional morbidity. In those cases where the mandible is not involved as in tumors of the tuberosity of the maxilla or upper gingivo-buccal sulcus, similar compartmental infratemporal fossa could be carried out by paramedian mandibulotomy approach (Fig. 6.30a–h). However, it was observed that large proportion of the patients after postoperative radiotherapy develop significant trismus. To minimize trismus, one may consider osteotomy at the angle of the mandible to expose the ITF (Fig. 6.31). After completion of the resection, the osteotomized segments of the mandible is approximated using a Prolene suture. This produces pseudo-joint at the mandibular angle region. Since lingual and mandibular nerves are sacrificed as part of compartmental resection of the ITF, sacrificing these nerves at the time of angle osteotomy does not cause additional morbidity.

Associated trismus is a major limiting factor for improved functional outcome for buccal mucosal cancer. Trismus can be due to associated submucous fibrosis, disease in the ITF, or postoperative scarring. Perform coronoidectomy (unilateral or bilateral if severe trismus) along with resection and try to reconstruct defect with a flap to prevent contracture.

Lymph node dissection is performed electively for cancers staged T2 and above. Selective neck dissection from level I to III is sufficient for N0 neck and level I to IV for majority of N+ necks. Level V lymph node clearance is performed only when level IV–V lymph nodes are positive.

6.4.2.4 Upper Alveolus and Hard Palate

Surgical Anatomy and Pattern of Spread

Cancer affecting the upper alveolus and hard palate is not as common as that of the mandible, tongue, or buccal mucosa. Many lesions of the hard palate are of minor salivary gland etiology and often malignant. These cancers need special attention because

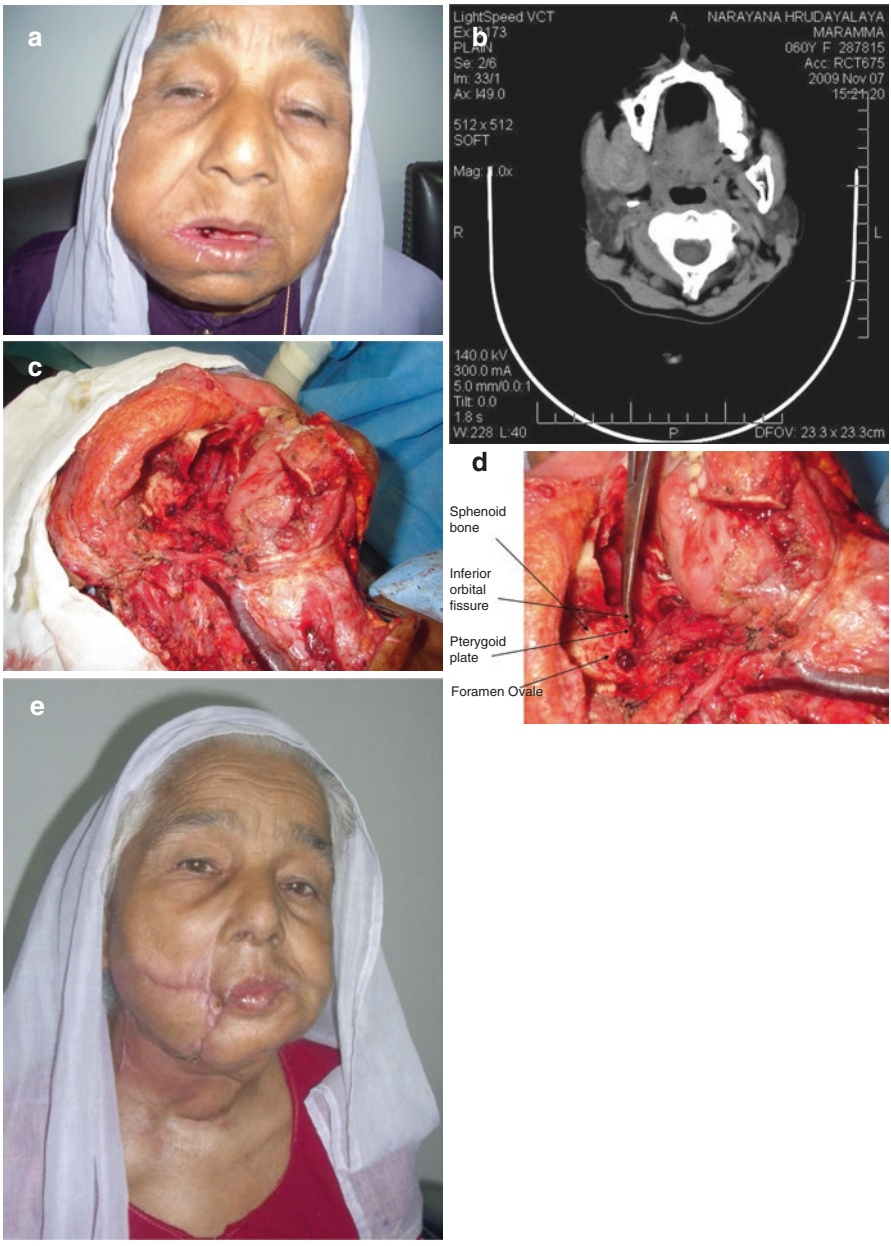


Fig. 6.29 (**a**–**d**) Compartmental resection of the infratemporal fossa for advanced buccal mucosal carcinoma with infratemporal fossa involvement. (**a**) Preoperative image, (**b**) CT scan showing involvement of medial pterygoid muscle, (**c**) post ablation defect, (**d**) close-up view of the skull base and cut end of the root of pterygoid plates, (**e**) postoperative appearance following anterolateral thigh flap reconstruction

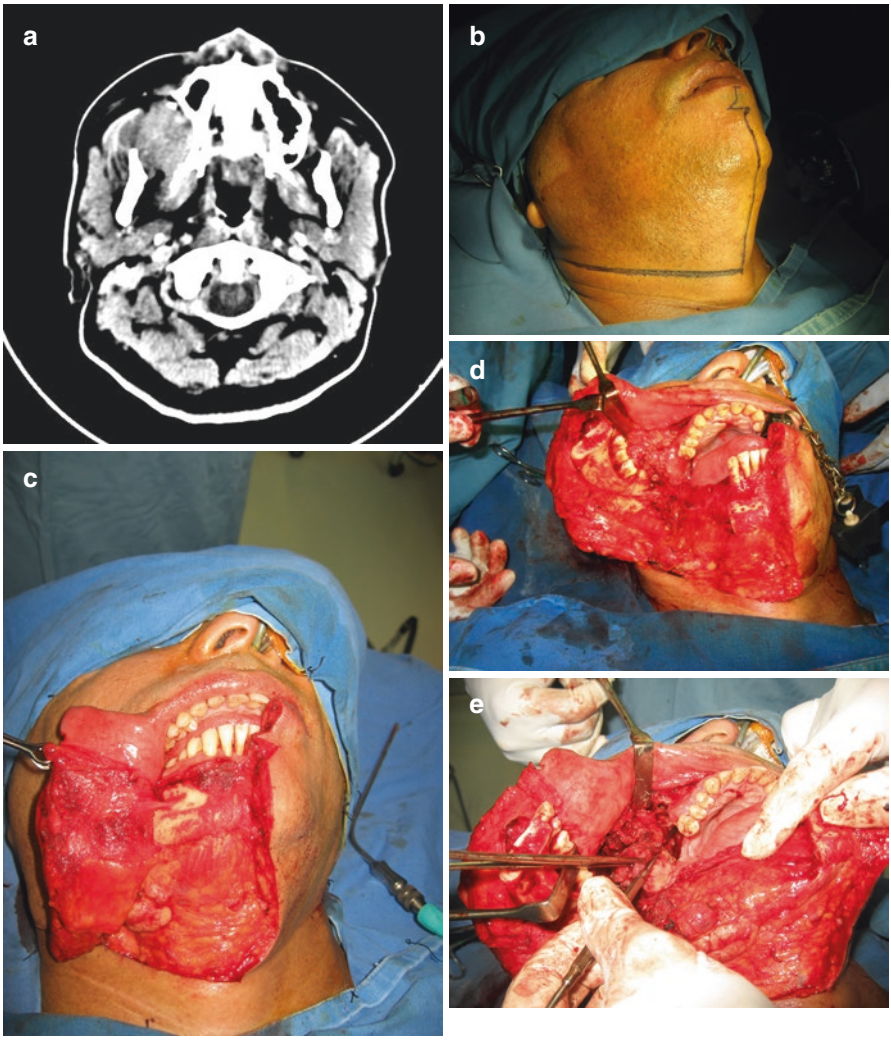


Fig. 6.30 Steps involved in performing compartmental resection of infratemporal fossa by mandibulotomy approach. (**a**) CT scan showing involvement of the medial pterygoid muscle, (**b**) incision, (**c**) exposure of the mandible, (**d**) paramedian mandibulotomy, (**e**) exposure of the infratemporal fossa, (**f**) surgical defect, (**g**) postoperative appearance, (**h**) trismus following surgery and adjuvant radiation

of their anatomical location. Lesions of the anterior palate and alveolus are very close to the premaxilla which provides support for the nose and midface. Lesions of the posterior alveolus and palate have a higher tendency to spread to the orbital floor and skull base due to anatomical proximity or through various neurovascular bundles. It is essential to evaluate preoperative disease extent with imaging studies. CT scan is the preferred mode of imaging but in select cases to evaluate skull base involvement. MRI can add value to determine perineural and intracranial invasion.

Fig. 6.30 (continued)

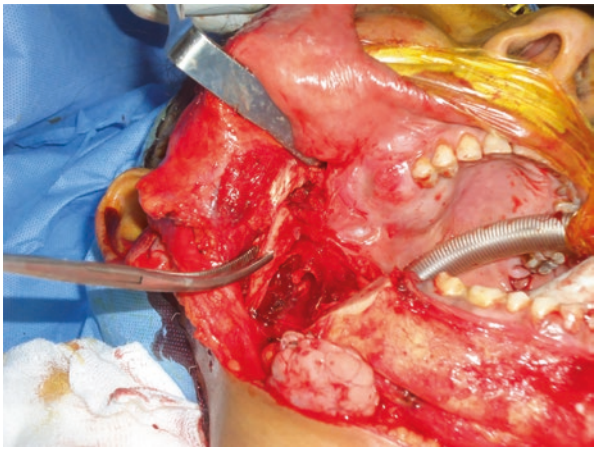


Fig. 6.31 Infratemporal fossa excision through mandibular angle osteotomy approach

Lymph node involvement is very rare for salivary neoplasm of the palate, and neck dissection is reserved only for node-positive disease. However, maxillary alveolar carcinoma has a high propensity for occult lymph node metastasis (15–20 %). Therefore, elective neck dissection is recommended. It is important to clear perifacial group of lymph nodes to have effective disease control for the upper alveolus.

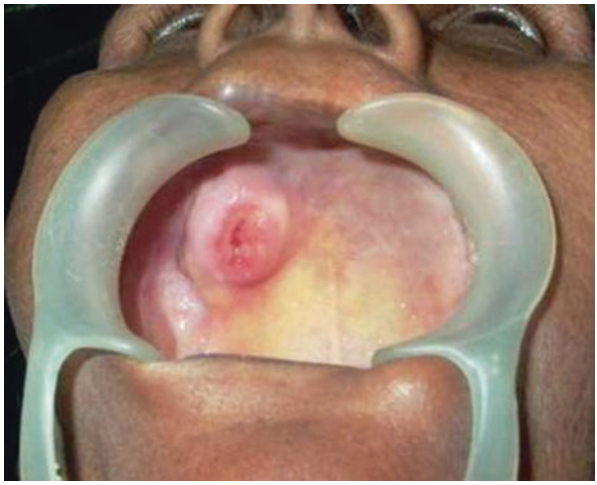


Fig. 6.32 Minor salivary gland tumor or the right posterior hard plate region in an edentulous patient

6.4.3 Surgery

Imaging studies are required to understand extent of disease especially to the infratemporal fossa. Isolated lesion of the hard palate can be managed by peroral WLE (Fig. 6.32). The bone of the palate is generally resected for malignant cases. Reconstruction can be achieved by one of local flaps in majority of cases. For palatal lesion involving part of the alveolus, an infrastructure maxillectomy is required. This can be performed either through peroral or with upper lip-split and lateral rhinotomy approach. Reconstruction can be achieved either by a dental obturator or by obturating defect with free flaps.

Upper alveolus lesion involving the last molars and infiltrating maxillary tuberosity area is a surgical challenge. They quite commonly have associated trismus due to ITF involvement. An infrastructure maxillectomy with compartmental resection of ITF is necessary for adequate surgical excision. Transmandibular approach offers optimal exposure for surgical excision than require maxillectomy and infratemporal fossa resection [57] (Figs. 6.30 and 6.31). Reconstruction is often performed with the use of a free flap. Lesion extending superiorly and involving the orbital floor requires a total maxillectomy. Weber Ferguson approach is a standard approach for this resection, but many surgeons perform this procedure with less extensive skin incisions. Reconstruction is necessary to support the orbit and provide oronasal separation and is generally achieved by free flaps. In cases of free-flap reconstruction, dental rehabilitation is achieved at a later date after completion of adjuvant treatment.

6.5 Summary

Surgery for oral cancer is challenging and needs multidisciplinary team approach with ablative and reconstructive surgeon working as a team. Each lesion is different in its behavior and proper preoperative planning is essential for complete tumor

removal. The primary determinant of improved locoregional control is the removal of tumor including areas of potential tumor spread to obtain three-dimensional tumor clearance. Appropriate approach should be selected to obtain adequate exposure for efficient tumor removal. The choice of reconstruction varies with extent of tumor resection, and free-flap reconstruction has become an integral part of surgical armamentarium. Effective functional rehabilitation helps in significantly reducing postoperative surgical morbidity.

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Management of the Neck in Oral Cavity Cancer

7

Robert A. Ord and J. Lubek

7.1 Introduction

Oral cancer is unusual in the Western countries, with an estimated 27,450 new cases for 2013 in the USA [1]. There has been a significant increase in 5-year relative survival rate between 1975–1978 and 2002–2008 of 53 % vs 65 % for all races, 54 % vs 67 % for whites, and 36 % vs 45 % for blacks. All of these were statistically significant ($p < .05$), although survival is still worse in blacks than whites [1]. This data is not true on global scale, and in many countries such as the Indian subcontinent, oral cavity cancer is more commonly seen due to habits such as the chewing of Betel Nut.

The majority of these oral cancers represent squamous cell carcinomas (SCCs), and this chapter will only discuss SCC. The oral cavity by definition includes the lips, but SCC of the lips is related to sun exposure and is in essence a skin cancer which does not behave like the mucosal intraoral SCC, so it will not be dealt with in this chapter.

This chapter will discuss the anatomy, staging, diagnosis, and management of regional metastasis of oral cavity cancer. The important topics of managing the N0 neck, the N+ neck, and recurrent disease in the neck will be dealt with separately. The preeminence in neck disease determining outcomes for patients with oral cavity cancer can be seen in the commonly quoted statement that a single positive node will reduce survival by 50 %.

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7.2 Anatomy

The anatomy of neck node drainage classically was based on postmortem cadaver studies and more recently on surgical studies of neck dissection specimens. Most authorities agree that neck disease usually progresses in a logical fashion from the first echelon nodes to the second echelon nodes, although skip metastasis can occur. Virtually all oral cavity cancers will drain to levels I and II in the neck, before passing to lower levels. Skip metastasis to level III can occur and is important, and rarely intraoral sublingual nodes may be the first sentinel nodes to be involved which has implications for sentinel node biopsy. Level I is now divided into level IA, the submental triangle, and level IB the submandibular triangle. The submental triangle drains the anterior portion of the oral cavity in the incisor region, and its nodes can be involved by SCC of the anterior floor of mouth or anterior mandibular gingival/alveolar cancers. Occasionally buccal or anterior tongue SCC may metastasize to the submental region. Level IB can be involved by the floor of the mouth, tongue, buccal, or mandibular and maxillary gingiva SCC.

The level II nodes are found between the level of the hyoid bone inferiorly and anteriorly, the posterior belly of the digastric muscle superiorly, and the posterior border of the sternocleidomastoid muscle (SCM) posteriorly. Level II is also now divided into level IIA inferior to the accessory nerve which contains the important jugulodigastric node through which virtually all of the oral cavity (and oropharyngeal) lymphatic drainage will pass and level IIB posterosuperior to the accessory nerve. Level I nodes will drain into level IIA, and the posterior floor of the mouth, posterior tongue, mandibular/maxillary gingiva in the molar region, and the retromolar fossa may all drain directly to level II.

Level III is demarcated inferiorly by the omohyoid muscle as it crosses the internal jugular vein (IJV) and contains the mid-jugular lymph nodes particularly the prominent omohyoid node lying in close relationship to the muscle. Although level III drains lymph from levels I and II, it can also exhibit "skip" nodes which directly involve level III nodes without involving nodes at levels II and III. This is especially true for tongue cancers.

Level IV and V nodes are very rarely directly involved by early initial spread of oral SCC but will become involved as neck disease progresses through levels I, II, and III.

In addition to these classical patterns of spread, buccal cancers may present with parotid nodes, and the posterior maxillary alveolus/hard palate may spread initially to retropharyngeal nodes. Although lymph node spread is usually ipsilateral, the floor of mouth cancers that approach or cross the midline may show contralateral spread as may SCC of the tongue tip or deeply invasive SCC of the tongue.

In a definitive study in 1990, Shah et al. examined 192 patients who underwent elective radical neck dissection (i.e., dissection of levels I–V) in the absence of any clinical/radiologic evidence of regional disease, i.e., N0 necks [2]. Sixty five patients (34 %) showed occult positive nodes, with 20 % at level I, 17 % at level II, and 9 % at level III. The tongue showed the highest involvement of level III with 16 %.

Also noted were 2–6 % positive nodes at level IV, the retromolar being the highest site, and a 0–2 % of level V nodes. This mirrored other studies which found an approximate 3 % incidence of level IV nodes in N0 necks [3–5]. These anatomic studies were later used to propose that a supraomohyoid neck dissection (SOND) would be sufficient for the NO neck in oral cancer.

7.3 Diagnosis and Staging

The initial clinical TNM staging of cancer uses clinical, radiologic, and any pathologic data (biopsy) that is available prior to the first definitive treatment [6]. If the patient undergoes surgery and more definitive histopathologic information is available, the pathologic staging pTMN may upstage or downstage the initial clinical TNM stage. At the current time, the N stage of the neck for oral cavity cancer is divided into five categories. NX indicates that the regional lymph nodes cannot be assessed. N0 indicates no regional metastases. N1 indicates metastasis in a single ipsilateral node, 3 cm or less in greatest dimension. The N2 category is the most complex and is subdivided into three groups. N2a indicates a metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension. N2b indicates metastasis in multiple ipsilateral lymph nodes, not more than 6 cm in greatest dimension. N2c indicates metastasis in bilateral or contralateral nodes, not more than 5 cm in greatest dimension. N3 indicates metastasis in a lymph node more than 6 cm in greatest dimension [6].

The value of the TNM system is that it allows different institutions in different countries to evaluate research and collaborate as well as providing a guideline for overall patient management through tumor boards. However, it is by no means a perfect system and is being regularly revised as new data regarding prognostic factors becomes available. At the present time, the N staging for oral cancer staging can be criticized for lacking information that is vital in dictating therapy such as the presence of extracapsular spread (ECS), the levels at which nodes are involved, and how to classify SCC in muscle or fat separate to any node. In addition to the data not included in the TNM system, there are inconsistencies within the system. Stage III for oral cavity cancer, for instance, includes both T3N0M0 and T3N1M0 patients. The N1 patients would be expected to have a 50 % less survival than the N0, yet both are classified as stage III. Nevertheless the TNM system has overall been validated as the most useful way of staging most cancers. In one classical retrospective study of 352 head and neck cancer patients, 5-year survival rates for N0, N1, N2, and N3 neck disease were 69 %, 39 %, 28 %, and 0 %, respectively [7].

In order to clinically stage neck disease in oral cavity SCC, clinical examination, imaging, and fine needle aspiration biopsy are all utilized. Clinical palpation of the neck is reported as having an accuracy of only 70 % [8]. Obviously in obese patients or patients with previously treated necks, examination is more difficult.

Imaging techniques have been used in the neck for over 40 years, but despite initial optimism, there are still areas of controversy regarding where it is useful and which techniques should be used to give the best information. Imaging with CT

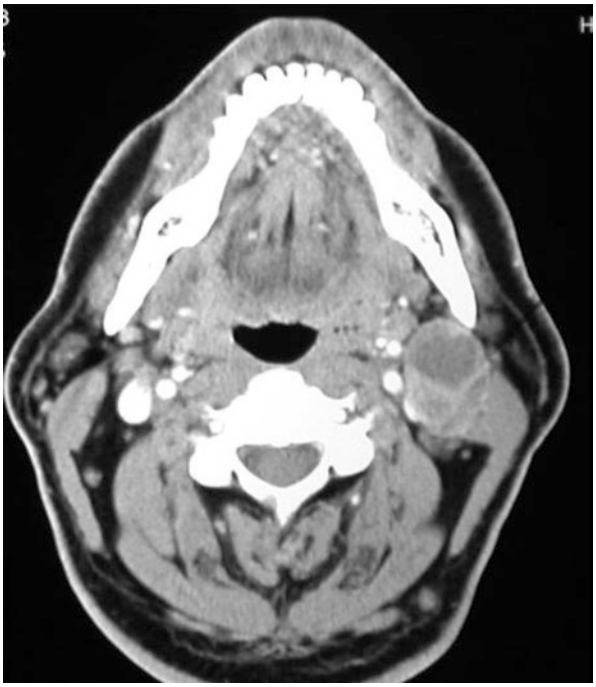

Fig. 7.1 Axial CT shows two enlarged nodes on the left at level II. The nodes are rounded, and there is central necrosis. The nodes appear fused and fixed to the sternocleidomastoid muscle

scan or MR has been said to improve accuracy for metastatic neck disease to approximately 90 % [9, 10]. It was Som in 1987 who outlined the CT criteria for diagnosing lymph nodes [11]. He defined three areas: size, submandibular or jugulodigastric node >1.5 cm or any other cervical node >1 cm; shape, metastatic nodes are more rounded or spherical; and appearance, central nodal necrosis is always pathologic (Fig. 7.1). Ultrasound imaging of the neck has been advocated as inexpensive and can be combined with fine needle aspiration to improve accuracy; however, it is time-consuming and very technique sensitive. In 1993 Erkan et al. reported a sensitivity of 94.4 % and a specificity of 95.7 % for ultrasound imaging of cervical metastases [12]. When the PET scan was developed, it seemed to give the clinician even greater ability to accurately diagnose and stage head and neck cancer (Fig. 7.2). In addition the whole body imaging of PEt allows diagnosis of distant metastases or second primary cancers. As fused PET/CT and PET/MR have become available, the number of options for imaging has increased; however, in critical areas of concern especially the N0 neck, recent studies do not indicate that imaging has superseded surgical staging.

A number of studies in the last 10 years have shown that PET scans in N0 necks cannot be used to define surgical management due to a limited sensitivity for small deposits and a relatively high number of false positives [13, 14]. These findings have not changed in recent published work with research in 2012 showing PET/CT

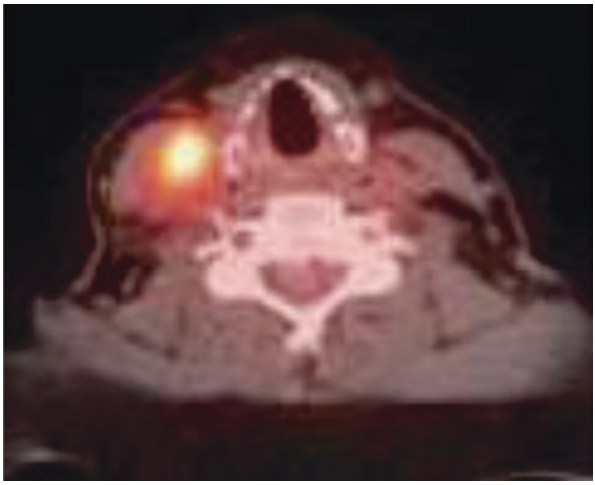

Fig. 7.2 Axial cut fused PET/CT shows node with increased SUV on the right side adjacent to the external thyroid cartilage of the larynx

having a much reduced rate of efficiency for N0 necks as opposed to N+ necks and concluding that it has little advantage in staging N0 necks [15]. PET/MR seems to have no advantage over PET/CT [16].

In comparing different imaging techniques, conclusions are somewhat varied. One 2014 prospective study examined patients deemed N0 by CT and/or MR who were then examined with ultrasound (US) and found that the number of patients with undiagnosed occult metastases decreased from 31 to 16 %, while 6 % of patients were over-staged by US [17]. In another study using multiple studies, it was concluded that fusion of (18)F-FDG-PET/MRI and (18)F-FDG-MRI plus DWI (diffusion-weighted imaging) may not increase nodal detection and N staging in oral cancer compared to US and (18) F-FDG-PET/CT [18]. Chaukar et al. found contrast-enhanced CT to give better concordance with histology in the N0 neck than either US or PET/CT [19].

In 2012 a meta-analysis comparing imaging modalities for the N0 neck identified 168 articles of which 7 studies fulfilled the inclusion criteria for CT, 6 studies for MR, 11 studies for PET, and 8 studies for US. The study conclusion was "modern imaging modalities offer similar diagnostic accuracy to define and diagnose clinically N0 neck." However, they could only state that avoiding elective neck dissection was acceptable in certain select cases [20]. In clinical practice, it appears that CT scan is most likely to be the initial study chosen for the N0 neck [21], despite the fact that "diagnostic accuracy of CT is limited among N0 oral cavity SCC patients" [22].

Although imaging has not provided an answer to diagnosis and staging of the N0 neck, there is evidence that it may provide prognostic information regarding outcomes. Joo et al. in 2013 showed that SUV max in PET/CT scanning was raised in lymph nodes with extracapsular spread; the ability to detect ECS also allowed prediction of 5-year worse survival [23]. The same authors also found a correlation

between resection margin involvement and an SUV >8.5 to be associated with adverse outcome [24]. Other authors have found SUV (mean) increase in the primary tumor to predict inferior disease-free survival [25]. In addition to raised SUV, metabolic tumor volume (MTV) as measured on PET has been found to be a significant prognostic factor for disease recurrence and mortality [26], as well as disease-free and overall survival [27].

Another area where PET has proved superior in neck evaluation is in recurrent regional disease. Lee et al. found that sensitivity and NPV for PET scan for recurrence was 92.5 % and 94.8 %, respectively, compared to 55 % and 76.9 % for CT scan. They recommend PET scan for routine surveillance [28]. PET/CT was also found to be superior to CT/MRI in detecting residual nodal disease in patients undergoing salvage surgery allowing better preoperative diagnosis [29].

US-guided fine needle aspiration biopsy (FNAB) has been shown to be very accurate in diagnosing lymph node status of the neck. Battenburg de Jong et al. [30] reported sensitivity of 98 % and specificity of 95 %, while Van de Brekel published a 96 % success rate in aspirating nodes >5 mm in diameter [31]. A 2012 prospective study compared CT, PET/CT, and US-guided FNAB to the final pathology obtained by neck dissection. Although US-guided FNAB showed the highest correlation with exact N classification and the smallest number of over-staged patients, it was concluded that none of the three modalities was reliable enough to replace neck dissection in N0 necks [32].

In addition to being used for diagnosis, FNAB has been used to guide therapy by assessing immunocytochemical profiles of cells to predict radiation response [33] and more recently to assess p16 status in possible HPV-associated head and neck cancers. HPV status can not only be useful in allowing de-escalating of therapy, but in nodes with an unknown primary, it may guide radiation fields to the oropharyngeal region reducing wide field radiation.

It is still felt by most head and neck surgeons that open biopsy of a neck node will compromise subsequent treatment and reduce outcomes [34], although Parsons et al. in 1985 showed that excisional removal of the entire node followed by radiation therapy gave a 96 % control of neck disease and a 75 % disease-free survival [35]. His work also demonstrated that incisional biopsy led to very poor outcomes.

7.4 The N0 Neck

7.4.1 Management

It can be seen from the above literature review that current clinical, imaging and FNAB techniques are not sufficiently accurate enough to diagnose occult disease (micrometastasis) in the N0 neck. The question becomes whether to treat the neck or observe and if we decide to treat then whether to give radiation therapy or elective neck dissection. As either treatment modality is associated with morbidity then clearly there must be a benefit to the patient as opposed to just observing. There are four randomized controlled trials in the literature which have examined survival in

early oral cancer patients with N0 necks treated either with elective neck dissection or observation. The first two trials were undertaken in France [36] and India [37] in the 1980s both with approximately 70 patients and oral tongue cancers. Neither trial demonstrated a significant survival benefit for neck dissection although there was a trend toward improved survival in tumors deeper than 4 mm in the Indian study. In 1994 Kligerman et al. published their trial of 67 patients with T1-2 N0 carcinomas of the tongue/floor of mouth and showed that disease-free survival rates at 3.5 years were 49 % for the observation and 72 % for the elective neck dissection cohort. The study also stratified patients into those with tumors >4 mm or <4 mm. Results demonstrated that stage II (T2) and >4 mm thick tumors were significantly associated with treatment failures. The trial concluded that neck dissection was mandatory in early stage oral SCC because of better survival than resection of the primary alone with observation of the neck and the poor salvage rates for neck relapse. This trial also provided the evidence for an elective SOHND approach to the N0 neck which remains the standard of care [38]. It is important, however, to appreciate that the 2009 prospective randomized trial by Yeun et al. failed to show any survival advantage for elective neck dissection [39].

Why should this early occult disease impact survival? One explanation is that ECS can occur at an early stage with very small deposits. Two large retrospective studies of 300 and 103 elective neck dissections for N0 disease showed similar rates of positive nodes 33 and 34 %, with rates of ECS of 24 and 49 %. ECS impacted rates of recurrence and disease-free survival [40, 41]. Another reason is that despite close observation patients tend to be diagnosed at a late stage rarely with N1 disease [42]. This may also be the reason why Yeun et al. in an initial retrospective study found salvage surgery for recurrence in "observed" necks to have poor outcomes [43]. However, even metastasis so small that were only detected by IHS or QRT-PCR can affect recurrence and/or survival [44, 45]. Primarily because of Kligerman et al.'s study [38] elective SOHND neck dissection became the standard of care for the "at-risk" N0 neck.

As evidence showed only approximately 33 % of elective neck dissections for N0 disease, it was not obvious which patients with oral cancer and N0 neck disease were at most risk for occult regional disease. Again from Kligerman et al.'s study [38], it appeared that patients having T2 tumors with thickness of 4 mm or greater had significantly lower survival. The initial studies on tumor thickness in SCC of the oral cavity being correlated with lymph node metastases were published in 1981 [46, 47]. Using the technique of decision analysis, Weiss et al. proposed that any patient with a risk above 20 % should undergo selective neck dissection [48]. This 20 % guideline covered all T2-4 tumors of the oral cavity plus any T1 tumors thicker than 4 mm.

Controversy has been generated over whether level IIB nodes or level IV nodes require to be removed in SOHND for an oral cavity primary and whether the neck dissection should be in-continuity or discontinuity with resection of the primary tumor. Regarding level IIB, the incidence of nodal involvement in the N0 neck is 6 % for all SOHNDs [49, 50] but is as high as 18 % in positive SOHND [50]. In a prospective study of 74 patients with oral cancer the occult positivity in the neck

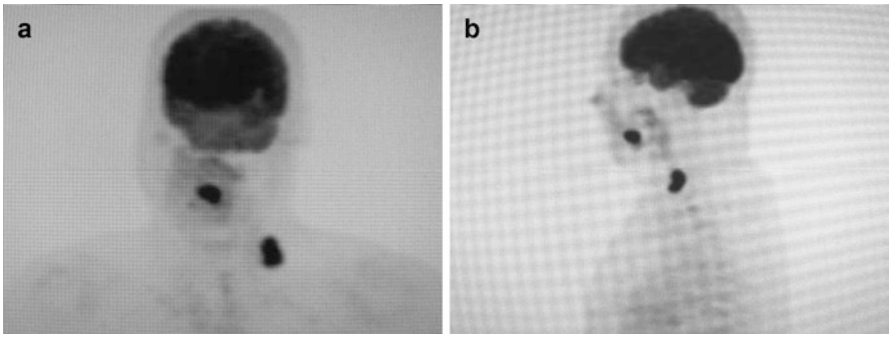

Fig. 7.3 (**a**, **b**) Coronal and sagittal PET shows primary tongue cancer with "skip" metastasis to level III

was 32 % (only 5 % of nodes at level IIB). In the final histopathologic examination of the neck dissection specimens, patients with positive nodes at level IIB all also had positive nodes at level IIA. In oral SCC the dissection of level IIB nodes is therefore not essential unless other palpable positive nodes at level IIA are discovered intraoperatively; this is important as dissection of level IIB is associated with some accessory nerve morbidity.

In 1997 Byers et al. advocated adding level IV dissection to the SOHND in cases of oral tongue cancer. His argument was based on retrospective data which showed a high level of "skip metastases" for oral tongue with 15.8 % of his series showing only level III or IV involvement [51] (Fig. 7.3). This conclusion was not upheld by a prospective trial which found an incidence of level IV nodes to be 4 % for oral tongue cancer and recommended only dissection of levels I–III [52]. The argument for in-continuity dissection revolves around the potential for missing important lymphatic tissue or nodes if a separate glossectomy and SOHND are performed with consequent higher recurrence rates. In one study, patients with discontinuous dissection had a 63 % 5-year survival compared to 80 % for patients where the primary resection and neck dissection was carried out in-continuity [53]. However, the in-continuity approach does sacrifice more normal tissue and creates an open tract between the mouth and neck leading to a greater potential for complications. A large Brazilian study with 193 patients showed no difference in disease-free or disease-specific survival associated with in-continuity versus discontinuity resections [54]. At the current time in the USA, discontinuous dissection appears to be the standard of care. This approach will miss removing sublingual lymph nodes which are rare but are reported to occasionally be the first echelon nodes for oral tongue cancer [55].

In patients who are medically unfit or refuse surgery with N0 neck at high risk of occult disease, there is good evidence that 50 Gy of radiation can effectively sterilize the neck [56, 57]. Indeed as long ago as 1972, Fletcher compared 187 cases with no elective irradiation to 187 cases with elective irradiation to the N0 contralateral neck and showed the incidence of delayed nodes to be 24 % and 3 %, respectively [58]. However, as most oral cancers are primarily dealt with surgically, it seems to make sense to undertake elective neck dissection in high-risk patients at the same time, as well as the staging information that is obtained. The argument can be made that patients

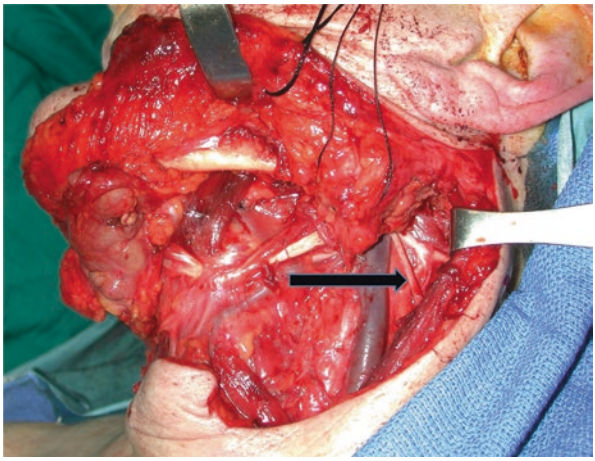

Fig. 7.4 The completed SOHND. The sternocleidomastoid muscle is retracted with an army-navy retractor. The *long arrow* crosses the carotid and IJV and points to the accessory nerve

with subclinically positive disease with ECS who only receive elective radiation do not get the benefit of chemoradiation which is indicated for ECS and that staging the neck by elective neck dissection can more accurately define the need for and type of adjuvant therapy. In the future sentinel node, biopsy may become the method of choice for staging the N0 neck, and this subject is addressed in another chapter.

7.4.2 Surgical Technique

The author uses a similar approach to SOHND as that reported by Medina and Byers [59] as he has previously described [60] (Fig. 7.4). The initial incision is made from the mastoid to the midline of the neck, placed in a mid-neck skin crease. The flaps are raised in a sub-platysmal plane from the area where the omohyoid muscle crosses the internal jugular vein (IJV) to the lower border of the mandible. The fascia is raised off the sternocleidomastoid muscle (SCM) over its anterior border and deep to the muscle. The posterior belly of the digastric muscle is identified deep to the SCM and close to the mastoid. Dissection of the fat beneath the inferior border of the digastric will identify the proximal end of the IJV and the accessory nerve as it crosses the posterior IJV at the level of the atlas vertebra. If there are no palpable hard nodes at level IIA, the level IIB triangle will not be dissected. The fatty tissue at the apex of the triangle between the accessory nerve and IJV is dissected down to the prevertebral fascia. This fat is mobilized from the accessory nerve and the posterior border of the IJV. Dissection continuous inferiorly releasing the fat from the SCM posteriorly and the IJV anteriorly till the omohyoid muscle superior border is seen. Care is taken to leave the nerves of the deep cervical plexus intact.

The fatty tissue is mobilized anteriorly to the IJV by dissecting the fascia off the IJV. Dissection continues anterosuperior in the anterior triangle of the neck with the anterior belly of the omohyoid delineating its anterior extent. Once the anterior belly

of the digastric is identified, level I will be dissected. If the level IA nodes are to be removed (submental), this will be done starting from the contralateral anterior belly of the digastric muscle and mobilizing the fat and adipose tissue to the ipsilateral submandibular triangle. The mandibular branch of the facial nerve is identified by careful dissection below the mandible and mobilized cephalad superior to the lower border of the mandible. The common facial vein and facial artery are tied off at the lower border (unless they are to be used for free flap reconstruction). The level IB fat and nodes including the submandibular gland are mobilized off the mylohyoid muscle identifying the posterior border of that muscle as dissection proceed posteriorly toward the mandibular angle. A vein retractor is used to retract the mylohyoid muscle anteriorly to identify the lingual nerve. The branch from the lingual nerve to the submandibular gland is clipped and cut, and Wharton duct is clipped and cut. The specimen is now pedicled on the proximal trunk of the facial artery as it emerges from deep to the posterior belly of the digastric muscle to pass superiorly to the muscle. This is doubly ligated and cut and the specimen removed. The platysma and skin are closed in two layers. Large round suction drains are placed prior to closure.

The specimen is oriented and pinned on a cork board with a diagram for the pathologist.

7.4.3 Adjuvant Therapy

It is currently a standard of care to examine histopathologic data at multidisciplinary tumor boards. Adjuvant therapy is usually recommended based on the current NCCN guidelines [61]. The guidelines for adjuvant therapy in the postoperative neck at are based upon two large prospective, randomized trials (RTOG 9501 in the USA and EORTC 22931 in Europe) comparing postoperative radiation to postoperative chemoradiation in patients at high risk for locoregional relapse [62, 63]. Long-term follow-up of the cohorts of these two trials have served to refine the criteria for the use of both radiation and chemo/radiation [64–66]. Current recommendations recommend no adjuvant therapy if the neck dissection is N0 or N1 histopathologically without extracapsular spread. Any N2 neck or greater histopathologically will be recommended for adjuvant radiotherapy if there is no ECS. If there is ECS in any neck dissection, then chemo/radiation is recommended.

7.5 The N-positive Neck

7.5.1 Management

The neck with clinically positive nodes was treated by radical neck dissection based upon Crile's classic description in 1906 [67]. The radical neck dissection (RND) encompassed levels I–V with the removal of the SCM, IJV, and spinal accessory nerve. The removal of these three structures especially the accessory nerve did lead to a significant morbidity for patients, and modified radical neck dissections

(MRND) were developed that still allowed complete dissection of levels I–V while sparing one or more of the SCM, IJV, and spinal accessory nerve. Lingeman et al. studied outcomes of patients who underwent either RND or MRND, finding that regional recurrence rates for N0, N1, and N2 necks were 14, 15, and 26 % in patients who had RND and 0, 16, and 25 % for MRND patients [68]. The MRND was demonstrated to be oncologically safe for N0 and N1 necks [69, 70], and it was also shown that the spinal accessory nerve could usually be safely preserved even with advanced neck disease, ECS and nodes along its course unless directly invaded by tumor [71]. Between 1984 and 1990, there was much discussion whether the N1 neck could be safely treated by SOHND [72], whether selective neck dissection levels I–IV [73] was required or whether MRND was essential [74]. In view of Shah's earlier study which showed an incidence of 20 % level IV nodes in the N-positive neck [2], it appears that at least a selective neck levels I–IV or MRND is essential. Other recent studies confirm this data and emphasize that positive nodes at level IIA are a predictor for positivity at both levels IV and IIB [75].

More recent studies have looked at outcomes for selective neck dissection for clinical N1 neck disease. Pellitteri et al. found that for pathologic N0, 1 of 33 patients (3 %) recurred in the neck, and for proven N1 disease, 1 of 8 patients (12.5 %) recurred. They felt selective neck dissection was suitable for the N1 neck, provided radiation was given for patients with N2 disease or ECS [76]. In another study of SOHND for N-positive necks, regional control was 88 % for N0 necks and 71 % for N-positive necks, and this was significantly improved by radiation therapy for the N-positive group [77]. Control rates in the SOHND cases with positive nodes who were irradiated were comparable to those patients with level I–V neck dissections and radiation. Further studies have confirmed these results using a variety of different selective neck dissections, showing comparable outcomes to MRND and RND provided radiation was given for greater than N1 disease and chemo/radiation for ECS [78–80]. It is difficult to assess whether SOHND is adequate as a selective neck dissection for the N-positive neck as many of these studies used a variety of selective neck dissections. In Givi et al.'s paper, 80 % of their selective neck dissections included level IV which they felt was particularly indicated for oral cavity primaries [81]. As MRND has more morbidity than selective neck dissection [82], level V nodes should only be removed when they are at high risk due to clinically evident ECS, multiple LN involvement and cN1 with deep jugular chain of LN involvement [83]. The IJV is usually retained in selective neck dissection especially if microvascular reconstruction is required; however, there are some studies that show an increased rate of neck failure with preservation of the IJV [84].

In concluding recommendations for the N-positive neck for an oral cancer primary, it appears that for the clinically N1 neck, a selective neck dissection levels I–IV or an MRND can be used. If the neck is found to be N2 or greater histopathologically, then adjuvant radiation is indicated, while for ECS chemo/radiation should be given. In countries where cost is a major driver of health care, MRND may be a more cost-effective choice [85]. In the clinically N2- or N3-positive neck, then MRND or RND is the method of choice. The accessory nerve can usually be spared except in extensive disease [71], and all cases will have adjuvant radiation

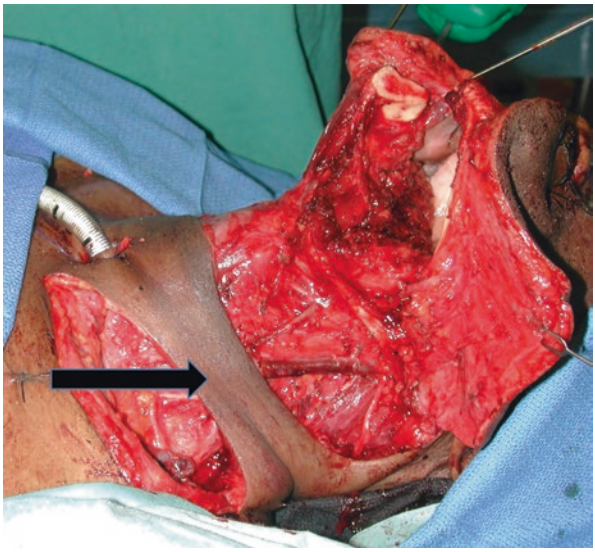

Fig. 7.5 MacFee incision for a MRND note the bi-pedicled skin flap (*large arrow*). Patient has had an in-continuity resection of the left tongue/hemi-mandible and MRND

with chemo/radiation used for ECS. Prognosis is poor in advanced neck disease with multiple nodes and ECS, and approximately 50 % of these patients will develop distant metastases, most frequently to the lung. Whether contralateral neck dissection is indicated has been debated but the rate of contralateral neck disease is only around 4 % [86], and the majority of patients will receive radiation to the contralateral neck as part of their adjuvant regime. Nodal disease <3 cm is well controlled by radiation therapy, and any microscopic disease in the contralateral neck should be sterilized with 50 Gy of radiation.

7.5.2 Surgical Technique

The author's preferred methods for RND [87] and MRND [60] are published in the literature. The author prefers a MacFee incision (Fig. 7.5), for all level I–V dissections to prevent trifurcation breakdown and carotid blowout (Fig. 7.6). If the sternocleidomastoid muscle is to be kept in MRND, then a wine glass (Schobinger) incision is usually safe. The skin flaps are raised in a sub-platysmal plane (if ECS involves platysma or skin, it will of course be sacrificed). The author begins the dissection posteriorly finding the anterior belly of the trapezius muscle 1 cm above the clavicle and defining this structure as the posterior limit of the dissection. The accessory nerve is identified as it passes beneath the trapezius 2–4 cm above the clavicle, in an RND this will be sacrificed in an MRND usually dissected and preserved. The supraclavicular fat and nodes are mobilized off the prevertebral fascia taking care not to damage branches of the brachial plexus. The location of the brachial plexus is at the

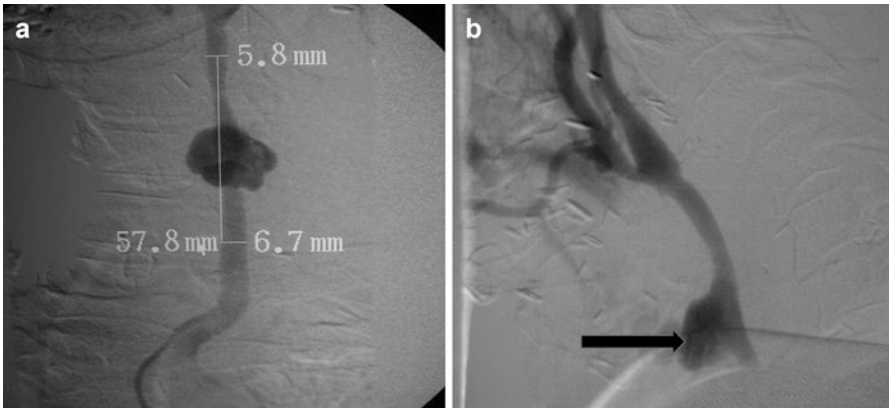

Fig. 7.6 (**a**, **b**) Angiogram demonstrates pseudo-aneurysm of common carotid artery following a premonitory bleed during radiation therapy. Carotid pseudoaneurysm (*arrow*)

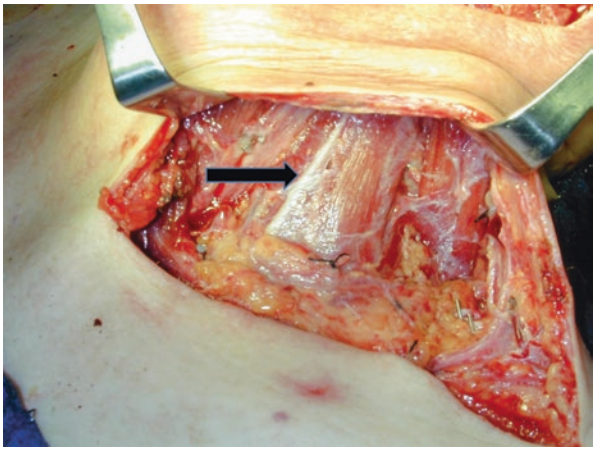

Fig. 7.7 The bi-pedicled portion of the MacFee incision is retracted cephalad. The accessory nerve, sternocleidomastoid, and IJV have been sacrificed. The *arrow* points to the phrenic nerve. The common carotid is retracted medially

point where the omohyoid muscle passes under the clavicle. The omohyoid is sacrificed in the RND but may be retained in the MRND. The sternocleidomastoid muscle is divided off the clavicle and sternum and dissected cephalad. The remaining supraclavicular fat is mobilized off the prevertebral fascia and mobilized cephalad. The transverse cervical artery and vein runs about 2 cm above the clavicle and may be preserved; it lies superficial to the phrenic nerve as it crosses the anterior scalene muscle. Care should be taken when mobilizing the level IV fat/nodes close to the IJV on the left side not to damage the thoracic duct (Fig. 7.7). At this point the IJV is identified in the base of the neck. If it is to be sacrificed and ligated, care is taken to separate its deep surface from the vagus nerve. The block of tissue fat with IJV and

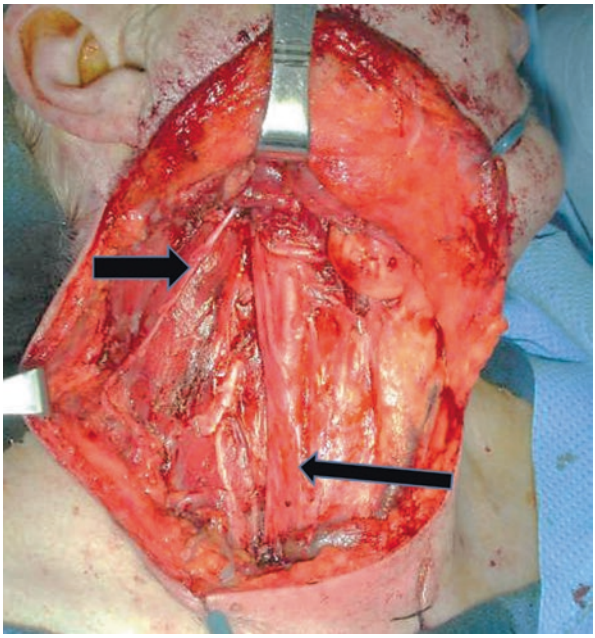

Fig. 7.8 MRND, the sternocleidomastoid muscle, and IJV have been sacrificed. The *long thin arrow* points to the common carotid and the *short thick arrow* to the intact accessory nerve

sternocleidomastoid muscle are now dissected superiorly along the prevertebral fascia sacrificing the large cervical nerve branches of the phrenic nerve (C 3, 4 and 5) as they pass into the specimen. In the RND this is a quick and easy dissection to the level II area. At this point the sternocleidomastoid muscle is sectioned off the mastoid from the apex of the posterior triangle. Then following a line from the tip of the mastoid to the angle of the mandible, the sternocleidomastoid is sectioned superiorly along with the tail of the parotid to the depth of the underlying posterior belly of digastric muscle. The superior end of the accessory nerve is identified and cut and the superior portion of the IJV ligated and cut at the level of the digastric. The specimen is mobilized forward to level I, and dissection proceeds as described for the SOND.

In the case of the MRND, dissection is more complex. If the accessory nerve is to be retained, it is dissected to its entry beneath the sternocleidomastoid muscle and mobilized from the underlying fat. The fat at the apex of the posterior triangle which lies superiorly (cephalad) to the nerve is mobilized from the prevertebral fascia and passed deep to the nerve to remain in continuity with the level V fat (Figs. 7.8 and 7.9). At this point if the sternocleidomastoid muscle is to be preserved, its fascia at the posterior border is raised and dissected to allow a tunnel to be created under the muscle to pass the contents from level IV and V to be passed anterior to the sternocleidomastoid into level III. Usually the author leaves the contents of levels IV and V in the posterior neck and completes the SOHND as already described (above) but leaving level III attached to level IV fat. When this is finished, it is easier to pass the

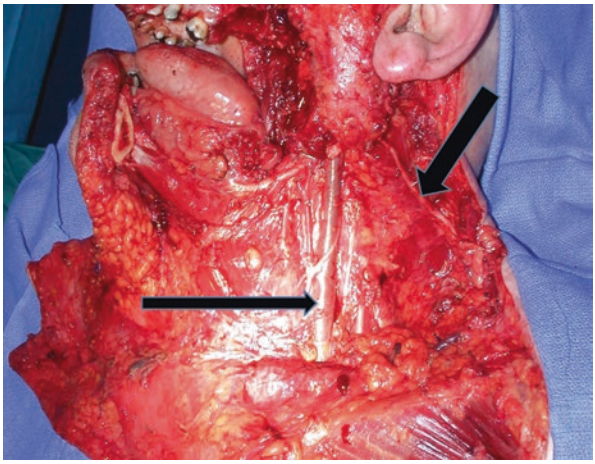

Fig. 7.9 In this MRND the sternocleidomastoid muscle has been sacrificed due to ECS into the muscle. The IJV (*long thin arrow*) is intact, and the accessory nerve (*short thick arrow*) is preserved

contents from the posterior neck (levels IV and V) in-continuity with the SOHND, although there are usually a few irritating attachments that need to be sectioned to mobilize the specimen easily.

7.6 Recurrent Neck Disease

Recurrent disease in the neck is a complex problem, and its outcome and management depends on many factors. It is important where the regional failure occurs, on the ipsilateral or contra lateral neck, and whether the ipsilateral neck has already been treated. If the neck has been treated surgically, then did the failure occur in the previous dissected field (Fig. 7.10) or outside the dissected levels? Factors that are important in regard to the initial disease include whether the neck was initially positive (especially N2 or greater), if there was ECS, the type of previous neck dissection, and whether radiation therapy had been given. In addition the time to recurrence is important in regional recurrence. In local recurrence early recurrence <6 months gives a much worse prognosis and worse survival; however, in regional failure, late recurrence appears to carry a worse prognosis [88].

It is very clear that the only salvage therapy that offers patients a meaningful chance at survival is surgery. Wong et al. found a 5-year survival of 26 % (mean 28 months) for regional failure with surgical salvage and 0 % – 5-year survival for radiation (mean 7 months), 0 % – 5-year survival for chemotherapy (mean 6 months), and 0 % – 5-year survival for supportive treatment only (mean 3 months) [89]. Interestingly in patients with no previous neck dissection, 56 % were able to be surgically salvaged with a 32 % – 5-year survival, but in ipsilateral recurrence with a previous neck dissection, only 32 % could be surgically

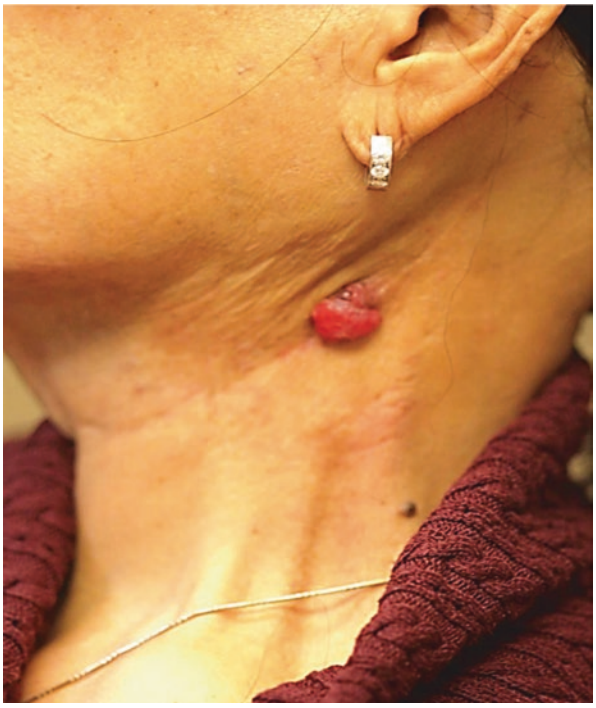

Fig. 7.10 Patient presents with squamous cell carcinoma fungating through neck dissection incision of previous supraomohyoid neck dissection

salvaged with an 18 % – 5-year survival. Kowalski also found that the type of prior neck dissection and previous radiation therapy to have a significantly worse effect on survival [88]. Mabanta et al. reviewed 51 patients who failed in the neck after being treated primarily with radiotherapy for positive nodal disease [90]. Only 33 % of this cohort could be offered salvage and the control of neck disease at 5 years was 9 % with a mean salvage survival time of 8.75 months. The authors concluded the likelihood of successful salvage treatment after a neck recurrence following radiotherapy is remote. Gleich et al. found that salvage in patients who had a previous neck dissection and adjuvant radiation was zero [91]. In this study salvage rates for radiation alone were also zero (mean <6 months), but the mean survival time for surgical salvage was 31.1 month, and 6 of 14 patients had prolonged survival.

In our own series of patients, we had 30 patients with regional recurrence and 19 (63 %) had a previously untreated neck, and we were able to salvage 13 patients (68 %), but in patients with recurrence in a previously dissected field or who received previous radiation therapy, our salvage rate was only 33 %. Our overall salvage rate was 50 % which was high as most of our cohort had untreated necks. All of our salvage patients had RND, and we were most successful using a combination of RND + radiation therapy (70.6 % salvage for this treatment) [92]. It should be noted

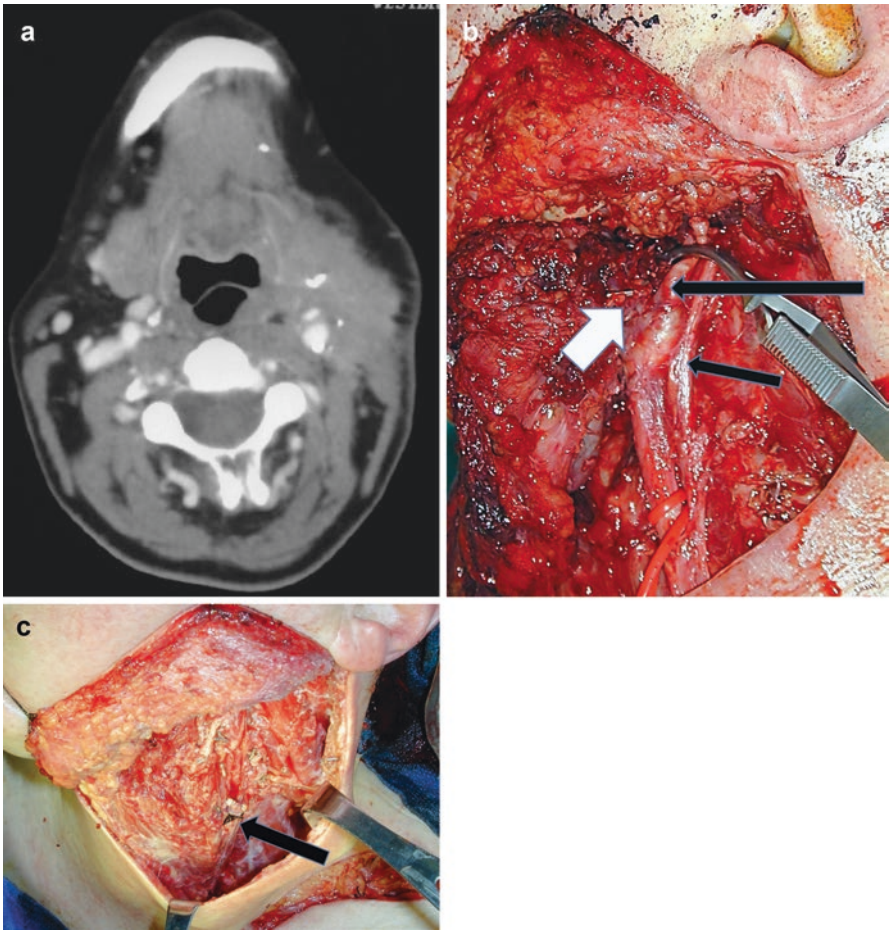

Fig. 7.11 (**a**) Shows axial CT of recurrent regional disease encasing IJV and part of the carotid. (**b**) intraoperative view shows the internal carotid artery has been preserved (*long thin black arrow*) and the vagus nerve also dissected free of tumor (*short thin black arrow*). The external carotid artery is encased by tumor (*thick white arrow*) and will be sacrificed. (**c**) The *arrow* points to the ligated external carotid artery stump. The digastric muscle has also been sacrificed

that frequently extended RND to remove involved structures that are preserved in a standard RND is essential (Fig. 7.11).

In conclusion regional failure is a difficult problem. Outcomes are poor, and a recent study from 2012 showed only 51 % of ipsilateral recurrent neck disease underwent salvage therapy, with control of the disease in 25 % of cases 12 months postsalvage surgery [93]. The best results are with early recurrence in an untreated neck. Late recurrence and previous treatment with surgery, radiation, or a combination of the two will all lower the expected survival rates. Radiation or chemotherapy used without surgery gives zero salvage, and the best treatment in this

situation is RND followed by radiation therapy if the patient has not been previously irradiated.

Conclusions

- At the current time, clinical, imaging, and other diagnostic techniques cannot accurately stage the N0 neck, so that elective SOHND has become the method of choice for staging the neck and planning subsequent management. Whether this policy results in a better overall survival has not been proved. In the future sentinel node biopsy may play an important role.
- The N1 neck can be treated by a selective neck dissection levels I–IV or MRND. If the neck is pathologically N2 or greater, adjuvant therapy will be indicated.
- The N2 and N3 necks are best treated by MRND or RND with adjuvant therapy as dictated by the pathology.
- In a neck dissection with pathologic N0 or N1 disease, no adjuvant therapy is required. In N2 or greater pathologic disease, radiation therapy is required postoperatively. If ECS is present in any neck dissection, chemo/radiation is required.

In recurrent neck disease, neck dissection offers the only hope of salvage. RND is usually required and postoperative adjuvant therapy given as indicated by pathology and previous therapy.

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Sentinel Node Biopsy in Oral Cancer

8

Krishnakumar Thankappan and Moni Abraham Kuriakose

8.1 Introduction

The status of the cervical nodes is an important prognosticator in patients with oral cavity squamous cell carcinoma (OSCC) [1]. There is a high incidence of occult metastasis, even in patients with no clinical or radiological evidence of lymph nodal metastasis (N0). This ranges from 10 to 50 % depending on the primary tumor characteristics [2–4]. Despite this, we currently have no accepted noninvasive diagnostic modality for identification of occult regional disease [1].

Management of N0 neck in OSCC is controversial. There is difference of opinion in choosing an elective neck dissection versus a "watch and see" policy [5, 6]. There is a chance of overtreating more than 70 % by doing an elective neck dissection resulting in avoidable morbidity. So, a strategy to identify patients at risk of metastasis in N0 neck allows accurate staging and implementation of appropriate adjuvant treatment. Presently, pathological evaluation is the most reliable method of staging cervical nodes [7]. As in case of many solid tumors [8, 9], sentinel lymph node biopsy (SNB) is emerging as a potential method for staging of lymphatic metastasis in OSCC. This paper will review the current understanding of the mechanism of lymphatic metastasis, concept of SNB, evolution of the concept, current status of SNB in OSCC, technique of isolation of the sentinel lymph node (SLN), intraoperative assessment of sentinel

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nodes, and pathological evaluation of the SLN including the histologic and molecular markers in identifying occult disease in sentinel nodes. This will also review the studies reporting the outcomes in SNB, the morbidity of the technique compared to selective neck dissection, and the controversies and latest developments in SNB in OSCC.

8.2 The Concept

Tumor cells enter the lymphatic system through the peritumoral lymphatics. Tumor cell motility and rich lymph vessel density are the key factors that determine this initial lymphatic permeation [10]. The absence of basement membrane and the large number of gap junctions between the endothelial cells assist the access of tumor cells to the lymphatics. The tumor emboli are then disseminated in the lymphatic system in an orderly fashion, beginning with the SLN and then to the remaining lymph nodes within the nodal basin [11] (Fig. 8.1). The nodal basins in oral cavity cancer are well characterized [12, 13]. The status of the sentinel node predicts the presence of metastasis in the rest of the nodes within the nodal basin. This forms the basis of SNB. The tumor emboli enter the sentinel node through afferent lymph vessels to the subcapsular sinus as single cells or small clusters of tumor cells. The tumor cells proliferate and result in stromal reaction. The tumor replaces the interfollicular sinuses of the cortical area and then invades the medullary sinuses of the node. Finally, the proliferating tumor replaces the architecture of the node. As the initial tumor cells are filtered at the subcapsular sinuses, the tumor can invade the capsule at any stage of its intranodal growth. The tumor emboli, after filtering through the sentinel node, exit through the efferent lymph vessels located at the hilum to other nodes within the nodal basin. The tumor deposit, when replacing the nodal architecture and filtering mechanism, can cause an increase in hydrostatic pressure within the afferent lymph vessels. Any further tumor emboli will be directed to other nodes within the primary tumor nodal basin, bypassing the first echelon node. The pattern of growth of tumor emboli filtering through the SLN is also well established, starting as isolated tumor cells (ITCs), micrometastasis, and macrometastasis [14].

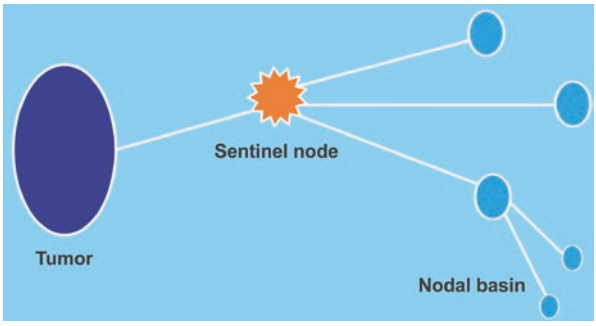

Fig. 8.1 Concept of sentinel node biopsy

8.3 The Evolution

Seaman and Powers [15], in 1955, for the first time demonstrated the concept of the first echelon node and nodal basin using radioactive colloid gold. Gould et al. [16] subsequently coined the term "SLN" in case of malignant parotid tumor. Cabanas [17] established the basis of SLN theory. In penile cancer, he showed that a specific node in each groin received lymphatic drainage, and the pathologic status of this SLN can be used as a guide to determine the need for lymph node dissection. However, subsequent studies failed to corroborate this finding, and therefore, the concept did not receive clinical attention [18]. In 1992, Morton et al. [19] demonstrated the clinical feasibility of the SNB in cutaneous malignant melanoma using isosulfan blue dye. They were able to identify the SLN in 82 % of patients. Alex and Krag [20] proposed the use of lymphoscintigraphy and the use of a handheld gamma probe for intraoperative identification of the SLN in cutaneous malignant melanoma. With a handheld gamma probe, they were able to identify SLNs in 90 % of the cases. Morton et al. [21] later concluded in a randomized clinical trial that blue dye and lymphoscintigraphy are superior to blue dye alone in cutaneous malignant melanoma. With the combined technique, the SLN could be identified in over 95 % of the patients. More importantly, these studies have demonstrated that when the SLN is negative for metastasis, the remaining nodes within the nodal basin are also negative for metastasis [22]. SNB has become the standard of care in melanoma [8, 23] and cancer of the breast [9, 24]. SNB for early-stage oral cavity cancer continues to gain acceptance worldwide as an effective alternative to elective neck dissection for staging the N0 neck [25].

8.4 Technique

SNB consists of two steps, identification of the SLN and pathological evaluation of the isolated SLN. SLNs can be identified by three techniques: blue dye, preoperative dynamic lymphoscintigraphy, and intraoperative static lymphoscintigraphy. The success rate of identification of the SLN is dependent on the experience of the surgeons. The recommendations of cutaneous melanoma are 30 cases [21]. Ross et al. [26, 27] noted that in experienced hands, the SLN detection rate was 96 %. However, for surgeons who had performed fewer than ten operations, the successful SLN detection rate was only 57 %.

8.4.1 Blue Dye Technique

Isosulfan blue dye is used most widely. The dye is injected submucosally around the tumor. The SLNs are stained blue 15–45 min after the injection. The technique needs visualization, and hence, it is essential to expose the entire nodal basin, thereby increasing the invasiveness of the procedure. Moreover, blue dye consists of small particles with a very poor retention in the sentinel lymph node, and the blue color is therefore retained for a short period of time. This is probably because of the

fast lymphatic drainage in the head and neck area. Besides, isosulfan blue dye has lower reliability than lymphoscintigraphy. Staining of the mucosa around the tumor may make the surgical excision of the primary tumor difficult. So, this technique is not preferred now for identification of the SLN.

8.4.2 Lymphoscintigraphy

Preoperative dynamic lymphoscintigraphy involves the injection of radiolabeled colloid at the periphery of the tumor. The flow of radiolabeled dye from the primary tumor to the sentinel nodes can be visualized in real time using a gamma camera operating in a continuous mode in both the anteroposterior and lateral views (Fig. 8.2). The position of these nodes where the radioactivity localizes can be marked on the skin. Intraoperative static lymphoscintigraphy involves identifying the nodes with highest radioactivity using a handheld gamma probe. An incision is made at the region of the nodes marked by the preoperative dynamic lymphoscintigraphy (Figs. 8.3 and 8.4). It is important that the incision should be planned in such way that it may be extended to do a neck dissection, should it be required, based on the SLN biopsy result. There is no threshold radioactivity value for the SLN. It varies by the time of injection, quantity of radioisotope used, and the location of the lesion. The nodes with the peak radioactive reading as well as any adjacent nodes that are more than 10 % as hot as the SLN are also removed. After removal, the node has to be checked for radioactivity. The surgical bed should not have radioactivity higher than the background reading. The 10 % rule was developed on the basis of the observation that about 13 % of the metastatic nodes are not those that are the hottest nodes [28]. There is controversy about the number of SLNs to be biopsied for accurately

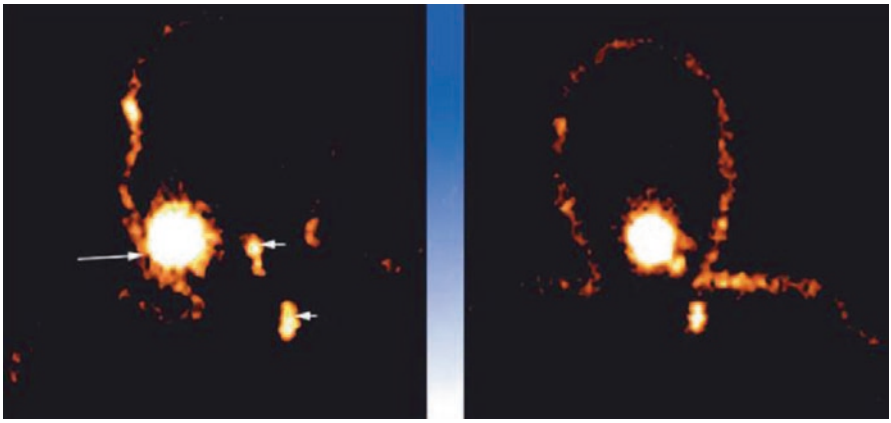

Fig. 8.2 Preoperative dynamic lymphoscintigraphy: lateral and frontal view (*long arrow* indicates primary tumor and *short arrows* indicate sentinel lymph nodes) [83]

determining the pathological nodal status [29]. This question was addressed by Werner et al. [30]. They performed SNB in 90 patients with clinically N0 head and neck cancer. Up to three SLNs were biopsied in these patients. Overall, 23 of the 90 patients (25.6 %) showed evidence of occult metastasis. It was observed that if only the node with the strongest tracer uptake had been biopsied, the histological evidence of metastasis would have been missed in nine of 23 (39 %) patients. This study clearly suggested that the node with highest radioactivity may not be the pathologically positive SLN, and more than one SLN needs to be harvested for accurate pathological evaluation [31, 32]. Detection of the SLN at level I becomes difficult at times due to the "shine-through" effect of the primary tumor. This is especially true in case of a primary tumor in the floor of the mouth. In this scenario, it is recommended that the primary tumor be removed first before localizing the SLN [33–35].

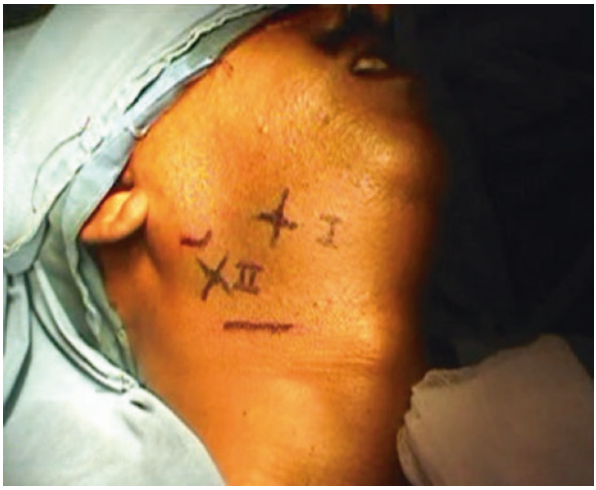

Fig. 8.3 Sentinel nodes marked on the neck

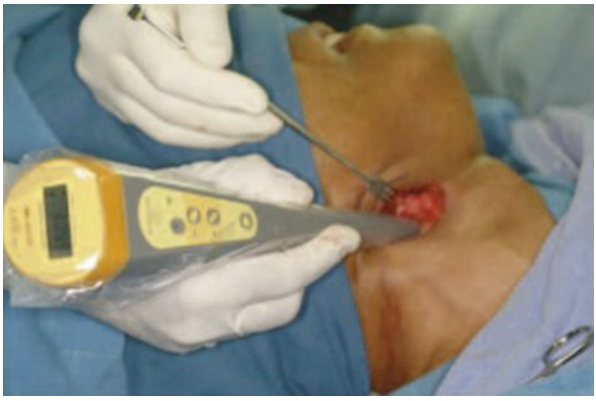

Fig. 8.4 Intraoperative handheld gamma probe localization of the sentinel lymph node [82]

8.4.3 Radioisotopes for Lymphoscintigraphy

Lymphoscintigraphy and intraoperative gamma probe identification of the SLN depend upon the ability of the injected radiotracer to be selectively retained within the sentinel node, while minimizing retention at the primary site and transit to downstream lymphatics. Once injected interstitially, radiotracers travel in lymphatic channels to the first echelon nodes, where they are taken up by macrophages. In order to be phagocytosed, these particulates must be within certain size limits. The size of the particle also influences clearance rates from the primary tumor site, transit time through the lymphatics, and retention time within the sentinel node. Larger particles achieve higher retention within the sentinel node and lower transit to second-echelon lymphatics and higher retention within the primary tumor site.

Gold-198 was the first material used for the purpose. This had a particle size of 5 nm. Although this material has greater and faster uptake than any other subsequently developed radioisotopes, the high dose of radiation thwarted its broader clinical use [36]. Iodine-131 and 99mTc were later introduced for lymphoscintigraphy. The 99m Tc attached to sulfur colloid is now the most widely used for lymphoscintigraphy. The advantages of 99mTc sulfur colloids are that they emit only gamma rays and have low radiation exposure, the half-life of 99mTc is only 6 h, and it has a peak energy emission peak of 140 keV. This is within the detection range of most of the gamma camera and handheld gamma probes. The particle size and the attached molecules are the primary factors that determine the rate of uptake into the lymphatics and the filtration within the sentinel node. The optimal particle size of radioisotopes is between 5 and 10 nm [37]. A particle size smaller than 5 nm may be taken up by the vascular system. The radioisotopes may be used as either filtered or unfiltered forms. The filtration allows control of the particle size to a specific size (15–50 nm). The unfiltered nanocolloids have a particle size raging from 5 to 1000 nm [36, 37]. The dose of radioisotope used also varies from 0.5 to 0.8 mCi. Using a 99mTc sulfur colloid in cutaneous lesions, the transit time to the lymph node is less than 1 h. The radioactivity may be retained in the lymph node for an additional 3–6 h. However, for mucosal head and neck tumors, the transit time is less than 30 min. The radioactivity can be detected for 3–6 h after the injection. Ideally, the injection, dynamic scintigraphy, and intraoperative gamma probe localization should be done on the same day.

Tilmanocept is a novel agent. It is a 99mTc-labeled non-particulate radiotracer that contains multiple mannose moieties with high affinity for the CD206 receptor found on macrophages and dendritic cells, enhancing targeting to these cells within the SLN. Studies in breast cancer and melanoma showed that tilmanocept may have improved clearance from the site of the primary tumor and enhanced retention within the sentinel node when compared to sulfur colloid [38, 39]. Because of the rapid clearance and prolonged retention within the sentinel nodes, patients could be injected preoperatively from immediately prior to surgery up to 30 h preceding surgery. A single institution reported their experience as part of this larger multicenter trial in their initial report of 20 clinically node-negative patients [40]. The NPV was 100 % for five patients with floor-of-mouth tumors. Complete results of the multicenter phase III trial are yet to be published.

8.5 Pathological Evaluation

One of the major advantages of SNB is the opportunity to undertake extensive histopathologic investigation of the limited number of nodes available for evaluation, in comparison with a large number of nodes, which need to be studied in neck dissection specimens. The identified SLNs can be subjected to different pathologic investigations with varying stringency, sensitivity, and clinical utility. This includes frozen section, imprint cytology, standard histopathology, serial step sectioning (SSS), standard histopathology and SSS, and immunohistochemistry (IHC). Of these, frozen section and imprint cytology can be used for intraoperative evaluation.

8.5.1 Frozen Section

Intraoperative detection of metastatic deposits in sentinel node biopsy is important to make the sentinel node biopsy procedure patient friendly and to avoid a staged second procedure. Recent studies have shown reasonable negative predictive value with frozen section analysis (83 %) [41–43]. Intraoperative evaluation with frozen section was accurate in detecting macrometastasis but was not effective in detecting micrometastasis and isolated tumor cell deposits [44]. Moreover, if smaller deposits (mainly isolated tumor cells) [41] are located within the tissue used for frozen section analysis, it would be missed in eventual analysis for micrometastasis. It has been argued that frozen section analysis prolongs the duration of the procedure. But, by coordinating with the histopathology service, the frozen section result can be made available during the resection of primary tumor.

8.5.2 Imprint Cytology

Imprint cytology as an alternative to frozen section analysis of lymph nodes is reported [45]. In the study by Trivedi et al. [44], the detection rates of imprint cytology and frozen section were identical. As in frozen section, imprint cytology failed to detect micrometastasis and isolated tumor cells. For better utilization of SLN biopsy, it is essential to develop a novel technology that can detect smaller deposits intraoperatively in SLNs. Intraoperative ultrarapid IHC and intraoperative real-time reverse transcriptase–polymerase chain reaction (RT–PCR) evaluation [46] may aid in the future to improve the sensitivity of intraoperative detection of occult metastasis.

8.5.3 Routine Histopathologic Evaluation (HPE) and Serial Step Sectioning (SSS)

Routine pathologic evaluation of a neck node consists of identifying each individual node, bisecting the node at its center and then staining one or two sections to find light microscopic evidence of metastatic deposits [47]. This, in reality, is an incomplete

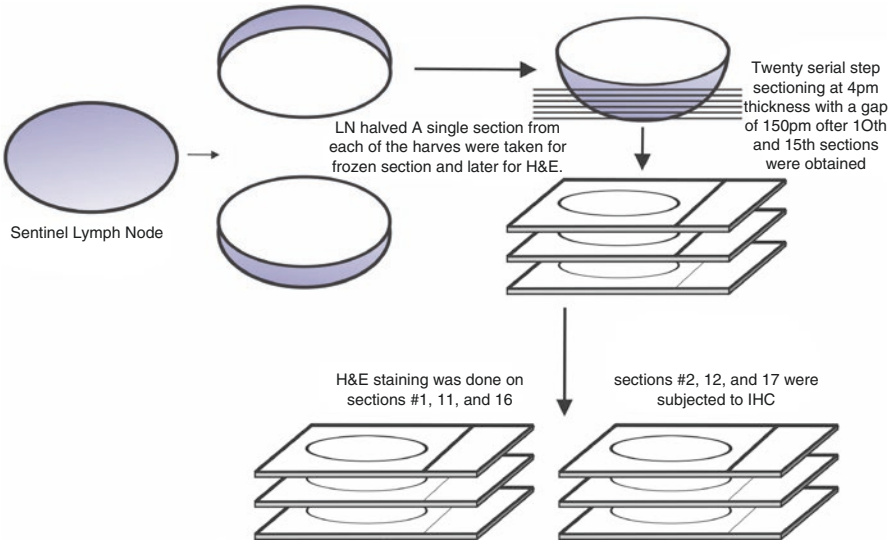

Fig. 8.5 Schema for pathological evaluation of SLN

examination, where central sections serve as a proxy for the whole node. If deposits were small and present in other regions of the node, they would be missed. Studies have shown that routine evaluation misses up to 21 % of disease nodes in breast cancer [48]. It has been shown that SSS with hematoxylin–eosin stain and IHC and molecular methods identify smaller metastasis more accurately. Nelson [49] has reported that hematoxylin–eosin staining with step sections identifies one cancer cell among 10,000 normal cells. IHC identifies one tumor cell among 100,000 normal cells. RT–PCR is the most sensitive of all. It identifies one cell among 1 million normal cells. In clinical practice, SSS with hematoxylin-eosin staining upstages the tumor in 10 %, whereas IHC further upstages it up to 10 % more [26, 27]. In a study by Trivedi et al. [44], routine pathologic evaluation detected occult metastasis in 13 cases (16.2 %) but missed metastasis in seven cases. SSS with hematoxylin–eosin stain and IHC identified the metastasis in 20 cases (25 %) and hence further upstaged the neck by about 9 %. Other studies [26, 27] also have reported similar results. SSS was necessary to detect micrometastatic deposits. The routine pathologic evaluation was not sufficient to detect this metastasis. IHC was needed only to identify isolated tumor cells. The clinical significance of these smaller foci of metastasis is not established.

There is now a standard recommendation for pathological evaluation of the SLN [50]. The node is dissected free of any fat and bisected through its long axis. If each half of the node is more than 2.5-mm wide, they are then further sectioned longitudinally so that each section is not more than 2.5 mm. SSS is then carried out at 150-mm intervals. At each step, four sections are obtained. One section will be stained by H&E and the other by IHC for cytokeratin. The remaining sections are retained for any additional or repeat study (Fig. 8.5). If any cytokeratin-positive cells are identified, they are compared with the adjacent H&E section to confirm that the positivity was due to tumor cells. It has been recognized that individual cells

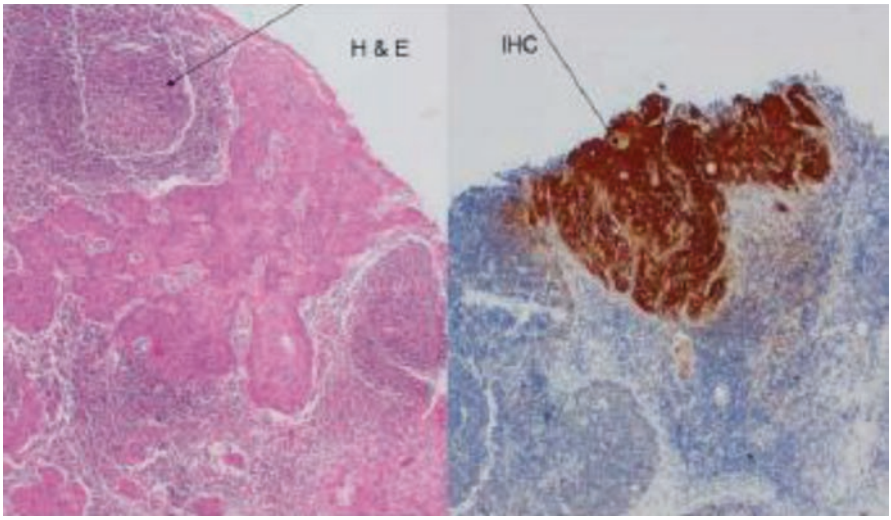

Fig. 8.6 Macrometastasis [44]

indigenous to lymph node milieu may be keratin positive and hence present a risk of false-positive detection in some instances [51, 52]. Once recognized, this problem can be solved by judicious application of interpretation skills. A standard and uniform reporting of the SLN needs to be adopted to compare results [50].

The term micrometastasis is erroneously used for any metastasis detected by histologic analysis of clinically negative (N0) neck. However, histologically detected metastases are correctly termed as occult metastases, which can be further stratified based on histopathologic criteria. Hermanek et al. [53] proposed histopathologic classification of occult metastasis for breast cancer into macrometastasis, micrometastasis, and isolated tumor cells. Widely used staging scheme for breast cancer formally defines macrometastasis (Fig. 8.6) as those metastatic deposits more than 2 mm in diameter. The micrometastasis is defined as metastatic deposit between 2 and 0.2 mm in diameter (Fig. 8.7). Deposits less than 0.2 mm are defined as isolated tumor cells [54] (Fig. 8.8). This can be either single cell deposits or a cluster of tumor cells. Unlike in breast cancer, there is no uniform histopathologic staging available for occult metastases in head and neck cancer. Some studies have included 3 mm as the upper limit of size of micrometastasis [55], but these studies do not always mention lower limit for micrometastasis. Most studies though use 2 mm as the upper limit and 0.2 mm as the lower limit for micrometastasis [56]. Metastatic deposits less than 0.2 mm are generally defined as isolated tumor cells [53, 54, 56, 57].

8.6 Morbidity

The morbidity of elective neck dissection is well studied. Common problems are shoulder dysfunction, pain, paresis/paralysis of the marginal branch of the facial nerve, scar, and postoperative sensory deficits. SNB is described as a minimally

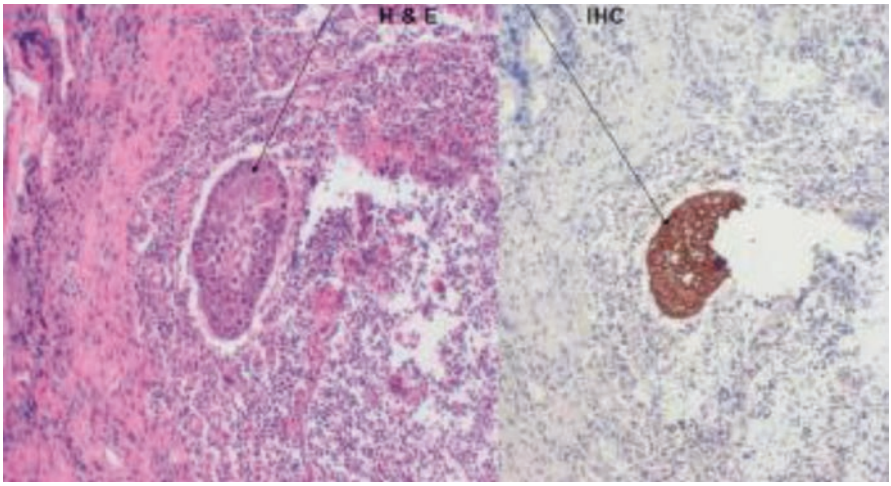

Fig. 8.7 Micrometastasis [44]

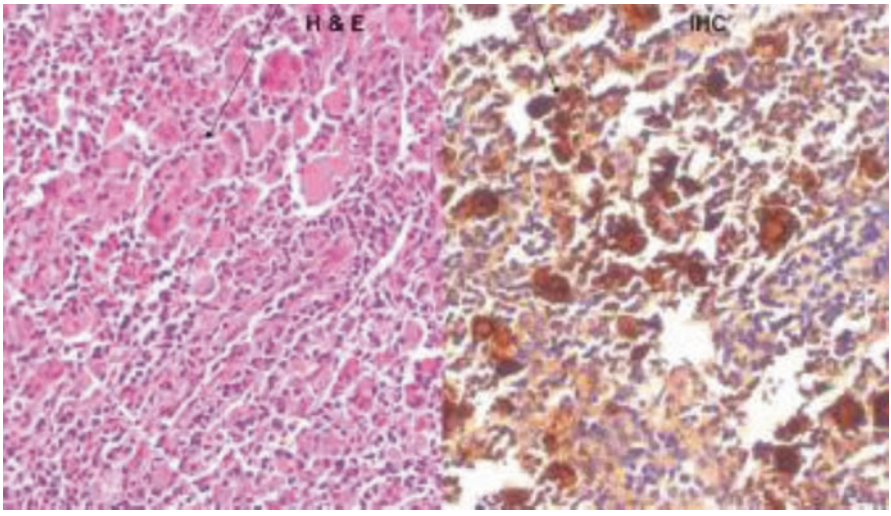

Fig. 8.8 Isolated tumor cell [44]

invasive procedure. It is assumed to be a less morbid procedure SND. Schiefke et al. [58] reported a cross-sectional retrospective study. The study measured 24 patients who had SLNB for oral cavity cancer and 25 patients who underwent elective neck dissections of levels I–III for oral cavity, oropharyngeal, and one hypopharyngeal cancer. Data were taken for health-related and disease-specific QOL measurements, depression and anxiety scales, as well as functional measurements relating to shoulder function, hypoglossal and facial nerve function, scarring, sensory function, and lymphedema. Reduced shoulder dysfunction, sensory disturbance, and impairment

from cervical scars were noted in the SNB cohort. QOL measurements indicated similar health-related QOL but a reduction in swallowing subscales on the disease-specific measurements in patients who underwent elective neck dissection. A similar decrease in functional morbidity was noted in a study by Murer et al. [59], comparing 62 patients undergoing SNB alone ($n=33$) versus elective neck dissection for a positive SLNB ($n=29$). Reductions in shoulder function, increased postoperative complications, and longer incisions were noted in patients undergoing neck dissections compared to those undergoing SNB alone. The findings from these limited studies show that SNB is less morbid than a selective neck dissection. This reduction seems to be most significant as related to the functional impact on the shoulder. Hernando et al. [60] in a recent study compared the postoperative morbidity in patients who had undergone SNB and elective neck dissection (END). Seventy-three consecutive patients were included. Shoulder function, length of the surgical scar, and the degree of cervical lymphedema were assessed. Neck hematoma and the presence of oro-cervical communication were also analyzed. Thirty-two patients underwent SNB, and 41 underwent an END (levels I–III). There were statistically significant differences between the groups in shoulder function and average scar length, favoring SNB. However, differences in degree of lymphedema were not statistically significant. Neck hematomas and oro-cervical communications occurred only in the END group.

8.7 Diagnostic Efficacy

SNB has to be evaluated in three aspects, namely, first, to determine the feasibility of the procedure to identify sentinel lymph nodes; second, the extent to which metastasis can be detected within those nodes; and lastly, the accuracy of the procedure in determining the status of the neck.

8.7.1 Sentinel Lymph Node Identification

The technical feasibility of SNB is ascertained by the probability of identifying sentinel lymph nodes with preoperative lymphoscintigraphy and intraoperative detection using a handheld gamma probe. High rates of sentinel lymph node identification in oral cancer have been reported suggesting that the procedure is feasible. Pilot studies from 20 centers contributing to the Second International Conference on Sentinel Node Biopsy in Mucosal Head and Neck Cancer were collectively analyzed [50]. Among 379 patients with clinically N0 disease, sentinel lymph nodes were identified in 366 patients, for an identification rate of 97 %. A systematic review and diagnostic meta-analysis of all published literature on SNB in oral cancer through 2003 were performed by Paleri and colleagues [61]. The analysis included 301 patients with oral cavity primary tumors from 19 studies. The study reported an overall sentinel lymph node identification rate of 97.7 %. A European multi-institutional study was initiated in 2002. The 5-year results of this study [35]

showed that, of the 227 SLNBs reported, 134 were performed on early-stage (T1-2) oral cavity cancer. In these patients, sentinel nodes were correctly identified in 93 % (124 of 135) of patients. The ability to identify the sentinel node was lower in patients with floor-of-mouth tumors compared to all other subsites (88 % vs. 96 %, $p = 0.138$). The meta-analysis by Govers et al. [62] had 847 cases of early-stage oral cavity or oropharynx in total. At least one sentinel node was detected in almost all patients included from the studies, and a sentinel node biopsy could thus be performed in 835 patients. The sentinel node detection rates ranged from 91 to 100 %.

8.7.2 Detection of Occult Metastasis

The next step in evaluating SNB lies in determining the extent to which occult metastases are identified. The finding of occult metastasis within the sentinel node on pathologic evaluation results in upstaging of the node-negative N0 neck. The rate of upstaging by SNB must be compared with that by elective neck dissection, which is currently the best available method of detecting occult metastasis. Pathologic evaluation of specimens stained with H&E and elective neck dissection upstages approximately 30 % of patients. In the Canniesburn trial [26], where the sentinel lymph nodes were examined by a routine H&E staining, serial sectioning, and immunohistochemical analysis for cytokeratin, upstaging of disease occurred in 34 % of cases. Nodal metastasis was identified by H&E staining alone in 26 % of cases and by additional pathologic means in 11 % of cases. Therefore, although the extent to which SNB upstages the neck by traditional pathologic methods seems similar to that with elective neck dissection, the use of additional pathologic methods results in perhaps an even greater level of detection of disease. Additional pathologic methods, such as serial sectioning and immunohistochemical analysis, may increase the identification of micrometastasis. The identification of micrometastases creates a problem for the current staging system for oral cancer. Patients with micrometastatic disease found by additional pathologic methods and with no additional disease in the neck specimen are upstaged from clinically N0 to a new classification of pNmi, or pathologic nodal micrometastasis, for which the prognosis is unknown.

8.7.3 Accuracy of Sentinel Node Biopsy

Many single-institution series have published the results of sentinel lymph to accurately stage the neck compared to elective neck dissection [63–76]. In the European multi-institutional study [35], with a minimum 5-year follow-up, the overall sensitivity of the procedure was 91 %. The patients with floor-of-mouth tumors demonstrated lower negative predictive values (NPV) compared to other oral cavity sites (88 % vs. 98 %). These findings led the authors to recommend the use of SLNB as a reliable staging procedure in all oral cavity sites with the exception of the floor of the mouth. The ACOSOG trial [77], a multi-institutional trial from the United States, (Z0360) included 140 patients with early-stage (T1-2) oral cavity cancer. SNB was performed, followed by immediate elective lymph node dissection. The negative

predictive value for SNB in this study, which consisted primarily of oral tongue and floor-of-mouth carcinomas, was 94 % (95 % CI: 0.88–0.98) on routine histologic analysis, with improvement to 96 % with immunohistochemical staining. SNB appeared to perform slightly better for smaller lesions, with NPV of 100 % for T1 lesions compared to 94 % for T2 lesions. The similar conclusions of these multiple published experiences support SNB as an accurate procedure for staging the neck in early-stage oral tongue cancer. In the meta-analysis by Paleri et al. including 301 patients with oral cavity squamous cell carcinoma as well as a smaller subset of 49 patients with oropharynx cancer [61], the pooled sensitivity of SNB for the study group was 0.926 (95 % CI: 0.852–0.964) using a random effects model, with individual ranges of 0.75–1. A more recent meta-analysis examining the diagnostic accuracy of SNB in head and neck cancer [78] included 766 patients in 26 studies between 1970 and 2011, in which the pooled NPV was 96 % (95 % CI: 94– 99 %). In the subset of 593 patients with early-stage (T1/2) consistency of the findings across the multiple studies included in these meta-analyses demonstrates that the accuracy of SLNB is reproducible. As with most procedures, however, surgeon experience does seem to affect the results. In the ACOSOG trial, increased surgeon experience with SLNB correlated with a higher negative predictive value when compared with surgeons with less experience (100 % vs. 95 %) [77]. In a yet another meta-analysis by Govers et al. [62], 21 studies (847 patients) could be included. Most of these patients had oral cavity squamous cell carcinoma (OCSCC). The pooled data showed an overall sensitivity of 0.93 [95 % CI 0.90–0.95]. Negative predictive values were ranging from 0.88 to 1. Subgroup analysis showed no significant differences in subgroups. As with most procedures, however, surgeon experience does seem to affect the results. In the ACOSOG trial [77], increased surgeon experience with SLNB correlated with a higher negative predictive value when compared with surgeons with less experience (100 % vs. 95 %). A single-center study of 79 patients with clinically (after ultrasound-guided FNAC) N0 early oral cancer found a sentinel lymph node detection rate of 99 %, a sensitivity of 91 %, and a negative predictive value of 90 % [79]. This study showed evidence that the previously reported promising short-term results can be sustained through long-term follow-up.

In summary, based on the sensitivity and specificity of SLNB in early-stage oral cancer, it seems that the accuracy of SNB is similar to that of elective neck dissection. Based upon the data, the performance of SNB is best for small oral tongue lesions and for floor-of-mouth lesions; the procedure appears to be less accurate.

8.8 Recurrence and Survival Outcomes

There are very few studies reporting the oncological outcomes in SNB. Oncological outcomes can be the results regarding the nodal recurrences or the survival outcomes. There can be comparison between SNB versus SND in the management of N0 neck or a comparison between SLN negative versus positive group of patients. In a retrospective study by Fan et al., 82 patients underwent elective neck dissection ($n=52$) or SNB ($n=30$) for cT1-2 N0 oral cancer. The use of SNB was not associated with a difference in either 10-year recurrence-free (72.3 % vs.73.3 %; $p=0.81$)

or overall survival (43.3 % vs. 44.2 %; $p=0.83$) when compared to elective neck dissection [70]. Alvarez et al., in a study of 63 patients with floor-of-mouth carcinoma, reported no significant differences in disease-specific or disease-free survival for patients undergoing SLNB compared to a standard cohort of elective neck dissection and observation [63]. There is a similar paucity of data of studies comparing SNB-positive and SNB-negative patients. In a European multicenter trial [35], no significant difference between SNB-positive and SLNB-negative patients could be shown. There was a numerical reduction in locoregional disease-free survival in the SNB-positive patients. But no significant difference was demonstrated in survival between patients undergoing SNB-assisted neck dissection and SNB alone.

Hernando et al. [60] compared 32 patients who underwent SNB and 41 who underwent an END (levels I–III). Seven regional recurrences were recorded in the END group. Three neck recurrences occurred in the SNB group. No significant differences were found in DFS or OS between the groups. Fan et al. reported a retrospective review of 82 patients with cT1-2 N0 oral tongue SCC. Thirty patients underwent SLNB, and 52 patients underwent END. There was a significant difference between the SLNB and END groups in the incidence of occult cervical lymph node metastasis in initial specimens (30 % vs. 11.5 %; p, .037). However, there were no significant differences between the groups for 10-year overall and cervical recurrence-free survival rates and 10-year overall survival rate. They concluded that SNB is superior to END for the prediction of cervical lymph node metastasis in patients with cT1-2 N0 oral tongue SCC. Neck dissection may be reduced for SLN-negative patients, owing to the comparable prognosis of SLNB.

The results of a Dutch multicentric trial by Flach et al. [80] were recently published. Patients were consecutively enrolled from four institutions, with T1/T2 oral cancer and cN0 neck based on palpation and ultrasound-guided fine needle aspiration cytology. SLN-negative patients were carefully observed, and SLN-positive patients were treated by neck dissection, radiotherapy, or a combination of both. Twenty of 62 patients (32 %) had positive SLNs. Macrometastases were found in nine patients, micrometastases in eight, and isolated tumor cells in three patients. Median follow-up was 52.5 months. Of the 42 SLN-negative patients, five developed a regional recurrence of whom four patients could be successfully salvaged. DFS, OS, and DSS of SLN-negative patients were 72.0 %, 92.7 %, and 97.4 %, and for SLN-positive patients, these numbers were 73.7 %, 79.7 %, and 85.0 %, respectively (DFS: $p=0.916$, OS: $p=0.134$, DSS: $p=0.059$, respectively). Neck control rate was 97 % in SLN-negative patients and 95 % in SLN-positive patients. They concluded that SNB is able to reduce the risk of occult lymph node metastases in T1/T2 oral cancer patients from 40 to 8 % and enables excellent control of the neck.

8.9 Advantages of SNB

The key advantages of SNB over SND are decreased morbidity, improved identification of “skip” metastases, and improved histologic evaluation of surgical specimens which are all advantages of SLN biopsy. The decreased morbidity relates to a

more limited dissection, placing fewer structures at risk, while still providing adequate diagnostic material. The ability to identify "skip" metastases and unpredictable lymphatic drainage patterns is another advantage of SNB. In 2006, Civantos et al. [81] showed that 14 of 103 (13.6 %) cases revealed sentinel nodes outside expected lymph node basins. They comment that these nodes would not have been dissected with standard neck dissection. A third advantage of SNB is related to the pathologic handling of the specimen. Although SND examines more lymph nodes, the specimen is embedded and sectioned in total, but only single sections are studied. Missed micrometastases often occur. In contrast, step sectioning of the entire sentinel lymph node(s) followed by systematic staining with H&E and immunohistochemistry can be performed for the small numbers of nodes harvested with SLN biopsy, thus enhancing identification of microscopic disease [77]. There are limitations to perform the same analysis on full neck dissection specimens.

8.10 Limitations of SNB

Five main limitations of SNB are: (1) Lack of confirmatory data. Apart from few prospective trials, much of the data are single-center retrospective studies. (2) Weakness in assessing FOM tumors. The obvious drawback of SNB is its poor performance identifying true sentinel nodes in patients with FOM tumors due to shine-through radioactivity due to the close proximity in anatomy, thus masking signal from the relevant sentinel node(s) [77]. This could be overcome by excising the primary tumor first. Part of the problem is also due to the properties of the radiolabeled agent. The detection of the sentinel lymph node is more difficult in patients with FOM cancers; the sentinel lymph node(s) are harvested successfully in 88 % of the cases compared to 96 % for tumors in other sites of the oral cavity. Likewise, sensitivity of SNB is lower for FOM tumors compared to other sites (80 % vs. 97 %). (3) Surgeon's learning curve. (4) Operating room logistics for performing the procedure and performing the completion of neck dissection in cases in which the SLN biopsy is positive. The sulfur colloid agent injection into the primary tumor site and lymphoscintigraphic imaging of the neck has to be performed within minutes to several hours. Additionally, SLN biopsy ideally is performed within 3–6 h from the time of injection. This imposes challenges related to operating room management and coordination with the nuclear imaging service. (5) Lack of spatial resolution of gamma camera [82]. One of the major limitations of the current single-photon emission CT (SPECT) scans used in lymphoscintigraphy is the limited spatial resolution. Novel methods for SLN detection, such as magnetic resonance lymphangiography using a carbon dye labeling technique [83] and use of SPECT–CT, are presently under investigation, to improve the spatial resolution of the lymphoscintigraphy technique [84].

Another issue is the prognostic significance of the micrometastases. Micrometastasis and molecular staging are found to have clinical significance in melanoma [48]. It was recommended that an intensive search should be undertaken for small foci of lymph node metastasis in head and neck cancer [65]. The clinical

significance of occult metastasis in head and neck cancer is not well established. There is a difference of opinion in literature regarding the prognostic significance. While some studies showed no difference in outcome of patients with macro or micrometastases [85], a few others [86, 87] have shown some prognostic value of micrometastases. However, larger studies with long-term follow-up are required to address this issue. If SNB is negative for micrometastasis, there is a high chance that the rest of the neck nodes will be negative as well. If SNB is positive, how many and which other neck nodes, if any, would harbor metastasis is not clearly established. For melanoma, Morton [88] showed that less than 1 % of patients had disease in non-sentinel nodes when micrometastasis was present in the SLN. So in those patients, SNB only would be enough, avoiding further nodal dissection. There are no prognostic indicators available in head and neck cancer, which predict the presence of micrometastases in the rest of nodes when micrometastasis is present in the SLN.

8.11 Recent Advances

A PET tracer, 89-zirconium nanocolloidal albumin, dedicated to lymphatic mapping and sentinel lymph node detection using high-resolution PET–CT was developed recently. Compared with gamma-based techniques, improved detection and precise localization of SLNs could be achieved on PET-CT in recently conducted clinical feasibility studies. PET–CT was able to identify sentinel lymph nodes close to the injection site and lymphatic vessels, which were not visualized on SPECT–CT [89].

Technical innovations to improve intraoperative SLN localization include intraoperative real-time imaging, freehand SPECT, and fluorescence imaging. Intraoperative real-time imaging with the portable gamma camera provides an overview of all radioactive spots and can show SLNs near the injection site by adjusting its position [90]. Also, it can provide a certainty about the completeness and accuracy of SLN excision by showing the remaining activity. Freehand SPECT can determine the position of the detector relative to the patient through generated 3D images. This provides the information about the direction and depth of the sentinel lymph node in relation to the probe. The possibility of generating images in the operating room after removing the sentinel lymph nodes, but before closing the wounds, may be useful to confirm harvesting of all hotspots. Promising results in patients with OSCC have been reported [91]. Near-infrared (NIR) fluorescence imaging may also be a very attractive option to facilitate intraoperative detection. The feasibility of NIR fluorescence-guided sentinel lymph node detection has been demonstrated in head and neck cancer, where the fluorescence imaging of indocyanine green was used as the fluorescent tracer [92]. Other tracers with improved optical properties have been tested in HNSCC in preclinical settings [93]. The clinical use of these agents is still to be evaluated.

Van den Berg et al. [92] reported a small study of 14 patients with oral cavity squamous cell carcinoma who were peritumorally injected with ICG-(99m) Tc-nanocolloid. They concluded that combined preoperative SLN identification and intraoperative radio and fluorescence guidance during SLN biopsies for oral cavity cancer proved feasible using ICG-(99m)Tc-nanocolloid. The addition of fluorescence imaging was shown to be of particular value when SLNs were located in close proximity to the primary tumor.

8.12 A Randomized Comparison with SND: The Need and the Hurdles

There are very few prospective studies on SNB. Of these only very few have specifically looked into the efficacy of SNB compared to SND. There exists a need for randomized controlled trial comparing SNB-directed approach to that of SND. The authors have completed a randomized controlled clinical trial, and the results are expected. Figure 8.9 shows the study schema of the trial. The primary objective of this trial was also to see the diagnostic efficacy of the procedure. But the oncological efficacy was also studied, though not enough statistically powered to do so. The sample size limitations may be a hindrance to such a study to prove the non-inferiority of SNB over SND. To prove a non-inferiority of SNB over SND, with an assumption of risk of neck failure in the standard arm (SND) as 10 % and a margin of risk of neck failure in the test arm (SNB) as 5 % on either side, the minimum sample size required in each arm would be 650 patients each (SamanthS 2015, Clinical Trial SND Vs SNB, personal communication).

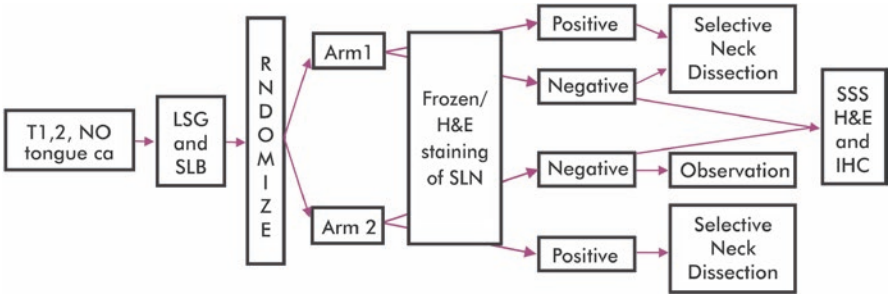

Fig. 8.9 Randomized trial schema from authors' institution. The trial has completed accrual and the results are expected

Conclusion

There are no methods presently available that can accurately predict the negative status of neck nodes other than by pathologic analysis of SND. SNB with lymphoscintigraphy is a potential tool to stage patients with clinically N0 neck nodes. The advantages are the reduced morbidity and better cosmetic outcomes. SNB is studied most in patients with previously untreated early-stage (T1/2) oral cavity cancer with clinical N0 stage. As in other solid tumors, existing data suggest that the status of the SLN predicts the pathologic stage of the nodal basin. The procedure is technically demanding especially in floor-of-mouth cancers. The isolated SLN should be subjected to SSS and staining by H&E and IHC. Intraoperative frozen section and imprint cytology are not sensitive to identify small foci of micrometastasis and ITCs within the SLN. The clinical relevance of micrometastasis and ITC needs to be established. The accuracy of SNB has been tested in multiple single-center studies and two multicentric trials. The pooled data showed an overall sensitivity of 93 %. Negative predictive values ranged from 88 to 100 %. There exists no randomized clinical trial with adequate power, comparing SNB and elective neck dissection in oral cancer. Though established guidelines have recommended SNB for early-stage tongue cancers, confirmatory data still do not exist justifying its routine use in the management of N0 neck.

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Pearls and Pitfalls in Oral Cancer Management

9

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9.1 Introduction

Complications are an integral part of any medical interventions, however they are potentially avoidable. Sequelae on the other hand are inevitable. The art of medical practice aims to recognize high-risk scenarios and take measures to minimize pitfalls. The clinical outcome should be periodically audited to recognize patterns of complications and to implement remedial actions to correct these errors. The effectiveness of the remedial actions also needs to be evaluated. This is a continuous process.

The spectrum of head and neck surgery has a higher incidence of complications than other disciplines. This is attributed to high comorbidities, poor nutritional status and sequelae from associated cancer treatment. Complications adversely affect the patient's recovery and delay further adjuvant treatment. Patients need to be counselled preoperatively about the anticipated adverse events and obtain appropriate informed consent.

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With the advent of better imaging modalities, diagnostic aids, better reconstructive armamentarium and supportive medical care, it is now possible to have predictable outcome and/or anticipate adverse outcomes.

This chapter is aimed at highlighting common complications that may be encountered at various stages of management of patients from patient evaluation, surgery with ablation and reconstruction, adjuvant radiation and chemotherapy and surveillance.

The authors have tried to assess it in the form of series of questions which clinicians are frequently challenged with and the best answers based on clinical evidence.

We have attempted to classify complications into various categories based on the temporal framework in which they are commonly encountered.

1. Patient evaluation
2. Surgical Complications:
   (a) General
   (b) Neck dissections
   (c) Primary tumor resection
   (d) Previously treated patient
   (e) Reconstruction
3. Adjuvant radiation
4. Adjuvant chemotherapy
5. Surveillance

9.2 Patient Evaluation

The aspect of patient evaluation will be addressed as two aspects namely the general evaluation of the patient and the evaluation with respect to the oral cavity malignancy.

9.2.1 General Evaluation

Comorbidities have been documented to have a major role in the treatment, outcome and prognosis in patients with head and neck malignancies. These also have a significant bearing on complications related to treatment. Comorbidities coexist with the index disease but are unrelated to it; however they are an important prognostic indicator when age and tumor, regional lymph nodes, distant metastasis stage (TNM) have been controlled for. Patients suffering from head and neck cancer have a history of tobacco and alcohol consumption with a significant risk of concomitant cardiac and respiratory disease [1].

Pulmonary complications are a major contributor to increased morbidity and mortality in patients undergoing head and neck surgery. These manifest as the need for prolonged ventilatory support, postoperative pneumonia and acute respiratory distress syndrome (ARDS). Weymuller et al. retrospectively reviewed data of 144 patients who had undergone head and neck surgical procedures at the University of Washington and tried to identify preoperative and peroperative variables which are important indicators for postoperative pulmonary complications. On univariate

analysis, smoking and weight loss are significant factors associated with pulmonary complications. However on multivariate analysis, it is only smoking and perioperative antibiotic which are the significant variables [1]. Smoking cessation has a positive effect on postoperative wound healing [2].

This chapter will not be detailing the cardiac, pulmonary and general surgical complications as these have been outlined extensively in other manuscripts.

To address the prediction of postoperative complications, the authors have looked at the following:

1. *Are there any designed predictor models to identify patients who are at a high risk for complications?*

The WHO performance scale and the Karnofsky performance scale are routinely used tools for this means. In addition the Adult Comorbidity Evaluation 27 Index (ACE-27 Index), American Society of Anesthesiologists (ASA) system is in vogue.

The scales are outlined below:

WHO performance scale:

Scale	
0	Able to carry out all normal activities without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out light work
2	Ambulatory and capable of all self-care, but unable to carry out work; up and about more than 50 % of waking hours
3	Capable only of limited self-care; confined to bed more than 50 % of waking hours
4	Completely disabled; cannot carry out any self-care, totally confined to bed or chair

Karnofsky performance scale

100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity: minor symptoms of disease
80	Normal activity with effort: some symptoms of disease
70	Cares for self: unable to carry on normal activity or active work
60	Requires occasional assistance but is able to care for needs
50	Requires considerable assistance and frequent medical care
40	Disabled: requires special care and assistance
30	Severely disabled: hospitalisation is indicated, death not imminent
20	Very sick, hospitalisation necessary: active treatment necessary
10	Moribund, fatal progressing rapidly

In addition to the above tools, the ACE-27 Index and the ASA risk classification systems have been used to describe comorbidity [3, 4].

The disadvantage of the ACE-27 Index is that it can be time consuming. The ASA stratification though routinely used preoperatively only signifies risk under anesthesia and not as predictor for complications.

Ferrier et al. reviewed 120 patients with head and neck squamous cell carcinoma (HNSCC) and used the ACE-27 and ASA grades to describe comorbidities. They also analysed various other parameters (totally 17 clinical variables) that could be predictors of complications in head and neck surgery. On multivariate analysis duration of anesthesia longer than 360 min, ACE-27 grades and ASA class are reliable predictors of complications and prolonged hospitalization. The authors have however mentioned the need to incorporate the presence of anemia and its correction in any predictor model. This was reflected by its absence in the current ACE-27 [5].

Age itself does not correlate with the incidence of complications. This has been extensively studied in the paper by Boruk et al. [6] This fact has also been corroborated by the study of Myers and Johnson analyzing the effect of advanced age and comorbidities on outcomes in microvascular reconstruction of head and neck defects. Their study showed no significance with advanced chronologic age, though complications were significantly higher in patients with preoperative comorbidities [7].

Determinants of operative risk include:

(a) General health status
(b) Severity of underlying illness
(c) Nutritional status which can be assessed by weight, body mass index, skin fold measurements, serum albumin and lymphocyte count [8]
(d) Degree to which surgery will disrupt normal physiologic functions
(e) Technical complexity of the procedure
(f) Experience of the treatment team

(a) and (b) can be best assessed by the two scales mentioned above.

9.2.2 Evaluation of the Tumor and the Neck and Surgical Planning

1. *What is the appropriate modality to image the neck in patients with oral squamous carcinoma?*

   For routine evaluation, a contrast-enhanced computed tomographic (CECT) scan which images the primary tumor in the oral cavity, neck and chest is the recommended protocol. A slice thickness of 3–4 mm with spiral scan is preferred.

   In evaluation of the neck, important prognostic indicators are the assessment of tumor necrosis, tumor volume, extranodal spread, involvement of level IV and V, and retropharyngeal lymph nodes. The relation of the mass to the carotid artery is also an important prognosticator indicator with encasement more than 270° suggestive of carotid invasion.

   In salvage and recurrent cases, positron emission tomography-computed tomography (PET-CT) scan along with an ultrasound-guided fine needle aspiration cytology (USGFNAC) can detect metastases greater than 5–6 mm [9].

2. *Issues with occult metastases and how to avoid pitfalls*
   (a) Computed tomography (CT) scan or Magnetic Resonance Imaging (MRI) has poor sensitivity to detect metastases smaller than 8–9 mm.
   (b) Is USG FNAC an alternate option for the clinically node negative (N0) neck?
   It is an ideal technique for the initial assessment and follow up. However its sensitivity varies from 42 to 73 %. It is operator dependent and requires a skilled sonologist and cytologist.
   (c) If the option of observing the neck is being considered, a strict protocol for follow up and imaging should be adhered to, as regional failure in advanced stages has poorer salvage rates [10, 11].
   (d) What is the role of sentinel lymph node biopsy?
   Currently sentinel node biopsy needs to be considered as an investigational tool and not the standard of care. It may be an alternative option to elective neck dissection in early T1 and T2 oral carcinoma. However it requires expertise in the technique. It does avoid the morbidity of a neck dissection, however a positive node in the sentinel nodal basin has to be converted into an elective neck dissection in a second operation. Intra-operative frozen section of sentinel node is not dependable. It should be used with caution in tumors of the floor of mouth, upper gingiva and palate. Single institutional studies and two multi-institutional trials have reported a pooled estimate of sensitivity of 0.93 and negative predictive values ranging from 0.88 to 1 [12–14].
3. *Planning for the neck dissection*
   (a) In a N0 neck, Levels I–III need to be dissected. It is to be extended to Level IV for tongue carcinomas. There is no role for supra-hyoid neck dissection in oral squamous cell carcinoma [15–17]
   (b) The predominant nodal basins that need to be addressed based on the patterns of metastasis are Levels I–IV and Vb. The involvement of Level V is less than 5 %. Dissection of this level can be avoided to minimize injury to the spinal accessory nerve due to devascularization and stretch injury.
   (c) Though it is has been proposed that Level IIb dissection can be avoided in N0 neck to minimize injury to accessory nerve; it is to be noted that predominant pattern of neck failure is at Level II in oral cavity cancer. For complete clearance of Level IIa group of nodes, it may be necessary to dissect Level IIb.
   (d) The use of a single transverse neck crease incision affords accessibility to all neck nodal levels [18].
   (e) When performing bilateral neck dissections, address the neck with the lesser tumor burden first trying to preserve the ipsilateral internal jugular vein (IJV), in case the contralateral IJV needs to be sacrificed. Consider reconstruction of the IJV or a staging of the neck dissection if the need to sacrifice both IJV arises. Complications specific to the sacrifice of the IJV are extensive facial and neck edema, raised intracranial pressure, blindness due to intra-cranial hypertension or ischemic optic neuropathy [19].

9.3 Surgical Complications

9.3.1 General

1. Management of the airway

   Evaluation and management of the airway is of utmost importance in oral cancer surgery, as patients with resection of tumors of the oral cavity especially involving part of the base of tongue hinders the oral phase of swallowing resulting in increased chances of aspiration. Secondly, postoperative edema and a bulky flap can result in compromise of the airway. Finally, in case the patient needs re-exploration under general anesthesia, airway access may become difficult due to compromised mouth opening and distortion of the anatomy of the oral cavity following the initial surgery.

   What would be the mandatory indications for a tracheostomy in oral cavity tumor resections?

   1. Extensive tongue resection especially including part of base of tongue and anterior tongue with the arch of the mandible (Fig. 9.1a)
   2. Bulky flap reconstruction with obliteration of the infratemporal fossa and nasopharynx and sinuses. There is an increased chance of silent aspiration due to secretions from the nasopharynx (Fig. 9.1b–d)
   3. Compromised mouth opening
   4. Perceived need for re-exploration

2. Non-functioning surgical drains

   Suction drains commonly employed during surgery can malfunction due to air-leak. This can lead to major complications such as accumulation of hematoma causing compression of flap pedicle and neck flaps not adhering to the surgical bed causing delay in wound healing. Air leaks in the suction drain can occur due to a number of causes.

   1. Inadequate skin closure technique
   2. Inappropriate placement and fixation of the drain
   3. Lack of water-tight mucosal closure
   4. Neck wound communicating with the tracheostomy site

      Air leaks usually become evident either immediately after surgery during reversal of anesthesia or in the first postoperative day when the patient starts moving his neck. Leaks due to inappropriate skin closure or faulty drain placement can be easily managed by the bedside. However, mucosal leaks and neck wounds communicating with the tracheostomy site can be a serious complication owing to the contaminated oral and tracheal secretions draining into the neck which may lead to vascular blow outs. Thus early identification and closure of the site of leak is desirable which may require re-exploration of the surgical wound in the operating room.

9.3.2 Complications Arising During Neck Dissection

1. Chyle fistula

   The thoracic duct is an endothelial lined vascular structure transporting chylous material into the inferior portion of the internal jugular vein. Although

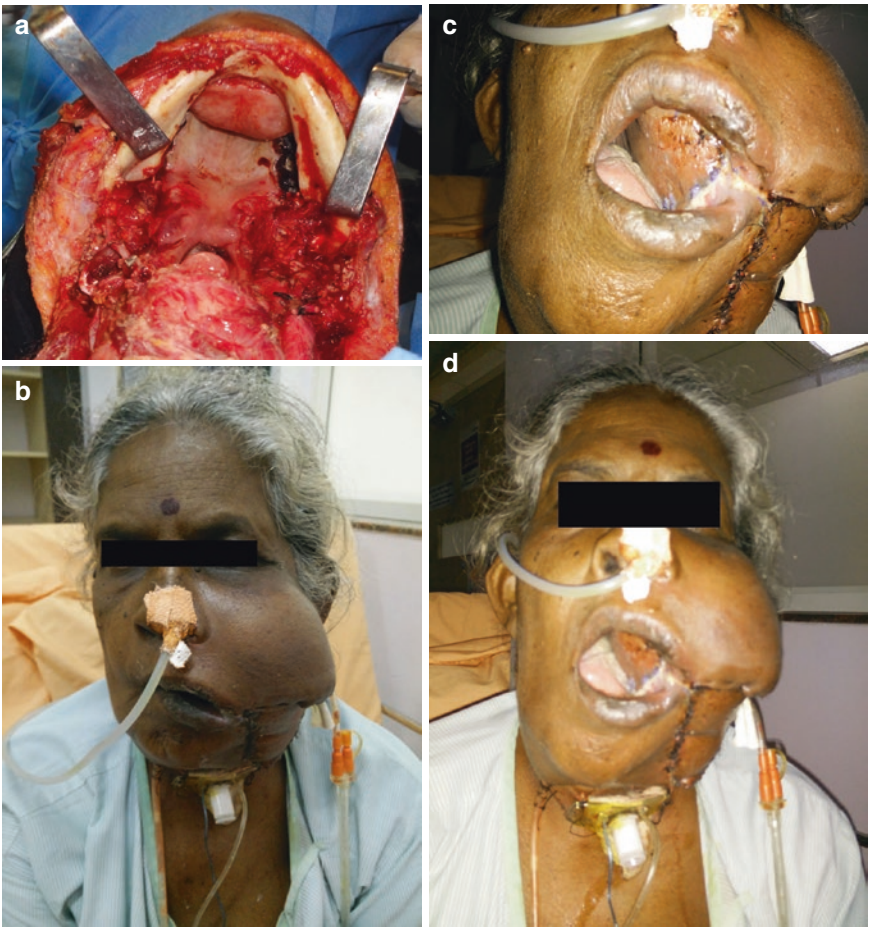

Fig. 9.1 (**a**) Total glossectomy defect that necessitates tracheostomy. (**b**) Initial bulk of the flap used to obliterate the infratemporal fossa and maxilla necessitating tracheostomy. (**c**) Intraoral view showing the bulk of the flap with restricted tongue mobility. (**d**) Bulk of the flap that restricts ability to expectorate secretions and also more prone to secretions from the nasopharynx necessitating a tracheostomy

named as a single structure, it is in fact an arborized series of chylous vessels intermingling with the lymphatic vessels. Mostly encountered in the left side, similar structure can also be seen on the right side along with the level IV lymphatics.

Chyle leak can occur while carrying out neck dissections at level IV region. In a review of 823 neck dissections (which included level IV nodal clearance), Spiro and Strong reported 1.9 % incidence of chyle leak [20]. This and other studies found that most patients developing postoperative chylous fistula had the leak identified and repaired intraoperatively. This fact highlights the importance of meticulous intra-operative assessment and management of chyle leak [21].

How to prevent and manage a chyle leak intra operatively

1. Meticulous surgical dissection at level IV region preferably under loupe magnification.

   The lymphatics in the medial aspect of level IV nodal basin overlying the phrenic nerve and extending even more medially to the posterior aspect of carotid sheath is the area where chyle duct (s) are mostly encountered. Dissection from lateral to medial direction with ligation of all fatty and lymphatic structures should be undertaken to prevent a leak.
2. At the end of the surgery, the area should be inspected during Valsalva manoeuvre with head end of the table lowered. This should be done for about 20–30 s and any suspected leak should be identified and ligated.
3. A non-absorbable suture material should be used to ligate the chyle duct. Reliable ligation of the fine chyle duct may not be always possible; transfixation with the aid of a piece of free skeletal muscle graft to the surgical bed is advised.
4. No suction drain should be placed in direct contact with the chylous vessel. A small piece of gelfoam may be placed over the area for additional protection.
5. Finally, the right side of the root of neck should also be inspected before closure

Management of postoperative chyle leak

Chyle leak detected postoperatively is managed as per the daily output. Conservative treatment is preferred when the daily output is less than 600 ml. It includes

1. Head elevation
2. Continuous suction drain
3. Pressure dressing
4. Maintenance of nutrition

This is achieved by an enteral diet rich in medium chain fatty acids or total parenteral diet. The rationale for the former is that long chain fatty acids are broken down into fatty acids and glycerol. The fatty acids are packed in chylomicrons and absorbed into lymphatic ducts. Medium chain fatty acids, on the other hand, are absorbed in the portal system directly bypassing the lymphatics. Martin et al. showed that the use of enteral medium chain fatty acids are effective in the management of postoperative chyle fistula and prevented the need for parenteral nutrition [22].

Surgical management is reserved for daily output more than 600 ml. Early surgery is warranted as the tissues surrounding the site of leak will get inflamed on exposure to chyle and resuturing will get more difficult with passage of time. Various agents have been used locally which includes fibrin glue, sclerosants like tetracycline and doxycycline and muscle transposition flaps [23]. If there is failure to obtain complete seal of chyle leak, thoracoscopic ligation of thoracic duct is an alternative.

2. Nerve injury

Although multiple nerves encountered in oral cavity and neck surgery, those at risk of injury are the marginal mandibular branch of facial nerve and the spinal accessory nerve.

The marginal mandibular nerve (MMN) supplies motor fibers to the depressorangulioris and the depressor labii inferioris. Injury to this nerve results in sagging of the ipsilateral lip giving a bad cosmetic outcome. At times however, division of the platysma results in pseudoparalysis of the MMN which usually recovers spontaneously [24].

Relevant anatomy

At the region of the facial artery crossing the mandible, the nerve lies above the inferior border of the mandible, in 81 % lateral to the vessels. It dips 1 cm or less below the inferior border of the mandible in 19 % of the patients [25]. Anterior to the facial artery, all branches of the MMN lie above the inferior border of the mandible. However in elderly patients, due to ptosis of the submandibular gland, the nerve may lie 3–4 cms below the lower border of the mandible [26].

Following neck dissection involving level I, the reported incidence of neuropraxia is 29 % and persistent paralysis 16 % [27]. Neuropraxia usually resolves in 3–6 months.

Prevention of nerve injury

1. Neck incision

   The neck incision should be made 3 cms below lower border of the mandible along a neck crease.

   The neck flap should be elevated in a plane immediately medial to the platysma (subplatysmal plane) and submandibular gland capsule.

2. "Indirect technique" of preservation of the nerve:

   As the submandibular gland is approached, the superficial layer of the deep cervical fascia is incised and elevated with the neck flap. As the MMN lies above the fascia, it gets retracted along with the fascia preventing its injury. Although this is a safe technique of preserving the nerve, metastatic prefacial nodes may be missed and separate dissection and removal of these nodes need to be performed, which will be along the facial vessels and close proximity to the MMN.

3. "Direct technique" of preservation of the nerve

   The skin flap is elevated in the subplatysmal plane upto the lower border of the mandible. The nerve is dissected immediately below the lower border of the mandible for about 2–3 cms upto the crossing with the facial artery. Suspicious prefacial nodes are dissected free of the nerve and removed. Level IB nodal clearance is done with the nerve under direct vision.

   Although the "direct technique" has more chances of neurapraxia, it is oncologically safer in patients having a high risk of metastatic pre facial nodes.

The spinal accessory nerve (SAN) exits the anterior wall of jugular foramen and courses medially to enter the upper third of the sternocleidomastoid muscle.

Fig. 9.2 Patient showing the delayed sequelae of spinal accessory nerve paresis with restricted abduction at the left shoulder and the drooping

The nerve crosses the internal jugular vein at the skull base either superficial (70 %) or deep (30 %) to the vein. The SAN gives off muscular branches to the sternocleidomastoid muscle and enters the posterior triangle of the neck 1 cm above the Erb's point [28]. It traverses the posterior triangle in the sub-fascial plane and enters the deep surface of the trapezius 2–5 cms above the clavicle.

The nerve is most prone to damage during level IIB and V nodal clearance. (Fig. 9.2)

Prevention of nerve injury

1. As the nerve traverses the posterior triangle, care should be taken during elevation of the neck flap. The nerve is more superficial than assumed.
2. The nerve is identified 1 cm superior to the Erb's point and traced as it enters the deep surface of the trapezius. There can be multiple terminal branches of the nerve which need to be preserved.
3. There may be contributions from cervical nerves. With gentle traction of the nerve at the posterior triangle, the cervical nerve roots can be identified and preserved.

4. During dissection of level II nodes, dissection should be done between the sternocleidomastoid muscle (SCM) and enveloping deep cervical fascia. The nerve is seen entering the muscle approximately at the junction of upper 1/3rd and lower 2/3rd. The nerve is dissected either anterograde or retrograde from the posterior belly of digastric to the entry point in SCM. With gentle traction on the nerve using a vessel loop or a nerve hook, level IIB nodes are cleared.
5. Electrocautery is best avoided near the nerve
6. If a segment of the nerve is sacrificed due to oncologic reasons, it may be reconstructed using the sural or the greater auricular nerve after confirming no perineural spread (by frozen section) along the preserved segments of the nerve.

3. Vascular complications

Major vascular blow out is a culmination of several complications.

1. Salivary fistula resulting in saliva trickling into neck wound is the major cause.
2. Improperly planned skin incisions especially in postradiated patients resulting in wound break down and exposure of the vessels.
3. Sub-adventitial dissection of the carotids resulting in deprivation of the vessels of the vasovasorum

Carotid blow out is a lethal complication with a mortality of spontaneous rupture being as high as 50 % [29].

Prevention and management

1. In established oro-cutaneous fistula, the neck wound should be explored and divert the salivary flow away from the great vessels. SCM muscle or scalene muscles may be used to protect the carotid artery.
2. In case of exposed vessels due to skin wound breakdown, the vessels should be covered with moist dressing and all slough should be debrided.
3. Carotid rupture is mostly preceded by a "sentinel bleed". This should receive prompt attention and elective ligation. Endovascular stenting is an alternative for impending rupture. Pre-emptive stenting of the internal carotid artery and detachable balloon occlusion of external carotid artery may be carried out. It is necessary to cover the exposed carotid vessel with a muscle flap. (Fig. 9.3a–d)
4. In case of established carotid blow out, bleeding should be secured with digital pressure of the artery against the spine at the bedside. Transfer of the patient to operating room without controlling major bleeding at the bedside may be fatal. In the operating room, if adequate hemostasis can be achieved by digital pressure or clamping the artery, the patient should be hemodynamically stabilized before further exploration of the neck wound. If the blow out has occurred from a branch of the external carotid, it can be ligated. However in case of blow out of the main vessel (commonly occurring at the region of the carotid bulb), repair is mostly futile as the vessel wall is very fragile owing to the pre-existing tissue conditions. In cases, where the carotid needs to be ligated, it is

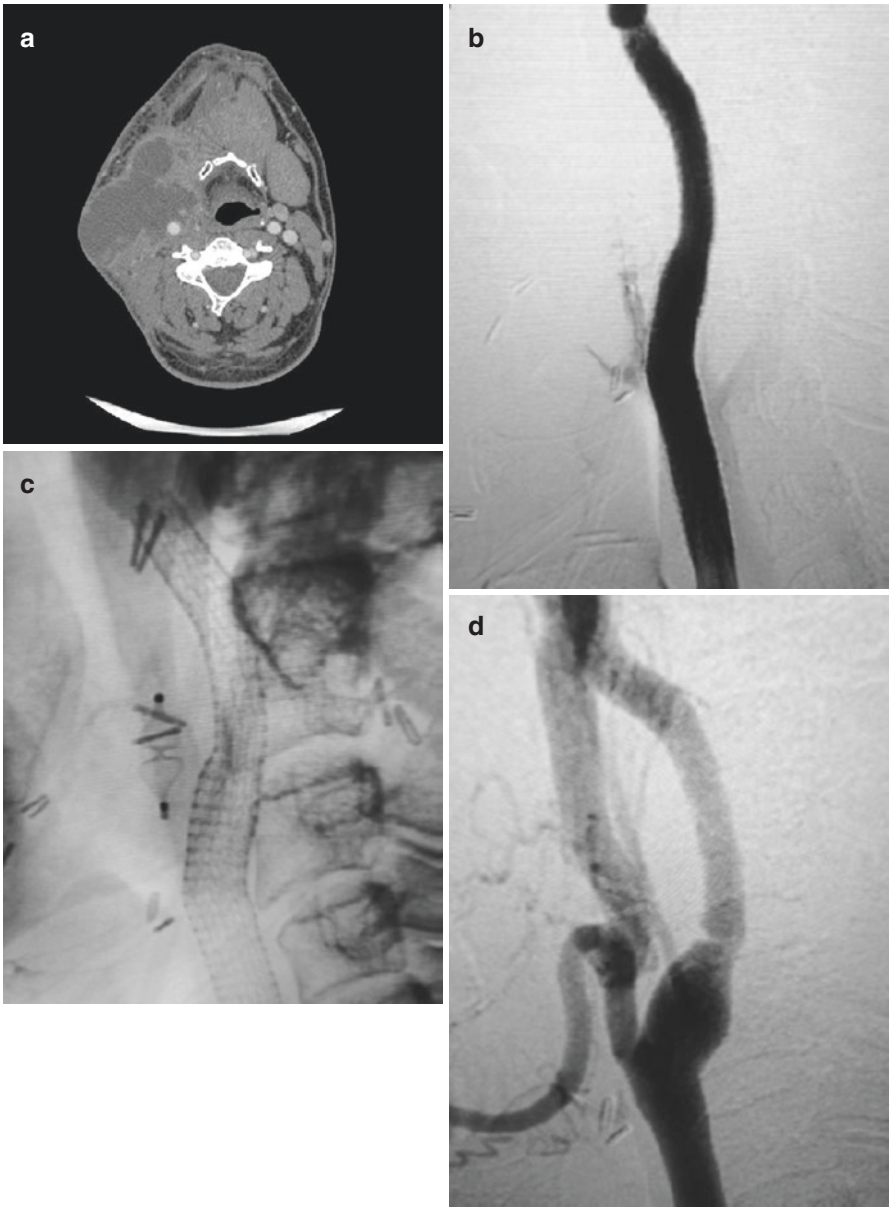

Fig. 9.3 (**a**) Computed tomographic scan showing more than 270° encasement of common carotid artery by metastatic lymph node. (**b**) Preoperative carotid angiogram. (**c**) Detachable balloon to occlude external carotid artery and stenting of internal carotid artery. (**d**) Poststent angiogram showing lack of flow through eternal carotid artery and patent internal carotid artery

preferred to ligate the vessel away from the contaminated site to prevent further blow outs. The vessel ends can be covered with muscle tissue for further protection.

Significant difference has been reported by Moore et al. in the incidence of death and neurological sequel in patients undergoing elective versus emergency ligation of the carotids [30]. They reported 23 % risk of neurologic complications after elective ligation versus 50 % after emergency ligation. The risk of death was 17 % in the elective ligation group versus 38 % in the emergency ligation group. This difference is mainly as a result of massive sudden hemodynamic compromise as a result of carotid blow out.

Internal jugular vein blow out is much less fatal and managed with either repair or ligation of the vessel.

9.3.3 Complications Arising During Primary Tumor Resection

1. *Planning access to avoid complications during ablation*

Failure to properly plan access for the ablation results in intraoperative complications with failure to obtain a three-dimensional clearance of the tumor.

Depending on the location of the primary tumor and the deeper extent, the incisions should be planned for accessibility.

The main consideration is whether the ablation can be done per orally or needs a lip split for access.

Design of the lip split either incorporating a chevron, step ladder with a Z plasty or along the mental prominence ensures good postoperative cosmesis.

Skin and mucosal slough can be prevented by planning of incisions to avoid acute angles, atraumatic handling of tissues and planned placement of sutures to avoid devitalizing tissues. It is imperative that incisions be made with a knife and deepened atleast till the dermis prior to using cautery. The division of the muscle fibers along the lip and chin with the skin and dermis ensures good postoperative viability [31–33]. (Fig. 9.4a–g)

Access for lesions depending on the site:

(a) Buccal mucosa and gingivobuccal sulcus tumors:

For early T1 and T2 lesions of the buccal mucosa and gingivobuccal sulcus excision can be done through per oral approach with the deeper margin of resection including the buccinator muscle but safeguarding the facial nerve branches. Lesions abutting the mandible need to have a concomitant marginal mandibulectomy done. If the lesion is abutting the upper alveolus, this necessitates either an alveolectomy or an infrastructural maxillectomy.

While performing a marginal mandibulectomy avoid sharp angles as they are prone to occlusal stresses and subsequent fractures. The angle of the mandible is the area most prone to these forces. Rounding off the angles to obtain a smooth contour prevents the concentration of these

unfavorable forces. Preserve atleast 8–10 mm of the lower border of the mandible in marginal mandibulectomy resections (Fig. 9.5a–c).

For advanced lesions extending posteriorly to the retromolar trigone or T3 and T4 lesions with involvement of the infratemporal fossa, a lower lip split with a cheek flap gives access to the tumor and infratemporal fossa clearance. Lesions with paramandibular involvement and cortical erosion need a segmental bone resection. Lesions abutting the retromolar trigone have a pattern of spread along the pterygomandibular raphae to the infratemporal fossa. The bone margin should include either a marginal mandibulectomy or a posterior segmental mandibulectomy.

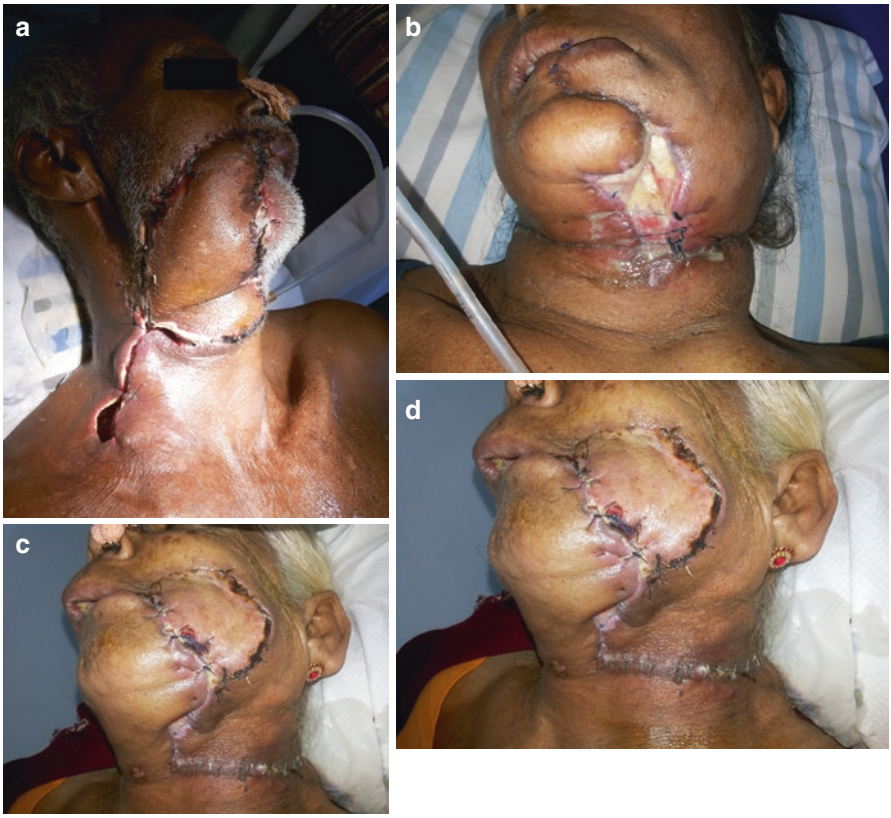

Fig. 9.4 (**a**) Trifurcation incision breakdown due to non-functioning suction drains that keep the skin flaps adhered to the bed. (**b**) Improperly designed lower lip split with skin wound dehiscence. (**c**) Dehiscence at neck wound at multiple points as the flap has failed to obliterate the dead space. (**d**) Marginal necrosis of the pectoralis major skin paddle. (**e**) Neck wound dehiscence due to wound infection and contamination from the tracheostomy site. (**f**) Multiple neck wound dehiscence due to neck haematomas. (**g**) Neck wound dehiscence due to thin skin flaps especially posteriorly with a deficient platysma muscle

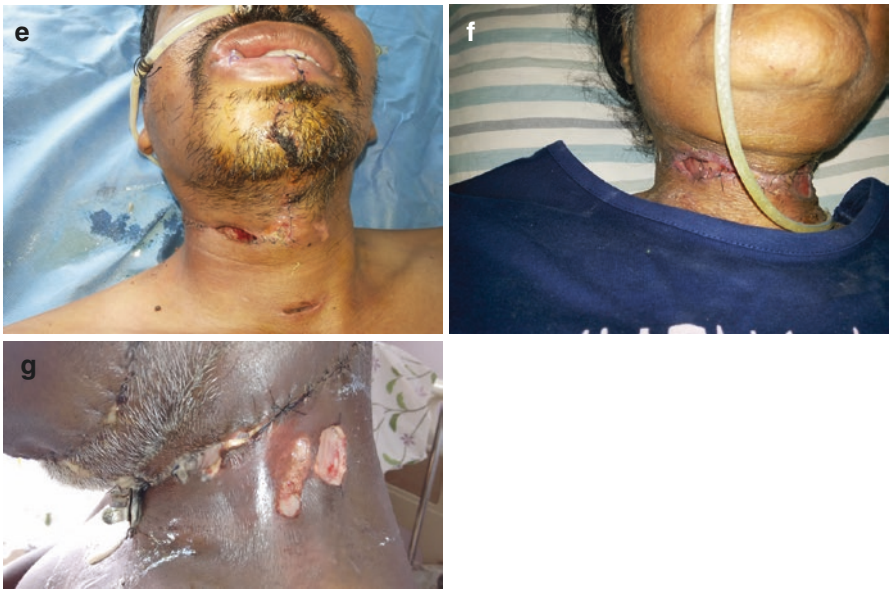

Fig. 9.4 (continued)

If the resection includes a mandible angle osteotomy, the proximal and distal fragments are repositioned with a semirigid fixation using a heavy prolene suture rather than plate fixation. The former facilitates a pseudojoint creation which significantly reduces the postoperative trismus [34, 35].

A lower lip split is also needed in patients with inadequate mouth opening due to submucous fibrosis.

It is imperative to plan the lip split according to the mucosal or skin margins required depending on the lesion to avoid lip necrosis due to inadequate supply through the inferior labial vessels which get transected. In these instances, an angle split is more appropriate.

(b) Upper alveolus and gingivobuccal sulcus tumors

Depending on the location of the tumors, the incisions need to be planned. Lesions requiring clearance of the infratemporal fossa need a lower lip split with a cheek flap. A Weber Ferguson with its modifications and upper cheek flap does not give access to the posterior compartment. Resection of these tumors needs a composite resection of the alveolus, hard palate, soft palate, tonsillar pillars and mucosa depending on the extent and margins needed. Due consideration should be given to the pattern of spread of these tumors along the neurovascular bundle of both the greater palatine and posterior superior alveolar. As these branches of the maxillary nerve (V2) extend into the pterygomaxillary fissure, it is this structure along with

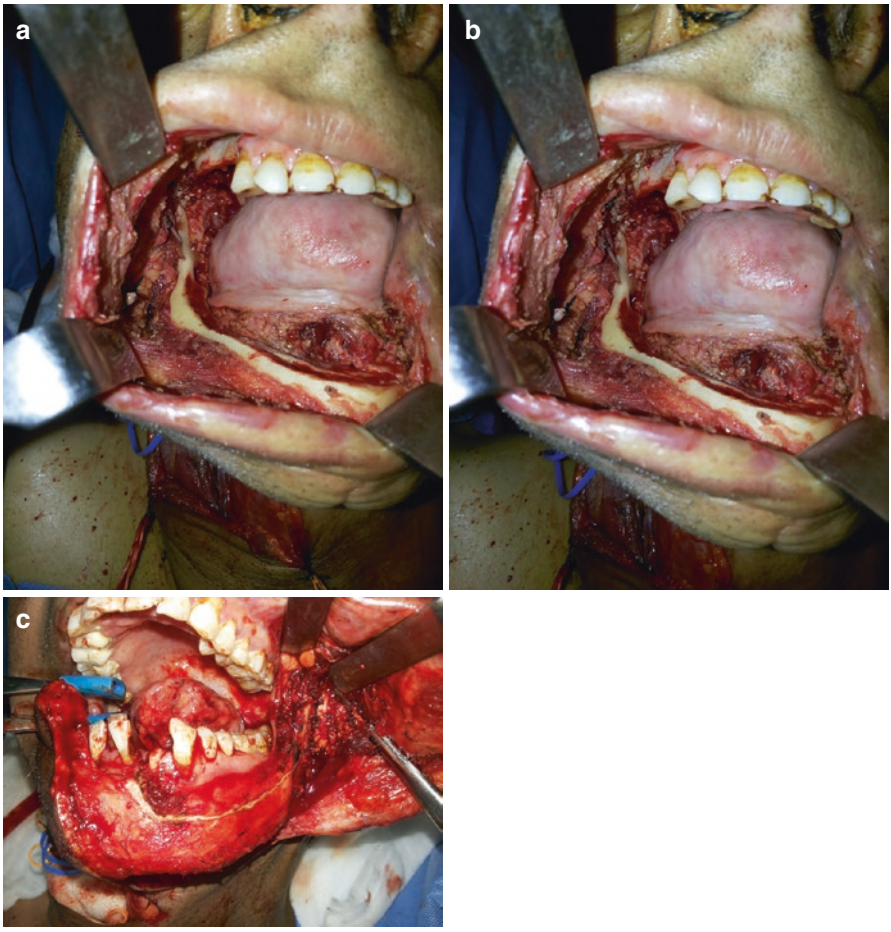

Fig. 9.5 (**a**) Sharp angles to be avoided in a marginal mandibulectomy that are prone to stress concentration and fracture. (**b**) Sharp angles to be avoided as these bony spurs can also damage the pedicle of the free flap as it passes along the lingual surface of the mandible. (**c**) Preserve at least 8–10 mm of the lower border of the mandible to prevent pathologic fracture

the inferior orbital fissure that needs to be assessed preoperatively in scans. Ensuring negative surgical margins along these structures might be difficult in advanced tumors and need to be considered in the inclusion of the treatment portals during postoperative adjuvant radiation [34, 35].

(c) Tongue tumors

For early lesions T1 and T2 a per oral glossectomy provides good access. If the floor of the mouth with the mylohyoid diaphragm needs to be removed enbloc, a planned compartment resection is possible through the per oral and neck approach by detaching of the suprahyoid muscles from the hyoid bone. Troublesome bleeding from the lingual artery can

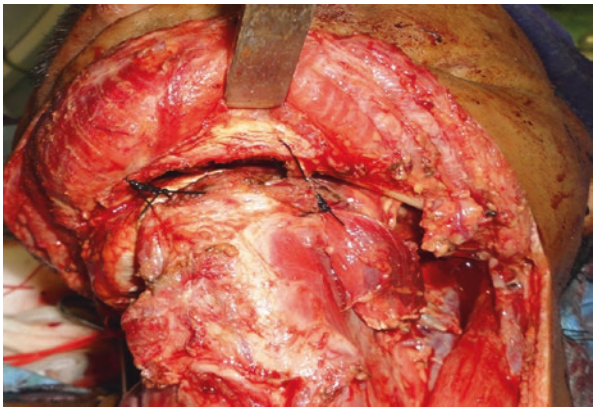

Fig. 9.6 Laryngeal suspension performed after total glossectomy to ensure minimal postoperative aspiration

be avoided by identifying it and obtaining vascular control before it passes deep to the hyoglossus.

In advanced T3 and T4 lesions necessitating a total glossectomy, the tumor is delivered transcervically along with the mandible component (marginal or segmental) and once dropped into the neck through a pull-through approach the posterior mucosal and tonsillolingual sulcus extension can be visualized and palpated before placing the cuts.

Access for lesions on the posterior tongue may necessitate either a lateral pharyngotomy or mandibulotomy approach.

Preserve the lingual neurovascular pedicle on the contralateral side. Keeping a viable base tongue remnant with the lingual artery enables good postoperative recovery of swallowing.

In total glossectomy, consider a percutaneous endoscopic gastrostomy for the long-term nutritional considerations and a laryngeal suspension with an infrahyoid detachment to align the larynx and prevent post operative aspiration. (Fig. 9.6)

2. *Other intraoperative complications during resection*
   (a) Margin assessment :
   - 5 mm is the shortest vivo margin recommended in resections for tongue carcinoma [36–39].
   - A careful bimanual intraoral palpation preoperatively with the patient under anesthesia should be done to assess the three dimensional extent of the tumor.
   - Mark the area of resection atleast 1.5–2 cm beyond the palpable induration to compensate for the natural tissue retraction that accounts for 25–30 % lesser than the invivo evaluation.
   - Intraoperative frozen section can be used to detect the adequacy of margins.

- Keep the mucosal margins of the excision free of preinvasive changes.
- For mandible resections assess preoperatively from imaging the pattern of bone invasion: erosive, infiltrative or mixed. The infiltrative pattern is associated with higher positive margins, recurrence, higher tumor grade and lower disease free survival.
- Plan the resection to obtain a 1.5–2 cm margin.
- Consider segmental mandibulectomy in prior radiated fields, paramandibular involvement, breach of the outer cortex and reaching the medullary space, paraesthesia or numbness along the inferior alveolar nerve.
- Intraoperative frozen section of the curetted cancellous marrow from both the proximal and distal stumps of the resection can be used to check the margin. Also assess the proximal stump of the inferior alveolar nerve [40–44].
- Surgical beds with close margins along neurovascular bundles or vital structures such as the carotid artery need to be tagged with ligature clips to ensure they are included in the planning fields of postoperative radiation.
- The margins of resection should not be altered based on shrinkage patterns seen in patients who have received neoadjuvant chemotherapy. This is not the standard of care. The resection has to be planned based on the original tumor volume prior to any treatment.

(b) Pitfalls during infratemporal fossa clearance

- Reflect the cheek flap deep to the fascia overlying the masseter. This maneuver safeguards the facial nerve branches.
- Avoid dissecting the flap over the zygomatic arch as the temporal branch of the facial nerve crosses the arch and damage can result in postoperative difficulty in eye closure.
- Attempt to identify the maxillary artery medial to the condyle along the lower border of the lateral pterygoid muscle and obtain control it prior to clearing the infratemporal fossa
- Trace the mandibular nerve (V3) either lingual or inferior alveolar nerve superiorly to the skull base at the foramen ovale. This serves as a guide and landmark and also avoids injury to the carotid vessels.
- The other landmarks for the carotid vessels are the parapharynx fat plane deep to the medial pterygoid and the Eustachian tube.
- The foramen ovale is in direct continuity with the lateral pterygoid plate.
- The resection and osteotomy of the pterygoid plates should be done after carefully assessing the scans as they can be pneumatized to a variable extent by the sphenoid sinus.
- Troublesome oozing from the skull base and pterygoid venous plexus can be reduced by intraoperative hypotension, delivering the contents from the skull base and foramen ovale, clipping the structures exiting from the foramen ovale and packing the bed with gel foam and oxidized cellulose and bone wax. Surgical tamponade with these agents and pressure is the best method to control bleeding.

9.3.4 Complications Arising in the Previously Treated Patient

In the recurrent tumor setting, surgical salvage represents the primary curative option if the disease is resectable [45–50].

What are the points to be considered from the previous disease before considering salvage?

- Stage of the initial and recurrent tumor
- Disease free interval from radiation therapy
- Presence of neck disease
- Positive surgical margins
  Oral cavity recurrences have an intermediate prognosis when compared to other head and neck cancer subsites.
  Which features would make the recurrent disease unresectable ?
- Prevertebral fascia involvement
- Skull base involvement
- Encasing the carotid vessels
  What complications can be expected in patients undergoing salvage?
- Tumor related
  Aggressive tumor biology with radioresistant lines are poor prognostic indicators as also shorter time to recurrence with short disease free intervals.
  Concomitant nodal disease needing neck dissections increases chances of poor wound healing, carotid exposure and skin necrosis.
- Reconstruction related
  The need for microvascular flaps with need for double flaps to reconstruct the defects.
  The neck might be a vessel depleted neck and will need to be assessed preoperatively with Magnetic Resonance (MR) angiograms to look for suitable donor vessels or vein grafts need to be considered.
  Patients need to be counseled appropriately about the chances of flap failure and a definitive salvage plan with regional flaps needs to be kept in the armamentarium.
- Adjuvant treatment related
  Reradiation should be offered to patients who have completed 1 year following definitive radiation but has its own morbidity. It definitely improves the local control and disease-free survival. If reradiation is not feasible brachytherapy to the tumor bed improves the local and regional control.
- Patient related
  Evaluate the patient for comorbidities, performance status, social support system and attitude towards surgical salvage.
  Patients in the salvage scenario take atleast 6–12 months to return to the base line functional status and quality of life. Patients need to be counseled appropriately about this.
  Long-term PEG tube dependence with inability to take orally and tracheostomy dependence are common in the salvage setting.
- Surgical and postoperative complications

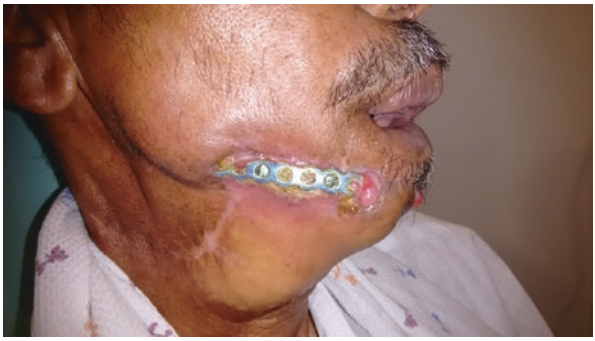

Fig. 9.7 Osteoradionecrosis of the mandible with implant exposure

Fibrosed necks with difficulty in dissecting the vessels making them prone to iatrogenic injury. Every attempt must be made to isolate a good stump of the carotid and internal jugular vein both proximally and distally to have good control for haemostasis.

Preserve the neural structures namely the vagus and hypoglossal nerves.

Osteoradionecrosis (ORN) in the setting of previous radiation.

ORN is exposed irradiated bone that fails to heal over a period of 3 months [51] (Fig. 9.7).

Mandibular ORN could have iatrogenic causes (81 %) such as surgical trauma, tooth extraction and poor oral hygiene with 19 % being spontaneous [52].

Clinically it presents as an exposed necrotic mandible or discharging fistula under the area of disease with foul odor and pain. Recurrent or persistent cancer can mimic ORN. Literature reports as much as 21 % of ORN being finally diagnosed as recurrent cancer after repeated debridements and radical surgery [52].

Management of ORN:

- The best method to avoid osteoradionecrosis is prevention. In the radiated bed consider placement of bone flaps with good vascularized soft tissue flaps, local flaps are also prone to the radiation effects and will not provide healthy vascularized cover. Proper implant placement with rigid and adequate fixation to the native mandible is required (atleast three screws on the proximal fragment). Ensure good bone contact between the osteotomized segments to obtain osseous healing not a fibrous callus.
- In the initial management of diagnosis and delineating the extent of the disease, MR imaging is superior as it has a better ability to define the bone marrow and surrounding soft tissue changes.
- Conservative management with debridement and sequestrectomy to remove the foci is essential. ORN is a surgical challenge and adjuncts like hyperbaric oxygen may elevate the oxygen tension in the devitalized tissue but are not the primary treatment modalities. Debrided tissue needs to be pathologically analyzed to rule out foci of malignancy.

- Radical sequestrectomy in recalcitrant cases with vascularized osseous flap is the corrective surgical procedure [53].
- The use of pentoxifylline-tocopherol combination along with clodronate is efficacious in decreasing the fibrosis of previous radiotherapy and enhances the mucosal healing. This combination is prophylactically recommended in patients with irradiated bone planned for extractions and implant placement [54].

Key points in salvage surgery:

- Disease-free interval is the most important prognostic indicator in the success of salvage. Liao et al. considers 10 months to be a crucial determinant, 54 % vs 12 % 5 year overall survival.
- Multi institutional studies have reported overall 5 year survival ranging from 30 to 45 % in salvage of oral squamous cell carcinoma.

9.3.5 Complications Encountered During Reconstruction

1. What are the predictive factors of free flap failure that need to be anticipated in head and neck reconstruction?

   Patient related factors such as age, smoking and radiation are universally applicable across all head and neck cancer patients undergoing reconstruction and have not been demonstrated to have an impact on overall flap survival [55].

   In a retrospective review of head and neck free flaps performed at the MD Anderson Cancer Center, muscle only flaps, combined arteriovenous thrombosis were associated with significantly worse outcomes. Multiple takebacks and late takebacks (>3 days) had a worse outcome. Anticoagulation, thrombolytics and thrombectomy did not improve overall survival [56].
2. What are the appropriate modalities of reconstruction to be selected based on site specificity?
   (a) Oral tongue: Partial glossectomies involving less than one third of the tongue, not involving the floor of the mouth and preserving the tip can be repaired by direct primary closure or allowed to heal secondarily if ablated with laser.

   Defects greater than one third only restricted to the tongue are best reconstructed with a lateral arm flap [57]. With the floor of the mouth involved a radial forearm free flap is a better option to provide pliable tissue and avoid tethering. In total glossectomy, defects options can be customized depending on the extent of the defect as to whether it includes a concomitant laryngectomy. Options include the anterolateral thigh flap, rectus abdominis and pectoralis major flap.

   (b) Mandible reconstruction: Lateral defects in dentate patients and involving the anterior mandible need skeletal reconstruction. Lateral defects distal to the premolar teeth in edentulous patients can be reconstructed with pedicled flaps.

   (c) Buccal mucosa defects: These defects come in varying combinations with other adjacent sites.

Small lesions upto 2 cm can be closed primarily or closed with the buccal pad of fat. Other options include submental flap, facial artery myomucosal flap and nasolabial flap.

Larger defects with bone resection and also in patients with submucous fibrosis benefit from thin pliable soft tissue flaps like the radial forearm flap.

Composite defects with infratemporal fossa clearance need soft tissue obliteration of the cavity with flaps such as the anterolateral thigh flap [58–60].

(d) Hard palate: Superficial lesions can be left to granulate and heal secondarily. Other options are palatal mucoperiosteal flaps based on the greater palatine vessels, tongue flaps, radial forearm flap and temporalis flap.

3. What are the common pitfalls encountered during flap harvesting and inset?

(a) Pectoralis major flap:

- Large skin paddles especially for full thickness cheek defects make the distal most part of the flap prone to necrosis as the skin paddle becomes random over the rectus sheath. A few tacking sutures of the skin paddle to the dermis and underlying muscle ensure the paddle does not get sheared off its blood supply (Fig. 9.4d).
- The subcutaneous tunnel according to the rule of thumb should be atleast four fingers wide to accommodate the flap without any tension on the pedicle.
- Always check the lie of the pedicle and avoid any torsion prior to inset.
- Use of a non-absorbable suture like 3–0 nylon along the palatal mucosa and interdental areas ensures stability of the flap and prevents its natural sag and dehiscence.
- If a marginal mandibulectomy has been done preferably take the flap over the mandible rather than on the lingual aspect to avoid any compression.
- A natural sequelae with this flap is the characteristic neck contracture tendency to sag, palatal dehiscence and hollow on the face.
- The bulk of the flap can be quite bothersome and can cause a sag and deviation of the commissure (Fig. 9.8a–d).

(b) Radial forearm flap

- Preoperatively perform the Allens test and always check the backflow through the radial stump at the end of flap harvest.
- Monitor tourniquet application, removal, pressure settings and time of application.
- Perform a suprafascial dissection with preservation of the paratenon to ensure good take of the skin graft over the donor bed.
- Secure the skin graft adequately to the donor site and immobilize appropriately in a plaster cast for atleast 5–7 days (Fig. 9.9a–c).

(c) Anterolateral thigh flap

- Try to base the flap on a single perforator than take muscle along with the flap.
- Avoid too tight closure of the defect and graft the remaining donor site.

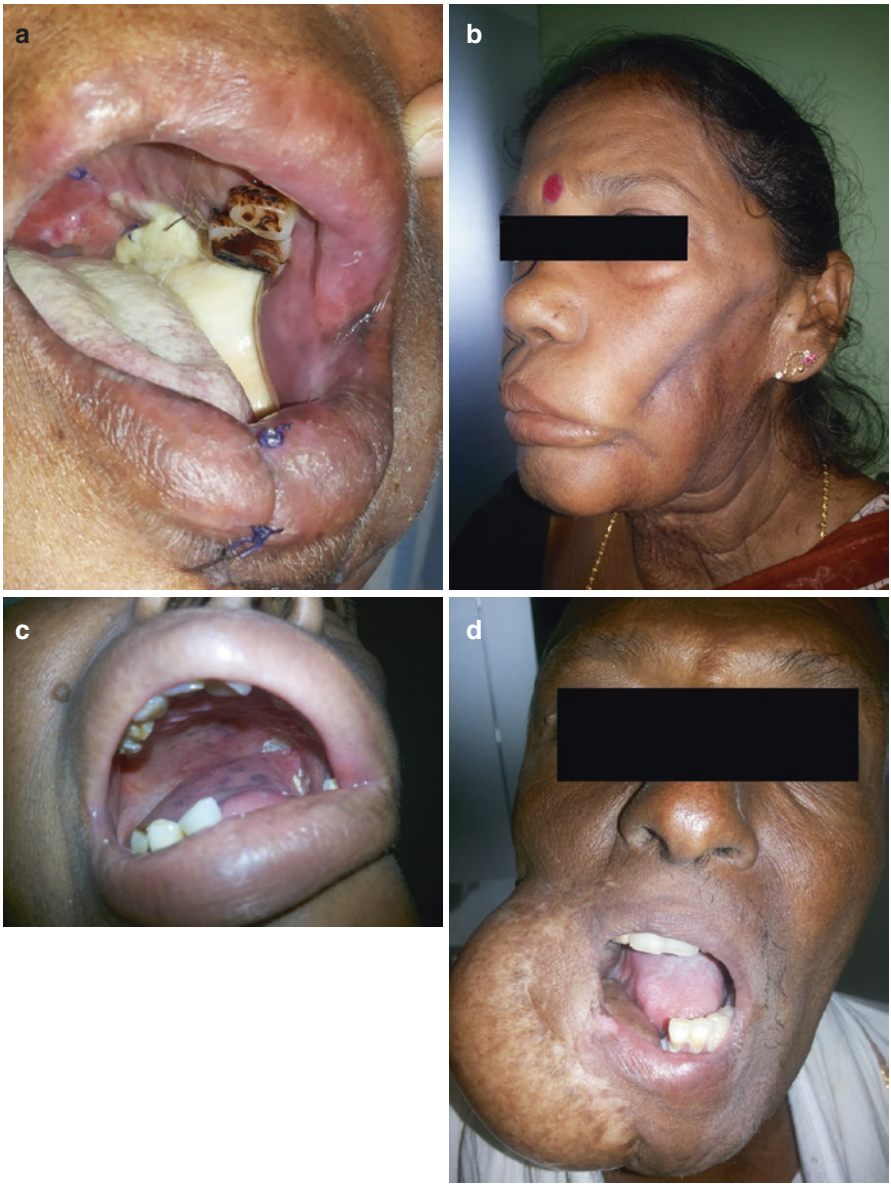

Fig. 9.8 (**a**) Intraoral sloughing of the skin paddle of the pectoralis major flap due to sheared off blood supply. (**b**) Characteristic hollow and neck contracture on long-term follow up with the pectoralis major flap. (**c**) Intraoral dehiscence seen with the pectoralis flap. (**d**) Bulk of the pectoralis flap with the characteristic commissural deviation and incompetence

- Preoperatively mark the perforator with Doppler ultrasound and identify the septum between the rectus femoris and vastus lateralis looking for perforators before committing the skin paddle incision (Fig. 9.10a, b).

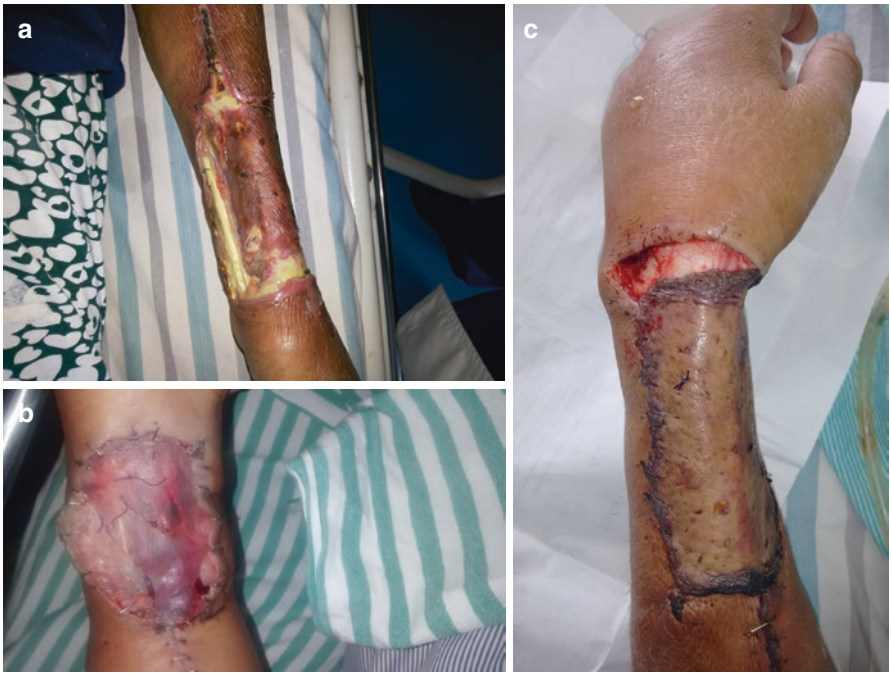

Fig. 9.9 (**a**) Skin graft dehiscence in the radial forearm donor site due to exposed paratenon and failure of graft take. (**b**) Unhealthy skin graft due to hematoma under the graft which has not been drained properly due to inadequate rents in the graft. (**c**) Improper immobilization of the forearm leading to graft displacement

(d) Fibula free flap
- Preoperatively do an MR angiogram or arterial Doppler to exclude peronea magna.
- Always preserve 4–6 cm bone proximally and distally to keep the stability of the ankle mortise and injury to the common peroneal nerve.
- Dissection at the proximal end should be performed carefully as the peroneal artery arises in close proximity to the posterior tibial artery.
- Always preplate the mandible with atleast three screws into the native mandible proximally and distally to ensure good stability.(Fig. 9.11)

(e) General Considerations
- Prior to inset, position the flap along the natural lie of the pedicle.
- Ensure there is no kinking or twist of the pedicle, the position of the ligaclips can be used to verify this.
- Avoid sharp angles along the lingual aspect of the mandible.
- Ensure that the anastomosis is stable with either suture stability or a piece of gel foam.
- Check the optimal position of the patient's head which needs to be maintained postoperatively avoiding any kink or twist of the pedicle.

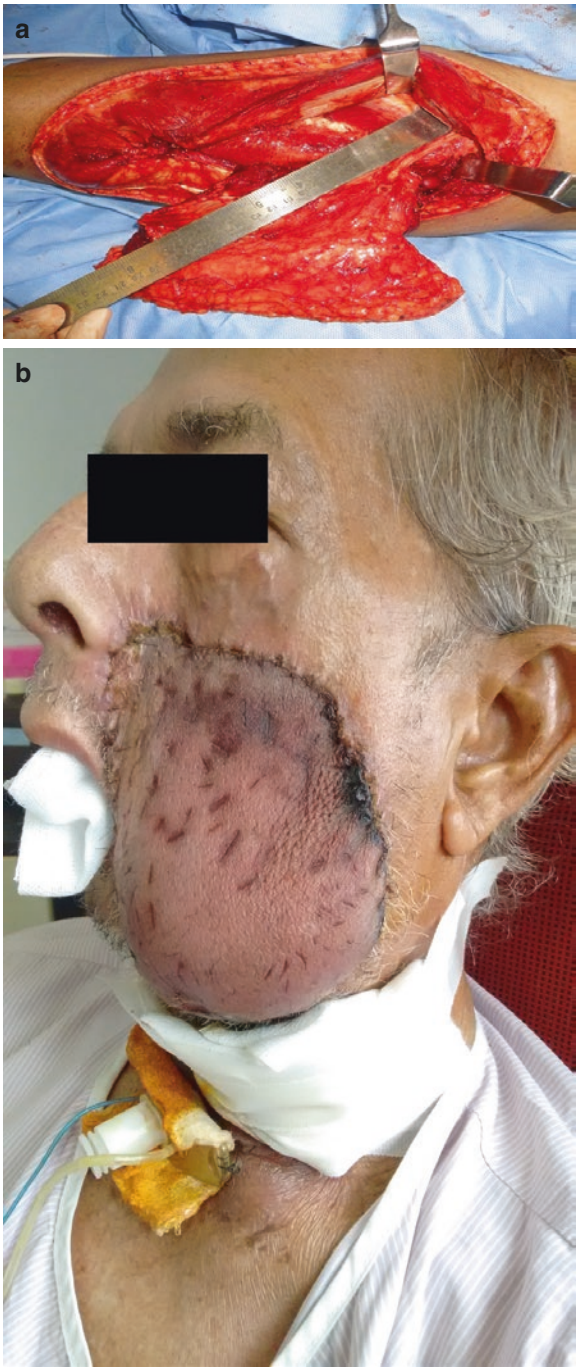

Fig. 9.10 (**a**) Anterolateral thigh flap harvested on a single perforator. (**b**) Venous congestion as seen developing in a large anterolateral thigh flap

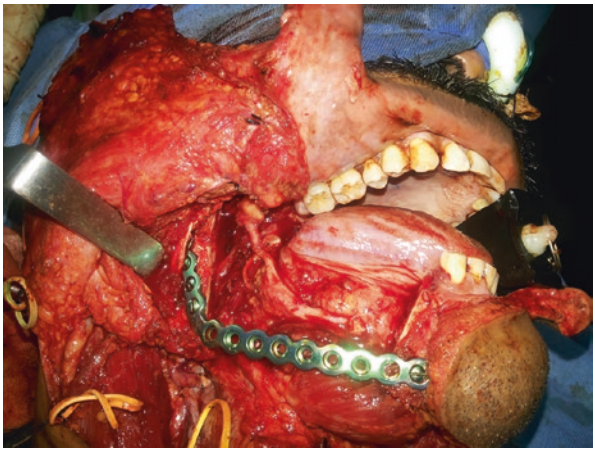

Fig. 9.11 Plating the mandible with three screws in the proximal and distal segments

9.4 Adjuvant Treatment

Adjuvant radiotherapy with or without chemotherapy is an integral part of treatment of advanced head and neck squamous cell carcinoma. Coupled with the adverse functional outcomes of major resections, adjuvant treatment adds significantly to treatment related toxicities.

9.5 Adjuvant Radiation

Since its inception a 100 years back, there has been revolutionary developments in the field of radiation therapy. Attempts have been made to improve the efficacy while decreasing the toxicity. For instance, Intensity Modulated Radiotherapy (IMRT) has significantly reduced the incidence of xerostomia and lead to recovery of salivary function as compared to conventional radiotherapy [61]. The common complications of radiotherapy in oral cancer are briefed in this section.

1. Mucositis

   How does radiotherapy cause mucositis?

   Apart from damaging the tumor cells, radiotherapy has deleterious effect on normal cells – however to a lesser extent. The effect of radiotherapy on normal cells is complemented by the addition of chemotherapy. Mucositis begins within 2 weeks of starting of radiation and continues with symptoms till 4–5 weeks posttreatment completion. It is divided into four phases:

   Initiation phase – begins immediately following the tissue insult. The epithelial cell DNA is damaged and this leads to cell death.

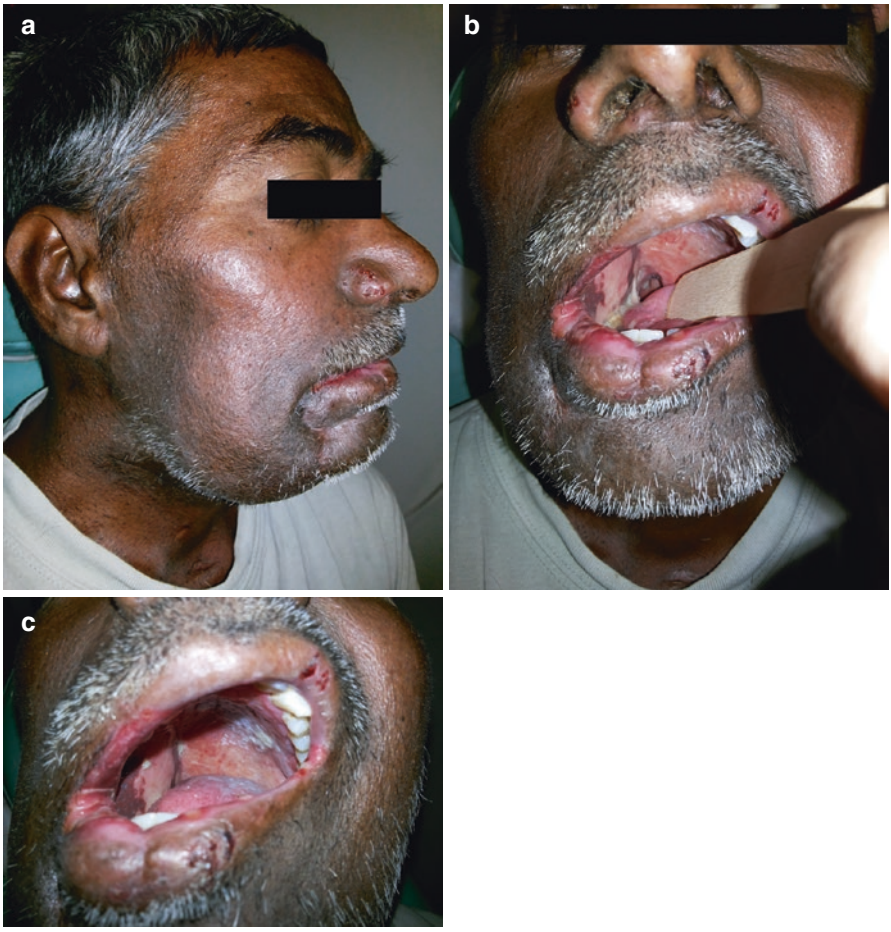

Fig. 9.12 (**a**) Skin changes seen during adjuvant radiotherapy. (**b**) Mucosal ulceration during adjuvant radiotherapy. (**c**) Mucosal changes seen during adjuvant radiotherapy

The upregulation and messenger generation phase – begins 2–3 days after the treatment initiation. There is activation of biological switches like nuclear factor κβ which results in increased activation of cytokines. The inflammatory cascade is thus switched on causes the mucosa to become thin, reddened and painful [62].

Amplification and signalling phase – further activation of proinflammatory cytokines and TNF-α results in profound submucosal damage

Phase of ulceration – clinically evident ulcers extending downwards from the epithelium to the submucosa are formed thus exposing the nerve endings resulting in severe pain. Bacterial colonization occurs in the ulcer troughs resulting in halitosis and bleeding. From the initiation to the ulceration, it takes around 10–15 days (Fig. 9.12b, c).

Healing starts by around the 14th to 21st day after mucosal assault and is completed by 4–5 weeks of completion of treatment.

Prevention of symptoms of mucositis – Handy tips:

Maintenance of oral hygiene-mouth rinse with salt and baking soda mixed with lukewarm water 4–6 times a day before and after meals.

Avoidance of chemical irritants like tobacco, alcohol, spices, citrus fruits and commercial alcohol-based mouth wash

Avoidance of physical irritants like extremes of hot and cold food, hard and coarse foods and ill-fitting dentures.

Certain pharmacotherapeutic agents like benzydamine, sucralfate and glutamine have been tried to treat mucositis but their effectiveness is not established due to lack of clinical trial support.

2. Skin reactions – an unavoidable but manageable complication

Skin reactions occur in 87–90 % of all patients receiving radiation [63].

The acute reactions usually begins 2–3 weeks after starting of therapy and continue 3–4 weeks after completion of treatment [63, 64]. Ionizing radiation damages the mitotic activity of stem cells of the basal layer of the epidermis. This disturbs the turnover and cells are more rapidly lost than produced. There is decreased thickness of the cornified cell layer at the skin surface which makes it more vulnerable to radiation insults. Increased release of serotonin and histamine leads to edema. Increased blood flow as a result of inflammation leads to erythema. Melanin rises to the surface causing darkening of the skin. The hair follicles are permanently destroyed resulting in permanent alopecia. Radiation effects start from mild erythema and progress to hyperpigmentation, dry desquamation and moist desquamation (Fig. 9.12a).

Moist desquamation leads to fluid losses, infection and most importantly treatment breaks resulting in decreased effectiveness of treatment.

Proper skin care is essential to reduce the burden of skin toxicity. This includes:

- Gentle washing of skin with warm water and mild soaps and rinsing well before patting the skin with clean soft cloth [65]. Use of a gentle baby shampoo is also permitted [66].
- Aquaphore ointment can be applied to the skin immediately after each radiotherapy sitting and at bedtime. However, the skin should be free of any ointment before each treatment.
- Avoidance of any skin cream, make up, after shave or cologne in the area to be treated.
- Avoidance of constrictive clothing, tight ties, starched collars or similar physical irritants during treatment.
- Direct sun exposure to be avoided using sunscreen, SPF-45 or face shading hat.

Xerostomia

The acinar cells of the parotid are highly sensitive to the effects of radiotherapy and clinically reversible transient xerostomia occurs at a dose of as less as 6 Gy. Doses greater than 30 Gy to the whole gland can result in permanent xerostomia. Xerostomia is more in patients with midline tumors like tongue, floor of

mouth, palate, midline lip and middle 1/3rd of mandible due to bilateral radiation fields causing damage of both parotid glands. Xerostomia leads to dryness of the oral mucosa which in turn makes the mucosa more vulnerable to mucositis and infection. Sparing of the parotids by IMRT significantly reduces the incidence of xerostomia [67].

Xerostomia can partially be managed by the use of salivary substitutes like carboxymethyl cellulose and sialogogues. Pilocarpine is the only sialogogue approved by the FDA. In a randomized Radiation Therapy Oncology Group (RTOG) trial, there was some objective improvement in saliva measurements in patients receiving pilocarpine; however there was no difference in patient perception of xerostomia [67].

9.6 Adjuvant Chemotherapy

Chemotherapy plays a supportive role in head and neck squamous cell carcinoma. The main drug used in the adjuvant setting is cisplatin. The recommended dosage of cisplatin in head and neck squamous cell cancer in the adjuvant setting is 100mg/sq metre body surface area every 3 weeks for three cycles. However, a weekly dose of 30 mg/m has been used and is supposed to be less toxic although there is no substantial data to support this. The major toxicity of cisplatin is nausea and vomiting and this may persist upto 1 week after the completion of treatment. Nausea should be managed symptomatically with anti-emetics.

Nephrotoxicity is a major dose limiting toxicity of cisplatin. It usually occurs in the second week of treatment with cisplatin. The incidence of renal insufficiency using saline hydration and diuresis is in the range 20–30 % of patients [68]. Typically, the onset of renal insufficiency begins several days after the dose of cisplatin, as revealed by increases in the serum creatinine and blood urea nitrogen concentrations. The urine output is usually preserved (non-oliguric) and the urine may contain glucose and small amounts of protein, indicative of proximal tubular dysfunction. Hypomagnesemia is also common, particularly after repeated doses of cisplatin, even in the absence of a fall in the glomerular filtration rate. Recovery of renal function usually occurs over a period of 2–4 weeks.

How to prevent cisplatin induced nephrotoxicity?

Adequate hydration in the peri-treatment period is the key to prevent cisplatin-induced nephrotoxicity. Usually patient is hydrated with 1 litre of normal saline (NS) with 2 ml of potassium chloride (KCl) intravenous infusion over 2 h. This is followed by injection (inj.) Cisplatin in 500 ml NS intravenous (i.v) over 1–2 h. Finally, 1 L of NS with 4 ml of magnesium sulphate is infused over 1–2 h.

High frequency sensorineural deafness is another potential complication of cisplatin. There is no effective treatment and serial audiometric assessment is required during therapy.

Other rare complications include peripheral neuropathy, anemia, leucopenia and loss of taste.

9.7 Surveillance in Oral Squamous Cell Carcinoma

The key points that need to be addressed to avoid pitfalls are:

(a) What should be the follow up protocol?
(b) What are the danger signs that need evaluation?
(c) What are the adjuvant and ancillary procedures that patients can undergo during follow up?
(d) What are the appropriate imaging and laboratory evaluation tests that need to be undertaken?

The above issues have been addressed in a manuscript by Roman et al. from the Education Committee of the American Head and Neck Society [69].

(a) The follow up protocol recommended by the National Comprehensive Cancer Network (NCCN) Guidelines available online (version 1.2015) suggests:
- History and physical examination with a complete head and neck, mirror and fiberoptic examination:
  Year 1: Every 1–3 months
  Year 2: Every 2–6 months
  Year 3: Every 5–8 months
  5 years: every 12 months
- Baseline imaging within 6 months of treatment and further imaging based on smoking history, worrisome or equivocal signs and symptoms, and areas inaccessible to clinical examination.
- Chest imaging for patients with smoking history.
- Thyroid stimulating hormone in irradiated patients at 6–12 months.
- Speech, hearing and swallow evaluation and rehabilitation.
- Smoking cessation and alcohol counselling as indicated.
- Dental evaluation especially for areas exposed to intraoral radiation.
- Nutritional evaluation and rehabilitation as indicated
- Ongoing surveillance for depression [70].
  Elango et al. showed that mouth self-examination (MSE) is an effective screening tool for oral cancers. It had a low sensitivity of 18 % with a high specificity of 99.9 %. It identified high risk lesions such as red patches (66.7 %), non-healing ulcers (42.9 %) and a low detection rate of white patches (12.7 %) [71].
  The same author did a questionnaire evaluation to assess the awareness of oral cancer, its risk factors and prevalence in a high risk population in India. Awareness was proportional to educational level and inversely proportional to prevalence of high risk factors. Both these parameters attained statistical significance [72].
  Critical review of certain guidelines recommended by the NCCN is mentioned here:

- The impact of surveillance office visits on survival is not related to the intensity of follow up. However, the guideline recommendations with regard to follow-up intervals are adhered to at most institutions.
- There is very little evidence to support long-term surveillance of asymptomatic head and neck cancer survivors with imaging especially PET CT scans. The pros and cons of this practice need to be considered in decision making. Imaging provides patients with a psychological reassurance but has additional financial implications, contributes anxiety among cancer survivors, additional care might be incurred based on imaging findings, unnecessary radiation exposure and deviates from the standard of care [69].
- Chest imaging is only recommended for patients with significant smoking history and in patients over 50 years of age with significant smoking history more than 20 pack years. The recommended screening is a low-dose CT scan followed by annual low dose CT scan for 2 years as long as the patient is eligible for definitive treatment [73].

(b) *Flag signs that need evaluation*

The cardinal signs that need evaluation include:

- General symptoms such as significant weight loss, cough and dyspnea, bone pain with low back ache, pain diffuse and radiating (manifests as otalgia, odynophagia) and dyspnea.
- Loco regional lesions manifesting as non-healing ulcer, white or red mucosal patches, skin nodules, persistent neck swelling manifesting into a sinus tract and delayed wound healing.
- Many of these changes may be difficult to distinguish from the radiation-induced fibrosis and changes during the initial 3 months posttreatment completion but need to be on close surveillance.

It is also imperative to perform a close surveillance on patients' at least weekly during chemoradiation to ensure the adequacy of the general condition in terms of weight and nutrition, airway, pain control for the mucositis, skin changes, counseling on dysphagia and pain and evaluation of hematologic parameters. Patients are highly susceptible to aspiration, pneumonia and febrile neutropenia which can result in intensive care hospitalization with break in the planned treatment regimen.

(c) Adjuvant and ancillary procedures that patients can undergo during follow up:

- Long-term sequelae of dysphagia and aspiration are seen in head and neck cancer patients. Speech and swallowing exercises improves function in these patients [74, 75]. Dysphagia and silent aspiration are more prone to occur in head and neck cancer patients.
- Smoking cessation with counseling and support measures and referral for professional help should be provided to all patients [76, 77].
- Dental care and rehabilitation:

Manage xerostomia with salivary substitutes, hydration and salivary stimulation

Prevent trismus with mouth stretching exercises

Check periodically for oral candidiasis

Dental evaluation with dental hygiene every 6 months and extraction being performed by surgeons with expertise in managing irradiated patients and in close consultation with the oncology team

Regular surveillance for osteoradionecrosis

Conclusion

The authors have tried to assess various commonly encountered complications specific to the management of oral cancer patients through a series of common clinical questions that need to be posed. The spectrum of complications can be seen from patient evaluation till follow up. Though this chapter might overlook many common complications like wound infection, flap-related complications, radiation and chemotherapy related complications, it has been done with intent as these are available for reference in other manuscripts.

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Salvage Treatment for Recurrent Oral Cancer

10

Mark D. DeLacure and Nicholas J. Sanfilippo

10.1 The Surgical Treatment and Reconstruction of Recurrent Oral Cavity Malignancy

Mark D. DeLacure

The surgical treatment of recurrent or previously treated malignancies of the oral cavity presents one of the greatest challenges known to the head and neck surgeon and reconstructive oncologist. These problems are faced with unfortunate frequency and bring oft-devastating functional cost along with the very real threat of death from uncontrolled locoregional disease. The "successful" (long-term locoregional control, effective palliation, the occasional cure) treatment of these cases requires technical expertise and judgment known only to the most experienced head and neck surgeon. Despite this, treatment failure is common and humbling.

10.1.1 Detection of Recurrence

When there is apparent delayed failure in the neck, it is incumbent to prove that the primary site in the oral cavity is inactive. While neck failure may represent the clinical emergence of metastatic cells that had been present in the node(s) throughout/despite treatment, this phenomenon may also represent continued seeding of the

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neck from a clinically inapparent, uncontrolled, primary. Deep submucosal recurrences or latent persistent tumor is not uncommonly clinically confused with postoperative scar tissue, particularly in the oral tongue.

The palpatory exam, while imperfect, is often the most accurate or the sentinel way to detect this unfortunately common circumstance. Regular surveillance postoperative exams during the first several years of posttreatment increase the accuracy and value of this essential tool and allow one to contextualize subtle changes, particularly when coupled with vague evolving or intermittent patient complaints such as pain, or observed misarticulations.

Cross-sectional imaging studies, particularly MRI, may be helpful, but are often confusing. Similarly, PET scanning, while overcoming many of the inaccuracies of posttreatment anatomical studies, may render equivocal results, with low SUV values that are non-compelling due to physiologic or background activity (speaking, swallowing), etc.

If such studies prove unhelpful, finger-guided dermatologic punch or incisional biopsy under anesthesia may be necessary to reveal the true status of the primary site. Clinically obtained biopsies are often inadequate due to a patient's ability to cooperate with such efforts due to pain, bleeding, and gag reflex. Unfortunately such biopsy results are often relied upon to reflect disease status and often add several additional months of delay in treatment due to complacency over a "normal" result.

The need to reoperate on the tongue primary site may profoundly change what began as an apparent neck salvage procedure, particularly with the significant reconstructive requirements that such surgery usually requires.

Accurate presurgical planning is essential in the successful conduct of salvage efforts.

10.1.2 Modifications of Surgical Technique for the Treatment of Recurrent Oral Cancer

Dissection – Blunt dissection techniques utilizing clamps or scissors or gauze dissectors are fraught with failure of effectiveness in the reoperative case as they rely on the separation of naturally occurring tissue planes that have been dissociated in primary treatment efforts. More often, the electrocautery is used to "carve" structures out of encasing scar to allow rapid progress and minimal frustration and collateral damage in such cases. Nowhere is the absolute knowledge of anatomy more important than in such cases in order to avoid catastrophic entry into major vascular structures, the pharynx, oral cavity, or esophagus.

Effective hemostasis – The considered use of a variety of techniques should be used appropriate to vessel size and flow, avoiding overreliance on any one method which might result in acute return to the operating room for hematoma, pedicle compression, or, in the longer term, obfuscation of subsequent surveillance imaging studies (metallic signal artifact). All too often, simple electrocautery or bipolar cautery is used for high-flow or large-caliber vessels, and over- or undersized metallic clips are reflexively or

thoughtlessly used and occasionally become regrettable choices. At every activation, cautery techniques create necrosis, inflammation, and, ultimately, scar – all rarely considered if one falls into mindless robotic use of such instruments.

Closure – While closure is of critical importance, idiosyncratic techniques abound (type of suture, knotting technique, type of bite, etc.) often take the place of sound general principles. Minimization of foreign body (even resorbables), prevention of ischemia (distance between sutures, suture placement, tightness of knotting), and minimization of tissue handling (forceps crush) should be a regular part of mindful surgical technique, among others.

Margin delineation – Frozen section control of margins from the patient defect side is critical to effective salvage surgery. Margins must be grossly cleared at a minimum and preferably microscopically. This should include major nerve sampling. Resection margins should be marked with metallic clips that can be later used to target postoperative adjuvant radiotherapy efforts.

Exposure/surgical access – On occasion, primary treatment failure may reflect an overly conservative approach to resection, or the failure to employ advanced access techniques (mandibulotomy), or to avoid visible incisions (lip splitting, trifurcated neck dissection incision) that might better ensure adequate exposure. The trauma concept of "zone of injury" should be modified and transposed to reoperative surgery, in which all fields previously dissected and all access incisions are resected, the salvage operation taking place through undisturbed, previously unoperated tissues.

10.1.3 Subsite-Based Biologic Behavior

The biologic behavior of the oral tongue and buccal mucosal subsites is particularly aggressive, and this must be reflected in the design of salvage efforts. I have rarely obtained durable control from cases requiring total glossectomy, no matter how elegantly reconstructed. While this operation can be often performed with preservation of the larynx, total glossectomy for the oral tongue, or p16-negative tumors, should be always be carefully considered.

Similarly, it appears that only up-front radical full-thickness cheek excision might achieve control of even early staged buccal SCCA's of the North American variety. This, of course, is an unacceptable and overly radical concept to most and often leads to the ultimate failure to control this disease site over three or more sequential operations over as many years, all increasingly radical and debilitating, eventuating in death from uncontrolled locoregional disease. Reoperative surgery of these sites, even with palliative intent, is often met with failure.

10.1.4 Functional Surgery

Though single-joint function may be acceptable for some, the maintenance of two-joint function may be desirable for others. The more posterior the mandibular

defect, the more predictable and acceptable are plate-only reconstructions, allowing often efficacious surgery where masticatory demands will be minimal. Habitually guided occlusion, where there are enough residual teeth arrayed in opposition, is often adequate, with early range of motion, in unreconstructed cases. Reconstructions involving TMJ prostheses should be properly suspended from residual condylar fossa structures to properly mimic capsular support and to prevent clanging on occlusion or the undersupported joint to dropout of the fossa, particularly during early healing. This can be accomplished with large permanent sutures (0-Prolene) or stainless wires in a cerclage technique.

Trismus/coronoidectomy – Is often the unavoidable result of surgery and/or radiation involving the pterygoids and temporalis muscles and their attachments. Surgical efforts to improve mouth opening are usually futile due to the etiology of the problem which lies in muscle fibrosis. Procedures aimed at simple orthognathic skeletal correction will usually fail, including creation of pseudarthrosis via subcondylar osteotomy, coronoidectomy, etc. Muscles of mastication, or those of the tongue, which have been detached, dissected, denervated, or otherwise disturbed in previous treatment efforts, will be irretrievably scarred in malposition (contraction, retraction) and cannot be later functionally replaced or recruited. Prevention, through early active range of motion with quantitative benchmarking, is most effective, even in patients treated nonsurgically at their index effort.

In cases requiring mandibulotomy or the rare partial mandibulectomy, defect bridging and load-sharing reconstruction plate constructs should be engineered with at least four holes per segment distally and mesially. Strict attention to detail when applying hardware, in particular irrigation during all sawing, drilling, and screw insertion, will minimize technique-related hardware failure (most commonly manifest as screw loosening (several months post-op), then late migration extrusion). Coverage of hardware by uncompromised tissue, where possible, may minimize problems for those who survive longer term.

10.1.5 Technical Modifications for Reoperative Head and Neck Surgery

It is more commonly than not the case that microvascular free tissue transfer techniques will be relied upon to reconstruct hemi- to major tongue and floor of mouth defects and/or skeletal and soft tissue defects resulting from the surgical salvage treatment of recurrence. Such challenges present the need to perform secondary or tertiary flaps in vessel-depleted necks. Facility with lower neck recipient vessels such as transverse cervical, reverse flow through distal superior thyroid, interposition reversed saphenous vein grafts to contralateral neck vessels, cephalic vein harvest, A-V loop construction, and/or IMA vessel transposition (Fig. 10.1) may be

required and escalate the level of expertise that must be brought to these reoperative cases. In general, techniques that rely on locoregional tissues, grafts, etc., are condemned to failure or at least entrain unacceptable additional loss of already limited functional reserve.

There are few, if any, circumstances that should require simultaneous multiple free tissue transfers and their inherent increased risk, regardless of extent. Microsurgical transfers may be combined with regional flap transfers (pectoralis major) to accomplish many goals. The sheet-grafted muscle-only pectoralis major flap is particularly useful for the resurfacing of the neck skin where neck failure and imminent tumor breakthrough is a problem. My strong preference has been to avoid "pie crusting" techniques, meshing, and bolsters as they are unnecessary, and the former lead to compromised aesthetics for those fortunate to achieve long-term control.

Nowhere is reconstructive expertise more important so as to minimize days-of-life lost for those who may not experience long-term survival.

10.1.6 Special Considerations: Vascular

Failure in the neck from oral cavity cancer commonly occurs in proximity to or at/involving the carotid bifurcation. Preemptive techniques to control catastrophic hemorrhage and to prepare for proximal external carotid sacrifice should be made and anticipated. Proximal and distal arterial control, where possible, should be secured preparatory to efforts to "peel" recurrent tumor from major structures. I have found that the steel scalpel may be the best instrument to perform such "carve-out" procedures as traditional dissection methods rely on undisturbed tissue planes that are nonexistent in these cases. I have also found the thermal "Shaw" scalpel to be used in this situation. In cases where in advertent major vascular entry results, mass ligation or bypass techniques may be required to avoid exsanguinating hemorrhage. I have had covered stents placed in such cases where carotid exarterectomy may be required. This requires presurgical planning, the availability of consultant physicians, and appropriate vascular imaging studies to assess the feasibility of such endeavors.

Extra-anatomic bypass for malignancies, while technically possible, has generally failed to extend control of disease and has often eventuated in catastrophe. Such ultra radical technical exercises should be avoided in this patient population, particularly in view of their grave prognoses.

Implications for microvascular technique should be realized preoperatively. The use of proper vascular technique and instrumentation (Gerald forceps, Satinsky and other partially occluding vascular clamps, Prolene suture material, round bevel (RB) needles, etc.) should be used and suture ligation applied to all major vascular structures that are sacrificed in these efforts.

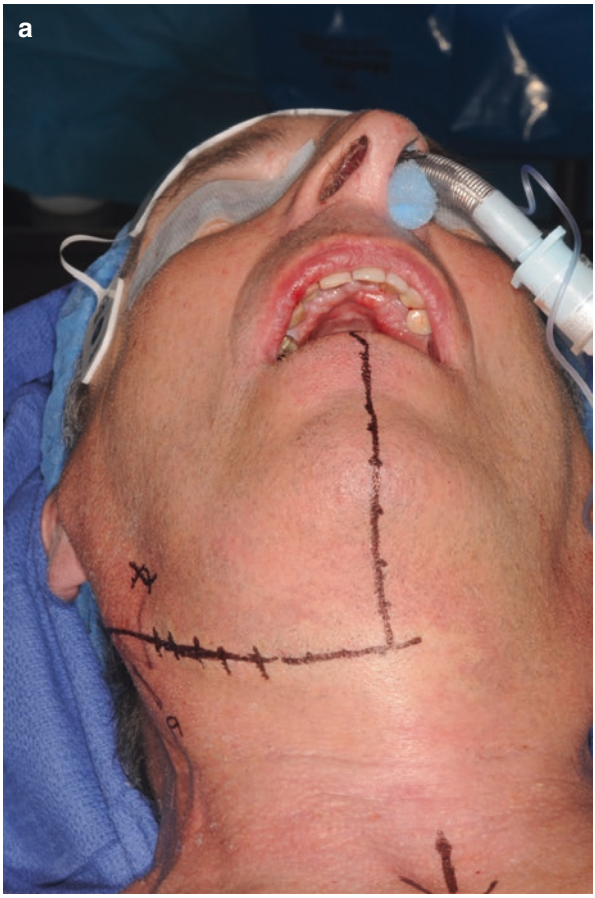
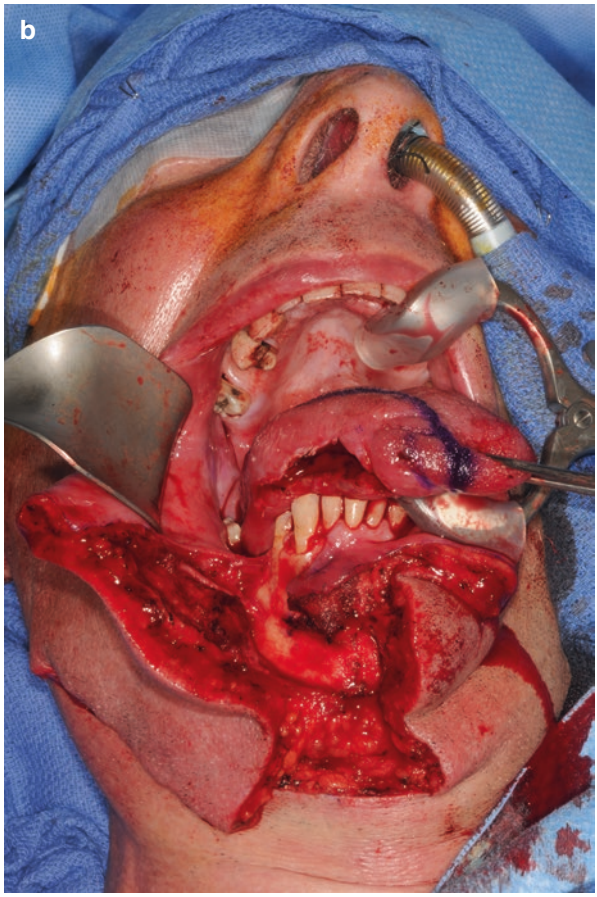


Fig. 10.1 *Patient 1*: (**a**) Incisional design for cheek flap and neck dissection procedures. This straight line, right angle at the level of the hyoid, will yield superior aesthetic results to all other designs. I had previously added an angle plasty to the cervical portion in order to discourage linear scar contracture, which never materialized, and which seemed to complicate wound healing. As the platysma is diastatic in the midline of many, this may be an explanation, as it is a watershed area in terms of vascularity. Designs, which curve into the neck portion characteristically, have a "trap door" or "pincushion" effect where upper flap edema persists and contributes an unnatural appearance and shadow. Incisions, which curve around the mentalis, tend to denervate that muscle on one side, resulting in abnormal dynamics in function. Radical salvage composite resection defect including upper neck skin. The treatment history rendered him vessel depleted in the search for recipient vessels. (**b**) Exposure for salvage hemiglossectomy – purple line denotes planned resection. (**c**) Hemiglossectomy defect. (**d**) Lateral arm flap reconstruction of glossectomy, inset, and closure. (**e**) Long-term peroral view, edentulous segment with osseointegrated implant in place, lateral arm glossectomy reconstruction. (**f**) Chronic trauma (protrusion) of the flap through edentulous segment led to fibromatous reaction which might resemble recurrent SCCA to some. This was treated with placement of the prosthodontic applicance, preventing protrusion. The area completely resolved over the following months. (**g–i**) Long-term aesthetic results after three surgical procedures, free flap reconstruction, RT, and CT. The patient remains active in the practice of law, his speech, articulation, and swallowing near-normal. He remains in NED status despite a PET scan that suggested recurrence in the interface tongue – likely representing actual relative hyperactivity in the retained native segment, relative to the hypometabolic fasciocutaneous flap

Fig. 10.1 (continued)



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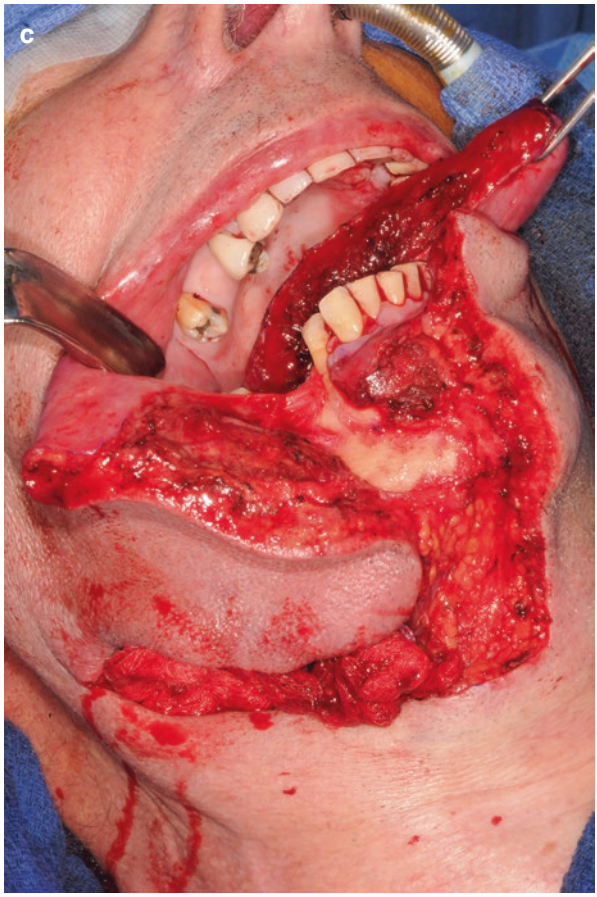

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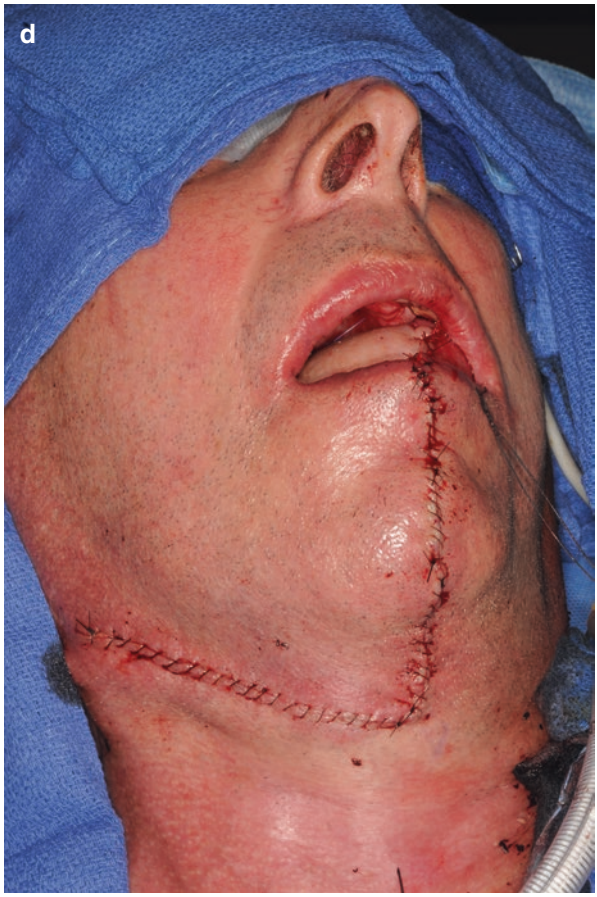

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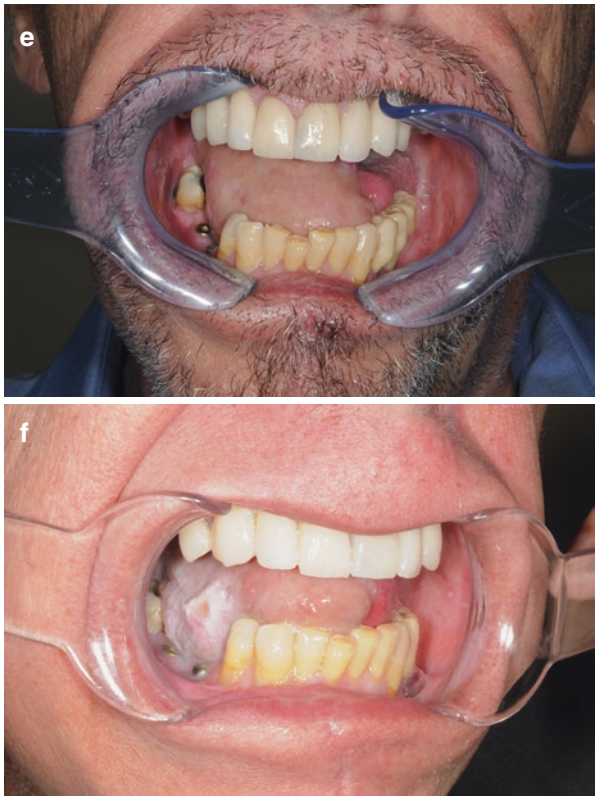

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10.1.7 The Role of Chemotherapy in the Treatment of Recurrent Oral Cavity SCCA

Active agents for palliative chemotherapy: Cytotoxic and targeted agents have shown activity in metastatic and recurrent head and neck cancer. Commonly used agents include platinum compounds (e.g., cisplatin, carboplatin), taxanes (docetaxel, paclitaxel), methotrexate, fluorouracil (5FU), and cetuximab, a monoclonal antibody that targets the epidermal growth factor receptor(EGFR). Small molecule tyrosine kinase inhibitors and checkpoint inhibition immunotherapy have shown activity in a second- or third- line setting.

The choice of therapy for patients with recurrent and metastatic head and neck cancer who have not received prior systemic therapy is dependent on the patient's performance status and comorbidities. For patients with good performance status, combined cytotoxic chemotherapy regimens, usually combining a platinum agent with a taxane or 5FU [1], show increased objective response rates compared to single-agent chemotherapy, although no improvement in overall survival has been demonstrated. However, the addition of cetuximab to cisplatin or carboplatin plus fluorouracil increased overall survival compared with cisplatin or carboplatin plus fluorouracil in a phase III trial [5]. In the study, chemotherapy plus cetuximab significantly prolonged overall survival compared with chemotherapy alone (median 10.1 versus 7.4 months, HR for death 0.80, 95 % CI 0.64–0.99). Small molecule tyrosine kinase inhibitors, gefitinib [2] and afatinib [3], have shown some activity in second- and third-line treatment.

Checkpoint inhibition immunotherapy: Multiple studies are ongoing in patients with advanced head and neck cancer with checkpoint inhibition. In a phase I/II study [4], in which 132 patients with advanced head and neck squamous cell carcinoma were treated with pembrolizumab (Keytruda – an anti-PD-1 antibody). In the study, 83 % of patients had received prior systemic therapy, and 59 % had received two or more regimens. Objective response rate was 25 %, and 56 % of patients had at least some evidence of tumor regression. Some of the responses were durable, and response rates were similar in those with HPV-positive and HPV-negative disease. Preliminary results of the recent international Phase III CheckMate 141 Trial examined the anti-PD-1 agent nivolumab (Opdivo) versus investigator's choice of cetuximab, methotrexate, or docetaxel in platinum-refractory head and neck SCCA were recently presented at the 2016 Annual ASCO Meeting [6]. The study was stopped early after increased overall survival (primary endpoint) was demonstrated. This class of drugs is of ever-increasing interest in the treatment of head and neck cancer after a decade (cetuximab the first targeted drug, and last FDA-approved, for HN SCCA, was approved for this indication in 2006) of limited progress in therapeutics for treating this previously hopeless, palliative-intent subset of unfortunate patients.

10.1.8 Perioperative Care

Aggressive attention to perioperative care is not insignificant in maximizing all efforts directed at such retreatment efforts and avoiding returns to the operative theater for related, avoidable complications. This includes the use of active suction drains, thoughtful placement, their meticulous post-op management, and the use of antibiotic mouth rinses to suppress oral flora during the healing of critical suture lines. Special attention to tracheotomy tubes, their maintenance, and the straps which secure them may avoid the occasional catastrophic obstructive or dislodgement event or flap outflow compromise.

10.1.9 Conclusion

While circumstances often appear dire, it is possible to achieve long-term control, effective palliation, and even cure (10–30 %) in these cases. More difficult is the unpredictability of which these outcomes will be the result of these substantial salvage efforts (Fig. 7–15). Patient selection is key, as is thoughtful planning and execution of surgery, particularly in preempting reconstructive catastrophes. The intersection of surgical palliation and decisions to proceed with nonsurgical approaches or end-of-life care and comfort measures requires a high level of experience and judgment. The mere technical ability to perform and reconstruct these challenging cases does not in and of itself justify their application in hopeless cases. Enthusiasm to treat must be tempered with reality-based and dispassionate decision making which is informed by realistic and measurable expectations and goals, all of which focus upon the patient and their needs, rather than reductively as a technically challenging "case."

Many of the principles contained herein apply equally well to cases where an adjacent second primary appears after the effective control of an index oral cavity primary or in the case of radiation-induced soft tissue sarcoma presenting after a long latency period.

10.2 Role of Radiation Therapy in Recurrent Oral Cavity Carcinoma

Nicholas J. Sanfilippo

Local recurrence of any solid tumor is a clinical dilemma for radiation oncologists. Oral cavity carcinoma is, however, particularly challenging given that radiation therapy (RT) has often been delivered during primary treatment and radiation tolerance of normal structures, including the mandible and spinal cord, at or near their tolerance limit. Still, the propensity of the disease to remain localized and cause debilitating symptoms and death offers a strong rationale to consider re-irradiation in selected patients at high risk for subsequent recurrence or progression (Figs. 10.2 and 10.3).

In the absence of prior RT, most investigators would consider adjuvant RT after surgical resection of a recurrence, even in the absence of high-risk features, as the recurrence itself is indicative of aggressive biologic behavior. If the lesion is believed to represent a new primary, it can be evaluated as such, using typical criteria for postoperative RT or chemoradiation (CRT). A more common and more complicated situation, however, arises when patients have already received RT to therapeutic doses of 50–60 Gy. Such cases require multidisciplinary discussion of the overall treatment goals and strategy to achieve them. Key factors to consider include resectability, pathologic features (if resectable), anticipated RT volume and critical structure dosimetry, disease-free interval, and the performance status of the patient. Specific indications for postoperative RT in resectable cases are unclear, but some data exist on the topic. De Crevoisier and colleagues (*Cancer*. 2001;91(11):2071–2076) reported on 25 patients

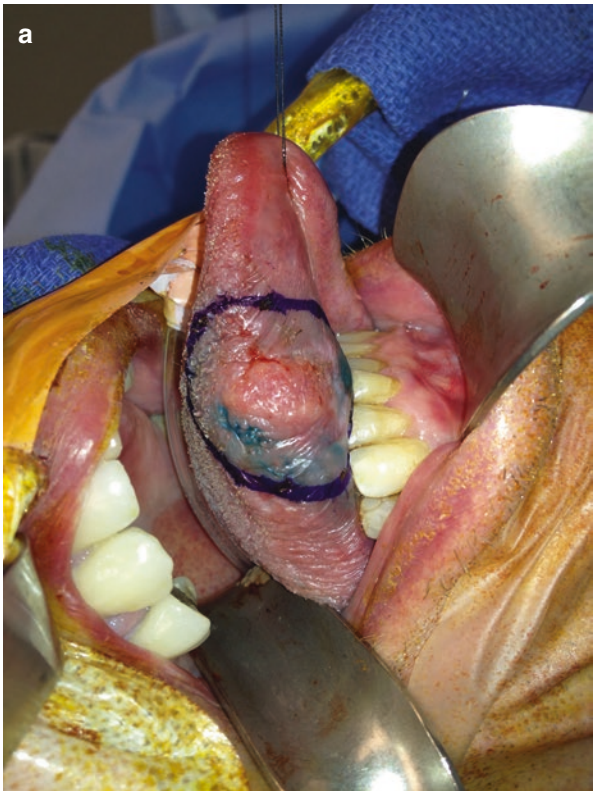

Fig. 10.2 *Patient 2*: (**a**) Right superior oblique view of recurrent T2N1M0 SCCA of the oral tongue, previously treated by surgery and adjuvant radiation. Recurrence at primary site as well as level I lymph node. (**b**) The level I node was adherent to the mandible. Salvage inferior mandibulectomy (as superior margin) for recurrence in neck soft tissues/lymph nodes after primary surgery, RT, and CT. Previous access incisions and intervening tissues must be included en bloc with the resection

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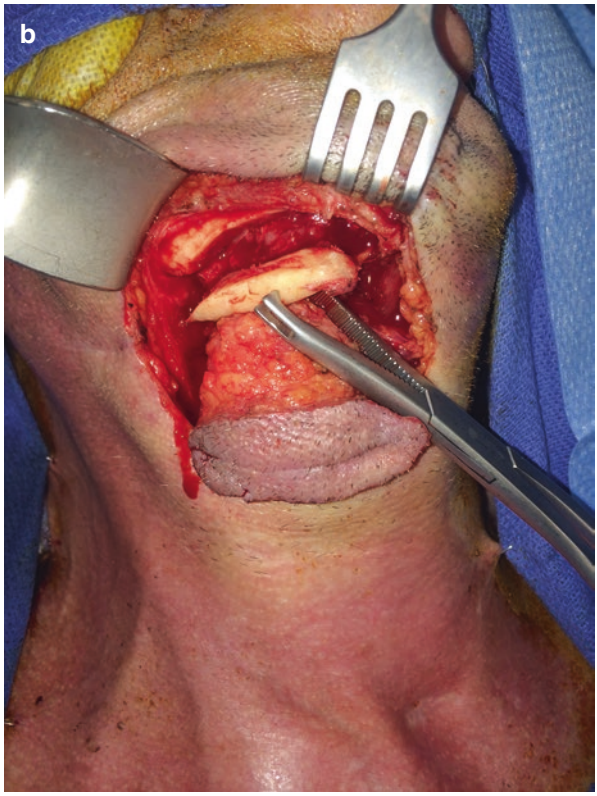

with recurrent head and neck cancer (any subsite) who received at least 45 Gy during primary therapy. Indications in this series were positive surgical margin or extranodal extension. Patients were treated postoperatively with 5-FU and hydroxyurea and concurrent RT to a total dose of 60 Gy. The patterns of failure were local only in nine patients, lymph node only two, local and lymph node only one, and metastatic in four. The 4-year survival rate after re-irradiation was 43 %. Sixteen percent had osteoradionecrosis and 40 % had late cervical fibrosis. Thus, moderate levels of local control and survival were achieved, albeit at the expense of substantial toxicity.

In the unresectable setting, the Radiation Therapy Oncology Group (RTOG) conducted a prospective study of re-irradiation with chemotherapy for recurrent head and neck squamous cell carcinoma (*Head Neck*. 2008 Mar;30(3):281–288). Eligibility included unresectable disease with >75 % of the tumor volume in tissue that received at least 45 Gy. Treatment included twice-daily RT (1.5 Gy per fraction) and concurrent hydroxyurea for 4 weekly cycles separated by 1 week of rest: a total of 60 Gy in 40 fractions. Radiation technique utilized parallel-opposed portals which were typically opposed laterals or obliques. Oral cavity lesions constituted 29.5 % of cases with oropharynx tumors representing 36 %. Seventy-nine of the 86 patients enrolled were

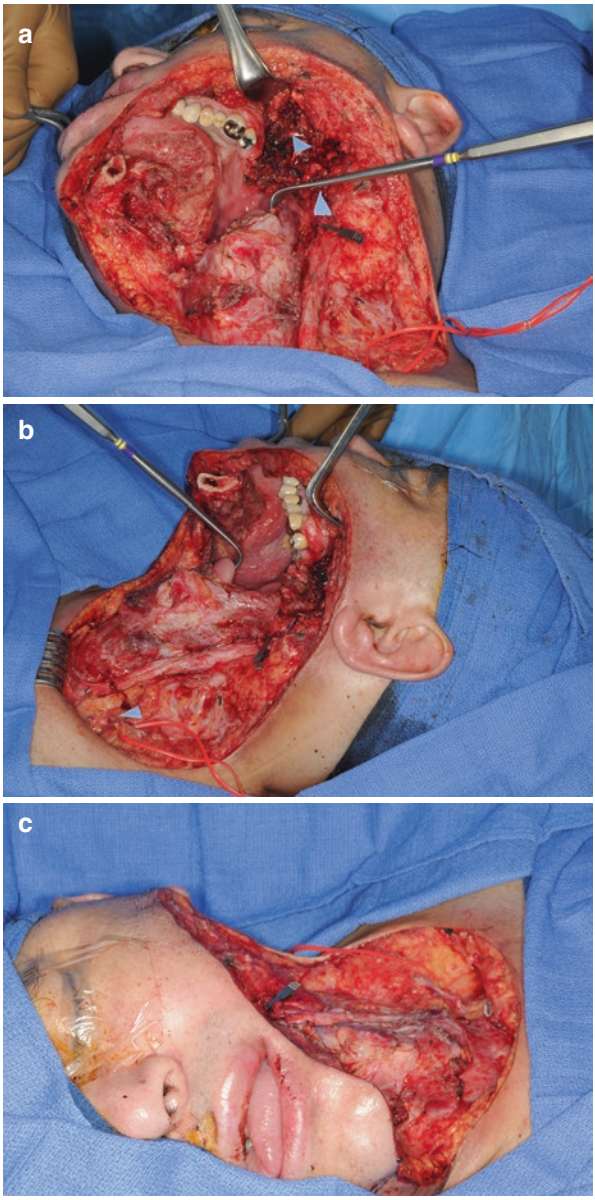

Fig. 10.3 *Patient 3*: (**a–c**) Recurrent carcinoma of left retromolar trigone involving mandible, overlying skin, and masticatory space; inferior, anterior, and lateral views of the surgical defect. (**d–f**) As previous surgery had depleted vessels in the neck, internal mammary artery was chosen as recipient vessel. A top-down view showing extrathoracic anastomosis of reversed saphenous vein graft to transposed internal mammary artery (IMA), self-retaining retractor at chest wall, "valley" cut in pectoralis major attachment to allow compression-free closure of skin over the interposition graft. Modified transverse rectus abdominis myocutaneous (TRAM) microvascular free flap final inset. Vertical component of abdominal flap closed in foreground, vertical thoracotomy incision joining neck incisions, adjacent to tracheotomy

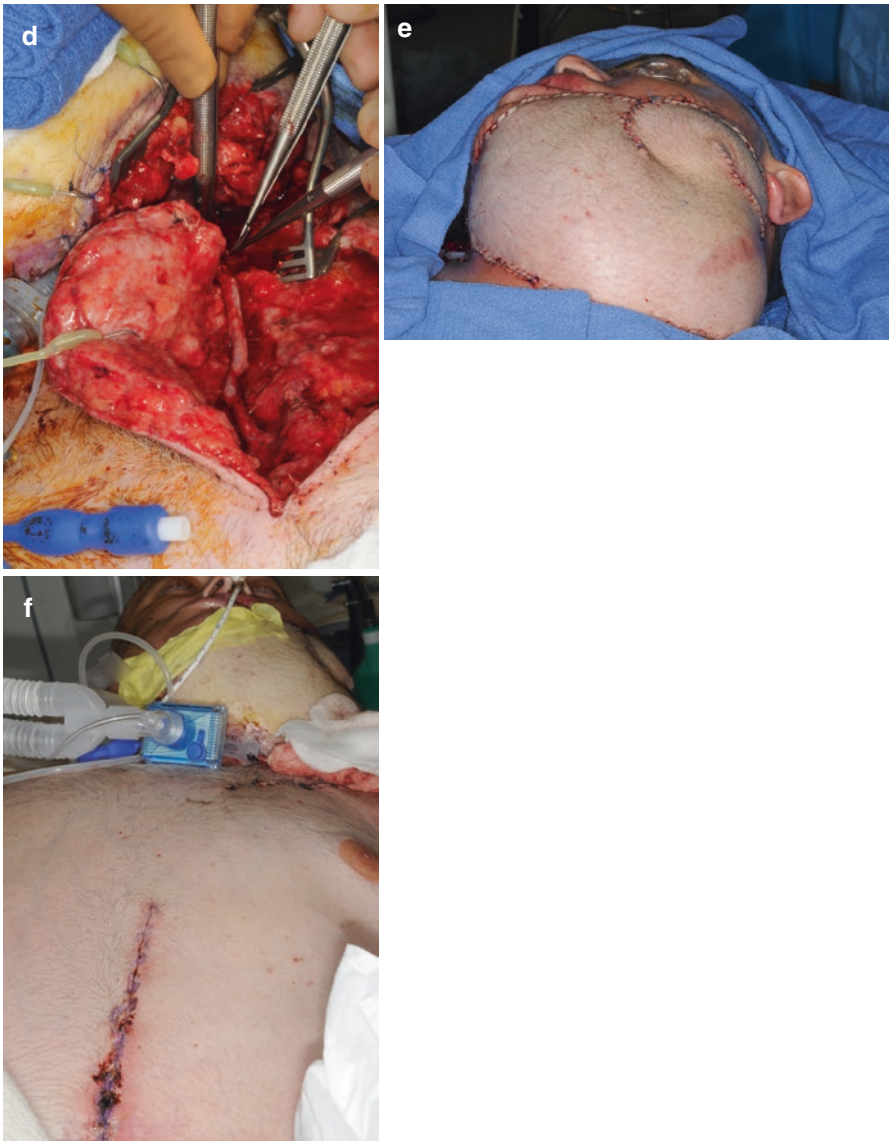

Fig. 10.3 (continued)

analyzable. The worst acute toxicity was grade 4 in 17.7 % and grade 5 in 7.6 %. Grade 3 and 4 late toxicities were found in 19.4 % and 3.0 %, respectively, and the estimated cumulative incidence of grade 3–4 late effects occurring at >1 year was 9.4. The estimated 2- and 5-year survival rates were 15.2 % and 3.8 %, respectively. Three patients were alive at 5 years. In a subsequent study, RTOG 9911, the same cooperative group tested the same re-irradiation regimen with concurrent low-dose cisplatin and paclitaxel. A total of 105 patients enrolled between 2000 and 2003 and 27 % had oral cavity recurrences. Median prior radiation dose was 65.4 Gy. Seventy-four percent of patients completed chemotherapy. Toxicities were pronounced, with grade 4 or worse acute toxicity occurring in 28 % and grade 4 or worse acute hematologic toxicity in 21 %. Eight treatment-related deaths (8 %) occurred: five in the acute setting, three late (including two carotid hemorrhages). Still despite these adverse events, estimated 1- and 2-year overall survival rates were 50.2 % and 25.9 %, respectively.

Advances in radiation treatment delivery, namely, intensity-modulated radiation therapy (IMRT), can mitigate concerns for toxicity as tumor dose escalation is possible while limiting normal tissue exposure. Duprez et al. (*Radiother Oncol*. 2014 Jun 111(3):388–392) reported on 60 patients treated with high-dose re-irradiation with IMRT. Patient characteristics were heterogeneous: oral cavity recurrences accounted for 25 % of cases, while oropharynx and sinonasal tumors accounted for 23 and 20 %, respectively. Treatment was similarly heterogeneous, with only 22 % having surgery prior to RT and 33 % receiving concurrent systemic chemotherapy. The median prescribed dose was 70 Gy in 35 fractions until 2004 and 69.12 Gy in 32 fractions afterward and the median cumulative dose was 132 Gy. With median follow-up of 18.5 months, actuarial 2-year locoregional control was 48 % and median overall survival was 9.6 months. Despite more sophisticated treatment technique, late toxicities were not insignificant. Twenty two (56 %) experienced late grade >3 toxicity, which included four deaths (grade 5) due to two cases of arterial rupture, one case of pneumonia, and one case of soft tissue necrosis and associated sepsis. The Dana Farber Cancer Institute also reported on 35 patient with recurrent or second primary head and neck cancer (*Cancer*. 2010 Oct 15 116(20):4761–4768) treated with IMRT and concurrent chemotherapy. Oral cavity tumors represented only 11 % of cases in this series. Treatments included surgery and postoperative CRT (49 %), definitive CRT (23 %), and induction chemotherapy plus CRT (28 %). Median follow-up was 2.3 years and 2-year actuarial overall survival and locoregional control were 48 % and 67 %, respectively. Four treatment-related deaths were observed including two aspiration events, one fatal oropharyngeal hemorrhage, and one infection. Overall 72 % experienced at least one grade >3 late toxicity with esophageal toxicity being the most common (17 cases, 49 %). Thus IMRT appears to increase feasibility of delivering full-dose re-irradiation in the setting of recurrence carcinoma with respectable rates of local control given the high-risk characteristics of these patients. Still, late toxicities are quite common despite more precise RT delivery, and further research is needed to improve the therapeutic ratio.

Brachytherapy (BRT) is another option that can be used for recurrent oral cavity carcinoma. Advantages are that radiation dose decreases dramatically as the distance from the radiation source increases, so a high dose can be delivered to a

small volume with limited dose to structures at greater distance from the sources. An obvious requirement for BRT is that the entire volume of tissue at risk must be accessible with intracavitary, or more likely, interstitial implantation. As recurrent cancers are often diffuse and infiltrative in nature, the radiation oncologists must be selective when considering BRT so as avoid underdosing tissue at risk if it is located even a small distance away from the implanted source. BRT can be done exclusively (*Int J Radiat Oncol Biol Phys*. 2001 Oct 1 51(2):354–362.) perioperatively with catheter placement at the time of tumor resection (*Arch Otolaryngol Head Neck Surg*. 1994 Sep 120(9):965–972), or in conjunction with external-beam RT with or without chemotherapy (*Radiother Oncol*. 1992 Jan 23(1):6–15). As seen in the external-beam experience in re-irradiation, case selection in BRT reports is not limited to oral cavity and typically includes a number of head and neck subsites with variable results. Strnad reported on 104 patients with recurrent head and neck cancer who were treated with interstitial pulsed dose rate brachytherapy. Head and neck subsites were mixed but oral tongue lesions represented 37.5 % of cases and floor of mouth 21 %. Salvage was done in 53/104 (51 %) patients. Salvage brachytherapy alone was administered in 81 patients (78 %), with a median total dose of 56.7 Gy. Salvage brachytherapy in combination with external-beam radiotherapy (EBRT) was performed in 23/104 patients (32 %). Simultaneously to PDR brachytherapy, concomitant chemotherapy was administered in 58/104 (55.8 %) patients. A single session of interstitial hyperthermia was also used to treat 33/104 (31.7 %) patients. With median follow-up of 60 months, local control rates at 2, 5, and 10 years were 92.5, 82.4, and 58.9 %, respectively. Local control was significantly improved with the addition of chemotherapy to BRT. Soft tissue necrosis or bone necrosis developed in 18/104 (17.3 %) and 11/104 (9.6 %) patients, respectively, but only 3 % of patients required surgical treatment. The superiority of these results compared to external RT is likely related to patient selection: tumors which are larger and in more precarious locations are less amenable to BRT and are more likely treated with external RT. Generally, the local control rates after salvage BRT in previously irradiated head and neck can vary widely between 14 and 90 % at 2–5 years which highlights heterogeneity of patient selection and treatment technique (*Laryngoscope* 112:1366–1371; *Laryngorhinootologie* 81:106–110; *Int J Radiat Oncol Biol Phys* 51:354–362; *Brachytherapy* 8:284–289; *J Otolaryngol* 36:327–335; *Cancer* 109:2052–2057).

Despite the aggressive nature of recurrent oral cavity carcinoma, a number of tools exist so that patients may achieve local tumor control and, in few cases, long-term survival. Salvage surgery should be employed whenever possible, and external RT, CRT, and BRT may be considered as salvage adjuvant retreatment techniques. In cases of unresectable disease, treatment is rarely curative, but medium-term (1–2 years) local control may be achieved and should be considered, especially in patients with good performance status. Precise indications for integration of surgery, RT, BRT, and chemotherapy are largely individualized and should be tailored to each patient's goals with a full discussion of anticipated acute and late toxicity.

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Biological Basis of Treatment Failure

11

Amritha Suresh, Ram Bhupal Reddy, Bonney Lee James, and Moni Abraham Kuriakose

11.1 Introduction

Despite aggressive multi-modality treatment, 50 % of oral cancers develop disease recurrence, a majority of them being at the primary site. PMID: 16731029, PMID: 25795179. However, with the intensification of locoregional therapy, especially with the use of postoperative adjuvant chemoradiotherapy, a higher proportion of disease failures is seen at the distant site PMID: 23079695, PMID: 20934766. Recurrent disease is often resistant to treatment and is often an indicator of incurability, especially in the case of patients with metastatic disease. Additionally, the mechanism of disease recurrence following surgery and chemoradiotherapy is different making it further difficult to manage the disease. It is thereby essential to understand the mechanisms of treatment response and recurrence post different modalities of treatment.

11.2 Mechanism of Local Recurrence After Surgery

Although surgery with positive margin is a strong predictor of local recurrence, negative margin does not usually, mean lack of disease relapse. This can be observed in cancers of the oral cavity, wherein, Over 50 % of the cancers, despite negative margin (R0 resection), develop disease recurrence PMID: 25376116, PMID: 15644773.

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Hockel and Dornhofer [1] have identified two patterns of local recurrences: those tumors that recur within the surgical site called "scar recurrences" and those that develop tissue adjacent to the initial tumor called "in situ recurrences."

Scar Recurrence The scar recurrence is a true local tumor recurrence when the minimal residual cancer after surgery regrows as recurrent tumor. As contamination of the surgical wound with tumor cells is a fairly common event, one would expect to see much higher incidence of local tumor recurrence than that observed clinically. Though incomplete removal of tumor may be the likely source of minimal residual tumor within the surgical bed, there exists an alternate hypothesis. It has been shown that the leaky tumor-associated blood vessels may favor reentry of circulating tumor cells (cancer stem cells) into the wound, thereby facilitating local recurrence [2].

The establishment of a relation between the minimal residual cancer and recurrent disease depends on the interaction of the tumor tissue with the surgical wound milieu. There is considerable similarity between wound healing and carcinogenesis; the factors that promote wound healing might also favor tumor growth PMID: 24415402.

The surgical wound healing progresses through four phases: coagulation, inflammation, proliferation, and remodeling. The coagulation and inflammation phase sets in during the first 72 hrs. The constriction of blood vessels and platelet plug leads to hemostasis-, while Neutrophils and macrophages are attracted to the field through the release of chemoattractants. This prevents infection, breaks down necrotic debris, and activates fibroblast response. The chemoattractants and pro-migratory factors may also attract cancer stem cells to the surgical wound, which are known to have receptors (CXCR2, CXCR4, CCR3, CCR4, CCR5, CCR7 and CCR10) for inflammatory cytokines [3].

The proliferation phase is between 72 hrs and 2 weeks. Activation of epithelial stem cells leads to the development of differentiated epithelial cells that promote healing of the epithelium. This process requires a concerted interplay between epithelial stem cells, fibroblasts and endothelial cells, a process similar to the one resulting in the activation of cancer stem cells in the tumor [4]. The fibroblasts and endothelial cells proliferate in the deeper tissue, with the collagen synthesized from the fibroblasts acting as a scaffold for further stromal regeneration. This granulation tissue, the term given to the newly formed connective tissue with new blood vessels, consists of capillary loops with leaky endothelium and collagen matrix. Various extracellular matrix degradation products and growth factors generated in the surgical wound can promote tumor cell growth. These include TGF beta, bFGF, EGF, PDGF, IL-1 and IL-6 [5]. In addition to this, the surgical wound milieu can promote epithelial-mesenchymal transformation (EMT) and angiogenesis which are important steps required for cancer development and progression [6] (Fig. 11.1).

The third phase of remodeling and maturation occurs between 2 weeks and several months. This process involves production of collagen and proteoglycan from the activated fibroblasts PMID: 24931397. During maturation phase, the fibroblasts disappear from the wound and are replaced by well-organized collagen scaffold.

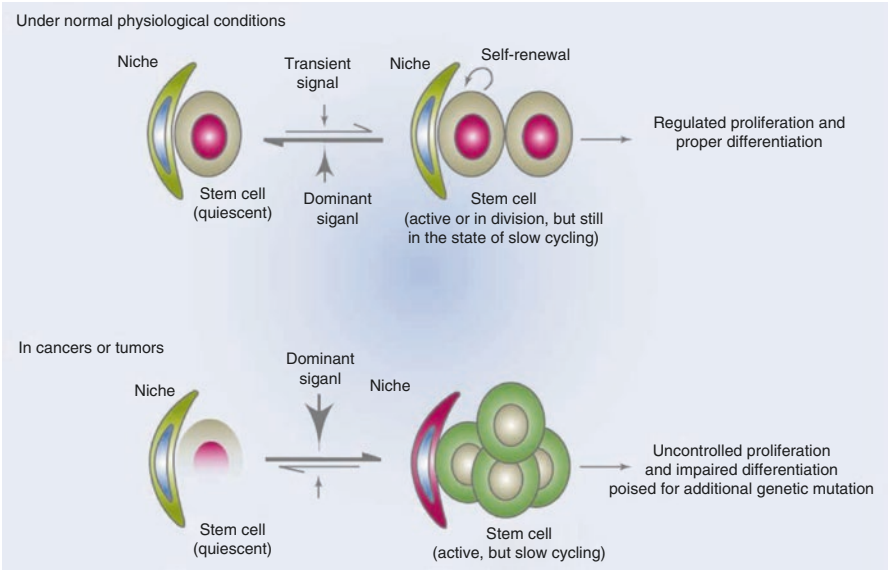

Fig. 11.1 From Li and Neaves [4]. Comparison of stem cell activation during wound healing and carcinogenesis (needs copyright approval)

In addition to the local wound milieu, immunosuppression observed during the postoperative period may contribute to the progression of minimal residual tumors into local recurrence.

In an experimental study in the hamster carcinoma model, surgery has caused increase in the incidence of cancer development. It is also speculated that surgical intervention of oral leukoplakia may increase the incidence of carcinogenesis within the lesion compared to observation [7]. The possible mechanisms of tumor initiation in the field surrounding the tumor, CSC-mediated and otherwise, have been detailed in other chapters (Chapter 1 and Chapter 14).

11.3 Biologic Basis of Tumor Recurrence Following Genotoxic/Cytotoxic Chemoradiotherapy

Recurrence post chemo-radiotherapy, as is the case of surgery, also signifies the escape of the cells from treatment. Although, in this case, the cells escape from the chemotherapy insult by adopting multiple cellular and molecular pathways. Treatment failure post chemo or radiotherapy, is hence, primarily dependent on the underlying molecular profile; a deeper understanding of the mechanisms of drug action and the targeted pathways is mandatory if resistance-response patterns are to be understood. The redundancy of most molecular pathways, a feature adapted to maintain major functions of the body, is also the tool adopted by the cancerous cells to escape the inhibitory effects of cytotoxic or targeted therapy, leading to resistance and treatment

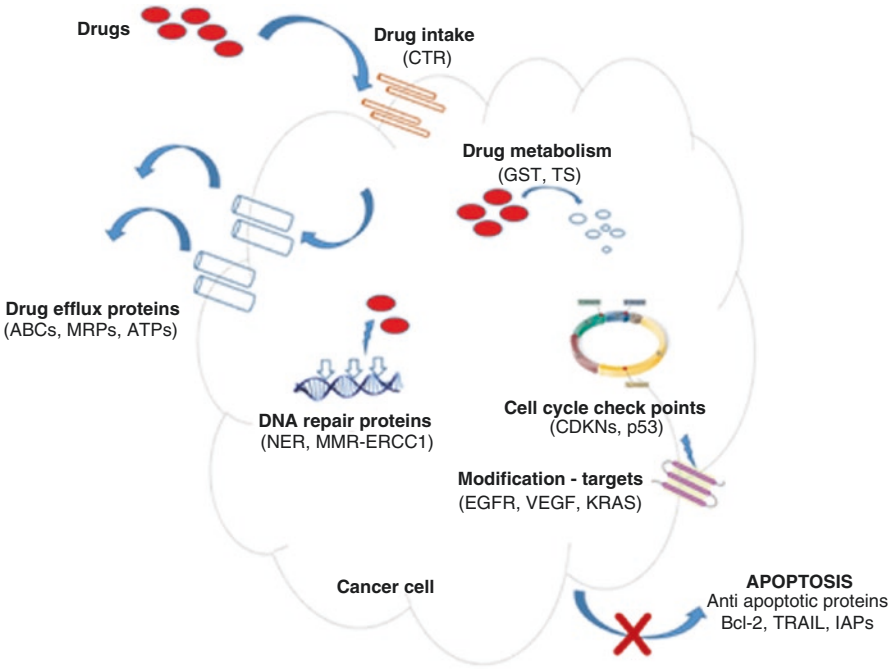

Fig. 11.2 Mechanisms of drug resistance to genotoxic/cytotoxic therapy. The levels at which resistance to cytotoxic therapy is achieved by the cancer cells are elucidated

failure. An understanding of the major pathways that contribute toward drug resistance may enable selection of patients based on the molecular profile of the patients, activity of the targets, and other associated biomarkers, thereby improving treatment outcome.

Genotoxic and/or cytotoxic therapy forms a major approach toward cancer treatment and along with targeted therapy has contributed towards improving the survival rates of cancers including oral cancer. Nevertheless, drug resistance is a major challenge, and studies down the decades have documented many molecular players that affect the process (Fig. 11.2).

11.3.1 Molecular Basis of Drug Resistance

Cancer cells adopt varied mechanisms (Fig. 11.2) to evade the cytotoxic action of the chemotherapeutic drugs administered to the patients. These operate at multiple levels that work either individually or in combination toward providing an escape route to the cells from drug action. Resistance to genotoxic drugs is reported to be achieved by several methods such as DNA repair, drug efflux, metabolism and anti-apoptotic machinery in addition to other approaches like p53-dependent ER/Golgi

pathways, epigenetic modifications of HDAC and transcription of alternative splice forms that enable the cells to escape targeting by the drugs [8].

Uptake and Efflux of the Drug The primary and first level of resistance mechanisms involves decreasing the uptake of the drug as well as facilitating their increased efflux out of the cell PMID: 25757878, PMID: 2564628. The latter is facilitated by the increased expression of several drug transporters such as the MRPs, ABC family genes and ATP7 PMID: 16815813. In case of cisplatin, the intake controlled by CTR1 while the efflux is regulated by ATP7A and ATP7B, the expression levels of these transporters, hence play a major role in the availability of the drug within the cell.

Alteration of Targets The next level at which cells can acquire resistance to the drugs that are administered is by alteration of targets; these can be modifications in microtubules/associated proteins (taxanes), thymidylate synthases (5-FU), or specific molecules as in the case of targeted therapy. Taxanes are known to induce polymerization of microtubules and thereby causing a G2/M phase arrest in the cells PMID: 24306928; modifications in tubulin proteins (mutation/expression) itself, regulation of the microtubule-associated proteins (MAPs), and posttranslational modifications of tubulin are known to contribute toward taxane resistance PMID: 22390762, PMID: 18068131, PMID: 11728383.

Deregulation of DNA Repair Pathways Platinum-based drugs act by generating DNA adducts PMID: 24810023, PMID: 24510227; the effect of this targeted action is nullified due to an increased expression of DNA repair genes PMID: 22659329. XRCC, ERCC and MLH families of genes involved in nucleotide excision repair and are known to be a major causal factor behind cisplatin resistance in the cells PMID: 20189873. DNA polymerases such as POLH and POLB involved in translesional replication, a repair process that facilitates replication past the lesions that are present on the DNA (thymidine dimers), are another class of molecules that can help to alter or bypass the cytotoxic action of the drugs.

Drug Metabolism Another level of resistance mechanism adopted by the cancer cell is with regard to the drug metabolism by detoxifying enzymes. Glutathione transferases (GST), superoxide dismutases (SOD) and myeloperoxidases are enzymes that regulate the levels of the drugs in the cell thereby contributing toward the resistance of the cell PMID: 25372413.

Anti-apoptotic and Cell Cycle Check Points The final consequence of the resistance mechanisms adopted by the resistant cell is prevention of apoptosis and continued proliferation. At this level, differential expression of proapoptotic (p53) and antiapoptotic molecules (Bcl-XL) in combination with the cell cycle proteins (CDKs and ATR) further ensures that the cancer cell maintains its resistant property PMID: 14576837, PMID: 17848273, PMID: 16020667.

11.3.2 Markers of Resistance/Response

11.3.2.1 *In Vitro* Evidence

Studies using cell lines have been invaluable in providing information with regard to the molecular basis of drug resistance in most solid tumors. Studies in HNSCC cell lines have identified several classes of genes as paramount in drug resistance. Global transcript profiling of sensitive and resistant cell lines identified MMP-7 and MMP-13 as important for intrinsic cisplatin sensitivity (ICS) [9]. Correlation of marker profiles between the cisplatin-sensitive and resistant cell lines also indicated a deregulation of markers involved in DNA repair (RECQL, [10]; PMID: 25327479), cell cycle (CCND1, CCND3) [11] and miRNA profiles [12]. Studies in cell lines have implicated other pathways involved in EMT and metastasis (Twist-miR181-a; MACC1, YAP1), glucose transport (GLUT1) and CSC marker (CD147, CD44) [PMIDs: 25846049, 25501015, 24148247, 25421538, 25327479, 23617290, 23413783]. EGFR is another molecule that has been identified to influence the resistance to the TPF regimen *in vitro*; knockdown of the molecule in cell lines increases sensitivity to the drugs [13]. TPF-resistant cell lines are also known to overexpress markers of cell cycle regulation (survivin), DNA repair (ERCC1) and MDR (MDR1 and PgP-2) [14]. *In vitro* studies have also revealed the HNSCC cells with varied genetic background may need modified approaches; cells with mutant p53 can be sensitized to cisplatin by inhibition of checkpoint kinases such as Wee-1 [PMID: 25504633] (Tables 11.1 and 11.2).

11.3.2.2 Correlation of Molecular Evidence with Survival and Prognosis

In vitro studies are extremely valuable in terms of delineating the underlying mechanisms of drug resistance; nevertheless, assessment of patient-related data and clinical trials have provided essential information with regard to the correlation between the markers and treatment response. These studies have emphasized on the prognostic role of sequence based alterations, expression of transcripts/proteins regulating cell cycle, apoptosis and DNA repair.

Alterations in p53, one of the most prevalent in HNSCC, as per The Cancer Genome Atlas (TCGA), have been identified as prime in resistance to drug. Assessment of loss of heterozygosity (LOH) and microsatellite instability (MSI) in HNSCC patients, identified LOH at 9p or 17p (location of p53) to be significantly associated with drug resistance, LOH at 17p being predictive of low response to platinum-5-FU chemotherapy [15]. Mutations in exons 4–9 of p53 were of high prevalence in HNSCC (~68 %) with these patients showing no response to neoadjuvant therapy [16], mutations being more specifically predictive of response in patients with laryngeal [17] and maxillary squamous cell cancers [18]. Alterations in the codon 72 of p53, encoding either arginine (72R) or proline (72P), effect response to cisplatin; patients with 72R showing extremely low response rates [19].

Expression of p53 (at protein level) in combination with thymidylate synthase (TS) and GST-pi also significantly correlated with response and survival to cisplatin-based neo-adjuvant chemotherapy NACT [20]. Immunohistochemical levels of

Table 11.1 Markers of resistance/sensitivity toward chemotherapy in head and neck cancer

Sl No	Marker	Alteration	Drug	Resistance	Sensitivity	Evidence level
	Mutation					
1	MMP3	1612ins A	Cisplatin-5Fu		+	P
2	p53	72R	Cisplatin	+		P
3		Exon2-4	NACT	+		P
4	p53	Mutation exon 4–9	Platinum	+		P
5	LOH 17p/9p		Platinum, 5-FU	+		P
6	ERCC1	Exon2–4	Cisplatin	+		In vitro
	Expression					
10	p53	High expression protein	Platinum	+		P
11	CCND1	High expression	Cisplatin	+		In vitro
12	EGFR	High expression	TPF	+		In vitro
13	c-erbB2	High expression	TPF	+		P
14	SNAIL	High expression	Cisplatin	+		In vitro
15	XPF4, ERCC4	High	TPF	+		P
16	Bcl2, XIAP	High	Platinum	+		P
17	Pgp, MDR1, MRP	High	Platinum	+		P
18	CD44, CD133	Expression	TPF	+		P
20	Thymidine phosphorylase	Low	TPF		+	P
21	GST-pi	High-expression protein	Platinum	+		P
22	Acetylated tubulin	High	TPF	+		P
23	GDF15	Low	TPF		+	P
24	Annexin	Low expression	TPF		+	Patient data
26	miR 100, miR-130a, miR-197	Low	Cisplatin	+		In vitro
27	miR-101m, miR-181b, miR-181d, miR-195	High expression	Cisplatin			In vitro
28	miR34a	Downregulation	Cisplatin	+		Patient data

TPF cisplatin, taxol, 5-FU, *P* patient data

Table 11.2 Markers of resistance/sensitivity toward targeted chemotherapy in head and neck cancer

Sl No	Marker	Alteration	Drug	Resistance	Sensitivity	Evidence level
	EGFR inhibitors					
1	EGFR-T790M, T590M	Mutation exon 20	Cetuximab		+	In vitro, In vivo
2	EGFR-T790M, T590M	Mutation exon 20	TKI	+		In vitro, in vivo
3	KRAS	p.Gly12Val	Cetuximab + RT	+		Patient data
4	G2607A	Mutation exon 20	TKI		+	Patient data
5	PP2A	Low	Cetuximab	+		In vitro
6	CIP2A	Overexpressed	Cetuximab	+		In vitro
7	NF1	Low	Cetuximab	+		In vitro
8	DUSP5	Low	Cetuximab	+		In vitro
9	VEGF, IL6	High (serum)	Cetuximan + platinum/taxol	+		Patient data
10	p21	High	Erlotinib	+		Patient data
	COX-2 inhibitors					
1	PGE2	High expression	NSAIDS		+	Patient data
2	PPAR-gamma	Low	NSAIDS		+	Patient data
3	EGFR	High expression	Celecoxib + erlotinib		+	In vitro + patient data
4	pERK	High expression	Celecoxib + erlotinib		+	In vitro + patient data
5	pS6	High expression	Celecoxib + erlotinib		+	In vitro + patient data
6	pAKT	High expression	Celecoxib + erlotinib		+	In vivo *and* in vitro
7	pSTAT3	High expression	Celecoxib + erlotinib		+	In vivo *and* in vitro
	mTOR inhibitors					
1	PTEN	Knockdown	Rapamycin		+	In vitro data
2	VEGF	High expression	Rapamycin + erlotinib		+	Patient data
	VEGFR1, IGN-gamma	High expression	Sirolimus + erlotinib	+		Patient data
	Bcl-2, MDR1	Absence	Rapamycin		+	In vitro data

GSTs when scored against chemotherapy response of patients showed that overall response rate (CR + PR) in patients with low GST was 88 %, while those with high GST scores only showed 19 % response ($p = 0.0001$). Among the subset treated with NACT, 100 % response was observed in GST low patients, while in patients treated with chemotherapy for relapsed disease, the response rate was 70 % [21]. When the genes involved in thymidine synthesis and metabolism were assessed for their association with response to combination therapy (radiation with induction CT of platinum/5-FU or concurrent platinum therapy), it was observed that lesser percentage of cells with nuclear thymidine phosphorylase (TP) in pretreatment biopsies was associated with high rate of complete response (CR). These patients also showed a high relapse-free survival ($p = 0.001$) [22].

Multidrug resistance proteins, MDR1 and MRP, are associated with resistance to therapy in oral cancer; expression of these proteins was high in the nonresponders as compared to responders in patients with tongue cancer [23]. Another study reported the induction of PgP by radiation and may explain the low response rates of patients who are subjected to concurrent chemotherapy [24]. Assessment of patients with advanced cancers of the head and neck also showed that nonresponders had a high expression of PgP and MDR-3 [25].

Markers of DNA repair are extensively correlated to treatment response; studies associating response to molecular profile in patients showed that increased co-expression of SNAIL and ERCC1 (SNAIL is a known activator of ERCC1) contributes toward resistance to cisplatin and was also found to correlate with prognosis in patients with HNSCC [26]. Expression of ERCC1 along with Bcl-2 and other multidrug-resistant genes (MDR-1, MRP-1 and ATP7B) were downregulated in recurrent maxillary disease [18]. Analysis of ERCC1 alterations at mutation, protein and transcript levels indicated an increased association with treatment outcome. In patients treated with adjuvant cisplatin-based chemoradiation, high IHC scores (H-score) of ERCC1 protein correlated with response and survival [27]. Further, in patients treated with cisplatin-based induction therapy followed by concurrent chemoradiation, low immunohistochemical levels of ERCC1 correlated with increased 12-month disease-free (73.3 % vs. 42.3 %, $p < 0.001$) and overall survival [28]. Other members of the ERCC family, XPF, or ERCC4 levels in IHC are also shown to correlate with progression-free survival in patients treated with DNA-damaging agents [29].

Deregulation of cell cycle and apoptotic proteins plays a major role in carcinogenesis as well as resistance to drugs. In patients exposed to neoadjuvant therapy (cisplatin based), low CCND1 expression indicated better response ($p < 0.0001$) with significantly better OS and DFS (73 % vs. 8 %, $p < 0.001$; 63 % vs. 6 %, $p < 0.001$); there was no correlation in patients treated with surgery and radiation indicating that this marker might be predictive in selecting patients for NACT [30]. Tumors treated with cisplatin, positive for the apoptotic protein, Bcl-2, prior to treatment had a high risk of treatment failure with high hazard ratio (hazard ratio, 5.99; 95 % confidence interval, 1.73–20.8; $P = 0.0014$) [31]. Studies have also shown increased expression of the Bcl-XL to correlate with low DFS in patients with advanced disease [25]. X-linked inhibitor of apoptosis (XIAP) was also

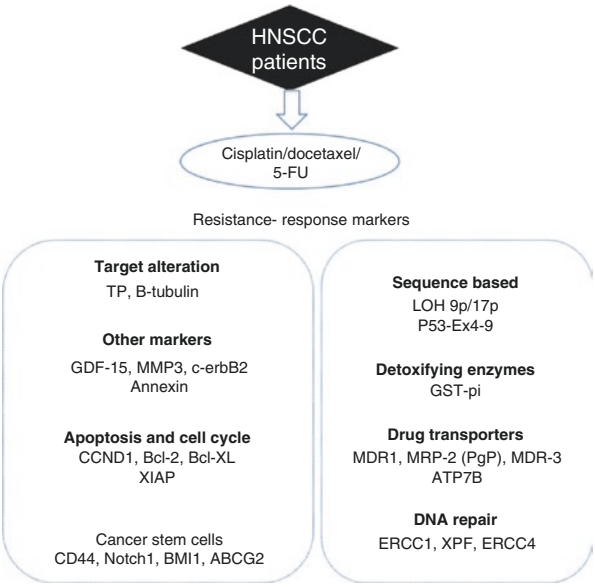

Fig. 11.3 Cytotoxic Therapy markers: Markers associated with resistance and response to cytotoxic therapy in head and neck and oral cancer markers identified in HNSCC to be associated with treatment response and prognosis are listed

associated with resistance to cisplatin ($p = 0.036$) and outcome. Additionally, it was observed that the expression of this gene was further induced in patients exposed to the therapy, which lead to a poorer outcome in this subset [32].

Alterations in the targets of the cytotoxic agents are a major mechanism of drug resistance adopted, especially in cases of taxanes. Increased expression of acetylated tubulin is known to correlate with occurrence of lymph node metastasis in HNSCC patients treated with docetaxel along with cisplatin and 5-FU. Extensive evidence correlating tubulin modifications with taxane resistance is available in other cancers; β-tubulin mutations in serum DNA were associated with paclitaxel resistance in non-small cell lung cancer (NSCLC) [33].

Many other markers have shown correlation with treatment response; polymorphisms in matrix metalloproteinase 3 (1612insA) promoter; 6A/6A genotype (wherein both the alleles have 6 adenosines at the position due to the insertion) was an independent response factor for patients treated with 5-FU-cisplatin therapy as compared to 5A/6A (heterozygous with one allele having no insertion) or 5A/5A genotypes (wild type allele with no insertions at the position) [34]. Other studies in patients, treated with 5-FU or cisplatin and paclitaxel, have shown increased expression of c-erbB2 to correlate with progression-free and overall survival [35]. Among other markers, downregulation of miR34a, involved in regulation of silent information regulator 1 (SIRT1) and thereby p53, was associated with poor DFS and local control rates in HNSCC patients treated with cisplatin [36] (Fig. 11.3).

The TPF combination therapy regime is considered as the gold standard of induction chemotherapy in head and neck cancer, but resistance to this regime has also been a major challenge. In patients with clinically positive nodes (clinically node positive, cN+), high cyclin D1 expression was shown to predict benefit from

addition of TPF regimen to standard treatment [37]. Expression of growth-dependent factor (GDF15) is shown to correlate with poor prognosis in patients treated with TPF therapy [38]. Low GDF predicts good overall as well as distant metastasis-free survival in these patients. Other studies in TPF-treated patients, evaluating marker correlation with response, indicated that acetylated tubulin (AT), annexin (low) and CDK1 (high) were predictors of response [39, 40]. In advanced recurrent patients treated with taxol and platinum, low levels of ERCC1 and increased RASSF1A were predictive of good prognosis [41]. Molecular profiling of oropharyngeal patients in the TAX324 trial (comparing TPF against PF in locally advanced HNSCC) showed that low beta tubulin II (beta T-2) was predictive of therapy benefit [42]. Categorization of the oropharyngeal patients of this trial based on their HPV status indicated that the presence of a specific molecular profile (high beta T-II, GST-pi and p53 along with low Bcl-2) was predictive of survival rates when treated with TPF/PF [43]. This observation emphasized the significance of risk stratification prior to treatment selection. A concept further gaining significance is the role of cancer stem cells in imparting drug resistance in cancers including head and neck cancer; studies have shown that in patients treated with the TPF regimen of drugs, expression levels of CD44, BMI1 and Notch1 correlated with recurrence. In resistant patients, a consequent enrichment of these markers posttreatment is a further indicator of poor response [44]. This aspect of the CSC-mediated drug resistance has been discussed in detail in the chapter 14.

11.4 Resistance to Targeted Therapy

Targeted therapies currently under investigation in HNSCC include anti-EGFR therapy (cetuximab), anti-VEGF (bevacizumab), and anti-COX-2 (celecoxib) [45–51]. Despite the advantage of targeting molecules/their alterations highly prevalent in head and neck cancer and being extremely specific to the cancer cells, these targeted therapies, in most cancers, including HNSCC fail to provide high rates of response in the patients. Unlike in the case of cytotoxic chemotherapy, in these cases, the resistant mechanisms are more pathway-specific and thereby unique to each targeted therapy.

11.4.1 Anti-EGFR Therapy

11.4.1.1 EGFR Pathway

EGFR, 170 KDa cell surface receptor protein with extracellular ligand binding and an intracellular domain with tyrosine kinase activity [47], aids in the normal development and proliferation of epithelial tissue and is found to be overexpressed in 80–90 % of head and neck cancer. EGFR overexpression, correlated with reduced survival, poor prognosis, and aggressive disease [52], is reported to be responsible for cell proliferation, differentiation, antiapoptotic signaling, angiogenesis and metastasis in various malignancies. EGFR is activated through ligand binding which

leads to autophosphorylation of the tyrosine kinase domain. The various EGFR ligands are TGF-α, amphiregulin, epiregulin, EGF, epigen, betacellulin and heparin-binding EGFR. The EGFR pathway has different signaling routes: P13K-PDK1-AKT, Ras-Raf-MEK-ERK (mediates transcription and activates other proteins), PLCγ-PKC (cell cycle progression), and JAK-STAT (cell proliferation, survival, transformation) [53, 54] (Fig. 11.4).

11.4.1.2 Markers of Resistance to Anti-EGFR Therapy

Targeting EGFR pathway, in patients wherein it is dysregulated, is hence considered a viable therapeutic option due to its increased prevalence in the patients as well it is functional relevance. The approaches towards EGFR targeting includes i) blockage of ligand binding using monoclonal antibodies (Cetuximab and Panitumumab) ii) blockage of its TKI domain (Geftinib, Erlotinib) activity thereby blocking the downstream signaling molecules. Nevertheless, the response rates in patients to these various therapies ranges between 10–40%, either due to primary or acquired resistance. The possible resistance mechanisms for EGFR therapy include mutation of EGFR, oncogenic shift or activation of a bypass pathway, and/or due to modification of any pathway/molecule essential for EGFR TKI-mediated apoptosis [55] (Fig. 11.5).

Targeting the EGFR protein is primarily through the use of monoclonal antibodies; Cetuximab and panitumumab are used for blocking the ligand binding to the receptor; they bind with a higher affinity as compared with the regular ligands. Cetuximab binds specifically to the extracellular domain [56]. Correlation of the

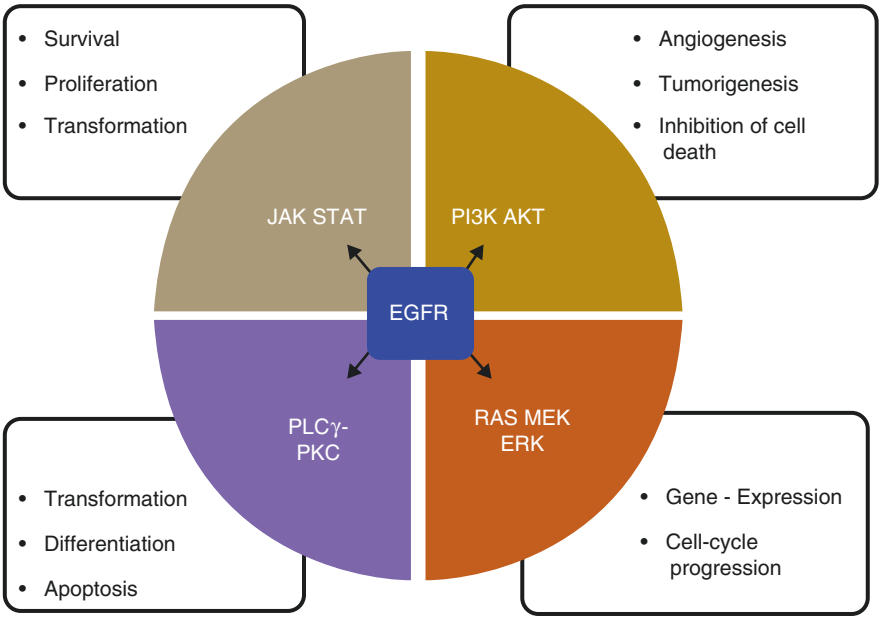

Fig. 11.4 EGFR signaling routes and the resulting downstream processes (From Loeffler-Ragg et al. [47])

marker profile with response to the drug indicated that expression of EFGR protein was indicative of response in the trials such as E2303 [Eastern Cooperative Oncology Group (ECOG)], Erbitux in First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer (EXTREME), and Cetuximab combined with Irinotecan in first line therapy for metastatic colorectal cancer(CRYSTAL) carried out in patients [57, 58]. Further assessment of the patients identified extracellular ERK1/2 and activated RAS/MAPK/ERK and/or PI3K/AKT pathways as indicative of PFS and OS [59]. However, marker evaluation in EXTREME trial patients showed no association of EGFR copy number with response in metastatic patients [60, 61]. Studies also revealed that serum biomarkers (VEGF, IL-6) were associated with response to cetuximab combination therapy with platinum/taxol) [62]. KRAS mutation (p.Gly12Val) and somatic EGFR mutation located in exon 19 is also suggested to contribute to the limited clinical response to cetuximab therapy in combination with radiotherapy; in the same study, high EGFR expression was indicative of increased treatment response [63]. Additionally, mutation in the 3′ UTR of KRAS have been associated with treatment response; patients (recurrent/metastatic HNSCC with mutation in 3′ UTR KRAS) showed improved response when treated with cetuximab and platinum as compared to cisplatin treatment alone [64].

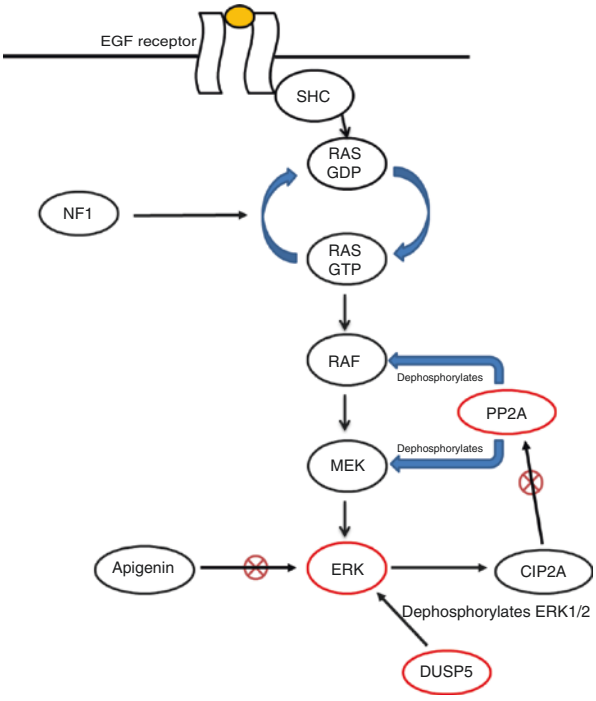

Fig. 11.5 Markers of resistance and response to EGFR therapy. The primary EGFR pathway is shown in addition to the associated molecules that might be involved in resistance to the drug. The markers with clinical evidence are indicated in *red*

Various *in vitro* studies have also established the role of the other molecules that contribute towards resistance to anti-EGFR therapy using monoclonal antibodies. Increased expression of CIP2A (cancerous inhibitor of PP2A), observed in HNSCC and colon cancer [65, 66], is suggested to be indicative of resistance to anti-EGFR therapy. CIP2A inhibits PP2A (protein phosphatase 2A) which, in normal cells, inhibits phosphorylation of RAF/MEF and thus controls the signaling downstream to EGFR. Neurofibromin 1 (NF1) is another molecule that converts activated RAS-GTP to RAS-GDP and thus bypasses the EGFR-mediated downstream signaling [67–69]. Dual-specificity protein phosphatase 5 (DUSP5) is a negative regulator of ERK1/2, inactivating the molecule by dephosphorylation; downregulation of the molecule might be indicative of resistance [70, 71], suggesting that resistance to cetuximab can be treated with ERK inhibitor apigenin. PI3K/mTOR inhibitor PF-05212384 (PKI-587) enhances sensitivity to cetuximab *in vitro* and this combination inhibits cell survival, impairs activation of signaling pathways and induces apoptosis in head and neck cancer models [72]. Aurora Kinase A and B are serine/threonine kinases reported to be involved in mitosis, are upregulated in HNSCC tumours. A T91A polymorphism in Aurora kinase A (AurkA) is found to impart resistance to Cetuximab; an *in vitro* study showed that HNSCC cell lines CAL27, UD5 and UD7 which do not show this polymorphism are sensitive to Cetuximab treatment whereas cell lines such as HN, UD3 and UD4 with the polymorphism were resistant to the drug [73]. This study further showed that combining Cetuximab with siRNA silencing of AurkA and AurkB increased the apoptotic rate as compared to Cetuximab alone. A validation of these markers in patients is mandatory to establish their clinical relevance.

Tyrosine kinase inhibitors such as gefitinib, erlotinib and lapatinib hinder the phosphorylation of EGFR. The patients show comparatively high response rates initially, but a majority of them relapse within a year. Studies have shown a correlation of p21 expression with response to erlotinib in nonmetastatic HNSCC patients [74]. *In vitro* evidences have correlated acquisition of EMT characteristics with resistance to TKIs, though a validation in patients is warranted [75, 76]. The resistance was caused due to an acquired T790M mutation in the gene, which reduces the binding affinity to the drug while preserving the catalytic site [77].

These evidences point indicate that targeting the EGFR pathway, though a beneficial approach, needs to adopted in context with the patient molecular profile. This will enable administration of the treatment to the patients who have a increasing chance of treatment benefit. In additionally, the evidences also suggest the need of targeting multiple molecules/pathways, based on the patients molecular profile, as a step towards reversing the resistance to the drugs.

11.4.2 Cox-2 Pathway (Celecoxib/NSAIDs)

11.4.2.1 COX-2 Pathway

Cyclooxygenase (COX) is one of the major enzymes involved in the conversion of arachidonic acid (AA), a polyunsaturated omega 6 fatty acid present in the

membrane phospholipids of cells into prostanoids (prostaglandins, prostacyclins, and thromboxane). There are two enzymes involved in the conversion of AA, namely, COX-1 and COX-2. COX-1 (constitutively expressed) is involved in the production of all the prostanoids, while COX-2 (inducible) is involved in the production of Prostaglandin E2 alone (PMID: 15821352, PMID: 16115954). Prostaglandin, the active lipid, is involved in the inflammation, pain, growth and mitosis. COX-2 levels are induced highly in response to inflammation, pain or other mitogenic stimuli and have been associated with carcinogenesis in many human neoplasms, including head and neck cancer [78–81]. Primarily, evidence points out to COX-2 being implicated in increased angiogenesis [49, 82] and cell proliferation [83], the main processes involved in carcinogenesis. A close association of COX2 expression was observed with postoperatively disease free survival (DFS) and overall survival (OS). Multivariate analysis revealed expression was independent predictor of DFS rather than OS (PMID: 13679206). Higher levels of PGE2 was observed with increased COX2 expression in HNSCC which stimulate the proliferation of cell, angiogenesis, cell survival and motility (PMID: 15128893). Expression profiling at transcript and protein levels of COX-2 in the HNSCC patients detected an overexpression as compared to COX 1, this increased expression was also observed in patients with premalignant conditions (oral leukoplakia) indicating an association of the marker with carcinogenesis. Similar observation has been reported in other studies wherein patients with premalignant lesions showed higher expression of COX 2 in dysplastic lesions which was accompanied by aneuploidy/other molecular alterations (PMID: 12196922, PMID: 12747975, PMID: 14626203, PMID: 12203806). Expression profiling at the transcript level by Real time PCT (qPCR) of Hypopharynx SCC indicated that a higher percentage (87 %) of patient tumors showed elevated COX-2 expression, which was further associated with increased lymphatic invasion (PMID: 12196922). The release of pro-inflammatory mediators like PGE2 acts on the cell surface receptors like EP1, EP2, EP3, and EP4 resulting in the growth of tumor cells in an autocrine or paracrine fashion [83]. The inhibition of COX enzymes results in the reduction of prostaglandins and thromboxane and thereby reduces the inflammation and pain. Increased COX 2 enzyme results in the production of carcinogens which plays an important role in angiogenesis, apoptosis, invasion and Metastasis (PMID: 11905709) (Fig. 11.6).

11.4.2.2 Targeting COX-2

Targeting COX-2 pathway has been explored both in the context of chemoprevention as well as therapy in HNSCC, due to the role of the pathway during initiation as well as progression of the disease. Non-steroidal anti-inflammatory Drugs (NSAIDs) which are pan-COX inhibitors and selective COX-2 inhibitors (Celecoxib) are the major approaches of targeting the pathway. Various preclinical studies have investigated COX inhibitors and have shown a response in terms of decreased angiogenesis [84, 85], increased tumor growth inhibition, apoptosis [84–88] and other anticarcinogenic effects [88, 89]. Treatment of patient derived xenograft models with Celecoxib, the selective COX-2 inhibitor currently approved,

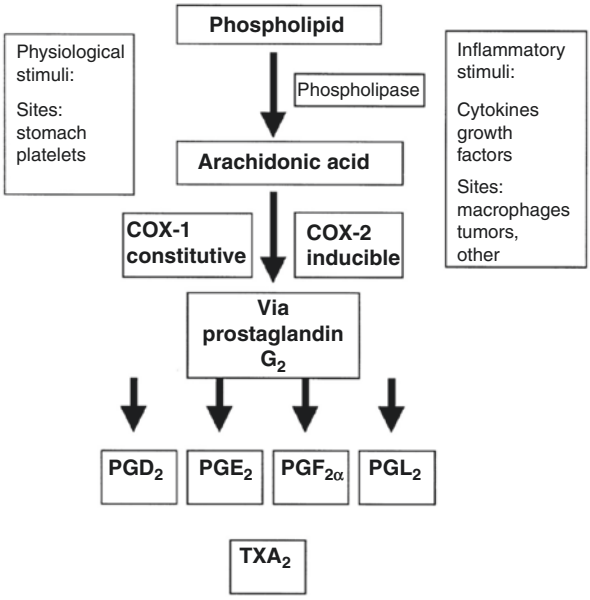

Fig. 11.6 COX-2 pathway and associated molecules (G. Davies et al., *Annals of Oncology* 13: 669–678, 2002)

COX-2 showed a reduction in the tumor volume and delayed growth of the cells [90]. Further, additionally, *in vitro*, studies have reported the role of Celecoxib in improving sensitivity to other chemotherapeutic drugs. Celecoxib is reported to enhance the sensitivity of HNSCC cell lines to drugs like doxorubicin, cisplatin and 5-fluorouracil, possibly by enhancing the inhibition of cell proliferation and by inducing apoptosis [92]. The combination of erlotinib, celecoxib and ionizing radiation showed increased apoptosis and inhibition of the tumor growth due to the parallel inhibition of multiple proteins like p-ERK1/2, pEGF, pAKT, p-STAT3 and PGE2 [93]. Other studies have also shown celecoxib to exhibit anticarcinogenic effect on SCC by inhibiting the EGFR and AKT pathways [50, 94–96].

Molecular analysis investigating the mechanism of resistance to COX-2 inhibitors are comparatively few. However, marker association studies in clinical trials using the COX-2 inhibitors in combination with other targeted therapies (anti-EGFR), have primarily correlated EGFR and AKT pathways [50, 97] with the response to treatment [100]. Chemopreventive trials have shown a similar phenomenon; the down-regulation of EGFR, pERK and pS6 levels correlated with an increased clinical response to celecoxib, when administered in combination with erlotinib in HNSCC [50]. A significant decrease in the levels of VEGF [49, 90] was observed in phase II trials with high COX-2 expression in HNSCC patients, when treated with celecoxib or in combination with radiotherapy [101, 102] (Fig. 11.7). Studies using *in vitro* systems have also identified alternate pathways that can possibly contribute towards resistance to COX inhibitors. COX2 expression can be induced by other pathways such as PI3K/mTOR and MEK/ERK1-2 (PMID: 25674239, PMID: 20206688, PMID: 21882257). An upregulation of these pathways/molecules may suggest a possible resistance to COX-2 inhibition. In addition to COX-2 mediated synthesis of PGE2, this molecule is also regulated by its own degradation; the down regulation of

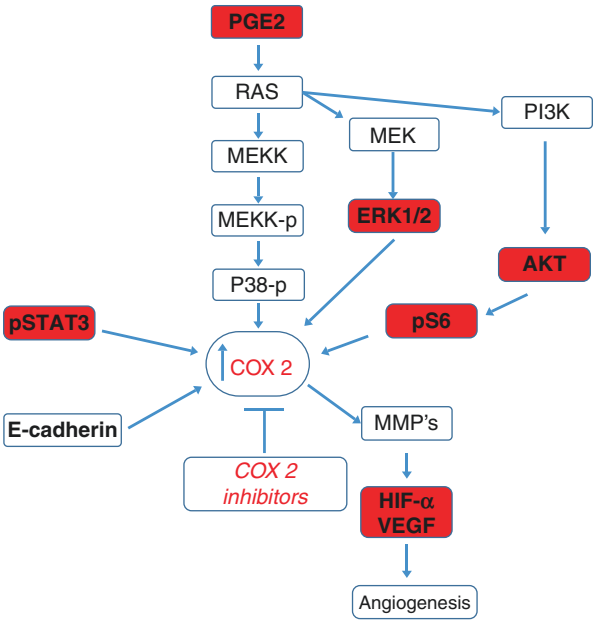

Fig. 11.7 Markers associated with resistance/response to COX-2 inhibitors. The various pathways leading to upregulation of COX-2 are shown. The markers with clinical evidence of resistance/response to COX-2 inhibitors are indicated in *red*

prostaglandin dehydrogenase (enzyme that catalyzes the catabolism of PGE2) (PMID: 25433169, PMID: 24839005, PMID: 20304053) is observed in many cancers and be indicative of resistance (PMID: 19136477). The relevance of these markers in terms of their predictive value clinically needs to be investigated further.

The presence of pathways that are redundant in terms of their end product also suggests that use of multiple targeted therapies may be a better option. The COX-2 inhibitors also, in combination with standard chemotherapeutic drugs such as monoclonal antibodies targeting EGFR and TK inhibitors, show a better and promising mode of treatment against various cancers including head and neck cancers [50, 93, 95, 96, 99]. As is the case with the other targeted pathways, the regulation/synthesis of the downstream molecules of the COX-2 pathway will have to be taken into consideration and validated extensively to establish their correlation with resistance and response to inhibition of COX-2 pathway. This will enable administration of the drug specifically to patients who will benefit from the treatment.

11.4.3 Targeting mTOR Pathway (Rapamycin/Sirolimus)

11.4.3.1 Mammalian Targets of Rapamycin (mTOR) Signaling

PI3K/AKT/mTOR signaling pathway is frequently altered in human cancers including the HNSCC and under normal physiological conditions is known to regulate cell survival, growth and metabolism. mTOR, a serine/threonine protein kinase

molecule which plays an important role in the execution of the downstream signaling of the PI3K pathway is encoded by FK506 binding protein 12 Rapamycin associated protein 1 gene (PMID: 8660990) and plays a critical role in tumor development, invasion, metastasis and angiogenesis, processes which are implicated in local recurrence and metastasis [103–105].

The two distinctive complexes of mTOR, *mTORC1 and mTORC2,* are known to have varied functions (PMID: 15122205); mTORC1 is the rapamycin-sensitive, protumorigenic complex, promoting cell proliferation, angiogenesis, migration and invasion [106–108], while mTORC2 is known to be resistant to rapamycin and is generally involved in the regulation of the cytoskeleton. Profiling of the mTOR pathway in head and neck tumors showed downregulation of TSC1, TSC2, 4EBP1 and PTEN while PIK3C2A, AKT1, PDPK1, RHEB, FRAP1, RPS6KB1, EIF4E, and RPS6 showed up regulation [109]. pS6K and/or p-4eBP1 overexpression was observed in 42 % of patients, suggesting frequent activation of the PIK3CA/AKT/mTOR pathway [111] (Fig. 11.8). In this context, targeting the mTOR pathway is one of the approaches under trial for treatment of head and neck cancer.

11.4.3.2 Targeting the mTOR Pathway

Extensive studies have shown the prognostic significance of mTORC1 and other upstream/downstream molecules such as pS6, 4EBP1 and eIF4E (PMID: 15355912, PMID: 18652687, PMID: 23226094). Its role in HNSCC progression hence provides a strong rationale for the evaluation of mTOR inhibitors as a treament strategy in HNSCC [112]. Rapamycin/Sirolimus and their derivatives are the currently in use drugs that target the activity of mTOR, thereby inhibiting the downstream

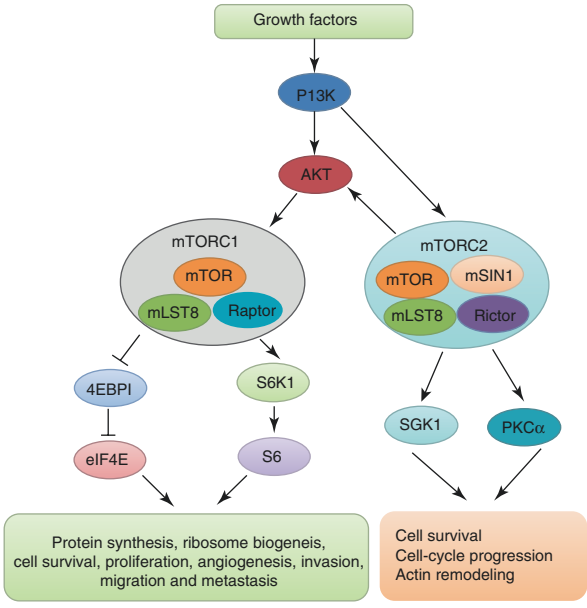

Fig. 11.8 mTOR pathway and its downstream signaling molecules of mTORC1 and mTORC2 complexes with their physiological functions [110]

signaling. Initial studies (*in vitro and in vivo*) using these potential inhibitors (rapamycin and its derivatives temsirolimus and everolimus) showed they suppress tumor growth and sensitize HNSCC to radiation, chemotherapy, and EGFR inhibitors [113]. *In vitro* studies revealed increased nuclei apoptosis and reduced neovascularization with Rapamycin treatment (PMID: 19114562). Studies also revealed that Rapamycin displayed a potent antitumor effect by inhibiting DNA synthesis and apoptosis in HNSCC cell lines and xenografts with decreasing the phospho-S6 levels (PMID: 16267020). Rapamycin showed an inhibition of HNSCC mice induced apoptosis and inhibited cell proliferation, upregulation of Akt and S6, decreased Survivin expression, which further led to deceased tumor progression (PMCID: PMC3463723). Rapamycin was further evaluated in the lymphatic endothelial cell lines and orthotropic mouse models which showed reduced lymphatic vessels invasion by tumor cells in the mouse tongue ($p=0.013$) and decreased metastasis within the lymph nodes (PMCID: PMC3702388). Treatment with rapamycin and the rapalog RAD001 diminished lymph angiogenesis in the primary tumors and prevented the dissemination of HNSCC cancer cells and thereby prolonging survival in animal models [114]. As is the case with targeted therapies, the efficacy is improved when used in combination with other drugs; similar results were reported with Rapamycin- significant increase in the number of apoptotic cells were observed in tumors treated with Cisplatin and mTOR inhibitors as compared to individual treatment, thus demonstrating that the latter can also sensitizes tumor cells to chemotherapy agents (PMID: 17912526, PMID: 19484784, PMID: 21950487, PMID: 20066897, PMID: 18971185, PMID: 19690197, PMID: 18824293).

Biomarkers that correlated with the treatment outcome of Rapamycin have been explored by various studies. The members of the pathway, specifically mTOR are suggested to be a biomarker for selection of patients for therapy. The increased expression of eIF4E and pS6, the active downstream members of the mTOR pathway is known to correlated with tumorigenesis and survival in HNSCC patients (PMID: 10561370), (PMID: 9890352, PMID: 15217935); these markers can be indicators of the possible response to mTOR inhibition. In addition to biomarker-based segregation, functional assessment of a patient's tumor before treatment with mTOR/AKT inhibitors has been suggested to be useful for patient stratification (PMID: 23361299). Phospho-proteomic profiling of tumors resistant to dual AKT/mTOR inhibitors revealed differential activation of multiple pathways involved in proliferation and survival.

Multiple alternate pathways are known to activate/inhibit the PI3K/mTOR pathway and hence can define the response/resistance to mTOR inhibitors. The CCL2-AMPK-mTORC1-survivin pathway is an alternate pathway that is known to activate mTORC1 and promotes cancer development/progression in a PI3K-independent manner [115]. Endogenous and exogenous EGFR activation is also known to act in both mTOR-dependent and independent manner to induce expression of the angiogenic factors, VEGF-A and VEGF-C, respectively [116]. PTEN, the tumor suppressor, inhibits PI3K, and downregulation of this gene is known to contribute toward drug resistance in multiple cancers [117–119]. Phosphatidic acid (PA) is a chemoattractant that binds to and signals inside the cell through the ribosomal S6 kinases

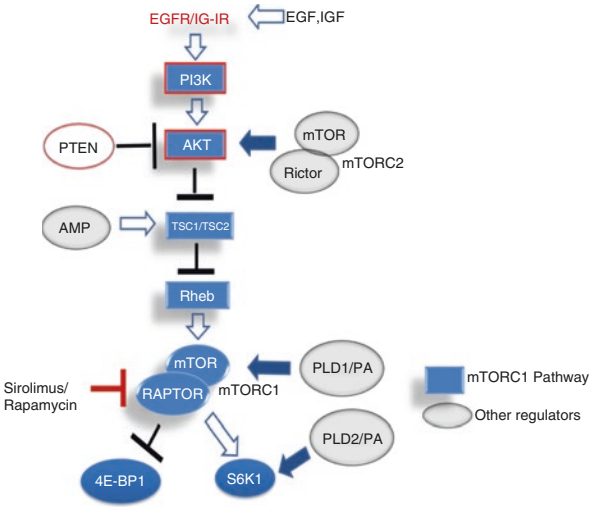

Fig. 11.9 Markers associated with resistance/response to mTOR inhibitors. The mTOR pathway along with the associated molecules that might lead to resistance to mTOR inhibitors is indicated. The markers with evidence in other cancers are indicated in *red*

(S6K) [120–123]. Levels of PA directly increase the S6K activity both in an mTOR-dependent (through PLD1) and independent (through PLD2) manner [122, 124, 125]. PA also regulates the expression of 4E-BP1, the downstream target of mTOR, via an ERK-dependent mechanism [126] (Fig. 11.9). These evidences suggest that the expression pattern of these markers in patients might be indicative of resistance/response to mTOR inhibitors.

The effects of mTOR inhibition are currently under investigation in multiple preclinical and clinical trials. Combination therapy including PI3K/mTOR inhibitors along with anti-EGFR therapy is known to improve response indicating the significance of targeting multiple pathways; patients treated with rapamycin in combination with erlotinib showed high response with VEGF levels correlating with overall survival [127]. Studies that can evaluate the expression profile of the markers of the pathway as well as those of the alternate pathways in the responders/non-responders to the therapy in these trials may provide insights into the predictive value of these markers in a clinical setting.

The other targeted therapies currently under investigation in patients with head and neck cancer are bevacizumab (anti-VEGF), sunitinib and sorafenib; the use of marker based information to categorize the patients into possible responders and non-responders is yet to be investigated extensively in oral cancer. Substantial evidence of marker correlation with response to genotoxic or cytotoxic drugs is available in head and neck cancer; nevertheless their use for clinical prediction and categorization of the patients prior to treatment requires further validation. With regard to targeted therapy, investigations into the reasons of low response and the possible underlying molecular mechanisms need to further explored. Investigation of the primary and associated pathways contributing toward drug resistance to conventional and targeted therapy or a combination is essential if the approach of marker-based personalized therapy is to be made a common practice. As in the case of other solid tumors, this necessitates retrospective and prospective studies/trials

that can establish the association of these markers with the response to therapy and prognosis, and further pathway based clinical trials to establish the efficacy of a marker based patient segregation approach prior to drug administration.

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