McGraw-Hill Manual

Endocrine Surgery

Shane Y. Morita • Alan P. B. Dackiw
Martha A. Zeiger

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Endocrine Surgery

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This book is dedicated to my family.
I thank them for their selflessness.
I am indebted to my late father and hero, Garry Takao Morita, as well as to my beloved mother, Soon Sun Morita, who sacrificed relentlessly in order to provide me with opportunities to succeed.
I am truly blessed to have the best parents in the world.
Mom, thank you for all of your prayers.
I am thankful to my late grandfather, Nick Shizuichi Morita, who along with my parents helped raise me in Hilo.
I am grateful to have two wonderful boys, Josiah David Morita and Elijah Garry Morita, they inspire me daily.
I am honored to be married to my beautiful wife, Jaimie Shannen Tom, MD, who never ceases to amaze me with her ability to be an outstanding doctor, mother, daughter, granddaughter, sister, and spouse.
I love you unconditionally!

Shane Young Morita, MD

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FOREWORD

It is an honor and great pleasure to write the foreword for this exciting new *McGraw-Hill Manual Endocrine Surgery* by Drs. Morita, Dackiw, and Zeiger.

This publication brings together many of the leaders in the field of endocrine surgery, along with their respective fellows, in a project that highlights essential information in the diagnosis and management of endocrine surgical patients. Each chapter contains numerous clinical pearls passed on to young endocrine surgical fellows by their respective mentors and will undoubtedly be of great value to those in training and practice. This group of fellows represents our inaugural year under the auspices of the Fellowship Committee of the American Association of Endocrine Surgeons. The field of endocrine surgery is becoming ever more complex, necessitating specialized training for those whose careers will focus on the surgical disorders that arise within the thyroid, parathyroid, and adrenal glands, as well as the vast gastroenteropancreatic neuroendocrine tumor system. The authors have clearly succeeded in synthesizing a very practical and reader-friendly manual of 21st century endocrine surgery. This will be a valuable resource for medical students, surgical residents, fellows, and consulting surgeons alike.

Geoffrey B. Thompson, MD
Professor of Surgery
College of Medicine, Mayo Clinic

PREFACE

McGraw-Hill Manual Endocrine Surgery was written to provide a succinct yet comprehensive resource for a wide variety of endocrine disorders. The topics are based on diseases and conditions that affect the thyroid, parathyroids, adrenals, pancreas, and gastrointestinal tract. The focus of this book is to ensure that pertinent information, including management of patients, is provided; hence, each chapter concludes with a section titled "Practical Pearls."

Endocrine surgery is now recognized as a distinct discipline of general surgery. Accordingly, the American Association of Endocrine Surgeons had its initial Endocrine Surgery Fellowship Match in 2007, and this manual was primarily written by fellows of the inaugural class. All were mentored by senior faculty at their respective academic facilities who are experienced endocrine surgeons, and each participating program from the class of 2007–2008 was represented. Every effort was made to ensure that institutions that had an expertise in a particular field authored that chapter.

This book does not encompass endocrine surgery in its entirety. It is beyond the scope of this publication to cover every aspect of this vast field. However, whenever possible, the authors have addressed controversies in the management of particular endocrine surgical conditions.

It is the intent of the editors that any health care provider may use this manual. We hope that nursing students, medical students, medical residents, surgical residents, fellows, practicing clinicians, and other personnel interested in endocrine surgery will both enjoy reading this manual and find it to be a useful resource.

Shane Y. Morita, MD
Alan P.B. Dackiw, MD, PhD
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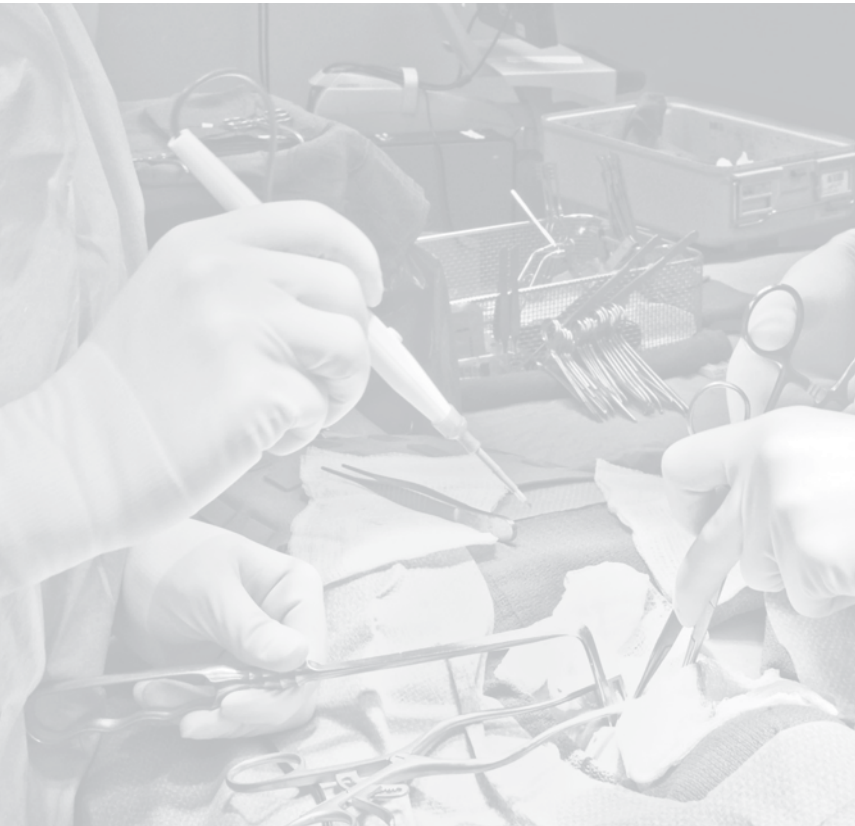
Shane Y. Morita, MD

SECTION I
Thyroid



Chapter 1

Thyroid Nodule

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Leigh Delbridge, MD, FRACS

EMBRYOLOGY

To treat thyroid disease, it is essential to have a thorough knowledge of its embryology. The thyroid is derived from the primitive pharynx as well as the neural crest with the main body arising from epithelial cells of the endoderm and forming the follicles of the gland. Arising as a diverticulum from the floor of the primitive pharynx, the thyroid transforms into a bilobed structure and descends in the midline of the neck. This tract remains attached to the posterior inferior tongue as the thyroglossal duct, and its distal end may go on to form a pyramidal lobe. This serves as the embryologic basis for the formation of a thyroglossal duct cyst as well as nodules within the pyramidal lobe, and underscores the need to completely excise the thyroglossal tract through the hyoid bone to the level of the foramen cecum when the aforementioned cyst is present. It also requires the surgeon to systematically search for a pyramidal lobe when performing a total thyroidectomy because it is present in 30% to 40% of patients and will be the point of persistent or recurrent disease if not identified at the time of operation.[1]

The neural crest serves as the basis for the formation of the parafollicular cells (C cells). The C cells, which secrete calcitonin, migrate from the fourth and fifth branchial pouches. The combination of these two branchial pouches leads to the formation of the caudal pharyngeal complex, which serves as the precursor to the lateral thyroid lobes (ultimobranchial bodies). Eventually, the lateral lobes join the main body on each side as they descend from the buccal cavity. The C cells ultimately populate the entire gland. The fusion of the ultimobranchial body and the main thyroid body forms the tubercle of Zuckerkandl and can be seen as a slight nodular thickening at the junction of the superior and middle third on the posterior surface of the gland where the lateral lobes meet the main thyroid body.

During development, the third branchial pouch (source of the thymus) is gradually separated caudally. As the thymus, heart, and great vessels descend, it is drawn toward the superior mediastinum. The thymus dissociates, leaving the thyrothymic ligaments as vestigial remnants of their connection. The track of descent of the thymus and great vessels into the superior mediastinum forms the thyrothymic ligaments. Along this path, thyroid rests are formed when the endoderm from the fourth branchial pouch may be pulled down in the descent of the primitive thymus to form retrosternal thyroid components.[2] As with the pyramidal lobe, care must be taken to search for these extensions of thyroid tissue to prevent persistence or recurrence of disease when total thyroidectomy is being performed.

ANATOMY

General

The normal thyroid gland lies caudal to the larynx and encircles the anterior and lateral aspects of the first several rings of the trachea. It normally weighs approximately 20 g and is composed of right and left lateral lobes; the isthmus; and at times, a superior extension of it, the pyramidal lobe (which occurs more often on the left). The strap muscles (sternohyoid, sternothyroid, and superior belly of the omohyoid) cover the anterolateral surface of the gland. The oblique upper insertion of the sternothyroid muscle to the thyroid cartilage prevents the lateral lobes from medializing and encroaching onto the underlying thyrohyoid muscle. The upper pole of the lateral lobe is attached medially to the inferior constrictor complex and to the posterior aspect of the cricothyroid muscle. The ansa cervicalis formed from the descendens hypoglossi (C1) and the descendens cervicalis (C2 and C3) innervate the strap muscles and should be preserved whenever possible. The obliterated thyroglossal duct may go on to form a muscular band (levator glandulae superioris) connecting the pyramidal lobe to the hyoid bone.[3]

The entire thyroid gland is enveloped in a thin, fibrous pretracheal capsular fascia. Dissection of this fascia from the surface of the gland serves as the basis for the term "capsular dissection." The fascia coalesces near the cricoid cartilage and upper tracheal rings on the posterior aspect of the thyroid gland to form the ligament of Berry.

Arterial Blood Supply

The superior pole of the gland is supplied by multiple branches of the superior thyroid artery as it originates from the external carotid artery and gives off terminal branches enveloping the superior pole of the gland in a variable course. Great care must be taken to expose the avascular space between the

cricothyroid muscle and the superior pole of the gland. The branches of the superior thyroid artery should be ligated as close to the gland as possible to prevent inadvertent incorporation of the external branch of the superior laryngeal nerve. This nerve often runs in a similar path with the superior thyroid artery; its anatomic variations are well described by Cernea et al.[4] In addition to exposing the avascular cricothyroid space, the lateral aspect of the superior pole needs to be dissected free of the overlying sternothyroid muscle. Inferolateral traction on the gland is crucial in exposing both of these planes of dissection to safely ligate the superior pole.

The inferior thyroid artery arises from the thyrocervical trunk and gives off terminal branches entering the posterolateral aspect of the thyroid at the junction of the upper and middle third of the gland. It is intimately associated with the recurrent laryngeal nerve and runs along a course that generally intersects the nerve as its branches terminate in the gland.

Venous Drainage

Venous drainage of the thyroid gland is variable and occurs through a variety of intercommunicating vessels. The venous network may be divided into three separate regions: the superior veins (draining the superior pole and adjacent to the superior thyroid arteries); the middle thyroid veins (which may be absent in some patients), traveling laterally from each lobe and emptying into the internal jugular vein; and the inferior thyroid veins, draining the inferior pole and adjacent to and coursing with the thyrothymic ligament.

Nerves

Three major components of the nervous system are encountered in thyroid surgery. At the superior pole of the thyroid is the external branch of the superior laryngeal nerve (EBSLN). It is a branch of the vagus nerve and is the motor nerve supplying the cricothyroid muscle. As previously noted, its close but variable course to the superior pole vessels place it at risk for injury during thyroidectomy.[4] When effort is taken to identify it as it courses through the cricothyroid space, the nerve may be found in more than 90% of cases.

The recurrent laryngeal nerves (RLNs) ascend from the thoracic inlet along the right and left tracheoesophageal grooves. Compared with the nerve on the left, the nerve on the right courses in a more lateral to medial oblique path. The nerves may give off anterior or posterior branches before entering the larynx. There are many variations of the nerve and its relation to the ligament of Berry as well as the inferior thyroid artery; however, it can generally be encountered passing into the pharynx in a cleft just medial to the tubercle of Zuckerkandl.[1] A nonrecurrent laryngeal nerve is rare (<1%); if present, it is usually found on the right. Left-sided nonrecurrent laryngeal nerves are extremely uncommon, although a recent case report noted

a patient with a right aortic arch, an aberrant left innominate artery, and the absence of a ductus arteriosus.[5] A nonrecurrent nerve tracks along the same course as the vagus and sweeps from lateral to medial in the jugulocarotid groove. It is most commonly associated with a retroesophageal aberrant subclavian artery (lusorian artery).

An additional set of nerves that deserves mention are the sympathetic–inferior laryngeal nerve anastomotic branch (SILABs), which run between the cervical sympathetic ganglia and the recurrent laryngeal nerve with fine direct anastomosis and then run onto the surface of the gland itself. The SILAB may be larger than the RLN and as such leads to confusion in identification of the RLN, thus placing it at risk for injury. SILABs may be divided with impunity during capsular dissection, but their visualization is necessary to ensure proper identification and preservation of the RLN.[1]

EPIDEMIOLOGY

Thyroid nodules are common in the general population. They may be found by physical examination in approximately 7% of the general population; if ultrasonography is used, thyroid nodules may be found in more than half of the general population over 50 years of age.[6,7] The prevalence of nodules increases with age and is generally higher in women than men. The principal concern of a thyroid nodule is malignancy. In 80% of cases, solitary nodules are most commonly benign and include colloid nodules, thyroid cysts, or thyroiditis. The remaining 10% to 15% of thyroid nodules are follicular lesions; approximately 5% of thyroid nodules are malignant.[7] Because of the large incidence of thyroid nodules in the general population, a concise scheme to approach thyroid nodules is important. This strategy should incorporate the characteristics of the nodule as well as the clinical history of the patient.

RISK FACTORS

Exposure to ionizing radiation has been shown to increase the risk of malignancy for a thyroid nodule to approximately 40%.[8] Medullary thyroid cancers (MTCs) may be familial 20% of the time, occurring in the multiple endocrine neoplasia (MEN) syndromes, or may be sporadic. Familial non-MTCs are rare, and the diagnosis is made when thyroid cancers occur in two first-degree relatives. Some of the conditions associated with differentiated thyroid cancer include familial adenomatous polyposis (FAP), phosphatase and tensin homolog hamartoma tumor syndrome (PHTS), Carney complex, Werner syndrome, and papillary renal cell carcinoma.[9] Table 1-1 lists both high- and moderate-risk features that may be associated with thyroid cancer. A general rule to follow is that for any nodule associated with two or more high-risk characteristics, the malignancy rate may be greater than 70%. All

TABLE 1-1. Suspicious Clinical Characteristics of Thyroid Nodules

High Risk
Family history of medullary thyroid cancer or MEN syndrome
Rapid growth, especially during levothyroxine therapy
Hard or firm nodule
Fixation of the nodule to adjacent structures
Cervical lymphadenopathy
History of head or neck irradiation
Moderate Risk
Age younger than 20 years or older than 60 years
Male gender
Nodule >4 cm
Complex cystic nodule
Mass effect symptoms (dysphagia, voice change, dyspnea, cough)

MEN = multiple endocrine neoplasia.

nodules that are hard, fixed to adjacent structures, rapidly growing, or associated with lymphadenopathy should be removed.

Patients presenting with other traditional benign thyroid disease may be at higher risk of harboring a malignant nodule. Cold nodules found on radionuclide scanning in patients with Graves' disease may be malignant 15% to 38% of the time depending on the nodule's size and the patient's gender. Complex cysts in thyroid disease may also have an associated malignancy approximately 17% of the time. In patients with goiter, the malignancy risk is actually higher in patients who have one or two nodules than in patients with more than three nodules. However, it must be noted that patients with goiter are not at an increased risk of malignancy compared with the general population. Finally, patients with a nodule of 4 cm or greater should undergo diagnostic thyroid lobectomy because fine-needle aspiration (FNA) biopsy in this group of patients has been shown to have up to a 34% false-negative rate; 40% of indeterminate lesions diagnosed on FNA were later found on histologic section to be malignant.[10]

A final population at an increased risk of malignancy is children with thyroid nodules. Thyroid nodules occur in children in an average of 1% of the population. The rate of malignancy varies among studies at between 20% and 50%. The rate of malignancy is similar for both palpable as well as nonpalpable nodules as it is in adults.

CLINICAL PRESENTATION

Evaluation of a patient with a thyroid nodule initially begins with a comprehensive history to evaluate the risk factors for malignancy. In general, patients commonly report a lump in the neck found during palpation. They may indicate a gradual feeling of tightness in the neck or chest that has developed over the past several months and a subjective sensation of shortness of breath or difficulty turning the neck. Other patients may present with a thyroid nodule detected incidentally on imaging ordered for a different medical reason (thyroid incidentaloma). Key aspects of the history include the presence of symptoms (dysphagia, voice change, coughing, choking, dyspnea, pain, and sudden increase in size) as well as exposure to ionizing radiation and a family history of thyroid disease or cancer. Additionally, the patient must be asked about any family history of thyroid disease, parathyroid disease, and other endocrinopathies. The patient should also be asked whether he or she has any coexisting medical illnesses such as an autoimmune disorder. Physical examination should assess for features of the nodule(s) as well as any cervical lymphadenopathy. Concerning features include nodules that are hard, fixed, irregular, or 4 cm or larger or lesions with associated lymphadenopathy.

DIAGNOSTIC EVALUATION

Biochemical Tests

The initial investigation required in all patients with a thyroid nodule is biochemical assessment of thyroid function because clinical assessment is not a reliable indicator of thyroid status. An unequivocal biochemical test that is necessary is the thyroid-stimulating hormone (TSH) level. If the patient is euthyroid or even hypothyroid, FNA biopsy may be used to assess the pathology of the thyroid nodule. A suppressed TSH level should alert the clinician to the possibility that the nodule may be a hyperfunctioning nodule. Alternatively, it may be part of Plummer's syndrome (toxic multinodular goiter) or a single nodule present in a patient with Graves' disease. Regardless, FNA should be carried out selectively. If the FNA is obtained in the hyperfunctioning state, then the result may be reported as "atypical" because of associated hypercellularity within the autonomously functioning nodule(s). Atypical nodules generally require excision; as described later, the incidence of malignancy in a hyperfunctioning nodule is so low that excision to rule out malignancy is rarely, if ever, warranted.

Additionally, recent data have suggested that obtaining a serum calcium level in patients who present with thyroid nodules should be considered because the rate of concomitant primary hyperparathyroidism has been reported to be 3%.[11]

Imaging

Ultrasonography

It cannot be overemphasized that manual palpation of thyroid nodules is extremely variable between even experienced clinicians, and as such, imaging with ultrasonography, especially performed by the surgeon, has become essential to the evaluation of the thyroid gland. Ultrasonography is able to detect nodules and lymphadenopathy with a much greater sensitivity than physical examination. However, the degree to which this may alter management is controversial. Although more nodules are likely to be found, the risk of malignancy in additional nodules detected does not change. Furthermore, although some ultrasound characteristics may indicate a higher risk of malignancy (intrinsic calcification, blurred or ill-defined margin, hypervascularity, hypoechoic), none so far have proven reliable enough to surpass FNA as the principal method of detecting malignant pathology within a suspicious nodule.[12] Ultrasonography is best used as imaging guidance for FNA and readily increases its accuracy, sensitivity, and specificity.[1] When a diagnosis of cancer is made on FNA, neck ultrasonography by an ultrasonographer with expert experience is mandatory to evaluate for lymphadenopathy that may not be detected by physical examination.[13]

Limitations of ultrasonography include imaging thyroid tissue in a substernal, retroclavicular, intrathoracic, and retrotracheal position. In these areas, computed tomography (CT) scanning is the best imaging modality.

Other Imaging: Computed Tomography, Magnetic Resonance Imaging and Positron Emission Tomography Scanning

Although ultrasonography is the imaging study of choice in evaluation of the thyroid gland, CT scanning has a limited but important role. CT is best used as an adjunct modality in imaging advanced thyroid pathology when retrosternal, intrathoracic, or retrotracheal extension of the gland is present. As noted previously, these are areas in which ultrasound imaging is limited as a result of acoustic distortion attributed to bone or air. CT scanning may also be very helpful in the preoperative assessment of advanced thyroid malignancies because it is reliable at discerning the development of lymphadenopathy (especially in the retroclavicluar area where ultrasonography is limited), as well as in determining invasion or compression of the aerodigestive tracts. It is essential to avoid administering iodinated contrast because it may complicate adjuvant radioactive iodine therapy if the thyroid nodule requiring resection is diagnosed as malignant. Magnetic resonance imaging may provide the same information as CT, although at a much higher cost.

Positron emission computed tomography (PET) scanning is currently being investigated for use in determining malignancy status of thyroid nodules. PET scanning is increasingly being used for staging and for surveillance

of other malignancies. As a result, it may occasionally identify a thyroid lesion. Some studies have reported that these lesions have a higher incidence of malignancy; as such, until further data are obtained, it is necessary to perform FNA biopsy of these lesions.[14]

Radionuclide Scanning

Apart from the setting of a suppressed TSH, radionuclide scanning plays a minimal role in the assessment of thyroid nodules. As already noted, radionuclide scanning may be important to determine an autonomously functioning nodule in the setting of hyperthyroidism or thyrotoxicosis. Nodules may be classified as hot (hyperfunction), cold (hypofunction), or warm (normal function) depending on the pattern of isotope uptake. The incidence of malignancy in cold nodules is approximately 15% compared with 9% for warm nodules; the incidence of malignancy in hot nodules is about 5%.[7] Thus, this information in and of itself is insufficient to allow for informed management of the patient. If radionuclide scanning is concordant with ultrasonography for the identification of a hot nodule, then that nodule does not require further evaluation via FNA because the incidence of malignancy is extremely low.[15] Just as with ultrasonography, the finding of additional nodules on radionuclide scanning does not change the risk of malignancy in a palpable nodule.

Laryngoscopy

Laryngoscopy is increasingly being advocated for routine use before thyroid surgery for both benign and malignant disease. Flexible laryngoscopy is easily performed in the office setting with topical nasal anesthetics and a fiberoptic scope. In the case of a patient with preexisting voice changes or in the presence of a suspected thyroid cancer, it is essential to determine the status of the vocal cords preoperatively.

Fine Needle Aspiration

FNA biopsy (or fine needle biopsy [FNB]) is the gold standard for evaluation of the pathology of a thyroid nodule. It provides quick and specific information about the cytology of a nodule from which the histology may be inferred. FNA is best performed with image guidance via ultrasonography. Contraindications are very few and complications rare. The technique involves choosing the proper size needle (25- to 27-gauge for solid nodules; 22- to 23-gauge for cystic component) and using ultrasound guidance, taking two to four passes of the needle into the targeted nodule. When targeting cystic lesions with solid components, ultrasonography should be used to obtain samples from the solid component.[16] Controversy exists over whether the best samples are obtained with passage of the needle through the lesion with or without

continuous suction. Obtaining an insufficient specimen for diagnosis is minimized by having immediate cytopathologic interpretation of the results. The acceptable FNA results and recommended management are shown in Figure 1-1. The incidence of each category of cytopathology is as follows: malignant, 5%; atypical (follicular), 15%; benign, 65%; and inadequate, 15%.[15]

In 2007, a consensus conference hosted by the National Cancer Institute proposed further classification of FNA results based on a six-tiered system.[17] Those categories and their risks of malignancy are listed in Table 1-2. The main feature of this system is that it serves to further classify the atypical (follicular) lesions by risk of malignancy and thus potentially spare unnecessary surgery to patients with "low-risk," atypical lesions. In this manner, the surgeon and patient may discuss the risks and benefits of surgical excision of the atypical lesion.

No test is available to identify malignancy from benign disease in follicular lesions; the diagnosis rests solely on the demonstration of follicular cells outside the capsule or within blood vessels on histologic specimen. If the specimen is inadequate, FNA should be repeated. If it is again inadequate, the patient should proceed with undergoing surgical excision. Additionally, if the lesion is cystic and recurs after aspiration or the practitioner is unable to obtain a diagnosis, the lesion should be excised because FNA has an accuracy of only 80% in these cases, and these cysts may degenerate or harbor an occult carcinoma.[8] FNA should generally be performed on nodules larger than 1 cm because any nodule harboring a carcinoma smaller than 1 cm is clinically insignificant (with the exception of those associated with lymphadenopathy).

MANAGEMENT

Overall, the natural history of thyroid nodules is not well characterized. Nodules that are suspicious for malignancy, cause pain or pressure, or enlarge should be promptly excised. Previous studies have shown that thyroid cancer rarely, if ever, comes from a previously benign nodule degenerating to a malignancy. Rather, thyroid cancer is likely from a monoclonal origin commencing from an initial mutation at the cellular level. However, carcinoma may still develop within an otherwise benign nodule.

Surgical Management

If malignancy is known before surgical excision (as evidenced by FNA), then total thyroidectomy is the procedure of choice. An ipsilateral central lymph node dissection is strongly recommended if malignancy is present. If a cytologic diagnosis cannot be obtained (inadequate FNA after repeat biopsy) or if there is a low risk of malignancy in an atypical nodule, then thyroid lobectomy is the procedure of choice. For lesions smaller than 3 cm in diameter, a minimally invasive approach may be used for diagnostic

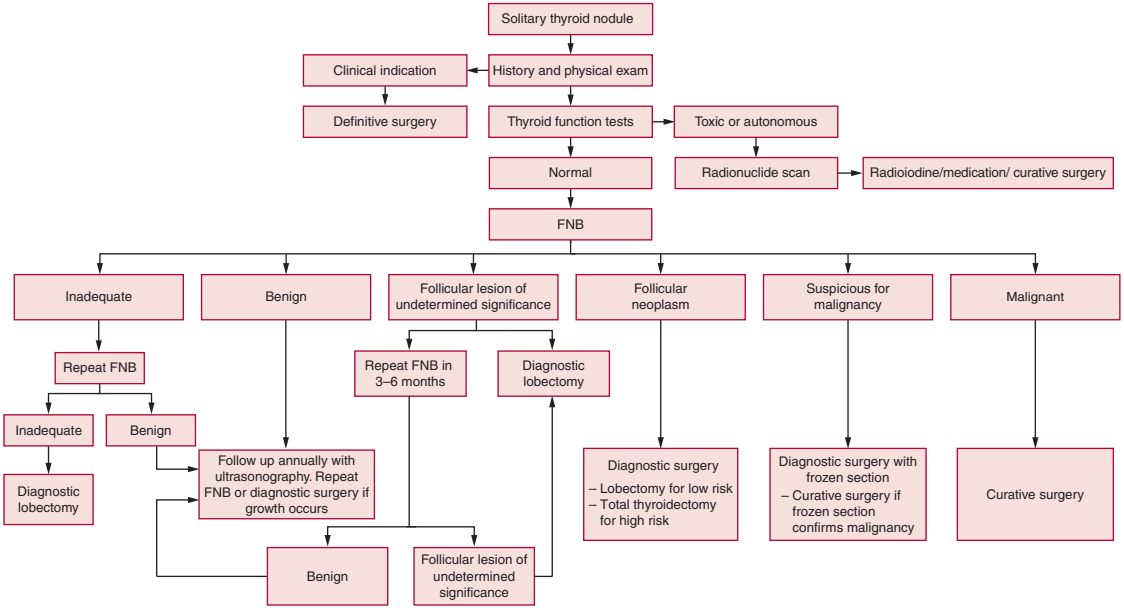

Figure 1-1. Management of a solitary thyroid nodule. For a follicular lesion of undetermined significance, the decision to proceed with either repeat fine-needle aspiration (FNA) or diagnostic surgery should be made with consultation between the patient and surgeon.

TABLE 1-2. Cytopathologic Diagnosis and Risk of Malignancy

NCI 2007 Traditional FNA Category	*Conference FNA Category*	*Risk of Alternate Category Terms*	*Malignancy (%)*
Benign	Benign		<1
Atypical or indeterminate	Follicular lesion of undetermined significance	Atypia of undetermined significance, atypical follicular lesion, cellular follicular lesion	5–10
	Neoplasm	Suspicious for neoplasm	20–30
	Follicular neoplasm	Suspicious for follicular neoplasm	
	Hürthle cell neoplasm	Suspicious for Hürthle cell neoplasm	
	Suspicious for malignancy		50–75
Malignant	Malignant		100
Inadequate	Nondiagnostic Inadequate	Unsatisfactory	

FNA = fine-needle aspiration; NCI = National Cancer Institute.

lobectomy.[18] If the lesion is confirmed to be benign on histologic examination, then no further treatment is necessary. Frozen section is rarely useful because almost all papillary thyroid carcinomas are diagnosed on initial FNA, papillary microcarcinomas present in the final specimen are of no clinical significance, and minimally invasive follicular carcinoma cannot be diagnosed on frozen section alone.[8]

Completion thyroidectomy is rarely required but is needed when there is a widely invasive follicular carcinoma that was not suspected preoperatively, a minimally invasive follicular carcinoma with angioinvasion, or a papillary

thyroid cancer that was not diagnosed on preoperative FNA. Timing of the interval completion thyroidectomy is such that it can be performed within several days of the initial thyroid lobectomy or deferred until 6 weeks later.

Medical Management

Medical management consists of two options, TSH suppression via levothyroxine treatment or ablation with radioiodine (I^{131}). Each option has different advantages and disadvantages.

Treatment with levothyroxine requires suppression of the serum TSH level to less than 0.3 mU/L. The likelihood of reducing the nodule size by more than 50% is increased if TSH is suppressed to less than 1 mU/L. Additionally, suppression to this level reduces the frequency with which new nodules form. Unfortunately, however, efficacy is limited. Castro et al.[19] noted in their meta-analysis that overall, there was no statistically significant difference in decrease of nodule size between groups undergoing suppression therapy and those taking placebo, although a higher proportion of patients in the treatment group had diminished nodule size. Furthermore, high doses of levothyroxine required for TSH suppression may induce cardiac arrhythmias such as atrial fibrillation and may also cause reduced bone density. With cessation of therapy, the nodules will continue to grow.

I^{131} therapy is an option for the treatment of a hyperfunctioning nodule or gland. However, its use is contraindicated in women who are pregnant or breastfeeding and generally requires women of childbearing age undergoing treatment to take oral contraceptives. I^{131} therapy requires very high doses to treat large goiters, and as such, patients may require hospitalization. I^{131} is effective at treating hyperfunctioning nodules, and the desired result is obtained in 75% of patients and with a 40% reduction in volume of the gland.[20] However, after 5 years, a significant number of patients are rendered hypothyroid, and this proportion increases with time. Additionally, the treatment may cause the nodules to become hard on palpation (a worrisome finding), and upon biopsy, unusual cytologic characteristics may be found. Nodules rarely regrow, but when they do, they require repeat FNA.[21] The final cytology of these nodules may be interpreted as atypical and lead to the need for excision.

Follow-up

Benign nodules diagnosed on FNA need no specific treatment but do require follow-up with annual examination and repeat ultrasonography. Because FNA has a 5% false-negative rate, it is necessary to continue to follow the nodules over time. Additionally, evidence in the literature suggests that depending on the technique and the practitioner's experience with FNA, the false-negative rate may be higher. Depending on the facility, FNA may have as high as a

20% incidence of false-negative results.[12] Although many nodules regress, others may enlarge. Kuma et al. [22] prospectively evaluated a large number of cytologically benign thyroid nodules and found that although slightly more than 20% of nodules grow within 10 years' time, more than 99% of nodules remain benign. The American Thyroid Association defines growth as a 20% increase in nodule diameter with a minimum increase in two or more dimensions of greater than or equal to 2 mm.[21] If there is evidence of enlargement either by physical examination or ultrasonography, repeat FNA is warranted. Additionally, if repeat ultrasonography displays any other worrisome features (intrinsic calcifications, blurred or irregular margins), then repeat FNA is also warranted, irrespective of the nodule's size.

SUMMARY

Thyroid nodules are common in the general population and are being detected with increasing frequency. The majority of nodules are benign. However, each patient with a thyroid nodule must be individually evaluated and risk stratified to determine the optimal strategy of management. Malignant lesions or lesions with a high risk of malignancy are treated with curative surgery. Low-risk lesions requiring diagnostic excision are treated with thyroid lobectomy via a traditional technique or a minimally invasive approach if feasible.

PRACTICAL PEARLS

- Nodule formation in the presence of a history of ionizing radiation exposure carries a 40% risk of malignancy and warrants excision via total thyroidectomy.
- Thyroid cancer rarely, if ever, forms from benign nodules, but because of the false-negative rate of FNA nodules, it requires yearly follow-up with ultrasonography and physical examination.
- Atypical or follicular lesions may be treated via thyroid lobectomy because their risk of malignancy is low; however, discussion with the patient regarding a completion thyroidectomy should be done preoperatively because the pathology may demonstrate malignancy. Some patients do not prefer the possibility of an interval completion thyroidectomy. If contralateral nodularity is present, the patient may initially be offered a total thyroidectomy.

(*Continued*)

- Nodules with a high risk of malignancy should be treated via total thyroidectomy.
- Curative surgery for malignancy generally includes total thyroidectomy with ipsilateral central lymph node dissection on the side of the malignancy.
- Although rare, children with clinically detected thyroid nodules are at higher risk of malignancy than adults and as such warrant careful workup and evaluation.

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Chapter 2

Goiter

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DEFINITION

Goiter is defined as enlargement of the thyroid gland. It generally results from focal follicular cell hyperplasia at one or multiple sites within the thyroid gland, and it usually develops over years. *Endemic goiter* refers to enlargement of the thyroid gland secondary to iodine deficiency affecting more than 10% of the population in a defined geographic area. *Sporadic goiter* develops in subjects living in iodine-sufficient areas. Goiter encompasses a spectrum of entities, including diffuse, uninodular, or multinodular enlargement of the thyroid gland. The overall hormonal status of the thyroid nodules within the goiter determines the function of the gland and the definition. When enlargement of the thyroid gland is present without clinical or laboratory evidence of thyroid dysfunction, it is euthyroid multinodular goiter (MNG); when accompanied by hyperthyroidism, it is toxic nodular goiter (TNG). Less frequently, thyroid enlargement is caused by two other disorders such as fibrous chronic Hashimoto's thyroiditis, Graves' disease, or neoplasia. *Retrosternal* or *substernal goiter* refers to goiter that is associated with extension into the mediastinum.

This chapter discusses the pathogenesis, clinical manifestations, and management of nontoxic goiter.

EPIDEMIOLOGY

Goiter prevalence in the general population is estimated to be 15.8%, varying between 4.7% in the Americas to 28.3% in Africa. When comparing current total goiter prevalence (TGP) estimates with the data from 1993, TGP has increased by 31.7% worldwide, but when analysis is restricted to surveys carried out in the past 5 years, TGP shows a decrease of 28.9% compared with 1993.[1] Sporadic goiter is the most common form of goiter

in the United States, affecting 5% of the population. Goiter is 2- to 10-fold more prevalent in women than in men.[2] The association between age and goiter prevalence is dependent on iodine status: in areas of severe iodine deficiency, the prevalence of goiter is maximal in the teenage years,[3] but the peak appears around middle age or later in mildly iodine deficient areas.[2] African-American ethnicity has been shown to be an independent risk factor for the development of large nodular goiter.[4]

RISK FACTORS

Iodine deficiency is the most important risk factor for goiter worldwide. The mechanism by which the thyroid gland adapts to an insufficient iodine supply is to increase the trapping of iodide, as well as the subsequent steps of the intrathyroidal metabolism of iodine. This process is triggered and maintained by increased secretion of thyroid-stimulating hormone (TSH), which is ultimately responsible for the development of goiter. The acceleration of the main steps of iodine kinetics and the degree of hyperstimulation by TSH are greater in the pediatric age groups than in adults, and the development of goiter appears as an unfavorable side effect in the process of adaptation to iodine deficiency during growth.[3]

In patients with sporadic goiter, the cause is usually unknown and involves a combination of environmental and genetic factors. TSH is considered to be the main growth factor in goiter development, but goiter is frequently seen in patients with normal or low TSH levels. It has been suggested that an imbalance in the interactions between the various growth factor axes that favors cell replication exists in patients with MNG.[5]

The role of naturally occurring goitrogens has been documented in the case of certain foods (e.g., milk, cassava, millet, nuts), smoking, and bacterial and chemical water pollutants. The goitergenic effects of tobacco smoke on the thyroid could be explained by the generation of thiocyanate, which competitively inhibits iodine uptake and organification, thereby mimicking a lower iodine intake.[2] Lithium has also been associated with the development of goiter.

A genetic predisposition for goiter development is evident from family and twin paired studies. The genes coding for proteins involved in thyroid hormone synthesis, such as thyroglobulin (Tg), thyroid peroxidase, sodium iodide symporter, pendrin, and the TSH receptor, are thought to be involved in the molecular etiology of familial euthyroid goiter. Familial euthyroid goiter has been linked to a multinodular nontoxic goiter locus (MNG-1) on chromosome 14q[6] and to defects in Xp22 with an X-linked autosomal pattern.[7] Recently, genetic factors on chromosomes 2q, 3p, 7q, and 8p have been suggested to confer susceptibility for euthyroid goiter in some families.[8] These data suggest genetic heterogeneity in euthyroid familial goiter.

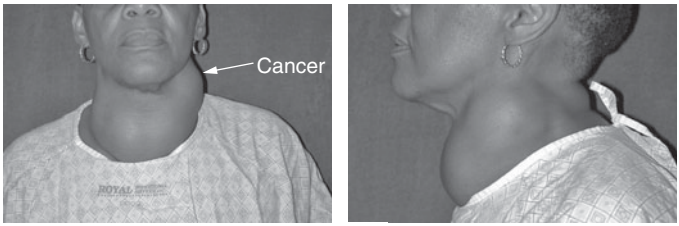

Figure 2-1. A 53-year-old woman with anaplastic thyroid cancer (left upper nodule) that developed within a long-standing goiter.

CLINICAL PRESENTATION

Goiters vary greatly in their size, growth rate, and symptomatology. Most patients with MNG are asymptomatic. Clinical manifestations of nontoxic goiter are usually attributed to thyroid enlargement. Patients may present with a neck lump or disfigurement of the neck (Figure 2-1) or with pressure symptoms, including dysphagia and breathing difficulties because of local esophageal or tracheal compression, respectively. The compression symptoms are most often seen when an intrathoracic extension of the goiter, termed a *substernal* or *retrosternal goiter*, is present. This is more common in elderly individuals with long-standing goiters. Dyspnea and stridor initially develop on exertion and later may also occur at rest. Vocal cord paralysis is rare in patients with benign goiter but may be caused by stretching or compression of the recurrent laryngeal nerves (RLNs). More rarely, compression of the phrenic nerve or the cervical sympathetic chain resulting in Horner's syndrome has been described. Bleeding within the goiter is associated with acute painful swelling in the neck and may cause dyspnea. Rapidly enlarging goiter that appears within weeks to months must increase the suspicion of anaplastic or lymphomatous malignancy. Patients with nontoxic nodular goiter may become hyperthyroid or, less commonly, hypothyroid. However, thyroid dysfunction usually develops only after the nontoxic goiter has existed for many years.[9] Hyperthyroidism often develops insidiously with a prolonged period of subclinical hyperthyroidism.

DIAGNOSTIC EVALUATION

The differential diagnosis of a patient with nontoxic nodular goiter includes diffuse goiter, benign nodular goiter, Hashimoto's thyroiditis, follicular adenoma, and carcinoma. The history should include any symptoms of thyroid

dysfunction, including hypo- or hyperthyroidism; family history of thyroid disease; multiple endocrine neoplasia (MEN) syndrome; thyroid cancer; and history of radiation exposure to the head or neck.

Thyroid enlargement is often best observed when the patient swallows. With practice, the thyroid gland can be palpated in normal size, but for most clinicians, the thyroid gland does not become palpable until the volume has doubled. Examination of the goiter should focus on symmetry, solitary nodule versus MNG, fixation of the goiter, presence of tracheal deviation, consistency of the nodules, and associated lymphadenopathy. The presence of a retrosternal extension is suggested by an inability to palpate the lower thyroid border. Venous outflow obstruction may be evident by Pemberton's sign. The Pemberton maneuver is a physical examination method that elicits manifestations of latent increased pressure in the thoracic inlet by altering the patient's arm position to further narrow the aperture. The maneuver involves extending both arms over the head, and a positive sign occurs when the patient experiences marked facial congestion, cyanosis, and venous engorgement. Physical examination should include findings compatible with Graves' disease that may coexist and may require a different therapeutic approach. The patient should also be examined for the presence of wheezing or stridor.

The diagnosis of thyroid carcinoma should be strongly considered when there is a family history of medullary thyroid cancer (MTC) or MEN, rapid tumor growth, a firm nodule within the goiter, vocal cord paralysis, or the presence of regional lymphadenopathy.

Laboratory evaluation should include TSH measurement to determine whether the patient is euthyroid, hypothyroid, or hyperthyroid. Patients with endemic goiter are usually euthyroid; however, mildly elevated TSH, low thyroxine (T4), and normal or moderately elevated triiodothyronine (T3) serum levels are common. With sporadic goiter, many patients who are clinically euthyroid have biochemical evidence of hypo- or hyperthyroidism. The degree of thyroid dysfunction is often mild or subclinical and evidenced only by an isolated TSH abnormality. If the TSH level is found to be outside the normal range, assays for T3 and T4 are also justified. With a moderately enlarged and firm gland, one should consider Hashimoto's thyroiditis. Increased levels of antithyroid peroxidase antibodies or Tg antibodies help confirm the diagnosis.

The routine use of calcitonin measurement in patients with nodular goiter is controversial but should be considered in any patient with a family history of thyroid cancer. Hahm et al.[10] performed routine measurement of serum calcitonin in 1448 patients with nodular thyroid diseases, with fine-needle aspiration (FNA) done in all patients with palpable or ultrasound-visible nodules. Ten cases of histologically confirmed MTC were detected by routine measurement of serum calcitonin; FNA suggested MTC in only two

patients. The authors concluded that routine measurement of serum calcitonin is useful in the early detection of MTC among patients with nodular thyroid disease.

Ultrasonography has become a first-line method in thyroid imaging. Ultrasound examination is used to measure the size of the gland, establish the presence and size of thyroid nodules, and provide a baseline for follow-up. Many patients who present with a solitary palpable nodule are found to have multiple nodules on ultrasonography. A diffuse goiter appears with normal echogenicity, but degenerative alterations usually lead to a more heterogeneous appearance to the gland. Thyroid nodules may appear hypoechoic, isoechoic, or hyperechoic. Features seen on ultrasonography that are suspicious for thyroid cancer include microcalcifications, local invasion, lymph node metastases, a nodule with anteroposterior dimension greater than its transverse dimension, markedly reduced echogenicity, absence of a halo, ill-defined or irregular margins, solid composition, and central vascular flow.[11]

Thyroid scintigraphy with 123-iodine or technetium pertechnetate (^{99m}Tc) is optional to confirm the extent and functional status of the gland. These scans have a particular role when considering a limited operation in the presence of hyperthyroidism. In a patient with a MNG and concomitant Graves' disease, the scan shows globally enhanced uptake. In most patients with MNG, the scan demonstrates a heterogeneous uptake pattern that includes cold and hot areas, which is typical for multinodular thyroid disease. Radionuclide imaging may also be used when treatment with iodine 131 (^{131}I) is being considered.

Chest radiography (posteroanterior and lateral views) should be obtained to evaluate the position of the trachea (Figure 2-2).

FNA biopsy may be indicated if discrete nodules suspicious for malignancy are present or if the patient has a history of rapid goiter growth. The incidence of carcinoma in patients with MNG has been reported to vary between 4% and 17%.[12–14] The prevalence of thyroid cancer is similar between patients with a solitary nodule and patients with multiple nodules;[15] therefore, a dominant or suspicious nodule in a patient with MNG should be evaluated in the same manner as a solitary nodule (i.e., suspicious nodules and nodules >15 mm in size should be considered for FNA), and characteristics seen on ultrasonography, as previously detailed, should be used to prioritize the biopsy of nodules.

Computed tomography (CT) scanning or magnetic resonance imaging (MRI) of the neck and superior mediastinum should be used selectively in patients with very large, fixed, or substernal goiters and in patients with obstructive symptoms. The anatomic relationships between the goiter, trachea, esophagus, jugular vein, and superior vena cava may be defined by CT or MRI (see Figure 2-2).

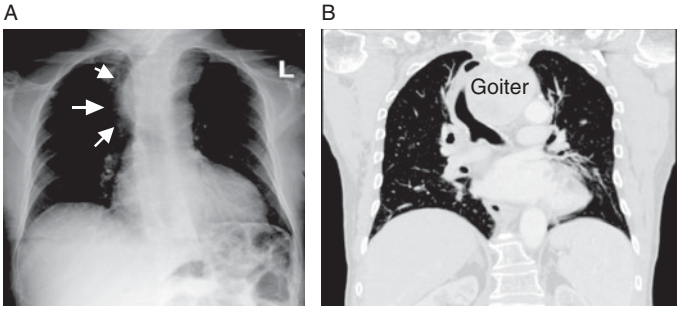

Figure 2-2. Chest radiograph (**A**) and coronal view chest computed tomography scan (**B**) showing a large substernal goiter (*arrows* in A) deviating the trachea to the right. L = left.

Pulmonary function tests with a flow–volume loop study may be used to document airway obstruction. Fiberoptic laryngoscopy may provide information regarding the appearance of the larynx, including the presence of deviation and vocal cord paralysis. These parameters should be brought to the attention of the anesthesia staff in patients undergoing surgery (Figure 2-3).

MANAGEMENT

The administration of iodine in the diet is used to prevent the development of endemic goiter. Salt is the most commonly used vehicle. There has been substantial progress in the past decade toward the elimination of iodine deficiency; despite this, it is estimated that nearly two billion individuals have insufficient iodine intake, with the most affected regions being Southeast Asia, Africa, and the Western Pacific.[1]

The natural history of sporadic nontoxic goiter appears to involve continuous growth with increasing thyroid nodularity and autonomy of thyroid function.[16] A decrease in goiter prevalence after age 75 years has been shown in an iodine-deficient community.[17] Patients may also have a stable goiter size for many years. Nevertheless, it is difficult to predict the natural history of a goiter in a given patient and therefore to decide whether an individual patient can be monitored without treatment or should be treated before the goiter grows any further.

The therapeutic goals for a patient with goiter include relief of local compressive symptoms and cosmetic deformity, prevention of progressive thyroid enlargement, treatment of associated thyroid dysfunction, and

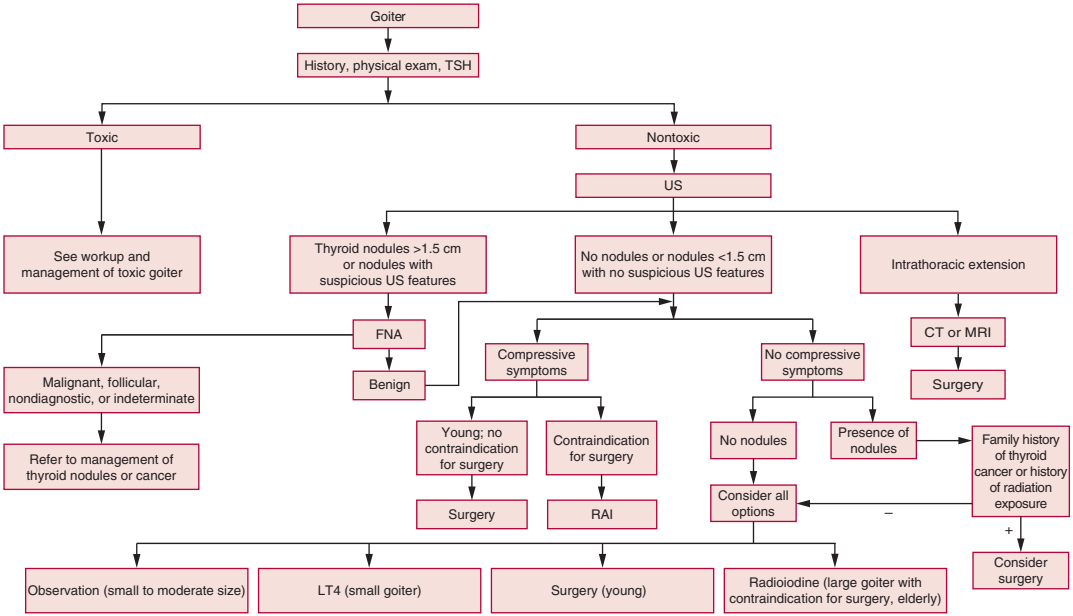

Figure 2-3. Diagnostic evaluation and management of goiter. CT = computed tomography; FNA = fine-needle aspiration; LT4 = levothyroxine; MRI = magnetic resonance imaging; RAI = radioactive iodine; US = ultrasonography.

removal of possible coexistent thyroid cancer. The symptoms of goiter vary widely among patients such that treatment must be individualized. The four main treatment options for nontoxic goiter are observation, levothyroxine (LT4) suppression, radioactive iodine, and surgical resection.

Asymptomatic euthyroid patients with small- to moderate-sized goiters without other risk factors for malignancy can be safely observed. These patients should be periodically examined with ultrasound measurement of overall thyroid and nodule size. If progressive growth is documented, surgery or radioiodine treatment should be considered. When there is any concern that malignancy may be present, the patient should undergo an FNA biopsy.

Patients with goiter accompanied by overt or subclinical hypothyroidism should be treated with LT4 to prevent symptoms and further goiter growth. The value of thyroid hormone suppression to decrease and control the size of euthyroid MNG is controversial. The idea is that by suppressing TSH, the main growth stimulus of the goiter is removed. In a questionnaire distributed to all North American members of the American Thyroid Association, LT4 therapy was used by 56% of respondents, with a TSH level between 0.1 and 0.3 mU/L as the appropriate target.[18]

In a prospective, double-blind, randomized trial, Berghout et al.[19] showed a response to treatment in 58% of the LT4-treated group, with a 25% decrease in volume after 9 months of therapy. After discontinuation of treatment, thyroid volume increased and returned to baseline within 9 months.

A more recent randomized trial from the Netherlands comparing the efficacy and side effects of suppressive LT4 therapy with ^{131}I therapy in patients with sporadic nontoxic nodular goiter showed a response rate of 43% with a decrease in goiter size by 22% at 2 years in the LT4-treated group. The chance of goiter reduction was lower if pretreatment TSH was already suppressed. Of note, there was a significant bone loss seen in this group of patients.[20] Goiters generally regrow after discontinuation of treatment, so patients need to receive indefinite treatment. Such patients may have subclinical hyperthyroidism for many years, which is associated with bone loss and an increased risk of atrial fibrillation. Because of these concerns, there has been a decline in the use of long-term T4 therapy for patients with nontoxic goiter.

^{131}I therapy may be considered for large goiters in older patients, especially those considered at high operative risk and for those who refuse surgery. Studies have shown a reduction of approximately 40% in goiter size after treatment with ^{131}I. Wesche et al.[20] showed a response rate of 97% in ^{131}I-treated patients with a decrease in goiter size of 46%. Therapeutic ^{131}I doses ranged from 12 to 90 mCi. The outcome of ^{131}I treatment was inversely related to goiter size (i.e., the larger the goiter, the smaller the relative decrease in size).

Posttherapy acute swelling of the gland with respiratory compromise is a rare complication. Long-term complications of ^{131}I therapy for patients with

nontoxic MNG include hypothyroidism, which has been shown to occur in up to 50% of patients; the development of autoimmune hyperthyroidism; and the potential risk for induction of thyroidal and extrathyroidal cancers. The literature on cancer incidences after ^{131}I therapy for nodular goiter is sparse, but a slightly higher overall cancer incidence (including stomach and bladder cancer) was suggested in patients with TNG treated with ^{131}I. The risks of leukemia and thyroid cancer do not appear to be elevated in this range of ^{131}I dose therapy.[21] Based on estimated absorbed doses in the thyroid and in the remainder of the body after therapeutic administration of ^{131}I in hyperthyroid and euthyroid patients with large MNGs, a 1.6% lifetime risk of development of fatal and nonfatal cancer outside the thyroid gland was calculated.[22] These values may be compared with the natural lifetime risk for cancer death of 20%.

Indications for surgical therapy in patients with MNG include compressive symptoms, intrathoracic extension of the goiter, suspected malignancy, hyperthyroidism, prevention of future complications, uncertainty of diagnosis, and improvement of cosmetic appearance. In patients with large cervical and substernal goiters, intubation may occasionally be difficult. Preoperative laryngoscopy findings and CT scan images should be carefully reviewed before surgery. However, laryngeal deviation generally does not represent a problem, and even with tracheal compression, a reasonably sized endotracheal tube can almost always be used. If there is any doubt as to the adequacy of a sedated mask anesthesia airway, an alternative method is an awake, sitting up, fiberoptic transnasal intubation.[23]

Because of its presumed lower complication rate, subtotal thyroidectomy has historically been the procedure of choice for patients with bilateral MNG. More recently, as surgical technique and expertise have advanced, total thyroidectomy is more commonly performed by many surgeons to prevent recurrence. In a single-institution study of 3468 patients with bilateral MNG treated with total or subtotal thyroidectomy over a 40-year period, there was no significant difference in the incidence of permanent complications between the two groups.[24]

When the goiter is unilateral, there is still controversy regarding the extent of surgery. Theoretically, when a goiter is unilateral, a unilateral lobectomy may be sufficient. However, many practitioners consider the pathologic process of the goiter to involve the entire gland and therefore perform total or near-total thyroidectomy to prevent recurrence.

The advantages of total thyroidectomy for benign goiter include avoiding the risk of leaving abnormal thyroid tissue that could potentially grow in the future and the need for a second thyroid operation that carries a higher risk for injury to the RLN and hypoparathyroidism. A high rate of recurrence has been reported after subtotal thyroidectomy for MNG (10% to 30%). Bellantone et al.[25] looked at the recurrence rate and predictive factors

for recurrence in 268 patients who underwent a lobectomy for unilateral nontoxic goiter in an endemic region after a mean follow-up of 79.9 months. They found a recurrence rate of 33.9% and a reoperation rate for recurrence of 7.4%. Predictive factors for recurrence were female gender, the presence of multiple nodules in the resected thyroid, and a lack of postoperative LT4 therapy. The authors suggested that these factors should be considered to determine an individualized surgical strategy. For patients with history of radiation exposure or a family history of thyroid cancer, total thyroidectomy should be considered independent of the extent of goiter.

Because of the risks of compression of adjacent organs, including the trachea, esophagus, and superior vena cava, resection of an intrathoracic goiter is nearly always indicated even in asymptomatic patients except in the presence of compelling contraindications. In addition, with large retrosternal goiters, FNA biopsy is frequently not applicable, and establishment of the diagnosis may be an important indication for surgery. Most intrathoracic goiters are located anteriorly in front of the subclavian and innominate vessels, but posterior mediastinal goiters with a retrotracheal component constitute 10% to 15% of all intrathoracic goiters. In experienced hands, more than 95% of retrosternal goiters can be resected with a standard collar incision. After the RLN is identified and dissected away from the goiter, either careful finger dissection or the use of a long-handled spoon in a strictly capsular plane allows for safe goiter delivery. Indications for sternotomy include recurrent intrathoracic goiter, a low-lying carcinoma with lymph node involvement, and any unsuccessful cervical delivery of a large goiter. In these cases, an upper midline sternotomy is done in addition to the collar incision.

Total thyroidectomy is a safe operation with minimal complications when performed by surgeons highly experienced in endocrine surgery. The most common complications of thyroid surgery include neck hematoma, RLN injury, and transient or permanent hypoparathyroidism. Overall, the complication rate of total thyroidectomy for benign MNG does not seem to differ from the rate for total thyroidectomy for other indications, including permanent RLN injury between 0% and 1% and permanent hypoparathyroidism between 0% and 2.7%.

In a prospective study of 301 total thyroidectomies for MNGs, postoperative complications occurred in 21% of patients with 9.6% hypoparathyroidism (0.7% permanent), 8.6% RLN injury (0.3% permanent), 1.3% superior laryngeal nerve lesions, 1% cervical hematomas, and 0.3% cervical wound infection. In a multivariate analysis, hyperthyroidism and intrathoracic component of the goiter were independent risk factors for the development of complications.[26] However, very large goiters may represent unique surgical challenges, especially because some goiters may significantly distort the position of the RLN. The nerve may be entrapped or splayed over the surface of the goiter so

that significant traction or goiter delivery would risk injury either by stretching or avulsion. It is therefore important to identify the nerve as an initial step. In retrotracheal cervical goiters and posterior mediastinal goiters, thyroid tissue is present posterior and deep to the RLN, necessitating extremely careful dissection. The superior parathyroid glands are more constant in position and are more frequently seen during thyroidectomy for goiter. The inferior parathyroid glands are more widely distributed and more likely to be significantly displaced by the goiter. Therefore, emphasis should be placed on preserving the superior parathyroid glands. In addition, a strict capsular dissection can usually preserve the displaced inferior parathyroid glands.[23]

In a retrospective record review of 29 patients with marked thyroid enlargement (unilateral or bilateral), McHenry and Piotrowski[27] showed an increase in postoperative transient hypoparathyroidism in patients with markedly enlarged thyroids compared with patients with lesser thyroid enlargement. No permanent hypocalcemia or nerve injury occurred, and the ease of intubation was unrelated to the extent of abnormality seen on imaging studies of the neck.

The role of postoperative LT4 therapy to reduce the TSH stimulation of the remnant gland and to prevent recurrence remains to be defined. Miccoli et al.[28] randomized patients after thyroidectomy to receive a substitutive dosage of LT4 (100 μg), placebo, or a suppressive dose of LT4 (2.2–3 μg/kg/day) and found the suppressive therapy to be effective in preventing recurrence of goiter in an iodine-deficient region. Previous studies have shown that suppressive therapy is effective in areas of mild or severe iodine deficiency and ineffective in iodine-sufficient areas. However, in an area of iodine deficiency, substitution with iodide has been shown to be just as effective as treating the patients with L-thyroxine for preventing recurrences.[29] Certainly, postoperative T4 medication is required in patients who have undergone extensive thyroid resection to prevent hypothyroidism.

PRACTICAL PEARLS

- Sudden growth of a nodule in the background of a long-standing goiter should raise the suspicion of cancer.
- Surgery should be recommended for younger patients, those with very large or intrathoracic goiters, those with compressive symptoms, and those with any case of clinical or cytologic suspicion of malignancy.

(*Continued*)

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Chapter 3

Hyperthyroidism

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The term *hyperthyroidism* refers to an overproduction of hormone by the thyroid gland. The resulting physiologic syndrome of excess thyroid hormone is termed *thyrotoxicosis*, although the two terms should not be used synonymously. *Hyperthyroidism* should be used to describe conditions associated with a sustained overproduction of thyroid hormone, such as Graves' disease or toxic multinodular goiter (TMNG). Several other conditions or situations result in transient increases in circulating thyroid hormone, which may result in thyrotoxicosis, but they do not cause hyperthyroidism in the strict sense of the term (Table 3-1). This chapter reviews the epidemiology, clinical presentation, evaluation, and management of patients with hyperthyroidism, focusing on surgical management.

EPIDEMIOLOGY

Hyperthyroidism is present in approximately 0.5% of the population.[1,2] An additional 0.8% of the population has mildly suppressed or undetectable serum thyroid-stimulating hormone (TSH) levels but circulating thyroid hormone levels in the normal range.[2] Additionally, the rate of development of the various causes of hyperthyroidism varies according to geographic location and is believed to be related to the iodine intake of the population. For example, an epidemiologic survey comparing an area of normal iodine intake to one with insufficient iodine intake found that Graves' disease accounted for 80% of cases of hyperthyroidism in the iodine-sufficient population but toxic uninodular and multinodular goiter accounted for the majority of cases in the iodine-deficient population.[3]

CLINICAL PRESENTATION

The clinical presentation of this disorder involves multiple symptoms that vary depending on the degree of hormone excess, the duration of illness,

TABLE 3-1. Causes of Thyrotoxicosis

Hyperthyroidism (sustained hormone excess)
Graves' disease
Toxic multinodular goiter
Toxic adenoma
HCG induced
Gestational hyperthyroidism
Trophoblastic tumors
Iodine-induced hyperthyroidism (Jod-Basedow effect)
Drug induced
Struma ovarii
TSH-secreting pituitary tumors
Metastatic functioning thyroid carcinoma
Thyrotoxicosis (transient hormone excess)
Thyroiditis
Infectious
Autoimmune
Drug induced
Iatrogenic hormone overreplacement
Thyrotoxicosis factitia

HCG = human chorionic gonadotropin; TSH = thyroid-stimulating hormone.

and the presence of other medical comorbidities. Additionally, the patient's age may affect the clinical presentation because elderly patients with thyrotoxicosis often have minimal clinical symptoms, a phenomenon termed *apathetic hyperthyroidism*.[4] Thyroid hormones, namely thyroxine (T4) and triiodothyronine (T3), are involved in the production of heat and energy; the development of the nervous system; the regulation of somatic growth and puberty; and the coordination of the synthesis of proteins involved in normal hepatic, cardiovascular, neurologic, and muscular functions. The wide range of actions of T3 and T4 on multiple organ systems accounts for the number and variability of symptoms that may accompany thyrotoxicosis (Table 3-2). Typically, patients complain of nervousness or anxiety, restlessness, palpitations, weight loss, and sensitivity to heat. Women may have irregular menses or problems with decreased fertility, and men may develop painful gynecomastia or reduced libido.[5,6]

Clinical findings frequently include tachycardia; warm, moist skin; and mild tremor. An enlarged thyroid gland is variably present. Other physical examination findings include "lid lag," which refers to a slight delay of the

TABLE 3-2. Common Signs and Symptom of Thyrotoxicosis

System	*Signs and Symptoms*
Constitutional	Weight loss or gain
	Fatigue
	Heat intolerance
Psychological	Anxiety
	Emotional lability
	Insomnia
Cardiovascular	Palpitations
	Tachycardia
	Arrhythmia
	Widened pulse pressure
Gastrointestinal	Diarrhea
	Dysphagia
	Increased appetite
Musculoskeletal	Proximal muscle weakness
	Osteopenia, osteoporosis
Respiratory	Air hunger
Integumentary	Warm, moist skin
	Onycholysis
	Pretibial myxedema
Ophthalmologic	Eyelid retraction, stare
	"Lid lag"
	Infiltrative ophthalmopathy (Graves' disease)
Reproductive	Oligomenorhea, decreased fertility (women)
	Gynecomastia (men)

eyelid in following the eye itself when having a patient look down; it is caused by increased sympathetic activity. Exophthalmos (protrusion of the eye), pretibial myxedema, and acropachy (clubbing of the fingers and toes) are specific physical examination findings in patients with hyperthyroidism caused by Graves' disease and are discussed in more detail in subsequent sections.

As previously mentioned, these clinical findings are frequently much more subtle in elderly individuals. These patients may present with congestive heart failure with an arrhythmia. Approximately 25% to 35% of these elderly patients with thyrotoxicosis develop atrial fibrillation, which is resistant to treatment until the thyroid disorder has been treated.[7] Additionally, 15% of elderly individuals with atrial fibrillation have underlying

thyrotoxicosis.[8] Another common clinical presentation of elderly patients with thyrotoxicosis is unexplained weight loss, which is commonly associated with anorexia, rather than the corresponding increase in appetite seen in younger individuals. These findings frequently initiate an exhaustive search for an underlying malignancy before thyrotoxicosis is diagnosed.[9]

Patients with thyrotoxicosis may also present with a potentially life-threatening constellation of signs and symptoms referred to as *thyroid storm*. This condition typically occurs in patients with known or undiagnosed thyrotoxicosis after a precipitating event such as surgery, trauma, childbirth, or infection. Signs and symptoms include severe tachycardia, fever, arrhythmias, congestive heart failure, agitation, psychosis, and coma.[10]

LABORATORY DIAGNOSIS

The laboratory diagnosis is relatively unambiguous and typically includes elevated serum concentrations of unbound T3 and T4 with a suppressed TSH hormone level. Measuring levels of the unbound or free fractions of T3 and T4 is preferable to measuring total serum levels because using T3 and T4 levels avoids diagnostic confusion in the setting of changing levels of thyroid-binding proteins. A minority of patients (~1%) have normal serum concentrations of T4 and elevated T3 concentrations known as T3 toxicosis.[11] Elevated T3 and T4 levels in the setting of elevated TSH levels may be seen in patients with an inappropriate TSH syndrome, such as a thyrotropin-secreting pituitary tumor or thyroid hormone resistance.[12,13]

Measurement of thyroid autoantibodies may play a role in elucidating the cause of hyperthyroidism or thyrotoxicosis. Antithyroid microsomal antibodies are antibodies to microsomes that may be released into the circulation with thyroid cell destruction (also known as *antimicrosomal* or *antithyroid peroxidase antibodies*). Increased serum levels are usually associated with Hashimoto's (chronic lymphocytic) thyroiditis but may also be seen in patients with other autoimmune conditions such as hemolytic anemia and Sjögren's syndrome.[14] Antibodies to the TSH receptor (also known as *thyroid-stimulating immunoglobulins*) are elevated in the majority (80%) of patients with Graves' disease.[15,16]

IMAGING STUDIES

Ultrasonography

All patients with evidence of thyrotoxicosis should undergo thyroid ultrasonography. This simple, noninvasive test may reveal the presence of diffuse thyromegaly, a multinodular goiter, or a solitary nodule. It may also show the characteristic ultrasound findings of thyroiditis, all of which may provide a

great deal of information to the clinician concerning the cause of the patient's thyrotoxicosis. Ultrasonography may be performed in the office and is an extremely useful aspect of the physical examination of patients presenting with symptoms of hyperthyroidism.

Thyroid Scintigraphy

With proven biochemical evidence of hyperthyroidism, thyroid scintigraphy with radioactive iodine (RAI) uptake measurement provides useful information that may direct clinical management. This nuclear medicine test typically uses iodine 123 or technetium-99m pertechnetate as radiopharmaceuticals and is a measure of the iodine avidity of the thyroid gland. Diffusely elevated uptake throughout the thyroid gland suggests Graves' disease, although focal areas of increased uptake with relative suppression of the remaining thyroid gland are indicative of toxic solitary nodule or TMNG. A diffusely low pattern of uptake is seen in thyrotoxicosis caused by thyroiditis, with excess release of preformed hormone because of cellular destruction. This is different from thyrotoxicosis caused by the excess formation of new hormone, as is the case with hyperthyroidism caused by Graves' disease, toxic adenoma, and TMNG. Thyroid scintigraphy may also reveal the presence of discrete nodules with low uptake, or "cold" nodules, necessitating additional investigation to rule out malignancy.

FINE-NEEDLE ASPIRATION BIOPSY

The role of fine-needle aspiration biopsy (FNA) in the setting of hyperthyroidism is useful when "cold" nodules, or nodules that do not show any uptake on RAI uptake scans, are present in a patient with Graves' disease or TMNG who prefers treatment with RAI ablation rather than surgery. Ruling out malignancy in cold nodules in these instances is important before proceeding with ablation therapy. In the absence of cold nodules, FNA is less important because the incidence of malignant nodules that are hyperfunctioning is extremely rare.

A thorough history and physical examination in addition to the previously mentioned biochemical and imaging studies should lead the clinician to the cause of thyrotoxicosis. The following sections go into additional detail about the causes of hyperthyroidism in which surgical resection has a role in treatment.

GRAVES' DISEASE

Epidemiology

Graves' disease is hyperthyroidism caused by the presence of circulating IgG autoantibodies that bind to and stimulate the G-protein–coupled TSH

receptor. Graves' disease affects approximately 0.5% of the population and is responsible for the majority (50% to 80%) of cases of hyperthyroidism. There is a 5:1 to 10:1 female predominance, and the peak incidence is between 40 and 60 years of age.[16,17]

A hereditary component appears to confer susceptibility to Graves' disease; its presence in a maternal relative is associated with an increased incidence of the disease and younger age at onset.[18,19] Environmental factors remain important, however, with only a 35% concordance rate between monozygotic twins.[19] Events believed to be associated with triggering Graves' disease in susceptible individuals include the use of sex steroids or immune-modulating drugs such as interferon-α, life stresses, smoking, and dietary iodine intake.[20–22]

Pathophysiology

Hyperthyroidism caused by Graves' disease is attributable to an autoimmune process, whereby constitutive stimulation of the TSH receptor by autoantibodies leads to follicular hypertrophy and hyperplasia with enlargement of the thyroid gland. This also leads to thyroid hormone overproduction with a relative increase in the production and secretion of T3 relative to T4 and consequently a suppression of TSH.[23] Iodine uptake and clearance are greatly enhanced, and the vascularity of the thyroid gland is significantly increased.

It is not entirely clear what mechanism is responsible for the autoimmune process in individuals with Graves' disease. Theories include the presence of abnormal clones of autoreactive T cells and abnormal antigen presentation by follicular cells independently or in response to cytokines released by infiltrating T-cell populations, but there is no concrete evidence that clearly delineates the exact mechanism.[16]

Clinical Presentation

The clinical presentation of patients with Graves' disease is similar in most respects to those with other forms of hyperthyroidism as previously outlined. However, several clinical features are unique to these patients. The most common of these, occurring in approximately 30% of patients, is ophthalmopathy, which presents as exophthalmos, or proptosis of the eye because of enlargement of the extraocular musculature and retrobulbar tissues caused by lymphocyte infiltration with resultant increases in connective tissue and edema. This is present variably, and the degree of protrusion as well as progression of disease can be measured with an exophthalmometer. More serious cases can be cosmetically significant and may lead to chronic desiccation of the cornea because of constant exposure, sometimes requiring orbital decompression or radiotherapy.[24]

The pathogenesis of Graves' ophthalmopathy is incompletely understood, but current hypotheses include the idea that it is another manifestation

of the autoimmune process whereby autoreactive T lymphocytes react with one or more antigens shared by thyroid cells and orbital tissues.[25] Although the identity of this antigen is not known with certainty, the TSH receptor is a logical candidate because autoantibodies to this receptor are known to be responsible for the hyperthyroidism associated with this disorder and because the TSH receptor is known to be expressed in orbital connective tissues.[26,27] After antigen recognition, a cascade of events occurs, including cytokine release, adipocyte differentiation, and fibroblast proliferation. These fibroblasts secrete glycosaminoglycans, whose hydrophilic properties attract water into these tissues, leading to edema. The resulting increase in orbital content leads to the clinical manifestations observed.[28]

Another clinical feature unique to Graves' disease is dermopathy, also known as pretibial myxedema. This is not seen as commonly as ophthalmopathy, only occurring in around 1% of these patients. Dermopathy presents as areas of nonpitting edema and thickening of the skin, typically on the anterior surfaces of the lower extremities, although it may occur in other areas of the body in advanced cases. The pathophysiology is thought to be similar to the mechanism responsible for ophthalmopathy, with antigen recognition and activation of fibroblasts and differentiation of adipocytes, leading to compression of the dermal lymphatics. TSH receptor expression has also been show to occur in dermal fibroblasts and adipocytes.[29]

Finally, thyroid acropachy is the characteristic changes in the digits seen in some patients with Graves' disease. This is also a rare finding, occurring in less than 1% of these patients, with usually only those with ophthalmopathy or long-standing hyperthyroidism developing this clinical finding. Thyroid acropachy presents as soft tissue swelling of the digits and clubbing of the distal phalanges, usually of the upper extremities, and is thought to be caused by subperiosteal bone formation.[30]

Therapy

The treatment of patients with Graves' disease involves three primary modalities, including pharmacologic therapy, RAI ablation therapy, and surgical excision. All three modalities have roles according to the clinical situation and patient preference, differing in the risks of the therapy themselves as well as the risks of recurrence of clinical hyperthyroidism.

Pharmacologic Therapy

Antithyroid drugs are frequently used as initial therapy in patients diagnosed with Graves' disease. The most common antithyroid drugs are thionamides, which include methimizole and propylthiouracil. They work primarily by inhibiting the oxidation and organic binding of thyroid iodide. Additionally, propylthiouracil inhibits the peripheral conversion of T4 to T3 by inhibiting

type 1 deiodinase.[31] Methimizole has a longer half-life than propylthiouracil (6 hours vs. 1.5 hours) and can be given once daily compared with three times a day. The most serious side effect is agranulocytosis, which occurs in only 1% to 3% of patients. Signs of agranulocytosis include the development of fever, sore throat, and oral ulcers. Patients should be advised to discontinue these medications if any of these side effects occur.

A significant reduction in symptoms of thyrotoxicosis is usually seen within 3 to 4 weeks of therapy, and β-adrenergic blocking drugs may be used in the interim for more immediate control of symptoms such as tachycardia, palpitations, tremor, and sweating. Dosages of antithyroid medications should be tailored to achieve normalization of serum T3 and T4 levels and eventually TSH levels in the normal range. Among patients with Graves' disease treated with antithyroid medications, remission is achieved 30% to 50% of the time, meaning TSH in the normal range while the patient is not receiving therapy. However, more than 50% of these patients experience a relapse.[32]

Radioiodine Therapy

RAI therapy with iodine 131 (^{131}I) may be used as an initial treatment modality or after treatment with antithyroid medications, which should be discontinued 3 days to 1 week before treatment to avoid diminishing its effect. Before treatment, a 24-hour radioiodine uptake study is frequently performed, and if the diagnosis is in question, the finding of diffuse increased uptake throughout the entire gland confirms the diagnosis. This test may also be used to calculate the dose of radioiodine.[33]

The goal of RAI therapy is to induce hypothyroidism and hopefully prevent recurrence of Graves' hyperthyroidism, which is successful in approximately 80% of cases.[34] Various dosing regimens have been tried, but there seems to be no significant difference in efficacy with standard doses compared with those calculated by dosimetry.[35] These doses vary between 55 and 200 μCi per estimated gram of thyroid tissue, which delivers a dose of radiation to the thyroid between 50 and 100 Gy.[36] Patients with persistent hyperthyroidism after initial therapy should undergo a second ablation in approximately 6 months. Recurrent hyperthyroidism occurs at a rate of 3% per year, so patients must continue to be monitored.

RAI therapy is contraindicated in pregnant women, and all women of childbearing age must have a pregnancy test before undergoing treatment. RAI is excreted in the urine, so the pelvic contents are exposed to radiation. Additionally, radioiodine crosses the placenta and can be taken up by the fetal thyroid gland after the late stages of the first trimester. Despite only having a half-life of 1 week, women are encouraged not to attempt conception for 6 to 12 months after undergoing RAI.[35]

Other side effects and adverse reactions to RAI include radiation thyroiditis, which may cause neck tenderness and the release of preformed hormone 10 to 14 days after treatment.[37] Several studies have shown that RAI may worsen ophthalmopathy in approximately 10% of patients,[38] although other studies suggest this is not the case in patients with mild orbitopathy.[39] Treatment with corticosteroids may decrease this effect,[40] but some clinicians believe the presence of ophthalmopathy is a relative contraindication to RAI therapy and that surgical resection should be recommended in these patients.[41] Some published studies show that surgical resection improves the symptoms of ophthalmopathy in up to 64% of patients, although the extent of resection (total vs. subtotal thyroidectomy) did not seem to influence symptomatic improvement; therefore, the authors advocate surgical resection as the therapy of choice in Graves' disease patients with significant eye disease.[42,43] Previously held beliefs that RAI therapy increased the incidence of other malignancies such as thyroid cancer or lymphoproliferative disorders have not appeared to be justified.[44]

Surgery

Thyroidectomy has been the least used modality in the treatment of patients with Graves' disease. Surgery has been reserved for selected patients, including those with complications or side effects from antithyroid medications, pregnant or nursing women, patients with large goiters or suspicious nodules, patients who do not wish to have exposure to even a low dose of radioactivity, and patients who want definitive treatment in a short time frame. Patients with suspicious nodules should undergo FNA to rule out malignancy before undergoing RAI therapy. A growing school of thought believes that patients with Graves' disease and discrete nodules should be treated with surgical resection because of the high risk of malignancy in this setting (as high 40% in some studies).[45] Also, as previously mentioned, more clinicians now favor surgical resection in patients with significant ophthalmopathy.

The type of surgery used to treat patients with Graves' disease traditionally involved subtotal thyroidectomy with an attempt to leave approximately 2 g of tissue overlying the recurrent laryngeal nerves (RLNs). This method was believed to offer the best chance at cure of hyperthyroidism while minimizing the risk of injury to the parathyroids and RLNs, as well as minimizing the incidence of hypothyroidism. More recently, total thyroidectomy has become the accepted surgical therapy for patients with Graves' disease because of the avoidance of the 2% to 20% reported recurrence rate of hyperthyroidism with subtotal resection,[41] with studies showing no increase in complication rates.[46]

Patients undergoing surgical resection for Graves' disease should be rendered euthyroid with antithyroid drugs preoperatively. This should be

TABLE 3-3. Advantages and Disadvantages of Therapeutic Options for Hyperthyroidism Caused by Graves' disease.

Treatment	*Pros*	*Cons*
Medication	No radiation exposure Noninvasive Lower initial cost Low risk of permanent hypothyroidism	Low cure rate Long-term compliance Adverse drug reactions
RAI therapy	Most cost effective May worsen ophthalmopathy Must defer pregnancy for 6 to 12 months; no breastfeeding 80% cure rate	Permanent hypothyroidism is frequent May worsen thyrotoxicosis
Surgery	Rapid, effective cure rate May improve ophthalmopathy Better option in the presence of worrisome nodules or large goiters	Small risk of injury to RLN and parathyroids Permanent hypothyroidism

RAI = radioactive iodine; RLN = recurrent laryngeal nerve.

established by following the patient's serum free T3 and free T4 because the serum TSH levels take longer to normalize. Additionally, these patients should receive a saturated solution of potassium iodide (SSKI) for 7 to 10 days before surgery. This has been shown to decrease the size and vascularity of the gland, making the surgery less technically challenging (Table 3-3).

TOXIC MULTINODULAR GOITER (PLUMMER'S DISEASE)

TMNG occurs in the setting of preexisting nontoxic multinodular goiter where structural and functional heterogeneity and subsequent autonomy develop slowly over time and ultimately lead to hyperthyroidism and clinical thyrotoxicosis. TMNG is responsible for approximately 5% of cases of hyperthyroidism in the United States, but it may be much more common in areas of endemic goiter caused by iodine deficiency.[47] TMNG usually presents in patients older than 50 years of age who have had a long-standing multinodular goiter. Nodules are frequently monoclonal, and TSH receptor mutations leading to constitutive activation have been identified in 60% of nodules in patients with TMNG.[48]

Although the development of thyrotoxicosis is typically gradual, it may be more rapid in the setting of iodine administration in the form of iodinated contrast during radiology studies and with medications such as amiodarone, the so-called *Jod-Basedow effect*. These patients present with the typical symptoms and signs of hyperthyroidism and are found to have a multinodular goiter on examination or ultrasonography. RAI uptake scans show overall normal uptake of radioiodine, with several areas of increased uptake and suppression of the remaining gland.

In the United States, treatment of patients with TMNG has typically been with RAI therapy. This often requires higher doses of radioiodine with consequent higher levels of radiation exposure than in RAI therapy for Graves' disease because of the overall normal uptake of iodine by the thyroid gland. The risk of recurrence of hyperthyroidism after RAI therapy is similar to that in patients with Graves' disease.[49]

Surgery, again, is usually reserved for patients with compressive symptoms, those who wish to avoid exposure to radioactivity, and those who have failed medical therapy or RAI therapy. Suspicious cold nodules should be evaluated with FNA before RAI therapy to rule out malignancy. If biopsy results are suspicious or positive for malignancy, surgical resection should ensue. Although patients should be rendered euthyroid with antithyroid medications before surgery, these do not tend to be significantly hypervascular, so treatment with SSKI is not necessary.

TOXIC SOLITARY ADENOMA

Toxic adenomas are true follicular adenomas and are the least common cause of hyperthyroidism after Graves' disease and TMNG (<5%). Again, activating mutations in the TSH receptor have been identified in the pathogenesis of the functional autonomy of these nodules, as well as downstream in the stimulatory G-protein signaling pathway linked to cyclic AMP production.[50] The frequency increases with age, although these present in a younger age group than TMNG (30s to 40s), and they are more common in women than men.

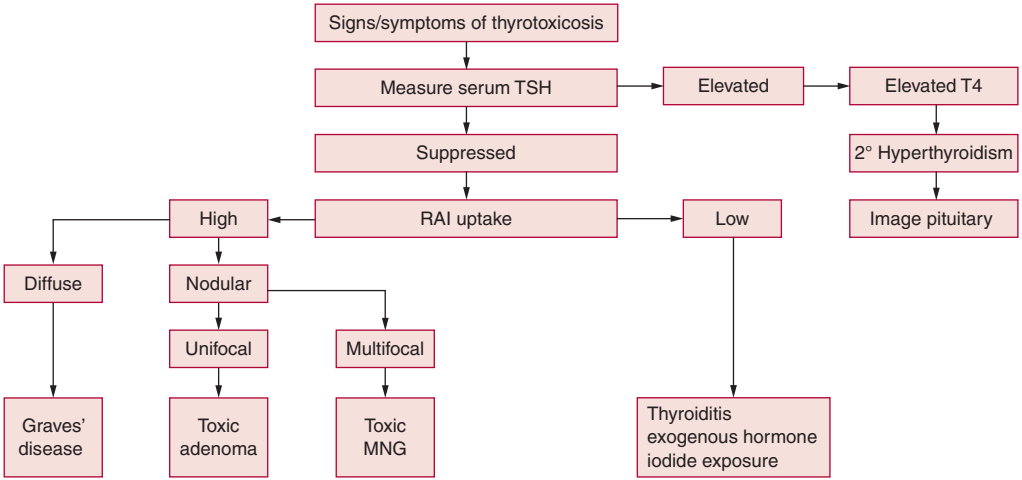
Clinical presentation is usually in the setting of a solitary nodule with a suppressed TSH level and normal or mildly elevated free T3 and T4 levels. RAI uptake scans show a single focus of increased uptake with suppression of the remaining gland. Thyrotoxicosis is rare in nodules less than 3 cm in size. As with Graves' disease and TMNG, treatment consists of RAI therapy and surgery; medical therapy alone is rarely used for patients with this condition. RAI therapy is used frequently in the United States, with surgery performed more often in other parts of the world.

When performed, surgery involves total thyroid lobectomy and isthmusectomy. FNA is generally not indicated in the setting of toxic solitary

nodule because the risk for malignancy in a hyperfunctioning nodule is extremely low. Patients should be rendered euthyroid before surgery with antithyroid medications as necessary until free T3 and free T4 are in the normal range. As is the case with TMNG, SSKI is not necessary in these patients before surgery.

PRACTICAL PEARLS

- Recurrence rates after treatment of Graves' disease are as follows:
  - Medical therapy: Remission is seen in 30% to 50% of patients treated with antithyroid medications; however, 50% of these patients develop recurrent hyperthyroidism.
  - RAI: Recurrence after treatment occurs in approximately 20% of patients, with recurrence of thyrotoxicosis occurring at about a rate of 3% per year.
  - Surgery: Recurrence after total thyroidectomy is essentially 0%. Rates of recurrent symptoms after subtotal thyroidectomy have been reported to be as high as 20%.
- Surgery and Graves' ophthalmopathy: A growing number of clinicians believe that the presence of ophthalmopathy is a relative contraindication to RAI treatment because it has been shown to worsen the retrobulbar inflammatory process; these clinicians recommend surgical resection instead. This area remains controversial, with several published reports showing improvement in orbitopathy in most patients after surgical resection and others showing no increase in incidence of worsening eye pathology after RAI therapy, especially if the patient is treated with corticosteroids.
- Initial evaluation of a patient with thyrotoxicosis: The first test to obtain after history and physical examination is the TSH level. If this is found to be suppressed, then one can proceed along the diagnostic algorithm (Figure 3-1).
- Use of RAI uptake scans: These should be obtained only when the cause of the thyrotoxicosis remains uncertain after history, physical examination, and initial laboratory tests. For example, in patients with thyrotoxicosis and several thyroid nodules, an uptake scan may be used to differentiate between TMNG, Graves' disease with the presence of discrete nodules, and toxic adenoma in the presence of other cold nodules.



RAI = radioactive iodine; TSH = thyroid stimulating hormone; MNG = multinodular goiter

Figure 3-1. Diagnostic algorithm for thyrotoxicosis. MNG = multinodular goiter; RAI = radioactive iodine; TSH = thyroid-stimulating hormone.

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Chapter 4

Papillary Thyroid Carcinoma

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EPIDEMIOLOGY

Thyroid cancer was expected to have an annual incidence in the United States of 37,340 cases in 2008 and has become the sixth most common cancer in women.[1] There has been a 2.4-fold increase in the incidence of thyroid cancer in the United States over the past 30 years, from 3.6 per 100,000 in 1973 to 8.7 per 100,000 in 2003, with virtually the entire increase attributable to the papillary type, particularly cancers smaller than 2 cm in diameter.[2]

Papillary thyroid cancer (PTC), which is a differentiated type of thyroid cancer derived from follicular epithelial cells, is the most common histologic type of thyroid cancer, occurring in about 80% of cases.[3] Multiple subtypes of PTC have been described and include the classical form that contains areas of a predominantly papillary growth pattern as well as follicles; a follicular variant of PTC (FVPTC) that grows in a follicular pattern; and more aggressive variants, including the tall cell, columnar cell, diffuse sclerosing, and insular variants of PTC.[4]

RISK FACTORS

Both genetic and environmental factors may increase the risk of developing PTC. About 3% of cases of PTC are familial.[5] Some familial syndromes known to be associated with PTC include familial adenomatous polyposis (FAP) and its variant, Gardner syndrome (both caused by a mutation in the *APC* gene); Cowden syndrome (also known as multiple hamartoma syndrome; caused by a mutation in the *PTEN* gene); and Carney complex (caused by a mutation in the *PRKAR1A* gene).[6,7] A family history of PTC in two first-degree relatives increases the risk of PTC three- to nine-fold, and these families

are likely part of a familial nonmedullary thyroid cancer (FNMTC) kindred, whose specific genetic defect has not yet been determined.[8]

The strongest evidence linking thyroid cancer to an environmental cause exists for exposure to ionizing radiation.[9] These data are derived from studies of children who were exposed to the nuclear fallout from Chernobyl, adult survivors of the atomic bombings of Hiroshima and Nagasaki, and patients who received head and neck radiotherapy in childhood for the treatment of a variety of benign conditions such as enlarged tonsils, tinea capitis, acne, or an enlarged thymus.

Other factors that have been investigated to determine their impact on the risk of developing thyroid cancer include hormonal factors, iodine intake, and the presence of Hashimoto's thyroiditis. Even though the majority of patients with PTC are women, no convincing hormonal associations have been elucidated.[10] Studies examining the influence of iodine intake on the risk of thyroid cancer have shown conflicting results, and at the present time, iodine intake is generally not considered to affect a patient's risk of developing thyroid cancer.[11] The influence of Hashimoto's thyroiditis on thyroid cancer risk is controversial, but large studies have shown an increased prevalence of Hashimoto's thyroiditis in patients with PTC.[12,13]

CLINICAL PRESENTATION

PTC is more common in women than men by a ratio of approximately 3:1 and has a median age of diagnosis of 45 years.[1,14] Patients with PTC are usually asymptomatic and present with a solitary thyroid nodule or with a gland that contains multiple thyroid nodules. These nodules are usually palpated on routine physical examination or discovered during an imaging study done for another reason. Some patients present with a palpable cervical lymph node. Occasionally, a patient presents with symptoms worrisome for an aggressive or invasive thyroid cancer such as hoarseness, dysphagia, or hemoptysis. In contrast, many PTCs incidentally discovered during the pathologic examination of a thyroid gland after surgery for benign disease, are usually less than 1 cm in diameter, and are termed *papillary microcarcinomas*. Even when patients present with cervical lymph node metastases or invasion into surrounding neck structures, PTC is largely a localized disease; distant metastases are uncommon, occurring in fewer than 4% of patients at the time of initial diagnosis.[15]

STAGING AND PROGNOSIS

The prognosis of PTC is excellent, with an overall 20- to 25-year cancer-specific mortality rate of 5%.[16] Some patients, however, have a worse prognosis than others, and multiple prognostic scoring systems have been

promulgated since the late 1970s in an attempt to distinguish patients at low versus high risk of death from thyroid cancer. The most well-known scoring systems include AGES (age, grade, extent, size), AMES (age, metastasis, extent, size); MACIS (metastasis, age, completeness of resection, invasion, size); and the EORTC (European Organization for Research and Treatment of Cancer) score, which takes into account gender, histology, invasion, and metastasis. For the most part, all of these scoring systems have been replaced by the American Joint Committee on Cancer's TNM (tumor, node, metastasis) system, which is based on the size and extent of the primary tumor (extrathyroidal extension will upstage the T stage), lymph node involvement, and the presence of distant metastasis.[17] Regardless of the classification scheme used, most patients with PTC (~80%) fall into a low-risk group, with 10-year cancer-specific survival rates of 97% to 100%.[16,18,19]

In contrast to staging systems for other cancers, most of those for PTC take into account the patient's age, which has been found to influence prognosis. In the TNM system, patients younger than 45 years are classified as having stage I or II disease, with only the presence of distant metastases distinguishing the two. It is imperative to note that patients in this age group who have lymph node metastases are still classified as having stage I disease. Patients who are age 45 years or older are categorized into having stage I, II, II, or IV disease depending on tumor size or invasion as well as lymph node or distant metastases.

In addition to the prognostic factors examined in these staging systems, other factors such as histologic subtype of PTC, as well as genetic factors, have been associated with a worse prognosis. The tall cell, columnar cell, diffuse sclerosing, and insular histologic variants of PTC, as well as PTCs that contain a mutation in the gene for the B-type isoform of RAF kinase (BRAF), are considered more aggressive.[4,20]

DIAGNOSTIC EVALUATION

The diagnostic investigation of a patient with PTC usually begins with the evaluation of a thyroid nodule, which includes ultrasonography of the thyroid gland and measurement of serum thyroid-stimulating hormone (TSH) level. A diagnosis of PTC is usually made by fine-needle aspiration (FNA) biopsy. Although most patients with thyroid cancer are euthyroid, higher TSH concentrations, even within the normal range, may be associated with an increased risk of cancer in a thyroid nodule.[21]

After a diagnosis of thyroid cancer has been established, the patient should then undergo preoperative staging (Figure 4-1). Because the pattern of spread of PTC is usually lymphatogenous, ultrasound examination of the cervical lymph nodes may help determine the extent of disease. Studies have

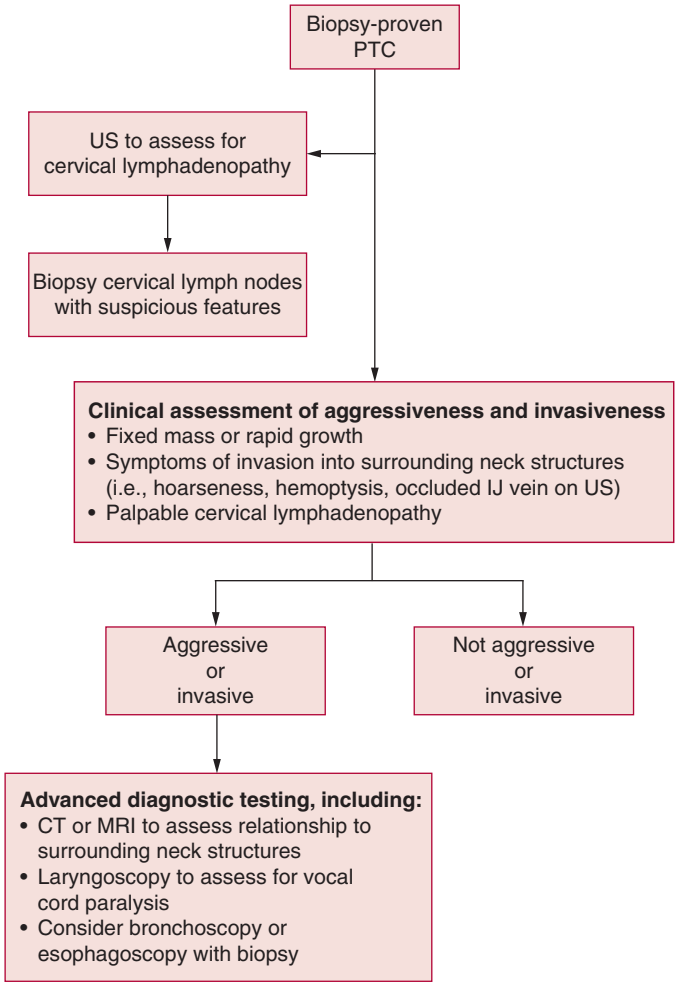


Figure 4-1. Diagnostic algorithm for the evaluation of patients with biopsy-proven papillary thyroid cancer (PTC). All patients should undergo cervical ultrasonography (US) to assess for suspicious lymphadenopathy. A clinical assessment of the aggressiveness or invasiveness of the thyroid cancer should be done, with further diagnostic testing ordered based on patient history, symptoms, and physical examination findings. IJ = internal jugular.

shown that routine preoperative ultrasonography can detect nonpalpable lymph node metastases in 14% to 20% of patients, which then changes the planned initial operation.[22,23] In addition, ultrasonography may demonstrate the patency of the internal jugular veins. The guidelines of the American Thyroid Association (ATA) and American Association of Clinical Endocrinologists both recommend the routine use of preoperative neck ultrasonography to evaluate the cervical lymph nodes in patients with a diagnosis of PTC,[24,25] but the guidelines of the National Comprehensive Cancer Network (NCCN) recommend only consideration of this test.[7] If a suspicious-appearing lymph node is detected by ultrasonography, FNA biopsy should be performed.

Other diagnostic tests should be tailored to the clinical assessment of how aggressive or invasive the thyroid cancer is suspected to be (see Figure 4-1). Features that should increase the preoperative suspicion of an aggressive or invasive thyroid cancer include rapid growth of the tumor, fixation to surrounding structures, symptoms of invasion into surrounding neck structures (e.g., hoarseness or hemoptysis), occluded internal jugular veins, and palpable cervical lymphadenopathy. In these patients, other cross-sectional imaging tests such as computed tomography (CT) or magnetic resonance imaging (MRI) may be helpful in determining the extent of the tumor and planning the extent of resection. Cross-sectional imaging studies are also useful when a substernal extension of the thyroid gland is present. It is important to note that CT imaging should be done without intravenous contrast because the administration of iodinated contrast agents may obviate the use of postoperative radioactive iodine (RAI) for several months. Other imaging, such as fluorodeoxyglucose positron emission tomography (FDG-PET) scanning, may be useful in patients with poorly differentiated PTC, who are at increased risk of distant metastases. The use of CT, MRI, and FDG-PET in the routine evaluation of patients with PTC, however, is not recommended.[25]

In addition to cross-sectional imaging, endoscopic examination via laryngoscopy, bronchoscopy, or esophagoscopy is recommended if there is a preoperative suspicion for invasion into the recurrent laryngeal nerve (RLN), trachea, or esophagus, respectively. The role of routine vocal cord examination in the evaluation of patients with PTC is controversial. Some experts recommend selective preoperative laryngoscopy only for symptomatic patients or for patients who have previously undergone a cervical operation because studies examining this issue have shown that most patients with a preoperatively identified RLN palsy were symptomatic, had previously undergone thyroid surgery, or had an invasive thyroid cancer.[26–28] Others recommend routine laryngoscopy because patients with thyroid malignancies may have a "silent" (i.e., compensated) preoperative RLN palsy. Discovery of a preoperative RLN palsy suggests extrathyroidal extension of the tumor and may change the operative plan, and routine

postoperative laryngoscopy allows surgeons to accurately analyze their RLN-related complication rates.

MANAGEMENT

The management of patients with PTC consists of four main components: adequate surgical extirpation of disease, adjunctive RAI ablation in selected cases, TSH suppression, and surveillance. The overall management strategy for any individual patient depends on preoperative and intraoperative findings as well as the final TNM classification and postoperative evaluation (Figures 4-2 and 4-3).

The surgical options for resection of the primary cancer include thyroid lobectomy versus total or near-total thyroidectomy. One of the ongoing debates in the treatment of patients with PTC over the past several decades has been the extent of thyroidectomy, particularly for small, intrathyroidal, low-risk, well-differentiated PTCs. Because of the low incidence of thyroid cancer and its overall good prognosis, no controlled, prospective studies have compared the surgical treatment options, so these debates are thus likely to continue. Those supporting thyroid lobectomy as the treatment of choice argue that some studies have shown no survival benefit to more extensive thyroidectomy[19,29,30] and that lobectomy is associated with lower rates of complications, such as RLN injury and permanent hypoparathyroidism. Arguments supporting total thyroidectomy include reports that have shown that more extensive thyroidectomy is associated with lower recurrence rates and a survival benefit compared with lobectomy.[31,32] Also, in the hands of experienced endocrine surgeons, the complication rates are comparable for total thyroidectomy and lobectomy.[33,34] PTC is multifocal in up to 80% of cases and bilateral in up to 60%,[35,36] and removal of the entire thyroid gland facilitates the use of postoperative RAI to treat residual microscopic or metastatic disease and allows for the use of serum thyroglobulin (Tg) postoperatively as a sensitive marker for recurrent disease.

Consensus guidelines recommend total or near-total thyroidectomy as the preferred initial procedure for patients with PTC, with absolute indications including a history of radiation exposure, familial thyroid cancer, tumor size greater than 4 cm, known extrathyroidal extension, cervical lymph node or distant metastasis, or an aggressive histologic variant of PTC.[7,25]

Another area of controversy in the treatment of patients with PTC is the extent of lymphadenectomy. Lymph node metastases from PTC are very common, with contemporary series of prophylactic neck dissections demonstrating a prevalence of 33% to 63% for central neck (pre- or paratracheal [level VI]) nodal metastases, and a prevalence of 57% to 64% for lateral neck (internal jugular vein [levels II, III, and IV]) nodal metastases not

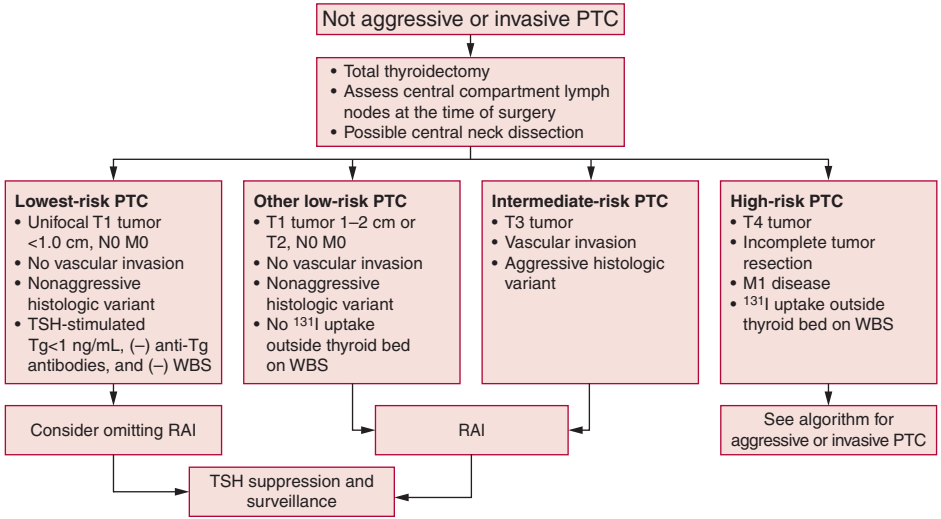
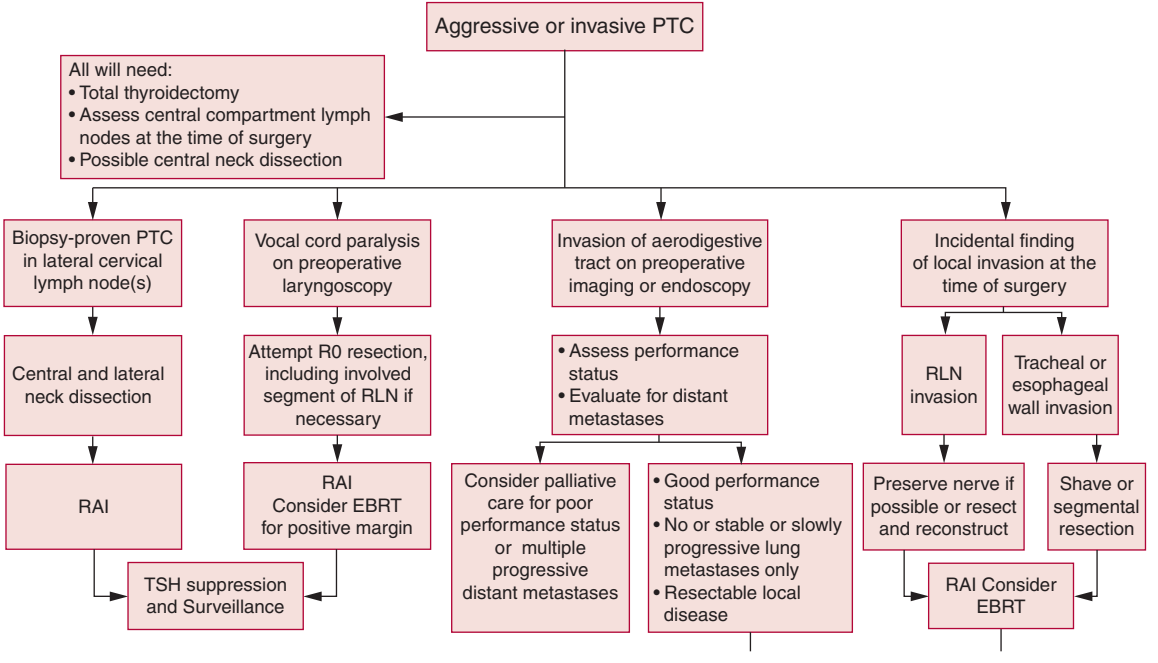


Figure 4-2. Management algorithm for papillary thyroid cancers (PTCs) that are not aggressive or invasive based on preoperative assessment. All patients should undergo total or near-total thyroidectomy with evaluation of central compartment lymph nodes at the time of surgery and central neck dissection for biopsy-proven nodal metastases. Radioactive iodine (RAI) ablation may be omitted in patients with PTC who are at the lowest risk for having persistent or recurrent disease. Other low-risk or intermediate-risk patients[25] should undergo RAI ablation followed by thyroid-stimulating hormone (TSH) suppression and surveillance. High-risk patients[25] should be treated according to the algorithm for aggressive or invasive PTC. ^{131}I = iodine 131; Tg = thyroglobulin; WBS = whole-body radioactive iodine scan.


Aggressive or invasive PTC
All will need:
• Total thyroidectomy
• Assess central compartment lymph nodes at the time of surgery
• Possible central neck dissection
Biopsy-proven PTC in lateral cervical lymph node(s)
Vocal cord paralysis on preoperative laryngoscopy
Invasion of aerodigestive tract on preoperative imaging or endoscopy
Incidental finding of local invasion at the time of surgery
Central and lateral neck dissection
Attempt R0 resection, including involved segment of RLN if necessary
• Assess performance status
• Evaluate for distant metastases
RLN invasion
Tracheal or esophageal wall invasion
RAI
RAI
Consider EBRT for positive margin
Consider palliative care for poor performance status or multiple progressive distant metastases
• Good performance status
• No or stable or slowly progressive lung metastases only
• Resectable local disease
Preserve nerve if possible or resect and reconstruct
Shave or segmental resection
TSH suppression and Surveillance
RAI Consider EBRT

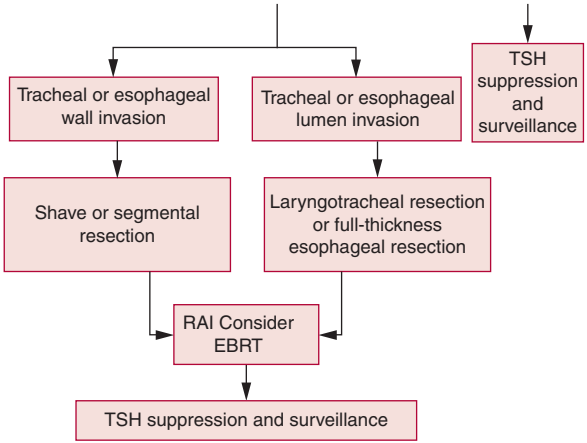


Figure 4-3. Management algorithm for papillary thyroid cancers (PTCs) that are aggressive or invasive based on preoperative assessment. All patients should undergo total or near-total thyroidectomy with evaluation of central compartment lymph nodes at the time of surgery. Central neck dissection should be done for biopsy-proven nodal metastases and in patients who require a lateral neck dissection for biopsy-proven disease. Treatment of recurrent laryngeal nerve (RLN) invasion should depend on the patient's preoperative function. Treatment of aerodigestive tract invasion should depend on the extent of invasion, the extent and progression of distant metastatic disease, and the performance status. All patients should undergo radioactive iodine (RAI) ablation followed by thyroid-stimulating hormone (TSH) suppression and surveillance. External beam radiation therapy (EBRT) should be considered in select patients.

detected by preoperative ultrasonography.[37–40] Despite these high numbers, however, the significance of lymph node metastases is unclear because some studies have shown that lymph node metastases have no impact on overall survival, particularly in patients younger than age 45 years.[17,30,41]

Therapeutic compartment-oriented lymph node dissection is indicated for patients with known cervical nodal metastases. Selective node removal, or "berry picking," should not be done because patients with PTC may develop recurrent disease within a previously dissected compartment, possibly necessitating high-risk revisional lymphadenectomy. Lymph node metastases are usually identified preoperatively by palpation or by ultrasonography and confirmed by FNA biopsy. The central compartment of the neck is less completely evaluated by preoperative ultrasonography[23] and should also be evaluated at the time of thyroidectomy, with a central neck dissection performed if a suspicious-appearing lymph node is confirmed to contain metastatic PTC on frozen section analysis.

The role of prophylactic lymphadenectomy in the treatment of patients with PTC is controversial. Prophylactic lateral neck dissection is not done in Europe and the United States. Prophylactic central neck dissection, however, remains an area of controversy. Proponents of routine prophylactic central neck dissection argue that central neck nodal metastases are common.[37–39] Some studies have shown that regional lymph node metastases are associated with higher rates of recurrent disease,[42–44] and patients who develop recurrent disease have higher rates of cancer-specific mortality.[42,44,45] Opponents of routine prophylactic central neck dissection argue that other studies have shown that lymph node metastases have no impact on overall survival[17,30,41] and that this procedure is associated with a higher risk of complications, with reported rates of transient vocal cord paralysis of 2% to 7%, rates of transient hypoparathyroidism of 14% to 60%, and rates of permanent hypoparathyroidism of 2% to 5%.[39,46,47] Major consensus guidelines disagree with respect to prophylactic central neck dissection: the ATA guidelines recommend considering routine central compartment neck dissection for patients with PTC but state that near-total or total thyroidectomy without central neck dissection may be an alternative approach when followed by RAI.[25] On the other hand, the NCCN guidelines do not advocate routine central neck dissection and only recommend it if lymph nodes are palpable or biopsy-proven positive for metastatic disease.[7]

Locally advanced disease may be overt or found incidentally at the time of thyroidectomy. If aerodigestive tract invasion is seen on preoperative imaging or endoscopy, the patient's performance status and extent and progression of metastatic disease should help guide the decision to perform an extensive laryngotracheal or full-thickness esophageal resection versus palliation with intraluminal laser tumor debulking or stenting. If just the

tracheal or esophageal wall is involved, it may be reasonable to shave the tumor off these structures, resect the outer muscular wall of the esophagus, or perform a limited segmental resection. Management of patients with RLN invasion depends on the preoperative function; if the ipsilateral vocal cord is paralyzed, then an R0 resection should be attempted, which may include resecting the involved segment of the nerve. If, however, the ipsilateral vocal cord is functioning, then the nerve should be preserved if possible. Resection and reconstruction may be necessary. Internal jugular vein invasion should be managed by unilateral resection; the rare circumstance of bilateral internal jugular vein invasion may be managed with bilateral resection, but these two procedures should be staged at least 6 weeks apart. External-beam radiotherapy should be considered for positive margins.

The second component of the global treatment strategy for patients with PTC is RAI ablation. It is usually administered 4 to 12 weeks after surgery, and its purpose is to destroy any remnant thyroid tissue after thyroidectomy and to treat occult or known metastatic disease. A controversy in the use of RAI is that although some studies show that it reduces rates of recurrence and cancer-specific mortality,[45,48–50] other studies have shown no benefit,[3,16,30,50] particularly for patients classified as having low-risk PTC. Both the ATA and NCCN consensus guidelines recommend RAI ablation for all patients with PTC except select patients with stage I disease who are at very low risk for recurrence (e.g., those with well-differentiated, unifocal tumors smaller than 1 cm, no extrathyroidal extension or vascular invasion, and no lymph node or distant metastases).[7,25] In addition, the NCCN guidelines recommend omitting RAI ablation in patients who have a negative whole-body RAI scan with Tg levels below 1 ng/mL and negative anti-Tg antibodies under conditions of adequate TSH stimulation.[7]

The isotope used for ablation is iodine 131 (I^{131}), which is administered in oral form as sodium iodide and has a half-life of 8 days. Contraindications to the use of RAI include pregnancy and lactation. Women of childbearing age should have a negative pregnancy test result before treatment and are advised to not become pregnant for at least 6 to 12 months after treatment. Preparation for treatment includes following a low-iodine diet for 1 to 2 weeks and discontinuing all iodide-containing products (including multivitamins), thyroid hormones, and amiodarone to allow the TSH to increase to above 30 mIU/mL and stimulate maximal uptake of the I^{131}.[51] Some physicians treat patients after administration of recombinant human TSH (rhTSH) rather than after withdrawal of thyroid hormone. Based on a prospective, international, multicenter trial, the US Food and Drug Administration approved the use of rhTSH to facilitate RAI ablation of thyroid tissue remnants in patients who have undergone near-total or total thyroidectomy for well-differentiated thyroid cancer in the absence of metastatic disease.[52]

The third component in the global treatment strategy for patients with PTC is administration of supraphysiologic doses of thyroid hormone in the form of levothyroxine (LT4). The rationale behind this therapy is to suppress TSH, which is a known stimulator of thyroid cell proliferation. Large retrospective and prospective studies, as well as a meta-analysis, have demonstrated that patients treated with TSH suppressive doses of LT4 have a decreased risk of major clinical adverse events, particularly in patients with PTC who fall into a high-risk group.[45,53,54] The ATA consensus guidelines recommend TSH suppression to below 0.1 mIU/mL for high-risk patients and to between 0.1 and 0.5 mIU/mL for those in the low-risk group.[25]

The last component in the global treatment strategy for patients with PTC is surveillance. Tumor burden should be monitored periodically by experienced physicians. The measurement of serum TSH, Tg, and anti-Tg levels; cervical ultrasonography; and RAI scanning are all sensitive for the presence of residual or recurrent disease. Anti-Tg antibodies, which are present in about 25% of patients with thyroid cancer and can falsely lower serum Tg levels,[55] should always be measured concurrently with TSH and Tg. Serial anti-Tg antibody levels may be followed as a surrogate marker for Tg.[25]

The strategies used for PTC surveillance are highly variable and institution specific. What follows is a basic strategy based on consensus guidelines. Initial follow-up should occur at 6 and 12 months after RAI remnant ablation and should consist of measurement of TSH, Tg, anti-Tg antibodies, and cervical ultrasonography. If the unstimulated Tg level is undetectable (<1 ng/mL) and the cervical ultrasonography results are negative, Tg should be remeasured under conditions of LT4 withdrawal or rhTSH stimulation.[7,25] If the patient is disease free (Tg <2 ng/mL), retesting should be done on an annual basis. If the stimulated Tg is detectable (>2–5 ng/mL), however, then the patient should undergo a whole-body RAI scan (WBS). If the WBS results are positive, further management depends on the site(s) of recurrent disease. If the WBS results are negative, FDG-PET scanning should be considered for further evaluation.[7]

Patients with a locoregional recurrence should have it confirmed by FNA biopsy and then undergo surgery if the recurrence is resectable. These locoregional recurrences are usually lymph node metastases that survived the initial RAI ablation, and appropriate treatment consists of a formal lymph node dissection of the involved lateral or central compartment. If the recurrence is in a previously dissected compartment, then excision of the solitary recurrence is appropriate, although other surrounding lymph nodes are often found to be positive at the time of surgery. This is recommended even in the presence of distant metastatic disease to palliate symptoms or to prevent subsequent airway or esophageal obstruction. Resection of locoregional recurrences should be followed by another treatment dose of RAI if the tumor is iodine avid.

Surgery may also be appropriate for selected patients with distant metastatic disease. Patients with central nervous system metastases may be treated with neurosurgical resection or stereotactic radiosurgery.[7] Patients with bony metastases may be treated with surgical resection or external-beam radiation therapy for palliation.[7] Surgical resection may also be considered for select extracervical sites of metastatic disease (most commonly the lung) if these lesions are solitary, enlarging, or causing symptoms.[7] Total thyroidectomy should be considered in the setting of metastatic differentiated thyroid cancer to facilitate efficacy of RAI. After surgical resection, RAI therapy should be considered for iodine-avid tumors in patients who have not reached the radiation exposure limits.[7]

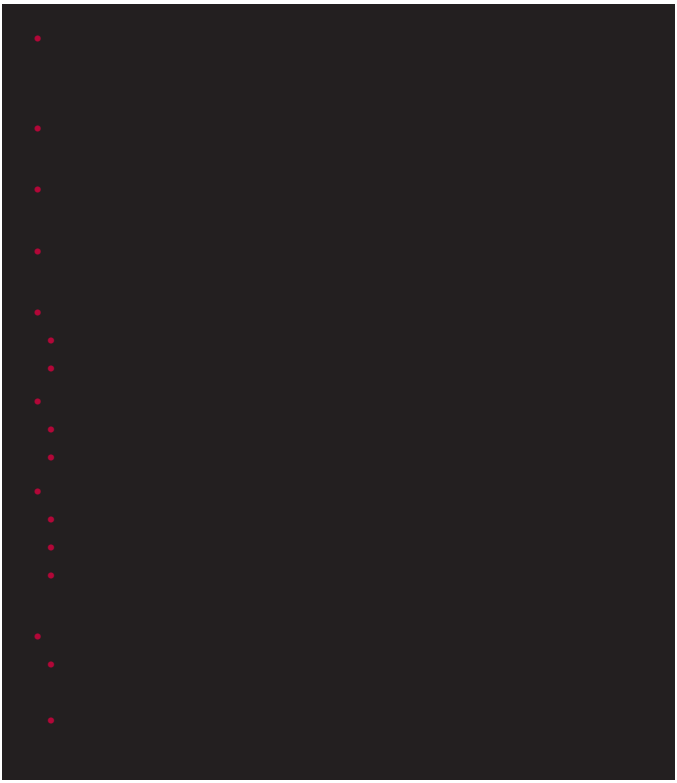
Cytotoxic chemotherapy has not traditionally been found to be effective in the treatment of patients with PTC.[56] It is not indicated in the adjuvant treatment of patients with resected PTC. For advanced, RAI-resistant differentiated thyroid carcinoma, the agent that has historically been implemented is doxorubicin. Response rates of up to 40% have been reported, although the duration is short lived.[57] In essence, cytotoxic chemotherapy has a limited role in the armamentarium for metastatic disease.

Novel therapies for the treatment of patients with advanced or metastatic PTC include redifferentiation agents, which are agents that target the Ras pathway, the BRAF pathway, vascular endothelial growth factor and its receptors, the epidermal growth factor receptor pathway, and other angiogenic pathways with agents such as thalidomide and proteasomes.[58,59] Some agents, such as sunitinib and sorafenib, inhibit multiple receptor tyrosine kinases and thus target multiple pathways involved in tumor growth. A recent phase II trial implementing sorafenib for patients with metastatic, iodine-refractory thyroid carcinoma demonstrated an overall clinical benefit rate (partial response or stable disease) of 77%.[60] The data are preliminary, and further trials are needed to validate the drug's long-term efficacy. Enrollment in clinical trials for patients with advanced thyroid cancer is strongly encouraged.

PRACTICAL PEARLS

- The operation may be truncated at hemithyroidectomy for patients with inadvertent RLN injury, especially in those with low-risk PTC.
- Parathyroid tissue with questionable viability may be autotransplanted, but it should first be proven with frozen section that it is not cancerous.

(*Continued*)



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Chapter 5

Follicular Thyroid Carcinoma and Oncocytic (Hürthle Cell) Carcinoma

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EPIDEMIOLOGY

A normal human thyroid gland contains 20 to 30 million spherical follicles lined with follicular epithelial cells filled with colloid and stores a 3 months' supply of thyroid hormone.[1] Among the several differentiated thyroid cancers that originate from thyroid follicular cells, 10% to 15% are follicular thyroid carcinomas (FTCs) and 3% to 5% are oncocytic (Hürthle) cell carcinomas (HCCs).[2] Recent studies suggest that FTC may represent only 5% of differentiated thyroid cancer in geographical regions with well-supplemented iodine diets. In iodine-deficient regions, however, FTC may account for up to 25% to 40% of thyroid carcinomas.[3] In contrast, HCC may be more common in areas with iodine-rich diets.[4] The mean age at presentation is higher for HCC (55 years) than for FTC (48 years). In most reports, both disorders are approximately twofold more common in women than men.[5]

Hürthle cells are also called *oncocytic* or *oxyphilic cells*. According to the most recent World Health Organization (WHO) classification, the current correct term for HCC is actually *oncocytic carcinoma*.[6] Hürthle cells were first described by Hürthle in 1894. Although it is now thought that the cells he described were actually parafollicular C cells, what we today call Hürthle cells are derived from follicular cells and may develop in response to defects in mitochondrial DNA.[7] Histologically, they are large and characterized by abundant eosinophilic (pink) cytoplasm with a large nucleus.

Hürthle cells are seen in patients with benign reactive thyroid diseases such as autoimmune thyroiditis, multinodular goiter, and Graves' disease and in patients treated with systemic chemotherapy.[8]

HCC is often classified as a variant of FTC, but a number of differences are seen (Table 5-1). Compared with FTC, HCC is associated with a higher risk of local recurrence (24% vs. 3%),[5] and unlike other differentiated thyroid carcinomas, HCC is not as iodine avid.[9] Distant metastatic disease develops in up to 20% of FTC patients (most commonly to the bone and lung) and in 30% of HCC patients (to the lung and lymph nodes). Survival

TABLE 5-1. Characteristic Features of Follicular and Oncocytic (Hürthle Cell) Carcinomas

Histologic Subtype	*Follicular*	*Oncocytic (Hürthle Cell)*	*References*
Age at presentation (mean)	40–50 years	50–60 years	5, 52, 54, 48, 49
Risk factors	Iodine deficiency Radiation exposure Genetic disorders	Radiation exposure	3, 4, 14, 15, 18, 19
Ras mutation or *PAX8-PPARγ* rearrangement	≤85%	10%	38, 39, 42, 43, 46
Multifocal	<2%	10% to 30%	4, 49, 52
Lymph node metastasis	<10%	20% to 25%	49, 52, 68, 72
Local recurrence	5% to 30%	25% to 50%	5, 71, 94
Distant metastatic rate	10% to 20%	30% to 35%	5, 48, 52
Common metastatic sites	Bone, lung	Lung	5, 48, 52, 94
Iodine avidity	50% to 75%	<10%	53, 75
10-year mortality	85%	75%	2

is equivalent when stratified by stage and at 5 years, but at 10 years, patients with HCC have a poorer survival (76% vs. 85%).[2,10]

Based on studies identifying regions of differentiated thyroid carcinoma within anaplastic tumor, FTC or HCC may dedifferentiate into more aggressive poorly differentiated or anaplastic thyroid carcinoma. The molecular mechanisms that cause this progression of malignancy are the subject of ongoing study.[11,12]

RISK FACTORS

Ionizing Radiation

Exposure to ionizing radiation is a risk factor for both Hürthle cell and follicular thyroid neoplasms, with exposed women at higher risk than men. The risk is also dependent on the dose received and the individual's age at the time of exposure.[13] After exposure, the risk appears to peak at 25 to 30 years but continues to be significant for up to 40 years.[14] The mean latency period for FTC is shorter (21 years) than for benign follicular adenoma (FA) (35 years), and radiation exposure does not alter the prognosis in either HCC or FTC.[15]

Inherited Syndromes

Isolated familial FTC and familial HCC are both very rare. In a study from Japan, the incidence of FTC among patients who had one or more first-degree relatives with FTC was 1.9%, and familial cases had no prognostic differences compared with sporadic cases.[16] In a study from the Swedish Family-Cancer Database evaluating 3292 patients with thyroid cancer, there were no cases of FTC when parents were diagnosed with any thyroid cancer.[17] There was a significant association between HCC and lymphoma; in four patients with HCC, two had parents diagnosed with Hodgkin's lymphoma and two had siblings diagnosed with non-Hodgkin's lymphoma. Additional studies are needed to validate this association.[17]

FTC has been associated with Cowden syndrome and Carney complex type 1. Cowden syndrome is an unusual autosomal dominant adult-onset inherited disorder that is caused by germline mutations in the *PTEN* tumor suppressor gene and is associated with an increased risk of breast cancer (25% to 50%) and thyroid cancer, particularly FTC (3% to 10%). In the practice of endocrine surgery, however, the presence of macrocephaly (head circumference that is >99th percentile for age) and characteristic mucocutaneous lesions on physical examination are common and should always raise clinical suspicion for the disorder.[18]

Carney complex type 1 is associated with an increased risk of differentiated thyroid carcinoma (DTC) (4%), either FTC or papillary thyroid cancer

(PTC), and benign FA (6%).[19] Other characteristics include cardiac myxomas and pigmentations of the skin and mucosa. Mutations of the protein kinase A regulatory subunit type 1α gene have been identified in affected patients.[19]

Other Genetic Susceptibilities

Genetic linkage analyses of large kindreds have identified possible chromosomal regions that may be associated with benign thyroid nodules and familial nonmedullary thyroid cancers. These loci include chromosome 1q21 (fPTC/PRN), 2q21 (fNMTC1), and19p13 (TCO).[20] Linkage to TCO, in particular, has been associated with familial HCC.[21]

Mitochondrial DNA mutations have been proposed to be a cause in the formation of HCC.[7] Approximately 15% of Hürthle cell variants of follicular and PTC have a mutation in *GRIM-19*, a regulatory gene involved in apoptosis and mitochondrial metabolism.[21]

CLINICAL PRESENTATION AND DIAGNOSTIC EVALUATION

The majority of FTC and HCC present as solitary thyroid nodules first identified on physical examination by the patient or physician or incidentally on imaging. Most patients are asymptomatic. The routine evaluation of patients with thyroid nodules should include assessment for symptoms such as dysphagia (to solids), positional dyspnea, orthopnea, anterior neck pain, and hoarseness. A history of supine dyspnea relieved by turning onto one's side is suggestive of a substernal component causing tracheal compression (Carty, unpublished data). Symptoms of hyperthyroidism or hypothyroidism should be queried, but these diagnoses will ultimately be determined with thyroid function testing, which should include thyroid-stimulating hormone (TSH), thyroxine (T4), triiodothyronine (T3), and free thyroxine index (FTI) levels within the past 3 months. A history of observed nodule growth, either on serial imaging or physical examination, suggests thyroid malignancy. The neck examination should focus on the size of the nodule, firmness, mobility, presence of contralateral thyroid nodules, tracheal deviation, signs of hyperthyroidism, and lymphadenopathy. Patients who are hoarse or who have had prior cervical exploration should always undergo preoperative laryngoscopy to evaluate vocal fold function.

Neck ultrasonography is very useful in determining nodule size and characteristics. Worrisome sonographic characteristics include irregular margins, microcalcifications, increased intranodular vascularity, height greater than width, and hypoechogenicity.[22] Ultrasonography can also easily distinguish cystic from solid nodules, determine if a nodule originates from the thyroid or is perithyroidal, and detect or exclude cervical

lymphadenopathy. Lymph nodes are considered enlarged if they are larger than 1 cm in size. Irrespective of size, suspicious characteristics, including round shape, loss of echogenic hilum, and calcifications, should prompt aspiration sampling for cytologic evaluation.[23] Ultrasonography may be limited by operator experience and may not be useful in the evaluation of mediastinal or low-level VI nodes.

Computed tomography may also be used with comparable sensitivity and specificity to assess for the presence of metastatic nodal disease, but it is more expensive, involves exposure to radiation, and occasionally results in a mistaken use of iodinated contrast, which may significantly delay the therapeutic administration of iodine 131 (^{131}I) if thyroid cancer is diagnosed.[24] Magnetic resonance imaging has been also shown to accurately identify nodal disease.[25] Ultimately, the advantages of using ultrasonography, most notably its decreased cost and biopsy capability, have made it the modality of choice for preoperative staging.[26,27]

In the evaluation of thyroid nodules, fine-needle aspiration (FNA) biopsy should be the initial diagnostic test. FNA results determine clinical management. In general, all nodules that are sonographically suspicious, larger than 1 cm, or clinical concerning should undergo FNA.[28] FNA may be performed guided by palpation or ultrasonography. Although palpation-guided biopsy is convenient and may be more cost effective, ultrasound guidance decreases the rate of inadequate yield and ensures that the nodule of interest is actually being accurately sampled.[29,30] FNA is performed by introducing a 25-gauge, long, beveled needle attached to a syringe (with or without a pistol-grip device) into the nodule. A series of rapid advance and withdrawal motions (at a rate of ~3 excursions/sec) over 2 to 5 seconds is usually sufficient to obtain adequate sampling. The sample is then smeared onto one or two slides and immediately preserved with fixative.[31] Inadequate FNA rates are usually less than 5%.[29,32] These rates should be monitored by those who routinely perform FNA to ensure that equivalent rates are maintained.

Follicular neoplasms (FNs) are diagnosed in 10% to 20% of FNA biopsies and are characterized by follicular cells with a paucity of colloid. The cells may be arranged in groups or in microfollicles.[33] Although Hürthle cell neoplasm (HCN) should be categorized as a distinct category separate from FN, historically this has not always been the case. The differentiation between FN and HCN is important because clinical factors may alter the risk of malignancy, potentially affecting the extent of initial diagnostic thyroid surgery. On FNA, HCN usually demonstrates minimal colloid with a hypercellular population of Hürthle cells arranged as a monolayer, groups, or single cells.[33]

One of the current limitations of thyroid cytology is the inability to differentiate between benign and malignant disease when an FN and HCN is diagnosed. The differential diagnosis is broad and includes FA, oncocytic

adenoma, parathyroid adenoma, follicular or oncocytic variant of PTC, FTC, and HTC, and tissue histopathology is required to make the differentiation (Figure 5-1). Subsequently, the presence of FN or HCN results should prompt diagnostic thyroidectomy. Carcinoma is diagnosed in approximately 20% of FN cases and up to 35% of HCN cases.[33]

Cytologic and histologic differentiation between FTC and follicular variant of PTC (FVPTC) can be challenging. FVPTC is diagnosed when characteristic PTC cells have a follicular growth pattern, and it often occurs in a background of nodular goiter.[3] Even among expert pathologists, the degree of concordance in differentiating between FTC, FA, and FVPTC is below 50%.[34,35] Being able to differentiate between the histologic subtypes is important for clinical management; for example, whereas PTC has a propensity for lymph node metastases, distant metastatic disease is more commonly seen in patients with FTC. Immunohistochemical markers, such as CK-19, HBME-1, and Galectin-3, are expressed strongly in patients with DTC but more so in those with FVPTC than FTC and may be used to help differentiate between the three types of lesions. These markers are also sometimes expressed in patients with benign lesions.[36]

Recent advances in molecular pathology have identified genetic changes that may help to differentiate thyroid carcinomas from adenomas before cervical exploration. Loss of heterozygosity (LOH) as a marker of genetic instability has been used to differentiate between FA and FTC. In a panel of markers corresponding to known tumor suppressor genes, LOH was increased in FTC compared with FA. In addition, poor patient outcome was correlated with increasing genetic instability.[37]

Other genetic changes implicated in thyroid carcinogenesis are summarized in Table 5-2. Point mutations in the *Ras* gene have been associated with 40% to 50% of patients with FTC but are also seen in those with benign adenomas and FVPTC[38–40] as well as in up to 50% of patients with poorly differentiated carcinomas.[41] *Ras* mutations are likely an initiating factor contributing to thyroid carcinogenesis and may predispose individuals to aggressive tumor behavior; this is under ongoing study.[41,42]

PAX8-PPARγ rearrangement occurs in up to 35% of patients with FTC and 10% of those with HCC.[38,43] The incidence in FA is variable, ranging from 0% to 50%.[43,44] *BRAF* mutations and *RET/PTC* rearrangements are rare in patients with FTC and HCC. The presence of either should alert the practitioner to the possibility of a PTC.[45] A diagnostic evaluation that screens FNA for these and other genetic changes commonly implicated in thyroid carcinogenesis, such as *Rb*, *P16INK4a*, and *c-erbAβ* may eventually prove to be very important in clinical management[42,46] and could even obviate the need for diagnostic lobectomy for many patients with FN or HCN cytology results.

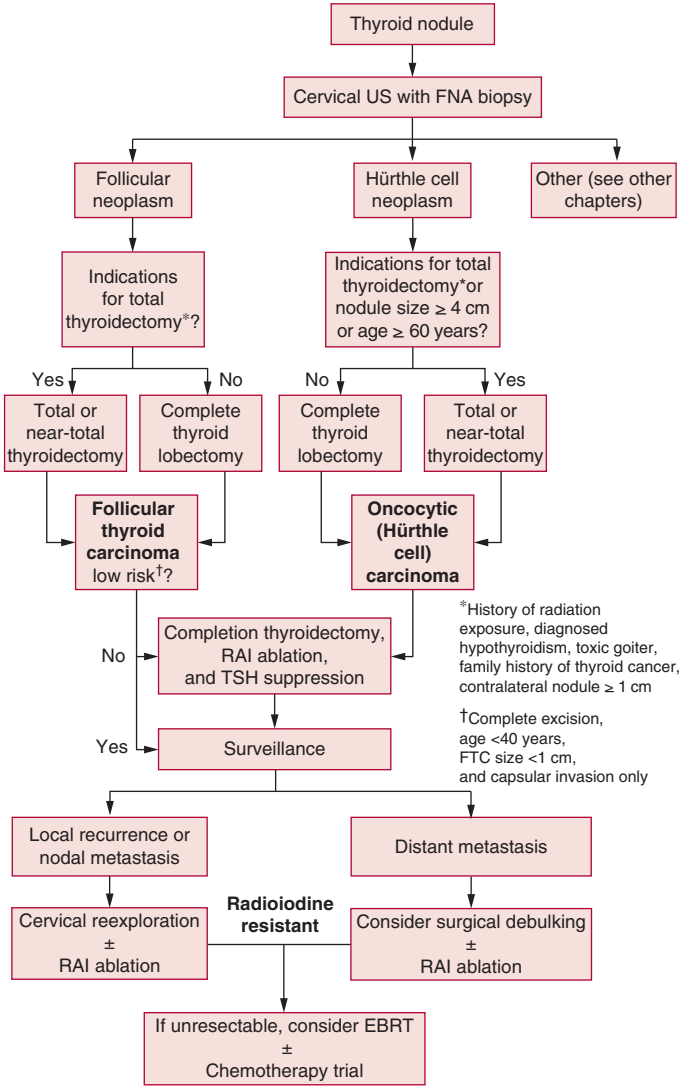

Figure 5-1. Algorithm for the diagnosis of follicular thyroid carcinoma (FTC) and oncocytic (Hürthle cell) carcinoma. EBRT = external-beam radiation therapy; NA = fine-needle aspiration; RAI = radioiodine; TSH = thyroid-stimulating hormone; US = ultrasonography.

TABLE 5-2. Genetic Alterations Implicated in Differentiated Thyroid Carcinoma[21,42,45,46]

Histologic Subtype	*Associations*
Papillary	
BRAF mutations	Tall-cell, conventional, and oncocytic variants Aggressive tumor features
RET/PTC rearrangements	Classic variant Pediatric patients Radiation exposure
NTRK1 rearrangement	Radiation exposure
Ras mutations	Follicular variant
Follicular	
Ras mutations	Follicular adenomas
PAX8-PPARγ rearrangement	Radiation exposure
Oncocytic (Hürthle cell)	
PAX8-PPARγ rearrangement	
GRIM-19?	Also in oncocytic variant PTC
Medullary	
RET mutations	Germline mutations associated with MEN types 2A and 2B and familial medullary thyroid carcinoma
Poorly Differentiated or Anaplastic	
Ras or *BRAF* mutations	Possibly predispose patients with DTC to malignant progression
p53 mutations	Less commonly seen in patients with PTC and FTC
CTNNB1 (β-catenin) mutations	Not found in patients with DTC

DTC = differentiated thyroid carcinoma; FTC = follicular thyroid carcinoma; MEN = multiple endocrine neoplasia; PTC = papillary thyroid cancer.

STAGING AND PROGNOSIS

A number of prognostic scoring systems exist for differentiated thyroid cancer, including metastases, age, completeness of resection, invasion, size (MACIS); age, grade, extent, size (AGES); age, metastases, extent, size (AMES); and the European Organization for Research and Treatment of Cancer (EORTC) score. The most commonly used staging system is the American Joint Committee on Cancer, 6th edition TNM (tumor, node, metastasis) (Table 5-3).[47] Although most of the scoring systems were validated for patients with either PTC or all differentiated thyroid cancers, studies have demonstrated that they still provide some predictive recurrence and survival information when applied to patients with FTC and HCC.[48,49] All thyroid cancer clinical scoring systems are imprecise, however, and it must be kept in mind that patients in low-risk groups can still die of thyroid cancer.[2,48]

The histologic classification of FTC correlates with prognosis. The 2004 WHO guidelines classify FTC into minimally invasive (capsular or vascular invasion) and widely invasive.[6] However, studies have demonstrated that whereas FTC with capsular invasion alone is associated with excellent long-term survival, FTC with vascular invasion is associated with a poorer prognosis, prompting some to propose that the histologic classification of FTC should be differentiated into three groups (capsular invasion, vascular invasion, or widely invasive).[50,51] Widely invasive follicular carcinoma is rare and is associated with poor 5-year survival (40%). Similar findings are reported in HCC. Whereas HCC with minimal to no capsular invasion is associated with up to 100% survival, greater than 50% mortality is seen among patients with widely invasive HCC, with a median disease-free survival of 86 months.[52]

In multivariate analyses, poor long-term prognosis is also associated with older age, presence of distant metastases, lymph node metastases, extrathyroidal extension, and incomplete resection.[48,49] In patients with HCC, large primary tumors and male gender have also been shown to be poor prognostic indicators.[53,54]

MANAGEMENT

Surgical Indications

Diagnostic thyroid lobectomy should be considered when FNA specimens are diagnosed as either FN or HCN. Nodule size is also an important consideration. A number of studies have demonstrated that as the nodule size increases, there is also an increased risk of thyroid malignancy. In a recent series of 639 patients, nodules that were 2.5 cm in size had the lowest risk of malignancy. In nodules that were larger than 2.5 cm, it was estimated that there was a significant association between malignancy and nodule size;

TABLE 5-3. American Joint Committee on Cancer (AJCC) 6th Edition, TNM Staging for Papillary or Follicular Thyroid Cancer

Primary Tumor (T)

Tx Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Tumor 2 cm or less in greatest dimension limited to the thyroid
T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension limited to the thyroid
T3 Tumor more than 4 cm in greatest dimension limited to the thyroid or any tumor with minimal extrathyroid extension (e.g., extension to sternothyroid muscle or perithyroid soft tissues)
T4a Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4b Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels

Regional Lymph Nodes (N)

Regional lymph nodes are the central compartment, lateral cervical, and upper mediastinal lymph nodes.
Nx Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis
N1a Metastasis to Level VI (pretracheal, paratracheal, prelaryngeal/Delphian lymph nodes)
N1b Metastasis to unilateral, bilateral, or contralateral cervical or superior mediastinal lymph nodes

Distant Metastasis (M)

Mx Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Stage Grouping	*Under 45 Years*			*45 Years and Older*		
I	Any T	Any N	M0	T1	N0	M0
II	Any T	Any N	M1	T2	N0	M0
III				T3	N0	M0
				T1	N1a	M0
				T2	N1a	M0
				T3	N1a	M0
IVa				T4a	N0	M0
				T4a	N1a	M0
				T1	N1b	M0
				T2	N1b	M0
				T3	N1b	M0
				T4a	N1b	M0
IVb				T4b	Any N	M0
IVc				Any T	Any N	M1

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for every 1-cm increase in nodule size, there was a 40% increased risk of malignancy.[55] In another large recent series, patients with thyroid nodules larger than 4 cm that were benign on ultrasound-directed FNA biopsy had a clinically significant thyroid cancer of the biopsied nodule in 13% of cases, most commonly FVPTC or FTC.[56] It was concluded that nodule size larger than 4 cm is an independent indication for diagnostic thyroidectomy.

Extent of Thyroidectomy

The initial surgical treatment of patients with FN or HCN is, at the minimum, an ipsilateral complete or near-total thyroid lobectomy. Partial, or subtotal, lobectomy is an outmoded and unsafe procedure that places the ipsilateral recurrent laryngeal nerve (RLN) at higher risk if further surgery is necessary immediately or later in life.[57] A near-total thyroid lobectomy leaves less than 50 mg of thyroid tissue at the ligament of Berry, a fragment the size of a normal parathyroid gland.

Factors such as a history of radiation exposure, diagnosed hypothyroidism, toxic goiter, or a family history of thyroid cancer are currently considered to prompt an upfront total thyroidectomy. We also consider the presence of a contralateral macronodule (≥1 cm) another factor that could prompt an initial total thyroidectomy. Clinical factors that increase the risk of malignancy may also indicate an initial total thyroidectomy. HCN larger than 4 cm has been shown to have a 50% to 65% risk of malignancy.[58,59] Older age (≥40 years) has also been associated with a higher risk of HCC.[60,61] Among 73 patients with a biopsy diagnosis of FN, nodule size larger than 2 cm was the only clinical factor associated with malignancy in one series.[32] In a larger series evaluating FN and malignancy risk, nodule size larger than 4 cm was associated with a threefold higher risk of malignancy compared with nodules smaller than 4 cm.[62]

In the absence of a recognized indication for initial total thyroidectomy, the extent of surgery for FTC or HCC otherwise remains controversial. The usual approach is diagnostic lobectomy followed by completion total thyroidectomy if HCC or FTC is diagnosed on permanent histologic sections. In this approach, the risk of hypothyroidism is weighed against the likelihood and risks of reoperation. After lobectomy, approximately 35% of patients are permanently hypothyroid compared with 100% of patients after total thyroidectomy.[63] Rates of permanent hypoparathyroidism after reoperative total thyroidectomy range from 2% to 10%; rates RLN injury range from 2% to 5%. The complications and costs of thyroidectomy are reduced when the procedure is performed by high-volume surgeons (>100 cases/year).[64]

The relative indolence of FTC and HCC means that the number of patients needed to conduct a prospective, randomized clinical trial would be high, requiring long follow-up; current surgical recommendations are thus

based on retrospective, mixed-tumor histology, and single-institution studies. Among low-risk patients with DTC receiving lobectomy only, studies suggest a higher rate of local (≤30%) and contralateral lobe (5% to 10%) recurrence; however, this group includes many patients with PTC,[65,66] which is considerably more likely to be multifocal (≤50%) compared with HCC (10% to 30%) and FTC (<2%).[49,52,67] For patients younger than 40 years old with small (<1 cm) FTCs that are completely excised and have capsular invasion only, lobectomy alone is generally considered to be adequate. Most recommend that FTC in older (>40 years old) patients and with more aggressive features, such as angiolymphatic invasion and extrathyroidal extension, receive total thyroidectomy.[51,68,69] Several small studies have suggested a better prognosis in patients with HCC after total thyroidectomy.[70] Completion total thyroidectomy allows for radioactive iodine (RAI) ablation, subsequent thyroglobulin (Tg) surveillance, and TSH suppression.

Lymphadenectomy

Synchronous lymph node metastasis is seen rarely (<10%) in patients with FCC and HCC,[48] is a poor prognostic indicator, and may be more likely in larger (T3 or T4) tumors.[71] The presence of lymph node metastasis is associated with an increased risk of recurrent disease in patients with both FTC or HCC.[52,53,71] Routine use of preoperative ultrasonography may identify suspicious lymph nodes. When grossly involved lymph nodes are present, they should be resected, but whether a formal neck dissection is required has not been well studied. Prophylactic neck dissection is not recommended for patients with FTC.

In long-term follow-up, lymph node metastasis develops in up to 25% of HCC patients compared with 2% to 4% of FTC patients.[72] Some have therefore recommended prophylactic neck dissection for patients with HCC, although this is by no means the standard, and no study has shown improved locoregional control or survival with neck dissection in HCC.

Radioactive Iodine Ablation

Among patients with DTC larger than 1.0 to 1.5 cm, thyroid remnant ablation with ^{131}I has been shown to decrease disease recurrence in large retrospective reviews.[65,66] In patients with FTC, thyroid remnant ablation has been associated with an up to 20-fold decrease in locoregional recurrence.[73] The effects of RAI ablation on cancer-specific survival are mixed. There has never been a randomized trial demonstrating a survival benefit of radioiodine in patients with FTC or HCC.[74] Less than 10% of HCCs are iodine avid,[53,75] and studies consistently demonstrate low uptake by HCC metastatic lesions with no overall improvement in local recurrence or survival after RAI.[54,75] However, because some patients do exhibit response to ablation, particularly with the use of dosimetry, HCC should never be considered to be a contraindication to RAI. Most also

agree that in both HCC and FTC, RAI of remnant thyroid tissue allows for improved disease surveillance and ease of long-term TSH suppression.

In preparation for RAI, serum TSH levels should be above 30 mU/L to stimulate thyroid tissue for ^{131}I uptake. This can be achieved either through levothyroxine (LT4) withdrawal or recombinant human TSH (rhTSH) administration. A low-iodine diet (<50 µg/day) for 2 weeks maximizes radioiodine uptake. ^{131}I may be administered by three methods: (1) as an empiric fixed dose, either low (30–50 mCi) or high (75–200 mCi); (2) by quantitative tumor dosimetry based on the calculated amount of thyroid or thyroid cancer tissue remaining; or (3) by quantitative whole-body dosimetry calculated to deliver 200 cGy to the whole blood, keeping whole-body retention below 120 mCi at 48 hours or below 80 mCi when pulmonary uptake is seen. Fixed doses are most commonly used because of the ease and patient tolerance; whole-body dosimetry is usually reserved for patients with widely metastatic disease.

Common complications related to RAI include transient nausea, sialadenitis, and dysgeusia (loss of taste). Patients with large thyroid remnants that are ablated may develop radiation thyroiditis characterized by ear and neck pain, remnant swelling, and even mild thyrotoxicosis. The condition is usually self-limiting but may require treatment with nonsteroidal antiinflammatory medications or corticosteroids. Transient testicular failure may develop if large (>300 mCi) doses of ^{131}I are administered. Large long-term studies of women who became pregnant after receiving ^{131}I have demonstrated no differences in infertility, miscarriage, or premature births.[76] In earlier studies, an observed low but increased frequency of second malignancies in DTC patients who received RAI led to the estimation that 100 mCi ^{131}I will induce 53 solid malignant tumors and three leukemias in 10,000 patients during 10 years of follow-up.[77] However, the increased risk for secondary cancers may also be attributable to an inherent epidemiologic or genetic predisposition to malignancy in DTC patients rather than to a causative RAI effect.[78,79]

Chronic Thyroid-Stimulating Hormone Suppression

Suppression of TSH after total thyroidectomy and RAI ablation may reduce recurrence (25%) and improve cancer-specific survival (50%) among patients with DTC. The degree of TSH suppression is controversial; some studies have reported that the degree of TSH suppression (<0.1 mU/L vs. 1 mU/L) correlates with recurrence,[80] but others have not replicated these results.[81] High-risk patients and those with persistent disease may obtain greater benefit from long-term TSH suppression.

TSH suppression, even to just subclinical hyperthyroidism, has been associated with cardiovascular complications, such as atrial fibrillation and impaired cardiac reserve, and with decreased bone mass in postmenopausal women.[82,83] LT4 dosing for TSH suppression is to lean body weight at 2.2 to 2.5 µg/kg for

adults. For most patients, the goal is TSH of less than 0.5 mU/L while keeping free T3 in the normal range except for high-risk patients who can be maintained at a target low TSH of less than 0.1 mU/L but at still detectable levels.[84]

Surveillance and Follow-up

Elevation in serum Tg levels after total thyroidectomy and ^{131}I ablation is useful in deducing the presence of locoregional and distant metastatic disease. The presence of Tg antibodies may invalidate serum Tg measurements and should always be simultaneously assessed. Tg measurements are most accurate when TSH is high (>25 mU/L), which is achieved by either LT4 withdrawal or by administration of rhTSH. Approximately 35% of patients with TSH-stimulated Tg levels above 2 ng/mL have metastatic disease.[85] Patients with FTC and HCC have higher Tg levels than patients with PTC.[86,87] Under TSH suppression, Tg levels below 10 ng/mL rarely indicate extracervical disease, and FTC Tg levels above 300 ng/mL are associated with three or more metastatic sites, which may include bone metastases.[87]

After initial ablation, whole-body scans are less sensitive than Tg level (although more specific) in detecting the presence of metastases. Among patients with metastatic disease, approximately 90% were identified by rhTSH-stimulated Tg level above ng/mL, but only 20% were identified by whole-body scans.[85] Failure of whole-body scans to identify recurrent or metastatic disease is usually because of either a small volume of recurrent disease or a failure of tumor deposits to sequester iodine (iodine insensitivity). Rarely, metastases may be associated with low Tg level and yet be identified on whole-body scan, and the majority of those lesions are cervical nodal metastases.[88] Good evidence now suggests that routine whole-body scans do not need to be performed when results of the first scan after radioiodine ablation and the TSH-stimulated Tg level are both negative.

Ultrasonography is an important surveillance adjunct for DTC patients. Metastatic lymph nodes can be identified with high sensitivity (≤92%) even among patients with low Tg level and negative whole-body scans,[89] and in association with an elevated TSH-stimulated Tg level, the sensitivity of ultrasonography increases to 96%.[90] All suspicious cervical lesions should be assessed with an FNA biopsy.

Positron emission computed tomography (PET) should be considered for patients with high Tg levels but negative whole-body scans and has been demonstrated to detect recurrent disease with a sensitivity of up to 70%. The sensitivity improves with higher Tg levels (>10 ng/mL) regardless of whether the TSH is suppressed or stimulated.[91] HCC, in particular, has high avidity for ^{18}F-FDG (18F-fluoro-deoxy-glucose), which is the radiotracer used in PET. This avidity may also have prognostic significance: metastatic HCC lesions with a higher maximum standardized uptake value (SUV)

(>10) have been associated with a poorer outcome than those with a lower maximum SUV (5-year mortality of 64% vs. 92%).[92]

To summarize, current guidelines for follow-up of FTC and HCC depend on the risk of recurrence. Low-risk patients who have no metastases, complete tumor resection, no extrathyroidal extension, no vascular invasion, and a negative whole-body scan after initial ^{131}I treatment may be monitored for 3 to 5 years with TSH-stimulated Tg level every 6 to 12 months and yearly cervical ultrasonography. All other FTC and HCC patients should be monitored indefinitely with yearly Tg level and ultrasonography and use of other modalities as required.[93]

Local Recurrence

Locally recurrent FTC or HCC may occur within 5 years of initial treatment.[94] Local recurrence, in either the thyroid bed or in cervical lymph nodes, occurs in 5% to 30% of FTC patients[95] and 25% to 50% of HCC patients and is associated with lymph node metastasis at presentation, extrathyroidal extension, and widely invasive histologies.[53,71,94] In one series, 24 of 33 (70%) patients with widely invasive HCC developed recurrent disease; of the nine (38%) patients who had locoregional recurrence, only eight patients had surgically resectable disease, and seven of nine patients eventually died from the disease.[52] FTC recurrences are more amenable to treatment, either surgical or RAI ablation, and appear to have better survival than HCC recurrences.[68] The optimal treatment for patients with locally recurrent FTC or HCC is unknown. Locally recurrent disease may be a result of iodine resistance, so some advocate surgical resection.

Reoperative cervical surgery is associated with an increased risk of RLN injury and permanent hypoparathyroidism.[57,96] In patients with DTC, resection of recurrent nodal compartment disease may be facilitated with same-day ultrasound localization to help guide safe and successful resection in the previously operated field and may even produce a decrease in postoperative Tg levels, although the duration is unknown.[97] Patients with lateral nodal disease may be treated with a modified radical neck dissection with subsequent ^{131}I if residual disease is still present. If suspected on imaging, patients with tracheal involvement should be evaluated preoperatively with bronchoscopy.

Patients with unresectable FTC or HCC recurrences may be treated with external-beam radiation therapy (EBRT), although response rates are not encouraging. EBRT may achieve good locoregional control of HCC, but most patients subsequently develop distant metastatic disease.[98]

Distant Metastasectomy

Patients who present with synchronous metastases are usually older. Age is a strong prognostic indicator for DTC synchronous distant metastasis.

Whereas pediatric patients with DTC who present with metastatic disease have a reported 10-year survival of 100%,[99] older patients have a 5-year survival of 35% to 50%.[100] HCC patients who present with distant metastases have a poorer prognosis (mortality rate of 80% at 5 years) compared with FTC patients (65% at 5 years).[9] Other prognostic indicators associated with better long-term survival are lung metastases and iodine avidity.[100] To optimize ^{131}I therapy, initial treatment should include total thyroidectomy.

Metachronous distant metastases may occur up to 10 years from initial treatment.[5,94] Distant metachronous metastases are more common in patients with HCC (27%) than FTC (12%).[5] The site of metachronous metastatic disease also differs; bone metastases are seen in patients with FTC, but pulmonary metastases are more common in those with HCC.

If possible, surgical debulking of metastatic lesions should be attempted first. Surgical resection of bone and brain DTC metastases has been associated with improved survival.[101,102] If the metastatic lesions are iodine avid, they should be treated with ^{131}I. EBRT may be used for palliation of metastatic bone pain.

Medical Management

For patients with radioiodine-resistant DTC metastases, the 10-year survival is less than 15%. Conventional cytotoxic chemotherapies have not been effective in treating patients with progressive metastatic disease, with response rates ranging from 6% to 26% for doxorubicin alone or in combination.[103,104] Partial responses have been achieved with newer chemotherapies, including the vascular endothelial growth factor receptor inhibitors motesanib diphosphate[105] and sorafenib.[106] Further studies are needed to determine if these partial responses translate into improvements in recurrence and overall survival.

PRACTICAL PEARLS

- HCC is a histologic variant of FTC, but biologic differences justify separate classification.
- Supine dyspnea relieved by turning on one's side is suggestive of substernal goiter.
- Ultrasonography is the best imaging test for thyroid nodules and cervical lymphadenopathy, and ultrasound-guided FNA is the best diagnostic tool.

(*Continued*)

- The cytologic diagnosis of FN or HCN should prompt diagnostic thyroid surgery, and the minimum thyroid operation should be a complete lobectomy.
- Patients with HCC or FTC1 cm or greater or with angiolymphatic invasion, extrathyroidal extension, or distant or locoregional metastasis should be treated with total thyroidectomy.
- Postoperative ^{131}I remnant ablation may facilitate TSH suppression and surveillance by Tg level and cervical ultrasonography.

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Chapter 6

Medullary Thyroid Carcinoma

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EPIDEMIOLOGY

Medullary thyroid carcinoma (MTC) is uncommon and accounts for only 5% of all thyroid cancers. MTC was first described in 1959 as a "peculiar" thyroid cancer with nonfollicular histology, amyloid-containing stroma, and a high incidence of lymph node metastases.[1] MTC arises from the parafollicular, or calcitonin-secreting, C cells of the thyroid gland. C cells are neural crest cells that are derived embryologically from the ultimobranchial bodies and migrate to the thyroid gland. They are found throughout the thyroid but often concentrate in the uppermost third of the thyroid lobes; therefore, MTC usually originates in this region[2] (Figure 6-1).

Approximately 25% of patients with MTC have the hereditary form of the disease, which results from germline activating missense mutations in the *RET* (*RE*arranged during *T*ransfection) proto-oncogene. The remaining 75% of patients with MTC have the sporadic form; however, somatic missense *RET* mutations may occur in up to 70% of the tumors in patients with sporadic MTC.[3]

RET is a 21-exon proto-oncogene located on chromosome 10q11.2. It encodes a receptor tyrosine kinase (RET) that functions as a signal transducer to regulate cell growth and survival.[4] Germline *RET* mutations cause the multiple endocrine neoplasia type 2 (MEN2) syndromes, which are inherited in an autosomal dominant fashion.

There are three recognized subtypes of MEN2 (Table 6-1), all of which are characterized by a very high lifetime risk of MTC. MEN2A, or Sipple's

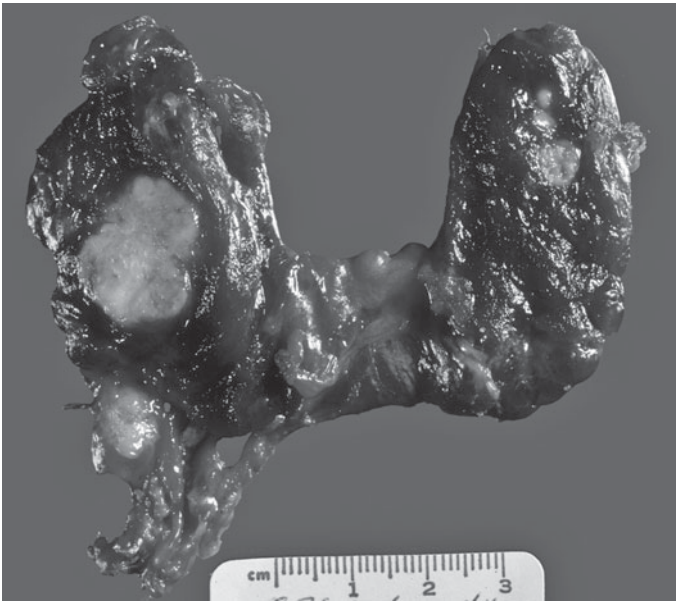

Figure 6-1. Photograph of resected thyroid showing medullary thyroid carcinoma (MTC) posteriorly in the uppermost third of both thyroid lobes.

syndrome, is the most common subtype of MEN2 and accounts for 80% to 90% of all cases of hereditary MTC. It is characterized by MTC in more than 90% of patients, pheochromocytoma in about 50% of patients, and hyperparathyroidism in about 20% of patients.[5] Rarely, MEN2A may be associated with cutaneous lichen amyloidosis (a pruritic plaque that develops on the skin overlying the scapula on the upper back; Figure 6-2)[6] or Hirschsprung disease.[7]

The second MEN2 subtype, MEN2B, accounts for about 5% of MEN2 cases and is characterized by MTC in more than 90% of patients, pheochromocytoma in about 50% of patients, and characteristic physical features. These physical features include a thin, lanky (marfanoid) body habitus; increased joint mobility; decreased subcutaneous fat; corneal nerve hypertrophy; ganglioneuromatosis of the gastrointestinal tract with megacolon; and mucosal neuromas of the lips, tongue, and eyelids (Figure 6-3).[8,9]

TABLE 6-1. Clinical Manifestations of the Hereditary Medullary Thyroid Carcinoma Syndromes

MEN2 Subtype	*Manifestations*
MEN2A	MTC (>90%)
	Pheochromocytoma (50%)
	Primary hyperparathyroidism (20%)
	Cutaneous lichen amyloidosis (rare)
	Hirschsprung disease (rare)
MEN2B	MTC (>90%)
	Pheochromocytoma (50%)
	Physical features (e.g., Marfanoid habitus, mucosal neuromas) Ganglioneuromatosis of the GI tract
FMTC	MTC in ≤four family members
	Documented absence of pheochromocytoma and hyperparathyroidism
	Adequate family history with long-term follow-up

FMTC = familial medullary thyroid cancer; GI = gastrointestinal; MEN = multiple endocrine neoplasia; MTC = medullary thyroid carcinoma.

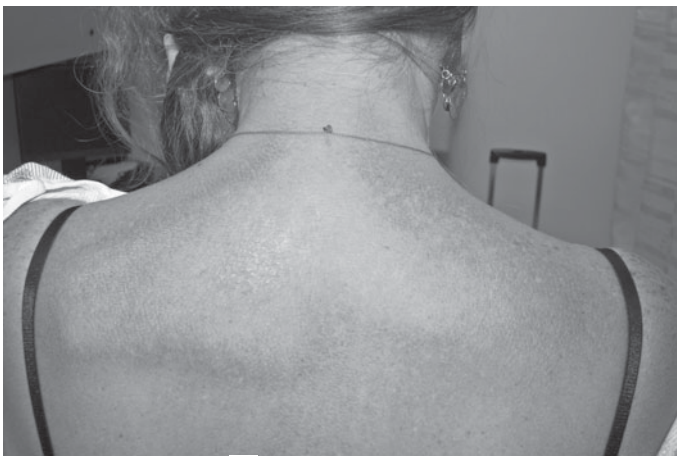

Figure 6-2. Cutaneous lichen amyloidosis in a patient with MEN2A. (Courtesy of Dr. Robert F. Gagel, MD Anderson Cancer Center.)

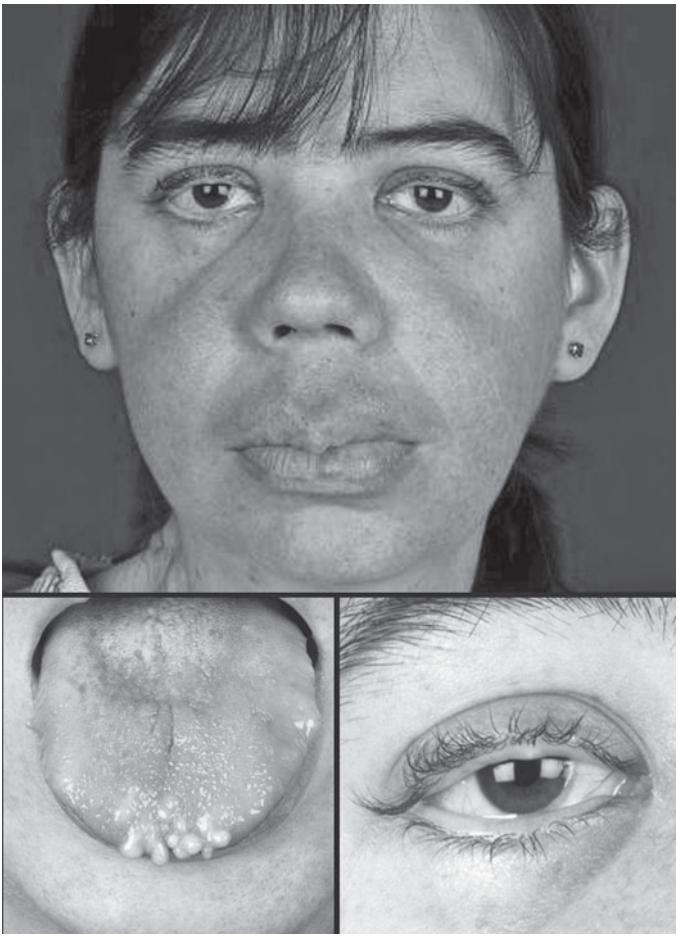

Figure 6-3. Patient with multiple endocrine neoplasia 2B (MEN2B) phenotype, including long, narrow facial features; thick, bumpy lips; neuromas of the anterior third of the tongue; and eyelid neuromas and eversion.

The third MEN2 subtype, familial medullary thyroid cancer (FMTC), accounts for 5% to 15% of MEN2 cases and is defined by the presence of MTC only.[10] However, because MTC is usually the first manifestation of MEN2, some patients with MEN2A may be initially misclassified as having FMTC if they are thought to have only MTC in the absence of adequate follow-up. This misdiagnosis results in a failure to screen for pheochromocytoma and hyperparathyroidism in these patients, which could have negative consequences, particularly if pheochromocytoma is present and not detected preoperatively. Thus, the classification of FMTC must adhere to strict guidelines. Some authors have advocated that only families with four or more cases of MTC, documented absence of pheochromocytoma and hyperparathyroidism, an adequate medical history, and long-term follow-up should be considered to have FMTC.[5] Other authors are even more conservative and define an FMTC kindred by more than 10 carriers, multiple carriers or affected members over the age of 50 years, and an adequate medical history.[11] Still other authors argue that FMTC should not be classified as a separate disease at all; instead, it should be considered a MEN2A variant with a greatly reduced penetrance of pheochromocytoma and hyperparathyroidism.

RISK FACTORS

Childhood exposure to ionizing radiation is a well-established risk factor for thyroid cancer in general and accounts for 9% of thyroid cancers, although most are papillary thyroid cancers (PTCs). The only identified risk factor specific to MTC is a *RET* proto-oncogene mutation. Up to 10% of patients with presumed sporadic MTC actually harbor de novo germline *RET* mutations and thus represent the index cases of MEN2 kindreds.[12] Because patients with sporadic and hereditary MTC are managed differently, genetic testing is essential in all patients who present with MTC.

Well-defined genotype–phenotype correlations exist in MEN2 patients. Specific *RET* mutations influence the MEN2 subtype, the age of disease onset, and the aggressiveness of MTC the patient will experience. Therefore, the specific *RET* mutation is used to determine the age at which a patient should undergo prophylactic thyroidectomy and whether screening for hyperparathyroidism or pheochromocytoma is necessary. The specific *RET* mutation also affects operative planning (extent of lymphadenectomy and intraoperative management of the parathyroid glands).

In 2001, an international conference of MEN experts published a consensus statement to help guide the management of patients with hereditary MTC according to their *RET* mutations.[11] The authors classified the

TABLE 6-2. Genotype–Phenotype Correlations in Hereditary Medullary Thyroid Carcinoma Syndromes[11,40]

RET Codon Mutations	*Risk Level for MTC Development and Aggressiveness*	*MEN2 Subtype*	*Recommended Age for Prophylactic Thyroidectomy*
768, 790, 791, 804, 891	Level 1 (lowest risk)	MEN2A or FMTC	Between 5 and 10 years
609, 611, 618, 620, 630, 634	Level 2 (intermediate risk)	MEN2A or FMTC	Before 5 years
883, 918, 922	Level 3 (highest risk)	MEN2B	Before 6 months

FMTC = familial medullary thyroid cancer; MEN = multiple endocrine neoplasia; RET = rearranged during transfection.

mutations into three levels based on aggressiveness of MTC (Table 6-2). Level 1 mutations are associated with the least aggressive form of MTC. There is significant variability in the age at onset of MTC associated with a level 1 mutation, so the timing of prophylactic thyroidectomy in carriers of these mutations is controversial; however, most experts recommend that carriers undergo prophylactic thyroidectomy by age 5 or 10 years. Level 2 mutations are associated with moderately aggressive MTC, and carriers of these mutations should undergo prophylactic thyroidectomy by age 5 years. Both level 1 and level 2 mutations give rise to MEN2A and FMTC, but there is considerable overlap between the mutations with regard to the phenotype displayed. Level 3 mutations are associated with the most aggressive form of MTC and result in the MEN2B phenotype. Prophylactic thyroidectomy in carriers with these mutations is recommended by age 6 months. However, it is usually quite difficult to make the diagnosis of MEN2B in the first few years of life, so prophylactic thyroidectomy should occur as soon as such a mutation is identified.

CLINICAL PRESENTATION

Patients who develop sporadic MTC or who represent an index case of MEN2A or FMTC may present as late as the fourth decade of life. Patients who represent index cases of MEN2B usually present with MTC within the

first two decades of life. Unlike other thyroid neoplasms, which occur more often among women, MTC is equally prevalent in men and women.[13]

Patients with sporadic MTC and patients who represent index cases of hereditary MTC almost always present with a palpable neck mass. Hereditary MTC is often multifocal and bilateral.[14] Approximately 15% of patients with MTC have symptoms of locally advanced disease at the time of presentation, including hoarseness, dyspnea, or dysphagia.[13] Bone pain or systemic symptoms related to hypercalcitoninemia, such as flushing or diarrhea, may be present in 10% of patients[13]; in such cases, the clinician should suspect metastatic disease, which is usually to the liver, lung, or bone. Occasionally, metastases may develop in the brain or subcutaneous tissue.[15] Patients with MEN2A or MEN2B may also present with symptoms of pheochromocytoma.[13]

Patients in known hereditary MTC kindreds are usually asymptomatic and are diagnosed by genetic testing and early screening. The disease is characterized by an age-related progression from a normal thyroid to C-cell hyperplasia to MTC,[16] and these patients may lie at any point along this spectrum at the time of diagnosis.

DIAGNOSTIC EVALUATION

Workup of Patients with Sporadic Medullary Thyroid Carcinoma or Index-Case Hereditary Medullary Thyroid Carcinoma

Obtaining a thorough history and physical examination is critical when evaluating patients with MTC. It is important to ask about voice changes, difficulty swallowing, increasing shirt size at the neck, flushing, diarrhea, and bone pain. Asking about kidney stones, pancreatitis, ulcers, osteoporosis, anxiety, tremor, panic attacks, "spells," and so on may help to determine whether a patient has a personal history of primary hyperparathyroidism or pheochromocytoma. A detailed family history must also be obtained. Family members with kidney stones, pancreatitis, ulcers, or osteoporosis may have had primary hyperparathyroidism, and family members who died of an unknown cause or had significant hypertension (especially at a young age) may have had pheochromocytoma.

The physical examination should include an evaluation of the size and mobility of the neck mass, as well as its relationship to surrounding structures, keeping in mind that MTC tumors are often posterior and may be locally aggressive, invading the trachea, recurrent laryngeal nerve (RLN), and great vessels of the neck. The cervical lymph nodes should also be carefully examined. At the time of diagnosis, 80% of patients with palpable MTC have central compartment lymph node metastases, and 75% and 47%

of patients have metastases to the ipsilateral and contralateral jugular nodes, respectively.[17] Because cutaneous lichen amyloidosis may be associated with MEN2A, the skin overlying the upper back should be examined (see Figure 6-2). It is also important to note any physical features characteristic of MEN2B, particularly a tall, thin body habitus and neuromas of the tongue and eyelids (see Figure 6-3).

The diagnosis is established by cytologic evaluation of a fine-needle aspiration (FNA) biopsy of a nodule that is palpable or visible by ultrasonography. The presence of an elevated calcitonin level confirms the diagnosis; a recent study found that calcitonin levels of 100 pg/mL or above have a 100% positive predictive value for MTC.[18] MTC also secretes carcinoembryonic antigen (CEA), and CEA levels may be a useful adjunct to calcitonin levels for determining the extent of disease. Neck ultrasonography is essential for obtaining anatomic information about the tumor or tumors and evaluating the central as well as lateral cervical lymph node compartments. Direct or indirect laryngoscopy should be performed to determine whether a locally invasive tumor has involved the RLN because this is important for operative planning and patient expectations.

Every patient who presents with MTC should undergo genetic counseling and then testing for a *RET* proto-oncogene mutation. Before undergoing genetic testing, patients should know how to interpret the results of genetic tests; understand the potential impact on health records and insurance; and realize the implications of positive results for other family members, particularly offspring. It is critical to identify MEN2 in patients before surgery for MTC because MEN2 patients may have additional neoplasms. Pheochromocytoma must be excluded in patients with MEN2A and MEN2B. Standard biochemical screening tests for pheochromocytoma include plasma-free metanephrine levels or 24-hour urine metanephrine and normetanephrine levels. Patients with elevated levels should undergo a dedicated adrenal-protocol computed tomography (CT) or magnetic resonance imaging (MRI) scan of the abdomen. It is of paramount importance that a pheochromocytoma be appropriately medically blocked and then resected before any neck operation is performed (although this may be done during the same anesthesia induction). MEN2A patients should also be screened for primary hyperparathyroidism before undergoing a neck operation for MTC. Measuring serum calcium and concomitant intact parathyroid hormone levels is an inexpensive, effective way to screen for primary hyperparathyroidism. If hyperparathyroidism is found, the parathyroid glands may be addressed at the same time as the initial cervical operation. However, most patients who are found to have MEN2A-related hyperparathyroidism are likely to have already undergone thyroidectomy with or without some level of neck dissection.

Standard imaging techniques are unlikely to detect distant metastatic disease if the patient's serum calcitonin level is 400 pg/mL or lower.[19] If distant metastatic disease is suspected because the patient has a serum calcitonin level greater than 400 pg/mL, lymph node metastases, bone pain, or symptoms such as flushing or diarrhea, staging evaluation should be performed. This should include CT of the neck and chest and CT or MRI of the abdomen. Although bone scintigraphy may be performed if metastases are strongly suspected, MRI of the axial skeleton is probably the best method of screening for bone metastases. In detecting metastatic MTC, [^{18}F]2-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) has been shown to be less sensitive than neck ultrasonography, chest CT, or abdominal CT or MRI[20]; however, because it may occasionally detect lesions not revealed by CT or MRI, FDG-PET may be useful when CT or MRI is negative; a very high serum calcitonin level suggests metastases.[21]

Workup of Asymptomatic Patients with Known Hereditary Medullary Thyroid Carcinoma

Asymptomatic MEN2 patients being considered for prophylactic thyroidectomy should undergo preoperative neck ultrasonography to evaluate the thyroid and regional lymph nodes. In addition, a baseline serum calcitonin level should be obtained. Generally, the potential for cure is very high if asymptomatic patients with MEN2A or FMTC undergo prophylactic thyroidectomy by age 5 years and MEN2B patients undergo prophylactic thyroidectomy by age 6 months. Patients with particularly indolent *RET* mutations in whom prophylactic thyroidectomy is intentionally delayed beyond age 5 years should undergo calcitonin level measurements and screening with neck ultrasonography annually; thyroidectomy should be performed as soon as any abnormality is detected. All MEN2 patients should be evaluated for pheochromocytoma and hyperparathyroidism before thyroidectomy; however, these diseases are uncommon in patients younger than age 12 years.

STAGING AND PROGNOSIS

Several staging systems have been described for MTC.[13] The 2002 American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) staging system[22] is used most often. Although the TNM staging system does not include prognostic factors such as age and postoperative calcitonin level, it has repeatedly been shown to correlate with survival (Tables 6-3 and 6-4). The prognosis for MTC patients is between that of patients with well-differentiated thyroid cancer (PTC or follicular thyroid cancer [FTC]) and that of patients with poorly differentiated (anaplastic) thyroid cancer.[23]

TABLE 6-3. American Joint Committee on Cancer Tumor, Node, Metastasis (TMN) Staging for Medullary Thyroid Carcinoma[22]

T Staging	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤2 cm in greatest dimension limited to the thyroid
T2	Tumor 2–4 cm limited to the thyroid
T3	Tumor >4 cm limited to the thyroid or any tumor with minimal extrathyroid extension (e.g., extension to sternothyroid muscle or perithyroid soft tissues)
T4a	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or RLN
T4b	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels
N Staging	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis (central compartment, lateral cervical, or upper mediastinal)
N1a	Metastasis to level VI lymph nodes (pretracheal, paratracheal, and prelaryngeal or Delphian lymph nodes)
N1b	Metastasis to unilateral, bilateral, or contralateral cervical, or upper mediastinal lymph nodes
M Staging	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

RLN = recurrent laryngeal nerve.
Reproduced with permission from Greene FL, Page DL, Fleming, ID, et al. AJCC Cancer Staging Manual, Sixth Edition. New York: Springer, 2002:78.

MANAGEMENT

Surgery

Surgery is the definitive therapy for patients with MTC. Total extracapsular thyroidectomy is the indicated procedure for addressing the disease within the thyroid in MTC patients and preventing the development of MTC in patients identified as

TABLE 6-4. American Joint Committee on Cancer Stage Grouping and Survival for Medullary Thyroid Carcinoma[22,23]

Stage Group	*T Stage*	*N Stage*	*M Stage*	*5-Year Survival (%)*
I	T1	N0	M0	98
II	T2	N0	M0	98
III	T3	N0	M0	73
	T1	N1a	M0	
	T2	N1a	M0	
	T3	N1a	M0	
IVA	T4a	N0	M0	40
	T4a	N1a	M0	
	T1	N1b	M0	
	T2	N1b	M0	
	T3	N1b	M0	
	T4a	N1b	M0	
IVB	T4b	Any N	M0	
IVC	Any T	Any N	M1	

MEN2 carriers. Regional lymph nodes are managed with compartment-oriented surgery consistent with the standard principles of surgical oncology.[24,25] However, the extent of cervical lymph node dissection depends on whether the thyroidectomy is prophylactic or therapeutic (Table 6-5).

Cervical lymph node dissection is usually not necessary when prophylactic thyroidectomy is performed by age 5 years in MEN2A or FMTC patients with normal serum calcitonin levels and normal ultrasonography findings. However, if the specific *RET* mutation, patient age, serum calcitonin level, or preoperative cervical ultrasonography findings suggest an increased likelihood of invasive cancer, bilateral central (level VI) neck dissection should be considered. Bilateral central (level VI) neck dissection is also usually performed in patients with the much more aggressive MEN2B phenotype because prophylactic thyroidectomy can rarely be performed in the first year of life. In addition, lateral (levels IIA, III, IV, and V) neck dissection should be considered in patients who are diagnosed with MEN2B later in childhood or in adolescence. Figure 6-4 illustrates the lymph node compartments of the neck.

The extent of neck dissection that should accompany therapeutic thyroidectomy in patients with hereditary MTC who have a thyroid nodule but

TABLE 6-5. Operative Management of Medullary Thyroid Carcinoma

Indication for Surgery	*Extent of Neck Dissection**	*Management of Devascularized Parathyroid Glands*
Prophylactic thyroidectomy in MEN2A or FMTC	Central (level VI) neck dissection based on *RET* mutation, patient's age, serum calcitonin level, and US findings	*RET* mutation consistent with MEN2A: Cryopreserve or autograft into forearm *RET* mutation consistent with FMTC: Autograft into neck (parathyroid glands are normal)
Prophylactic thyroidectomy in MEN2B	Central (level VI) neck dissection routinely; lateral (levels IIA, III, IV, and V) neck dissection based on patient's age, serum calcitonin level, and US findings	Autograft into neck (parathyroid glands are normal)
Therapeutic thyroidectomy in MEN2A or FMTC†	Central (level VI) neck dissection routinely; ipsilateral or bilateral lateral (levels IIA, III, IV, and V) neck dissection based on patient's age, serum calcitonin level, and US findings	*RET* mutation consistent with MEN2A: Cryopreserve or autograft into forearm *RET* mutation consistent with FMTC: Autograft into neck (parathyroid glands are normal)
Therapeutic thyroidectomy in MEN2B†	Central (level VI) and bilateral lateral (levels IIA, III, IV, and V) neck dissection	Autograft into neck (parathyroid glands are normal)
Therapeutic thyroidectomy in sporadic MTC†	Central (level VI) neck dissection routinely; ipsilateral or bilateral lateral (levels IIA, III, IV, and V) neck dissection based on serum calcitonin level and US findings	Autograft into neck (parathyroid glands are normal)

* Any disease visible by ultrasonography in the central or lateral neck requires a compartment-oriented dissection of that compartment.
† Patients with a malignant thyroid nodule and a normal ultrasonography of the lateral neck.
FMTC = familial medullary thyroid cancer; MEN = multiple endocrine neoplasia; US = ultrasonography.

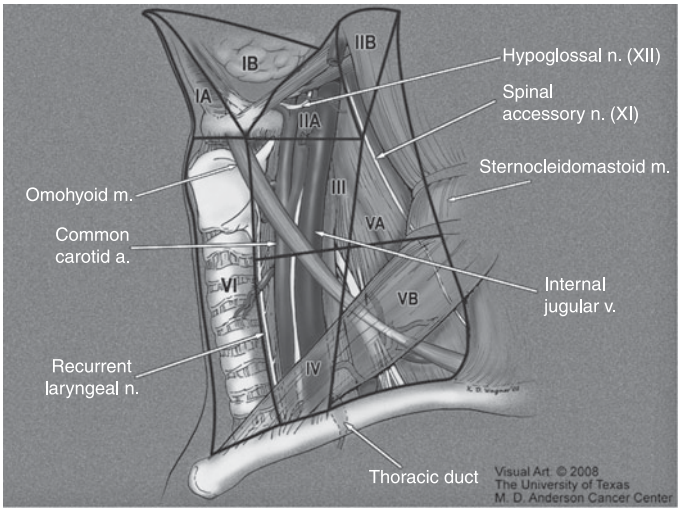

Figure 6-4. Lymph node compartments in the neck. The central compartment (level VI) is defined laterally by the carotid sheaths, superiorly by the hyoid bone, and inferiorly by the suprasternal notch. The lateral compartment contains superior jugular (level II), middle jugular (level III), and inferior jugular (level IV) lymph nodes, as well as the posterior triangle nodal tissue bound by the posterior border of the sternocleidomastoid, the anterior border of the trapezius, and the clavicle (level V). The division between levels II and III is a horizontal plane defined by the inferior body of the hyoid bone. The division between levels III and IV is a horizontal plane defined by the inferior border of the cricoid cartilage. Level I contains the submental and submandibular lymph nodes. (Reproduced with permission from The University of Texas MD Anderson Cancer Center.)

no ultrasonographic evidence of cervical lymphadenopathy is somewhat controversial in the current era of very high-resolution ultrasonography. In patients with biopsy-proven macroscopic MTC, bilateral central compartment (level VI) lymphadenectomy should always be performed. If high-quality ultrasonography of the lateral neck compartments (levels IIA, III, IV, and V) is completely normal, the lateral neck compartments are not dissected. This guideline of dissecting the lateral neck compartments only for image-positive disease is

new and is based on the improved sensitivity of ultrasonography and CT; the fact that many patients with established MTC cannot be biochemically cured (defined as an undetectable postoperative serum calcitonin level) through the use of elective lateral neck dissection anyway; and the known heterogeneity of MTC, both within kindreds and among families with identical RET mutations. Exceptions to this guideline include MEN2B patients diagnosed later in life and the rare patients with level 2 mutations and high serum calcitonin levels but no detectable distant metastases. Patients with level 1 mutations should not undergo elective lateral neck dissection in the absence of imaging evidence of nodal involvement.

Therapeutic thyroidectomy in patients with sporadic MTC who present with a thyroid nodule but no ultrasonographic evidence of cervical lymph node metastases should be accompanied by bilateral central (level VI) neck dissection. In the past, it was recommended that these patients undergo ipsilateral lateral (levels IIA, III, IV, and V) neck dissection, regardless of preoperative imaging findings, but at present, dissection of the lateral neck should be performed only in the setting of nodal disease visible by high-quality imaging. Rare exceptions to this guideline include patients who have high serum calcitonin levels and no detectable distant metastases. In such patients, an ipsilateral lateral neck dissection may be considered; however, high-quality CT imaging of the mediastinum is critically important to detect mediastinal adenopathy as the source of the high serum calcitonin level.

Intraoperative assessment cannot accurately predict whether lymph nodes are involved and therefore is not a reliable method for determining the extent of lymphadenectomy that needs to be performed. For example, in a study of 73 patients with palpable MTC who underwent thorough central and bilateral modified neck dissections, the sensitivity of intraoperative assessment by the surgeon was only 64%.[17] Relying on intraoperative assessment alone could thus miss about one third of patients with involved lymph nodes, which is clearly unacceptable for a disease that has few options for adjuvant therapy.

Patients with sporadic or hereditary MTC who have evidence of lymph node metastases in any cervical compartment are very likely to have coexisting metastases in another compartment. These patients should undergo central (level VI) and bilateral lateral (levels IIA, III, IV, and V) neck dissection.

The management of inferior parathyroid glands intentionally removed during central neck dissection or parathyroid glands accidentally devascularized during thyroidectomy depends on the patient's specific *RET* mutation. For example, patients with MEN2A-associated mutations are at an increased risk of future hyperparathyroidism. Portions of the devascularized parathyroid glands should be autografted into these patients' forearms with or without

cryopreservation; if hyperparathyroidism caused by autograft hypertrophy subsequently develops, it can be managed with a local procedure on the forearm instead of a neck reoperation. In contrast, patients with sporadic MTC or *RET* mutations consistent with FMTC or MEN2B are not at an increased risk of future hyperparathyroidism, and their devascularized parathyroid glands may simply be autografted into the sternocleidomastoid muscle in the neck. Prophylactic subtotal or total parathyroidectomy with autotransplantation in MEN2A patients is not recommended.

Follow-up and Surveillance

For patients who have undergone thyroidectomy for MTC, baseline calcitonin and CEA levels should be measured and neck ultrasonography performed 2 to 3 months after surgery and then annually. Patients with hereditary MTC should undergo annual screening for hyperparathyroidism and pheochromocytoma. This may consist of a history directed toward symptoms and a biochemical evaluation.

Calcitonin is an extremely sensitive biochemical marker, and serum calcitonin levels are used to follow MTC patients after their initial surgical therapy. Increased serum calcitonin levels may indicate microscopic persistent or recurrent MTC long before regional lymph node or distant metastases can be visualized by conventional imaging. After surgery, calcitonin levels may not reach their nadir for 3 to 6 months.[26] More than 50% of MTC patients will have persistent or recurrent disease as defined by elevated serum calcitonin levels.[13] Clinical management of patients with only biochemical evidence of persistent or recurrent disease is controversial. These patients often do well without evidence of disease for many years,[27] but observation alone is unsettling because MTC can also be a very aggressive tumor, with rapidly progressive metastatic disease in some patients. In patients with elevated postoperative calcitonin levels who did not undergo adequate cervical lymph node clearance at the time of thyroidectomy, standard management includes high-quality imaging along with serial observation until lymph node metastases are detectable, at which time reoperation is indicated.[15] Patients with postoperative calcitonin levels above 150 to 200 pg/mL, rapidly increasing calcitonin or CEA levels (or calcitonin doubling time <6 months)[28] should undergo a complete metastatic survey, which includes ultrasonography of the neck, CT of the neck and chest, and MRI of the liver and axial skeleton.

In patients who undergo prophylactic thyroidectomy and in whom pathology demonstrates normal thyroid or C-cell hyperplasia, the appropriate follow-up is unclear. The risk of persistent or recurrent disease in these patients is very low.[29] It is reasonable to follow them initially with an annual calcitonin level and less frequently after prolonged follow-up.

Unlike patients with PTC and FTC, those with MTC do not respond to thyroid suppression; therefore, patients who undergo thyroidectomy for MTC should receive replacement, not suppressive, thyroxine therapy. The goal should be to achieve thyroid-stimulating hormone (TSH) levels in the normal range. In addition, MTC cells do not concentrate iodine, so there is no role for postoperative radioactive iodine therapy.

Therapy for Systemic Disease

Distant metastatic MTC represents a therapeutic challenge; there are no curative options available at this time. Cytotoxic chemotherapy for systemic disease has been nonspecific and of limited effectiveness. Even the best results with dacarbazine-based regimens have demonstrated few actual responses and some long-term stabilizations, but these studies have involved very small numbers of patients, and regimens were significantly limited by their toxicity.[30,31] Overall, combinations of chemotherapeutic agents have demonstrated partial responses in only about 20% of MTC patients. Other systemic therapies, such as somatostatin analogues, interferon-α, anti-CEA antibodies, and immunotherapy with calcitonin-pulsed dendritic cells, have yielded equally disappointing results.[32]

As a result of the success of tyrosine kinase inhibitors (TKIs) in the treatment of patients with other cancers (e.g., imatinib for gastrointestinal stromal tumors and chronic myelogenous leukemia and erlotinib for some non–small-cell lung carcinomas), RET has become an important potential therapeutic target for patients with MTC. TKIs are small molecules that compete with the adenosine triphosphate binding site of the catalytic domain of a RET, thereby inhibiting autophosphorylation and activation of downstream intracellular signaling pathways.[33] A TKI can be specific to one or many homologous kinases, including RET, B-RAF, RAS, VEGFR, PDGFR, EGFR, Kit, FLT-3, and MET.[34] Currently, at least eight kinase inhibitors are being evaluated in phase I, II, or III clinical trials for metastatic MTC. These include axitinib, gefitinib, imatinib, motesanib, sorafenib, sunitinib, vandetanib, and XL184.[34] Evidence to date suggests that clinical responses to these therapies are at least as good as those seen with standard chemotherapy, with significantly fewer side effects; the most common side effects seen are diarrhea, nausea, fatigue, rash, hypertension, and QTc interval prolongation.[35,36] Although their role in MTC remains unclear, TKIs offer some hope to patients with a disease that has essentially no effective systemic therapy.

Historically, external-beam radiation therapy (EBRT) was used only to palliate the symptoms caused by extensive cervical or mediastinal MTC and bone metastases. However, the role of EBRT as a postoperative adjuvant

therapy was recently investigated.[37] Thirty-four patients with stage IVa to IVc MTC underwent surgical resection followed by conformal EBRT or intensity-modulated radiotherapy. Although about one third of the patients had positive surgical margins, the estimated 5-year locoregional relapse-free survival rate was 87%, and only two patients (9%) had long-term side effects from the radiotherapy. These results suggest that EBRT may someday play a greater role in the management of patients with MTC.

Other treatments may be helpful in addressing specific forms of metastatic disease. An extensive metastatic burden may cause uncomfortable flushing episodes and debilitating diarrhea; somatostatin analogue therapy or surgical debulking may be somewhat effective in controlling these symptoms. The liver is a frequent site of MTC metastasis and may harbor bulky disease; hepatic chemoembolization has been shown to relieve some of the symptoms caused by liver metastases.[38,39] Patients with bone metastases can be treated with radiotherapy or intravenous bisphosphonate therapy.

PRACTICAL PEARLS

- MTC should be suspected in patients with neuroendocrine cells noted on FNA biopsy of the thyroid, and the serum calcitonin level should be obtained.
- During initial assessment, the practitioner should inquire about:
  - Voice change, difficulty swallowing (indicates locally advanced disease)
  - Flushing, diarrhea (indicates elevated serum calcitonin levels)
  - Panic attacks, anxiety, tremor, "spells" (indicates concomitant pheochromocytoma)
  - Kidney stones, pancreatitis, ulcers, osteoporosis (indicates concomitant hyperparathyroidism)
  - Family history of MEN2
- Every patient who presents with MTC should be tested for a *RET* proto-oncogene mutation.
- Known genotype–phenotype correlations help direct the extent and timing of surgery.
- Pheochromocytoma should be excluded before patients with MTC undergo surgery.

(*Continued*)

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Chapter 7

Anaplastic Thyroid Carcinoma, Metastases to the Thyroid Gland, and Thyroid Lymphoma

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EPIDEMIOLOGY

Anaplastic thyroid cancer (ATC) is a highly aggressive malignancy that accounts for more than 39% of all thyroid cancer deaths even though it represents less than 2% of all thyroid cancers diagnosed.[1,2] Although the incidence of well-differentiated thyroid cancer (WDTC) has increased in recent years, newly diagnosed ATC is decreasing in the United States. This may be because of improvements in histologic techniques, the elimination of endemic goiter, or advances in the treatment of patients with WDTC.[3] It is possible that a significant proportion of thyroid lymphomas, medullary thyroid carcinomas (MDCs), and other non-ATC were misdiagnosed as ATC in the past; histologic accuracy has benefited from developments in immunohistochemistry (Figure 7-1).[4] Because ATC is associated with WDTC in more than 80% of cases, earlier removal of WDTC could, in theory, reduce anaplastic transformation and ATC incidence.[5,6] Conversely, incomplete or delayed therapy for patients with WDTC increases the risk of anaplastic transformation.[7]

RISK FACTORS FOR ANAPLASTIC THYROID CANCER

Although no known familial syndromes are associated with ATC, we have observed a probable increase in the frequency of ATC in patients with

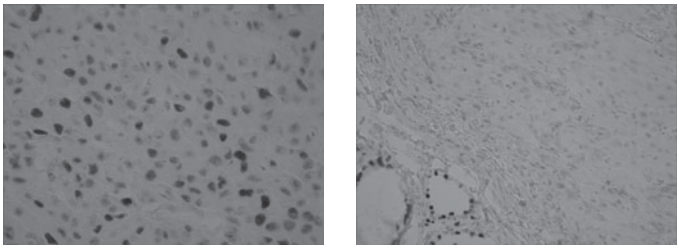


Figure 7-1. Immunohistochemistry of anaplastic thyroid cancer. Immunohistochemical profile demonstrating diffuse nuclear positivity for p53 (**A**) and negativity for TTF1 (**B**) characteristic of anaplastic thyroid cancer. In **B**, positive residual follicles are seen in the left lower corner. (Courtesy of Vania Nose, MD.)

familial nonmedullary thyroid cancer. Some studies have found associations between ATC incidence and environmental factors. ATC is more common in areas with endemic goiter and low socioeconomic status.[8] Furthermore, advanced age is a risk factor because ATC is primarily a disease of elderly people, and it typically occurs after the sixth decade of life.[9]

GENETICS OF ANAPLASTIC THYROID CANCER

Although some of the genetic alterations found in patients with ATC have been described, the essential changes that drive anaplastic transformation remain incompletely understood.[10,11] Anaplastic transformation likely entails both the loss of tumor suppressor function and oncogene activation.

Regarding tumor suppressor status, the majority of ATC studies have reported a loss of p53 function.[12] Mutations of p53 are common in patients with ATC but rare in those with WDTC, even when they are determined within the same surgical specimen. This suggests that p53 loss is an essential event in anaplastic transformation.[5]

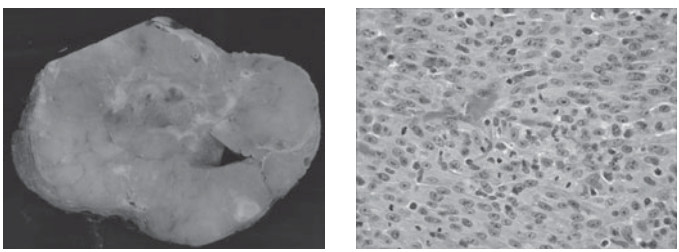
Regarding oncogene activation, several studies have compared global expression in WDTC with ATC, and others have investigated the expression of known oncogenes from other cancer types in those with ATC. Confirmed alterations in ATC include β-catenin, OEATC-1, Aurora B, c-myc, and NM23.[13–15]

CLINICAL PRESENTATION

Most patients with ATC present with a rapidly enlarging neck mass. Patients with long-standing goiters or indolent WDTC may abruptly develop new symptoms and an increase in size of the thyroid gland. These patients most likely had indolent, well-differentiated tumors that underwent anaplastic transformation. Some of the gross and histologic features of ATC are shown in Figure 7-2.

Furthermore, some patients also present with hyperthyroidism from pseudothyroiditis secondary to the rapid destruction of normal thyroid follicles by ATC invasion.[16] Because ATC has a tendency to be locally invasive, it is often fixed to surrounding structures; may cause regional pain; and may invade the recurrent laryngeal nerves (RLNs), resulting in vocal cord dysfunction. ATCs are generally large and cause local symptoms from their mass effect, including a sensation of pressure, dysphagia, and dysphonia. They also frequently cause respiratory problems because of their large size, including tracheal obstruction or recurrent or vagal nerve dysfunction.

In our experience with ATC, the average tumor size is greater than 7 cm in diameter, and nearly every patient presents with symptoms that may be attributed to the mass effect from the primary tumor. Clinicians should carry a high index of suspicion for ATC in all elderly patients with a symptomatic or rapidly enlarging neck mass.



A B

Figure 7-2. Gross and microscopic appearance of anaplastic thyroid cancer. **A.** Cut surface of a large tumor showing a heterogeneous, fleshy appearance with areas of necrosis. **B.** Microscopic picture of a spindle cell variant with numerous mitoses. (Courtesy of Vania Nose, MD.)

STAGING AND PROGNOSIS

Because the prognosis in ATC is generally poor, all ATC is considered stage IV disease. This is also true for occult ATCs that are incidentally discovered during thyroidectomy for WDTC or benign thyroid disease. The 2002 American Joint Committee on Cancer tumor, node, metastasis (TNM) staging system for thyroid cancer subdivides ATC into three different subcategories of stage IV disease. In stage IVa, the primary tumor has not extended beyond the thyroid capsule. Given the strong propensity for local invasion in ATC, stage IVa disease is found only when a small ATC lesion is incidentally discovered in a thyroidectomy specimen or during a radiologic workup for another medical problem. Stage IVb disease represents tumors with local invasion, which often precludes curative resection. Stage IVc disease includes all ATCs with distant metastases. In general, long-term survival is exceedingly rare in patients with stage IVb and IVc ATC.

Distant metastases are common at presentation and may be found in up to 43% of patients.[17] The common sites of distant ATC metastases are the lungs, bones, and brain. Although systemic metastases are common, the most frequent cause of death in ATC is caused by the primary tumor site.

Regarding prognosis, results are generally poor, and survival is typically measured on the order of months, rather than years. In a recent comprehensive review of the ATC literature from 1975 to 2002, the median survival from the time of diagnosis ranged from 4 to 12 months.[18] In our recent experience at the University of California, San Francisco, from 1981 to 2007, the median survival of patients with ATC was 6 months from the time of diagnosis. We have two patients who have lived without evidence of disease for longer than a decade after thyroidectomy. Both of these patients underwent aggressive multimodality therapy, including surgical extirpation, external-beam radiation therapy (EBRT), and systemic chemotherapy. The tumor specimens from these survivors have been independently reviewed by endocrine pathologists to confirm the diagnosis of ATC. In our experience, both distant and regional metastases preclude curative therapy for ATC patients despite multimodality therapy.

Several studies have identified clinical and pathologic features that are predictive of survival in patients with ATC. Because ATC is uncommon, most reports are small and retrospective. As such, reports have varied with respect to predictive clinical and pathologic determinants of survival for patients with ATC. Although some reports have found white blood cell count, serum albumin, and thyroid function to be independent predictors, multiple studies have implicated patient age, extent of disease, and tumor size as prognostic clinicopathologic markers for survival.[19–21]

One recent study included 516 patients from the Surveillance, Epidemiology and End Results (SEER) database and found that patients younger than 60 years with tumors without extracapsular extension have significantly longer survival.[22] In a recent Korean study of 121 cases of ATC, age younger than 60 years, tumor size less than 7 cm, and lesser extent of disease were independently predictive of lower mortality from ATC.[23] In one group's experience of 67 patients with ATC, young age, absence of symptoms, small tumor size, microvascular invasion, and surgical resection were independent predictors of improved survival.[24] In contrast, our group found that the ability to attempt curative surgery, rather than patient age or tumor size, was the only predictive factor for survival in patients with ATC.[25]

DIAGNOSTIC EVALUATION

As with any thyroid lesion, investigation should include a detailed history and physical examination. The interview should focus on the patient's history of endocrinopathy and the potential symptoms that could be attributed to ATC. The physical examination should evaluate for local invasion and metastastic disease. Thyroid function tests are typically unremarkable unless the burden of ATC has replaced most of the normal thyroid gland. ATC can be readily diagnosed by fine-needle aspiration (FNA) biopsy with cytologic review.[26]

All patients with the diagnosis of ATC by FNA should undergo a detailed workup to determine the extent of disease and the potential for curative resection. Because ATCs tend to be large, ultrasonography is generally not needed for accurate FNA sampling. However, formal neck ultrasonography can determine the local extent of the ATC and the presence of abnormal cervical lymph nodes. Computed tomography (CT) and magnetic resonance imaging of the neck can characterize the extent of locoregional disease and the presence of invasion into the esophagus, trachea, and soft tissues (Figure 7-3A). The evaluation should include direct laryngoscopy to determine if tracheal invasion exists and to evaluate for vocal cord dysfunction from possible invasion of the RLN. Esophagoscopy with or without endoscopic ultrasonography can evaluate for esophageal invasion. Although positron emission tomography (PET) may demonstrate increased [^{18}F]2-fluoro-2-deoxyglucose (FDG) avidity from the primary site and distant metastases (Figure 7-3B), not all ATCs are FDG avid.

SURGICAL MANAGEMENT

The treatment of patients with ATC is controversial regarding both curative and palliative intervention. Several groups have proposed multimodality therapy for patients with ATC, which includes surgical resection, chemotherapy, and radiation.[27–31]

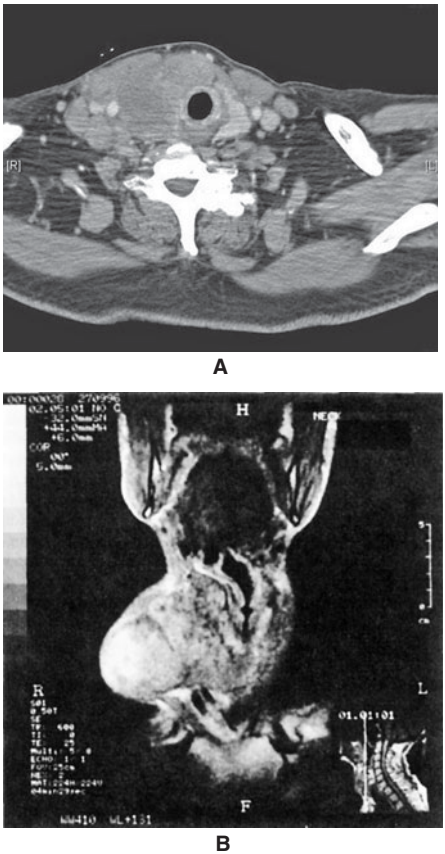


Figure 7-3. Preoperative imaging studies from a patient with locally invasive anaplastic thyroid cancer with distant metastases. **A.** CT scan of the neck demonstrating a large, heterogeneous primary tumor extending into the esophagus. Although this tumor displaces the trachea and the vessels of the carotid sheath, it does not invade the former or encase the latter. There is bilateral cervical lymphadenopathy. (Courtesy of Raphael Bueno, MD.) **B.** Positron emission computed tomography scan demonstrating an intensely ^{18}[F]2-fluoro-2-deoxyglucose (FDG)–avid primary tumor. FDG-avid cervical lymphadenopathy and multiple pulmonary metastases are present. Foci of tracer uptake is seen at the level of the dome of the liver, likely representing liver metastases. (Reproduced with permission from Brunicardi FC, Andersen DK, Billiar TR, et al. Schwartz's Principles of Surgery, 8th ed. New York, McGraw-Hill, 2005; p 1425.)

We concur with this approach for patients with ATC that is amenable to total thyroidectomy. Our treatment algorithm for ATC is depicted in Figure 7-4.

ATC often invades nearby organs and structures, such as the RLN, trachea, esophagus, and internal jugular vein. Locoregional invasion that fails to respect tissue margins usually precludes complete macroscopic resection. Some groups have even proposed debulking surgery when complete resection is not technically feasible.[20, 25,32] Of note, several reports have identified infrequent cases of long-term survival in patients who have undergone complete surgical resection. In our experience, aggressive tumor debulking followed by adjuvant therapy extends survival in patients with localized disease.[33] However, long-term survival in patients with confirmed ATC is truly rare.

In our opinion, surgical resection with combination chemoradiotherapy is beneficial in patients with ATC that is clinically amenable to complete resection. Although no studies have demonstrated reliable curative surgical therapy, several have demonstrated significant improvements in short-term survival.[20,25,34,35] Local control rates of 60% have been reported with multimodality therapy consisting of neoadjuvant chemoradiation followed by surgical resection.[36] The majority of patients in these series died from distant metastases, which questions the utility of aggressive local therapy for disease that is widely systemic. However, in addition to overall survival, control of cervical disease and the prevention of asphyxiation are also important treatment goals.

No prospective trials have demonstrated a long-term survival advantage in patients with ATC who have undergone aggressive surgical resection. There are few reports of long-term curative outcomes, and some have suggested that these were actually lymphoma or poorly differentiated MTC that were misdiagnosed as ATC.[4] In our opinion, complete surgical resection with adjuvant chemoradiation should be attempted whenever possible, without sacrificing major neurovascular structures. Although some authors have reported that extrathyroidal extension precludes curative resection,[37] in our experience, only regional and distant metastases preclude a curative outcome. Regardless, long-term survival in patients with ATC is extremely rare, and we have treated only a few patients who are disease free beyond 5 years after thyroidectomy.

Partial thyroidectomy, often with tracheostomy, should be performed only as a palliative measure to prevent asphyxiation in patients with local airway compression that is not amenable or responsive to EBRT. There is no role for prophylactic partial thyroidectomy or tracheostomy, which may actually shorten survival.[38]

Because no individual treatment has been proven effective for patients with ATC, aggressive combination therapy that includes adjuvant EBRT is often undertaken. In a large analysis that used the SEER database, combined

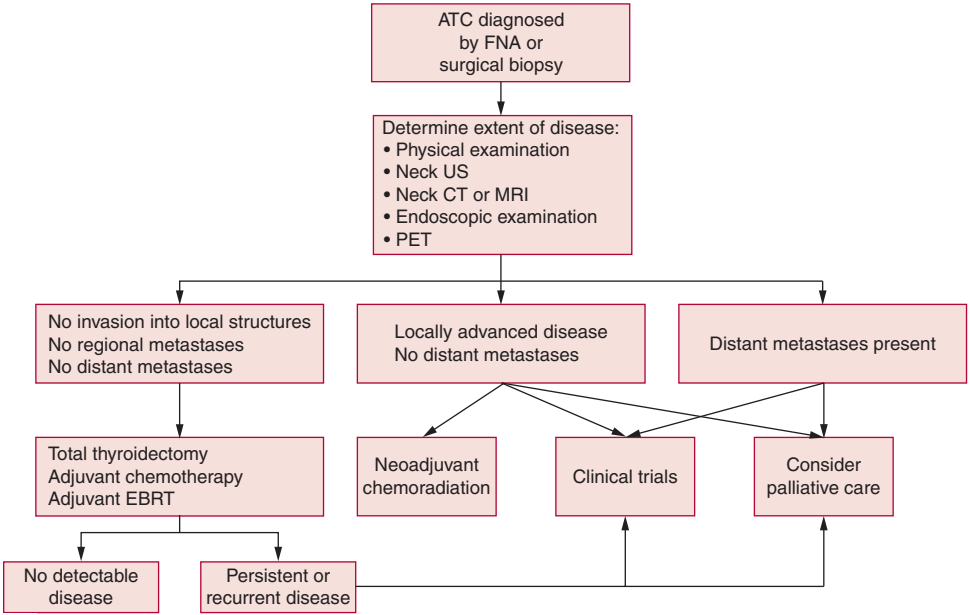


Figure 7-4. Treatment algorithm for patients with anaplastic thyroid cancer (ATC). CT = computed tomography; EBRT = external-beam radiation therapy; FNA = fine-needle aspiration; MRI = magnetic resonance imaging; PET = positron emission computed tomography; us = ultrasonography.

surgery and EBRT decreased cause-specific mortality in patients with regional and distant disease.[22] Although some reports of multimodality regimens that include EBRT have demonstrated some success, no combination therapy has demonstrated consistent long-term survival. Thus, EBRT is more often used as a palliative treatment for patients with ATC. EBRT may often reduce tumor bulk and relieve airway compression in patients with advanced ATC.[39]

Because the overall results are so poor for ATC patients after resection, multimodality therapy, including systemic chemotherapy, is commonly used. Although chemotherapy may add little to long-term survival in this patient population, the grave nature of the disease warrants aggressive adjuvant therapy. Results from conventional chemotherapy treatment for patients with ATC have been generally poor. Early studies of doxorubicin monotherapy demonstrated response rates approximating 22%, which was almost half that of the 42% response rate in those with MTC.[40] Combination chemotherapy regimens that include paclitaxel,[41] cisplatin,[42] vincristine,[43] bleomycin,[44] and gemcitabine[45] have demonstrated similarly disappointing results.

Targeted therapeutics have demonstrated some efficacy in in vitro and in vivo studies.[46–48] Other novel therapies that have demonstrated some promise in ATC either as single agents or in combination therapy include oncolytic virus therapy,[49] histone deacetylase inhibitors,[50] and combrestatins.[51]

SURVEILLANCE AND FOLLOW-UP

In the small subgroup of patients that can undergo complete surgical resection and adjuvant chemoradiation, close surveillance is indicated. Our practice is to have patients undergo follow-up physical examination and CT scanning 3 months, 6 months, and 1 year after curative surgery. We believe the same criteria for attempted curative extirpation should be followed if a patient has local recurrence or even distant isolated metastases when there has been a relatively long (= 12 months) tumor-free period.

METASTASES TO THE THYROID GLAND

Although metastases to the thyroid are considered rare, autopsy studies suggest that the prevalence is relatively common, with an incidence of 2% to 25%.[52–54] Metastases to the thyroid gland represent advanced systemic disease that cannot be cured by surgical extirpation. FNA biopsy with cytologic review can usually identify the primary cell type. Metastases to the thyroid gland most often originate from melanoma as well as bronchogenic, breast, gastrointestinal, prostate, and renal carcinomas.[55–57] Among all of the histologic sites, however, renal cell is the most frequent. Cytologic diagnosis

of metastases to the thyroid gland in asymptomatic patients can avoid unnecessary surgery in patients without local compressive symptoms.

Although controversial, some retrospective studies have reported that thyroidectomy can prolong disease-free survival in patients with isolated metastases to the thyroid.[58] A report by Heffess and colleagues[59] advocated surgical resection in patients with metastatic renal cell carcinoma to the thyroid. Palliative surgery is a reasonable treatment option for patients with thyroid-associated pain, dysphagia, or obstructed breathing from metastases. Thyroid lobectomy is generally the treatment of choice in this setting. Adjuvant combination chemotherapy and EBRT should be considered, depending on the primary cancer type.

An unusual primary tumor of the thyroid is lymphoma. It is a rare entity and comprises 1% to 2% of all thyroid malignancies.[60] It is more common in females with a greater than 3 to 1 propensity. A well-known risk factor for thyroid lymphoma is Hashimoto's thyroiditis. The typical patient presents in the seventh decade of life with a rapidly enlarging neck mass.[61] Nearly half of these patients have symptoms and signs attributed to local compression.

Thyroid Lymphoma

Thyroid lymphoma is most commonly non-Hodgkin's lymphoma of B-cell origin. Hodgkin's and T-cell lymphoma occur rarely. General subtypes include diffuse large B-cell lymphomas with or without marginal zone B-cell lymphoma, marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue, and follicular lymphoma.[62] Staging is categorized into IE (localized disease of the thyroid), IIE (disease confined to the thyroid and regional nodes), IIIE (disease on either aspect of the diaphragm), and IVE (disseminated disease). Prognosis is typically based on the clinicopathologic type. Patients with diffuse large B-cell or mixed lymphomas have worse outcomes than patients with pure mucosa-associated lymphoid tissue (MALT) lymphomas.

Because of the similar clinical presentation to ATC, it is imperative that a definitive diagnosis be made. FNA with adjunctive techniques is usually sufficient to diagnose thyroid lymphoma. However, in some instances, such as distinguishing MALT lymphomas from Hashimoto's thyroiditis, open surgical biopsy is sometimes necessary.

The management of patients with thyroid lymphoma is controversial.[62] Some evidence suggests that surgery or radiation alone may be beneficial in early stage (IE) disease, especially with a MALT subtype. However, the vast majority of patients with thyroid lymphoma are generally treated with a multimodality approach using cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)–based chemotherapy combined with radiation.

PRACTICAL PEARLS

- ATC is one of the most aggressive solid tumors in human oncology, and despite maximal multimodality therapy, outcomes are generally poor.
- Patients without evidence of regional or distant ATC should undergo aggressive multimodality therapy, including attempted complete surgical resection.
- Novel treatments are needed for ATC, and studies investigating the use of targeted therapies are currently underway.
- Patients with ATC should be enrolled in clinical oncology trials whenever possible.
- Metastases to the thyroid gland most often originate from bronchogenic, breast, gastrointestinal, melanoma, prostate, and renal carcinomas; the kidney is the most common primary site.
- Thyroid lymphomas are rare tumors and should be definitively diagnosed because the clinical presentation mimics ATC.

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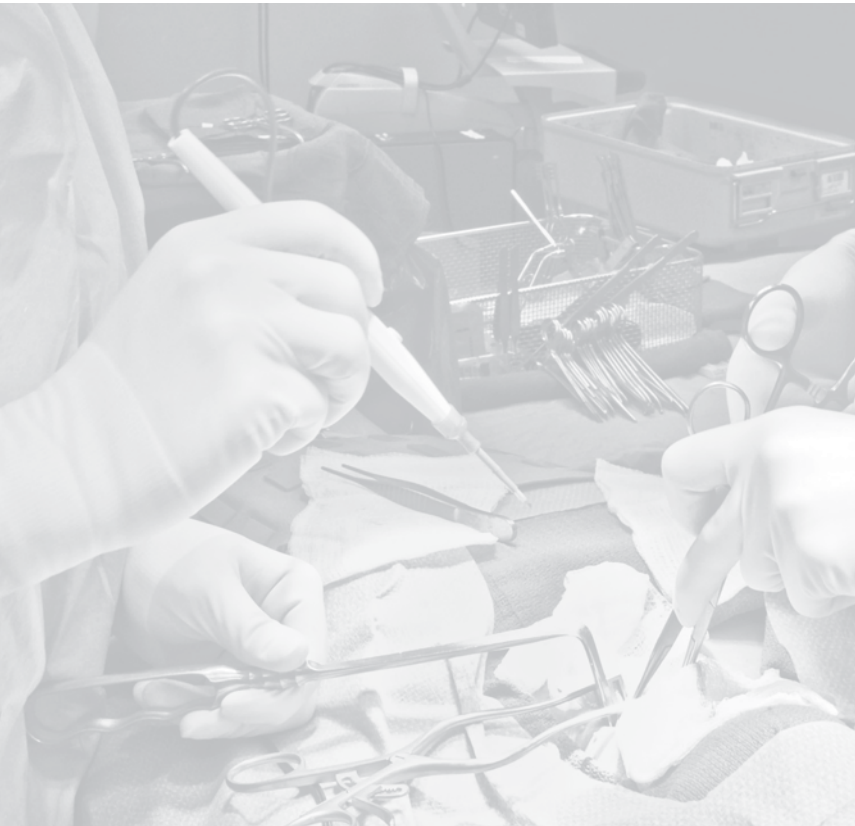
SECTION II
Parathyroid



Chapter 8

Primary Hyperparathyroidism

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EPIDEMIOLOGY

Primary hyperparathyroidism (PHPT) results from the overproduction of parathyroid hormone (PTH) by one or more autonomously hyperfunctioning parathyroid glands that usually causes hypercalcemia. PHPT is usually caused by a single parathyroid adenoma (85%); the remaining cases (15%) are caused by multigland disease (MGD) in which more than one parathyroid gland is hyperfunctional.

PHPT is the most common cause of hypercalcemia in the outpatient setting. Approximately 100,000 new cases per year of PHPT occur in the United States. Since the advent of routine laboratory testing, the prevalence of the disease has increased from 0.1% to 0.4%.[1] PHPT may present at any age, with the majority occurring in patients older than age 45 years. Furthermore, women are affected twice as often as men; this is believed to be secondary to estrogen deficiency after menopause that unmasks underlying hyperparathyroidism.[1].

RISK FACTORS

Definite risk factors for PHPT can be identified in only a few patients. More specifically, PHPT may be associated with genetic abnormalities such as multiple endocrine neoplasia (MEN) syndromes or familial isolated hyperparathyroidism (FIHPT) and a history of radiation exposure. Some patients have a history of therapeutic neck radiation 30 to 40 years before developing PHPT. In one study of 2555 patients followed for 50 years, even low doses of radiation exposure during the teenage years was associated with a slight risk of developing PHPT [2].

Several genetic anomalies, including tumor suppressor genes and proto-oncogenes, have been identified in the development of PHPT. A DNA mutation in a parathyroid cell may confer a proliferative advantage over normal neighboring cells, thus allowing for clonal growth. Large populations of these abnormal cells containing the same mutation within hyperfunctioning parathyroid tissue suggest that such glands are a result of clonal expansion.[3]

MEN1 is a tumor suppressor gene that may play a role in the development of PHPT. The *MEN1* gene, located on chromosome 11, encodes for the transcription factor menin. This gene has been found to be mutated in up to 16% of patients with sporadic PHPT.[4] *PRAD1* proto-oncogene abnormalities have also been found in approximately 20% to 40% of patients with parathyroid adenomas. *PRAD1*, which is located on chromosome 11, encodes for cyclin D1, which is an important regulator of the cell cycle. Inversion of the *PRAD1* gene allows for cyclin D1 overexpression, leading to adenoma formation.[5] In families with hyperparathyroidism–jaw tumor syndrome (HPT-JT), inactivation of the *HRPT2* gene that encodes the protein parafibromin has been established as a possible mechanism in the development of parathyroid tumors. *HRPT2* mutations that inactivate parafibromin and its tumor suppressor function are found in patients with HPT-JT and parathyroid carcinoma and in a few cases of parathyroid adenomas with cystic features. There is evidence to suggest that whereas parafibromin expression remains intact in benign parathyroid adenomas, its loss of expression is indicative of *HRPT2* mutations, which are highly associated with HPT-JT and parathyroid carcinoma.[6]

CLINICAL PRESENTATION

The clinical presentation of PHPT has evolved throughout the years. The classic descriptions of osteitis fibrosa cystica, nephrocalcinosis, peptic ulcer disease, and severe proximal myopathy are now infrequently encountered in the United States. Currently, the most common signs and symptoms identified are bone pain, nephrolithiasis, fatigue, weakness, mood swings, irritability, anxiety, depression, poor concentration, and memory loss. Other findings associated with this condition include polydipsia, polyuria, constipation, nocturia, and heartburn. Nonetheless, up to 80% of patients currently present with nonspecific symptoms and are often considered asymptomatic.[7]

DIAGNOSTIC EVALUATION

After PHPT is suspected or hypercalcemia is encountered, biochemical confirmation of the disease is necessary. Total serum calcium or ionized calcium levels are reliable laboratory measurements for hypercalcemia. Intact PTH levels are also measured, and if they are elevated, the diagnosis of PHPT is

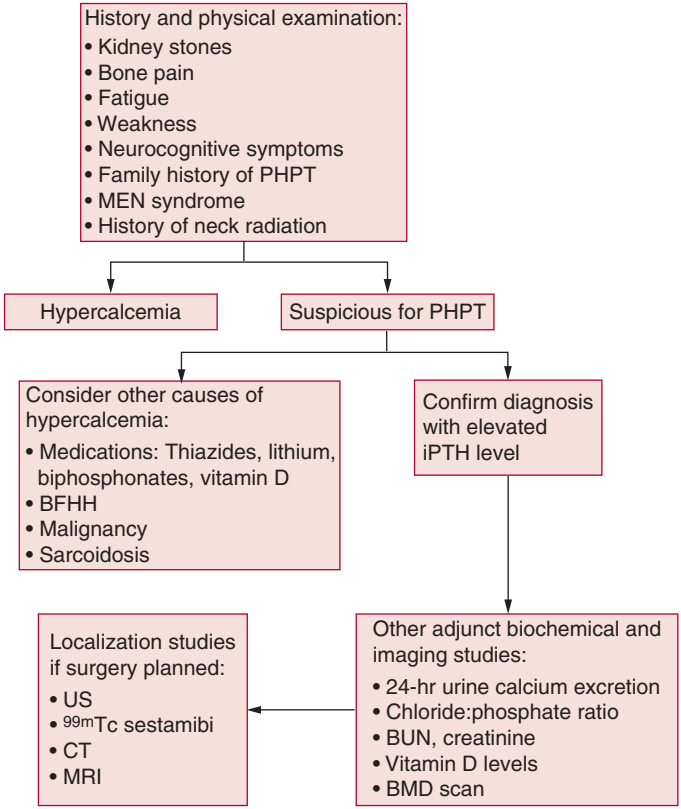

Figure 8-1. Diagnostic evaluation for patients with primary hyperparathyroidism. BFHH = benign familial hypocalciuric hypercalcemia; BMD = bone mineral density; BUN = blood urea nitrogen; CT = computed tomography; iPTH = intact parathyroid hormone; MEN = multiple endocrine neoplasia; MRI = magnetic resonance imaging; PHPT = primary hyperparathyroidism; PTH = parathyroid hormone; ^{99m}Tc = technetium pertechnetate; US = ultrasonography.

confirmed (Figure 8-1). However, up to 10% of patients with PHPT may actually have a "normal" or inappropriately elevated PTH level, possibly because of a different PTH "set point" within individuals that may vary with age or overall calcium levels.[8] Other causes of altered calcium levels also need to

be excluded, including use of thiazide diuretics, lithium, or biphosphonates; vitamin D excess; malignancy; sarcoidosis; and prolonged immobilization. Other biochemical studies that assist in making the diagnosis of PHPT include the chloride:phosphate ratio. Patients with PHPT have chloride levels in the high-normal range and phosphate levels in the low-normal range. A chloride: phosphate ratio greater than 33 is indicative of PHPT.[9]

Patients with PHPT may also present with normocalcemic hyperparathyroidism. In these patients, normal calcium levels are associated with elevated PTH levels. This condition is generally recognized in patients after they are evaluated for osteoporosis. In some patients, this may be the earliest presentation of symptomatic PHPT. Nevertheless, other causes of secondary PTH elevation, such as vitamin D deficiency, need to be excluded.[10]

Benign familial hypocalciuric hypercalcemia (BFHH) is a rare condition that must be considered in the differential diagnosis. Biochemically, BFHH may mimic PHPT, with patients presenting with elevated calcium and PTH levels. An autosomal dominant disease, BFHH is caused by a systemic underexpression of the calcium-sensing receptor gene. This condition is characterized by a long-standing history of hypercalcemia since birth along with decreased urine calcium excretion. Patients with BFHH may have a family history of hypercalcemia in relatives before age 10 years, a condition that is rarely seen in individuals with PHPT, FIHPT, or MEN syndrome. Furthermore, the urine calcium levels in these patients are usually less than 50 mg/24 hours. Similarly, the urinary calcium:creatinine clearance ratio is less than 0.01; in patients with PHPT, it is greater than 0.02.

Dual-energy x-ray absoptiometry (DEXA) measurement of bone mineral density (BMD) is widely used for the study of osteopenia and osteoporosis. Patients with decreased BMD should be monitored for hypercalcemia secondary to PHPT. Conversely, the majority of patients with PHPT should undergo BMD testing. If osteoporosis is documented (t-score < -2.5), parathyroidectomy should be considered. In patients with PHPT, bone density losses are greater in areas of cortical bone such as the radius, but they may occur at all bony sites. The benefit of parathyroidectomy, however, is more pronounced at the hip and spine because of the morbidity and mortality associated with bone fracture at these sites.

After PHPT is biochemically confirmed and the patient is a surgical candidate, the abnormal parathyroid gland(s) should be localized. Because the parathyroid glands can have varied anatomic locations, preoperative parathyroid localization can be invaluable. Ultrasonography and technetium pertechnetate (^{99m}Tc) sestamibi scans are most commonly used for parathyroid localization. Either imaging study alone can localize abnormal glands, with an accuracy nearing 80%. Ultrasonography has the advantages of being noninvasive and less costly than sestamibi scans and provides detailed information

regarding the anatomic relationships of the diseased parathyroid gland(s) that may be useful to the operating surgeon (Figure 8-2). Several studies have demonstrated that surgeon-performed ultrasonography has similar or better sensitivity to sestamibi scans and radiologist-performed ultrasonography.[11,12]

Sestamibi has been used for the past 20 years, and several variations have been developed (Figure 8-3). There is general agreement that sestamibi, especially when combined with single-photon emission computed tomography (SPECT), is the single best imaging study for parathyroid localization. Several studies report the sensitivity and specificity of sestamibi imaging to be around 91% to 99%, respectively. A limitation of sestamibi scans is related to the additional presence of thyroid nodules or lymph nodes that may cause false-positive findings and mimic the hyperactivity of parathyroid adenomas.[13]

MGD can be a challenge to localize preoperatively. Sestamibi scans alone fail to identify multiple abnormal parathyroid glands in up to 87% of patients, and ultrasonography cannot reliably visualize all enlarged glands.[14] Under

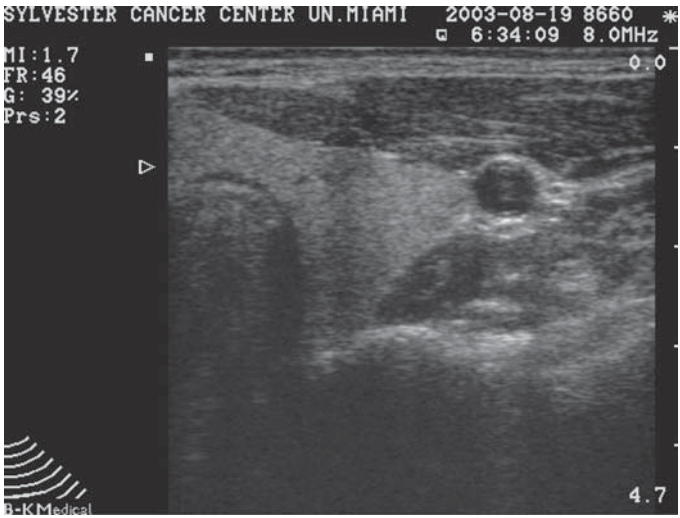

Figure 8-2. Parathyroid adenoma localized by surgeon-performed ultrasonography to the inferior left thyroid lobe (*arrow*). Typical characteristics include a well-demarcated hypoechoic mass lateral to the thyroid (*arrowheads* identify the anterior border of the left thyroid lobe) with increased flow on color-flow mapping.

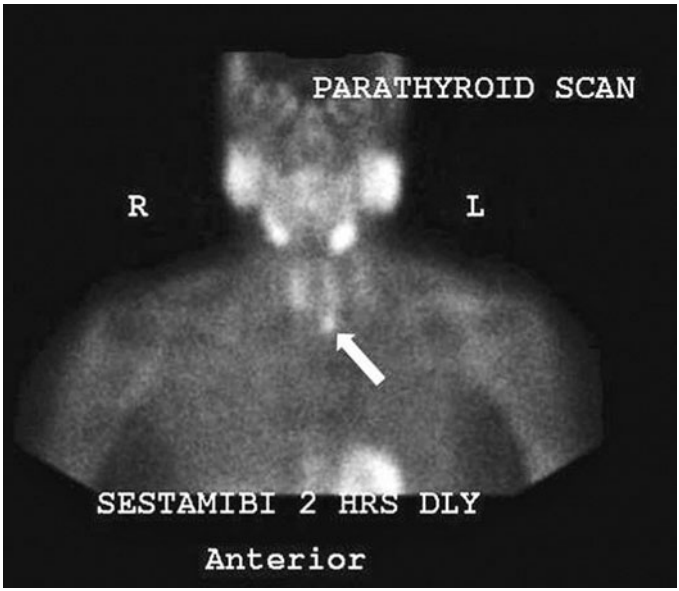

Figure 8-3. Parathyroid adenoma localized to the inferior pole of the left thyroid lobe (*arrow*) by sestamibi scan.

these circumstances, surgeons must rely on their judgment and experience and perform such parathyroidectomies based on the intraoperative findings.

In cases in which neither ultrasonography nor sestamibi provides adequate preoperative localization, computed tomography (CT) or magnetic resonance imaging has been used with variable success. Four-dimensional CT uses rapid wash-in and washout characteristics of parathyroid adenomas that allow for anatomic identification of hyperfunctioning glands with improved sensitivity greater than ultrasonography or sestamibi-SPECT.[15] For selected reoperative cases, four-dimensional CT may have additional value, although its role in preoperative localization is still under investigation.

In selected cases and most reoperative cases in which preoperative localization studies fail to identify an abnormal parathyroid gland, selective venous sampling for PTH levels can be helpful in lateralizing the location of hyperfunctioning parathyroid gland(s). A variation of this technique involves intraoperative percutaneous sampling of both internal

jugular veins using the rapid PTH assay.[16] This simple procedure measures PTH levels in the bilateral internal jugular veins just before incision, thereby identifying the side of the neck in which the diseased gland(s) reside. This technique, which has an accuracy of 79%, may be particularly helpful in patients without preoperative parathyroid localization.

MANAGEMENT

In 2002, the National Institutes of Health (NIH) revised its guidelines for the surgical treatment of patients with PHPT.[17] Parathyroidectomy is recommended in all symptomatic patients (Figure 8-4). In asymptomatic patients with PHPT, however, surgical treatment is recommended in individuals with any of the following:

1. Significant hypercalcemia (>1 mg/dL over the reference range)
2. 24-hour urine calcium >400 mg/dL
3. Renal insufficiency (creatinine clearance reduced by 30% compared with age-matched control subjects)
4. Osteoporosis (t-score at any site <–2.5)
5. Age younger than 50 years
6. Poor patient compliance
7. Patient desire for surgical treatment

Although there has been evidence for parathyroidectomy in patients with PHPT, most clinicians believe that there are no clear guidelines that address the neurocognitive symptoms in these patients. A majority of endocrine surgeons perform parathyroidectomy on patients who present with vague, nonspecific complaints that do not completely satisfy NIH guidelines.[18] Some evidence suggests clear improvement of neurocognitive symptoms in patients with PHPT after parathyroidectomy, particularly for depression and spatial working memory.[19]

The traditional surgical approach to PHPT has been bilateral neck exploration (BNE) under general anesthesia. This procedure usually involves identification of four parathyroid glands, removal of the enlarged gland(s), and biopsy of one or more normal parathyroid glands. When not identified initially during BNE, a diligent search for the abnormal parathyroid gland(s) in the neck is performed, involving exploration of the upper mediastinum, retroesophageal area, carotid sheaths, and thyroid gland. If the gland is still not found, mediastinotomy may be performed at a later date after reevaluation of initial diagnosis and further imaging to localize the unidentified gland. In experienced hands, BNE has classically been described to have a success rate above 95%, with strong advocacy by some groups.[20,21] However, with

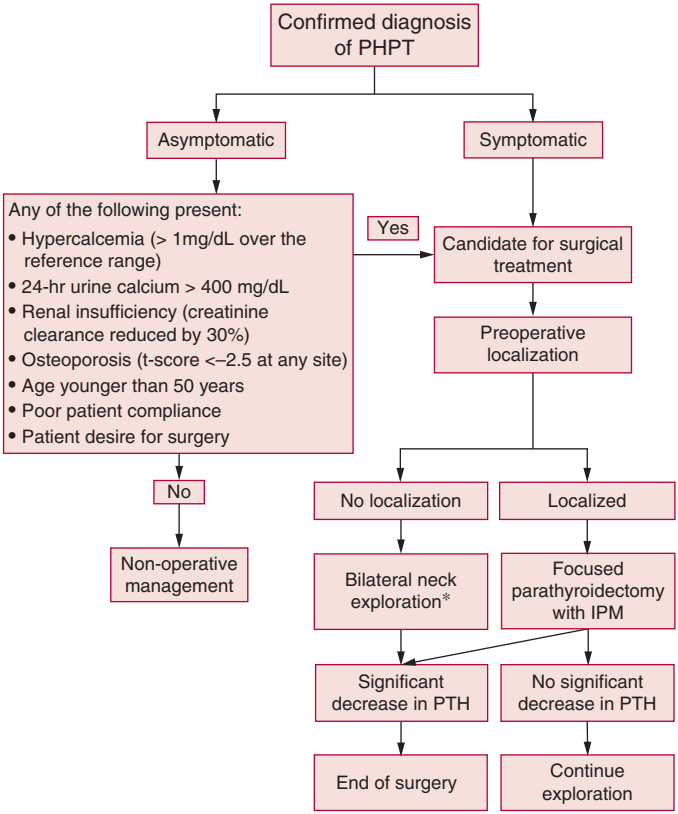

Figure 8-4. Management of patients with primary hyperparathyroidism. *Jugular venous sampling as discussed in text. IPM = intraoperative parathyroid hormone monitoring; PHPT = primary hyperparathyroidism; PTH = parathyroid hormone.

improved methods for preoperative parathyroid localization and the use of intraoperative PTH monitoring (IPM), less invasive parathyroidectomy has been described with similar or better outcomes. These less invasive procedures include unilateral neck exploration (UNE), focused parathyroidectomy (exploring and resecting only the diseased gland), and minimally invasive

video-assisted methods. A randomized, controlled trial comparing UNE with BNE in patients with PHPT demonstrated a 97% cure rate for both groups with no cost difference. UNE, however, was performed quicker and was associated with fewer cases of postoperative hypocalcemia than BNE.[22]

In 1991, Irvin and colleagues[23] popularized the use of IPM to confirm excision of all hypersecreting parathyroid tissue. Briefly, a baseline pre-incision level is drawn from peripheral blood. After the suspected abnormal parathyroid is identified, a second PTH level is drawn (pre-excision level) before its blood supply is clamped. Third and fourth samples are then drawn 5 and 10 minutes later, respectively. When peripheral PTH values decrease more than 50% from the highest either pre-incision or pre-excision level at 10 minutes, these criteria accurately predict postoperative eucalcemia, with an operative success of 97%.[24] Conversely, if the PTH level fails to decrease more than 50% at 10 minutes, hypersecreting parathyroid tissue remains present, requiring further surgical exploration. Further PTH measurements are obtained after excision of other abnormal parathyroid tissue until a significant decrease in the hormone level occurs.

IPM may not be necessary to perform focused parathyroidectomy in patients with single-gland disease in which the preoperative sestamibi and ultrasonography studies are concordant. Imaging studies are considered concordant when both tests localize the parathyroid gland(s) in the same neck location(s). Both imaging studies are considered discordant if one test localizes the abnormal parathyroid gland but the other does not, if one test localizes the gland inferiorly but the other test localizes it superiorly on the same side of the neck, if both tests localize glands on opposite sides of the neck, or if no glands are identified. Parathyroidectomy with concordant preoperative ultrasonography and sestamibi scans without IPM has a failure rate of 2%; if IPM is added, the failure rate decreases to 1%. Conversely, if these preoperative parathyroid localization studies are discordant, IPM may alter operative management in the majority of these patients while maintaining an excellent operative success rate in this potentially difficult-to-treat patient population.[25]

Minimally invasive radioguided parathyroidectomy (MIRP) is another modality used in the surgical treatment of patients with PHPT. Patients should ideally have a localizing preoperative sestamibi scan with washout from the thyroid gland to avoid significant signal interference. Patients are injected 2 hours preoperatively with 18 mCi of ^{99m}Tc sestamibi, and a gamma probe is then used to direct the incision site and localization of the adenoma. This method has been found to be most useful in cases when there is an absence of thyroid tissue, in reoperative cases, or in the presence of an ectopic parathyroid adenoma. IPM may be used as an adjunct to this technique to increase the operative success rate.

Recent interest has revolved around the development of video-assisted parathyroidectomy. The first case of endoscopic parathyroidectomy was reported in 1996.[26] Since then, several variations to this video-assisted technique have emerged. Some studies have compared video-assisted approaches with more conventional methods, uniformly concluding that video-assisted approaches are associated with less postoperative pain, fewer analgesic requirements, and increased patient satisfaction.[26,27]

The video-assisted technique is performed through a 1.5- to 2-cm transverse incision in the neck using a 5-mm, 30-degree laparoscope that is inserted through the incision. Dissection is performed with video magnification provided by an endoscope, which enables easy identification of the recurrent laryngeal nerve and abnormal parathyroid gland(s). However, the video-assisted technique requires two additional assistants, has a longer learning curve, and is contraindicated in patients with large thyroid nodules and in reoperative cases. Preoperative parathyroid localization and the use of IPM increase operative success in these patients. Importantly, the surgeon should already be experienced with the conventional approach before attempting video-assisted procedures.

Several operative techniques have been described for MGD. The usual operative technique first involves visualization of four parathyroid glands. In cases in which more than one parathyroid gland appears abnormal, only the involved glands are excised. If all four parathyroid glands appear abnormal, the gland closest to normal size should be biopsied and subtotally resected first. A remnant of approximately 50 mg should be left behind. If this remnant becomes ischemic or is of questionable viability, then it should be totally resected and the next normal-appearing gland should be subtotally resected. When the parathyroid remnant is viable, the remaining glands are removed. A thymectomy is recommended in all cases because of a 14% to 25% risk of having a fifth adenoma. If there is any question regarding the viability of the remaining parathyroid tissue, it can be autotransplanted in the ipsilateral sternocleidomastoid muscle or in the nondominant forearm. Because total parathyroidectomy with autotransplantation is associated with higher rates of hypoparathyroidism, subtotal parathyroidectomy ($3\,{}^{1}/_{2}$-gland resection) is the preferred approach.

The operative success rates for BNE and focused parathyroidectomy approach 98%.[21,24,28,29] Operative success is defined as eucalcemia for at least 6 months after surgery. Persistent disease, defined as hypercalcemia associated with elevated PTH levels within 6 months of surgery, may be caused by missed MGD or the presence of missed ectopic or supernumerary glands. Many studies report elevated PTH levels with eucalcemia after successful parathyroidectomy. Although its clinical significance remains unclear, advanced age, gender, disease severity, adenoma size, osteoporosis,

MGD, decreased peripheral sensitivity to PTH, vitamin D deficiency, and renal failure have all been described as possible underlying causes of postoperative elevated PTH levels in eucalcemic patients.[30]

Patients should undergo routine postoperative surveillance. Serum calcium levels should be obtained within the first 24 to 48 hours after surgery and measured at 2 and 6 months to confirm operative success. Vitamin D measurements should also be considered postoperatively, and vitamin D replacement should be given if vitamin D 25-OH levels are below normal. Patients can then be followed on a yearly basis with routine calcium, PTH, and vitamin D level measurements.

Parathyroidectomy is the only definitive treatment for PHPT, and it can be performed safely in patients with a high rate of success. Patients who are not surgical candidates or have failed parathyroidectomy, however, may be medically treated. Options include biphosphonates, corticosteroids, and calcimimetic agents such as cinacalcet. The most promising results have been achieved with cinacalcet, which binds to the calcium-sensing receptors on the parathyroid cells, increasing the receptors' sensitivity to calcium and decreasing PTH secretion. This medication may achieve long-term eucalcemia in some patients.[31]

PRACTICAL PEARLS

- PHPT is defined as hypercalcemia resulting from the overproduction of PTH by one or more hyperfunctioning parathyroid glands.
- PHPT is usually caused by a single parathyroid adenoma (85%); the remaining cases (15%) are caused by multigland disease (MGD).
- PHPT is the most common cause of hypercalcemia in the outpatient setting.
- PHPT may present at any age, but the great majority of cases occur in patients older than age 45 years, with women affected twice as often as men.
- Risk factors for PHPT can be identified in only a few patients, including those with genetic abnormalities and a history of neck radiation.
- Up to 80% of patients with PHPT are asymptomatic; however, signs and symptoms include bone pain, nephrolithiasis, fatigue, weakness, mood swings, irritability, anxiety, depression, poor concentration, and memory loss.

(*Continued*)

- After PHPT is suspected and hypercalcemia is found, elevated intact PTH levels confirm the diagnosis of PHPT; however, up to 10% of patients with PHPT may actually have high-normal PTH levels.
- The differential diagnosis includes other causes of calcium elevation, such as use of medications, malignancy, sarcoidosis, vitamin D excess, and BFHH.
- After the diagnosis of PHPT is made, localization of the hyperfunctioning parathyroid gland(s) is usually obtained with ultrasonography or a sestamibi scan.
- Parathyroidectomy is recommended in all symptomatic patients. In asymptomatic patients with PHPT, surgical consultation should be offered.
- The traditional operation for PHPT has been a bilateral neck exploration; however, with improved preoperative localization studies and the use of IPM, focused parathyroidectomy is performed with similar or greater success.
- When more than one parathyroid gland is abnormal, only the involved glands are excised. When all four parathyroid glands are abnormal, subtotal parathyroidectomy ($3^1/_2$-gland resection) and leaving a small parathyroid tissue remnant is the procedure of choice.
- Operative success, defined as eucalcemia for at least 6 months after surgery, by experienced surgeons approaches 98%.
- Patients who are not surgical candidates or have failed parathyroidectomy may be medically treated.

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Chapter 9

Persistent and Recurrent Hyperparathyroidism

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Richard A. Prinz, MD

EPIDEMIOLOGY

Primary hyperparathyroidism (PHPT) is the second most common disease treated by endocrine surgeons, with more than 100,000 new cases diagnosed annually in the United States.[1] Success rates for treating hyperparathyroidism are regularly reported to be in excess of 95% in the hands of experienced parathyroid surgeons. However, these rates decrease to approximately 70% when the initial surgery is performed by an inexperienced surgeon.[2] The morbidity associated with the initial operation for PHPT performed by a high-volume surgeon is minimal. Despite the excellent results reported for initial parathyroidectomies, those reported for reoperations are less impressive. After a failed initial operation, the success rate decreases, and the morbidity increases regardless of the experience of the operating surgeon. Claude Organ, MD, has been quoted as saying: "The decision to operate is the second hardest decision in surgery. The decision to reoperate is the hardest."

In 2002, the National Institutes of Health released a consensus statement regarding the treatment of patients with PHPT.[3] This statement specifically addressed the treatment of asymptomatic patients who have elevated calcium and parathyroid hormone (PTH) levels and represents a transition to a broader recommendation for surgery in hyperparathyroid patients. In conjunction with this tolerant recommendation for surgery in asymptomatic patients, many authors now suggest a more inclusive definition of symptomatic patients that allows for more global signs and symptoms, such as fatigue, sleep disturbances, difficulty with concentration, polydipsia, and

polyuria. Even with this paradigm shift, many surgeons remain more conservative when considering reoperation for patients with persistent or recurrent hyperparathyroidism. The indications for reoperation are less well defined and frequently depend on the overall condition of the patient and ability to localize abnormal parathyroid tissue.

Persistent hyperparathyroidism is defined as elevated calcium and PTH within 6 months of neck exploration for hyperparathyroidism, and recurrent hyperparathyroidism is defined as elevated calcium and PTH that occurs more than 6 to 12 months after a seemingly successful parathyroidectomy. Many factors have been implicated in persistent or recurrent hyperparathyroidism. Six major reasons for recurrent or persistent hyperparathyroidism have been identified.[4] These include multiple gland disease (MGD), ectopic gland location, supranumerary glands, surgeon inexperience, persistent or metastatic parathyroid carcinoma, and errors on frozen section or intraoperative PTH monitoring.

MGD has been implicated in 31% to 37% of patients with persistent or recurrent hyperparathyroidism.[2,5] Levine and Clark[4] reported that 37% of failures were the result of MGD, with 22% of patients having hyperplasia and 15% having double adenomas. These numbers are much higher than the 10% to 15% and 3% to 5%, respectively, that are typically quoted for patients undergoing first-time operations for PHPT. This increased incidence likely reflects the lower sensitivity of current localization measures in identifying MGD.

In recent years, intraoperative PTH monitoring has been added to endocrine surgeons' armamentarium in an attempt to identify patients with MGD. This technique, initially described by Dr. George Irvin, uses the short half-life of intact PTH to demonstrate physiologic surgical success while in the operating room.[6] This has promoted the development of focused, minimally invasive parathyroidectomy based on preoperative imaging for localization and documentation of decreased PTH levels while in the operating room. By combining these two elements, success rates similar to that for traditional four-gland exploration have been obtained by many surgeons. However, controversy remains regarding the interpretation of intraoperative PTH levels. Many authors advocate the initially described 50% reduction from the baseline level of intraoperative PTH as the determining factor for terminating the operation, but others espouse more rigorous criteria that include a decrease into the normal range. Proponents of this suggest that normalization of the intraoperative PTH would decrease the number of patients with persistent or recurrent hyperparathyroidism. Even with intraoperative PTH monitoring, missed MGD remains an important cause of recurrent or persistent hyperparathyroidism.

EMBRYOLOGY

The embryologic development of the parathyroid gland allows a wide array of anatomic variation. The classic anatomic location for the parathyroid glands is described as within a 1-cm radius centered at the junction of the recurrent laryngeal nerve (RLN) and the inferior thyroid artery. Whereas the superior parathyroid glands tend to be located dorsal to the RLN, the inferior parathyroids are typically located ventral to the nerve. The superior glands develop from the fourth branchial pouch along with neuroendocrine cells that will ultimately become the parafollicular C cells. They migrate inferiorly, where they are often intimately associated with the posterior–lateral portion of the thyroid. The inferior glands develop from the third branchial pouch along with the thymus. Both structures migrate inferiorly to their normal positions. The inferior glands tend to have more anatomic variation because of their long migratory path and may be located ectopically in the thymus, mediastinum, or carotid sheath. Between 25% and 55% of failures are attributed to ectopic location of the parathyroid adenomas.[2,7,8] Shen and associates[2] reported that 50% of ectopically located glands were in the neck and 50% were in the mediastinum. Seventeen percent of ectopically located glands required median sternotomy for removal and accounted for 9% of all reoperations in their series. The authors concluded that the majority of ectopically located glands in the mediastinum could be accessed through a traditional transverse cervicotomy. Other authors advocate a thoracoscopic approach to address mediastinal parathyroid adenomas. Nilubol et al.[9] reported that nine of 32 patients with mediastinal adenomas required either a limited sternotomy ($n = 3$) or a radioguided video-assisted thoracoscopic surgery (VATS; $n = 4$). Two patients required a conversion of VATS to conventional thoracotomy.

FACTORS FOR PERSISTENT OR RECURRENT DISEASE

Surgeon experience appears to be a very important factor in minimizing recurrent or persistent hyperparathyroidism. Surgeons at the Mayo Clinic demonstrated that the pattern of surgical failure was highly dependent on surgeon volume.[8] They reported that 82% of patients requiring reoperation who were initially treated at an outside center had single-gland disease versus 15% of those initially treated at the Mayo Clinic.[8] Furthermore, 76% of these single glands were located in a normal anatomic position. The authors hypothesized that the majority of the failures with normally located glands could have been avoided if the initial operation was performed by an experienced parathyroid surgeon.

Other factors that have been implicated in initial surgical failures include supranumerary glands, metastatic parathyroid carcinoma, recurrence

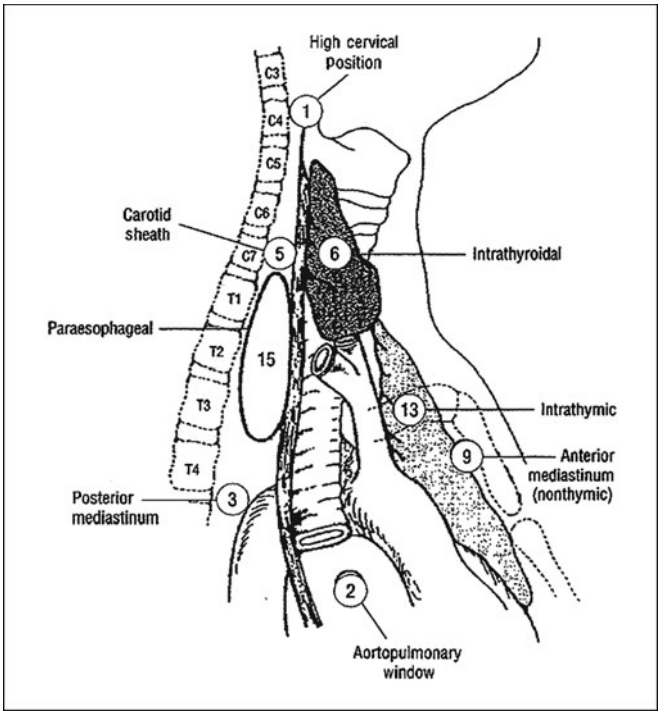

Figure 9-1. Anatomic locations of ectopic parathyroid glands, with numbers in each location given ($n = 54$). (Reproduced with permission from Shen W, Duren M, Morita E, Higgins C, et al. Reoperation for persistent or recurrent primary hyperparathyroidism. *Arch Surg* 1996;131:861-869.)

of partially resected adenomas, and errors on frozen section. Patients with either hyperplasia or adenomas may have supranumerary glands,[4] and they may be found in usual locations as well as in ectopic positions. Metastatic parathyroid carcinoma may cause recurrent hyperparathyroidism by either local recurrence or distant spread. Recurrence may result from the implantation of spilled parathyroid tissue or by the incomplete resection of parathyroid adenomas. Thyroid nodules have also been mistaken for parathyroid tissue on frozen section, resulting in the premature termination of neck exploration.

DIAGNOSIS

Although the success rates for initial operations for PHPT have expanded the indications for parathyroidectomy, a more cautious approach should be taken with patients who have persistent or recurrent disease. A planned algorithm for approaching these patients is necessary to optimize success. The first step in the algorithm is to confirm the diagnosis of hyperparathyroidism (Figure 9-2). This should include measurement of the serum calcium, intact PTH, and urinary calcium excretion. In an early report by Brennan and coworkers,[5] 9% of patients with persistent hypercalcemia were found to have familial hypocalciuric hypercalcemia (FHH), which is an autosomal dominant disease with hypercalcemia, normal or mildly elevated PTH, and low urinary calcium excretion. The presence of FHH is diagnosed by finding a urinary calcium:creatinine clearance ratio of less than 0.01.

The second step in the algorithm is to review all records available from the initial operation. This includes analyzing and correlating the original localization studies as well as operative reports, pathology reports, and pathology slides from the initial surgery. These reports may yield clues that will help guide further interventions and identify the offending gland.

Next, the focus should be localizing the abnormal parathyroid gland(s) by imaging techniques. The initial imaging modality should be one that is high yield yet cost effective. Ultrasonography has a sensitivity of 75% and an accuracy of 65% when used alone to identify missed or recurrent parathyroid adenomas. If fine-needle aspiration (FNA) of an identified lesion with cytology or measurement of PTH levels is used with ultrasonography, the accuracy improves to 82%.[5] Single-photon emission computed tomography sestamibi scanning with subtraction has a sensitivity of 82% and an accuracy of 67% but is more expensive than ultrasonography.

Other localization techniques have been described but have a more specialized role in identifying abnormal glands. Helical computed tomography (CT) and MRI may be used in conjunction with first-tier imaging modalities if the localization remains in question. These are particularly useful when sestamibi scanning suggests a mediastinal adenoma. These techniques are anatomic imaging modalities that define the relationship to surrounding structures. A third-tier imaging modality is selective venous sampling. This technique been used less frequently in recent years because it is more invasive than other imaging modalities. Selective venous sampling can still prove helpful when all other less invasive attempts at localization have failed. Ultrasonography should be the initial choice for localization, and sestamibi scanning may be used when missing glands cannot be localized successfully by ultrasonography or to confirm the ultrasonography findings.

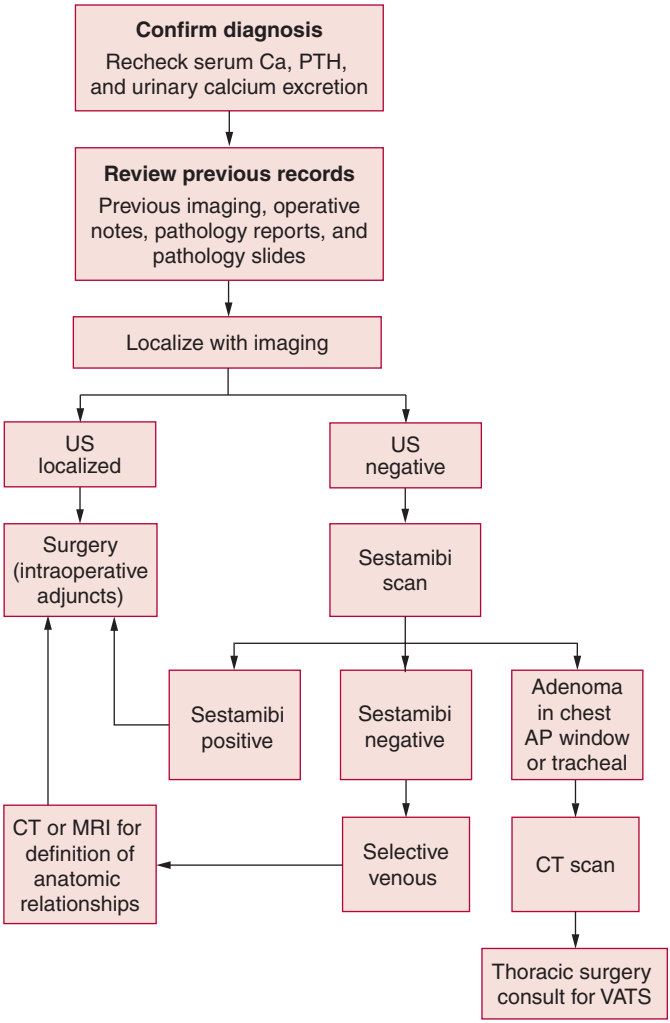

Figure 9-2. Algorithm for the diagnosis of hyperparathyroidism. AP = anteroposterior; CT = computed tomography; MRI = magnetic resonance imaging; PTH = parathyroid hormone; US = ultrasonography; VATS = video-assisted thoracoscopic surgery.

Other imaging techniques should be reserved for patients with mediastinal adenomas or lesions not localized by ultrasonography or sestamibi. It is preferable to have two positive noninvasive localizing test results that confirm the location of a missing gland before reoperation. A positive ultrasonography result with a positive FNA result would also suffice.

SURGICAL MANAGEMENT

After all preoperative preparations are complete, the next step in the algorithm is surgical exploration by a surgeon with a thorough knowledge of the anatomy and embryology of the parathyroid glands. Several intraoperative adjuncts have been described in an attempt to improve the success of reexploration; however, there does not appear to be a substitute for surgeon experience. Some of these adjuncts include gamma probe localization, intravenous methylene blue injection, intraoperative PTH monitoring, RLN monitoring, and methylene blue injection by ultrasound guidance. Each of these techniques has its proponents, but they also have pitfalls that can mislead surgeons. An understanding of the strengths and weaknesses of each adjunct allows surgeons to use these modalities to maximize surgical success.

The surgical approach can also be altered to allow for dissection in a tissue plane that has less scarring. By using a lateral approach, the surgeon avoids many of the adhesions that exist between the thyroid and the strap muscles. This approach starts by incising the investing layer of deep cervical fascia lateral to the strap muscles and retracting the sternocleidomastoid muscle laterally. This technique allows excellent exposure to the superior positions, including the retropharyngeal space and the tracheoesophageal groove. Another surgical maneuver that may help identify the RLN is incising the carotid sheath on the anterior surface of the artery. By staying on the anterior surface of the carotid, the surgeon can identify the nerve as it passes into the neck posterior to the artery. This area generally has less scarring from previous operations and allows identification of the nerve in normal undisturbed tissue. The nerve can then be traced cephalad and the surrounding tissue explored without fear of injuring it.

The surgeon must also have a thorough understanding of the typical ectopic locations of the parathyroid glands. Shen and associates[2] suggest that a systematic exploration of the known ectopic locations should be carried out, including "ipsilateral thymus, anterior superior mediastinum, carotid sheath, and upper cervical regions for lower glands and paraesophageal region, carotid sheath, and posterior mediastinum for missing upper glands. When examination results of these areas are negative, a partial or total thyroid lobectomy or thyroidotomy may be performed to remove possible intrathyroidal parathyroid tumors."[2]

For patients who have glands that have been localized within the mediastinum, the best approach must be determined preoperatively. It may be necessary to enlist the help of an experienced thoracic surgeon in planning these operations. Many of the glands that are located within the mediastinum at the level of the tracheal bifurcation or the aortopulmonary window may be successfully treated with a thoracoscopic approach. Prinz et al.[10] reported on two patients with persistent PHPT and two with persistent secondary hyperparathyroidism who were successfully treated with a thoracoscopic approach. All glands were localized with preoperative sestamibi scanning and confirmed with CT of the chest. These glands were found near the main pulmonary artery, ascending aorta, or aortic arch or in the aortopulmonary window. Each gland was resected thoracoscopically, and calcium levels returned to normal in both patients.

Failure of surgical intervention for PHPT is rare, but when it does occur, a systematic approach is needed to successfully resolve the issue. By following an algorithm, which includes confirming the diagnosis, reviewing records, localizing the glands with imaging, using various surgical adjuncts, dissecting in undisturbed tissue planes, and systematically searching known ectopic sites, endocrine surgeons can successfully cure recurrent or persistent hyperparathyroidism in nearly 90% of cases. Although a systematic approach may improve success and decrease morbidity, the best treatment for patients with persistent or recurrent hyperparathyroidism is prevention by thorough exploration at the initial operation by an experienced endocrine surgeon.

PRACTICAL PEARLS

- Persistent hyperparathyroidism is defined as elevated calcium and PTH within 6 months of neck exploration for hyperparathyroidism.
- Recurrent hyperparathyroidism is defined as elevated calcium and PTH that occurs more than 6 months after a seemingly successful parathyroidectomy.
- The diagnosis of persistent or recurrent hyperparathyroidism should always be confirmed biochemically with measurement of serum calcium, serum intact PTH, and urinary calcium excretion. During physical examination, the practitioner should consider performing flexible laryngoscopy to evaluate the function of the RLN.

(*Continued*)

- When operative intervention is indicated, all records available from the initial operation should be reviewed. This includes analyzing and correlating the original localization studies as well as operative reports, pathology reports, and pathology slides from the initial surgery.
- In additional to confirming the diagnosis as well as reviewing prior records, by using various surgical adjuncts, dissecting in undisturbed tissue planes, and systematically searching known ectopic sights, endocrine surgeons can successfully cure recurrent or persistent hyperparathyroidism in nearly 90% of cases.

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Chapter 10

Secondary and Tertiary Hyperparathyroidism

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Francis D. Moore Jr, MD

OVERVIEW AND DEFINITIONS

The precise regulation of the serum ionized calcium concentration is necessary to sustain human life. The calcium cation is central to a myriad of reactions, from enzymatic function to the coagulation cascade to muscle fiber contraction and neurotransmission to the dynamic buildup and breakdown of the scaffolding that houses it all. The majority of calcium in the human body is found in the skeleton and comprises approximately 2% of the average individual's body weight. Serum calcium levels are precisely maintained through an intricate interplay of checks and balances that begin and end with the parathyroid glands. The regulatory axis of calcium consists of the parathyroid glands, parathyroid hormone (PTH), membrane calcium receptors, the kidneys, the gut, and bone. Membrane calcium receptors on the cells of the parathyroid glands sense minute decreases in serum ionized calcium levels, triggering a cascade beginning with the secretion of PTH. This stimulates mobilization of calcium from bone, a reduction in renal calcium excretion, and an increase in renal hydroxylation of vitamin D, indirectly affecting calcium absorption in the duodenum and proximal jejunum. When calcium increases to within an acceptable range, calcium receptor-based stimulation of the parathyroids ceases, and secretion of PTH is inhibited. Thus, under normal conditions, the defining relationship between serum calcium and serum PTH is inverse: that is, high serum calcium begets low serum PTH and vice versa.

Diseases of the parathyroid are manifest almost exclusively as derangements in calcium metabolism. Hypercalcemia is the most common presentation, although the differential diagnosis of isolated hypercalcemia may be broad and complex. When hypercalcemia is associated with inappropriately

high serum PTH, it is considered *primary hyperparathyroidism* (PHPT). This presupposes no antecedent renal disease, lithium therapy, or malabsorptive syndrome. In PHPT, the calcium level is generally high-normal to significantly elevated, and PTH levels are moderately elevated. PHPT may come in the form of single- or multigland adenoma, four-gland hyperplasia, or (rarely) parathyroid carcinoma.

Secondary hyperparathyroidism (SHPT) refers to the situation in which a derangement in calcium homeostasis (of a nonparathyroid cause) leads to a compensatory increase in PTH secretion. Unlike with PHPT, in SHPT, the elevation of serum PTH is an appropriate physiologic response to a perceived calcium deficit. The serum calcium level is generally in the low-normal range, and PTH is proportionately elevated. This is seen most often in the setting of end-stage renal disease (ESRD) (Figure 10-1) but

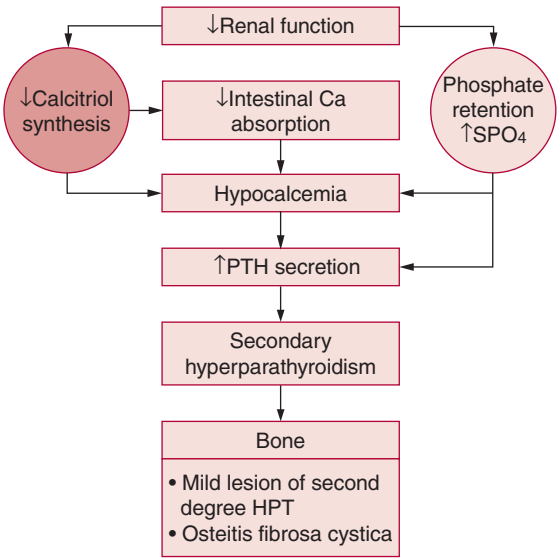

Figure 10-1. Pathogenesis of secondary hyperparathyroidism. PTH = parathyroid hormone; SPO_4 = serum phosphate (Reproduced with permission from Wesseling K, Coburn JW, Salusky IB. In: DeGroot LJ, Jameson J, DeKretser DM, eds. *Endocrinology*, 5th ed. Philadelphia: Elsevier Saunders; 2006:1697-1712.)

may also result from other disorders of bone metabolism and the gastrointestinal (GI) tract.

On occasion, after prolonged secondary stimulation, the hyperfunctioning parathyroids are rendered unresponsive to serum calcium concentrations via a loss of calcium-sensing receptors, and they enter into an autonomous secretory state, or *tertiary hyperparathyroidism* (THPT). The serum calcium level is usually in the high-normal to high range, with a markedly pronounced elevation of PTH. Tertiary disease may occur after correction of the underlying defect in calcium metabolism, which is most often achieved through renal transplantation. Both SHPT and THPT involve uniform overstimulation of the glands and therefore manifest almost exclusively as four-gland hyperplasia.[1] Histologically, whereas resected glands from patients with SHPT show either diffuse or nodular hyperplasia,[2] those taken from patients with tertiary disease may be hyperplastic or even adenomatous.

EPIDEMIOLOGY

The epidemiology of SHPT and THPT is best discussed within the context of the underlying process driving the disease. Most simply put, SHPT may occur in any individual with chronic hypocalcemia or chronic hyperphosphatemia. Chronic hypocalcemia may be the result of malnutrition, malabsorption, vitamin D deficiency, use of various drugs (including lithium), chronic cholestasis, and so on. Thus, three populations are generally at risk: patients with chronic kidney disease, patients with malabsorptive syndromes, and patients at the extremes of age. Overall, no racial predilection exists, and the incidence is equal in males and females, although racial and gender differences are thought to exist within certain subgroups of patients. THPT tends to occur in individuals exhibiting prolonged severe secondary disease.

SHPT occurs as a natural consequence of ESRD (see Figure 10-1), and the severity of derangement may only be ameliorated via aggressive medical management of calcium and phosphate metabolism. Approximately 65% to 75% of patients with renal failure have clinically apparent disease. Of these, only around 5% fail medical therapy, resulting in the need for surgical intervention. Of the patients with ESRD and SHPT who undergo transplantation, approximately 5% to 7% develop tertiary disease, requiring definitive surgical management.

Traditional discussions regarding SHPT and THPT focus primarily on disease resulting from progressive renal impairment because it is the most common cause of adult disease in the United States. However, with the increase of obesity surgery, the role of malabsorptive syndromes warrants mention here. The prevalence of SHPT in all individuals with malabsorptive

syndrome remains somewhat ill-defined. However, as the number of patients undergoing surgery for obesity continues to climb, there is a growing number of patients in which a malabsorptive state has been intentionally induced, and this population is clearly at risk. Much of the recent literature suggests that the prevalence of SHPT in the gastric bypass population may be as high as 20% to 30%.[3,4] The incidence of THPT in this group of patients appears to be negligible.

RISK FACTORS

Similar to the epidemiology, the risk factors for SHPT and THPT relate to the underlying metabolic derangement. Risk factors for secondary disease include chronic renal failure (CRF), malnutrition (including rickets), malabsorption (celiac disease, surgical manipulation of the GI tract), cholestatic liver disease, advanced age (lack of sunlight, poor nutrition, renal dysfunction), some cancers, lithium therapy, and aluminum toxicity. Additional but unusual risk factors include oral contraceptive use and idiopathic hypercalciuria. Essentially, any condition that stimulates the parathyroid glands to increase production and secretion of PTH can be a risk factor for SHPT, especially if it is a sustained stimulus. Thus, technically speaking, SHPT is not a true endocrine disorder. The only identifiable risk factor for progression to THPT is the duration of SHPT.

CLINICAL MANIFESTATIONS

Classically, patients with CRF-related SHPT experienced symptoms of bone pain, GI dysfunction, arthritis, myopathy, tendon rupture, pruritis, and extraskeletal calcifications. However, advances in the medical management of patients with renal failure together with earlier institution of medical therapy for those with metabolic derangements have rendered patients relatively asymptomatic until later in the disease course. Signs and symptoms are now relatively nonspecific and are usually predated by laboratory and radiologic evidence of disease. Despite a decrease in symptomatology, though, the impact of SHPT with respect to its effects on the skeleton, cardiovascular system, and integument must not be trivialized.

Skeletal abnormalities, most often caused by PTH-induced bone resorption, occur relatively early in patients with CRF. These bone disorders come in multiple varieties, including classic osteitis fibrosa cystica, osteomalacia, aluminum osteodystrophy, adynamic bone disease, and a mixed abnormality with characteristics of both osteitis and osteomalacia. Patients often experience skeletal deformation and frequent fractures.

Extraskeletal calcification results from tissue deposition of calcium in the setting of a markedly elevated calcium–phosphorus product. This process may manifest in three distinct types of tissues: visceral (including myocardial and valvular), periarticular, and vascular. Vascular calcification may affect both large and small vessels (including the coronary arteries) in at least one fifth of patients with ESRD[5] and is certainly a significant contributing factor in the high morbidity and mortality in this patient population. Overall, cardiovascular complications, often related to both visceral and vascular calcification, account for nearly half of mortality in patients with stage 5 kidney disease.[6]

Calciphylaxis is a unique syndrome characterized by focal lesions representing ischemic necrosis of skin, subcutaneous fat, and muscle, the pathogenesis of which remains uncertain. This process may occur in patients with advanced renal failure who are not yet receiving renal replacement therapy (RRT), those who are receiving regular RRT, and those who have undergone successful transplant.[7] The two distinct anatomic versions of this highly morbid syndrome are proximal (involving the trunk and thighs) and acral (involving the distal extremities and digits). The proximal form occurs with greater frequency in the white population as well as morbidly obese individuals and carries greater than 80% mortality. Acral disease is more mild and often improves after surgical intervention. Calciphylaxis in the setting of SHPT is an indication for urgent parathyroidectomy.

DIAGNOSTIC EVALUATION

A diagnosis of SHPT may not be established by any one single test. However, a persistently elevated intact PTH in the setting of a persistently low-normal or low calcium level is highly suggestive of the disease. In patients with CRF or ESRD, serum phosphorus and serum alkaline phosphatase (especially bone-specific fraction) are usually elevated. Conversely, phosphorus levels in patients with SHPT unrelated to renal dysfunction are often low. The most useful radiologic study remains radiography, which most commonly reveals subperiosteal erosion at multiple sites, including the clavicles, the sacroiliac joints, and the pelvis and at the junction between the metaphyses and diaphyses of the long bones.[7]

THPT may be very difficult to distinguish from PHPT because both disorders are characterized by inappropriately elevated PTH in the setting of hypercalcemia. The diagnosis must be made based on patient history and context of disease. For all practical purposes, THPT is almost exclusively a disease of patients with long-standing, advanced renal failure who have undergone successful renal transplant.

MANAGEMENT

Medical Management

The appropriate management of patients with SHPT depends on the cause of the disease. In patients with CRF, the primary goal is to prevent glandular hyperplasia rather than treat its consequences. Initial intervention aims to maintain serum calcium and phosphorus within near-normal limits (thus avoiding chronic parathyroid stimulation leading to hyperplasia), prevent accumulation of toxic substances, and avoid development or progression of extraskeletal calcification. The vast majority of patients with CRF are managed medically, with surgical intervention reserved for only the most refractory cases.

Medical management should be initiated very early in the course of CRF. Calcitriol levels begin to decrease even with very a modest reduction (<80) in glomerular filtration rate (GFR).[7] Initial measures should therefore include dietary manipulation of calcium and phosphate as well as adequate vitamin D supplementation. Addition of an oral phosphate-binding agent (sevelamer) becomes necessary as the GFR decreases and serum phosphate begins to increase. More recently, new therapies have aimed at manipulating the calcium-sensing receptors in parathyroid tissue. The calcimimetics, a relatively new class of drugs acting as allosteric activators of the calcium-sensing receptor, are now being used to control PTH levels more tightly than was possible with vitamin D and phosphate binding alone. It remains unclear whether these drugs may eventually obviate the need for parathyroidectomy (PTx) in patients with ESRD and severe SHPT who are not candidates for transplant.

Indications for Surgery

In cases of SHPT, surgical intervention should be reserved for failures of maximal medical therapy. Every effort should be made to determine and treat the underlying cause. Failure of medical management is rarely encountered outside of the ESRD population. In this context, failure implies severe symptoms (unrelenting bone pain or myalgias, intractable pruritis), renal osteodystrophy (which now falls under the broad category of chronic kidney disease–mineral and bone disorder [CKD-MBD]), and calciphylaxis. *CKD-MBD* is a comprehensive term that has been chosen to encompass both severe pathophysiologic consequences of SHPT in patients with ESRD, including the bony abnormalities as well as the extraskeletal calcification. Renal osteodystrophy (the bone component of CKD-MDB) manifests as bone pain, osteomalacia, pathologic fractures, and brown tumors of bone. The excessive morbidity and mortality related to calciphylaxis render this diagnosis a surgical "urgency" because PTx often results in a measurable positive response. Figure 10-2 depicts the complex algorithm that defines the threshold between ongoing medical management and surgical intervention in patients with ESRD-associated SHPT.

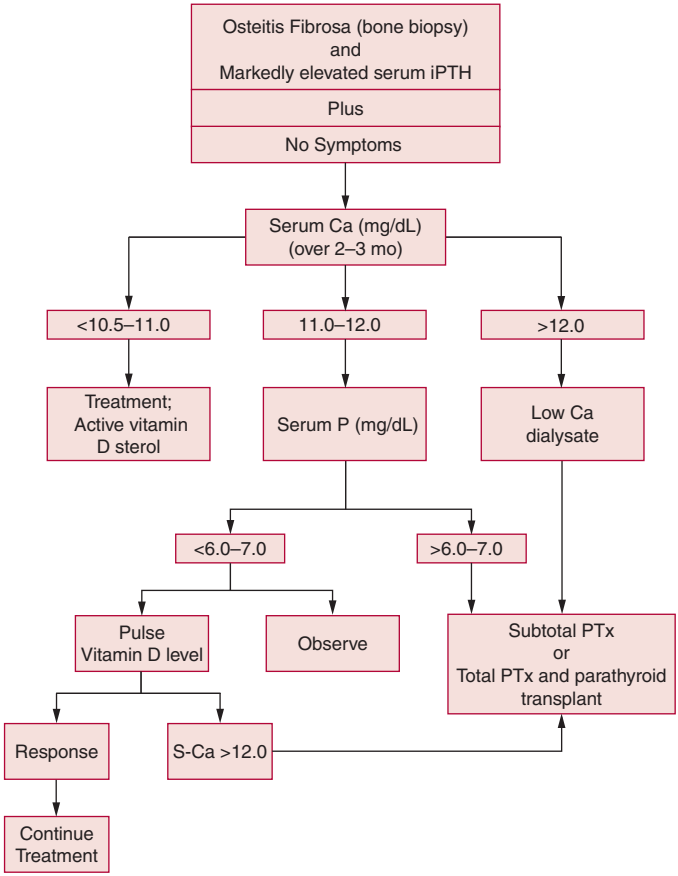

Figure 10-2. Decision-making algorithm for parathyroidectomy in patients with chronic kidney disease–mineral and bone disorder (CKD-MBD) who have asymptomatic secondary hyperparathyroidism (**A**) and symptomatic disease (**B**). iPTH = intact parathyroid hormone; PTx = parathyroidectomy. (Reproduced with permission. Wesseling K, Coburn JW, Salusky IB. In: DeGroot LJ, Jameson J, DeKretser DM, eds. *Endocrinology*, 5th ed. Philadelphia: Elsevier Saunders; 2006:1697-1712.)

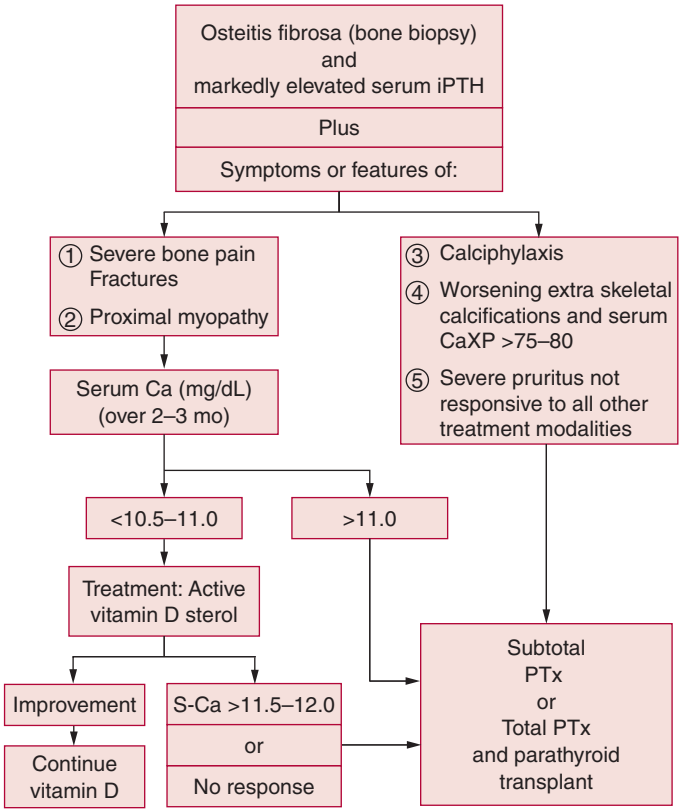

Figure 10-2. (*Continued*)

THPT, especially in the setting of renal transplant, is a surgical disease. An inappropriately elevated serum calcium level in a patient with protracted, severe SHPT is essentially diagnostic of autonomous glandular function, and the long-standing nature of this process ensures the presence of significant bone disease.

Preoperative Evaluation

Hemodialysis-dependent patients should undergo dialysis within the 24 hours preceding surgery. Special consideration should be given to cardiac

status in this group of patients because a high proportion of patients with ESRD have concurrent coronary artery disease. All bisphosphonates should be discontinued at least 3 weeks before surgery because these medications may interfere with postoperative calcium management. All anticoagulants and antiplatelet agents should be held according to the usual policies of the institution or surgeon. In patients who have undergone renal transplant, immunomodulators may be continued throughout the perioperative period, with stress dosing of steroids as appropriate.

Some authors advocate the use of preoperative imaging for localization of all parathyroid tissue, which is most helpful if the desire is to identify ectopic glands either in the posterior neck or the mediastinum. The available options include (but are not limited to) ultrasonography, computed tomography, technetium scanning, sestamibi scanning, and several new modalities that combine these techniques. It is the opinion of these authors that preoperative imaging is an unnecessary step before the *initial* operation because a four-gland exploration is mandatory in the setting of both SHPT and THPT, and the overall incidence of truly aberrant or intrathoracic tissue is low. However, preoperative imaging is an essential component of preoperative planning in the setting of reoperation for recurrent or persistent disease (Figure 10-3).

Surgical Approaches

It is now known that a critically important component of successful parathyroid surgery is a highly skilled surgeon who has a wealth of experience in this arena. In addition, every effort must be made to locate all parathyroid tissue, given that 15% of this patient population harbors supernumerary glands.[5] To start, we know we are doing a four-gland exploration, and we know that the majority of parathyroid tissue needs to be resected in hyperplastic disease. The questions that remain are how much parathyroid tissue is to be taken, and where should the remnant lie thereafter?

The two accepted approaches to surgical management are subtotal PTx and total PTx with autotransplantation. A small contingent remains that still advocates total PTx (without autotransplantation) based on lower recurrence rates. This is not an approach advocated by these authors because patients who are maintained on renal replacement therapy develop severe osteomalacia over time, and patients who undergo transplantation experience somewhat disabling persistent hypocalcemia.

Our operation of choice is subtotal PTx. Three glands are resected, and a small remnant of the fourth, most normal-appearing or most accessible gland is left on its vascular pedicle. A key consideration is that the size of the remnant left behind should be gauged based on the patient's underlying diagnosis. In patients with SHPT and THPT who are dialysis dependent,

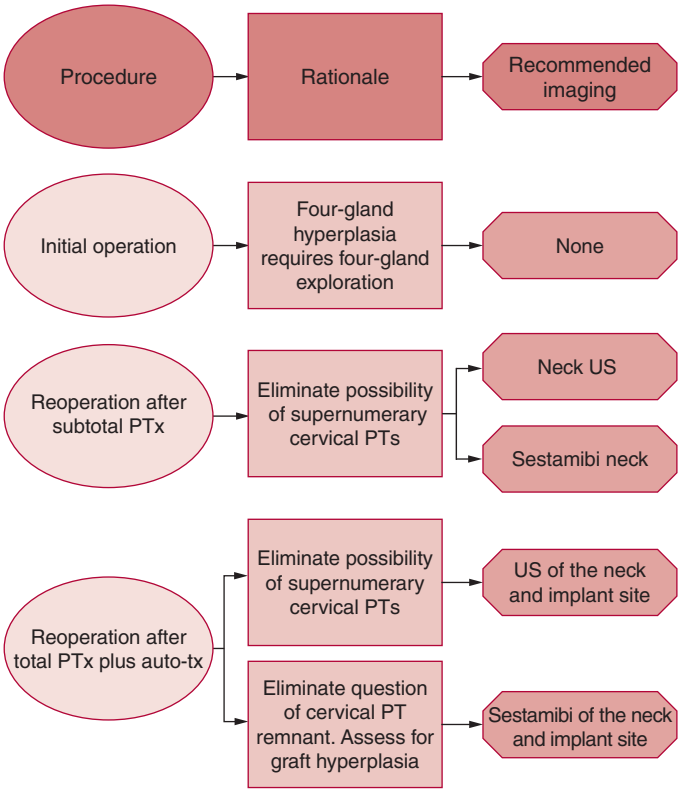

Figure 10-3. Recommendations for preoperative imaging studies. PT = parathyroid; PTx = parathyroidectomy; auto-tx = auto-transplantation.

it is reasonable to anticipate that the underlying path physiology driving their disease will not be altered with surgery. Thus, the stimulus toward hyperplasia will persist, and a minimal remnant should be left behind. This approach is designed to maximize time to recurrence. We recommend leaving a portion of gland that is roughly equivalent to the volume of a single normal parathyroid. However, in transplanted patients with THPT, a remnant this size might result in persistent hypoparathyroidism. In this setting, we advocate leaving a remnant roughly equivalent to the volume of four normal parathyroids.[1]

Total PTx with autotransplantation of a portion of the gland into the forearm or sternocleidomastoid muscle is a reasonable alternative to the approach recommended above. This obviates the need for a reoperation in the neck with disease recurrence, sparing risk to the recurrent laryngeal nerve(s) at the time of re-resection. However, parathyroid tissue tends toward local invasion, and re-resection may require excision of surrounding muscle, adding significant morbidity in the form weakness in the wrist or hand or visible neck deformity. Also of concern is the variable viability, or "take," of the autografted tissue, which may be a problem in the setting of wound difficulties or poor tissue blood supply in renal vasculopaths.

The issue of rapid intraoperative PTH testing has been raised in the context of these cases but is not a proven value-added practice. Another issue that has been raised is the altered metabolism of the hormone in renal failure. This element of unpredictability renders testing somewhat subjective because no established values define success in this situation. We do not routinely use this technology but do advocate its use in certain appropriate situations.

Postoperative Management

The vast majority of dialysis-dependent patients will experience a period of extreme bone hunger. For this reason, we prefer keeping these patients in the hospital for aggressive intravenous calcium replacement over a period of approximately 72 hours.[1] These patients are often asymptomatic despite extraordinarily low serum calcium levels. The purpose of hospital admission, however, is not to control symptoms but to provide adequate opportunity for calcium uptake and bone remodeling. Patients with nonrenal SHPT and posttransplant THPT, however, may be treated similarly to those with primary disease. These patients should receive both oral calcium and calcitriol supplementation for approximately 1 week postoperatively to prevent symptomatic hypocalcemia and promote bone uptake of calcium.

Recurrence of disease is common in dialysis-dependent patients who have undergone PTx for SHPT, and one can expect that a majority of these patients will experience recurrence of their disease over time in the absence of renal transplant. The stimulus toward parathyroid hyperplasia persists, and any gland remnant that remains (whether in the native position or an implant) will eventually become hyperplastic, occasionally requiring reoperation. Conversely, the recurrence rate in patients with successful renal transplants who have undergone PTx for THPT is very low, and one may expect the vast majority of these patients to be cured with the initial surgery. In both patient populations, a repeat bone density study should be performed approximately 12 to 18 months after surgery to ensure stabilization or even reversal of bone loss.

PRACTICAL PEARLS

- In subtotal PTx, the remnant size should be tailored to the underlying diagnosis. A volume equivalent to one normal parathyroid should be left behind in dialysis-dependent patients with SHPT versus a volume equivalent to four normal parathyroids in patients who have undergone renal transplant.
- Approach to a missing upper parathyroid (the "classical" location is posterior, even retroesophageal): The ipsilateral upper pole is mobilized, and the posterior surface of the thyroid, area of superior thyroid artery, space anteromedial to the recurrent laryngeal nerve as well as lateral and posterior to the esophagus, and the carotid sheath are searched. If the gland is not discovered, an ipsilateral thyroid lobectomy should be performed and the paratracheal fat pad removed.
- Approach to a missing lower parathyroid: It is located either within the thyroid substance or within the thymus. An ipsilateral cervical thymectomy is performed. If the missing gland is not recovered, the lower portion of the ipsilateral thyroid lobe is resected. If the gland is still not found, the paratracheal fat pad is removed.
- Approach to a missing parathyroid of ambiguous position: Steps from the previous two scenarios are combined.
- Approach when one "normal-appearing," small parathyroid is encountered: The normal-appearing gland is more likely a rudimentary supernumerary gland. Another hyperplastic gland will likely be found in the thymus. Cervical thymectomy is performed. The incidence of a thoracic (intrathymic) parathyroid gland that is not accessible through a cervical incision is extremely low.

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Chapter 11

Parathyroid Carcinoma

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EPIDEMIOLOGY

Carcinoma of the parathyroid gland is a rare endocrine malignancy, accounting for only 0.005% of all cancer registrations in the US National Cancer Database (NCDB).[1] Using information from the Surveillance, Epidemiology and End Results (SEER) database, the incidence in the United States is estimated to be 5.73 per 10 million population, increasing by 60% from 1988 to 2003.[2] Parathyroid cancer accounts for 0.5% to 1% of cases of primary hyperparathyroidism (PHPT) in series from Western nations and 2.8 to 5% of cases in Japan.[3–6] It affects males and females equally and is evenly distributed within different socioeconomic and racial groups in the NCBD.[1] The mean age of diagnosis of parathyroid cancer is 47 to 56 years, and 73% of cases occur in patients older than age 45 years.[1,2]

RISK FACTORS

Few risk factors have been identified for parathyroid cancer. Hyperparathyroidism–jaw tumor (HPT-JT) syndrome is a familial condition with an autosomal dominant pattern of inheritance caused by an inactivating mutation of the tumor suppressor gene *HRPT2*. The *HRPT2* gene is located on chromosome 1q, codes for the nuclear protein parafibromin, and is thought to be involved in cell growth cycle regulation.[7,8] Affected HPT-JT family members develop PHPT secondary to parathyroid adenomas, fibro-osseous tumors of the mandible and maxilla, renal hamartomas, renal stromal cell tumors, and cystic disease of the kidneys.[8] Patients with HPT-JT have a markedly increased risk of parathyroid cancer, which is seen in 10% to 17% of patients.[7,8] The *HRPT2* gene is also involved in the pathogenesis of sporadically occurring cases of parathyroid cancer, with somatic mutation of this gene identified in 67% of parathyroid cancers and germline mutations

identified in 20% of patients with parathyroid cancer without a family history of HPT-JT.[9]

Although parathyroid cancer has been reported in patients with other familial forms of hyperparathyroidism (HPT), namely multiple endocrine neoplasia syndrome types 1 and 2A and familial isolated hyperparathyroidism, there is no evidence to associate these conditions with an increased risk of this malignancy. A family history of HPT is present in only 4.7% of individuals with parathyroid cancer.[6] A history of previous head and neck irradiation is present in up to 7.4% of patients with parathyroid cancer, and this has also been suggested as a risk factor for this malignancy.[10]

Parathyroid cancer has been reported in patients with chronic renal failure receiving hemodialysis.[11] It has been suggested that patients with end-stage renal disease (ESRD) are at increased risk for this malignancy occurring within hyperplastic or adenomatous parathyroid glands because of chronic overstimulation. Such an association has not been proven, and if ESRD was a strong risk factor for parathyroid carcinoma, then the incidence of this malignancy would be expected to be much higher in North America than is presently seen. It is conceivable that differing pathologic criteria for the diagnosis between Japan and North America may account for the increased incidence of parathyroid cancer in studies such as this from Japanese centers.

CLINICAL PRESENTATION

Parathyroid cancer is biochemically functional in 96% of cases. For this reason, patients typically present with signs and symptoms of the metabolic disturbance of HPT and hypercalcemia rather than with those caused by local tumor growth or metastatic disease. Renal calculi occur in 30% to 64% of patients, and renal insufficiency is seen in up to 84% of patients because of the increased renal clearance of calcium.[6] Other symptoms include polydipsia, polyuria, dehydration, fatigue, and weakness. Abdominal complications of hypercalcemia, including peptic ulcer disease (10% to 18% of cases) and acute pancreatitis (10% of cases), may also occur.[6] Patients with parathyroid cancer may present emergently with a hypercalcemic crisis, characterized by severe dehydration, renal insufficiency, and reduced level of consciousness, in 8% to 17% of cases.[3,12]

Skeletal complications of HPT occur frequently in patients with parathyroid cancer. Radiographic changes consistent with osteitis fibrosa cystica, such as bone cysts and brown tumors of bone, are seen in 46% to 91% of patients as a result of the increased resorption of skeletal calcium, and symptoms of bone pain, deformity, or pathologic fracture may also occur.[3,6] This is in sharp contrast to benign causes of HPT, in which such

clinically significant bone disease occurs in only 5% of patients in North America. Parathyroid cancer should be suspected in all patients with a rapid onset of symptoms of HPT, severe hypercalcemia (>3.5 mmol/L or >14 mg/dL), or end-organ complications of HPT. Symptoms of local tumor growth, such as hoarseness of the voice from recurrent laryngeal nerve (RLN) involvement, are present in only 1.6% of patients.[12]

Unlike benign PHPT, parathyroid cancer may form a mass large enough to be palpable on physical examination in 21% to 45% of cases.[6,12,13] In most patients with HPT in whom a neck mass is palpable, it is because of a thyroid nodule or other cause unrelated to parathyroid cancer; however, a high index of suspicion for this malignancy should be maintained in this setting. Clinical features that are suspicious for parathyroid cancer and that should alert the treating physician to this possible diagnosis are shown in Table 11-1.

There is no generally accepted staging system for parathyroid cancer. Local invasion into surrounding structures is seen in 34% to 70% of patients at the time of operation with the adjacent lobe of the thyroid, overlying strap muscles, and adjacent soft tissues involved most commonly.[3,10,14] Invasion into the esophagus occurs in 2% to 14%, the trachea in 11%, the RLN in 7% to 13%, and carotid sheath structures in 2% of patients.[3,6,10] Regional nodal metastases from parathyroid cancer are uncommon, with clinical involvement of regional nodes present in only 3% to 8% of cases.[2,3,10,13] When involved, spread to both the central and lateral compartments of the neck may occur.[6,10] Distal metastatic disease was documented in 4.5% of cases in the SEER database and has been reported in 5% to 11% of cases in smaller series.[2,3] In a study of 27 patients with parathyroid cancer, distant metastases were present in 3.7% of patients at presentation but developed in 22% during long-term follow-up.[10] The lungs, bones, and liver are the most frequent sites of distant metastatic disease. Rare sites of metastatic disease include the pleura, pericardium, and pancreas.

Parathyroid cancer arising primarily from a gland in a mediastinal location has been reported rarely, accounting for 2.3% of cases.[6] Parathyroid cancer is nonfunctional in only 4% of patients.[5] In this rare clinical scenario, parathyroid hormone (PTH) and calcium levels are not elevated, and the tumor presents as a locally invasive neck mass or with complications of metastatic disease.

DIAGNOSTIC EVALUATION

The evaluation of patients with suspected parathyroid cancer involves biochemical and imaging investigations (Figure 11-1). The biochemical features of parathyroid cancer are those associated with HPT. Although

TABLE 11-1. Clinical Features Suspicious for Parathyroid Cancer and Benign Causes of Hyperparathyroidism

Parathyroid Cancer	*Benign Primary Hyperparathyroidism*
Rapid onset of symptoms (weeks to months)	Slow onset of symptoms (months to years)
Serum calcium >3.5mmol/L (14 mg/dL)	Serum calcium <3.0mmol (12 mg/dL)
iPTH >3x normal	iPTH 1x to 2x normal
Nephrolithiasis in 30% to 64% of patients	Nephrolithiasis in 10% to 15% of patients
Osteitis fibrosa cystica in 46% to 91% of patients	Osteitis fibrosa cystica in 5% of patients
May present with hypercalcemic crisis	Rarely presents with hypercalcemic crisis
Renal insufficiency common	Renal insufficiency rare
Palpable neck mass	No palpable neck mass
Lymphadenopathy	No lymphadenopathy
Age younger than 40 years	Rarely occurs in individuals younger than age 40 years without a family history of the disease
Family history of parathyroid cancer	No family history of parathyroid cancer
Hoarse voice or RLN involvement	No hoarse voice or RLN involvement
Lesion size >2 cm	Lesion size <2 cm
Firm lesion; white or grey color	Soft parathyroid; red or brown color

iPTH = intact parathyroid hormone; RLN = recurrent laryngeal nerve.

parathyroid cancer cannot be differentiated from benign causes of HPT on biochemical criteria alone, parathyroid cancer is associated with elevation of serum calcium and PTH to levels greater than those normally associated with benign disease. Serum calcium is elevated in all cases of functional tumors, with mean levels of 3.4 to 3.65 mmol/L (13.5 to 14.6 mg/dL). Serum calcium is highly elevated, with values exceeding 3.5 mmol/L (14 mg/dL) in 39% of cases. Serum phosphate is reduced in 71% of cases. Intact PTH is elevated to levels three to 10 times greater than the normal range in patients with functional tumors. Elevation of PTH differentiates parathyroid cancer from other causes of hypercalcemia (e.g., disseminated

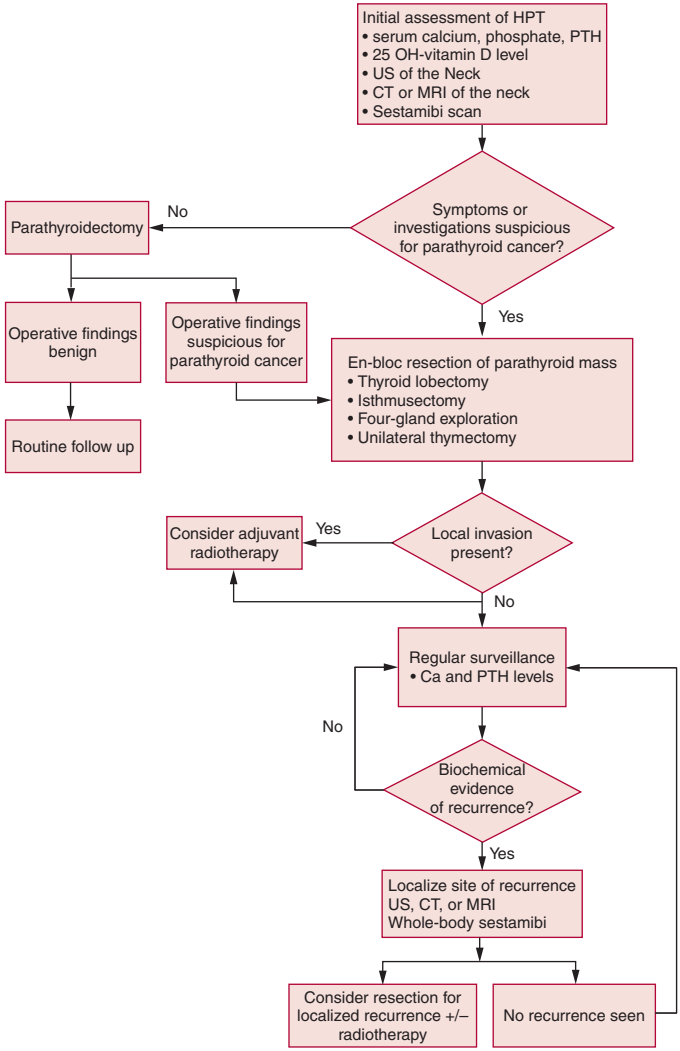


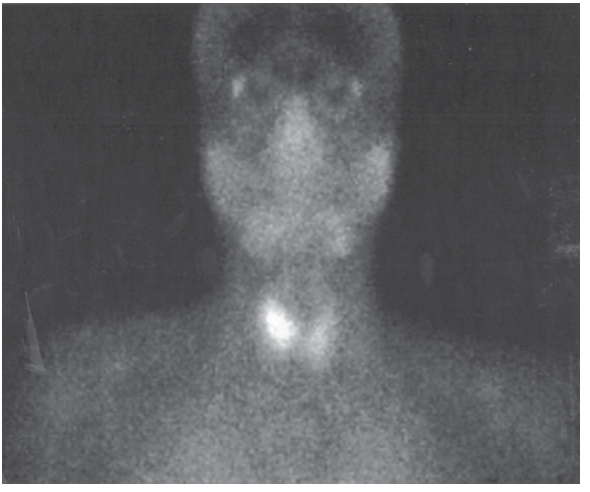
Figure 11-1. Algorithm showing the diagnostic evaluation and management of patients with suspected parathyroid cancer. CT = computed tomography; HPT = hyperparathyroidism; MRI =magnetic resonance imaging; PTH = parathyroid hormone; US = ultrasonography.

malignancy or PTH-related peptide secreting tumors) in which PTH levels should be suppressed. Alkaline phosphatase levels may be elevated because of the presence of PHPT-related bone disease, and serum creatinine may be elevated because of complications of renal insufficiency.

In all patients with HPT in whom a suspicion of parathyroid cancer exists, imaging with high-resolution ultrasonography of the neck, whole-body sestamibi scanning, and cross-sectional imaging of the neck and mediastinum with computed tomography (CT) or magnetic resonance imaging (MRI) is indicated to assess the extent of the disease. On ultrasonography, the presence of a hypoechoic mass with poorly defined margins indicates local invasion into surrounding structures and is characteristic of malignancy. Enlarged cervical lymph nodes may be seen in the rare cases of nodal metastases. Scintigraphy using radiolabeled sestamibi localizes abnormal parathyroid tissue in 85% to 95% of cases of HPT, including parathyroid cancer (Figure 11-2). No specific features can differentiate parathyroid cancer from benign disease on sestamibi scanning except for uptake within distant metastases seen in rare cases. CT or MRI of the neck is recommended in all patients with HPT in whom parathyroid cancer is suspected and may demonstrate a mass with poorly defined margins or infiltration into surrounding structures. Parathyroid cancer is best imaged with MRI using T1-weighted images postgadolinium contrast[15] (Figure 11-3). It is often not possible to differentiate parathyroid cancer from benign disease on imaging criteria because the classical features of local invasion are infrequently demonstrated, and the absence of such findings or normal imaging does not rule out malignancy in patients in whom this is otherwise suspected.[4] Because of the difficulty in differentiating benign from malignant causes of HPT preoperatively, many cases of parathyroid cancer will be recognized only at parathyroidectomy.

Intraoperative findings of a large, firm, white- or grey-colored parathyroid mass of atypical appearance or with local adherence to surrounding structures should alert the surgeon to this possible diagnosis, and an en-bloc resection of the lesion with the adjacent thyroid lobe and surrounding tissues should be performed (Figure 11-4). The difficulty involved in differentiating parathyroid cancer from large or atypical parathyroid adenomas based on their macroscopic appearance alone means that as many as 22% of patients may not be correctly diagnosed at the time of surgery.[4,13] The diagnosis in these patients instead becomes apparent either on histopathology or by the appearance of recurrent or metastatic disease during follow-up.

In contrast to other head and neck malignancies, fine-needle aspiration (FNA) biopsy of a neck mass is contraindicated when parathyroid cancer is suspected.[16] FNA may cause capsular disruption of the lesion and local seeding of tumor cells, compromising future surgical resection and increasing the



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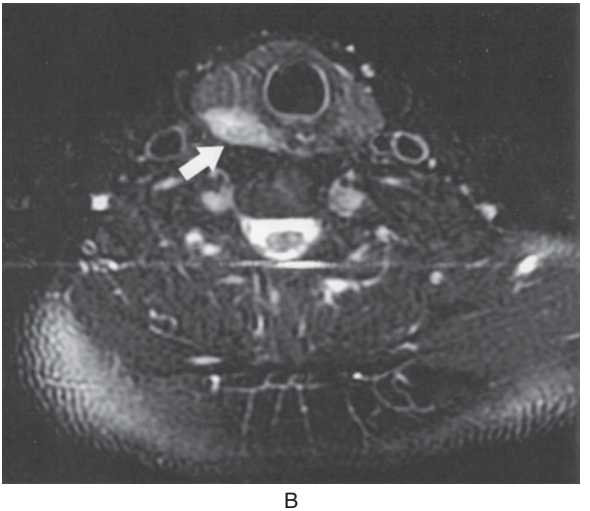

B

Figure 11-2. A. Sestamibi scan of a 28-year-old man presenting with hypercalcemic crisis demonstrating increased uptake in a right parathyroid carcinoma. **B.** Magnetic resonance imaging of the neck in the same patient demonstrating parathyroid carcinoma (*arrow*). The mass has indistinct margins, suggesting local invasion into the right lobe of the thyroid. The tumor was removed en bloc with the adjacent thyroid lobe and was confirmed on histopathology to be malignant.

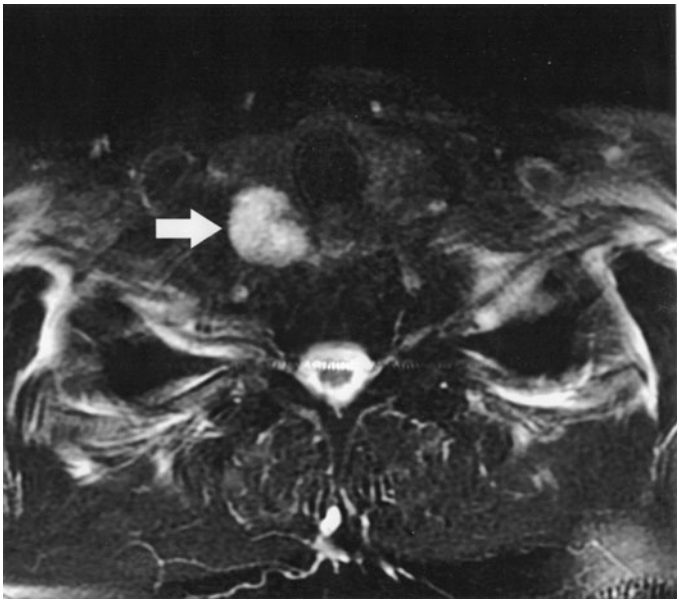

Figure 11-3. Magnetic resonance imaging of the neck of a 54-year-old man presenting with severe hypercalcemia demonstrating a 4-cm parathyroid cancer (*arrow*).

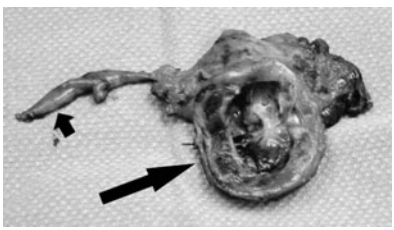

Figure 11-4. Resection specimen of a parathyroid carcinoma (*long arrow*) sectioned longitudinally. The lesion was resected en bloc with the adjacent thyroid lobe, isthmus, pyramidal lobe, and thymus (*short arrow*).

risk of local recurrence. Cutaneous implantation of tumor at the site of biopsy has also been reported. Because most parathyroid cancers are relatively well-differentiated tumors, distinguishing malignant from benign disease is rarely possible on FNA cytology and has a high incidence of false-negative results. FNA of enlarged cervical lymph nodes can be safely performed to diagnose or confirm regional nodal involvement with parathyroid cancer.

MANAGEMENT

To assist in surgical planning, preoperative assessment of vocal cord function with fiberoptic laryngoscopy should be performed in all patients in whom parathyroid cancer is suspected. In patients presenting with metabolic disturbance secondary to hypercalcemia, the initial management involves the control of calcium levels with intravenous (IV) fluid resuscitation and appropriate use of loop diuretic agents before surgical intervention. Curative resection of parathyroid cancer involves removal of the primary lesion en bloc with any adjacent involved structures to ensure complete resection of disease.[17] It is of paramount importance that disruption of the tumor capsule should not occur because this risks local seeding of cancer cells and local recurrence of disease.

Because of the rarity of the tumor and the high risk of recurrent disease, an oncologically complete resection should be performed for all patients with suspected parathyroid carcinoma. This is best managed by surgeons experienced in operative and reoperative parathyroid surgery at appropriately specialized institutions. Exploration of all four parathyroid glands should be performed in all cases.[5] It is important to identify the ipsilateral normal parathyroid gland and remove it to achieve clearance of all parathyroid tissue from the affected side of the neck.[17,18] For this reason, an ipsilateral thymectomy should also be performed from the affected side of the neck to include any supernumerary glands in this location.

As part of the operative approach to the tumor, the strap muscles overlying the region of the tumor should be resected en bloc with the lesion. An ipsilateral thyroid lobectomy, isthmusectomy, and removal of the pyramidal lobe should be performed en bloc with the primary tumor.[5,17,18] In a study of 95 patients with parathyroid cancer, en-bloc thyroid lobectomy was associated with a lower rate of local recurrence and improved survival compared with simple resection of the primary tumor.[13] Macroscopic invasion into surrounding structures such as the esophagus or trachea found at the time of operation requires en-bloc resection to achieve complete resection of disease, and this may require appropriate reconstruction, depending on the extent of invasion. When macroscopic invasion of the RLN is encountered during surgery, it should be sacrificed and resected en bloc.

In a review of parathyroid cancer management, Clayman and coworkers[14] recommended preservation of the normally functioning RLN unless circumferential involvement of the nerve by tumor is encountered. Regional cervical lymph nodes are involved in only 6% to 8% of cases; however, removal of ipsilateral tracheoesophageal and paratracheal nodes in the central compartment adjacent to the lesion is recommended.[5,14] This ensures an en-bloc resection and minimizes the risk of recurrent disease in the small percentage of patients with nodal metastases. The presence of clinically involved regional lymph nodes mandates formal dissection of the central and lateral compartment nodes. When parathyroid cancer is suspected preoperatively on clinical grounds, minimally invasive approaches to parathyroidectomy are contraindicated.

Intraoperative measurement of PTH (IOPTH) has proven useful to confirm the successful resection of all hyperfunctioning parathyroid tissue at the time of parathyroidectomy in patients with benign causes of HPT. The role of IOPTH in the resection of parathyroid cancer, however, has not been defined. Clayman and coworkers[14] at the MD Anderson Cancer Center have reported their experience with IOPTH in patients with parathyroid cancer. IOPTH levels reduced at a slow rate after resection of parathyroid cancer in this report and required a longer period of time to normalize than for IOPTH performed for benign disease. Persistent elevation of IOPTH after resection of parathyroid cancer may be caused by extensive involvement of adjacent soft tissues with tumor, the presence of residual metastatic disease, or poor renal clearance of PTH in the setting of renal impairment.

Pathology

The diagnosis of parathyroid carcinoma can be made with certainty when metastatic disease is confirmed or local invasion is demonstrated. When these features are not present, the diagnosis of parathyroid cancer on histopathology is difficult, particularly differentiating these malignancies from parathyroid adenoma with atypical features. Classic features that are described for parathyroid carcinoma on microscopy include trabecular cellular architecture, mitotic figures, fibrous hyaline bands, vascular invasion, and capsular invasion, yet these features are frequently absent in patients with this malignancy and are not specific for this.[18] Staining for Ki-67 antigen as a marker for cellular proliferation is higher in parathyroid cancer than in benign lesions, but overlap between these two entities limits the usefulness of this technique. Immunohistochemical staining for parafibromin, the nuclear protein product of the *HRPT2* gene, has been used to differentiate parathyroid carcinoma from benign lesions. Whereas parathyroid carcinoma demonstrates absent or weak nuclear staining for parafibromin in more than 90% of cases, staining is strongly positive in 98% of benign

parathyroid tumors.[19] All atypical parathyroid adenomas should be reviewed by an experienced tumor board, and immunohistochemical staining for parafibromin should be undertaken.

Postoperative Management and Surveillance

Serum calcium and phosphate levels should be closely monitored after resection of parathyroid cancer because of the risk for severe hypocalcemia secondary to hungry bone syndrome, which may be life threatening.[5] Sudden withdrawal of high levels of PTH, the presence of severe bone disease related to HPT, and the younger age of patients with parathyroid cancer relative to those with benign disease are all factors predisposing individuals to the development of this condition. All patients should be started on oral calcium and vitamin D supplementation after surgery, and replacement therapy may be required for months after surgery to meet the demands associated with hungry bone syndrome. IV supplementation of calcium is sometimes required and should be titrated to serum calcium levels and the patient's symptoms. It is important to monitor serum magnesium and phosphate levels while replacing calcium orally and intravenously. Excessive administration of oral calcium may drive down serum phosphate because of binding within the gastrointestinal tract. For this reason, in the presence of significant hungry bone syndrome, the amount of IV and oral calcium supplementation need to be individually titrated.

Even after macroscopically complete resection of parathyroid cancer, locoregional recurrence of disease occurs in 40% to 67% of cases because of the locally aggressive nature of this tumor.[3,10, 12,15] Rates of recurrence are higher where disruption of the tumor capsule occurred intraoperatively and where surgical margins are involved with tumor.[6,12] External-beam radiation therapy (EBRT) is given postoperatively at some institutions with the aim of reducing the incidence of locoregional recurrence.[12,14,16,20] In a series of six patients who had postoperative EBRT after macroscopically complete resection of parathyroid cancer, all patients were free of disease at a mean of 62 months follow-up.[20] EBRT has also been used as primary treatment for patients with locally advanced parathyroid cancer that is not surgically resectable. Munson and coworkers[12] at the Mayo Clinic reported on four patients with unresectable parathyroid cancer treated primarily with EBRT. They achieved locoregional control for all patients for periods ranging from 24 to 218 months.

Long-term surveillance of patients with parathyroid cancer is recommended because of the risk of locoregional and distant disease recurrence. The neck is the site of recurrence in 75% to 80% of cases, with mediastinal nodal involvement accounting for 25% of cases.[6,15] The mean time to recurrence is 28 to 33 months, but delayed recurrence as long as 20 years after resection has been reported.[5,6,12,15] Lifelong monitoring of serum

calcium and PTH levels should be performed at yearly intervals, and an increase in these biochemical markers indicates disease recurrence. It should be noted that persistent elevation of PTH levels immediately after surgery may be secondary to the increased demand associated with hungry bone syndrome and that it may take months to reduce to baseline levels. Because of the slow growth rate of these tumors, an increase in biochemical markers is an early indicator of recurrence at a stage when most recurrent lesions are not detectable on imaging studies.

Management of recurrent disease

When disease recurrence is suspected on biochemical testing, imaging with high-resolution ultrasonography of the neck should be undertaken to assess for the presence of locoregional disease; this has a sensitivity of 69%.[15] CT or MRI of the neck, thorax, and abdominal regions should be performed, looking for locoregional recurrence, mediastinal nodal disease, and distant metastases to the lungs or liver.[5,15] Total-body sestamibi scanning demonstrates uptake at sites of locoregional or distant metastases with a sensitivity of 79% and has the advantage that whole-body scanning can be performed.[15]

Recurrent disease may also manifest clinically as a return of symptoms and complications of hypercalcemia. Surgical resection has an important role in the management of patients with both locoregional and distant recurrence because of the difficulty in achieving control of hypercalcemia with medical management alone and the poor response of patients with parathyroid cancer to systemic chemotherapy. In a study by Kebebew and coworkers,[15] reoperation for recurrent disease was associated with normalization of serum calcium levels in 62% of patients, a significant reduction in serum calcium levels in 75%, and a relief of symptoms of hypercalcemia in 86%, with an acceptable rate of operative morbidity of 6.2%. In a report by Iihara and coworkers[3] of 14 patients undergoing surgical resection of locoregional recurrence, successful palliation was achieved in 11 patients, and five patients were disease free after a mean 48 months of follow-up. Surgical resection of recurrent disease is rarely, if ever, curative, with most patients developing further recurrence on long-term follow-up. Reoperation can be effective in the management of such repeat recurrences.[15] Recurrent disease has been associated with a mean survival duration of 28 months to 7.6 years from the time of first recurrence, and death occurs because of the eventual development of uncontrolled hypercalcemia.[13,15]

In patients with recurrent or metastatic disease that is not surgically resectable, control of hypercalcemia is dependent on medical therapies. Bisphosphonates, including zolendronate, pamidronate, and alendronate, are osteoclast inhibitors that may achieve control of hypercalcemia for relatively long periods with increasing dosage.[5] The calcimimetic agent cinacalcet

binds to calcium-sensing receptors on parathyroid tissue to reduce PTH release and has been approved by the US Food and Drug Administration for the management of patients with hypercalcemia caused by parathyroid cancer.[16] So far, this agent has been shown to be effective in reducing serum calcium levels in these patients, although studies are limited.

Calcitonin, mithramycin, gallium nitrate, and corticosteroids have also been used to assist in the control of hypercalcemia from advanced parathyroid cancer. Although isolated case reports exist in the literature describing clinical response of parathyroid cancer to systemic chemotherapy for periods of 12 to 18 months, combinations of 5-fluorouracil, doxorubicin, vincrystine, carboplatin, taxols, and cyclophosphamide have been used in this setting with little therapeutic benefit.[5,6,10] EBRT can be used in the palliation of painful bony metastases from parathyroid cancer.

Prognosis

Despite the relatively high rates of recurrent disease, parathyroid cancer is associated with 5-year overall survival rates of 77% to 85% and 10-year survival rates of 49% to 77%.[12-14] In a survival analysis of patients with parathyroid cancer from the SEER database, the 10-year cancer-specific mortality rate was 12.4%.[2] Older age at diagnosis, the presence of metastatic disease, and male gender were factors associated with reduced survival in this study.

PRACTICAL PEARLS

- The diagnosis of parathyroid cancer requires a high index of clinical suspicion preoperatively and intraoperatively, and biochemical and imaging studies frequently cannot distinguish benign from malignant disease.
- Preoperatively, parathyroid cancer should be suspected in all patients with HPT who present with a rapid onset of symptoms, severe symptoms, or markedly elevated serum calcium or PTH levels.
- Intraoperatively, parathyroid cancer should be suspected when a pale or firm parathyroid or invasive tumor is encountered.
- Patients with HPT-JT have an increased risk of parathyroid cancer, and genetic testing for mutation of the *HRPT2* gene should be performed in all patients with parathyroid cancer.

(*Continued*)

- When parathyroid cancer is suspected, four-gland parathyroid exploration and en-bloc resection of the tumor with the ipsilateral thyroid lobe, isthmus, adjacent soft tissues, lymph nodes, and overlying strap muscles should be performed to ensure complete oncologic resection. Disruption of the tumor capsule should be avoided at all costs.
- Because of the rarity of the condition, patients with parathyroid cancer should be managed by surgeons with specialized experience in both operative and reoperative parathyroid surgery.
- Specific staining of resection specimens for parafibromin and review by a specialized endocrine pathologist should be considered because of the difficulty of diagnosing parathyroid carcinoma on histopathology in the absence of confirmed metastatic disease.
- Lifelong monitoring of serum calcium and PTH levels is required after definitive surgery because of the 40% to 67% risk of recurrence and because reoperation can be effective in control of recurrent disease.

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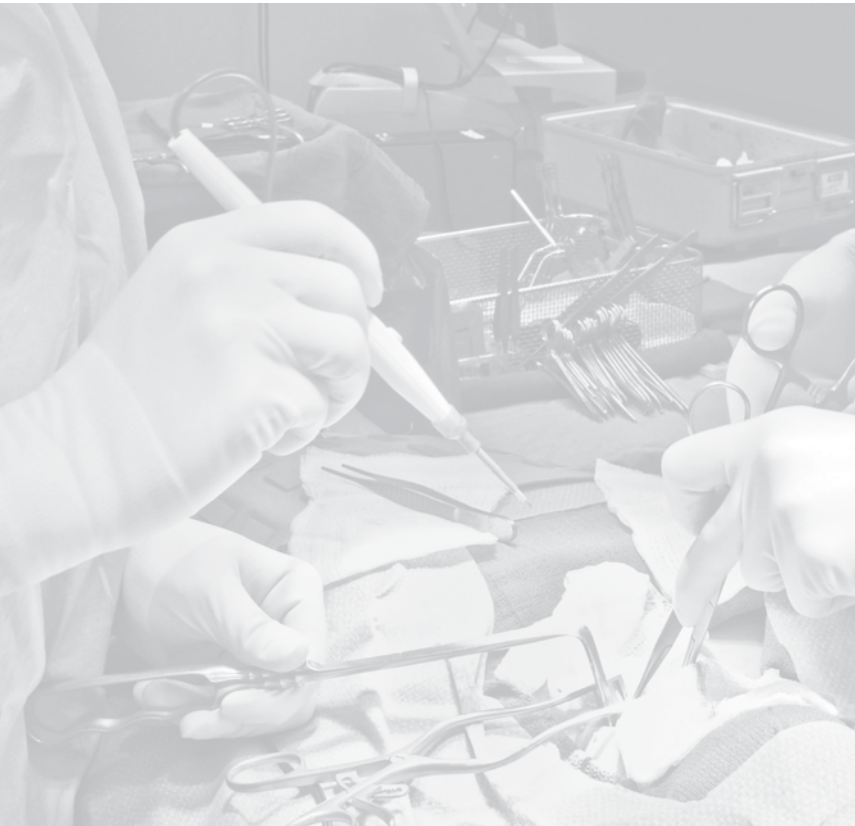
SECTION III
Adrenal



Chapter 12

Incidentalomas and Metastases to the Adrenal Gland

Jacob Moalem, MD
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Incidentalomas, unsuspected adrenal tumors that are encountered during radiographic testing done for unrelated causes, are among the most common solid organ tumors in humans. This classification carries a very broad differential diagnosis (Table 12-1) and spans the spectrum of aggressiveness in tumors. Although most incidentalomas are benign and require no intervention, adrenocortical cancer (ACC) is among the most aggressive cancers in humans. Moreover, a significant subset of incidentalomas is hormonally functional, and although these tumors are histologically benign, failure to diagnose and treat patients with these tumors results in increased morbidity and may risk mortality.

With the increasing use of cross-sectional, sonographic, and other imaging technologies, incidentalomas are likely to be diagnosed even more frequently in the future. After they have been identified, these tumors must be characterized as benign or malignant (and if malignant, as primary vs. metastatic) and as hypersecretory or nonhypersecretory. Because the majority of incidentalomas are ultimately managed nonsurgically, their increasing incidence and their follow-up are likely to become an even more important diagnostic, logistic, financial, and therapeutic challenge for individual practitioners and for our health care system. This chapter discusses the prevalence, differential diagnosis, and diagnostic and therapeutic strategies of these fascinating tumors.

PREVALENCE

First described in the early 1980s,[1] the term *incidentaloma* refers to all clinically unapparent adrenal tumors that are incidentally discovered during

TABLE 12-1. The Most Common Incidentally Found Adrenal Tumors and Their Relative Frequencies in the Literature

Tumor Type	Frequency (%)
Adrenal Cortex	
Adenoma	36–94
Nodular hyperplasia	7–68
Carcinoma	0–25
Adrenal Medulla	
Pheochromocytoma	0–11
Ganglioneuroma	0–6
Metastases	
Patients without prior cancer diagnosis	0–21
Patients with known cancer diagnosis	32–73
Other Adrenal Masses	
Cysts	0–22
Hematoma	0–4
Lipoma	0–11
Myelolipoma	7–15
Pseudoadrenal masses	0–10

imaging studies that are done for other causes. Tumors that are discovered during the initial assessment or follow-up of patients with nonadrenal malignancies are excluded from this definition. Similarly, large adrenal tumors that are symptomatic because of mass effect are also excluded. The reported prevalence of these tumors ranges from 0.35% to 5%[2] and is affected by the sensitivity of the radiologic examination that is being used and the inclusion criteria of patients. Thin-cut helical computed tomography (CT) scanning and high-resolution magnetic resonance imaging (MRI) can now identify subcentimeter adrenal lesions that were previously undetectable. Moreover, studies that include many elderly patients or patients with symptoms that can retrospectively be attributed to their adrenal masses report a higher frequency of incidentalomas and have a higher frequency of malignant or metastatic tumors in the adrenal gland.

Similar to the variation seen in the prevalence reported by radiologic tests, autopsy data are also inconsistent. Depending on inclusion criteria, the reported prevalence of adrenal tumors is between 1.05%[3] and 32%.[4] Autopsies of hypertensive patients reveal an even higher prevalence of adrenal neoplasms, as high as 68%.[5] A recent report of pooled autopsy data suggested that the overall prevalence of adrenal adenomas is 5.9% in patients without premortem evidence of adrenal disease or malignancy. This prevalence was age related: although only 0.2% cadavers from patients younger than age 30 years had adrenal adenomas, 6.9% of cadavers from patients older than age 70 years had adrenal adenomas.[6]

BIOCHEMICAL EVALUATION

All adrenal tumors, regardless of their radiographic appearance or suspicion for malignancy, should be screened to exclude biochemical hyperfunction. A suggested algorithm is depicted in Figure 12-1.

Pheochromocytoma

Although the incidence of pheochromocytoma in the general population is only 2 to 8 per million,[7] these tumors account for 11% to 23% of incidentalomas.[2,5,8,9] The classic triad of symptoms attributable to pheochromocytoma is hypertension, headaches, and flushing, but this symptom complex is only present in approximately 40% of patients with an established diagnosis.[10,11] Partly because pheochromocytomas may be clinically silent,[10,11] up to 75% of pheochromocytomas are not diagnosed until after the patient's death.[12] Undiagnosed, the stimulation of a pheochromocytoma by the induction of anesthesia,[13] percutaneous biopsy, or surgery is associated with death rates up to 80%.[5,12] For 10% of all pheochromocytomas, the initial manifestation is pheochromocytoma crisis caused by spontaneous hemorrhage or rupture.[10]

Because the consequences of failure to recognize a pheochromocytoma are so dire, this entity must be definitively established or excluded in any patient who presents with an adrenal mass, irrespective of symptoms. Thus, considerable research has been done to determine which of the multiple available biochemical and radiographic tests most conclusively secures the diagnosis.

A recent multicenter cohort study compared all available biochemical (urine and plasma) tests for the diagnosis of pheochromocytoma.[14] The authors concluded that plasma-free metanephrines, with sensitivity of 99% and specificity of 89%, were the best tests for the confirmation or exclusion of pheochromocytoma. Moreover, because the addition of a second diagnostic test did little to improve the diagnostic accuracy in patients with negative plasma metanephrine test results, the authors recommended against

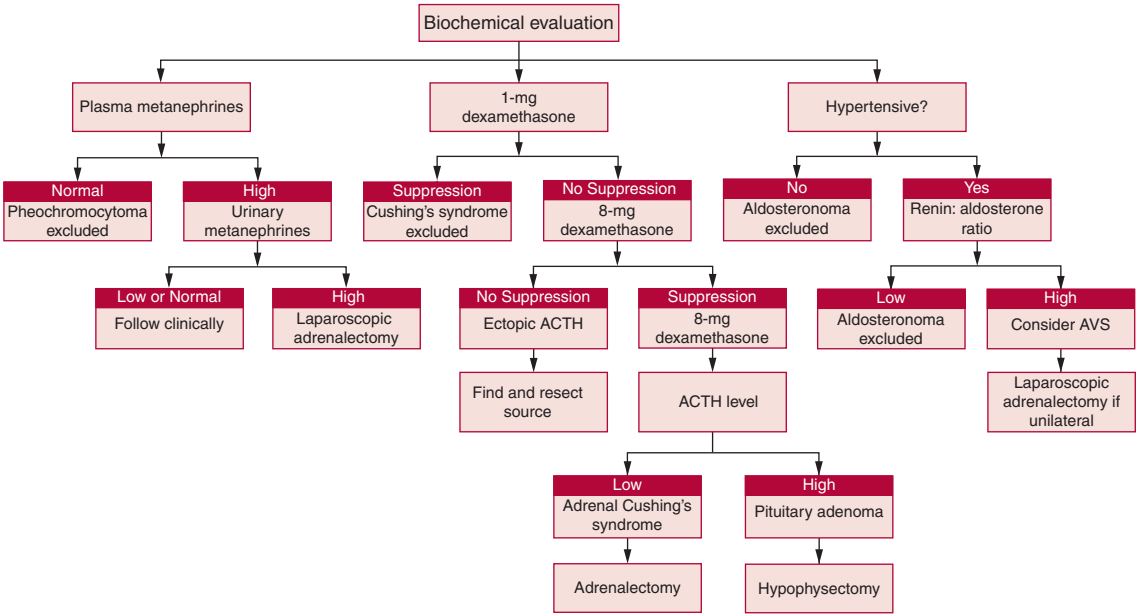

Figure 12-1. Algorithm for the evaluation of incidentalomas. ACTH = adrenocorticotropic hormone; AVS = adrenal vein sampling.

the use of confirmatory tests for most cases. This study formed the basis for the recent recommendations made at the National Institutes of Health (NIH) consensus conference.[15]

Researchers from the Mayo Clinic[7] disagree. They point out the role of pretest probability (prevalence) in the determination of the predictive value of a diagnostic test and suggest that for the general population, the routine use of plasma metanephrines would result in an unacceptably high (30%) number of patients with false-positive test results. Therefore, they recommend that this test be reserved only for situations with high pretest probability of pheochromocytoma (patients with a genetic syndrome, family history, or radiologic features) of pheochromocytoma. For the more typical scenario of a patient with a clinical suspicion (based on difficult-to-control hypertension, palpitations, or low-attenuation incidentalomas), they suggested that 24-hour urinary metanephrines and catecholamines, with significantly higher specificity and minimally lower sensitivity than plasma-free metanephrines, be used as the test of choice.

To minimize the number of false-positive results, a threshold of double the upper limit of normal is recommended.[16] Moreover, testing should be done under circumstances that avoid artificial elevations in catecholamine levels: the patients should be supine and relaxed, and the blood collection should be through an indwelling catheter rather than a direct venopuncture. Caffeine, nicotine, and acetaminophen are all known to increase catecholamine levels and should be withdrawn for 2 weeks before testing.[14]

Based on these studies, our practice is to use plasma metanephrines as a screening test only. Because of its better specificity, we confirm the diagnosis using 24-hour urine metanephrine measurements. We recently studied a group of 10 patients with adrenal incidentalomas and borderline elevated urine or plasma metanephrine levels.[17] Among this group of completely asymptomatic patients, three (30%) had a pheochromocytoma, highlighting the need for preoperative α-blockade in all patients who have any elevation in their metanephrine levels.

Cushing's Syndrome

Although the incidence of Cushing's syndrome (CS) is exceedingly low in the general population,[18] studies of specific high-risk subpopulations have revealed an unexpectedly high prevalence of unsuspected CS. In newly diagnosed diabetics; poorly controlled diabetics; and obese patients with hypertension, diabetes, or polycystic ovary syndrome, the frequency of unsuspected CS was 2.0% to 3.3%, 1.0%, and 5.8%, respectively.[19–21] Even among patients with hypertension, screening studies have found a 0.5% to 1.0% prevalence of unsuspected CS.[22,23]

Although a variety of biochemical tests are available for the evaluation of patients with suspected CS, they are all designed to detect aberrations in the normal hypothalamic–pituitary–adrenal axis. In normal individuals with typical sleep–wake cycles, serum adrenocorticotropic hormone (ACTH) and cortisol levels begin to increase in the early morning hours, peak between 7 and 9 AM, and decrease to a nadir for the remainder of the day as long as the patient remains unstressed or asleep. In these patients, the delivery of supraphysiologic doses of glucocorticoids results in suppression of ACTH and cortisol release. On the other hand, CS is characterized by the loss of diurnal variation in ACTH and cortisol release, and patients' serum cortisol levels remain persistently elevated throughout the day.[24,25] Moreover, their cortisol release is autonomous (either because of a primary adrenal tumor or because of an ACTH-secreting mass) and is not suppressed by low-dose glucocorticoid administration.[26]

Serum Cortisol Levels

Because results of serum cortisol testing are directly affected by patients' albumin and cortisol-binding globulin (CBG) levels, this test is prone to false-positive and false-negative results under a variety of conditions. Estrogen-containing birth control pills increase CBG levels, and women taking these medications have a 50% chance of a false-positive result.[27] They should therefore undergo testing after a 6-week withdrawal period whenever possible.[28] On the other hand, malnourished or critically ill patients and patients with the nephrotic syndrome will have falsely decreased serum cortisol levels owing to their low albumin levels.[29,30] Furthermore, because of the variation in the degree of hypercortisolism that patients with CS manifest, it is recommended that all testing be duplicated to decrease the likelihood of false-negative results.[18]

Dexamethasone Suppression Test

A number of published protocols have discussed the performance and interpretation of the dexamethasone suppression test (DST).[31–34] The overnight DST is the simplest version of this test and requires the administration of 1 mg of dexamethasone between 11 PM and midnight followed by measurement of serum cortisol between 8 and 9 AM on the following morning. Because patients with CS have variable degrees of responsiveness to dexamethasone, researchers have recommended that a low threshold (postsuppression cortisol level <1.8 μg/dL) be used to enhance the sensitivity of the test.[18,34]

The 48-hour, 2-mg/day low-dose DST is preferred by some endocrinologists because of its improved specificity over the 1-mg test.[18] During this examination, which can also be administered in the outpatient setting, 0.5 mg of dexamethasone is given every 6 hours for 2 days, and a final cortisol level is measured 6 hours after the last dose. As in the low-dose test, the cortisol level should be suppressed to less than 1.8 μg/dL in patients without CS.

Urinary-Free Cortisol Levels

Urinary-free cortisol (UFC) measurements, unlike serum cortisol measurements, are unaffected by patients' CBG or albumin levels. Measured over a 24-hour period, UFC provides a reliable evaluation of the patient's total daily cortisol secretion. Falsely low measurements of UFC may occur in patients whose creatinine clearance is less than 60 mL/min,[35] and elevated UFC is seen in patients with excessive (>5 L/day) fluid intake[36] and in patients with physiologically increased cortisol levels such as during pregnancy and in patients with depression, alcoholism, morbid obesity, or poorly controlled diabetes.[18]

To optimize the test's reliability, patients should be carefully instructed to avoid all glucocorticoid-containing medications during the collection period and to avoid excessive fluid intake. The collection should exclude the first morning's void but include all subsequent voids for the next 24 hours, including the second day's first morning void. During the test period, the specimen should be refrigerated. The test should be duplicated to increase its accuracy, particularly in children.[18]

Late Night Salivary Cortisol Level

This test relies on the fact that free serum cortisol rapidly (within a few minutes) equilibrates with salivary cortisol.[37] Although many methods can be used to measure salivary cortisol, the enzyme-linked immunosorbent assay (ELISA) and liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) tests are best validated and most commonly used.[18] Saliva is collected either passively (by collecting drool into a capillary tube) or actively (by placing a cotton pledget in the mouth while the patient is chewing). With a sensitivity and specificity between 92% and 100% for the detection of CS, late night salivary cortisol has accuracy that is similar to that of UFC.[38] This test's accuracy may be decreased in critically ill patients, patients in whom the circadian rhythm is blunted, elderly men, smokers, and heavy drinkers.[18]

Aldosteronoma

Primary hyperaldosteronism is the most common cause of secondary hypertension, and it is usually curable by adrenalectomy. Among patients with hypertension, the prevalence of aldosteronoma was estimated to be approximately 1%,[39] although more recent reports suggest that the true prevalence of aldosteronoma is at least 10 times higher than initially thought, even among normokalemic patients.[40] Among patients with incidentaloma, however, aldosteronoma is a relatively uncommon diagnosis. In a recent series of more than 1000 incidentalomas,[41] the prevalence of aldosteronoma was only 1.4%. This low frequency is likely because of patient selection because many aldosteronomas are discovered as part of a workup for hypertension.

Although the hallmark of primary hyperaldosteronism (Conn's syndrome) is hypertension and hypokalemia, neither finding is necessary for the diagnosis. There are scattered reports of normotensive primary hyperaldosteronism,[42] and even Conn himself described a large number of patients with normokalemia in the setting of aldosteronoma.[43,44] Nevertheless, the absence of hypertension effectively rules out the presence of an aldosterone-secreting tumor, and most experts recommend no biochemical workup to exclude aldosteronoma for normotensive patients who are found to have an incidentaloma.[5,8]

Biochemically, the test with the highest sensitivity and specificity for identifying patients with primary aldosteronism is the measurement of the aldosterone excretion rate during salt loading, in which a rate greater than 14 μg/24 hour is diagnostic of this condition.[45] Far more commonly used is the aldosterone:plasma renin activity (PRA) ratio, which, if greater than 30, is highly suggestive of aldosteronoma.[46] β-blockers and antisympathetic medications lower renin and thereby falsely elevate the aldosterone: PRA ratio, so their use may lead to false-positive results.[47] Some authors[2,8,47] advocate a confirmatory test (e.g., the saline suppression test) to verify the diagnosis. Although the aldosterone level in patients with aldosteronoma will not change after the infusion of 2 L of normal saline, it will decrease to less than 6 ng/L in patients without aldosteronoma.

Aldosteronomas are typically small (most <2 cm in size), but larger tumors are occasionally seen. Malignant mineralocorticoid-secreting tumors of the adrenal gland have been reported,[48] but these are exceedingly rare, are typically large and locally invasive, and often secrete other hormones.

Some controversy exists as to the necessity of adrenal vein sampling (AVS) to confirm tumor localization of a unilateral aldosteronoma in patients with a radiographically confirmed adrenal mass. Some authors view AVS as the gold standard test and advocate liberal use of this test before adrenalectomy because of the possibility of a coexistent nonfunctional adrenal tumor.[49,50] Others report excellent surgical outcomes when a single adrenal adenoma (>1 cm) is resected in a patient with biochemically proven primary hyperaldosteronism. They reserve AVS for patients with primary hyperaldosteronism with bilateral adrenal abnormalities on CT scan; no adrenal mass identified; or equivocal findings, such as an adrenal mass that is smaller than 1.0 cm. Using these criteria, only 5% of patients with hyperaldosteronism failed to improve after adrenalectomy.[51]

Radiographic Evaluation

Because of its widespread use, CT scanning is the most common radiographic test that may lead to the discovery of an incidentaloma[52] and is also the most studied. Irrespective of the imaging modality used, the most

straightforward tumor characteristic that has been used to differentiate ACC from other benign or malignant tumors of the adrenal gland is their size: A recent review from the Surveillance, Epidemiology and End Results (SEER) database[53] demonstrated that the mean size for malignant adrenal tumors was 11.2 ± 5.4 cm, significantly larger than the mean size for benign adrenal neoplasms (4.2 ± 1.9 cm). Overall, ACCs accounted for 5% of all incidentalomas.[54] When stratified by size, ACCs accounted for less than 2% of all incidentalomas smaller than 4.0 cm, 6% of incidentalomas 4.1 to 6.0 cm, and 25% of all incidentalomas larger than 6.0 cm. Conversely, benign cortical adenomas accounted for 65% of all incidentalomas smaller than 4.0 cm and only 18% of incidentalomas larger than 6.0 cm.[15]

Because significant overlap exists in the size distribution of benign and malignant adrenal neoplasms, no exact size cutoff exists. ACCs smaller than 2 cm have been resected,[53] and applying lower cutoffs for resection of adrenal tumors (≥4 cm; maximizing sensitivity) would do so at the expense of lower specificity (52%). Conversely, choosing a higher size cutoff (≥8 cm) would improve specificity to 95% but at the expense of a markedly diminished sensitivity of 79%.[53]

Additional radiologic features that are highly suggestive of malignancy include the presence of local invasion, tumor heterogeneity or irregular surface, regional lymphadenopathy, and tumor metastases. When present, these findings should prompt expeditious open resection.

Computed Tomography

Beyond these morphologic differences between ACCs and adenomas, much research has been done to determine whether CT scanning, with or without contrast enhancement, could reliably differentiate among the many clinical entities that an incidentally discovered adrenal lesion could represent. Much of this research relies on differences in cellular water and lipid content among the various tumors of the adrenal gland (Figure 12-2).

Benign adrenal adenomas, unlike malignant lesions of the adrenal gland, commonly have high intracytoplasmic lipid content. This feature leads to their having lower unenhanced CT density values[55] and a less-bright appearance on T2-weighted MRI images.[56] In their metaanalysis, Boland and coworkers[52] reviewed 10 studies that evaluated unenhanced CT's ability to differentiate adenomas from non-adenomas. Cumulatively, 495 adrenal lesions (272 benign and 223 malignant) were evaluated using noncontrast CT with sensitivity and specificity values of 71% and 98%, respectively, when a threshold of 10 Hounsfield units (HU) was used. A later series[55] of 73 adrenal lesions described a mean attenuation of 8 HU for adenomas compared with a mean of 68.6 HU for non-adenomas. Unfortunately, unenhanced CT's ability to differentiate among the adrenal

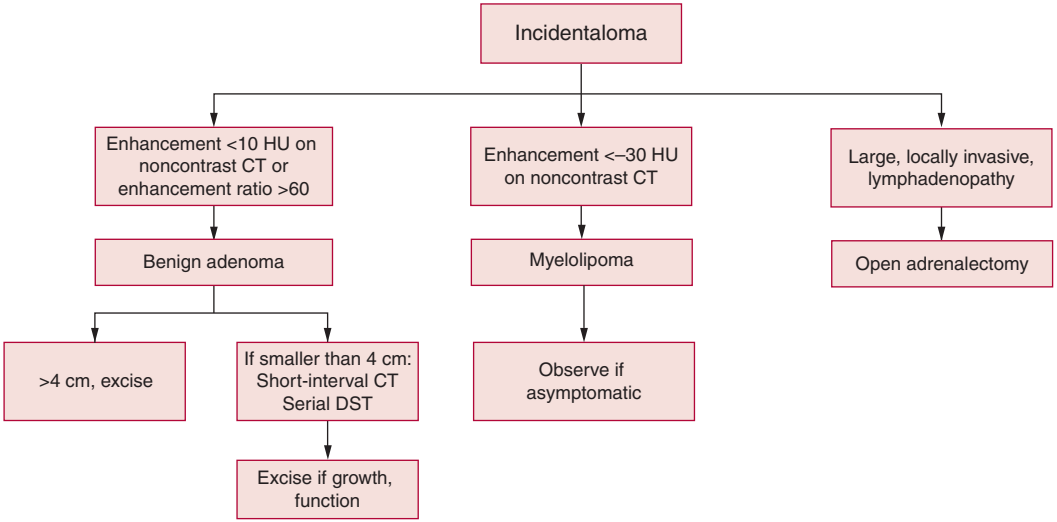

Figure 12-2. Differences in cellular water and lipid content among the various tumors of the adrenal gland. CT = computed tomography; DST = dexamethasone suppression test.

non-adenomas is poor, with mean enhancement values of 39, 44, and 34 HU for ACC, pheochromocytoma, and tumor metastasis, respectively. Nevertheless, most authorities agree that an enhancement value of 10 HU or less (on a noncontrast CT) is diagnostic of a benign adrenal adenoma and that no further diagnostic workup is necessary to secure the diagnosis.[57–59] Because up to 40% of benign adrenal adenomas are lipid poor[60] and because fatty tumors can metastasize to or originate from the adrenal gland, considerable overlap exists in these radiologic features as well.

Interestingly, the addition of intravenous (IV) contrast does little to improve CT's ability to segregate adrenal neoplasms.[55] Sixty seconds after injection, mean enhancement values for adenomas, ACCs, pheochromocytomas, and metastatic lesions were 60, 83, 94, and 81 HU, respectively. At 15 minutes after injection, the enhancement values were 32, 72, 83, and 66, respectively. This report is consistent with a prior study[59] that demonstrated that although both adenomas and non-adenomas demonstrate rapid enhancement after contrast administration, non-adenomas have a prolonged washout phase. Consequently, benign adenomas have much higher relative loss of enhancement (percent loss of enhancement compared with initial enhancement).[55] Because non-adenomas have similar retention of IV contrast, loss of enhancement ratios cannot be used to differentiate among adrenocortical adenoma, pheochromocytoma, and tumor metastasis.[55]

A recent study[58] was conducted to assess whether the combination of unenhanced CT and enhancement ratios obtained from contrast-enhanced CT improves the diagnostic accuracy of adrenal lesions. Using a dedicated adrenal protocol CT, the authors were able to correctly diagnose 124 of 127 cortical adenomas and 36 of 39 non-adenomas.

A proposed algorithm[60] is to perform a noncontrast CT scan initially, and if the attenuation value of the adrenal mass is greater than 10 HU, to administer IV contrast and repeat the scan at 1- and 15-minute delays. Enhancement washout calculations should then be performed. If the absolute enhancement ratio is greater than 60%, the lesion is characterized as an adenoma. If the enhancement ratio is less than 60%, additional testing is recommended.

Adrenal masses that contain grossly visible fatty components (attenuation values of –30 HU) can be definitively diagnosed as myelolipomas, which also have a characteristic appearance on CT scan.[58] Unless the patient is symptomatic, even when these lesions are large, they may be safely observed and require no specific treatment.

Magnetic Resonance Imaging

MRI also relies on the differences in intracellular lipid and water content to differentiate among adrenal tumors. The relatively higher water content of pheochromocytomas, ACCs, and tumor metastases causes them to appear

brighter on T2-weighted images than adenomas. By comparing the signal intensity of the adrenal tumor with the intensity of the liver, Reinig et al.[56] demonstrated that three subsets of adrenal tumors exist, differentiated by their adrenal or liver signal intensity ratios—pheochromocytomas, with the highest intensity ratios, tumors (ACC and metastases) with intermediate intensity ratios, and adenomas with the lowest intensity ratios.

Unfortunately, although pheochromocytomas could be definitively diagnosed by MRI (all had intensity ratios greater than 3.4, and no other tumor had a ratio greater than 2.7), the differentiation between adenoma and cancer was less definitive. All adrenal masses with intensity ratios between 1.4 and 2.6 were malignant (metastases), and all adrenal masses with intensity ratios less than 1.2 were adenomas. However, 21% of the nonpheochromocytoma adrenal masses had an adrenal:liver intensity ratio between 1.2 and 1.4 and could not be definitively diagnosed by radiographic criteria.[61] In these cases, if the patient has a known primary malignancy, this should be imaged as well, with the expectation of similar intensity for the primary and metastatic lesions. Thus, if the primary tumor is very bright on T2-weighted images, a less-bright adrenal lesion is more likely to be an adenoma.

Fluorodeoxyglucose Positron Emission Tomography

Although CT and MRI attempt to differentiate among adrenal lesions based on their differing lipid and water contents, positron emission tomography (PET) scanning differentiates among lesions based on their metabolic rate. Unlike benign adrenal adenomas, malignant lesions and pheochromocytomas, with their characteristically high metabolic rates, have increased fluorodeoxyglucose (FDG) uptake and appear bright on PET scans (high standardized uptake value). Pheochromocytomas, in turn, are readily diagnosed using biochemical testing.

Many studies have evaluated the utility of FDG-PET for the differentiation of benign versus malignant adrenal lesions in patients with known malignancy and have reported sensitivity of close to 100% and specificity ranging between 80% and 100%.[62] A recent prospective study[63] looked at the ability of PET scanning to differentiate benign from malignant tumors in patients without biochemical hypersecretion or a recent history (within 5 years) of malignancy. In 41 adrenal incidentalomas, PET scans had a 100% sensitivity and negative predictive value and were 86% specific.

OPERATIVE APPROACH

Since the introduction of laparoscopic adrenalectomy,[64] more than 30 studies (totaling more than 1600 patients) have compared open with

laparoscopic adrenalectomy.[47] Although the majority of these studies were retrospective in nature and were marred by large variations in methodology and patient populations, it is apparent that laparoscopic surgery is associated with a decreased operative time and blood loss, a shortened postoperative hospital stay, and more rapid return to work. Excellent results have been reported for laparoscopic surgery in the setting of incidentaloma, aldosteronoma,[65] CS,[66] pheochromocytoma,[10] and metastatic lesions to the adrenal gland.[67] Moreover, some authors have reported excellent results for laparoscopic adrenalectomy in the setting of bilateral disease[66] or large (>6 cm) adrenal tumors.[11,68] Studies of less commonly used approaches to adrenalectomy (e.g., posterior open and laparoscopic, robotic, and needlescopic) have also been published but are beyond the scope of this chapter.

Because of early reports of port-site metastasis of ACC after laparoscopic resection and the soft, friable nature of ACC, laparoscopic adrenalectomy is contraindicated in this setting. Therefore, if preoperative imaging is suggestive of ACC (large, locally invasive lesion; retroperitoneal lymphadenopathy), open adrenalectomy should be performed.

LONG-TERM FOLLOW-UP AND NATURAL HISTORY

Although the workup and management of patients with adrenal incidentalomas are fairly well established, the follow-up of patients with apparently benign, nonhypersecretory adrenal nodules remains controversial. Varying recommendations have been made regarding the necessity of regular interval biochemical evaluations and radiographic examinations. Some authors suggest that hormonal behavior and size are unlikely to change,[69] but others recommend serial biochemical testing and imaging.[70,71] Moreover, no consensus has been reached regarding the duration of follow-up.

A large study from the Mayo Clinic recently reported on 224 patients with incidentalomas who were followed for an average of 7 years.[69] The average tumor size in their cohort was 2 cm, and only nine of the patients had tumors larger than 4 cm on initial imaging. Ninety-one of the patients had follow-up CT scans (at an average of 49 months), and only four patients' tumors (4.4%) had grown. Although repeat biochemical testing was not routinely done, no patient who was originally euadrenal developed symptoms of an adrenal hypersecretory disorder. None of these patients developed ACC.

Another recent study, though, reported on 75 patients with incidentalomas who were followed for a mean of 4.6 years with serial imaging and

biochemical evaluations. The authors reported that 17 (29%) of the tumors grew ($n = 11$), became hormonally active ($n = 3$), or both ($n = 3$).[72] In this cohort, the cumulative risks for mass enlargement and adrenal hyperfunction were 22.8% and 9.5%, respectively, at 10 years. Most functional and growth change occurred during the first 3 years after diagnosis and did not continue to increase after the first 5 years from the diagnosis. Initial tumor size greater than 3 cm was predictive of future hyperfunction.

The NIH's consensus statement on this subject[15] reflects the paucity of data. Currently, the recommendation is for a single, short interval (6 to 12 months) CT scanning. No data support further radiographic surveillance for lesions that do not change in size. Because the risk for development of adrenal hyperfunction is greatest in lesions larger than 3 cm and cortisol hypersecretion is the most likely disorder to be diagnosed, our recommendation is to perform an annual 1-mg DST and reserve biochemical testing for patients with pheochromocytoma and aldosteronoma for the rare patients who develop suggestive symptoms. For nonfunctional incidentalomas, we recommend resection for tumors that demonstrate interval growth or are larger than 4 cm.

Patients with a History of Cancer and Concern for Metastases

Patients with a history of cancer who are found to have an adrenal lesion on follow-up imaging are a particularly challenging group. Even in this selected population, the majority of adrenal lesions are benign and nonsecreting.[63] Although these are technically not considered to be incidentalomas, the workup should be conducted in a similar fashion, as highlighted by a recent report of eight pheochromocytomas in 33 patients with a history of cancer who underwent adrenalectomy for isolated adrenal masses.[73]

We agree that in contrast to most patients with incidentalomas in whom fine-needle aspiration (FNA) is not recommended, FNA can sometimes be helpful in demonstrating whether an adrenal lesion that is suspicious for malignancy is a primary ACC or a tumor metastasis. FNA biopsy of adrenal glands, however, is associated with up to 50% nondiagnostic rate, and excluding these, its sensitivity rate is only about 80%.[47] Moreover, FNA is rarely associated with a variety of complications, including pneumo- or hemothorax; fever and bacteremia; adrenal, renal, and hepatic hematomas; hypotension; and pain. In situations in which this information might change the surgical management, FNA is recommended.[5,6,15,47]

PET scanning is generally accurate in differentiating benign from malignant lesions without the associated risks, so fewer adrenal tumor FNA biopsies are currently being done.

PRACTICAL PEARLS

- The reported prevalence of adrenal incidentalomas ranges from 0.35% to 5%.
- All adrenal incidentalomas, regardless of their radiographic appearance or suspicion for malignancy, should be screened to exclude biochemical hyperfunction.
- The three major functional tumors that should be accounted for are pheochromocytoma, hypercortisolism, and hyperaldosteronoma.
- Patients with a history of a nonadrenal cancer who present with an adrenal tumor must be biochemically evaluated in the same fashion as patients with adrenal incidentalomas. A recent study[73] reported eight pheochromocytomas in 33 patients with a history of cancer who underwent adrenalectomy for isolated adrenal masses

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Chapter 13

Hyperaldosteronism

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DEFINITION

Hyperaldosteronism is caused by the hypersecretion of the hormone aldosterone by the adrenal cortex, leading to the clinical syndrome of hypertension and hypokalemia. This syndrome was originally described by Conn in 1955 and thus is often referred to as Conn's syndrome.[1] In approximately 50% to 60% of cases, hyperaldosteronism is caused by a solitary adrenal nodule or "aldosteronoma." The remainder of cases (~30% to 40%) are caused by bilateral adrenal hyperplasia.[2] Unilateral adrenal hyperplasia and aldosterone-producing ovarian tumor may also cause hyperaldosteronism.

Approximately 5% of the time, patients present with an angiotensin-2–responsive adenoma, although this type of presentation is rare. In 1% of cases, familial hyperaldosteronism type I (FH1), also known as glucocorticoid-remediable hyperaldosteronism (GRA) and familial hyperaldosteronism type II, causes hyperaldosteronism. GRA is an autosomal dominant disease that is characterized by high aldosterone levels and low renin levels. With GRA, symptoms are reversed by glucocorticoid administration because aldosterone levels are controlled by adrenocorticotropic hormone (ACTH) rather than by normal angiotensin II (Figure 13-1). Adrenocortical carcinoma and metastatic disease may also cause high aldosterone levels. A quick and simplified schematic of the physiology of aldosterone is shown in Figure 13-1.

EPIDEMIOLOGY AND RISK FACTORS

Most cases of hyperaldosteronism affect younger adults between the ages of 30 and 50 years, with a female preponderance three times higher than that of males. Many studies have demonstrated evolving etiologies of

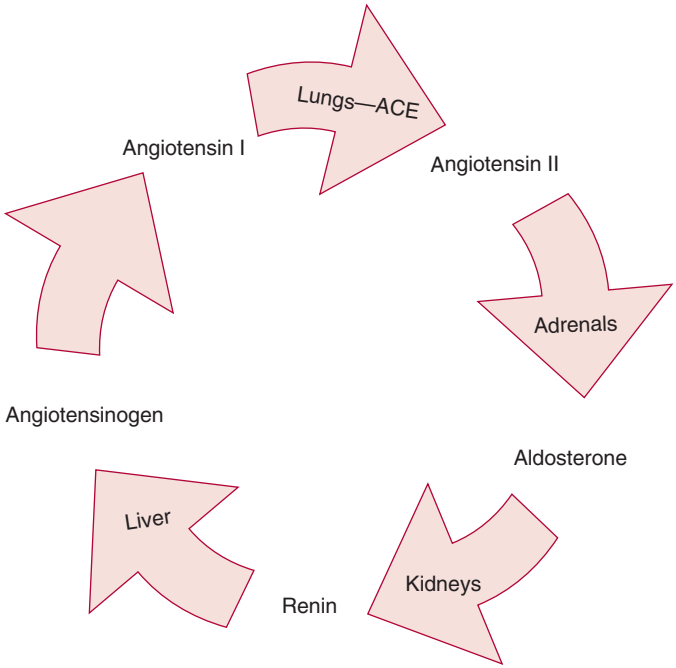

Figure 13-1. The physiology of aldosterone. ACE = angiotensin-converting enzyme.

hyperaldosteronism depending on how the disease is defined. Hypertensive patients who are at risk for increased aldosterone levels include very young patients with refractory hypertension and those with a strong family history of an aldosteronoma. According to the Joint National Committee, the prevalence of primary hyperaldosteronism is 1.99% in subjects with stage 1 hypertension, 8.02% in stage 2 hypertension, and 13.2% in stage 3 hypertension. In patients with resistant hypertension, the prevalence of primary aldosteronism has been reported to be 17% to 20%, but African-American and black South African subjects have lower renin levels than white subjects.[3] Ethnicity, age, and gender differences have not had a profound effect on the prevalence of hyperaldosteronism.

CLINICAL PRESENTATION

In most cases of hyperaldosteronism, mild to moderate hypertension occurs, making the diagnosis more elusive until essential hypertension is ruled out. Hypokalemia, as often seen in patients with hyperaldosteronism, may cause muscle weakness, cramping, paralysis, fatigue, and headaches.[4] It also has accompanying hypernatremia without pedal edema and may present with polyuria, polydipsia, and increased liability to urinary tract infections secondary to impairment of urinary concentration and acidification.[5] A thorough physical examination should be performed to look for signs of adrenal pathology, including obesity, short stature, striae, hirsutism, peripheral weakness, abdominal bruits (renal artery stenosis), and peripheral edema.

DIAGNOSTIC EVALUATION

Accurate diagnosis of aldosteronoma includes a combination of clinical suspicion, symptoms, biochemical testing, and imaging results. In patients with primary or secondary hyperaldosteronism, hypernatremia, hypokalemia (serum K+ <3.4 mEq/L), aldosteroneuria (12 ug/d), hypomagnesemia, hypophosphatemia, and increased urinary 17-hydroxysteroid may be seen.

Plasma renin activity is useful in differentiating primary from secondary hyperaldosteronism. A PAC:PRA (Plasma Aldosterone Concentration: Plasma Renin Activity) ratio above 25 ng/dL is sensitive and specific in the screening and diagnosis of primary hyperaldosteronism.[2] Classification of this ratio is as follows: low ratios (0.21 to 0.98) indicate adrenal insufficiency, normal ratios (2.8 to 23.2) indicate secondary hyperaldosteronism, and ratios above 105 indicate primary hyperaldosteronism.[6]

It is also important to remember that many antihypertensive drugs, such as spironolactone, angiotensin-converting enzyme inhibitors, and diuretics, affect renin aldosterone regulation and should be discontinued 4 to 6 weeks before diagnostic studies are performed.[4]

Historically, a postural stimulation, or "salt-loading," test (Table 13-1) was used to confirm the diagnosis; however, the sensitivities were low, and these studies have largely fallen into disuse. An iodocholesterol scan (NP-59) is also seldom used because of limited availability, low accuracy in detecting small lesions, and the requirement for dexamethasone suppression.[4] In the era of computed tomography (CT) scanning, NP-59 and postural stimulation testing (salt loading) are rarely necessary.

Imaging Studies

Localizing studies are mandatory for surgical decision making and may help differentiate between adenoma and hyperplasia. CT scanning is most

TABLE 13-1. The Postural Stimulation, or "Salt-Loading," Test for Hyperaldosteronism

Adenoma	*Hyperplasia*
Aldosterone varies:	Aldosterone increases:
With increased angiotensin	With increased angiotensin
On standing*	On standing

*Because adenomas are insensitive to angiotensin.

accurate for nodules that are larger than 1 cm in diameter. Smooth borders characterize CT findings of an adenoma, and lipid-rich adenomas are seen with low attenuation on noncontrasted CT scans. Lipid poor adenomas can be further differentiated by using delayed enhanced CT scans.[7] The adequate localization of bilateral masses may be further characterized by more invasive tests. Increased and rapid growth of an adrenal mass within a 6-month interval and an adrenal mass larger than 4 cm warrant more aggressive follow-up because the suspicion for malignancy is high in these cases. A CT scan can miss bilateral disease either because it is adrenal hyperplasia or the adrenal masses are smaller than 1 cm.

When CT scan findings are equivocal or the presence of bilateral adrenal nodules is suspected, adrenal venous sampling (AVS) may be used to accurately diagnose hyerplasia.[8] AVS can lateralize the "hyperfunctioning" gland, especially in cases of bilateral adrenal adenomas, whereby nonfunctioning and aldosterone-producing adenomas can coexist in the ipsilateral or contralateral gland. AVS uses blood samples from both adrenal veins and the inferior vena cava to measure aldosterone and cortisol before and after ACTH stimulation. An aldosterone:cortisol ratio fourfold greater than that in the other adrenal vein is considered indicative of a unilateral aldosterone-producing tumor.[9,10]

An important concept in classifying adrenal gland pathology is understanding the difference between primary and secondary hyperaldosteronism (Figure 13-2).

DIFFERENTIAL DIAGNOSIS

After essential and primary hypertension are ruled out, surgically correctable causes of hypertension, known as *secondary hypertension*, is investigated. These are more commonly seen in young individuals with difficult-to-treat hypertension who present with symptoms, clinical signs, or laboratory parameters associated with Cushing's syndrome, Conn's syndrome, or pheochromocytoma.[11] These secondary causes of hypertension include:

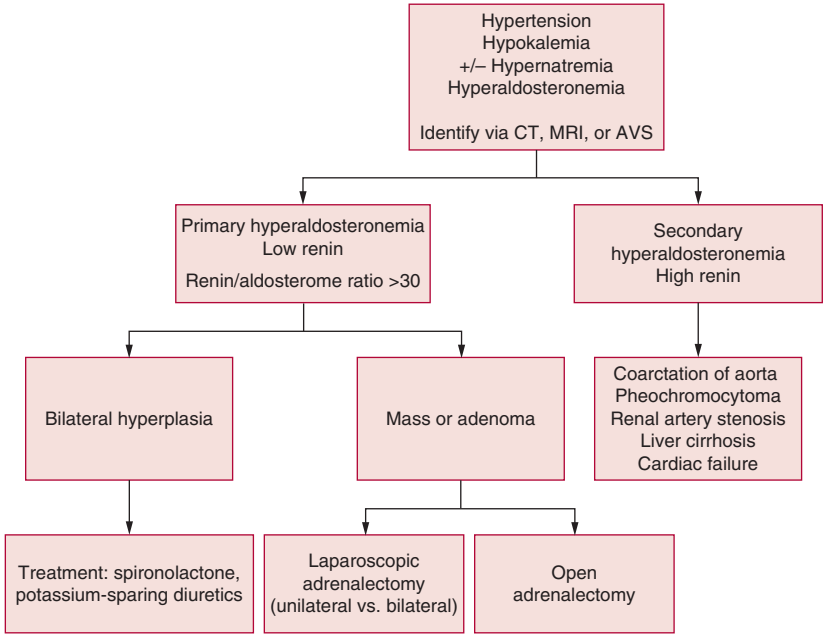

Figure 13-2. Workup for primary hyperaldosteronism. CT = computed tomography; MRI = magnetic resonance imaging; AVS = adrenal venous sampling.

- Coarctation of the aorta: arm blood pressure exceeds leg blood pressure
- Pheochromocytoma: accompanying palpitation, intermittent and profuse sweating, and urinary and serum biochemical evidence of catecholamine elevation
- Renal artery stenosis: suggested by hypertension onset younger than age 30 years that is refractory to three-drug antihypertensive medications, presence of accompanying epigastric or flank bruit, progressive worsening of hypertension, and worsening renal function; this is the most common cause is fibromuscular dysplasia in women and atherosclerosis in men
- Adrenal aldosteronoma

MANAGEMENT

Patients with bilateral adrenal hyperplasia are treated with spironolactone, an aldosterone antagonist. However, if there is clear-cut evidence of a unilateral adenoma or unilateral hyperplasia, then unilateral adrenalectomy is the treatment of choice. Because aldosteronomas are typically small and benign, most of these lesions can be resected by a laparoscopic approach. Several studies have shown that normalization of blood pressure with spironolactone and correction of hypokalemia before surgery is undertaken are good predictors for the successful treatment of hypertension after unilateral adrenalectomy.[4]

Two ways to approach an adrenal mass is by open adrenalectomy and laparoscopically. Open adrenalectomies are classified as either anterior (using a subcostal or midline approach) and posterior (thoracoabdominal approach). Anterior open adrenalectomy is the most commonly used open approach, but it is associated with a longer recovery time, poor wound healing risks, and cardiopulmonary postoperative complications.[12] The open thoracoabdominal approach has significant morbidity yet is acceptable for smaller tumors and is used when the patient has treacherous intraabdominal adhesions.[12]

As mentioned previously, for adrenal hyperaldosteronomas, laparoscopic adrenalectomy is now considered the approach of choice. Laparoscopic adrenalectomy may be performed using a lateral transabdominal (most common), lateral, or posterior retroperitoneal approach.[12] Techniques are summarized in Table 13-2. Laparoscopic retroperitoneal adrenalectomy is also gaining favor, considering that the adrenal glands are anatomically in the retroperitoneum.[13]

PROGNOSIS AND SURVEILLANCE

One way to measure the resolution of hypertension after an adrenalectomy is by a scoring system (Table 13-3), which can help clinicians objectively inform patients of likely clinical outcomes before surgical intervention.[14]

TABLE 13-2. Steps in Laparoscopic Adrenalectomy[12]

1. Exposure of the adrenal gland: division of lateral attachments to spleen, pancreas, liver
2. Dissection of the adrenal gland: starting from the diaphragm superiorly, to a clockwise manner for the right adrenal gland, a counterclockwise manner for the left adrenal gland, and identification of the adrenal vein
3. Mobilization of the adrenal gland from the renal hilum
4. Removal of the adrenal gland from the fat overlying the kidney

Based on the resulting four-item aldosteronoma resolution score (ARS), three likelihood levels for complete resolution were identified: low (0 to 1), medium (2 to 3), and high (4 to 5), with a predictive accuracy of 27%, 46%, and 75%, respectively.[14]

One specific measure of success of an adrenalectomy is the correction of hypertension or at least a reduction in the number of antihypertensive medications needed. Approximately one third of patients did not require antihypertensive medications after adrenalectomy for aldosteronoma, and half of the patients were able to reduce their number of medications.[12] However, a recent study indicated a direct relationship between aldosterone, insulin resistance, and hyperinsulinemia to possibly explain the link to hypertension and increased cardiovascular risk.[15] Further studies are needed

TABLE 13-3. Scoring System for Measuring the Resolution of Hypertension After Adrenalectomy

Predictors		
Need for two or fewer hypertensive medications		
BMI <25 kg/m^2		
<6 months' duration of hypertension		
Female gender		
Level	*No. of Predictors*	*Accuracy (%)*
Low	0–1	27
Medium	2–3	46
High	4	75

BMI = body mass index.

to clarify these issues as well as the ongoing research regarding the association between aldosterone in patients with obesity and metabolic syndrome.

PRACTICAL PEARLS

- Hyperaldosteronism, a rare cause of hypertension, is defined by either primary causes (adrenal adenoma and adrenal hyperplasia) or secondary causes (renal artery stenosis, coarctation of the aorta, liver or kidney diseases).
- In most cases, patients have mild hypertension. Hyperaldosteronism should be suspected in younger patients with hypertension, muscle weakness, and fatigue.
- Measuring PAC and PRA levels and using CT scans and AVS can help practitioners differentiate between an adrenal adenoma and hyperplasia.
- An aldosterone antagonist such as spironolactone is used to treat bilateral adrenal hyperplasia.
- Laparoscopic excision of an adrenal adenoma has an excellent cure rate and response to treatment.
- Direct relationships between aldosterone, insulin resistance, and hyperinsulinemia contribute to hypertension, increased cardiovascular risk, and metabolic syndrome.[15]

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Chapter 14

Hypercortisolism

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DEFINITION

Hypercortisolism is a disorder characterized by excessive circulating cortisol from either endogenous or exogenous sources, which can cause detrimental changes to nearly every organ system. Collectively, the ravages of hypercortisolism are best classified as *Cushing's syndrome* (CS). The term *Cushing's syndrome* is used for all causes of hypercortisolism, and the term *Cushing's disease* is reserved specifically for cases of pituitary-dependent CS. The most common cause of CS is exogenous administration of glucocorticoids, which are used for their beneficial antiinflammatory, antineoplastic, and immunosuppressive effects. This chapter focuses solely on endogenous CS and is a summary of our recent review at the Mayo Clinic in Rochester, Minnesota.[1]

EPIDEMIOLOGY

The incidence of CS is approximately two cases per 1 million persons per year.[1] Patients who are not cured by surgical intervention or with malignant disease have a poor prognosis, with a standard mortality ratio of 3.8 to 5.0 compared with normal control subjects. Adrenocorticotropic hormone (ACTH)–dependent causes account for 80% of all cases of endogenous CS, with the majority of them (85%) attributed to pituitary-dependent causes; only 15% of cases are caused by ectopic production of ACTH or corticotropin-releasing hormone (CRH). The remaining 20% of cases of endogenous CS are caused by ACTH-independent CS. Specifically, 10% of all cases of endogenous CS are attributed to adrenal adenomas, 5% to 8% are attributed to adrenocortical carcinomas (ACCs), and the remaining 2% to 5% to ACTH-independent macronodular adrenal hyperplasia (AIMAH) and primary pigmented nodular adrenal disease (PPNAD) (Figure 14-1).[1–3]

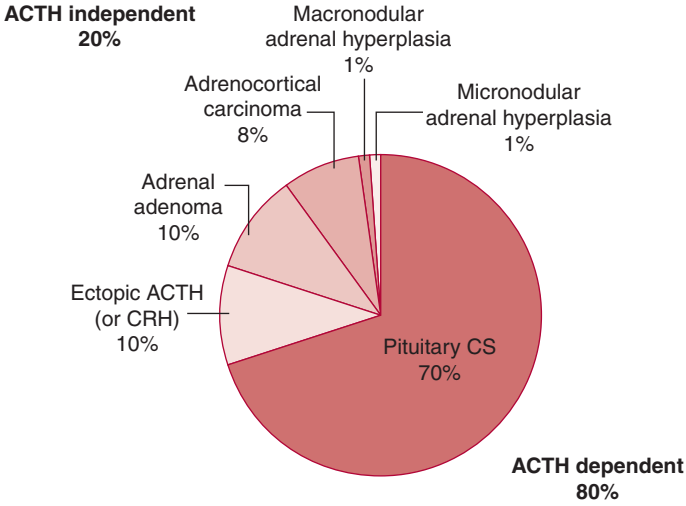


Figure 14-1. Classification of endogenous Cushing's syndrome (CS) in adults. ACTH = adrenocorticotropic hormone; CRH = corticotropin-releasing hormone. (Reproduced with permission from Porterfield JR, Thompson GB, Young WF, et al. Surgery for Cushing's syndrome: a historical review and recent ten-year experience. *World J Surg* 2008;32(5):659-677.)

RISK FACTORS

Because of the multiplicity of causes, there is no single risk factor or set of risk factors associated with CS. However, a common factor that is present in individuals with CS is a female predilection, with the exception being CS caused by ectopic ACTH production, which is slightly more common in men. In our recent 10-year review of 288 patients who underwent surgery for CS at the Mayo Clinic, women accounted for 79% of all cases of pituitary-dependent CS, 81% of adrenocortical adenomas, and 90% of ACCs. However, among patients with ectopic ACTH syndrome, men are affected slightly more often than women at 54%.[1]

CLINICAL PRESENTATION

In 1912, Harvey Cushing described a 23-year-old woman, "Minnie G.," with moon facies, obesity, amenorrhea, and hirsutism.[4] It was not until 20 years

later that he postulated that this "polyglandular syndrome" was caused by a primary pituitary abnormality that resulted in adrenal hyperplasia. This full-blown clinical picture is not always present, so one must maintain a high index of suspicion when this condition is suspected. In adults, weight gain and centripetal obesity are the most common signs. In children, short stature and generalized obesity should raise the suspicion of CS.[2] Excessive fat deposition occurs preferentially over the thoracocervical spine, supraclavicular fossae, cheeks, and temporal regions, giving rise to descriptions of a "buffalo hump," "moon-like facies," or the visual effect of "disappearing ears" when the patient is viewed in a series of facial photographs. Patients are often troubled by menstrual irregularity, infertility, and loss of libido.[2] Acne and hirsutism are common, particularly in women, because of excessive ACTH stimulation of the androgen-producing zona reticularis. The excess cortisol also has an inhibitory effect on gonadotropin production, resulting in hypogonadism.

More than half of patients with CS have psychiatric disturbances. The most common are agitated depression, lethargy, irritability, insomnia, and cognitive dysfunction. In extreme cases, severe paranoia and psychosis may be present.

In children, short stature is related to impaired linear growth in contrast to the loss of height seen in adults caused by vertebral compression fractures. Accelerated bone loss, osteoporosis, and skeletal fragility may result in asymptomatic rib and other atraumatic fractures. Aseptic necrosis of the femoral and humeral heads may also be seen. Proximal myopathy of the lower extremities and shoulder girdle are common and are a major discriminatory feature of CS. An inability to rise from a crouching position is often revealing.[1,2]

In the skin, cortisol excess results in thinning, separation, and exposure of underlying subcutaneous vascular tissue, giving rise to the plethoric features. Minimal trauma leads to "easy bruising," which is exacerbated by delays in wound healing. The typical 1- to 2-cm, wide, red-purple striae are virtually pathognomonic. They are most frequently found on the abdomen but may also be seen on the upper thighs, breasts, and arms.[1,2] Increased skin pigmentation, or "bronzing," is common in individuals with ectopic ACTH syndrome because of stimulation of skin melanocyte receptors from high levels of circulating ACTH. Fungal nail and skin infections, systemic fungal infections, and other opportunistic infections may also be seen in those with glucocorticoid excess.[1]

Three quarters of patients with CS have hypertension as part of their severe metabolic syndrome. The well-recognized consequences of diabetes and dyslipidemia contribute to increased cardiovascular morbidity and mortality.[1,2] Thromboembolic events and intestinal perforations are also more common in people with CS. Glucose intolerance and overt diabetes are seen in up to one third of patients with CS. Hypokalemic alkalosis, seen in 10% to 15% of patients with pituitary CS, is present in more than 95% of those

with ectopic ACTH syndrome because of marked increases in cortisol levels and its effect on the mineralocorticoid receptor. In addition to suppressing pituitary gonadotropins, glucocorticoids directly inhibit Leydig cell function. Excess cortisol may increase fat deposition in the retroorbital regions, leading to exophthalmos, and in the epidural space, leading to neurologic sequelae from spinal cord or cauda equina compression. Excess cortisol may also increase intraocular pressure, resulting in glaucoma.[1,2]

The often insidious onset of CS is one of the most challenging problems in endocrinology. It is common for the signs and symptoms to have been present for 3 to 5 years. In differentiating cases of CS from normal aging and simple weight gain, old photographs are particularly helpful. In obese individuals with type 2 diabetes who have poor glycemic control, the prevalence of CS may be as high as 4%.[2] After CS has been recognized, appropriate and cost-effective laboratory testing are required for confirmation, subtype determination, and (when possible) definitive cure.

DIAGNOSTIC EVALUATION

When hypercortisolism is suspected, our first test of choice is usually measurement of urinary-free cortisol (UFC) in a 24-hour collection. We also quantify urine creatinine for complete collection quality control. The suspicion for CS is elevated when the 24-hour UFC is greater than twice the upper limit of normal (normal range, 3.5 to 45 μg/24 hr or 9.7 to 124 nmol/d). Loss of diurnal variations in serum cortisol can be perturbed under many circumstances, including stress and hospitalization, and are thus less reliable than 24-hour urine collections. Even in patients with known CS, 10% to 15% of patients have one of four serial 24-hour UFCs in the normal range. All causes of CS can produce cortisol in an episodic fashion. Therefore, if suspicion is high based on the clinical assessment, repeated collections are indicated. Use of tandem mass spectrometry has avoided the falsely elevated 24-hour UFC caused by medications such as carbamazepine. Other scenarios in which the 24-hour UFC may be falsely elevated include high urine volumes (4 L/24 hr), severe illness, alcoholism, depression, and obstructive sleep apnea (OSA). When the clinical picture is consistent with CS and the baseline 24-hour UFC exceeds five times the upper limit of normal (300 μg or 828 nmol/d), no additional studies are needed to confirm CS (Figure 14-2).

An overnight 1-mg dexamethasone suppression test (DST) is a useful test for demonstrating the autonomy of an existing adrenocortical nodule.[5] The 8 AM plasma cortisol level in normal patients will suppress to below 5 μg/dL (138 nmol/L) with this test. There are, however, many causes of cortisol nonsuppression with the overnight 1-mg DST, including patient error,

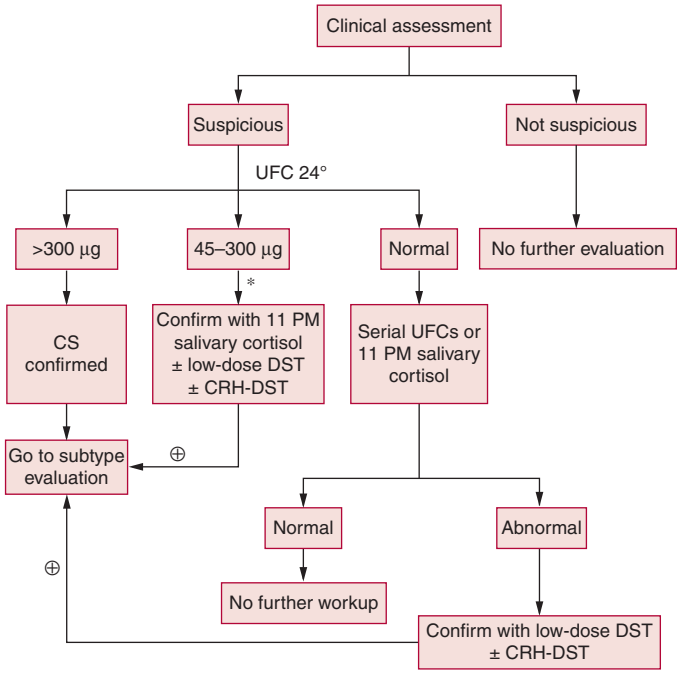


Figure 14-2. Algorithm for case finding and confirmation of Cushing's syndrome (CS). CRH = corticotropin-releasing hormone; DST = dexamethasone suppression test; UFC = urinary-free cortisol. *May go straight to subtype evaluation if clinical assessment is highly suggestive of pituitary-dependent CS. (Reproduced with permission from Porterfield JR, Thompson GB, Young WF, et al. Surgery for Cushing's syndrome: A historical review and recent ten-year experience. *World J Surg* 2008;32(5):659-677.)

increased corticosteroid-binding globulin (CBG) caused by estrogen therapy or pregnancy, alcoholism, OSA, depression, panic attacks, obsessive–compulsive disorder, obesity, drugs that accelerate dexamethasone metabolism (anticonvulsants, primidone, rifampin), renal failure, stress, cortisol assay insensitivity, and laboratory error. Another option is the 8-mg overnight DST. Normal patients should have a morning cortisol level of nearly 0. Failure to suppress is a positive test finding and warrants a 2-day, low-dose DST.

With equivocal findings and a 24-hour UFC below 300 µg (828 nmol/d), hypercortisolism should be confirmed with a 2-day, low-dose DST. Dexamethasone, 0.5 mg orally, is given every 6 hours for 48 hours. A 24-hour UFC collected during the second day of suppression of 3.5 µg (9.7 nmol/d) or above is consistent with the diagnosis of CS. This test is far from perfect, with a sensitivity of 79%, specificity of 74%, and overall accuracy of 71%. The test is most efficacious for ruling out CS in patients in whom the index of suspicion for CS is low. In addition, some patients with mild pituitary-dependent CS may suppress with a low-dose DST.[5]

In an effort to correct the suppression with a low-dose DST observed in some patients with pituitary CS, the CRH DST test was developed. A serum cortisol concentration above 1.4 µg/dL (37.6 nmol/L) at 15 minutes after CRH administration is consistent with CS. Although purported to be highly accurate, false-positive results have been seen in our clinic.

Other diagnostic tests include the measurement of late night plasma or salivary cortisol. A midnight sleeping plasma cortisol concentration above 1.8 µg/dL (50 nmol/L) is 100% sensitive in patients with CS.[1] However, for the test to be precise, hospitalization is usually required. Alternatively, measurement of salivary cortisol correlates well with serum cortisol levels. This is performed by giving the patient instructions to chew on a special cotton swab for 2 minutes and then place it in a specially designed container. Salivary cortisol levels obtained at 11 PM that are above 100 ng/dL (2.6 nmol/L) are highly sensitive for CS. This test is becoming increasingly more popular and is used as a first-line screening test in some centers despite problems with reproducibility, sensitivity, and precision of the assay.

No single test is satisfactory for case finding and confirmation of CS. The clinician should be certain of the diagnosis of CS before proceeding to subtype evaluation and localization. Patients whose clinical assessment suggests a possible diagnosis of CS when exogenous sources have been excluded should be evaluated with multiple tests for diagnostic confirmation. These include, at a minimum, a 24-hour UFC aided by an 11 PM salivary cortisol to be followed by the two-day, low-dose DST or CRH DST test. Patients with clinically evident CS and a 24-hour UFC above 300 µg (828 nmol/d) need no further confirmatory studies. Patients with an incidentally discovered adrenal mass and an 8 AM plasma cortisol concentration below 5 µg/dL (138 nmol/L) after an overnight 1-mg DST also need no further testing because autonomous cortisol production has been ruled out.

Subtype Evaluation and Imaging

With CS confirmed, subtype evaluation and localization should be done next. Because 70% of patients with endogenous hypercortisolism have pituitary-dependent CS and 80% have ACTH-dependent CS, the plasma

ACTH concentration is obtained as the next step. When measured with an immunoradiometric assay, normal plasma ACTH levels are 10 to 60 pg/mL (2.2 to 13.3 pmol/L). Plasma ACTH levels below 5 pg/mL indicate pituitary suppression by primary adrenal disease. ACTH levels in the 20 to 200 pg/mL range generally indicate pituitary-dependent disease, and ACTH levels in the 50 to above 200 pg/mL range are most often seen in patients with ectopic ACTH syndrome[3] (Figure 14-3).

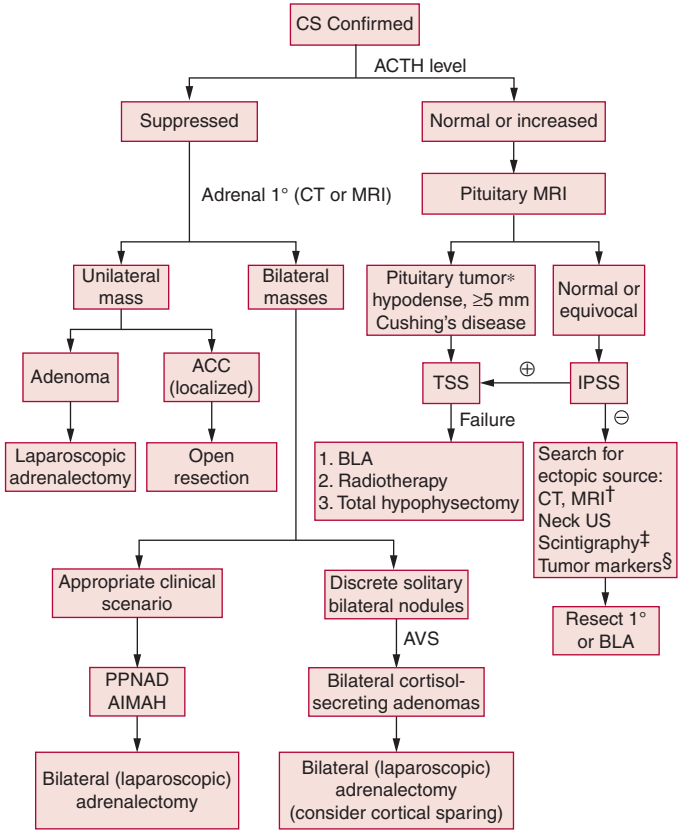
When ACTH levels are below 5 pg/mL, suggesting primary adrenal disease, cross-sectional imaging with computed tomography (CT) or (less often) magnetic resonance imaging (MRI) of the adrenal glands will usually delineate the site(s) of adrenal pathology. As with any high-resolution imaging, the presence of incidental and unrelated findings is common. About 5% to 10% of the population harbors incidentally discovered adrenal nodules that are smaller than 1 cm.[5] Typically, benign cortisol-secreting adrenal adenomas are 2 to 6 cm in diameter and have a smooth, regular border with a homogeneous appearance (Figure 14-4A). A homogeneous adrenal lesion with less than 18 Hounsfield units (HU) on unenhanced CT scans may be designated as a lipid-rich benign adenoma with a specificity of 85% and sensitivity of 100%.[6] Rarely, bilateral cortisol-secreting adenomas may be found.

ACCs smaller than 5 cm in size are rarely seen, but when present, they usually display a worrisome radiographic phenotype consisting of a heterogeneous mass with irregular borders by CT (Figure 14-4B). Other imaging characteristics of ACC include areas of necrosis, hemorrhage, calcification, delayed or incomplete washout of intravenous (IV) contrast, or bright areas on T2-weighted MRI sequences. ACC may also demonstrate regional lymphadenopathy; venous tumor thrombi; direct invasion of contiguous structures; or distant metastases to the lung, bone, and liver. MR angiography or venography may be particularly helpful in delineating the presence and extent of vascular involvement.

The presence of high intracellular lipid content, a characteristic of benign adenomas, may be seen by axial, in-phase and out-of-phase, fast, multiplanar spoiled, gradient-echo T1-weighted MRIs. Benign adenomas also appear isotense relative to the liver in axial fast spin-echo, T2-weighted MRIs.

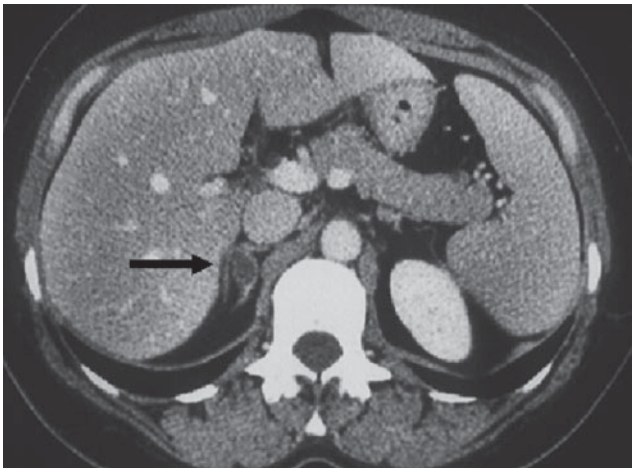
In patients with primary PPNAD, bilateral adrenal micronodularity ("string of beads" appearance) is a characteristic finding on high-resolution CT. The adrenal glands are usually normal in size.[7] After diagnosis, the patient and family members should be screened for cardiac myxomas, a common cause of sudden death in PPNAD patients with Carney complex (CNC). Genetic testing is available for the *PRKAR1A* mutations seen in 40% of patients with CNC.[7]

In AIMAH, CT scans (Figure 14-4C) demonstrate massive, often asymmetric, bilateral adrenal enlargement, with nodules reaching 5 cm in size. Research protocols are available to screen for abnormal adrenal expression

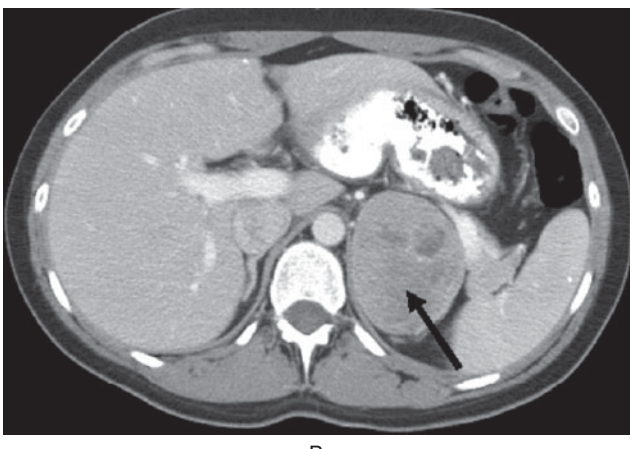


*TSS in appropriate clinical setting.
†Chest, abdomen.
‡Octreoscan, 123-I-metaiodobenzylguanidine scintigraphy, positron emission tornography scanning with ^{18}F-fluorodeoxyglucose.
§Calcitonin, urinary 5-hydroxyindoleacetic acid, gastrin, plasma fractionated metanephrines.

Figure 14-3. Algorithm for subtype evaluation of Cushing's syndrome (CS). ACC = adrenocortical carcinoma; ACTH = adrenocorticotropic hormone; AIMAH = adrenocorticotropic hormone–independent macronodular adrenal hyperplasia; AVS = adrenal venous sampling; BLA = bilateral laparoscopic adrenalectomy; CT = computed tomography; IPSS = inferior petrosal sinus sampling; MRI = magnetic resonance imaging; PPNAD = primary pigmented nodular adrenal disease; TSS = transsphenoidal surgery; US = ultrasonography. (Reproduced with permission from Porterfield JR, Thompson GB, Young WF, et al. Surgery for Cushing's syndrome: a historical review and recent ten-year experience. *World J Surg* 2008;32(5):659-677.)

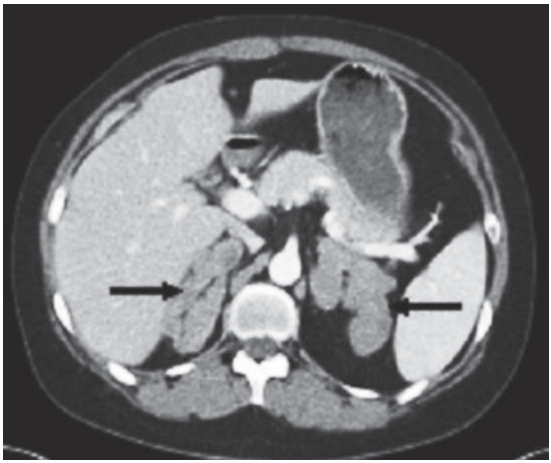


A



B

Figure 14-4. A. Axial computed tomography (CT) image showing a small adrenal cortical adenoma (*arrow*). **B.** Axial CT image showing a large left adrenocortical carcinoma (*arrow*). **C.** Axial CT image from a patient with adrenocorticotropic hormone–independent macronodular adrenal hyperplasia showing massively enlarged adrenal glands (*arrows*) bilaterally.



C

Figure 14-4. (*Continued*)

and function of receptors that include gastrointestinal polypeptide, interleukin-1, LH (Luteinizing Hormone), vasopressin, and β-adrenergic receptors. Unfortunately, to date, directed medical therapy with octreotide, V1a receptor antagonists, β-blockers, gonadotropin-releasing hormone agonists, $5HT_4$ or AT-1 antagonists, has generally proven unsuccessful. Thus, bilateral total adrenalectomy is often necessary to resolve the hypercortisolemic state.[1,7]

Normal to moderately elevated ACTH levels confirm ACTH-dependent CS. The clinical presentation however, cannot be underestimated for its predictive value. For example, a 55-year-old woman with an insidious onset of CS over many years possessing classic signs and symptoms almost certainly has pituitary-dependent CS (>95% probability). In contrast, a 55-year-old man with a 3-month history of fatigue, weight loss, marked skin pigmentation, hypokalemic alkalosis, glucose intolerance, an ACTH level above 100 pg/mL, and a 24-hour UFC above 500 μg almost certainly has ectopic ACTH syndrome until proven otherwise.

Because 85% of patients with ACTH-dependent CS have Cushing's disease, a dedicated pituitary MRI with gadolinium-enhancement is indicated

in all patients in this subgroup.[1] If a hypodense and nonenhancing pituitary tumor larger than 5 mm is identified in the correct clinical scenario (female gender, indolent disease, UFC <fivefold but >twofold elevated), further studies are not required before definitive treatment. Smaller (<5 mm) pituitary lesions occur in as many as 10% to 20% of normal individuals and are being detected with increasing frequency with each new generation of MRI scanner. Thus, patients with normal pituitary scans or very small lesions should be further studied with inferior petrosal sinus sampling (IPSS) because 50% of patients with Cushing's disease demonstrate a normal pituitary MRI.[1]

In IPSS with CRH stimulation, both inferior petrosal sinuses are sampled simultaneously because of pulsatile ACTH secretion. Sampling of the cavernous sinuses is more cumbersome and dangerous, and sampling of the internal jugular veins is less accurate. IPSS that demonstrates a central to peripheral vein gradient of more than 2:1 at baseline and more than 3:1 after CRH administration is diagnostic of Cushing's disease (95% sensitivity; 100% specificity). IPSS also assists in surgical lateralization if the side-to-side ACTH ratio is above 1.5:1. Factors that may cause misleading IPSS results include episodic disease (cyclical CS), incorrect catheter placement, anomalous venous drainage, and the rare ectopic CRH-secreting tumor. The risks associated with IPSS are not trivial and include venous thrombosis, pulmonary embolism, cranial nerve palsy, and brain stem infarction, thus mandating the availability of an experienced interventional neuroradiologist. IPSS is technically successful in 85% to 99% of procedures in experienced centers and is considered the most important advance in subtype evaluation of CS in the past quarter century.[8]

With ACTH-dependent CS and negative pituitary MRI and IPSS findings, a search for an ectopic ACTH-secreting tumor is then pursued. In our recent 10-year review, we were successful in locating the primary tumor in only 65% of cases.[1] IPSS can be avoided if the pituitary MRI results are negative and the clinical setting is typical for ectopic ACTH syndrome (i.e., male patient with rapid onset of CS, predominance of metabolic abnormalities, and very high cortisol and ACTH levels). CT or MRI of the neck, chest, abdomen, and pelvis is performed. Unfortunately, somatostatin receptor imaging with ^{111}In-DTPA-pentetreotide has not proven very accurate in localizing ectopic ACTH-secreting tumors, many of which remain occult for years. Diagnostic sensitivities ranging from 30% to 80% have been reported. [^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) has added little to the diagnostic armamentarium for ectopic ACTH-secreting tumors.[9] It is hoped that diagnostic accuracy of PET will improve with the use of additional isotopes ([^{11}C]5-HTP, [^{11}C]2-DOPA), but this has yet to be proven.[9] In rare situations, biochemical markers may be of assistance. These include calcitonin (medullary thyroid cancer), plasma and urinary fractionated metanephrines (pheochromocytoma), gastrin

(gastrinoma), and urinary 5-hydroxyindoleacetic acid (carcinoid tumors). However, when these markers are elevated, the source is usually readily apparent by conventional imaging. ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy can be helpful in localizing an ACTH-secreting (or CRH-secreting) pheochromocytoma and its metastases, if present.

MANAGEMENT

The goals of treatment of patients with CS includes resolution of the hypercortisolemic state, management of complications of CS (hypertension, osteoporosis, diabetes mellitus, and myopathy), and restoration of the normal hypothalamic–pituitary–adrenal (HPA) axis. All of these goals may take months to years to complete. Despite appropriate treatment, normalization of plasma cortisol levels and restoration of the HPA axis may not occur.

Pituitary Cushing's Syndrome

Transsphenoidal selective (TSS) pituitary adenomectomy via an endoscopic transnasal approach is the treatment of choice for patients with Cushing's disease. The sublabial approach has been largely replaced. The endonasal route has lower morbidity, eliminating the painful gingival incision and dental paresthesias often associated with the sublabial approach to the sphenoid sinus. The short-term cure rate for ACTH-secreting microadenomas is 80% to 85%. Success rates decrease appreciably for larger macroadenomas, locally invasive tumors, and treatment at less experienced centers. Perioperative mortality rates range from 0% to 2%. Morbidity from TSS includes diabetes insipidus, the syndrome of inappropriate antidiuretic hormone secretion, cerebrospinal fluid rhinorrhea, meningitis, optic nerve injury, other cranial nerve injuries, vascular accident, nasal septal perforations, epistaxis, sinusitis, and graft site dehiscence. Fortunately, morbidities are uncommon, and when present, they are often transient.[10]

Postoperative cortisol levels may remain normal to elevated for several days. Patients with readily measurable cortisol levels in the immediate postoperative period may still be cured. However, when plasma cortisol levels exceed 20 μg/dL (550 nmol/L) more than 4 days after TSS, the patient has not been cured. Histologically, cure cannot be predicted based on the presence or absence of an adenoma or hyperplasia. The development of secondary adrenal insufficiency may occur slowly such that careful postoperative steroid management and withdrawal should be performed under the guidance of an experienced endocrinologist. Full recovery of the HPA axis may require 6 to 24 months, and long-term physical rehabilitation may be necessary.

When initial TSS has failed, a second operation is considered but is curative in less than half of the cases. Total hypophysectomy is an option,

but concerns for future reproductive function in young women and panhypopituitarism make this a less than desirable option. In the case of severe CS, prompt bilateral (laparoscopic) adrenalectomy can be life saving.[11–13] In patients hospitalized with severe metabolic derangements, prompt aggressive institution of medical therapy, antibiotic coverage for opportunistic infections, and ulcer prophylaxis may reduce perioperative morbidity.

In cases in which bilateral adrenalectomy is required, there are two lifelong concerns, Addisonian crises and Nelson-Salassa syndrome. After bilateral adrenalectomy, lifelong oral glucocorticoid and mineralocorticoid replacement are required. Thus, patients must be educated and invested into their own health care to minimize episodes of Addisonian crises. Lairmore et al.[14] reported a 23% incidence of crises requiring hospitalization and one death after bilateral adrenalectomy. It is suspected that most retrospective studies underestimate its true incidence. Patient education is of paramount importance to minimize these occurrences. All patients should wear a medical ID bracelet and carry with them a prefilled glucocorticoid syringe for intramuscular injection when physiologic stress occurs or illness prevents oral steroid augmentation.

Prophylactic pituitary radiation after bilateral adrenalectomy for pituitary-dependent CS remains controversial. Nelson-Salassa syndrome is characterized by unrestrained growth of an untreated and unopposed corticotroph pituitary tumor. Eleven percent of such patients at the Mayo Clinic developed Nelson-Salassa syndrome. In nearly every case, there was clear evidence of invasive pituitary disease before adrenalectomy.[1,15] In the absence of advanced pituitary disease, most patients undergoing bilateral adrenalectomy never develop Nelson-Salassa syndrome. Instead, their ACTH-secreting pituitary microadenomas remain smaller than 10 mm, avoiding the need for tumor-directed therapy. Radiotherapy is associated with some risks. In our series, 3% of patients who underwent radiotherapy developed secondary central nervous system neoplasms and other morbidities listed below.[1] We reserve stereotactic radiotherapy for patients with large invasive pituitary tumors or residual pituitary tumors that demonstrate clinically important growth on serial MRI.

Radiotherapy

As an alternative to TSS, radiotherapy may be selected for the treatment of patients with recurrent or persistent Cushing's disease. Stereotactic radiosurgery with protons (gamma knife) or photons (linear accelerator) has provided the precision and the ability to deliver a higher dose to the target field compared with conventional radiotherapy. Radiotherapy is capable of controlling hypercortisolism. However, there is a significant delay between delivery and the subsequent decline in cortisol levels. In severe cases, this

may be unacceptable. A delay often requires the use of cortisol-lowering medications. The risk of delayed hypopituitarism is also significant. Other less common side effects include optic nerve atrophy with visual impairment, secondary tumor development, and cognitive dysfunction.

Ectopic Adrenocorticotropic Hormone Syndrome

Optimal management of patients with ectopic ACTH syndrome involves localization and resection of the primary tumor for cure. Unfortunately, in 35% of cases, the tumor cannot be localized at the time of diagnosis of CS. This is further complicated by the fact that among those whose primary site is identified, 85% have metastatic disease or incompletely resectable disease. The timing of tumor discovery is also quite variable, with some tumors discovered up to 20 years before or after the diagnosis of CS. In a recent series[16] from the Mayo Clinic, the most frequent causes for ectopic ACTH syndrome were bronchial carcinoid tumor (25%), islet cell carcinoma (16%), small cell lung cancer (8%), medullary thyroid carcinoma (7%), thymic carcinoid tumor (5%), metastatic neuroendocrine tumor of unknown primary (5%), pheochromocytoma (3%), and no tumor found (16%). As a result of the often occult or metastatic primary tumor, bilateral laparoscopic adrenalectomy has become the treatment of choice. This effectively addresses the ravages of hypercortisolism that pose a greater immediate risk to the patient than the malignancy itself. These patients are often quite ill and systemically more deranged than patients with either persistent or recurrent Cushing's disease and thus may benefit from a short period of medical preparation.

Adrenal Adenoma

Patients with cortisol-secreting adrenal adenomas are best treated with unilateral, laparoscopic, or posterior retroperitoneoscopic adrenalectomy. This choice is nearly completely dependent on the experience and preference of the operating surgeon.[17] Both have well-defined benefits over open approaches particularly with regard to wound healing. In the rare cases of bilateral functioning adenomas, these can be managed with a cortical-sparing approach in a minimally invasive or open fashion. Intraoperative ultrasonography assists with complete tumor resection.[18]

Primary Pigmented Nodular Adrenal Disease and Adrenocorticotropic Hormone–Independent Macronodular Adrenal Hyperplasia

Bilateral total adrenalectomy is the definitive cure for patients with PPNAD and AIMAH.[7] Rare reports of cures after unilateral adrenalectomy are suspect, and persistent glucocorticoid autonomy is likely. Unfortunately, medical

therapy in AIMAH, which is directed at abnormal receptor function and expression, has been disappointing.[7] PPNAD is ideally suited to bilateral laparoscopic adrenalectomy. Because of the benign, ACTH-independent nature of macronodular adrenal hyperplasia, select cases may be amenable to a laparoscopic approach as well.

Adrenocortical Carcinoma

ACC remains an enigma for endocrinologists, oncologists, and endocrine surgeons alike. It remains one of the most lethal solid tumors known to mankind, often striking individuals in the prime of life. Fortunately, its occurrence is a rarity. Half of ACCs are functional, with more than two thirds associated with excess cortisol production. Resection at an early stage coupled with adjuvant therapy (mitotane) and protocol-based therapy provide the best outlook for patients with this dismal disease.

Replacement Therapy After Surgery for Adrenocorticotropic Hormone–Independent Cushing's Syndrome

All patients undergoing surgery for CS require a standard perioperative steroid preparation. Successful surgery will ultimately render all patients hypocortisolemic, although there may occasionally be delays after TSS. In general, patients leave the hospital on supranormal replacement doses as directed by their clinical status. For patients who have undergone transsphenoidal adenomectomy or unilateral adrenalectomy, replacement doses of glucocorticoids are given and tapered over time until return of function of the HPA axis is documented. This is to be accomplished without the need of an ACTH stimulation test. The process of glucocorticoid tapering may take 2 to 24 months or longer to complete.

Patients undergoing bilateral total adrenalectomy need lifelong glucocorticoid and mineralocorticoid replacement after the perioperative steroid taper.

Medical Therapy for Cushing's Syndrome

Medical therapy has a clear role in the management of patients with endogenous hypercortisolism when definitive resection or radiotherapy is not an option. Preoperatively, it may also be used to optimize a patient's condition for a brief period of time before definitive surgical therapy. This is most common in the setting of ectopic ACTH syndrome and persistent or recurrent Cushing's disease.

Metyrapone inhibits 11β-hydroxylase and is given to lower cortisol concentrations before definitive therapy. Nausea and hypokalemia are the principal

side effects. Aminoglutethimide is more toxic than metyrapone and blocks enzymes earlier in steroidogenesis. It is often used in conjunction with metyrapone and causes nausea, marked lethargy, and skin rash. Ketoconazole, an antifungal agent, blocks a variety of steroidogenic cytochrome P450-dependent enzymes, lowering plasma cortisol levels. Daily doses of 400 to 1200 mg are required, and usage is often limited by the development of abnormal liver function tests. Fluconazole has similar activity. Mitotane, a derivative of DDT, is an adrenolytic agent that is taken up by normal and malignant adrenal tissue, resulting in adrenal necrosis and atrophy. Doses up to 10 to 20 g/day may be required, but such doses may be impossible to achieve because of nausea and other side effects, notably fatigue and skin rashes. Both glucocorticoid and mineralocorticoid replacement may be required.[2]

Etomidate, an IV anesthetic agent, is a member of the imidazole group that includes ketoconazole and fluconazole, agents with antifungal properties. Etomidate lowers plasma cortisol levels by a similar mechanism to that seen with ketoconazole. It can be used for patients unable to take oral ketoconazole or metyrapone or in conjunction with other forms of medical therapy.[19]

Cushing's Syndrome During Pregnancy

Because of the negative effect of cortisol excess on gonadotropins, pregnancy is uncommon in the setting of CS. CS in pregnancy is associated with increased fetal morbidity and mortality. The diagnosis can be challenging because of the profound effects of pregnancy on the HPA axis, normally leading to increased circulating cortisol and ACTH levels. The proportion of adrenal causes, however, in pregnancy is increased. Surgery, both pituitary and adrenal, can be carried out most safely during the second trimester. Medical therapy with metyrapone is also an option to bring the patient to full-term delivery before definitive surgical intervention.[20]

CONCLUSION

Surgery for CS is highly successful for pituitary-dependent CS and most ACTH-independent adrenal causes. Bilateral total adrenalectomy may also provide effective palliation from the ravages of hypercortisolism in patients with ectopic ACTH syndrome and for those who have failed transsphenoidal surgery. Unfortunately, to date, ACCs are rarely cured. Future successes in this area will likely depend on a better understanding of tumor biology, more effective adjuvant therapies, and earlier detection. Clearly, IPSS, advances in cross-sectional imaging, and developments in transsphenoidal and laparoscopic surgery have had the greatest impact on today's management of patients with this complex disorder.

PRACTICAL PEARLS

- Case finding in endogenous hypercortisolism requires a high index of clinical suspicion and usually requires multiple screening tests.
- The diagnosis of endogenous hypercortisolism can be made with confidence if the 24-hour urine cortisol level is greater than five times the upper limit of normal.
- Subtype evaluation requires plasma ACTH measurement followed by selective imaging.
- Seventy percent of patients with CS have pituitary Cushing's disease. Thus, all patients with either a normal or elevated plasma ACTH level should continue subtype evaluation with a dedicated pituitary MRI.
- Inferior petrosal sinus sampling is indicated when the MRI results are negative (>50% of patients with pituitary CS) and the clinical picture is compatible with Cushing's disease.
- Very high ACTH and urinary cortisol levels coupled with a short clinical course; hypokalemic metabolic alkalosis; and hyperpigmentation, especially in men suggests ectopic ACTH syndrome. After a negative MRI result, potential ectopic sites should be imaged with CT, MRI, scintigraphy, and PET.
- Ectopic sites of ACTH production (in decreasing order of frequency) include the chest (lungs, mediastinum), abdomen (pancreas, adrenal), and neck (medullary thyroid cancer).
- CT of the adrenal glands remains the best first-line imaging tool for ACTH-independent CS.
- Laparoscopic and posterior retroperitoneoscopic adrenalectomy are both excellent treatment modalities for primary benign, functioning, and nonfunctioning tumors; for failed transsphenoidal pituitary adenomectomies; and for most patients with ectopic ACTH syndrome.
- Larger tumors (>6 cm) and obviously malignant tumors are best managed with an open approach.
- Optimal management of patients with ACC requires complete surgical extirpation. The overall prognosis still remains poor and requires a better understanding of its unique tumor biology.
- Adjuvant treatment with mitotane should be considered for all patients with ACC. Patients with advanced disease should be offered protocol-based therapy.

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Chapter 15

Pheochromocytoma and Paraganglioma

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DEFINITION

Pheochromocytomas and paragangliomas, otherwise referred to as *extra-adrenal pheochromocytomas*, are rare neuroendocrine tumors that originate from neural crest cells of the autonomic nervous system.[1] They secrete catecholamines in variable amounts (e.g., those of the head and neck produce less than those located within the abdomen).[1] Sympathetic paraganglia are intimately associated with the adrenal medulla and organ of Zuckerkandl, and parasympathetic paraganglia are associated with the carotid bodies.[2] Neural crest tumors that arise from the adrenal medulla are referred to as *pheochromocytomas*, and those that occur extra-adrenally are called *paragangliomas*. In 2004, the World Health Organization (WHO) clarified the definition of pheochromocytomas as tumors that arise in the adrenal medulla and that are derived from chromaffin cells of neural crest origin.[3] Pheochromocytomas were first described in 1886 by Felix Fränkel.[4] Evidence suggests that the patient described, Ms. Minna Roll, had bilateral adrenal lesions and multiple endocrine neoplasia type 2 (MEN2). This is based on genetic analyses performed in 2007.[5]

The term *pheochromocytoma* was first coined in 1912 by Ludwig Pick. This was based on the dark color these tumors turned when exposed to chromaffin salts.[4] In 1926, Cesar Roux was the first to successfully remove a pheochromocytoma.[4] The term *paraganglioma* was first used by Drs. Alezais and Peyron of Marseilles in 1908.[4] Biochemically, only pheochromocytomas and paragangliomas of the organ of Zuckerkandl secrete epinephrine because the enzyme phenyl ethanolamine N-methyl transferase is only present in the

adrenal medulla and organ of Zuckerkandl. The organ of Zuckerkandl, also know as the para-aortic bodies, is located at the bifurcation of the aorta or origin of the inferior mesenteric artery. First described by Emil Zuckerkandl in 1901, it is the most common site for paragangliomas.[3]

Although generally described together, pheochromocytomas and paragangliomas should be kept distinct because they exhibit several differences. Pheochromocytomas tend to have a lower rate of malignancy (10%), an adrenergic phenotype, and a higher propensity to be associated with hereditary syndromes. Paragangliomas contain neurosecretory granules; however, only 1% to 3% have clinical evidence of oversecretion. In addition, paragangliomas are predominantly located in the abdomen (85%) and rarely (3%) in the head and neck. When found in the abdomen, 15% to 35% of paragangliomas are malignant.[6] When discovered in the head and neck region, they are likely to be carotid body tumors. These tumors are characterized clinically as painless masses that are laterally mobile but vertically fixed (Fontaine's sign). They tend to cause cranial nerve palsy via mass effect. Patients with pheochromocytomas and paragangliomas should always be managed surgically, if possible.[6]

EPIDEMIOLOGY

Both pheochromocytomas and paragangliomas are rare but may cause hypertension. The estimated prevalence of pheochromocytomas is as high as 0.05%.[7] However, the incidence of pheochromocytomas is less than 0.5% in patients with hypertensive symptoms and as high as 4% in patients with adrenal incidentalomas.[8] Pheochromocytoma was once called the *10% tumor*, because it was thought to be 10% familial, 10% malignant, 10% bilateral, and 10% extra-adrenal.[2] However, it has been recently reported that up to 30% of patients with pheochromocytoma and paraganglioma have a hereditary syndrome.[9] Paragangliomas alone have an estimated incidence of one in 30,000 individuals.[10] When both pheochromocytomas and paragangliomas are grouped together as catecholamine-producing tumors, the estimated incidence is two to eight cases per 1 million people.[11] Both pheochromocytomas and paragangliomas occur in equal frequency in men and women. It is uncommon for these tumors to develop in the pediatric population. If present in children, they are commonly multifocal and associated with a hereditary syndrome.

RISK FACTORS

Although it has been reported that pheochromocytomas and paragangliomas are more readily seen in smokers, it is difficult to unequivocally list tobacco as an etiologic agent. However, several known susceptibility genetic mutations have been identified. The more commonly known genes include von Hippel-Lindau

(VHL), rearranged during transfection (RET), MEN2, neurofibromatosis type 1 (NF1), and those encoding succinyl dehydrogenase (SDH).[9]

Genetics

Several familial syndromes are associated with the development of pheochromocytomas and paragangliomas.[9] VHL syndrome is an autosomal dominant disorder caused by a mutated tumor suppressor gene located on chromosome 3. The estimated prevalence is one in 35,000 individuals. The organs that may be affected include the brain, eye, ear, kidney, pancreas, prostate, and adrenal gland. Pheochromocytomas have been reported in 20% to 80% of these patients, and paragangliomas have been reported in 10%.[12] Typically, the adrenal lesions are bilateral and produce norepinephrine.

In MEN2, a syndrome associated with the RET proto-oncogene located on chromosome 10, approximately 50% of patients develop pheochromocytomas; paragangliomas are uncommon in people with this disorder. The estimated prevalence of this syndrome is also one in 35,000 individuals. The adrenal lesions are typically bilateral and tend to secrete epinephrine. Although extremely atypical, pheochromocytomas have been shown to occur in patients with MEN1, an autosomal disorder caused by mutations in the tumor suppressor gene located on chromosome 11. The prevalence of this disorder is one in 30,000 individuals.

NF1 is an autosomal dominant disorder caused by mutations in the tumor suppressor gene located on chromosome 17. The estimated prevalence is one in 3000 individuals. Both pheochromocytomas and paragangliomas occur in only 2% of these patients.

More recently, familial paraganglioma syndrome has been found to be associated with several mutations in the SDH gene.[13] Pathophysiologically, these mutations cause a chronic hypoxic signal in the mitochondrial II complex that leads to cellular proliferation and tumor growth.[10] The first germline mutation identified was in the SDH subunit D (SDHD) by Baysal and colleagues in 2000.[14] Additional mutations have been discovered in subunits B and C (SDHB and SDHC). When Neumann and colleagues[13] evaluated 271 patients with putative nonsyndromic pheochromocytomas and paragangliomas, 12 (4.4%) cases were attributed to SDHB and 11 (4.0%) were attributed to SDHD. The genes encoding SDHB and SDHD are both located on chromosome 1; SDHD is also located on chromosome 11. SDHB mutations are associated with thoracic or abdominal paragangliomas that are more likely to be malignant; pheochromocytomas are rare. SDHD mutations are generally associated with tumors located in the head and neck. SDHD mutations in the tumor suppressor gene on chromosome 11 also are associated with head and neck paragangliomas that are less likely to be malignant but more likely to be multifocal; pheochromocytomas are rare.

Interestingly, transmission of the SDH genes is autosomal dominant; however, SDHD has been noted to display maternal imprinting whereby transfer of the gene from the mother leads to a carrier state without pheonotypic expression.[15] In SDH-associated disease, if the adrenals are involved, the lesions tend to be bilateral. Other less common syndromes associated with pheochromocytomas and paragangliomas include Carney complex, tuberous sclerosis, Sturge-Weber, and ataxia-telangiectasia

CLINICAL PRESENTATION

Patients with pheochromocytoma and paraganglioma often present with hypertension that is of new onset, episodic, and persistent or refractory to standard pharmacologic agents. Additionally, more common signs and symptoms include headache, palpitations, and diaphoresis. Other findings may include anxiety, tremor, pallor, flushing, tachycardia, postural hypotension, visual disturbances, heat intolerance, fever, nausea, vomiting, abdominal pain, constipation, polyuria, hematuria (related to a paraganglioma of the bladder), polydypsia, hyperglycemia, and hypercalcemia.[16] Patients with pheochromocytomas may be asymptomatic even in the setting of extremely large tumors (50 g) because of their tendency for cystic degeneration (Figure 15-1). It is essential to note that malignant catecholamine-producing tumors have a clinical presentation identical to their benign counterparts. The most common metastatic sites are regional lymph nodes, bone, liver, and lung.[17] In the majority of cases, however, pheochromocytoma and paraganglioma are benign tumors. The malignancy rate is approximately 5% to 10% and 15% to 35%, respectively. According to the WHO, malignancy is defined by the presence of metastatic disease rather than by local invasion.[1] There is no single histologic feature, including capsular or vascular invasion or cytologic atypia, that solely identifies metastatic potential.[1] Other scoring systems have been used, including those developed by Linnoila and coworkers[18] in 1990, Thompson[19] in 2002, and Kimura and coworkers[20] in 2005; however, they have not been routinely implemented.

Pheochromocytomas may present as adrenal incidentalomas. Most that are serendipitously discovered in this way are smaller than 3 cm. The incidence of pheochromocytomas among patients who have adrenal incidentalomas is reported to be between 1.5% and 11%.[21] A recent multicenter study involving nearly 100 patients who had pheochromocytomas or paragangliomas reported that 40% of tumors were found incidentally.[22] In some cases, pheochromocytomas and paragangliomas are not associated with hypertension. One theory has included the desensitization of catecholamine receptors over time because of constant and chronic exposure that then leads to disruption of normal circadian variation in blood pressure.[23] In fact, the

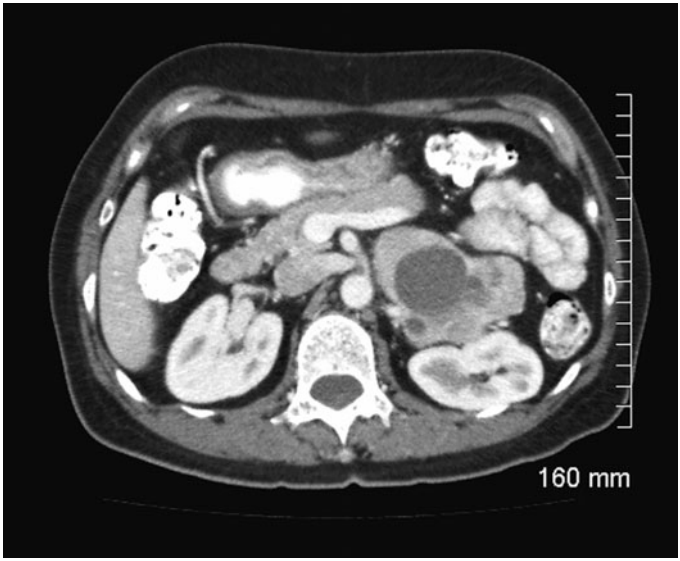

Figure 15-1. Computed tomography scan of a large left pheochromocytoma; note the areas of necrosis with cystic degeneration. (Courtesy of Darren P. Lum, MD.)

same authors have reported that up to 40% of patients with pheochromocytoma are asymptomatic and are considered "subclinical."[23]

DIAGNOSIS

Biochemical Tests

When a pheochromocytoma or paraganglioma is suspected, it is imperative that functional biochemical studies be performed before any radiologic imaging is done. The diagnosis of this entity is essential because if not identified, it could result in catastrophic consequences such as sudden death or stroke. Testing patients for excessive production of catecholamines should be the initial step in the differential diagnosis. Unfortunately, some of these tests, whether performed via blood or urine sampling, are plagued by false-positive results. Confounding factors include interfering substances and patient comorbidities that lead to inaccuracies. Specifically, levodopa, pseudoephedrine, amphetamines, reserpine, acetaminophen, ethanol, prochlorperazine,

tricyclic antidepressants, labetalol, and methylglucamine from iodine-containing contrast media should be avoided when doing an evaluation. Disorders such as acute myocardial infarction, acute stroke, severe congestive heart failure, acute clonidine withdrawal, and acute alcohol withdrawal may also cause falsely elevated catecholamine levels.[24]

A comprehensive multicenter cohort study involving 214 patients with and 644 patients without pheochromocytoma was performed.[25] The investigators compared the sensitivities and specificities of plasma-free metanephrines, plasma catecholamines, urinary fractionated metanephrines, urinary catecholamines, urinary total metanephrines, and vanillylmandelic acid. They reported that plasma-free metanephrine testing was the best initial test for patients being evaluated for pheochromocytoma. Sensitivities ranged from 97% to 99%, and specificities ranged from 82% to 96%. The false-negative plasma-free metanephrine rate was 1.4%, indicating that the probability of missing a pheochromocytoma with this test is extremely rare.[25]

In patients at low risk for pheochromocytoma or paraganglioma, others recommend urinary total catecholamines and metanephrines as the initial diagnostic test of choice, with plasma levels reserved for patients with a strong family history.[26] It is important to note that in general, whereas pheochromocytomas secrete epinephrine, paragangliomas primarily secrete norepinephrine. Phenylethanolamine N-methyltransferase, an enzyme primarily located in the adrenal gland, converts norepinephrine to epinephrine; therefore, patients with extra-adrenal paragangliomas tend to have higher levels of normetanephrine. Tumors associated with VHL produce mostly norepinephrine, and tumors associated with MEN2 produce both epinephrine and norepinephrine. In malignant disease, dopamine is often preferentially secreted because of alterations in catecholamine synthesis. Because pheochromocytomas and paragangliomas are neuroendocrine tumors, serum chromogranin A may also be used as a tumor marker.[27] It may be falsely elevated in patients with renal insufficiency, however. The sensitivity is 86%; and the specificity can be as high as 98% when combined with an elevated plasma catecholamine level in patients with normal renal function (patients with creatinine clearance at least 80 mL/min).[28]

Radiologic Studies

Computed tomography (CT), magnetic resonance imaging (MRI), and iodine-metaiodobenzylguanidine (MIBG) scintiscan are the most commonly used radiographic imaging modalities for the evaluation of pheochromocytomas and paragangliomas. CT is the anatomic imaging examination of choice in the evaluation of both pheochromocytomas and paragangliomas. The sensitivity of detecting pheochromocytomas measuring at least 0.5 cm in size is approximately 95% to 100%, and the sensitivity of identifying

extra-adrenal paragangliomas at least 1.0 cm in size is approximately 90%.[29] The specificity, however, is poor and may be as low as 50%.[30]

For pheochromocytomas, an adrenal protocol-based CT is recommended in which thin-sliced images are obtained before and after injection of intravenous (IV) contrast medium. For small pheochromocytomas that are typically homogenous in appearance, an unenhanced CT scan usually shows a soft tissue density of 40 to 50 Hounsfield units (HU) and uniform enhancement with contrast. Larger pheochromocytomas may undergo cystic degeneration, necrosis, or hemorrhage, causing an inhomogeneous appearance.[31] For paragangliomas, if no appreciative mass is identified intraabdominally near the inferior vena cava, abdominal aorta, organ of Zuckerkandl, or bladder, then a CT scan of the neck and chest should be obtained because paragangliomas may be located in the carotid body or mediastinum.[32] Because these paragangliomas are mainly derived from chromaffin cells, they have a soft tissue density of 40 to 50 HU.

Occasionally, CT scans may not be suitable for the anatomic assessment of pheochromocytomas and paragangliomas. For pregnant women, children, and patients who are allergic to contrast media, MRI may be more appropriate. Classically, MRI scans display increased signal intensity on T2-weighted images attributable to the vascular nature of pheochromocytomas and paragangliomas. However, in large tumors, MRI may depict low signal intensity on T2-weighted images if necrosis or hemorrhage is significant. For the detection of paragangliomas in comparison with pheochromocytomas, MRI has a higher sensitivity (90% to 100%) and a higher specificity (50% to 100%).[29] If biochemical studies suggest pheochromocytoma but CT does not localize the tumor, MRI should be used.

Another anatomic imaging study that may be used in select settings is ultrasonography. This entity can be initially applicable to paragangliomas of the head and neck such as carotid body tumors, which have characteristic findings of solid, well-defined, hypoechoic lesions with cephalad flow.[33]

In addition to anatomic imaging, functional imaging can be efficacious in the management of patients with pheochromocytoma and paraganglioma. The more conventional adjuncts include MIBG and fluorodeoxyglucose positron emission tomography (FDG-PET). MIBG should be used when CT or MRI do not identify the adrenal tumor. Additionally, it may be used for paragangliomas as well as for the assessment of recurrent or metastatic pheochromocytoma. MIBG is a norepinephrine analog. In the United States, iodine 131 (^{131}I) is the more commonly used isotope. For pheochromocytomas, the sensitivity of iodine 123 (^{123}I) is 83% to 100% and ^{131}I, 77% to 90%. For paragangliomas, the sensitivities are lower, and the specificity is 95% to 100%.[29] Implementing MIBG can be complicated. Patients need to ingest potassium iodide or potassium perchlorate to prevent thyroid uptake

that would otherwise obscure paragangliomas of the neck. Recent experiences at the National Institutes of Health suggest that fluorodopamine is an excellent agent to localize adrenal and extra-adrenal tumors, including metastatic lesions.[34] Compared with other amines, dopamine is a more specific substrate for the norepinephrine transporter. In some instances, patients with metastases who with negative MIBG results had positive PET results.[35]

In summary, CT scans should be used first for anatomic imaging for most pheochromocytomas and paragangliomas. If CT is unremarkable, MRI should be used. If available, the functional imaging modality of choice should be FDA-PET. If this test is not available, MIBG should be obtained for paragangliomas and for recurrent or metastatic disease.

MANAGEMENT

Although several options exist for the treatment of patients with pheochromocytomas and paragangliomas, the mainstay of treatment is surgical extirpation. Under no circumstances should a patient determined preoperatively to harbor a pheochromocytoma or paraganglioma, undergo a fine-needle aspiration biopsy (FNA). These tumors are highly vascular; furthermore, using FNA may precipitate a hypertensive crisis, hemorrhagic event, or death.[36]

The management of patients with pheochromocytomas and paragangliomas involves meticulous preoperative, intraoperative, and postoperative care. Patients should be started on α-blockade therapy preoperatively, preferably with phenoxybenzamine, an adrenergic inhibitor. Side effects include lightheadedness and sexual dysfunction. Phentolamine, another adrenergic inhibitor, can also be initiated in lieu of phenoxybenzamine. α-Blockade therapy should be implemented at least 2 weeks before operative intervention. If the patient develops tachycardia, β-blockade should also be added. Medical therapy, including α-blockade, should be continued until the morning of surgery.

Intraoperatively, it is essential that the patient has optimal IV access and is monitored hemodynamically because fluctuations in blood pressure are to be expected. Communication with the anesthesiologist is critical, especially when the tumor is manipulated. Venous control of the adrenal vein is important because it limits hemodynamic lability. Postoperatively, patients should be in a monitored setting because they often require norepinephrine to maintain adequate blood pressure.

For pheochromocytomas, the preferred method of resection consists of a transperitoneal laparoscopic approach unless a concern for malignancy or metastatic disease is evident preoperatively. The first laparoscopic adrenalectomy for a patient with pheochromocytoma was reported in 1992 by Gagner

and colleagues.[37] Studies, including those performed by Jaroszewski and colleagues,[38] support the laparoscopic approach, citing advantages such as smaller incisions, less pain, decreased length of hospital stay, and faster recovery. Although some surgeons have used laparoscopy in patients with paragangliomas, consideration for an open approach should be entertained because of the higher rate of malignancy. A recent multicenter study involving 74 patients with pheochromocytoma who underwent laparoscopy reported success in more than 90% of patients.[22] This same group of investigators offered laparoscopy to two of nine patients who had paragangliomas; one patient required conversion to open adrenalectomy because of bleeding, and another patient died postoperatively from unrecognized hemorrhage.[22]

Laparoscopic adrenalectomy is performed by first placing the patient in a lateral decubitus position followed by establishing a pneumoperitoneum placing four subcostal trochars. For right adrenal tumors, the liver is retracted medially to allow exposure. It is important that a plane between the inferior vena cava and medial margin of the gland be developed to facilitate exposure of the adrenal vein. For left-sided tumors, the spleen and pancreas are mobilized to allow exposure. It is essential that Gerota's fascia be incised medial to the superior pole of the kidney to expedite visualization of the adrenal vein.

Another minimally invasive approach is the retroperitoneoscopic approach. The patient is placed in a prone position. Walz and colleagues[39] reported excellent results with posterior retroperitoneoscopic adrenalectomy in 520 patients who had undergone 560 adrenalectomies. Of these, 119 (23%) had a preoperative diagnosis of pheochromocytoma. Four of these patients had malignant pheochromocytomas, and 13 had bilateral disease. The authors concluded that this procedure could be safely and easily performed.

Patients with hereditary pheochromocytomas can be challenging to manage. They frequently have bilateral tumors, but bilateral total adrenalectomy renders the patient Addisonian and on lifelong steroid replacement. Data from previous studies, including those from de Graaf et al.[40] in 1999, demonstrate significant morbidity and mortality from adrenal insufficiency after bilateral total adrenalectomy, although others have reported minimal morbidity associated with bilateral adrenalectomy. de Graaf et al.[40] reported that nine of 28 (32%) of their patients experienced Addisonian crises, including two patients (7%) who died. Therefore, some investigators have advocated cortical-sparing adrenalectomy.[41]

A recent study from MD Anderson Cancer Center reported their experience with the management of patients with hereditary pheochromocytomas and paragangliomas.[41] Among 59 patients, 56 (95%) had pheochromocytomas, and the remaining three (5%) had paragangliomas. Sixty-five percent of the patients who underwent cortical-sparing adrenalectomy did not require chronic steroid replacement therapy. The risk of recurrent disease in the

remnant gland was only 10%. The study depicted that for patients with bilateral disease, an open approach should be performed, with a cortical-sparing procedure performed on one gland and complete resection of the other gland.

It is widely accepted that pheochromocytomas smaller than 6 cm can be safely removed with a minimally invasive (laparoscopic transperitoneal) approach. However, laparoscopic adrenalectomy for larger tumors is controversial. Concern about laparoscopic adrenalectomy for larger lesions includes the fact that there is a higher rate of malignancy, there may be greater intraoperative hemodynamic instability, and the procedure is technically challenging. Analysis of a comprehensive multicenter study revealed that the operation can be safely performed; however, when patients who had tumors smaller than 4 cm were compared with patients with tumors larger than 6 cm, operative time, blood loss, and length of stay were all statistically significantly increased in the group with pheochromocytomas larger than 6 cm.[42]

Recently, investigators from France reported their experience with laparoscopic adrenalectomy in 17 patients with pheochromocytomas 6 cm or larger. They concluded that laparoscopic adrenalectomy for large pheochromocytomas is safe and effective as long as local invasion is not present.[43] However, four (23%) of these patients experienced complications, including capsular disruption and bleeding, and the average length of stay was 5.5 days.

Another study involving 90 malignant and 60 benign pheochromocytomas found that the mean tumor size for a malignancy was 7.6 cm; it was 5.3 cm for benign lesions.[44] The authors recommended that irrespective of size, conversion to an open technique should be done if there is evidence of local invasion, if adhesions are present or it is a difficult dissection, or if the surgeon is inexperienced.[44] In summary, although laparoscopic adrenalectomy can be performed for large tumors in select cases, it is often associated with greater morbidity and therefore cannot be routinely recommended.

Patients with pheochromocytomas or paragangliomas may also present with advanced disease. In these situations, surgical resection should be performed if feasible. Radiotherapy may be administered for unresectable disease, especially for bony metastases. Other methods of therapy include radiofrequency ablation for small hepatic lesions and hepatic artery embolization for large hepatic lesions. In approximately one third of patients, ^{131}I MIBG induced partial responses.[45] Some investigators have used octreotide analogs as another modality of treatment but have not consistently demonstrated its efficacy.[46] For patients with disseminated disease who are unresponsive to MIBG or octreotide analogs, cytotoxic chemotherapy with cyclophosphamide, vincristine, and dacarbazine may be used, with response rates in approximately two thirds of patients.[47] A more recent study

using this regimen demonstrated a complete response rate of 11% and a partial response rate of 44%.[48]

Although the mainstay of treatment for patients with pheochromocytomas and paragangliomas is primarily surgical resection, it is very important that genetic counseling be offered to any patient suspected of having a hereditary component. However, as stated at the First International Symposium on Pheochromocytoma and Paraganglioma in 2005, it is impractical to test every family member who has the disease.[49] Any patient who has a positive family history or is younger than 50 years of age should be tested for the VHL, RET, SDHB, and SDHD genes. Any patient with multiple tumors should be evaluated for SDHB, SDHD, and VHL. In summary, it is essential that a systematic and organized approach be implemented in the management of patients with pheochromocytomas and paragangliomas (Figure 15-2).

SURVEILLANCE AND FOLLOW-UP

Because both pheochromocytomas and paragangliomas can recur, patients should undergo lifelong follow-up, especially in the setting of inherited disease.[50] All patients should have biochemical testing, at a minimum, 1 month after surgery. If testing results are still abnormal, an MIBG scan should be obtained to evaluate for persistent or metastatic disease. If hypertension persists after surgery, concern should be raised for the presence of residual tumor.[24]

PROGNOSIS

Recurrence rates for pheochromocytomas and paragangliomas are difficult to predict. In one series[51] of 176 patients with a malignancy and at risk for recurrence, 29 (16%) had recurrent disease at a mean follow-up of 9 years. The authors identified several important factors associated with recurrence. Recurrence was 3.4-fold higher in patients with familial disease compared with patients with sporadic lesions. Patients who had right-sided tumors had a 3.1-fold risk of recurrence compared with those with left-sided lesions, perhaps because of initial inadequate resection. Patients with extra-adrenal tumors had an 11.2-fold increased risk of recurrence compared with patients with adrenal tumors.[51]

With respect to overall survival, patients with malignant pheochromocytomas have a less than 50% survival at 5-year follow-up.[52] However, the prognosis for these patients can be highly variable. Interestingly, 50% of patients have an indolent course with a life expectancy of more than 20 years, but the other 50% experience a rapid progression of disease within 1 to 3 years of the original diagnosis.

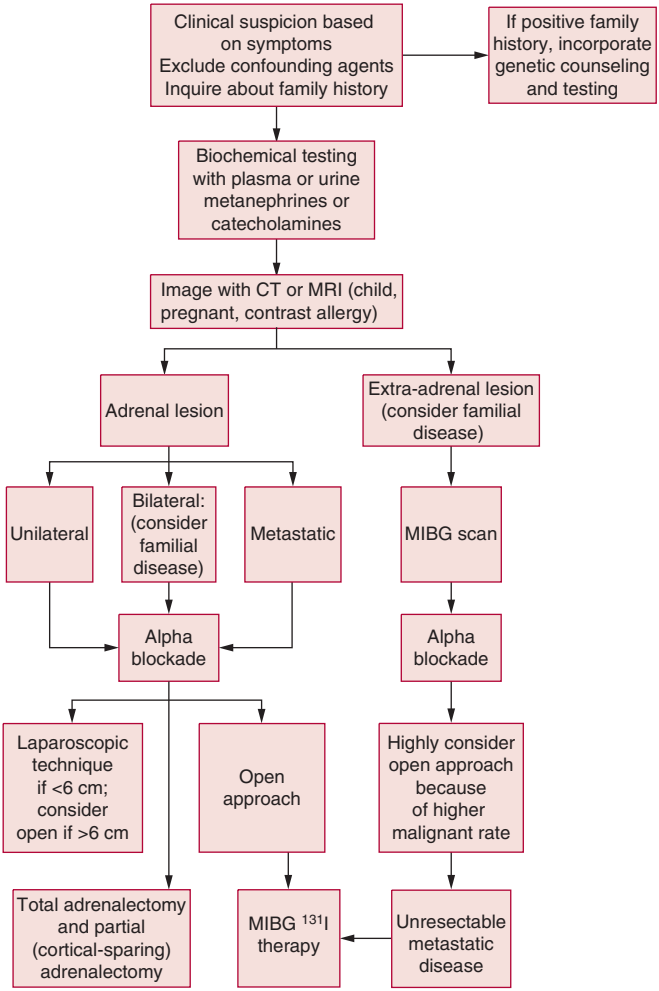

Figure 15-2. Algorithm for the management of pheochromocytoma and paraganglioma. CT = computed tomography; ^{131}I = iodine 131; MIBG = metaiodobenzylguanidine; MRI = magnetic resonance imaging.

SPECIAL CIRCUMSTANCES

Pheochromocytomas and paragangliomas in pregnancy are rare, with an estimated incidence of only 0.007%.[53] The diagnosis should be entertained in multigravid women who have severe hypertension, persistent glycosuria, and no history of preeclampsia. Patients should be diagnosed with biochemical testing. MRI is the imaging of choice because CT exposes the fetus to radiation. α-Blockade with phenoxybenzamine is safe. Patients should undergo surgical resection in the second trimester if possible, although successful resections before 24 weeks gestation have been reported.[54] Several options regarding approaches to resection and delivery are available and must be individualized. The patient can deliver vaginally followed by elective laparoscopic adrenalectomy 6 weeks postpartum[55] or can undergo simultaneous cesarean section and tumor resection.[56]

Pheochromocytomas and paragangliomas in children are rare. However, they represent the most common pediatric endocrine tumor.[57] The incidence is 1% in pediatric patients with hypertension.[58] Approximately 40% of pheochromocytomas and paragangliomas in children are hereditary.[59] The localization study of choice is MRI, with some advocating concomitant MIBG to confirm the diagnosis and evaluate for multiple paraganglioma syndrome.[60] α-Blockade with phenoxybenzamine is the preferred pharmacologic agent; if this is not sufficient, calcium channel blockers can be used.[61] Similar to the case in adults, laparoscopic adrenalectomy is the preferred method of choice for surgical resection.[62,63]

PRACTICAL PEARLS

- Pheochromocytomas are adrenal tumors derived from chromaffin tissue; similar tumors located extra-adrenally are paragangliomas.
- The most common site for a paraganglioma is the organ of Zuckerkandl.
- Pheochromocytoma should no longer be hailed as the "10% tumor" because 30% of them are associated with a hereditary syndrome.
- In addition to VHL, MEN1 and MEN2, and NF1, SDH mutations should be considered as genetic causes of pheochromocytoma and paraganglioma.

(*Continued*)

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Chapter 16

Adrenocortical Carcinoma

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DEFINITION AND EPIDEMIOLOGY

Adrenocortical carcinoma (ACC) is a rare malignant endocrine neoplasm with an estimated incidence of 0.5 to 2 cases per 1 million people annually in the United States,[1,2] accounting for 0.02% of all cancers reported annually.[1] The prognosis for most patients diagnosed with ACC is disappointingly poor because of delays in diagnosis and the absence of effective systemic therapy. Approximately 50% of affected patients do not survive beyond 2 years after diagnosis, and the 5-year mortality rate approaches 80%.[3] ACC has a bimodal age distribution with an increased incidence among children younger than 5 years of age and in individuals in their fourth and fifth decades of life. A slightly higher incidence rate is reported for women than for men.[4] Approximately 40% of ACCs produce clinically significant excess amounts of steroid hormones, resulting in characteristic signs and symptoms;[5] female patients are more likely to have an associated clinical endocrine syndrome. Surgery remains the only effective curative treatment for ACC. In a 1996 study of risk factors, cigarette smoking and the use of oral contraceptives were found to be associated with the development of ACC.[6] An association has also been described between ACC and congenital adrenal hyperplasia.[7]

MOLECULAR PATHOGENESIS

The etiology of ACC is unknown. A study of adrenocortical tumor clonality reported that whereas most benign adrenocortical lesions were polyclonal, ACCs were monoclonal, thus suggesting that ACC develops through the uncontrolled growth of a single cell.[8]

ACCs may be sporadic or occur as part of a hereditary tumor syndrome. Investigations of genetic alterations present in adrenocortical tumors have revealed the involvement of multiple chromosomal loci that correlate with regions that are abnormal in familial cancer syndromes. Such loci include those associated with Li-Fraumeni syndrome (LFS; *p53* gene on17p13), multiple endocrine neoplasia type I (MEN1; *MEN1* gene on 11q13), Beckwith-Wiedemann syndrome (11p15.5, correlated with the overproduction of insulin-like growth factor [IGF] II), and the Carney complex (loss of heterozygosity on 2p16).[9]

Although a multistep tumor progression model has been suggested in the etiology of sporadic ACC, proof of a hyperplasia-to-adenoma-to-carcinoma sequence is lacking.[10,11] Insights into the pathogenesis of sporadic ACC have been gained from the study of familial cancer syndromes that include ACC. For instance, the most frequently inherited p53 mutations associated with LFS are also found in sporadic cases of ACC.[12] One of the most common p53 point mutants, Arg 175 to His, fails to bind DNA and results in complete loss of p53 transcriptional activity. Although this mutation presents with a classic LFS cancer spectrum, including ACC, it also accounts for 6% of the missense mutations identified in all human cancers.[13] In Brazil, where the rate of pediatric ACC is 10 to 15 times greater than the overall worldwide incidence, the majority of patients have the same germline point mutation of p53 encoding an Arg 337 to His amino acid substitution in exon 10.[14] This mutation results in ACC development without the other associated tumor types seen in LFS. A pH-dependent destabilization of the mutant p53 tetramer in this R337H polymorphism allows for a adrenocortical-specific tumor formation.[15]

Sporadic ACCs, similar to hereditary ACCs associated with Beckwith-Wiedemann syndrome, have been found to overexpress the IGF-II gene. Several studies have identified a greater than 100-fold higher expression of IGF-II in 60% to 90% of sporadic ACCs compared with normal adrenal tissue and adrenal cortical adenomas.[16,17] Increased IGF-II is thought to play a role in the etiology of ACC but is most likely in conjunction with concominant changes in expression of other genes such as 11p15LOH.[18,19] Squamous cell carcinoma–related oncogene (SCCRO) is a novel gene involved in the hedgehog-signaling pathway, which is important in the development of the adrenal cortex. SCCRO is an "onco-developmental gene" important in both normal cellular function in the regulated state and in carcinogenesis in the dysregulated state; it may play a role in the development of adrenal cortical carcinoma.[20]

CLINICAL PRESENTATION

Approximatley 60% of ACCs in adults are hormonally functioning in that they produce measurable adrenal hormone excess; 40% of patients with ACC

TABLE 16-1. Endocrine Syndromes in Patients with Functioning Adrenocortical Carcinoma

Syndrome	*Frequency (%)*
Combined hormone excess	35
Hypercortisolism (CS)	30–40
Virilization (precocious puberty in children)	20–30
Feminization	10
Primary hyperaldosteronism (Conn's syndrome)	3–10
Other	<5
Adrenogenital syndrome	
Adrenal insufficiency (from primary adrenal lymphoma)	
Catecholamine excess (coexisting pheochromocytoma)	

CS = Cushing's syndrome.

present with symptoms of hormonal excess, and in an additional 20% of patients, the hormone excess is subclinical and detected only on biochemical evaluation .The most common excess hormones identified are cortisol, aldosterone, and sex steroids; each is associated with a well-defined clinical syndrome (Table 16-1). Most adrenal tumors that secrete excess amounts of multiple steroid hormones are malignant, so this may be the first clue to a diagnosis of ACC.

Cushing's syndrome (CS) is the most common clinical hormone excess syndrome associated with ACC (present in 30% to 40% of cases). It is caused by excess production of cortisol, and in ACC patients, it is often seen in combination with virilization caused by concomitant androgen hypersecretion. CS is characterized by truncal obesity; a rounded face (moon facies); violaceous striae on the abdominal wall; muscle weakness; and thin, fragile skin. Patients may have any combination of fatigue, proximal muscle weakness, osteoporosis, hypertension, and glucose intolerance. The rapid onset of CS with virilizing features is characterisitic of ACC.

Excess androgen production often goes unoticed in men; however, in women, it produces signs that may include hirsutism, a deepened voice, menstrual irregularity, male pattern baldness, and clitoromegaly. ACC-associated virilization is characteristically more pronounced than that associated with functioning adrenocortical adenomas; the severity of virilization in malignant adrenal tumors is correlated with a characteristically relatively high rate of cosecretion of 17-ketosteroids and dehydroepiandrosterone (DHEA).[21]

Excess production of estrogen is rare; when it occurs in women, it may result in menstrual irregularity or breast tenderness. Estrogen excess in men may present as feminization, with associated impotence, decreased libido, testicular atrophy, and gynecomastia.[22] Production of aldosterone by ACC is relatively uncommon, occurring as an isolated hormone elevation in only approximately 3% of patients and in up to 11% as part of a mixed hormone presentation. When present, aldosterone excess is usually associated with the typical findings of hypertension and hypokalemia (which may be profound).[23] Of note, these same symptoms may be caused by severe CS in the absence of excess aldosterone production; in such patients, the overwhelming excess levels of cortisol may stimulate mineralcorticoid receptors.[24] In children, ACCs are most commonly functioning tumors (90% of cases); most pediatric ACCs produce androgens, resulting in precocious puberty and virilization.

Patients with nonfunctioning ACC typically present with symptoms related to their large retroperitoneal mass, including abdominal pain, weight loss, nausea and vomiting, or early satiety, and they may have a palpable abdominal mass. Occasionally, a nonfunctioning ACC is discovered incidentally during adominal or thoracic imaging. Unfortunately, patients with nonfunctioning ACCs in particular may not present until they develop signs or symptoms of advanced or metastatic disease (e.g., severe fatigue, jaundice, bone pain, pulmonary embolism). At the time of initial presentation, 70% of cases have extra-adrenal spread, mostly to the lung (45% to 53% of cases), liver (42% to 46% of cases), and lymph nodes (18% to 40% of cases).[1,25] In a series of 160 consecutive operative patients evaluated for ACC by Lee et al., 142 (89%) patients had locoregional disease and 18 (11%) patients had distant disease at the time of presentation. Locoregional disease may include involvement of the ipsilateral kidney, retroperitoneal or peritoneal spaces, regional lymph nodes, diaphragm, inferior vena cava (IVC), or liver (on the right) or the pancreas, spleen, or colon (on the left).[26]

DIAGNOSTIC EVALUATION

The diagnostic evaluation of a patient with known or suspected ACC should always include a biochemical endocrine analysis and radiographic imaging. Endocrine evaluation is performed to identify or confirm excess hormone production (Table 16-2). Confirmation of excess hormone production is used as a guide to preoperative preparation (e.g., partial control of the effects of cortisol or aldosterone overproduction before laparotomy is done may be clinically very helpful in reducing the operative risk). Hormone levels, if documented as elevated preoperatively, can also be used as a "tumor marker" to monitor outcome after surgery, evaluate response to systemic therapy, assist in the interpretation of postoperative imaging studies, and guide interval follow-up.

TABLE 16-2. Biochemical Evaluation of Known or Suspected Adrenocortical Carcinoma

To Exclude Pheochromocytoma	
Pheochromocytoma	Fractionated plasma-free metanephrines or 24-hour urinary VMA, fractionated catecholamines, and fractionated metanephrines
To Assist in Preoperative Management and Follow-up Evaluation	
Cushing's syndrome	1-mg overnight DST 8 AM serum cortisol with paired ACTH 24-hour urinary cortisol
Hyperaldosteronism	Serum potassium Serum aldosterone Serum renin (calculate aldosterone:renin ratio)
Virilization or feminization	Serum androstenedione Serum testosterone Serum DHEAS Plasma 17-β-estradiol (men and postmenopausal women)

ACTH = adrenocorticotrophic hormone; DHEA-S: dihydroepiandrosterone sulfate; DST = dexamethasone suppression test; VMA = vanillylmandelic acid.

Listed in Table 16-2 and described below are options for testing. In patients presenting with an adrenal mass for which ACC (as well as pheochromocytoma) is in the differential diagnosis, we routinely perform biochemical evaluation of the major potential associated syndromes (pheochromocytoma, CS, virilization or feminization, and hyperaldosteronism). The recommendations included here assume that the patient is considered at relatively elevated risk for ACC based on the size of the adrenal tumor (generally at least 4 cm), its imaging characteristics (irregular, inhomogeneous, or locally invasive), or the presence of suggestive signs or symptoms (pain, clinical evidence of steroid hormone excess).

Every patient with a newly diagnosed adrenal mass should be assessed for excess cathecholamine production to rule out pheochromocytoma. Traditionally, this has been accomplished by measurement of fractionated metanephrines, fractionated catecholamines, and urine vanillylmandelic acid in a 24-hour urinary specimen. Alternatively (and increasingly commonly),

fractionated plasma-free metanephrines may be substituted for the timed urine collection as a screening test. In comparing the diagnostic efficacy of both tests, Sawka et al.[27] found that urinary tests yielded fewer false-positive results. However, the plasma test is somewhat more sensitive as well as somewhat more convenient for the patient than a timed urine collection; plasma screening may also be preferred in patients at risk for an inherited endocrine syndrome. At our institution, we routinely screen for pheochromocytoma by measurement of fractionated plasma-free metanephrines in patients with adrenal masses suspicious for ACC.

Cortisol is the hormone most frequently overexpressed by ACC, either alone or in combination with sex steroids or aldosterone. In patients without signs or symptoms of cortisol excess, an overnight 1-mg dexamethasone suppression test (DST) is a sensitive way to exclude the presence of cortisol overproduction. This test involves the administration of 1 mg of dexamethasone orally at 10 PM and the measurement of a plasma cortisol level the following morning at 8 AM. A normal response is a suppression of the morning cortisol level to 3 μg/dL or less. Failure of dexamethasone to suppress the plasma cortisol level below 3 g/dL suggests that the patient may have autonomous cortisol production. Because false-positive results with the 1-mg overnight DST are relatively common, patients with an elevated cortisol level after overnight testing should undergo confirmatory testing with the combination of paired 8 AM serum cortisol and adrenocorticotropic hormone (ACTH) levels together with a 24-hour urinary-free cortisol level.

Timed urine collection for cortisol determination should also be obtained in patients with obvious signs or symptoms of cortisol excess at presentation; screening via overnight DST is unnecessary in such patients. In equivocal circumstances, a formal 2-day low-dose DST (0.5 mg of dexamethasone every 6 hours for 2 days with pre- and post-DST 24-hour urinary-free cortisol determination) may be used to confirm the presence of subtle overproduction of cortisol by an adrenal tumor. However, in our experience, this test is rarely necessary in the diagnosis, preoperative preparation, or postoperative follow-up of patients with known or suspected ACC.

Evaluation for androgen and estrogen excess should include serum DHEA sulfate, androstenedione, testosterone, and 17-β-estradiol. Evaluation for hyperaldosteronism includes measurement of serum potassium (to identify hypokalemia) and serum level of aldosterone and renin activity (so that an aldosterone:renin ratio can be calculated).

Imaging

Computed tomography (CT) is the initial imaging modality of choice for the diagnosis and characterization of most adrenal tumors, including those possibly representing ACC (Table 16-3). Most ACCs are at least 5 cm in diameter,[28]

TABLE 16-3. Radiographic Characteristics of Adrenocortical Adenomas versus Carcinomas

	Adenoma	*Carcinoma*
CT scan	<10 HU (noncontrast) or <30 HU(contrast)	18 HU (noncontrast) or >30 HU (contrast)
	50% washout within 15 min of contrast injection	Greater contrast retention
	Small	Large
	Well-defined, homogenous	Ill-defined, inhomogeneous
		Calcification
		Necrosis
		Hemorrhage
MRI	Adrenal:liver ratio: <1.4*	Adrenal:liver ratio: 1.2–2.8*
PET	No uptake	High uptake

*Adrenal:liver ratio based on the differential resonance frequencies of protons in water and triglyceride molecules.

CT = computed tomography; HU = Hounsfield units; MRI = magnetic resonance imaging; PET: positron emission tomography.

so size is an important criterion when evaluating an adrenal cortical lesion with CT imaging. Only 2% of adrenal lesions 4 cm or smaller are ACCs, 6% of lesions 4.1 to 6.0 cm are ACCs, and 25% of lesions larger than 6 cm are ACCs. It is important to recognize that CT may underestimate the true size of a tumor (as measured from the surgical specimen) by up to 20%.[29] In a review by Barnett et al.,[29] the mean radiographic size estimate for ACCs was 9.5 cm (1.7 to 30 cm), but the mean pathologic measurement of the resected tumors was 11.7 cm (3.0 to 30 cm). This difference was significant ($P = 0.001$).

Using a cutoff of more than 30 Hounsfield units (HU), contrast-enhanced CT has been reported to have both a high sensitivity and a high positive predictive value in identifying malignant adrenal tumors.[30] The use of intravenous contrast material may also be helpful in characterizing and staging ACCs. On contrast-enhanced images, ACCs typically show peripheral enhancement of the mass with a central non-enhanced area of necrosis, giving the tumor a heterogenous appearance. Additionally, the measurement of contrast washout may also be helpful in distinguishing benign adrenocortical adenomas from ACCs; malignant cortical tumors characteristically demonstrate a slower washout.

ACCs are often irregular with poorly defined margins. Calcifications or cystic degeneration are seen in about 30% of these tumors. CT also provides essential staging information in allowing detection of metastatic disease in the regional lymph nodes, liver, and lungs. Finally, CT assists in surgical planning. Imaging occasionally demonstrates invasion of the upper pole of the kidney or the IVC; associated adjacent nodal metastasis are also occasionally identified.

Magnetic resonance imaging (MRI) is also an excellent alternative imaging modality for the characterization of adrenal tumors, including ACCs. On T1-weighted images, ACCs are typically hypointense relative to the liver, but on T2-weighted images, ACCs are hyperintense relative to the liver. However, it is important to recognize that ACCs may appear heterogeneous on both T1- and T2-weighted images owing to internal hemorrhage and necrosis, and blood products in areas of hemorrhage may cause portions of an ACC to appear bright on T1-weighted images. One advantage of MRI is its ability to demonstrate flow within major blood vessels, which may allow visualization of invasion of an ACC into the renal vein or IVC. Of note, right-sided ACCs in particular have a propensity to form venous tumor emboli, and vascular invasion and tumor thrombus can be seen with flow-sensitive MRI sequences.[31] Enhancement after MRI contrast agent administration is usually most pronounced around the periphery of ACCs in non-necrotic areas, and contrast washout is often prolonged.

[^{18}F]fluorodeoxyglucose (FDG) positron emission tomography (PET) is an important imaging modality in the evaluation of many different types of malignant processes. FDG-PET exploits the characteristically high glucose consumption of many tumor cells and can be a sensitive imaging modality in the identification of ACC recurrence and metastasis. However, FDG-PET has some limitations, including the fact that infections and inflammatory conditions (including postoperative inflammation) can result in prominent focal FDG uptake, potentially leading to false-positive findings on PET imaging. Nevertheless, FDG-PET, particularly when combined with non-contrast CT imaging (PET-CT), can be extremely useful in the detection of recurrence or metastases in patients with ACC. In particular, PET-CT can be helpful in excluding distant metastatic disease in patients with recurrent ACC being considered for surgery.

Size

As mentioned previously, perhaps the single most important predictor of malignancy in localized, nonmetastatic adrenocortical tumors is size. Most ACCs are more than 6 cm in diameter at the time of diagnosis,[32] but adrenal masses smaller than 4 cm in diameter are generally benign. These data have been incorporated into the National Institutes of Health's consensus

criteria for evaluation of incidental adrenal masses, which include a recommendation that any adrenal mass larger than 6 cm in diameter be resected, regardless of its functional status or imaging characteristics.[33] A review of the literature over a 30-year period found that 9% of reported ACCs were smaller than 5 cm in diameter at the time of diagnosis.[34] As a result, many surgeons have chosen to resect all tumors larger than 4 to 5 cm in size in patients who are good surgical candidates. Smaller lesions that have imaging characteristics suspicious for primary ACC (irregular borders, heterogenous enhancement) should also be resected, preferably by an open approach (as discussed below).

Histopathology

Characteristics that suggest a diagnosis of ACC include large tumor size with irregular margins, invasion of surrounding structures, and the presence of distant metastases; however, these are relatively nonspecific characteristics. ACC can be a difficult histologic diagnosis to confirm, so an experienced endocrine pathologist should review equivocal cases. On cross-section, ACCs are characteristically yellow and demonstrate hemorrhage, cyst formation, and necrosis. Histologically, ACCs are variable in appearance, ranging from mild degrees of atypia to anaplasia with giant cells. Trabeculations; nesting; and alveolar, solid, diffuse, or mixed features are common. ACCs usually consist of lipid-depleted cells with a compact eosinophilic cytoplasm; however, some ACCs contain an abundance of lipid-rich, pale-staining cells. Occasionally, a coarse, granular cytoplasmic pigment is seen. Nuclear pleomorphism and hyperchromasia may be present. On immunohistochemistry, ACCs usually stain positive for vimentin and negative for epithelial membrane antigen, cytokeratin, and blood group antigen. It is important to recognize that poorly differentiated ACC in particular can still represent a challenging diagnosis and may be confused with renal cell carcinoma, melanoma, small cell lung cancer, or hepatocellular carcinoma. This serves to emphasize the importance of a careful history, physical examination, and preoperative hormone evaluation in such patients.

In 1984, Weiss[35] proposed a histopathologic classification system for adrenocortical tumors based on his review of 43 patients with adrenocortical neoplasms, including 25 patients with benign tumors and 18 with ACC. The commonly applied Weiss criteria include nine features that can be helpful in distinguishing benign from malignant adrenocortical tumors and in grading ACC (Table 16-4). In Weiss' series, there was no recurrence or metastasis of any tumor exhibiting two or fewer criteria. All but one of the tumors exhibiting four or more criteria recurred or metastasized. Mitotic activity, particularly atypical mitoses, and venous invasion correlated best

TABLE 16-4. Weiss Criteria for Classification of Adrenocortical Tumors*

Criteria
Nuclear grade (III or IV)
Number of mitoses (>5/50 hpf)
Presence of atypical mitoses
Percentage of clear cells (≤25% tumor)
Diffuse architecture
Microscopic necrosis
Venous invasion
Sinusoidal invasion
Capsular invasion

*≥3 of these criteria is consistent with ACC; <3 suggests benign lesion.
hpf = high-power fields.
Data from Weiss LM. Comparative histologic study of 43 metastasizing and nonmetastasizing adrenocortical tumors. *Am J Surg Pathol* 1984;8:163-169.

with metastasizing or recurring tumors. Weiss subsequently used these same nine criteria (plus the weight and diameter of the tumor) to evaluate survival among 42 patients with ACC with the goal of distinguishing low- versus high-grade ACC.[36] Only one variable, mitotic rate, had a strong statistical correlation with patient outcome. Whereas 21 patients with carcinomas with more than 20 mitoses per 50 high power fields (hpf) had a median survival of 14 months, the 21 patients with carcinomas with 20 or fewer mitoses had a median survival of 58 months ($P < 0.02$). Based on these data, Weiss proposed that tumors with more than 20 mitoses be designated as high grade and those with 20 or fewer mitoses be designated as low grade. Although Weiss' histopathologic criteria are commonly used for evaluation of adrenal cortical neoplasms, this grading system (although potentially clinically important) has not been widely adopted.

STAGING AND PROGNOSIS

In 1958, Macfarlane[37] proposed a staging system based on tumor size (≤5 cm or >5 cm), the presence of local invasion, and the involvement of regional lymph nodes. Sullivan and colleagues[38] later modified this system. Further modifications have been proposed by Icard and coworkers[39] and Lee and coworkers[40] (Table 16-5). The most significant modification of the Lee staging system is the classification of all patients with either invasion of adjacent organs or nodal metastasis but without distant metastasis as stage III and the inclusion

TABLE 16-5. Staging Systems for Adrenocortical Cancer

	Macfarlane[37]	*Sullivan et al.*[38]	*Icard et al.*[39]	*Lee et al.*[40]
I	T1 (≤5 cm), N0, M0	T1 (≤5 cm), N0, M0	T1 (≤5 cm), N0, M0	T1 (≤5 cm), N0, M0
II	T2 (>5 cm), N0, M0	T2 (>5 cm), N0, M0	T2 (>5 cm), N0, M0	T2 (>5 cm), N0, M0
III	T3 (local invasion without involvement of adjacent organs) or mobile positive lymph nodes, M0	T3 (local invasion), N0, M0 or T1–T2, N1 (positive lymph nodes), M0	T3 (local invasion) or N1 (positive regional lymph nodes), M0	T3 or T4 (local invasion as shown by histologic evidence of adjacent organ invasion, direct tumor extension to IVC, or tumor thrombus within IVC or renal vein) or N1 (positive regional lymph nodes), M0
IV	T4 (invasion of adjacent organs) or fixed positive lymph nodes or M1 (distant metastases)	T4 (local invasion), N0, M0; T3, N1, M0; or T1–T4, N0–T1, M1 (distant metastases)	T1–T4, N0–N1, M1 (distant metastases)	T1–T4, N0–N1, M1 (distant metastases)

IVC = inferior vena cava; M0 = no distant metastasis; M1 = distant metastasis; N0 = no nodal involvement; N1 = involved nodes (fixed); T1 = tumor ≤5 cm; T2 = tumor >5 cm.

Modified with permission from Lee JE, Berger DH, el-Naggar AK, et al. Surgical management, DNA content, and patient survival in adrenal cortical carcinoma. *Surgery* 1995;118(6):1090-1098.

of only patients with distant metastasis as stage IV. The variability in staging systems used in individual studies complicates the comparison of these studies.[20] Importantly, there is no American Joint Committee on Cancer staging system for ACC. Gonzalez et al.[5] reviewed data on 186 patients with ACC and found the following stage system at diagnosis using the Lee classification system: stage I (5%), stage II (55%), stage III (20%), and stage IV (13%).

Several recent studies have reported 5-year survival rates of 35% to 38% for all patients with ACC and 5-year survival rates of 48% to 55% for patients who underwent curative resection.[41–43] In the MD Anderson Cancer Center's series of 186 patients with ACC who underwent initial surgical resection, independent predictors of a worse outcome included advanced stage at presentation and cortisol production by the primary tumor.[5] Our results thus support the association between tumor cortisol production and shorter overall survival as initially identified by Abiven et al.,[44] although the mechanism for this association remains unknown. Multiple authors have documented that complete resection is associated with an improved survival.[42,43] Comparison of overall survival between patients with large ACCs (≥5 cm) and small ACCs (<5 cm) at the time of presentation has not consistently demonstrated a difference in outcome.[5]

TREATMENT

Perioperative Management

Patients with ACC and associated CS are in a catabolic state with protein depletion. Adequate nutritional support before and after surgery is essential. Patients with ACC who have clinical or subclinical hypercortisolism should be treated with stress-dose steroids at the time of open surgery in the form 100 mg of hydrocortisone administered intravenously for one or two doses beginning at the time of division of the adrenal vein. Replacement steroids may be required for months after resection as discussed below. There is a fourfold increased risk of deep venous thrombosis in patients with hypercortisolism; therefore, perioperative prophylaxis against venous thrombosis is imperative.[45]

We administer a preoperative mechanical bowel preparation to all patients undergoing open adrenalectomy for known or suspected ACC. Patients with significant CS-associated signs and symptoms should be considered for preoperative treatment with agents to block excess cortisol production (e.g., metyrapone). Caution must be exercised in such circumstances, however; replacement steroids may be required to minimize the risk of development of an Addisonian state. Patients with hyperaldosteronism require aggressive correction of potassium deficiency, which may be facilitated through the administration of preoperative spironolactone, a competitive nonselective mineralocorticoid receptor antagonist (MRA). An alternative to

spironolactone is epleronone, a second-generation, competitive, more selective MRA derivative of spironolactone with none of the progestational and antiandrogen side effects of its predecessor. Epleronone may be used as a substitute for spironolactone if side effects of the latter medication are troublesome, although epleronone is considerably more expensive.[46] Correction of hypertension and electrolyte abnormalities in patients with aldosterone excess reduces the risk of perioperative arrhythmias.

Surgery

Complete surgical resection remains the only curative treatment for patients with ACC. Unfortunately, more than 65% of ACCs are unresectable at the time of presentation because of the presence of a locally advanced primary tumor process or the presence of distant metastasis.[4] The goal of surgery is complete resection without violation of the tumor capsule to minimize the risk of tumor seeding of the retroperitoneum and abdominal cavity. Invasion of surrounding structures may require en-bloc resection of the kidney, liver, diaphragm, pancreas, spleen, or bowel.

Primary areas of potential technical challenge during open adrenalectomy include involvement of the posterior segment of the right lobe of the liver and invasion of the IVC by a right-sided ACC. Therefore, complete mobilization of the liver together with proximal and distal control of the IVC should be routinely performed during right adrenalectomy. When the presence of a large right adrenal tumor prevents successful mobilization because of the presence of the overlying liver, we often involve our hepatic surgeons to consider early division of the hepatic parenchyma to allow direct access to the anterior aspect of the vena cava and the adrenal tumor. Performance of a "hanging maneuver" of the liver takes advantage of the avascular plane anterior to the vena cava and posterior to the liver. A tape is passed along this plane to assist with elevation of the liver, allowing the liver to be transected between the right and left lobes from front to back and subsequently opened up like a book. This maneuver exposes the IVC from the diaphragm to the subhepatic space, allowing total control of the IVC before the liver is mobilized and before adhesions and vascular connections between the adrenal tumor, diaphragm, and IVC are addressed. This approach is safe; may significantly reduce blood loss; provides complete access to the IVC; and facilitates complete resection of the posteriorly located tumor, diaphragm, and IVC with a significantly lower risk of tumor rupture.[47]

Incomplete resection of a left-sided ACC is usually caused by tumor extension along the mesenteric plexus at the origin of the celiac axis. Tumor encasement of the celiac axis, aorta, or proximal superior mesenteric artery represents definitive evidence of a locally unresectable tumor; these aspects of tumor invasion are best assessed on preoperative imaging studies rather

than in the operating room. This area is a site of potential iatrogenic injury to the arteries when the relationship of the tumor to these structures is not precisely identified, both on preoperative imaging and during surgery; in such patients, it can also be responsible for incomplete tumor resection.

The four methods for open adrenalectomy are anterior, lateral (flank), posterior, and thoracoabdominal. Each approach has specific advantages and disadvantages; in many cases (especially for medium-sized tumors without radiographic evidence of local invasion), the choice of an open approach may be based on the surgeon's comfort level and experience.[48] Factors to consider when choosing the appropriate approach include unilateral versus bilateral disease, the presence of multiple or extra-adrenal tumors, the size and site of the tumor, the presence of additional intraabdominal disease, any history of abdominal surgery, the patient's body habitus, and the anticipated risk of complications.[49] The posterior open approach is generally not recommended for known or suspected ACC because exposure is usually suboptimal for tumors larger than 5 cm in diameter.

The anterior approach is preferred for resection of most ACCs. It is performed via a midline incision, a bilateral subcostal incision, or a Makuuchi (hockey stick–shaped) incision. The anterior approach is particularly advantageous because any size tumor can be resected, and the entire peritoneal cavity can be evaluated and accessed. It is also the only open method allowing both adrenal glands to be exposed via a single incision and single position. Disadvantages of this approach include a potential for postoperative adhesions and subsequent intestinal obstruction.

The thoracoabdominal approach provides the widest exposure of very large ACCs. It is useful for tumors that may require en-bloc resection of adjacent organs, especially the liver or vena cava, or extensive lymph node dissection. The patient is placed in the decubitus position, the incision is created over the eleventh rib on the left or over the tenth rib on the right, and the rib is resected. A median sternotomy may be added to this approach for tumors with significant extension into the IVC, hepatic veins, or right atrium. One side effect of this approach is the decreased respiratory capacity associated with division of the diaphragm.

The lateral (flank) approach is limited by the length of the incision that can be performed and relatively limited flexibility regarding the approach to adjacent organs. It involves placing the patient in a lateral decubitus position and taking an extraperitoneal approach to the involved adrenal tumor. The lateral approach may be helpful in obese patients because gravity assists with retraction. A relatively large working space can be made available, and the approach can avoid any intraabdominal adhesions that may be present. However, only unilateral exposure is possible, and hemostasis of large vessels (including the IVC) can be difficult.[48]

The role of noncurative resection of ACC is contoversial, with survival after incomplete resection being poor overall and not measurably different from patients who do not undergo surgery.[40,50] However, there may be a role for palliative resection in highly selected patients with hormonally active tumors to improve their quality of life by minimizing hormone production, especially in patients whose hormone overproduction is poorly controlled by medical management and in whom systemic therapy has been maximized; such patients, however, are very uncommon.

Known or suspected ACC is still best treated by open resection rather than with a minimally invasive or laparoscopic approach. We have evaluated the pattern of recurrence after laparoscopic versus open resection of ACC and have identified a very high rate of peritoneal carcinomatosis in patients subjected to laparoscopic (compared with open) resection.[26] In a follow-up to that report, peritoneal carcinomatosis was identified in eight (89%) of nine patients who underwent laparoscopic resection of primary ACC compared with 19 of 127 (15%) patients who underwent open resection ($P < 0.001$).[5] The high incidence of peritoneal carcinomatosis in the laparoscopically treated patients was observed even though the average size of the adrenal tumors resected laparoscopically was only half that of the tumors resected by means of open adrenalectomy (6 cm vs. 13 cm, respectively).[26]

Surgical resection of recurrent or isolated metastatic disease may be a reasonable treatment option for highly selected patients. Improved patient survival has been reported by multiple groups for patients who have undergone resection of recurrent or limited metastatic ACC compared with those who have not undergo resection.[5,42] We recently reported that patients with recurrent ACC who had either stable disease or a response to mitotane had a significantly longer overall survival (18 months) than patients who progressed on mitotane (9 months; $P = 0.01$).[5] Based on these data, it may be preferable to treat patients with recurrent but potentially resectable ACC with a course of neoadjuvant mitotane followed by surgical resection rather than by immediate surgery followed by postoperative adjuvant mitotane. Patients with at least stable disease after mitotane treatment may have a more favorable tumor biology and are therefore more likely to benefit from reoperation. Patients with tumor progression on mitotane have an overall short survival duration, are unlikely to benefit from surgery, and are perhaps better candidates for combination systemic therapy or a clinical trial.

Postoperative Management

Intraoperative and postoperative administration of replacement steroids is essential in patients with cortisol-secreting tumors to avoid an Addisonian crisis caused by suppression of their opposite adrenal gland. We give 100 mg of hydrocortisone intravenously beginning intraoperatively when the adrenal

vein is divided and then every 6 hours for the first 24 hours after surgery. The dose is gradually decreased during the first postoperative week until the patient is on an oral maintenance dose of 25 to 50 mg of hydrocortisone daily. (An upward dose adjustment is necessary if the patient is on chronic mitotane therapy.) Steroid replacement should be tapered very slowly over 6 to 12 months in patients who do not require long-term steroid replacement because of concurrent adjuvant therapy with mitotane.[51] Patients with preoperative cortisol hypersecretion who undergo resection are at risk for postoperative Addisonian crisis, which may present as unexplained hypotension, fever, nausea and vomiting, or confusion. Although ACTH stimulation testing may be performed in the acute postoperative setting to evaluate for suppression of the opposite adrenal gland after surgery for ACC, exogenous administration of most steroid hormones (including hydrocortisone but excluding dexamethasone) interferes with plasma cortisol measurement. Therefore, if it is considered necessary to measure adrenal cortical function in patients on chronic steroid hormone supplementation, they should either be switched to dexamethasone for glucocorticoid support before ACTH stimulation testing or undergo measurement of 24-hour urinary-free cortisol.

After removal of an aldosterone-secreting ACC, adjustment of antihypertensive medications may be necessary. Relative hypoaldosteronism may result and may persist for up to 3 months after surgery.[51]

Surveillance and Follow-up

As many as 75% of patients undergoing potentially curative resection of ACC eventually develop local recurrence or distant metastases.[5] A reasonable restaging evaluation after resection of ACC includes at least CT of the chest and abdomen and chest radiography along with a laboratory evaluation that includes any hormones identified as elevated on preoperative testing (see Table 16-2). A reasonable schedule for follow-up evaluation is every 3 to 4 months for the first 2 years, every 6 months for 4 to 5 years, and then annually thereafter. Although late recurrence of ACC occurs occasionally, the majority of patients who survive recurrence free for 5 years appear to be cured.

Systemic Therapy

Because of the large proportion of patients who present with advanced, unresectable disease and the high recurrence rate after surgical resection, many patients with ACC ultimately require systemic therapy. Such treatment may include hormonal therapy if the disease is functional, as well as cytotoxic therapy with combination mitotane, chemotherapy, or both. Hormonal agents that may be useful in the management of patients with ACC are described in Table 16-6. Most treatments used in hormone management (with the notable exception of mitotane) do not result in an objective tumor

TABLE 16-6. Agents for Medical Management of Steroid Hormone Excess Syndromes in Patients with Adrenocortical Carcinoma

Agent	*Mechanism of Action*	*Common Side Effects*	*Advantages*	*Disadvantages*
Mitotane	Hormone suppression and antitumor activity Selective destruction of zona reticularis and fasciculata Inhibits 11 β-hydroxylation and cholesterol side chain cleavage Selective adrenocortical necrosis in adrenal tumor and metastases	Nausea Vomiting Diarrhea Depression Somnolence Vertigo Ataxia Hepatotoxicity Nephrotoxicity	Long-lasting effects Relatively specific adrenocortical cytotoxin Drug levels available for dose titration and reduction (goal, 14–20 ug/mL)	Slow to reach therapeutic level Dose-limiting toxicity Side effects in up to 57% of patients Hypercholesterolemia even with low doses
Metyrapone	Hormone suppression Inhibits 11 β-hydroxylation	Hirsutism Acne Virilism Nausea Vomiting Diarrhea	Rapid onset Reversible	Increase in adrenal androgens may result in female masculinization
Ketoconazole	Hormone suppression Weakly and nonselectively inhibits p450 enzymes involved in adrenal steroid synthesis	Hepatotoxicity	Useful in female patients with hirsutism Inhibits cholesterol synthesis	Slower onset Weak inhibition of cortisol synthesis Gynecomastia, reduced libido in males

(*Continued*)

TABLE 16-6. Agents for Medical Management of Steroid Hormone Excess Syndromes in Patients with Adrenocortical Carcinoma (Continued)

Agent	*Mechanism of Action*	*Common Side Effects*	*Advantages*	*Disadvantages*
Aminoglutethamide	Hormone suppression Inhibits conversion of cholesterol to pregnenolone (aromatase inhibitor) Reduces synthesis of cortisol, aldosterone, and estrogens	Rash Fever Dizziness Lethargy Antiestrogen effects Hypothyroidism	Useful in mixed hormonal syndromes	Side effects in up to 58% of patients Tolerance to cytotoxic effect
Mifepristone (RU486)	Hormone suppression Glucocorticoid receptor antagonist Progesterone receptor antagonist Blocks glucocorticoid-induced negative feedback at the hypothalamopituitary level	Medical abortion Menorrhagia Nausea Vomiting Diarrhea	Multiple mechanisms of action Blocks progesterone effects	Hypoadrenalism not easily identified (does not lower cortisol levels) and prolonged because of its long half-life

response; the goal of these therapies is to improve the quality of life rather than achieve a therapeutic tumor response.[20]

Mitotane is the only drug approved by the US Food and Drug Administration for the treatment of patients with ACC. It is unique because it may provide both hormonal control of functioning ACC and has utility as an antitumor agent. Mitotane measurably reduces steroid hormone levels in approximately 70% of patients with functioning ACC.[52,53] It is a difficult drug to manage because of its narrow therapeutic window; antitumor effects may require a plasma concentration of 14 mg/L or more, but toxic side effects are marked at levels at or above 22 mg/L. As an antitumor agent, mitotane has been used alone for the treatment of patients with recurrent, metastatic, and unresectable disease.[53–55] It has also been used as adjuvant therapy after surgical resection, although its use for this purpose remains controversial.[44,56–58] In a recent nonrandomized, interinstitutional study, adjuvant mitotane after surgery for ACC was associated with a decreased recurrence rate (49% with mitotane vs. 73% to 91% without mitotane).[59] A limitation of this study was its retrospective nature. The reported results are susceptible to selection bias, as well as inconsistency in standardized restaging among institutions over the 20 years of the study, which may have resulted in ascertainment or lead-time bias with regard to recurrences. In addition, limited details were provided by the authors regarding mitotane treatment, including no information regarding crossover treatment with mitotane among patients in the control group in whom disease recurred.[58] Large, randomized, prospective trials on the use of mitotane for ACC have not been performed. Therefore, we recommend that treatment decisions regarding adjuvant mitotane in patients who undergo resection of localized ACC be individualized. For many young, healthy patients, adjuvant mitotane is a reasonable treatment option; on the other hand, older patients with significant comorbidities are likely to tolerate mitotane poorly and may be better candidates for observation alone, with consideration for institution of mitotane at the first sign of any recurrence.[5]

Limited data are available regarding the choice and effectiveness of cytotoxic chemotherapy for ACC because of the rarity of the disease. Available evidence suggests that cisplatin-based chemotherapy may be effective, with response rates in the range of 20% to 30%.[60–62] An alternative regimen with lower overall associated toxicity consists of a combination of mitotane and streptozotocin, with a reported response rate of 36% in a total of eight patients.[63] Combinations of chemotherapy with mitotane have had a reported overall response rate of 32%; historical comparison suggests that the response rate of chemotherapy with mitotane is superior to that of chemotherapy alone.[20] Without data from a randomized trial, however, the optimal chemotherapy regimen for a patient with ACC cannot be determined.

An ongoing international trial, the First International Randomized Trial in locally advanced and Metastatic Adrenocortical Cancer Treatment (FIRM-ACT), is randomizing patients with advanced ACC to either mitotane with cisplatin-based therapy (cisplatin–etoposide–doxorubicin) or mitotane with streptozotocin. A total of 300 patients are being accrued, and results are expected in 2011.

Novel therapies for ACC are also being investigated. Epidermal growth factor receptor (EGFR) has been found to be expressed by the majority of ACCs. Unfortunately, a recent study of the EGFR tyrosine kinase inhibitor erlotinib in combination with the nucleoside analogue gemcitabine demonstrated little activity in a small group of patients with advanced ACC.[64] Advances in modern array-based molecular genetic technologies offer the opportunity to better understand adrenal cancer oncogenesis and enable the development of improved diagnostics and targeted therapies. Demeure's currently evaluating ACCs in comparison with benign adrenal cortical tumors using comparative genomic hybridization. This group has described patterns of genetic changes strongly associated with survival. Such investigations may identify novel molecular targets that may be exploited to develop novel therapies for this aggressive cancer.[65]

PRACTICAL PEARLS

- The rapid onset of CS, often together with virilizing features, is characterisitic of ACC.
- Complete surgical resection is the cornerstone of curative treatment of ACC.
- Known or suspected ACC is still best treated via an open operation. Minimally invasive or laparoscopic resection is best avoided.

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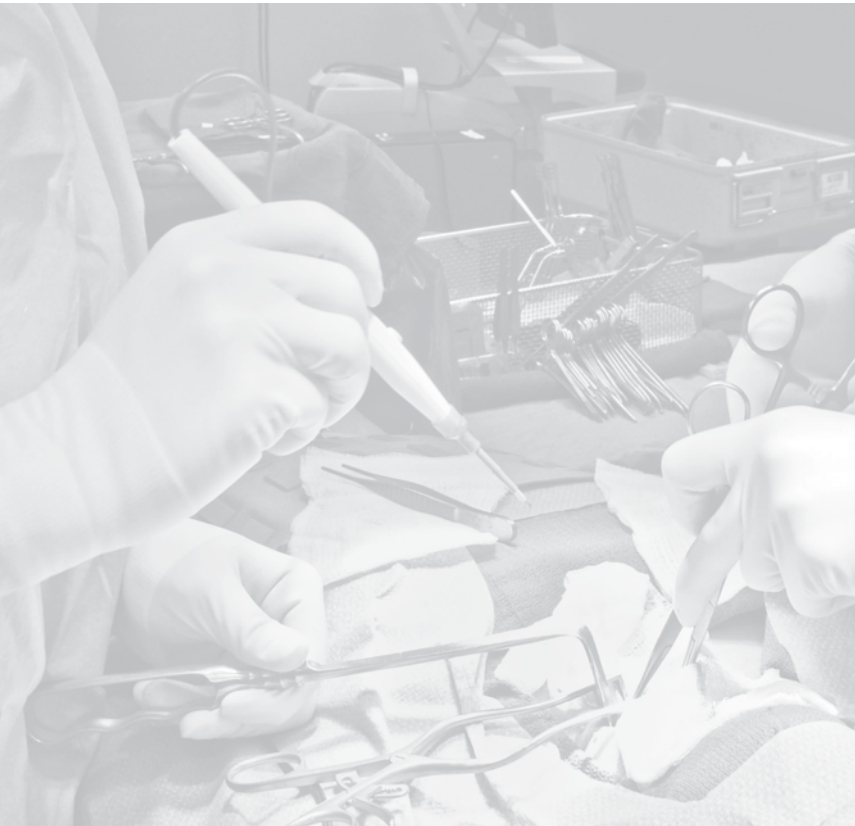
SECTION IV
Gastrointestinal



Chapter 17

Insulinoma

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Insulinomas are such rare tumors that even most specialists treat only a handful of these patients over their entire careers. Moreover, even most major referral centers treat only three or four cases per year. Nevertheless, the widely disparate clinical presentations as well as the complexity of diagnosis, localization, and treatment of these tumors continue to allure and sometimes perplex the team of physicians who care for these patients.

Resection of an insulinoma was first attempted by William J. Mayo in 1926.[1] Unfortunately, the patient, a surgeon, was found to have an unresectable metastatic insulinoma and died 1 month later. Two years later, Roscoe Graham of Toronto performed the first successful curative enucleation of a benign insulinoma.[2] In 1935, Frantz and Whipple characterized the classic symptoms of endogenous hyperinsulinemia, which subsequently became known as a "Whipple's triad."[3] This triad of hypoglycemia (plasma glucose <50 mg/dL), symptoms of hypoglycemia, and symptom resolution after glucose administration still serves as the fundamental basis for diagnosis.

Islet cells were first identified by a medical student, Paul Langerhans, in 1869.[4] Islets contain several different subtypes of secretory cells with different hormone production profiles. Insulin, which is secreted by the β cell, was discovered by Banting and Best in 1922, winning them a Nobel Prize.[5] Insulin is manufactured by the β cell as proinsulin, an inactive peptide made up of two subunits and a linking peptide (C peptide). Before secretion, proinsulin is cleaved into its active form, also releasing C peptide (an inactive, rapidly degraded peptide) in equimolar amounts.[6] C peptide is more rapidly degraded in the blood than insulin, with a half-life of about 4 to 6 minutes compared with a half-life of about 11 to 14 minutes for insulin.[7] Knowledge of this biochemistry is critical in evaluating patients with suspected hyperinsulinemia because the concomitant measurement of insulin and C-peptide levels may help distinguish between endogenous hyperinsulinemia and

exogenous insulin administration (e.g., malingering). Manufactured insulin compounds do not contain C peptide. Hyperinsulinemia with low or undetectable C-peptide levels indicates an exogenous source of insulin.

EPIDEMIOLOGY

Insulinoma is an islet cell neoplasm characterized by the excessive unregulated secretion of insulin, which results in the clinical symptoms of hypoglycemia. The incidence is estimated at four per 1 million person-years.[8] Table 17-1 presents the major reported series of surgically treated insulinomas. The mean age of presentation is typically in the fourth or fifth decade of life, with a slight predominance in women. Approximately 3% to 7% of tumors are associated with type 1 multiple endocrine neoplasia syndrome (MEN1).[9–16]

Sporadic insulinomas are almost always benign and single. Islet cell neoplasms in patients with MEN1 are almost universally multiple and scattered throughout the pancreas. The prognosis for patients with malignant insulinoma is better than for patients with exocrine pancreatic cancer, but most patients with liver metastases still have a relatively poor median survival of only 2 years.[8,17]

RISK FACTORS

The only documented risk factor for insulinoma is MEN1 syndrome. This syndrome results from a mutation in the *menin* gene on the long arm of chromosome 11, which predisposes patients to neuroendocrine tumors.[18] Neuroendocrine tumors of the pancreas and duodenum are the second most common manifestation of MEN1, affecting more than 50% of patients, and are the most common cause of death.[19] These tumors include insulinomas, gastrinomas, and other rare hormone-secreting tumors (glucagonomas, vasoactive intestinal peptide [VIP]-omas, carcinoid tumors) but predominantly are nonfunctional islet cell tumors (pancreatic polypeptide [PP]-omas, producing only pancreatic polypeptide, or nonsecreting tumors). Hyperparathyroidism and pituitary adenomas are also encountered in MEN1 patients, with hyperparathyroidism affecting 88% to 97% of patients.[19] Treatment of MEN1 patients must take into consideration the multicentric nature of the disease as well as the predilection for other tumors, especially hormonally active duodenal carcinoid tumors. These patients should have close lifelong surveillance.

CLINICAL PRESENTATION

The diagnosis of insulinoma is often delayed because of the vague and sometimes bizarre nature of the symptoms. The key to the diagnosis is clinical

TABLE 17-1. Summary of Insulinoma Experience at Major Referral Centers

Characteristics	Rothmund et al.[9]	Doherty et al.[10]	Pasieka et al.[11]	Menegaux et al.[12]	Pedrazzoli et al.[14]	Geoghegan et al.[13]	Kuzin et al.[15]	Chen et al.[16]	Mayo Clinic
Year	1990	1991	1992	1993	1994	1994	1998	2002	2007
Patients (*n*)	396	25	50	30	58	34	120	74	257
Operations (*n*)	419	25	47	29	63	34	117	77	261
Primary (%) reoperations (%)	89:11	92:8	—	—	95:5	93:6	—	96:4	89:11
Demographics									
Male (%): female (%)	—	36:64	48:52	40:60	41:59	38:62	32:68	50:50	42:58
Mean age (range) (years)	—	36 (21–60)	42 (19–81)	50 (23–74)	45 (7–75)	50 (18–78)	44	41 (21–73)	51 (12–86)
MEN1 diagnosis (%)	7.3	0	1	—	4	3	4	—	6.5
Presentation									
Duration of symptoms (range) (months)	—	24 (3–72)	62 > 24	37 (0–168)	—	30 (1–168)	—	40 (1–156)	42 (0–324)
Mean fasting glucose nadir (mg/dL)	—	35 (24–46)[†]	—	—	—	27	—	—	39 (14–60)

Mean insulin level (mU/L)	—	21 (11–230)[†]	—	—	—	60.3	—	—	—
Mean C-peptide level with glucose nadir (ng/mL)	—	2.5[†]	—	—	—	6.27	—	—	6.7
Tumor location									
Head (%)	36	36	50	37	37	16	32	32	39
Body (%)	30	32	32	24	32	41	36	30	32
Tail (%)	33	28	17	35	31	43	32	38	24
Tumor size									
Mean (cm)	—	1.7 (0.6–6.0)	—	—	1 (0.5–2.0)[†]	—	—	—	1.6 (0.1–7.0)
<1 cm (%)	—	12	—	—	19[‡]	7	—	—	20
1.0–1.5 cm (%)	—	58	—	—	62[‡]	80	—	—	38
1.6–2.0 cm (%)	—	8	—	—	19[‡]	—	—	—	22
>2.0 cm (%)	—	21	—	—	0[‡]	1	—	15	20
<2.0 cm (%)	—	71	66	90	100[‡]	87	—	85	80
Palpable at operation (%)	—	64	—	100	93	—	90	—	89
Multiple tumors (%)	10.6	—	4	3	7	—	5	3	7

(*Continued*)

TABLE 17-1. Summary of Insulinoma Experience at Major Referral Centers (Continued)

Characteristics	*Rothmund et al.*[9]	*Doherty et al.*[10]	*Pasieka et al.*[11]	*Menegaux et al.*[12]	*Pedrazzoli et al.*[14]	*Geoghegan et al.*[13]	*Kuzin et al.*[15]	*Chen et al.*[16]	*Mayo Clinic*
Nesideoblastosis (%)	—	—	4	3	7	6	8	3	1
Malignant disease (%)		—	4	11	—	6	7	3	0
Operative procedures									
Enucleation (%)	52	52	62	48	50‡	53	60	77	64
Distal pancreatectomy (+/- splenectomy) (%)	36	44	30	45	28‡	38	33	22	30
Total pancreatectomy (%)	<1	—	—	—	—	—	—	—	—
Pancreatico-duodenectomy	9	4	—	3.5	6‡	3	—	—	2
Laparoscopic resection (%)	—	—	—	—	—	—	—	—	1.5
Open/close (%)	1	—	—	—	—	—	—	—	1
Other (%)	1	—	7	3.5	16‡	6	7	1	1.5

Complications (overall) (%)	31	16	32	—	—	26	44	—	30
Pancreatic (leak, hemorrhage) (%)	24	12	30	41	—	12	31	36	18
Nonpancreatic (wounds, pneumonia) (%)	5	4	17	10	—	18	—	3	12
Mortality (%)	2	0	0	3	6‡	0	8	0	0
Cure rate (%)	98	96	96	92	97	94	—	97	97

* Author's personal experience with patients referred for benign insulinoma, Mayo Clinic, July 1982–February 2007 (261 operations in 258 patients).

† Data presented are medians rather than means.

‡ Data presented are on the most recently reported 18 patients.

suspicion and the presence of neuroglycopenic symptoms. Mild hypoglycemia stimulates both autonomic and adrenergic responses, resulting in symptoms of sweating, tachycardia, tremor, anxiety, palpitations, and weakness. This may progress as hypoglycemia worsens to neurologic dysfunction; the neurologic symptoms of hypoglycemia are the key to suspecting the diagnosis. The neurologic effects of hypoglycemia (<50 mg/dL) ranges from mild (e.g., confusion or forgetfulness, blurred vision) to severe (e.g., loss of consciousness, seizures). Rarely, focal neurologic deficits are seen and are confused with transient ischemic attacks.[8] Symptoms are typically encountered after fasting or exercise, are stereotypic for a given patient, and are often described as "spells." Family and friends typically confirm episodes of unusual behavior or disorientation. Confirmation of hypoglycemia while symptoms are present is critical to establishing the diagnosis. Many patients gain weight before diagnosis because of increased oral intake at the onset of hypoglycemic "spells" in an effort to prevent or abort their hypoglycemic symptoms.

In taking a patient's history, the social history (e.g., health care professional, close contact with diabetic family members) can be important because access to injectable insulin may raise the suspicion of surreptitious insulin self-administration. Timing of symptoms is also important because whereas those occurring early in the morning (e.g., from fasting overnight) and after exercise are suggestive of insulinoma, postprandial symptoms suggest non-insulinoma, pancreatogenous hyperinsulinemia syndrome (NIPHS; discussed later).

DIAGNOSTIC EVALUATION

Currently, four concomitant criteria must be met for the diagnosis of insulinoma:

1. Plasma glucose <45 to 50 mg/dL
2. Elevated insulin level (>6 μU/mL by IRMA or >3 μU/mL by ICMA)
3. C-peptide levels ≥200 pmol/L
4. Negative screening test results for sulfonylureas

A supervised fast (classically described but now rarely extending to 72 hours) is performed. This may be initiated and often completed in the outpatient setting if the patient begins the fast the evening before evaluation (with the start time dependent on the usual time to onset of symptoms and scheduled clinic appointment time). An intravenous (IV) line is started at the time of the patient's arrival at the hospital, and initial glucose levels are drawn and repeated periodically by reflectance meter until symptom onset. Biochemical tests that need to be obtained at the time the patient experiences symptoms (with concomitant reflectance meter glucose levels <50 mg/mL)

include serum levels of glucose, insulin, β-hydroxybutyrate, and C peptide. Glucagon (1 mg IV) is then administered, and glucose is monitored every 10 minutes for an additional 30 minutes to allow for measurement of insulin surrogates (discussed later). Low (or undetectable) C-peptide levels in the setting of hyperinsulinemic hypoglycemia suggests administration of exogenous insulin (and suppression of endogenous insulin or C-peptide production). Insulin:glucose ratios are not routinely helpful because fewer than 50% of patients with insulinomas have ratios of 0.30 or below. More important are the absolute levels of glucose and insulin because any measurable insulin in the setting of severe hypoglycemia (<45 to 50 mg/dL) is abnormal.

In some instances, measurement of the insulin level may be compromised and unreliable, such as with a hemolyzed sample or in patients with insulin levels at the lower limit of detection. Several biochemical surrogates of insulin activity can be used in these cases. Because the physiologic effects of insulin are glycogenic, antiketogenic, and antilipolytic, serum levels of β-hydroxybutyrate (a ketone) and the glucose response to glucagon administration can also be measured as surrogate markers of hyperinsulinemia. β-hydroxybutyrate level 2.7 mmol/L or below at the time of documented hypoglycemia (glucose ≤50 mg/dL) or an increase in the plasma glucose of above 25 mg/dL within 30 minutes of a 1-mg IV glucagon bolus also suggests hyperglycemia.[20]

Localization

Preoperative localization of these tumors is routinely undertaken because they can be quite small (typically <2 cm), sometimes multiple, and difficult to localize. No single localization study has demonstrated adequate sensitivity (or accuracy) to emerge as the preferred imaging modality. Table 17-2 presents a summary of the success of localization techniques at major referral centers.[9–16] Often, more than one study is required to successfully localize an insulinoma; however, almost all tumors can be successfully localized preoperatively. A suggested localization algorithm is presented in Figure 17-1.

Computed Tomography

Helical computed tomography (CT) has the advantage of being non-invasive and anatomically precise in identifying tumor size and location and the presence of lymphadenopathy or distant disease. Furthermore, CT images are generally easily interpreted by the surgeon. In the past, the sensitivity of CT was less than 40%; however, with the current generation of helical CT scanners (with improved speed, resolution, multiphase images, and the possibility of image reconstruction in multiple planes), sensitivity has greatly improved, now exceeding 60% (which is still less than ideal) (Figure 17-2A).

TABLE 17-2. Reported Sensitivities for Detection of Insulinoma with Different Localization Studies

Imaging Modality	*Rothmund et al.*[9]	*Doherty et al.*[10]	*Pasieka et al.*[11]	*Menegaux et al.*[12]	*Pedrazzoli et al.*[14]	*Geoghegan et al.*[13]	*Kuzin et al.*[15]	*Chen et al.*[16]	*Mayo Clinic**
Transabdominal US									
Studies (n)	142	23	—	12	21	13	78	47	232
Sensitivity (%)	39	26	—	40	33	15	30	30	63
CT									
Studies (*n*)	246	23	35	12	33	29	38	41	142
Sensitivity (%)	33	17	26	50	30	24	24	63	60
MRI									
Studies (*n*)	—	8	—	1	12	—	—	11	9
Sensitivity (%)	—	25	—	100	50	—	—	63	38
EUS									
Studies (*n*)	—	—	—	2	—	7	—	9	30
Sensitivity (%)	—	—	—	100	—	57	—	33	84
Percutaneous transhepatic portography									
Studies (*n*)	80	23	36	9	28	—	—	3	—
Sensitivity (%)	89	77	94	89	86	—	—	100	—
Angiography									
Studies (*n*)	305	26	41	25	57	33	118	11	40
Sensitivity (%)	62	35	44	44	32	93	56	27	61

SACS									
Studies (*n*)	22	—	—	—	—	—	17	10	26
Sensitivity (%)	—	—	—	—	—	—	90	90	100
IOUS									
Studies (*n*)	72	25	1	29	23	5	37	—	209
Sensitivity (%)	—	92	0	93	61	60	100	—	98

*Author's personal experience with patients referred for benign insulinoma, Mayo Clinic, July 1982–February 2007.

CT = computed tomography; EUS = endoscopic ultrasonography; IOUS = intraoperative ultrasonography; MRI = magnetic resonance imaging; SACS = selective arterial calcium stimulation; US = ultrasonography.

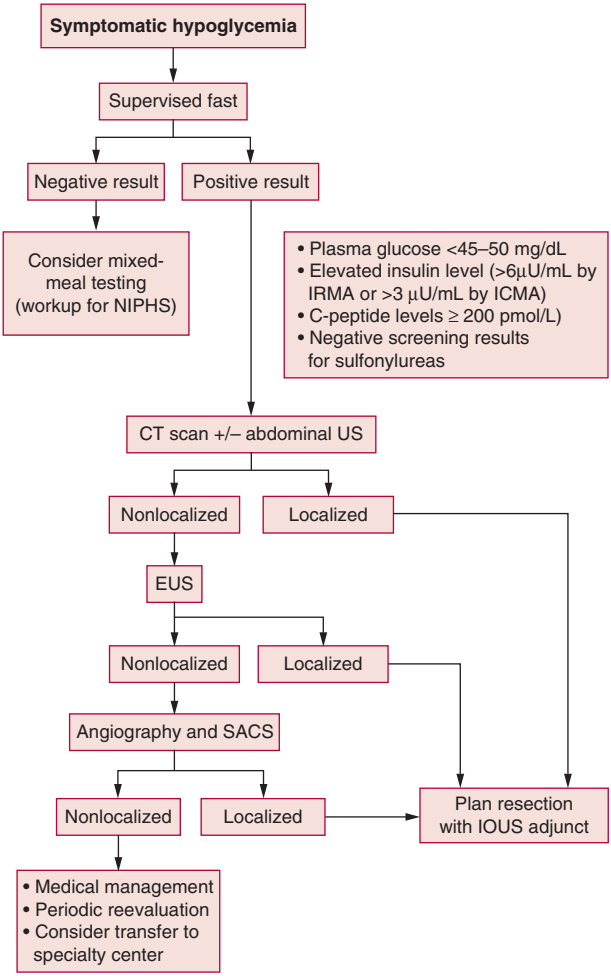
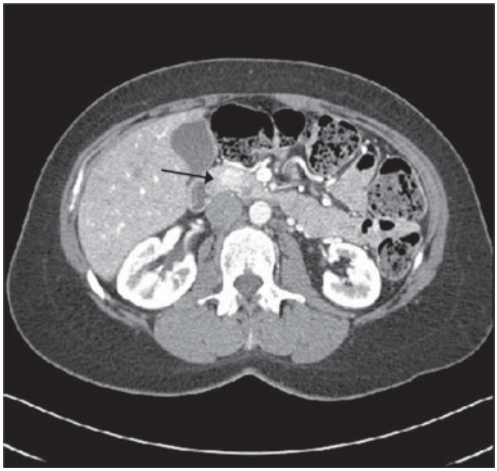
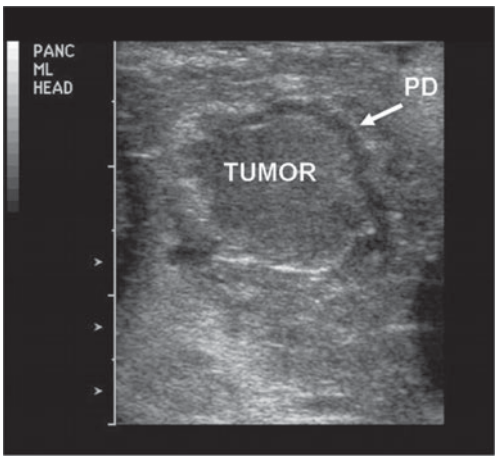


Figure 17-1. Diagnostic algorithm for patients with suspected hyperinsulinemic hypoglycemia. CT = computed tomography; ICMA = immunochemiluminometric assay; IOUS = intraoperative ultrasonography; IRMA = immunoradiometric assay; NIPHS= noninsulinoma, pancreatogenous hypoglycemia syndrome; SACS = selective arterial calcium stimulation; US = ultrasonography.



A



B

Figure 17-2 A. Computed tomography scan demonstrating a 1.4-cm hypervascular mass in the head of the pancreas in a patient diagnosed with insulinoma (*arrow*). **B.** Intraoperative ultrasonogram the demonstrating relationship of the pancreatic duct (PD) to insulinoma in the pancreatic head. The main PD was displaced and "draped" over the tumor. The tumor was successfully enucleated without difficulty or damage to the duct, and the patient was cured.

Transabdominal Ultrasonography

Success with transabdominal ultrasonography has varied by institution. Although ultrasonography may be limited by the experience of the technician and radiologist, the patient's body habitus, or bowel gas interference, most tumors can be identified by an experienced ultrasonographer. Patient ingestion of 12 oz of water just before scanning (to fill the stomach) is quite helpful in reducing bowel gas interference and improving the quality and sensitivity of the study.

Endoscopic Ultrasonography

For patients with tumors that cannot be localized either by CT or abdominal ultrasonography, endoscopic ultrasonography (EUS) is usually successful in identifying the tumor. EUS is modestly invasive, with rare complications (e.g., perforation, pancreatitis). The main drawback to EUS is that it requires operator expertise both in endoscopy and ultrasonography, and the images obtained are not as useful to the operating surgeon. EUS (when indicated) appears to be more sensitive than other imaging modalities and is most helpful in patients with small pancreatic head or uncinate tumors.

Arteriography with Selective Arterial Calcium Stimulation

There continue to be a few patients in whom CT, transabdominal ultrasonography, and EUS fail to localize the tumor. For such challenging cases, angiography combined with selective arterial calcium stimulation (SACS) testing is the next step. This technique involves selective catheterization of the gastroduodenal, splenic, and superior mesenteric arteries with simultaneous venous catheterization of the right hepatic vein for blood sampling. Selective arteriography may demonstrate a hypervascular "blush," suggesting the location of the tumor. Calcium gluconate is sequentially injected into the superior mesenteric, splenic, and gastroduodenal arteries with blood samples taken from the hepatic vein at 0, 20, 40, and 60 seconds after calcium injection (Figure 17-3). A greater than twofold increase in hepatic vein insulin levels is considered a positive result. This "regionalizes" the site of insulin secretion within the pancreas by its blood supply. Aberrant arterial anatomy must be recognized because it may affect the results. Success in this complex procedure requires an experienced and highly skilled interventional radiologist. Arteriography alone (without SACS) is of limited value because its sensitivity averages only somewhat better than 50%.

Before SACS was developed, percutaneous transhepatic portal venous sampling (for insulin) was briefly used with some success. However, the procedure is very difficult to perform and carries a higher complication risk. Its use has since been abandoned.

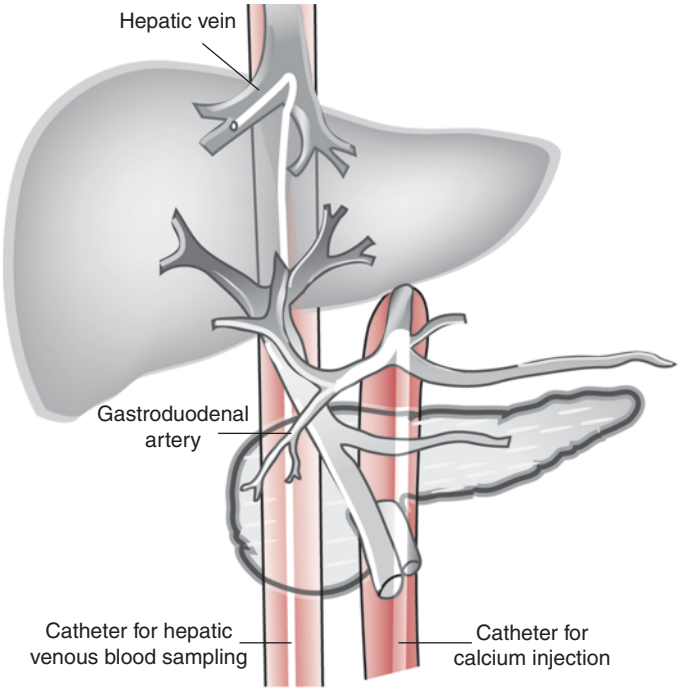
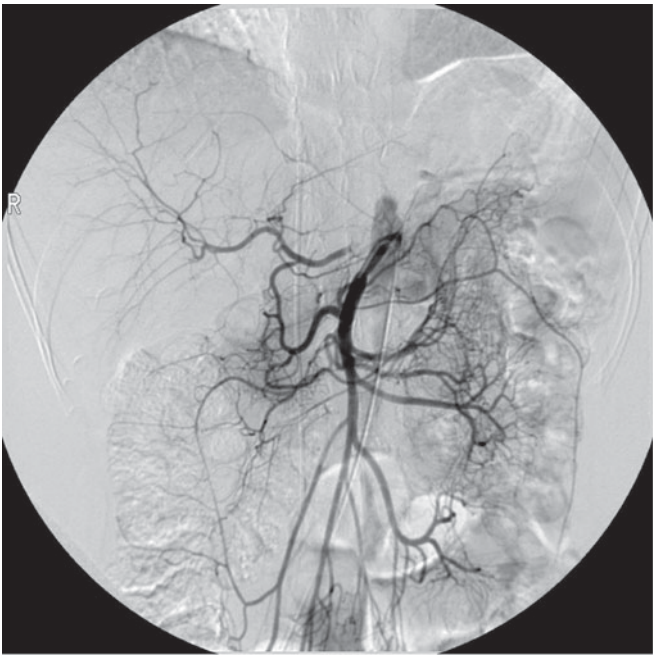
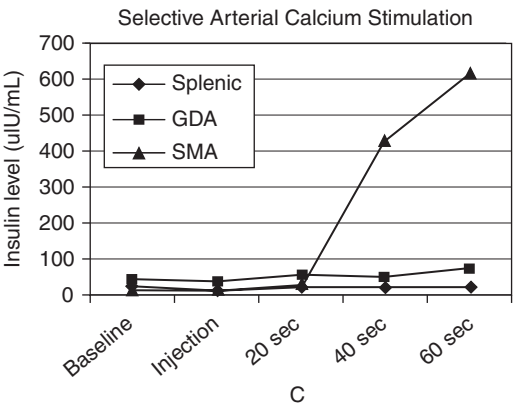


Figure 17-3. Arteriography with selective arterial calcium stimulation testing (SACS). **A.** Positioning of catheters for SACS. **B.** Angiogram of a patient with nonlocalizing transabdominal tumor. Ultrasonography, computed tomography, and endoscopic ultrasonography suggest a lesion in the tail of the pancreas (faint "blush" from the dorsal pancreatic artery branch from the SMA = superior mesenteric artery; *). **C.** Insulin levels in the hepatic vein after selective calcium injection of the GDA = gastroduodenal artery, SMA, and splenic arteries in the same patient demonstrate a marked insulin increase with injection of the SMA, confirming angiographic findings. The patient was taken to the operating room, and the tumor was confirmed by intraoperative ultrasonography and enucleated. The patient was cured.



B



C

Figure 17-3. (*Continued*)

Intraoperative Ultrasonography

Intraoperative ultrasonography is an extremely useful adjunct in guiding operative treatment. Its main benefits are in confirming the location of the tumor, elucidating the anatomic relationships of the tumor(s) (e.g., relationship to the pancreatic and biliary ducts and blood vessels; see Figure 17-2B) and detecting the presence of multiple tumors.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has similar (or slightly better) sensitivity to CT in localizing insulinomas. The main disadvantages of MRI include its increased cost (relative to CT and ultrasonography) and images that are more difficult to interpret by the surgeon. MRI may be useful in patients with contraindications to IV contrast (renal dysfunction, contrast dye sensitivity), when noncontrast CT scan is equivocal, and at centers without experience in pancreatic ultrasonography. MRI is contraindicated in patients with pacemakers or metallic foreign bodies.

Octreoscan

Octreoscan, although useful in other neuroendocrine tumors, is rarely used for insulinomas because the majority of tumors lack somatostatin receptors with high affinity for octreotide.[21]

Noninsulinoma, Pancreatogenous Hypoglycemia Syndrome

A subset of patients with endogenous hyerperinsulinism do not have an insulinoma but instead have NIPHS.[22] NIPHS is currently most commonly seen in patients who have undergone gastric or bariatric surgery. Patients present with profound postprandial rather than fasting hypoglycemia. The pathogenesis of NIPHS is thought to be reactive hypersecretion of insulin from diffuse β-cell hyperplasia or nesidioblastosis. These patients often experience symptoms 1 to 3 hours after eating but do not typically have morning (fasting) hypoglycemia. Their hypoglycemia can be quite profound, with glucose measurements into the low 20s (μU/mL), resulting in seizures and other debilitating neuroglycopenic symptoms.

Patients with suspected NIPHS should undergo mixed-meal testing, which involves a supervised ingestion of a premixed meal replacement, with blood samples taken at baseline and every 30 minutes for glucose, insulin, and C peptide. Documentation of symptom onset within several hours after a mixed meal associated with concomitant hypoglycemia, hyperinsulinemia, and elevated C-peptide levels suggests NIPHS. In contrast to patients with insulinoma, a 72-hour fast is negative in these patients. Additional confirmation by negative imaging study results and a positive calcium stimulation

test result in more than one arterial distribution (often all three distributions) suggests the diffuse nature of NIPHS rather than an isolated insulinoma.

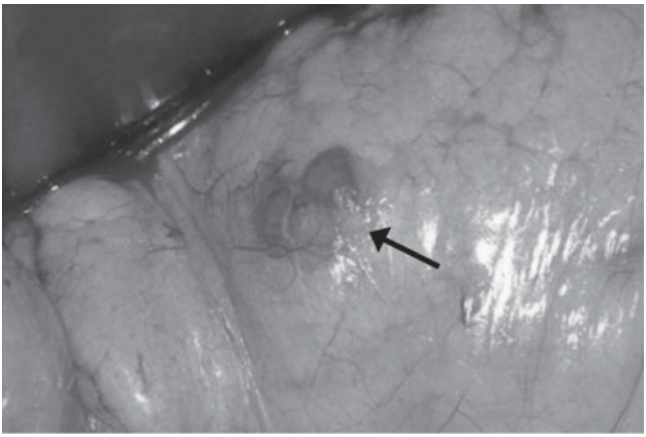
MANAGEMENT

Perioperative Care

Surgical therapy is guided by the tumor's location in the pancreas, the location in relation to the pancreatic duct, sporadic versus MEN1-associated disease, and malignancy. Patients may be admitted the night before surgery for IV dextrose administration to prevent fasting hypoglycemia, which may be discontinued shortly before surgery. Intraoperative monitoring of blood sugar at regular intervals (e.g., every 15 to 30 minutes) to prevent hypoglycemia is recommended if dextrose is not administered in the intraoperative fluids. Dextrose can be administered as a bolus if the glucose level decreases below 40 μU/mL. After tumor excision, close glucose monitoring should be continued, and a relatively prompt increase in glucose levels is expected. The development of hyperglycemia, although not always seen, is a reassuring sign of surgical cure.

Open Surgical Treatment

The abdomen is usually accessed through a bilateral subcostal incision. Complete mobilization of the pancreas is required both for palpation of the gland and to permit optimal intraoperative ultrasound visualization. Full mobilization of the gland involves both mobilization of the spleen to allow for posterior palpation of the gland as well as an extended Kocher maneuver of the duodenum to allow for adequate examination of the head and uncinate process. Bimanual palpation is then performed, and intraoperative ultrasonography can be used as an adjunct to identify the pancreatic ducts and any additional tumors. A good bimanual examination should identify almost 90% of tumors. Intraoperative ultrasonography is particularly useful in pancreatic head and neck tumors because it can identify the location of the main pancreatic duct relative to the tumor, which permits a safe plan for enucleation. Even when tumors are directly adjacent to the common bile duct or major pancreatic ducts, they can often still be enucleated safely because they typically displace but do not invade or constrict the duct (Figure 17-4). Benign insulinomas are typically well circumscribed. They tend to be firm, compressed tissue with a distinct plane adjacent to the surrounding normal pancreatic parenchyma. Enucleation, when feasible, is the procedure of choice for benign solitary tumors. The enucleation site may be oversewn or left open (provided there is no obvious leak or duct injury); however, drainage has usually been elected.



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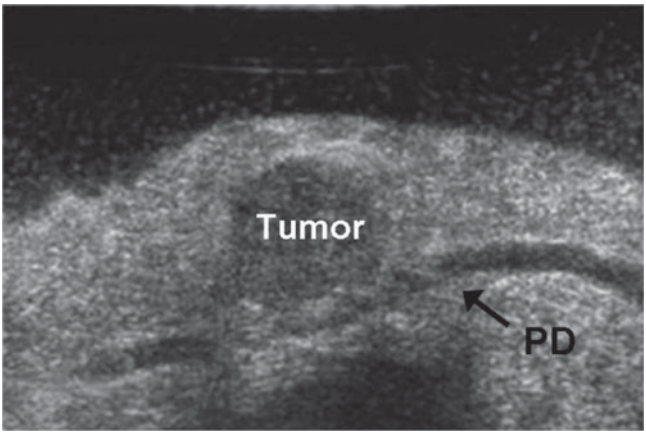
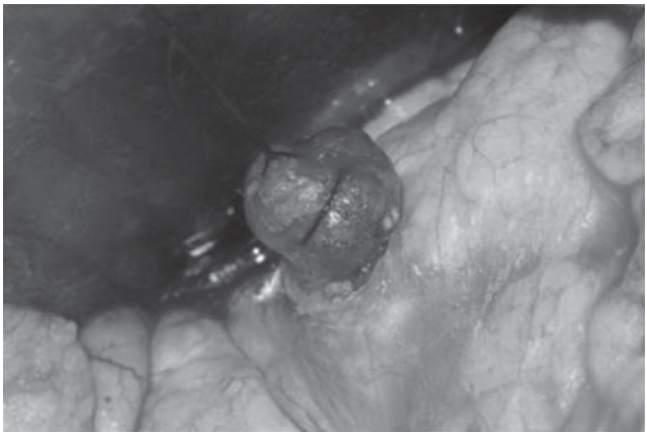


B

Figure 17-4. A. A pancreatic body tumor (*arrow*) is visible on the surface of the pancreas (uncommon). **B.** Intraoperative ultrasonography demonstrates close proximity of the pancreatic duct (PD) just deep to the tumor. **C.** The tumor is carefully enucleated without damage to the duct, and the patient is cured.



C

Figure 17-4. (*Continued*)

When enucleation is not possible because of the tumor's size or location, or because of concerns of malignancy (invasion of surrounding structures or metastatic disease), distal pancreatectomy (for body and tail lesions) or (rarely) pancreaticoduodenectomy (for head and uncinate lesions) may be preferable. Peripancreatic lymphadenectomy should also be performed in cases of suspected or proven malignancy. Spleen-sparing distal pancreatectomy may be performed when anatomically feasible and when malignancy is not a concern. Drainage of the pancreatic or splenic bed is generally performed but is not necessary as long as interventional radiology support is available for percutaneous drainage if a clinically significant leak becomes apparent. Splenectomy necessitates vaccination against encapsulated organisms (*Haemophilus* spp, pneumococci, and meningococci), which is ideally performed either 2 weeks before or 2 weeks after surgery.

In the past, progressive pancreatic resection starting from the tail and moving toward the head was performed in patients with occult tumors (i.e., "blind distal pancreatectomy"). This is no longer advised because these patients are found to have a high rate of surgical failure. For patients whose tumor is not localized by preoperative or intraoperative imaging and surgical palpation, abdominal closure and referral to a tertiary center is recommended.

Laparoscopic Resection

Laparoscopic resection of islet cell tumors was first reported in 1996 and is now offered at most tertiary referral centers for selected patients.[23] Principles of resection for laparoscopic resection should mirror those of open surgery. Both enucleation and distal pancreatectomy (with or without splenectomy) can be safely performed by experienced laparoscopists and require preoperative confirmation of tumor location and anatomy (which is confirmed with laparoscopic intraoperative ultrasonography). Enucleation may be performed either with electrocautery (e.g., Endo Shears, hook cautery) or a bipolar device (e.g., harmonic scalpel).

For distal pancreatectomies, an endoscopic stapling device is typically used to transect the pancreas and splenic vessels (although pancreatic transection can by accomplished with a variety of other devices). Conversion to an open procedure is required for bleeding, poor visualization, technical difficulty, or findings suggestive of malignant disease. Laparoscopic resections should not be attempted in patients with MEN1, questionable localization, or concern for duct or vascular proximity limiting safe laparoscopic feasibility.

Reoperation

For previously operated patients (either prior pancreatic resection or negative exploration), preoperative localization is absolutely critical. These patients are best treated at a tertiary referral center.

Complications

Pancreatic complications, such as hemorrhage, abscess, pancreatitis, and pancreatic fistula, occur in 12% to 41% of patients.[9–16] The majority of pancreatic fistulas close spontaneously within a few weeks as long as adequate drainage is maintained. An additional 3% to 18% of patients develop nonpancreatic complications (e.g., deep vein thrombosis, pulmonary embolism, pneumonia, wound infections).[9–16] Perioperative mortality is low, averaging around 2%.[9] Pancreatic complications from laparoscopic resection (a highly selected subgroup of patients) appear to be similar (or slightly higher) to those seen with open resections, with pancreatic fistula rates of 7% to 36%, but overall complications and length of stay may be slightly less.[23,24]

Special Considerations

In patients with MEN1, surgical treatment is individualized to the individual patient's pattern of disease. The goal is to excise the bulk of disease, remedy the hyperinsulinism, and decrease the risk of future pancreatic malignancy while preserving as much grossly normal pancreas as possible.[25] For most patients, distal pancreatectomy and enucleation of all accessible pancreatic head tumors is the option of choice. For patients with

bulky disease in the pancreatic head, pancreaticoduodenectomy with enucleation of additional tumors in the tail may be required. In addition, duodenotomy with palpation of the duodenal wall and excision of any palpable nodules (carcinoid tumors) in patients who have Zollinger-Ellison syndrome is advised. These patients are best managed at a tertiary referral center.

In patients with NIPHS who fail attempts at medical management and have debilitating symptoms, distal pancreatectomy (which reduces islet cell mass) may be indicated; however, long-term results of this strategy have yet to be reported.

Postoperative Care

After surgery, most patients develop transient hyperglycemia. Frequency of glucose monitoring can be gradually decreased as glucose levels stabilize. Dextrose is typically avoided in the patient's IV fluids for the first 24 hours, which helps confirm cure of hyperinsulinemia. Some patients require small doses of insulin in the early postoperative period; however, most patients are euglycemic or mildly hyperglycemic at the time of discharge. Drainage tubes are typically removed after the patient resumes a normal diet if the amount remains minimal with a benign (nonpancreatic) appearance.

Follow-up

Follow-up after excision of a benign sporadic insulinoma is basically unnecessary unless hypoglycemic signs and symptoms return. The prognosis is excellent, with more than 95% of patients achieving a long-term cure. Recurrence of symptoms at any time should prompt reevaluation and suspicion of recurrence in the previous enucleation site, MEN1 syndrome, or malignancy. Patients with MEN1 should have close follow-up with periodic imaging and biochemical screening for the various manifestations of their disease (discussed elsewhere).

MEDICAL TREATMENT

Medical management (e.g., diazoxide or somatostatin analogs) may help reduce insulin secretion and hypoglycemia in patients not amenable to undergoing resection (either because of unresectable malignancy or severe comorbid disease and high surgical risk).[26] Because of the typically slow progression of malignant tumors, aggressive surgical resection, radiofrequency ablation, or chemoembolization may help palliate symptoms and potentially increase life expectancy.[27,28] In the past 15 years, chemotherapeutic options (e.g., streptozocin monotherapy or in combination with 5-FU, doxorubicin, chlorozocin) have yielded reasonable response rates, both in tumor regression and symptom palliation, with some long-term survivors.[27,28]

PRACTICAL PEARLS

- Preoperative localization is critical; blind distal pancreatectomy should not be performed.
- EUS is probably the best modality for preoperative localization, but it is not required in the majority of patients because CT and ultrasonography identify the majority of tumors.
- Intraoperative ultrasonography is an extremely helpful adjunct for localization and to define pancreatic anatomy, particularly the pancreatic duct and its relation to the tumor.
- Patients with MEN1 syndrome have multiple pancreatic and duodenal tumors, and surgery should be planned accordingly.
- NIPHS should be distinguished from insulinoma because its pathogenesis and treatment are markedly different.

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Chapter 18

Gastrinoma

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EPIDEMIOLOGY

In 1955, Zollinger and Ellison[1] described two patients with jejunal ulceration, gastric acid hypersecretion, and a non-β pancreatic islet cell tumor. The diagnostic triad of gastric acid hypersecretion, recurrent peptic ulceration in the setting of adequate therapy, and a non-β islet cell tumor of the pancreas was proposed for the syndrome that now bears their names. The subsequent development of a sensitive radioimmunoassay resulted in the identification of gastrin overproduction as the underlying mechanism for this syndrome.

The incidence of gastrinoma is between one and three per 1 million people.[2,3] In patients with peptic ulcer disease (PUD), gastrinoma is thought to account for 0.1% to 1.0% of cases. However, these figures may be underestimates because these patients may have symptoms similar to those with typical PUD, attributed to *Helicobacter pylori* or the use of nonsteroidal antiinflammatory drugs (NSAIDs), and may go undiagnosed. Enteropancreatic neuroendocrine tumors are second in incidence only to insulinoma.

Although 75% to 80% of gastrinomas are sporadic, 20% to 25% are diagnosed in the setting of multiple endocrine neoplasia type 1 (MEN1).[2,3] This syndrome includes primary hyperparathyroidism and tumors of the pituitary gland in addition to pancreatic islets cell tumors and duodenal gastinomas. (Thymic carcinoids, adrenal adenomas, and some cutaneous tumors have also been associated.) This distinction is important to make because the diagnostic and management approaches to sporadic and familial disease differ significantly. The penetrance of pancreatic neuroendocrine tumors or duodenal gastrinomas in patients with MEN1 is approximately 60% to 70%. Gastrinoma is the most common of these tumors. In general, these tumors become clinically evident in the fourth or fifth decade of life in these patients.

These tumors arise from enteroendocrine cells found in the pancreas and duodenum. Histologically, they are well-differentiated tumors that resemble other pancreatic neuroendocrine tumors and demonstrate few mitoses with a proliferative (Ki-67) index of 2% to 10%. As with all gastroenteropancreatic neuroendocrine tumors, gastrinomas are classified by World Health Organization guidelines into well-differentiated endocrine tumors (benign), well-differentiated endocrine carcinomas (low malignant potential), and poorly differentiated endocrine carcinomas (high malignant potential).[4] The majority of gastrinomas (50% to 80%) fit into the well-differentiated endocrine carcinoma category. Ultimately, more than 60% of these tumors prove to be malignant. This distinction relies on evidence of local invasion or metastatic spread because no histologic feature exists that is diagnostic of malignancy.

Although initially described as a pancreatic neuroendocrine tumor, it is now recognized that the majority of gastrinomas (50% to 88%) arise in the duodenum.[2,3] In addition, these tumors are rarely found in the stomach, jejunum, biliary tract, liver, kidney, and ovary. Sporadic tumors of the duodenum are typically small (<1 cm). Despite this, 60% to 80% have metastasized to regional lymph nodes at the time of diagnosis. On occasion, gastrinoma is found in a lymph node when no primary tumor is evident. Most, if not all, of these "primary lymph node gastrinomas" have likely spread from a small duodenal tumor. With careful intraoperative examination, most of these primary tumors can be found. The existence of true lymph node primary tumors is currently controversial. The most common site of metastatic spread is the liver; the second most common is bone. In sporadic duodenal gastrinomas, liver metastases are seen in 10% of patients at the time of diagnosis.

In contrast to tumors in the duodenum, sporadic pancreatic gastrinomas are generally larger (>2 cm). Although spread to regional lymph nodes appears to occur at a similar rate to duodenal tumors, pancreatic gastrinomas are associated with a higher likelihood of distant liver metastases. Tumors associated with MEN1 are most commonly found in the duodenum (90%). Multiple tumors are the rule in these patients. Most of these tumors are small, and distant metastases are rare at the time of diagnosis.

RISK FACTORS

Few specific risk factors have been identified for gastrinoma. Perhaps the only widely acknowledged risk factor is family history in those with MEN1. More recently, it has been proposed that prolonged hypergastrinemia from antisecretory medications or other causes may increase the risk of developing not only gastric carcinoids but duodenal gastrinomas as well. This is postulated to be a result of long-standing G-cell stimulation.

CLINICAL PRESENTATION

The clinical presentation of patients with gastrinoma is relatively nonspecific. Roy et al.[5] from the National Institutes of Health (NIH) conducted a prospective evaluation of 261 patients with gastrinoma seen over a 25-year period. The mean age of presentation in this cohort was 41.1 ± 0.7 years. On average, patients with sporadic disease presented later than those with MEN1-associated gastrinomas. The most common complaint in this cohort was abdominal pain, which was seen in 75% of patients. Diarrhea was noted in 73% of patients, with symptoms of heartburn (44%), nausea (33%), vomiting (25%), and weight loss (17%) occurring in a lower percentage of patients. Abdominal pain was noted less frequently in those with MEN1-associated disease (66%).

DIAGNOSTIC EVALUATION

Biochemical Tests

Given its nonspecific presentation and relative rarity, it is not surprising that the diagnosis of gastrinoma is often significantly delayed. In fact, the mean delay from symptom onset to diagnosis is 5.2 years. This may be even longer in patients taking proton pump inhibitors (PPIs). Clinicians should have a heightened index of suspicion in patients with recurrent or severe cases of PUD, multiple ulcers, or ulcers in unusual locations (more distal small bowel). In addition, in patients with duodenal ulcers in the absence of *H. pylori* infection, PUD associated with prolonged diarrhea, and PUD in the setting of personal or family history of hypercalcemia, the possible diagnosis of gastrinoma should be considered.

In the appropriate clinical setting, the diagnosis of gastrinoma is made with biochemical testing. The biochemical hallmark of gastrinoma is an elevation of fasting serum gastrin (FSG) level in the presence of gastric acid hypersecretion. The demonstration of a low gastric pH is important given that a number of conditions with associated achlorhydria (or hypochlorhydria) manifest an elevated serum gastrin level (Table 18-1). These conditions include pernicious anemia, atrophic gastritis, PPI or H2-blocker use, and postvagotomy states. Even in the setting of elevated gastric acid secretion, hypergastrinemia may result from other conditions, such as gastric outlet obstruction, antral G-cell hyperplasia, renal failure, and short bowel syndrome. Patients taking antisecretory medications should discontinue them at least 1 week before the FSG level is measured. An algorithm for the diagnosis of gastrinomas is shown in Figure 18-1. Given the broad differential diagnosis and the confusion regarding the interpretation of diagnostic testing, patients referred to an endocrine surgeon with a provisional diagnosis should be reviewed thoroughly because many of these diagnoses may be incorrect.

TABLE 18-1. Differential Diagnosis of Hypergastrenemia with and without Gastric Acid Hypersecretion

Elevated Gastric Acid Secretion	*Normal or Decreased Gastric Acid Secretion*
Gastrinoma	Pernicious anemia
Gastric outlet obstruction	Atrophic gastritis
Antral G-cell hyperplasia	PPI or H2-blocker use
Renal failure	Postvagotomy
Short bowel syndrome	

PPI = proton pump inhibitor.

The interpretation of FSG levels has been the focus of some discussion in the literature.[3] Overall, it is generally accepted that an FSG level more than 10 times the upper limit of normal in the setting of a gastric pH below 2 is diagnostic of gastrinoma. In our laboratory, the upper limit of normal is 47 pg/mL. Unfortunately, in a significant portion of these patients, the elevation in FSG level is lower than this benchmark. In an effort to clarify this, a recent NIH study examined prospective data on 309 patients with Zollinger-Ellison syndrome and compared these results with 2209 patients in 513 series reported on in the literature.[6] In this study, a normal FSG level was seen in just 3% of patients with gastrinoma. If repeat testing was used, this number decreased to 0.3%. In addition, two thirds of these patients were found to have levels below 10 times the upper limit of normal.

Patients with suspected gastrinomas who have elevated FSG levels less than 10 times the upper limit of normal should undergo provocative testing. Secretin and calcium stimulation tests have been described for this disease. Although the mechanism remains unclear, secretin stimulates gastrin release in patients with gastrinoma but inhibits its release in those without this tumor. This test involves the administration of a 2-U/kg intravenous bolus infusion of secretin with FSG measurements at specific time points (−15, −5, 0, +2, +5, +10, + 15, +20 and +30 minutes) before and after infusion. Similarly, calcium infusion has been noted to produce an increase in gastrin level in these patients. This test is performed by administering an infusion of 5 mg/kg/hr of calcium (typically in the form of a 10% calcium gluconate solution) over 3 hours with FSG measurements at 30, 15, and 0 minutes before and 30-minute intervals after the start of this infusion for 3 hours.

For both tests, a number of protocols and standards have been used, so a global description of the performance of these tests has been elusive. More recently. however, Berna et al.[7] prospectively examined the results of

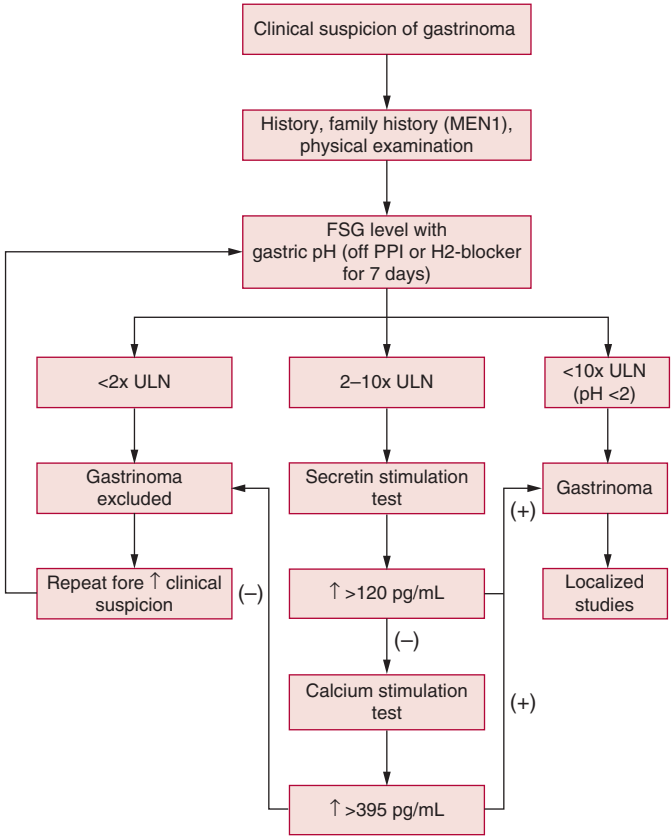

Figure 18-1. Algorithm for the workup and diagnosis of gastrinoma. FSG = serum gastrin; MEN = multiple endocrine neoplasia; PPI = proton pump inhibitor; ULN = upper limit of normal.

provocative gastrin testing in 293 patients from the NIH and made additional comparisons with published reports of an additional 537 cases. Several useful conclusions were made. Overall, secretin testing was found to be more sensitive than calcium infusion (94% vs. 62%, respectively). The optimum criterion for a positive secretin test result was found to be an increase

of 120 pg/mL or more (94% sensitivity;100% specificity). For the calcium stimulation test, this was found to be an increase of 395 pg/mL or more (62% sensitivity; 100% specificity).

Given the afore mentioned results, the secretin stimulation test should be considered the first choice in patients with suspected gastrinoma and a moderate (<10 times the upper limit of normal) elevation in gastrin level. However, a calcium stimulation test result is positive in 38% to 50% of patients with gastrinoma in whom the secretin test result is negative. Thus, when the index of suspicion is high, a negative secretin test result should be followed by a calcium stimulation test. This study also found that the traditional meal stimulation test was not a useful adjunct to the diagnostic algorithm for gastrinoma.[7]

Preoperative Localization

After a biochemical diagnosis, the focus should turn to localization of the tumor. Overall, up to 90% of gastrinomas are located in a triangular region that includes the head of pancreas, the first and second portions of the duodenum, and the hepatoduodenal ligament. Tumors of the pancreas tend to be larger than those found in the duodenum. Localization studies typically begin with conventional anatomic imaging using computed tomography (CT), magnetic resonance imaging (MRI), or ultrasonography (Figure 18-2). Unfortunately, although anatomic imaging can localize 50% to 72% of pancreatic tumors (often those >1 cm in size), these tests miss up to 80% of subcentimeter duodenal tumors. Overall, the sensitivity of these tests ranges from 20% to 60%.[2]

Receptors for somatostatin are commonly present on gastrinoma tumor cells. This realization has been exploited through the use of somatostatin receptor scintigraphy (SRS) using indium-111 labeled pentetreotide. This functional imaging modality has proven to be more sensitive than conventional anatomic tests.[8] The overall sensitivity for primary tumor localization ranges from 58% to 80%. Unfortunately, the sensitivity is directly related to the tumor size, and although SRS has a sensitivity of 96% for gastrinomas larger than 2 cm, the performance of this test in smaller tumors is significantly decreased. Additionally, SRS is highly sensitive for the detection of disease in the liver and may be useful in the pickup of spread to other sites, including the bones.

Endoscopic ultrasonography (EUS) has also been investigated as a modality for preoperative localization of gastrinomas. The strength of this test lies in its sensitivity for the detection of small intrapancreatic tumors and regional lymph nodes (80% to 95%).[9] However, EUS is a poor test for the detection of duodenal tumors, with a sensitivity of just 10% to 50%. Although an additional advantage of EUS lies in the ability to perform a needle biopsy, this is generally unnecessary because the biochemical diagnosis of gastrinoma has typically already been made. Thus, although EUS

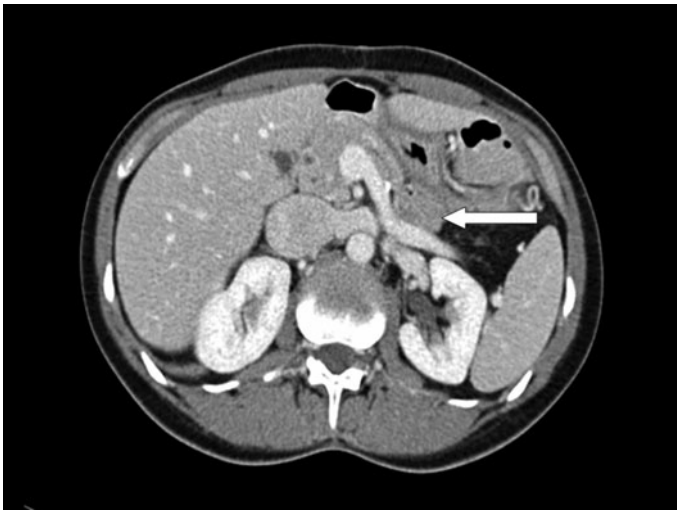

Figure 18-2. Computed tomography scan of the pancreas with intravenous contrast. *Arrow* indicates gastrinoma in the pancreatic tail. The patient had multiple endocrine neoplasia type 1, and two additional tumors of the pancreas (body and head, <1 cm each) and a small 3-mm duodenal tumor were found during surgery.

is an intriguing tool, practitioners are still searching for a firm indication in the workup of gastrinoma. Proye et al.[10] found that the routine combination of SRS and EUS in all gastrinoma patients resulted in an overall sensitivity of 93% for preoperative localization and argue that both modalities should be considered for preoperative imaging.

Invasive testing has also been used to aid localization in patients with gastrinomas. Portal vein sampling and selective arterial infusion of secretin with hepatic venous sampling both have sensitivities above 75%. The major drawbacks of these two tests are the ability to regionalize disease rather than specify tumor location and the invasive nature of the procedures and their potential complications.

Detecting Familial Disease

Of patients with gastrinomas, 20% to 25% have this diagnosis in the setting of MEN1. This syndrome is characterized by primary hyperparathyroidism,

pituitary tumors, and pancreatic islet cell tumors or gastrinomas. A thorough family history should be obtained. Even in the absence of a positive family history, hereditary disease remains a significant possibility because patients may represent an index case, other family members may have yet to be diagnosed, or the patient's knowledge of his or her family's medical history may be incomplete. Thus, all patients should have their calcium, parathyroid hormone, and prolactin levels measured. Patients suspected of having familial disease should be offered genetic testing after appropriate counseling.

MANAGEMENT

Management of patients with gastrinoma is aimed at controlling acid hypersecretion and managing the tumor itself (which may in and of itself accomplish the first goal). Historically, surgical therapy was used to reduce acid secretion (via vagotomy) or to remove the acid-secreting surface altogether (via gastrectomy). With the development of antisecretory medications (H2-blockers and subsequently PPIs), surgical antisecretory therapies are now rarely required. Initial therapy typically requires a twice-daily, high-dose PPI (e.g., omeprazole 40 mg twice daily). Some authors advocate the use of basal acid output measurements for titration of this therapy.[11] In the vast majority of patients, the dose of PPI used can be titrated downward after initial control of acid hypersecretion.[12] However, downward titration should only be attempted after endoscopic documentation of healing in ulcers or esophagitis.

Although long-term control of acid hypersecretion with PPIs is possible, there are several potential downsides to chronic therapy with these agents. Patients on long-term antisecretory therapy are at risk for vitamin B12 deficiency. In addition, prolonged hypergastrenemia predisposes patients to the development of gastric carcinoid tumors secondary to chronic stimulation and hyperplasia of the enterchromafin-like cells of the stomach. As such, yearly endoscopies are a prudent strategy in this group of patients. Finally, a significant portion of these tumors ultimately prove to be malignant. Medical therapy aimed at controlling acid secretion fails to address the primary tumor and may allow the tumor to spread to distant sites at a higher than acceptable rate.

In guiding the surgical therapy of patients with gastrinoma, the distinction between sporadic and familial disease is critical. In sporadic disease, surgery is potentially curative and should be offered to all patients with a biochemical diagnosis and acceptable surgical risk and without extensive, unresectable metastases. In one of the largest series published, Norton et al.[13] compared 160 patients undergoing resection for gastrinoma with 35 patients managed with non-operative therapy. The groups were similar with respect to stage and proportion of patients with familial disease

(21% to 26%). At 12 years follow-up, 41% of the surgical group was deemed cured, defined as a normal FSG level, normal secretin stimulation test result, and negative imaging study results. In addition, significantly more patients in the medical management group developed liver metastases (29% vs. 5%), and the 15-year disease-related survival was significantly higher in the surgery group (98% vs. 74%).

Surgery for patients with sporadic disease is typically offered irrespective of preoperative localization because most "occult" tumors can be found with careful intraoperative exploration. After examination of the abdominal cavity to exclude unexpected distant disease, exploration involves mobilization of the duodenum and pancreas by means of an extended Kocher maneuver and dissection along the inferior border of the pancreas. Careful palpation and intraoperative ultrasonography are then used to search the pancreas. The duodenum is then inspected and palpated. Endoscopic transillumination may facilitate this initial inspection. Performing a duodenotomy is a crucial step in the localization of gastrinomas given the small size and submucosal location of these tumors.[14] Norton et al.[15] compared localization rates and outcomes in 143 patients who had a duodenotomy ($n = 79$) or did not ($n = 64$) during operative exploration for gastrinoma. Operations in which a duodentomy was performed were significantly more successful in locating a gastrinoma compared with those not using this maneuver (98% vs. 76%). In addition, cure rates were significantly higher in the duodenotomy group at both the immediate postoperative check and at a median follow-up of 8.8 years.

Surgical Therapy for Patients with Sporadic Tumors

Solitary pancreatic gastrinomas are typically amenable to enucleation. Pancreatic resections should be reserved for larger tumors with evidence of local invasion. Distal pancreatectomy with lymph node dissection is appropriate for patients with tumors in the pancreatic tail. Larger tumors in the head of the pancreas may be managed with enucleation and lymph node dissection or, if necessary, a pancreaticoduodenectomy. Duodenal tumors can usually be enucleated if they are small or removed with a full-thickness resection of the duodenal wall.

Surgical Therapy for Patients with Multiple Endocrine Neoplasia Type 1

Recommendations in patients with MEN1-related gastrinomas are more controversial because of the common occurrence of multiple tumors and the rarity of cure after surgery. A number of treatment strategies have been proposed in the literature, including the recommendation for non-operative treatment of all of these patients. A more common approach is to recommend surgery for these patients in the setting of disease that is detectable on

preoperative imaging and is above a given size criterion (typically 2 to 3 cm).[3] This approach is based on the observation that liver metastases are a major prognostic factor for long-term survival and the risk of liver disease increases significantly with tumor size larger than 2 cm.

Some authors have proposed a more aggressive approach, recommending surgery in all patients with an unequivocal biochemical diagnosis of gastrinoma.[2] This is the approach we have adopted at our center. Proponents of this position cite the lower risk of liver metastases after surgery and the relatively low mortality of more aggressive procedures. Traditionally, the operative procedure in these patients, pioneered by Dr. Norman Thompson, has been a distal pancreatectomy, lymph node dissection, enucleation of pancreatic head tumors, and duodenotomy with enucleation or resection of duodenal tumors. Unfortunately, only a small proportion of these patients are biochemically free of disease in the immediate postoperative period. Given that the vast majority of tumors in these patients are found in the duodenum, some authors have more recently recommended a pylorus-preserving pancreaticoduodenectomy. Currently, only short-term follow-up with small numbers of patients is available. However, in one series,[16] 77% of patients managed with this approach were deemed free of disease at 6 months follow-up.

Management of Advanced Disease

Unfortunately, up to one third of patients with gastrinoma have distant metastases at the time of diagnosis, most commonly involving the liver. Aggressive surgical treatment is advocated by most authors because traditional chemotherapy has limited efficacy in these patients.[2,17] Formal anatomic or wedge resections are recommended when disease is confined to one lobe. Resection in combination with other modalities such as radiofrequency ablation may be used when complete resection of disease is not possible. In addition, many experts advocate "debulking" procedures when up to 90% of grossly visible disease can be resected. This is of particular utility in patients with poorly controlled symptoms.

In general, outcomes of surgical treatment for patients with advanced disease are reported within larger series that include other functional and nonfuctional neuroendocrine tumors. Aggressive surgical management appears to be associated with prolonged survival in these patients. In one series, 5-year survival was 72% for those undergoing aggressive surgical management compared with 25% in those treated medically.[17]

The goals of medical treatment in advanced disease are to control acid hypersecretion and symptoms and direct effects on the tumor. PPIs are highly effective at controlling acid hypersecretion. In addition to controlling acid hypersecretion and symptoms as well as to directly affect the tumor, octreotide has demonstrated direct antitumor effects, but the response is

more unpredictable than for other neuroendocrine tumors. In one series, 75% of patients responding to octreotide therapy were alive at 4- to 8-year follow up.[18] In patients who did not respond to this therapy, only 21% were alive at last follow-up. Traditional systemic chemotherapy has also been used in metastatic gastrinoma but with limited benefit.

Outcomes

Ultimately, gastrinomas prove to be malignant in at least 60% of patients. However, similar to other neuroendocrine tumors, slow disease progression and long-term survival are common. In a recent large series of 195 patients, 15-year disease-specific survival was 93% in patients treated surgically and 73% in those not undergoing surgery.[13] A number of factors have been linked to survival in individuals with gastrinoma. The most important one is the presence or absence of liver metastases. The 15-year survival in patients without liver disease is 90% compared with 30% in those with metastases.[19] Other factors potentially affecting survival include primary tumor size, tumor location, presence or absence of MEN1, and high initial FSG level. Patients with MEN1, although virtually incurable, tend to have smaller tumors, a lower incidence of metastatic disease, and 10- to 15-year survival that approximates 100%. Interestingly, lymph node status appears to have no effect on long-term survival in patients with gastrinoma.

PRACTICAL PEARLS

- The incidence of gastrinoma is between one and three per 1 million people.
- Twenty percent of gastrinomas occur in association with MEN1.
- Sixty percent of gastrinomas are malignant.
- Gastrinoma should be suspected in patients with severe, recurrent, or complicated PUD; PUD in the absence of *H. pylori* infection or NSAID use; PUD with diarrhea; multiple ulcers or odd locations on endoscopy; and family history compatible with MEN1.
- A FSG level more than 10 times the upper limit of normal in the setting of low gastric pH is diagnostic for gastrinoma.
- Patients with suspected gastrinoma and elevations of FSG one to 10 times the upper limit of normal should undergo secretin stimulation testing.

(*Continued*)

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Chapter 19

Carcinoid Tumors

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Carcinoid tumors were first described in a 1907 paper titled "Karzinoide Tumoren des Dünndarms," or "Cancer-like Tumors of the Gut," by the German pathologist Siegfried Oberndorfer.[1] He used the word *karzinoide* to illustrate the benign behavior of a tumor whose cells appeared malignant under the microscope.[1] Later in 1914, Gosset and Masson characterized the endocrine-related properties of carcinoid tumors.[2] Over the years, a considerable amount of confusion has developed over the definition of *carcinoid tumors*, largely because, historically, the name *carcinoid* was used in reference to all neuroendocrine tumors. In general, the term *carcinoid* refers to endocrine tumors of the gastrointestinal (GI) tract, bronchopulmonary epithelium, and rare other sites but not to pancreatic neuroendocrine tumors (PNETs), also called islet cell tumors. This chapter focuses on GI carcinoid tumors, which arise from enterochromaffin, enterochromaffin-like, or Kulchitsky cells that are part of the diffuse neuroendocrine cell types of the gut. These cells are distinguished by their ability to secrete bioactive peptides and amines, such as serotonin, somatostatin, gastrin, and histamine.

EPIDEMIOLOGY

In the United States, the overall age-adjusted incidence of carcinoid tumors has increased over the past 5 decades from about 1.5 to 2.75 per 100,000 people.[3] This trend has mirrored the increased incidence observed in all neuroendocrine tumors over the same time period from about 2.5 to 5.0 cases per 100,000.[3] Carcinoid tumors make up almost 50% of all neuroendocrine tumors, with the majority of carcinoid tumors (68%) occurring in the GI tract and the remainder in the bronchopulmonary system (25%).[3] Rarely, carcinoid tumors have been reported in other locations, including the esophagus, ovaries, testis, thymus, and other endocrine tissues of the body.[3] Classically, the appendix was thought to be the most predominant

site within the GI tract for these tumors. However, more recent studies reveal that the majority of GI carcinoid tumors occur in the small intestine (42%), rectum (27%), and stomach (9%), with only about 5% of these tumors being found in the appendix. In addition, approximately 1% of patients present with more than one primary site of disease.

The rates of carcinoid tumors have been examined in various subsets of the population. The age-adjusted incidence of carcinoid tumors is higher in African Americans compared with whites and is highest in African-American men.[3] Tumors with the highest rates of metastases include cecal, pancreatic, and small intestinal carcinoid tumors (82%, 72%, and 58%, respectively).

RISK FACTORS

The exact etiology of carcinoid tumors remains unknown. However, certain risk factors and conditions are associated with a predisposition for developing carcinoid tumors. Furthermore, genetic studies have revealed chromosomal abnormalities that occur more frequently in patients with these tumors. As mentioned, African-American men have the highest rate of developing GI carcinoid tumors.[3] People with well-educated social backgrounds (relative risk [RR] = 2.8), living in major metropolitan areas (RR = 1.39), or who have a family history of a first-degree relative with a carcinoid tumor (RR = 3.6) also have an increased risk for carcinoid development.[4] In addition, cigarette smoking and alcohol consumption are connected to an increased chance of having a GI, but not a pulmonary, carcinoid tumor.[5] Currently, no dietary risks have been identified. GI conditions, including peptic ulcer disease, pernicious anemia, chronic atrophic gastritis, and Zollinger-Ellison syndrome, are also known to increase the risk for carcinoid tumors of the GI tract, especially gastric carcinoid tumors.

Genetics

Specific genetic disorders and chromosomal abnormalities are associated with a predisposition for developing carcinoid tumors. Multiple endocrine neoplasia type 1 (MEN1) is one disorder that has been identified as a risk factor for neuroendocrine tumor development, including carcinoid tumors. Loss of heterozygosity at 11q13, which codes for the menin gene, has been observed in sporadic duodenal and Zollinger-Ellison syndrome–associated carcinoid tumors.[6,7] In addition, case reports of patients with neurofibromatosis type 1 and ampullary carcinoid tumors as well as von Hippel-Lindau syndrome and gallbladder carcinoid tumors have been published, but molecular data are lacking.[6] Increased use of gene sequencing techniques, comparative genomic hybridization, and microsatellite analysis has allowed identification of chromosomal abnormalities that occur with

increased frequency in GI carcinoid tumors. Chromosomal losses on chromosomes 9, 11, 16, and 18 and gains on chromosomes 4, 5, 17, and 19 all have been shown in GI carcinoid tumors. However, because of the rarity of these tumors, several of the studies examining risk factors and genetic alterations associated with carcinoid tumors are limited by sample size.

CLINICAL PRESENTATION

The majority of patients with carcinoid tumors are asymptomatic, and their tumors are found incidentally on imaging studies or during a procedure such as endoscopy or surgery. However, for patients with symptoms, the clinical behavior of GI carcinoid tumors varies greatly and depends largely on the origin of the primary tumor and whether or not the tumor is functioning (i.e., secretes bioactive hormones or peptides that cause symptoms). Traditionally, GI carcinoid tumors have been classified based on their embryologic origin—foregut (gastric and duodenal), midgut (small intestine, appendix, and proximal colon), or hindgut (distal colon and rectum). Functioning tumors secrete a myriad of substances, including (but not limited to) serotonin, histamine, somatostatin, chromogranin A, bradykinin, tachykinin, substance P, gherlin, secretin, melatonin, gastrin, motilin, and vasoactive intestinal peptide. These substances cause the symptoms that are associated with the carcinoid syndrome, including flushing, diarrhea, wheezing, heart disease, and pellagra. However, only about 10% of patients develop the carcinoid syndrome because the majority of carcinoid tumors are nonfunctioning.[4] Because of the indolent nature of these tumors and frequent nonspecific signs, patients commonly have symptoms for 1 to 2 years before diagnosis. At the time of diagnosis, 10% to 15% of patients with carcinoid tumors have distant metastases, and up to 80% of symptomatic patients are found to have metastatic or advanced disease.[3]

Patients with foregut carcinoid tumors may present with symptoms of GI or biliary obstruction, abdominal pain, duodenal or peptic ulcers, bleeding, atypical carcinoid syndrome, or a history of Zollinger-Ellison syndrome. However, these cancers are often found incidentally on upper endoscopy. The atypical symptoms of carcinoid syndrome are uncommon and include more intense, protracted, purplish flushing and the development of telangectasias on the extremities and upper body.[8] Gastric carcinoid tumors are usually multiple small tumors and have been classified into three main types with different characteristics. Type I represent the majority (80%) of these tumors and is associated with chronic atrophic gastritis and pernicious anemia.[6] Type I gastric carcinoid tumors rarely metastasize and are usually nonfunctional and asymptomatic.[6] Type II gastric carcinoid tumors are the least common (5%), are seen in patients with MEN1 or Zollinger-Ellison

syndrome, and exhibit more aggressive behavior.[6] Last, type III tumors are larger often single tumors with the most aggressive behavior.[6]

Midgut carcinoid tumors are the most common type of carcinoid tumors and, when in the small bowel, frequently cause abdominal pain, GI obstruction, bleeding, or diarrhea. Small bowel carcinoid tumors usually present in the fifth and sixth decades of life. These tumors may be multicentric and may cause mesenteric fibrosis, which may result in mesenteric kinking, mesenteric strangulation with ischemia, or ureteral obstruction. Tumors that originate in the jejunum, distal ileum, and cecum metastasize to the liver almost twice as often as other GI tumors, so they are associated with a higher rate of carcinoid syndrome.[3,4] When metastatic liver disease is present, the bioactive hormones secreted by these tumors reach the systemic circulation, resulting in the carcinoid syndrome. Appendiceal carcinoid tumors most commonly present as appendicitis or are found incidentally during surgery for another disease. Carcinoid tumors of the appendix are usually localized, small, and found during the fourth or fifth decades of life.[9]

Carcinoid tumors of the hindgut tend to be large cancers with frequent metastases when located in the distal colon but small and localized tumors when located in the rectum.[10] Symptoms of pain, anorexia, weight loss, and bleeding can been seen with colonic carcinoid tumors. These colonic hindgut carcinoid tumors are also present more commonly in women and during the seventh decade of life.[11] Many of these tumors metastasize to regional lymph nodes and to the liver but not as frequently as right-sided colonic carcinoid tumors.[3] Rectal carcinoid tumors, on the other hand, rarely metastasize and even more rarely lead to the carcinoid syndrome.[11] Patients with rectal carcinoid tumors may present with pain, bleeding, or constipation, but almost 50% of these patients are diagnosed during colonoscopy screening.[9]

DIAGNOSTIC EVALUATION

The wide spectrum of biologic and clinical characteristics of GI carcinoid tumors frequently makes diagnosis difficult. A high index of suspicion is needed to ensure timely diagnosis and treatment of these patients. Clinical presentation, laboratory tests, and histologic evaluation all play a role in the diagnosis of GI carcinoid tumors. However, microscopic confirmation of tumor pathology with immunohistochemical staining of neuroendocrine tumor markers provides the most definitive diagnosis. Figure 19-1 provides an algorithm for the diagnostic evaluation of carcinoid tumors of the GI tract.

Biochemical Tests

Several biochemical tests for various tumor markers may be performed to help diagnose carcinoid tumors. Classically, diagnosis of GI carcinoid

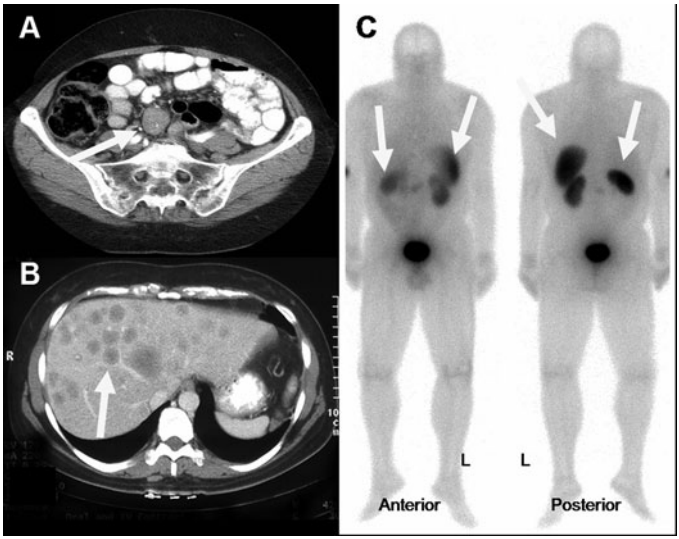

Figure 19-1. Abdomen and pelvic computed tomography scan showing an enlarged lymph node (*arrow*) of a patient whose primary small bowel tumor could not be localized (**A**) but whose multiple liver metastases are well visualized (**B**). Somatostatin receptor scintigraphy, a more sensitive and specific radiologic technique for carcinoid tumors, reveals a large tumor burden in the liver as well as a primary small bowel tumor (**C**).

tumors has been made by measuring 24-hour urinary 5-hyrdroyindolacetic acid (5-HIAA), the breakdown product of serotonin. In patients with symptoms of the carcinoid syndrome, the sensitivity and specificity of this test are both nearly 100%.[11] However, in the absence of carcinoid syndrome, the sensitivity is closer to 70%, and in patients with foregut or hindgut tumors, urinary 5-HIAA levels are even less sensitive.[8,11] To obtain accurate 5-HIAA measurements, certain dietary and drug restrictions must be followed. Both urinary and serum serotonin levels may also be elevated in patients with GI carcinoid tumors but are used infrequently.

Serum chromogranin A measurement is another commonly used test for the diagnosis of GI carcinoid tumors and has a similarly high sensitivity (80% to 100%), but is less specific than urinary 5-HIAA levels.[11] Renal failure, inflammatory bowel disease, atrophic gastritis, and chronic use of

proton pump inhibitors can all cause falsely elevated chromogranin A levels.[10,11] Unlike urinary 5-HIAA, chromogranin A is very sensitive in patients with foregut and hindgut carcinoid tumors (87% and 100%, respectively).[11] Chromogranin A is useful as a marker to follow for tumor recurrence as well because a direct correlation has been found with serum levels and tumor burden. In addition, chromogranin B has high specificity for patients with GI carcinoid tumors.[10]

Alternative biochemical tests for diagnosing GI carcinoid tumors are available. Additional biomarkers that can be tested for include pancreatic polypeptide, α-or β-human choriogonadotropin (α- or β-HCG), neuron-specific enolase, neuropeptide K, and substance P, among others.[12] The specificity of these tests is lower than for chromogranin A and depends on the location of the primary tumor.

Radiographic Studies

Multiple imaging modalities are available to localize GI carcinoid tumors and determine the extent of tumor burden. Because of the small size of many carcinoid tumors (primary or metastatic), they can be difficult to image. The site of the primary tumor may remain unknown in up to 20% of patients.[10,12] The most commonly used radiographic method is conventional computed tomography (CT). However, the sensitivity of CT and similar tests, such as magnetic resonance imaging (MRI), in detecting the primary tumor is approximately 50% (Figure 19-1A). These tests are more useful for identifying and monitoring hepatic metastases, with sensitivities in the range of 70% to 85% (Figure 19-1B).[10,12] CT images often reveal mesenteric stranding or fibrosis in addition to mesenteric lymphadenopathy. The sensitivity of CT may be increased when it is combined with other radiologic methods such as positron emission tomography. Because of the indolent nature and low metabolic rate of GI carcinoid tumors, [^{18}F]fluorodeoxyglucose (FDG) is not useful for imaging, but radiolabeled amine precursors (i.e., 18-flouro-levodopa and 11-carboxy-serotonin) show highly selective uptake by carcinoid tumors.[8,10]

The most sensitive radiographic study for GI carcinoid detection is somatostatin receptor scintigraphy (SRS) or OctreoScan (Figure 19-1C). The sensitivity and specificity of SRS is 80% to 90%, and the positive predictive value is 100%.[11] Almost 90% of carcinoid tumors express surface receptors that bind somatostatin or analogs of somatostatin. SRS uses uptake of ^{111}In-octreotide by these receptors to identify deposits of carcinoid tumors. This method is particularly useful for identifying bone metastases and has the advantage of imaging the whole body. Widespread availability of SRS is limited, however. Traditional bone scans also can be used to locate metastatic bony disease. Scintigraphy with ^{131}I-methyl iodobenzylguanidine (MIBG) is another nuclear imaging technique with slightly lower sensitivity and

specificity than SRS. In patients with SRS negative scans, particularly in those with hindgut tumors, ^{123}I-MIBG can be used as an alternative.[12]

Contrast-based studies, including upper GI and small bowel series, enterocolysis, and barium enemas, also are used to detect GI carcinoid tumors. Target signs of an ulcerated lesion, narrowing from fibrosis, and other filling defects can be visualized with these tests but are nonspecific findings. In general, contrast-based studies lack the sensitivity and specificity associated with alternative methods, particularly for hindgut carcinoid tumors. More recently, CT enterocolysis has been used.

Other radiographic studies that are available for localizing GI carcinoid tumors include upper or lower endoscopy, transabdominal ultrasonography, endoscopic ultrasonography (EUS), angiography, and video capsule endoscopy. For gastric, duodenal, and rectal carcinoid tumors, endoscopy with or without EUS can be very useful and allow for biopsy of the lesion.

MANAGEMENT

The treatment of choice for patients with GI carcinoid tumors is surgery because resection remains the only curative option. Medical and other nonsurgical therapies, such as hepatic artery embolization, are adjuncts to surgery and should be used alone when surgery is not an option (e.g., when the patient has unresectable disease or another condition that precludes surgery). Frequently, the treatment of patients with carcinoid tumors involves a multimodal approach that spans several medical specialties. One possible management algorithm is shown in Figure 19-2. However, data supporting a specific treatment protocol are lacking, and care should be individualized to each patient. Similar to the clinical presentation, management of patients with GI carcinoid tumors depends on the location of the primary tumor and whether metastatic disease is present.

Surgical

Similar to most cancers, en-bloc removal of the tumor with involved lymph node basins and any metastatic disease to achieve an R0 resection is the optimal treatment for the majority of GI carcinoid tumors. Fortunately, these tumors do not usually invade adjacent organs, so en-bloc resection of adjacent viscera is rarely necessary. However, certain exceptions and considerations should be made when operating on GI carcinoid tumors. Patients with type I and II gastric carcinoid tumors that are smaller than 2 cm can be observed with endoscopic surveillance or have their tumors removed either endoscopically or surgically.[11] If the tumors are larger than 2 cm, multiple, or recurrent, excision is recommended with consideration for antrectomy to remove the source of hypergastrinemia.[11] On the other hand, patients with

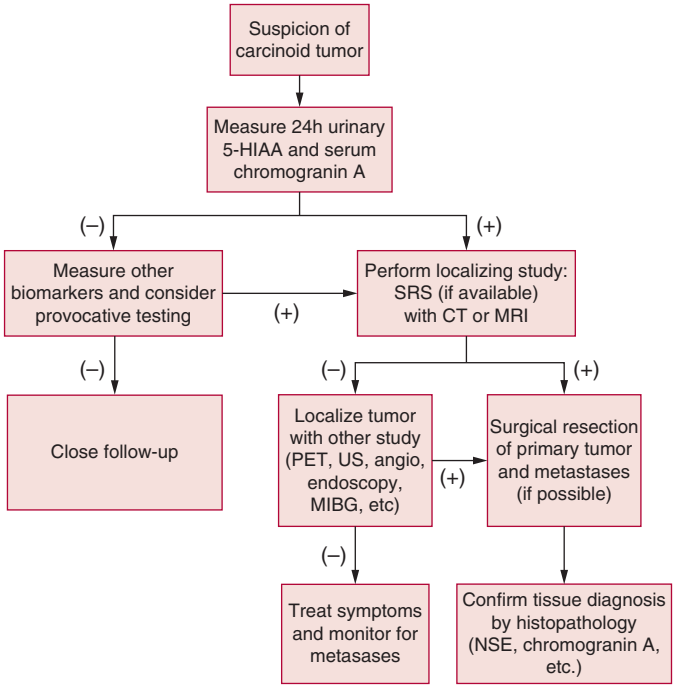

Figure 19-2. Suggested algorithm for the diagnosis of gastrointestinal carcinoid tumors. CT = computed tomography; 5-HIAA = 5-hyrdroyindolacetic acid; MIBG = ^{131}I-methyl iodobenzylguanidine; MRI = magnetic resonance imaging; NSE = neuron specific enolase; PET = positron emission tomography; SRS = somatostatin receptor scintigraphy; US = ultrasonography.

type III carcinoid tumors should undergo total gastrectomy because these tumors are much more aggressive.[11] Duodenal carcinoid tumors smaller than 1 cm also can be removed endoscopically or enucleated, but larger lesions require transduodenal resection or pancreaticoduodenectomy.

Midgut carcinoid tumors are frequently associated with nodal or metastatic disease. These tumors tend to cause a desmoplastic reaction with resultant fibrosis or encase mesenteric vessels that lead to mesenteric ischemia or bowel obstruction. En-bloc resection of small bowel carcinoid

tumors should include a generous wedge of the associated mesentery to remove mesenteric and lymph node disease and prevent future obstructive or ischemic complications. However, ligation of the superior mesenteric vessels should not be performed, and excessive resection that would result in short bowel syndrome should be avoided. Small bowel resection for carcinoid tumors can be technically challenging because the mesentery is often thickened and shortened. A decrease in tumor-related symptoms with an increase in overall survival has been associated with an aggressive surgical approach to mesenteric disease.[11] For appendiceal tumors smaller than 2 cm, simple appendectomy is an adequate resection as long as the margins are negative and no evidence of local or lymphatic invasion is present. A right hemicolectomy is the recommended treatment for appendiceal carcinoid tumors 2 cm or larger or when mesoappendiceal invasion is noted because more than 30% of these patients may have lymph node metastases.

Carcinoid tumors of the colon are treated like colon adenocarcinomas with formal hemicolectomy and appropriate mesenteric lymphadenectomy. Large rectal carcinoid tumors also require traditional surgeries such as a low anterior or abdominoperineal resection, depending on the exact tumor location. On the other hand, small rectal carcinoid tumors can be treated with local excision when the tumor is smaller than 2 cm and EUS shows no evidence of nodal disease. Several series of transanal endoscopic microsurgery (TEM) have been reported for rectal carcinoid tumors located between 4 and 18 cm from the anal verge.[13] These studies claim TEM to be advantageous over more invasive procedures because it provides better exposure, similar outcomes, and decreased length of hospital stay.[13]

Minimally invasive approaches have also been used for treatment of patients with other GI carcinoid tumors. Case reports and small series of laparoscopic resections for gastric, duodenal, small bowel, appendiceal, and colonic carcinoid tumors can be found in the literature. However, data on the safety and efficacy of these approaches compared with open procedures are lacking except for carcinoid tumors of the appendix. Because appendiceal carcinoid tumors are often found incidentally during appendectomy for appendicitis and because laparoscopy is the most common approach in these patients, retrospective comparisons with open appendectomy have been possible. Outcomes of laparoscopic appendectomies for carcinoid tumors are similar to those of open surgery.[14] Laparoscopic techniques can also be used in the treatment or diagnosis of metastatic disease. Both laparoscopic radiofrequency (RFA) and cryoablation of hepatic carcinoid metastases have been reported for local and symptomatic control of these patients.[15] Laparoscopic resection of carcinoid liver metastases is extremely rare because of the diffuse nature of metastatic disease and the difficulty of using laparoscopic intraoperative ultrasonography.

Open surgery is the mainstay of management for patients with metastatic GI carcinoid tumors. Even in the presence of known distant metastases, resection of the primary tumor is recommended because a survival benefit has been shown in these patients.[16] Studies examining curative and palliative hepatic resection of neuroendocrine metastases reveal a survival benefit when curative resection is achieved.[17] Furthermore, cytoreductive therapy and surgical debulking of these metastases provide symptom reduction and improved survival compared with patients not undergoing surgery.[17] Anatomic or wedge resection should be performed when feasible at the time of primary tumor removal. However, larger hepatectomies may require a staged procedure. Intraoperative ultrasonography is an important adjunct to assess for small metastases not seen on CT scan or other preoperative imaging studies.

Ablative procedures such as RFA or cryotherapy also offer excellent palliative alternatives, with the majority of patients experiencing symptomatic relief. A combination of hepatic resection and RFA or cryoablation is often needed to address bilobar disease and preserve hepatic function. These ablative techniques may be used during open or laparoscopic surgery or percutaneously under radiographic guidance. Orthotopic liver transplantation is another treatment option with an unclear role.[9] Because metastatic carcinoid tumors are frequently not amenable to complete resection, several nonsurgical therapies have been developed to address patients with symptomatic disease.

Embolization

Hepatic artery embolization is a nonsurgical invasive treatment indicated for the palliation of symptomatic patients with unresectable hepatic carcinoid metastases. Because the blood flow of these tumors comes primarily from the hepatic arteries, this method works by inducing tumor necrosis. The procedure can be performed with or without the addition of intraarterial chemotherapy. Symptomatic improvement is generally observed in 60% to 90% of patients, and tumor regression can be seen in up to 50% of patients.[16] Several studies also report a survival benefit for patients treated by embolization whether used alone or in combination with surgical resection.[16,17] Embolization with radiolabeled microspheres is a newer technique, so long-term data are lacking.

Medical

Medical management of patients with metastatic GI carcinoid tumors focuses primarily on symptomatic relief of those with carcinoid syndrome. Somatostatin analogs, such as octreotide, lantreotide, and the investigational agent SOM230, are used to treat the debilitating symptoms of flushing,

palpitations, and diarrhea. These analogs act by binding the somatostatin receptors on the surface of carcinoid tumors and inhibiting hormone production. Various short- and long-acting preparations are available that can be administered either subcutaneously or intramuscularly. These drugs are highly effective at reducing tumor markers and improving symptoms; however, tolerance can develop.[10,11] Some evidence suggests that octreotide may also have an antitumor effect, and actual tumor shrinkage has been observed but is rare.[11] Interferon-α (IFN-α) is another agent used for palliation of the symptoms of carcinoid syndrome; it has similar efficacy to the somatostatin analogs.[9,10] Control of symptoms, decrease in urinary 5-HIAA, and tumor regression are all possible with the use of IFN-α.[9] Unfortunately, this drug is poorly tolerated because it has substantial side effects, including fever, fatigue, anorexia, and weight loss. Combination therapy with somatostatin analogs and IFN-α may be effective for patients who do not respond to or tolerate either drug alone. Treatment of specific symptoms with targeted agents such as serotonin antagonist (i.e., odanesetron) for diarrhea is also often required.

Systemic chemotherapy has also been examined in patients with metastatic carcinoid tumors but has limited efficacy. Multiple agents, including streptozocin, fluorouracil, doxorubicin, cyclophosphamide, irinotecan, IFN-α, oxaliplatin, capcitabine, and others, have been studied.[10] Both single- and multi-agent regimens have limited response together with significant toxicities.[9,10] Newer antiangiogenic drugs, such as vascular endothelial growth factor monoclonal antibodies, tyrosine kinase inhibitors, epidermal growth factor receptor inhibitors, and mammalian target of rapamycin inhibitors, are currently under investigation.[10] A few examples of these newer investigational treatments are bevacizumab, sunutinib, sorafenib, vatalanib, temsirolimus, and everolimus.[18] Similar to the results seen with cytotoxic chemotherapy, several of these drugs appear more effective in islet cell tumors than carcinoid tumors.[10]

Other tumoristatic peptide-directed therapies are currently being investigated as well, namely radionuclide-labeled somatostatin analogs. These hormone receptor radiation therapies include treatment with ^{131}I-MIBG-octreotide, ^{111}In-pentetreotide, and other compounds.[8] Theoretically, internalization of the radionuclide segment into the carcinoid tumor can deliver high-dose localized radiation specifically to the tumor cells. These treatments are limited to patients with SRS-positive scans and are still investigational.

Prognosis

As with the clinical presentation, diagnosis, and management of GI carcinoid tumors, the prognosis for patients with this disease depends largely on where the primary tumor is located, the extent of the disease, and tumor

histology. In general, patients with carcinoid tumors have a favorable prognosis compared with patients with adenocarcinomas arising from the same organ. For instance, whereas patients with type I and II gastric carcinoid tumors have 5-year survival rates of more than 90%, 5-year survival rates for patients with stage I gastric adenocarcinoma range from 50% to 80%.[6] Type III gastric carcinoid tumors metastasize in more than 50% of patients and thus have a poorer prognosis (75% to 80% 5-year survival). Overall for duodenal carcinoid tumors, the other foregut GI location, approximately 60% of patients will be alive at 5 years.[19] The prognosis for patients with duodenal carcinoid tumors larger than 2 cm is worse because these patients have a higher rate of recurrence.[19]

Even for midgut carcinoid tumors that share embryologic origins, the prognosis varies widely depending on the location of the cancer. At the time of diagnosis, small bowel carcinoid tumors in the jejunum and ileum are associated with lymph node or distant metastases in up to 60% of patients and have the highest rate of associated noncarcinoid cancers (29%) according to recent Surveillance, Epidemiology and End Results (SEER) data.[3] Patients with small bowel carcinoid tumors that are localized and have not spread beyond regional lymph node basins have 5-year survival rates between 60% and 70%.[3] If distant metastases are present, survival decreases to 50% or less at 5 years.[3] On the contrary, whereas 80% to 90% of patients who have locoregional appendiceal carcinoid tumors are alive at 5 years, fewer than 30% of patients with distant metastases are alive at 5 years.[3] Cecal carcinoid tumors are similar to appendiceal carcinoid tumors in terms of prognosis. Five-year survival rates for patients with locoregional versus distant metastatic cecal carcinoid tumors are 78% and 44%, respectively.[3]

Patients with carcinoid tumors of the hindgut tend to have favorable prognoses, especially when the tumors are localized. Patients with localized carcinoid tumors of the descending or sigmoid colon have 5-year survival rates ranging from 75% to 80%, which decreases to 50% if regional spread has occurred.[3] SEER data from 1992 to 1999 reveal that overall, 65% to 75% of these patients at any stage are alive at 5 years.[3] Rectal carcinoid tumors have the best overall 5-year survival rates, with 88% of these patients still alive at 5 years.[3] The same SEER data show that localized anorectal lesions may have a 100% survival rate at 5 years but only 25% to 30% survival rates if metastases are present. The size of rectal tumors correlates closely with both metastatic risk and prognosis.[11]

Several factors have been identified that predict prognosis in patients with GI carcinoid tumors. These risk factors include both patient and tumor characteristics. Age older than 50 years, male gender, presence of the carcinoid syndrome, and elevated urinary and serum biomarkers have all been

described as negative prognostic indicators.[11] In addition, increased tumor size, increased depth of invasion, presence of lymph node or hepatic metastases, and greater than 50% liver involvement are predictors of poor outcome.[11] Patients with tumors of the small bowel and colon also tend to have worse prognoses. Other tumor characteristics that are unfavorable include increased proliferative index (higher K*i*-67) and elevated expression of *p53*. When tumors are discovered incidentally, patients generally have a better prognosis compared with patients who present with symptoms.[11]

SURVEILLANCE AND FOLLOW-UP

Specific recommendations for the surveillance and follow-up of patients with GI carcinoid tumors vary greatly. This phenomenon is likely because carcinoid tumors are a heterogeneous group of cancers that display a wide variety of biological behaviors. Management and subsequent monitoring of patients with GI carcinoid tumors needs to be tailored to each individual, and no single protocol should be used (See Figure 19-3).

Patients with residual disease and symptoms should be followed up with every 3 to 4 months. However, if their symptoms are well controlled, the duration between follow-up appointments can be up to every 6 months. The serum chromogranin A level should generally be monitored at these appointments every 3 to 4 months with an emphasis placed on the trend of the values rather than the specific values themselves. Substance P can also be checked and followed if it is initially elevated. Levels of urinary 5-HIAA may be monitored at the same time intervals as chromogranin A or less frequently (every 6 months). Imaging of liver metastases by CT or MRI with contrast is also recommended every 6 months. Some physicians advocate alternating CT or MRI with SRS, but others believe that SRS should only be performed after a baseline scan and if the results will change therapy. Echocardiography is another test that should be performed at baseline and then annually for early detection of valvular abnormalities associated with carcinoid heart disease. If the patient has normal serum or urinary serotonin and 5-HIAA levels, echocardiographic evaluation may not be necessary.

Patients without residual disease or with relatively benign carcinoid tumors should be followed with different regimens. Gastric carcinoid tumors are usually monitored endoscopically, and unless they are type III or have high metastatic potential, do not require additional imaging. On the other hand, appendiceal carcinoid tumors smaller than 2 cm require no follow-up if the tumor is confined within the wall of the appendix. Similarly, follow-up of rectal carcinoid tumors that are 1 cm or smaller and are completely excised is not necessary.

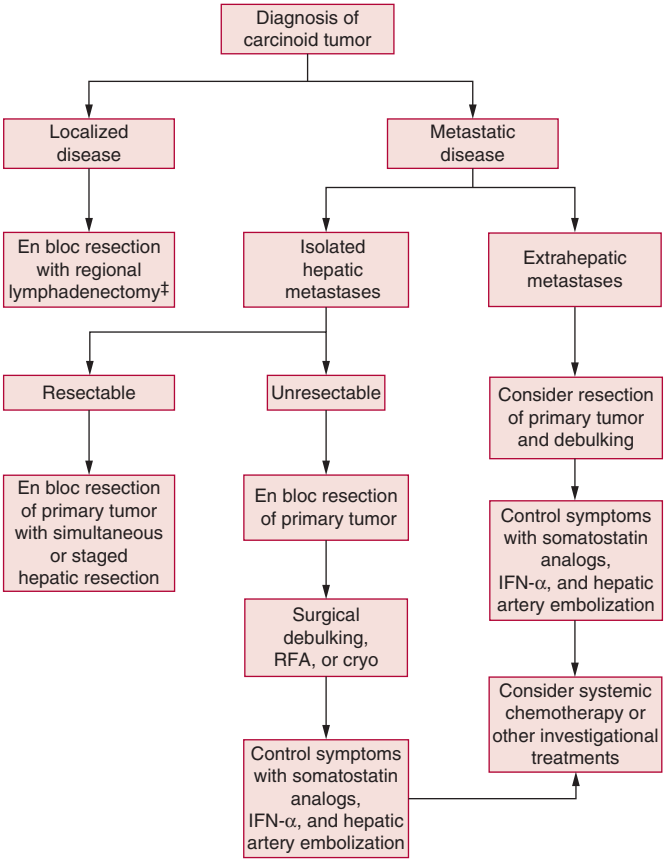

Figure 19-3. Suggested algorithm for the management of patients with gastrointestinal carcinoid tumors. IFN-α = interferon-α; RFA = radiofrequency.

PRACTICAL PEARLS

- Carcinoid tumors are thought to be derived from enterochromaffin or Kulchitsky cells and secrete bioactive substances such as serotonin, chromogranin, pancreatic polypeptide, and others.
- Carcinoid syndrome generally occurs when liver metastases have developed, is present in only 10% of individuals with carcinoid tumors, and classically causes flushing and diarrhea.
- The small intestine is the most common site of GI carcinoid tumor development followed by the rectum, stomach, and appendix.
- Diagnosis of GI carcinoid tumors is made by measuring serum biomarkers; localizing the tumor; and confirming tissue diagnosis with immunohistochemical staining for chromogranin A, neuron-specific enolase, and synaptophysin.
- Surgical resection is the only curative treatment option for patients with GI carcinoid tumors and should be performed with en-bloc resection of the primary tumor, including a wide area of mesentery when it is a small bowel carcinoid tumor.
- Hepatic metastases should be completely excised or debulked when possible. Residual hepatic tumor can be treated with RFA, cryoablation, or hepatic artery embolization.
- Simple appendectomy is adequate treatment for appendiceal carcinoid tumors smaller than 2 cm that are confined to the appendix and have negative margins; otherwise, right hemicolectomy is the treatment of choice.
- Symptoms of the carcinoid syndrome may be treated medically with octreotide or IFN-α.

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Chapter 20

Other Functional and Nonfunctional Neuroendocrine Tumors

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EPIDEMIOLOGY

The pancreas is a retroperitoneal organ that is composed of multiple lineages of neuroendocrine cells interspersed within the larger structure of its exocrine ductal system. The neuroendocrine cells are histologically grouped into islands known as *islets of Langerhaans*. These islet cells are differentiated such that they each synthesize and secrete only one of six pancreatic endocrine hormones. These hormones play an integral role in the fine balance of normal physiology. Both benign and malignant neoplastic processes can affect the pancreatic neuroendocrine cells. This tumor formation may be the result of a sporadic, somatic mutation or an inherited genetic predisposition to tumorigenesis. Although some of the tumors that develop retain sufficient differentiation to elicit the specific hormone made by the cell of origin, defects are often present in the normal feedback control of hormone release. This may result in a clinically detectable syndrome of hormone excess that may be diagnostically useful before detection of symptoms related to the primary tumor mass or metastatic burden. Pancreatic neuroendocrine tumors (PNETs) are relatively rare, with approximately five cases occurring per 1 million people annually.

PNETs are named relative to the chief hormone produced by the tumor cells. For example, there are insulinomas, gastrinomas, glucagonomas,

somatostatinomas, and vasoactive intestinal peptide (VIP)-omas. Insulinomas and gastrinomas are discussed elsewhere in this manual. Occasional functional PNETs elicit hormones not normally produced by the pancreatic islet cells, including neurotensin, adrenocorticotropic hormone, parathyroid hormone–related protein, and growth hormone–releasing factor. Tumors that do not produce a specific hormone product and yet are derived from a neuroendocrine progenitor cell are known as nonfunctional neuroendocrine tumors.[1] Roughly 75% of the nonfunctional neuroendocrine tumors produce pancreatic polypeptide but have no associated endocrine syndrome. Hence, these tumors could be referred to as pancreatic polypeptide or PP-omas. These nonfunctional tumors can be identified based on their histologic appearance, cell surface markers, and the presence of immunohistochemical staining for markers such as chromogranin A and neuron-specific enolase.[2] Each PNET can be characterized by a unique endocrine syndrome that includes hormone overproduction (with the exception of nonfunctional neuroendocrine tumors), the location of the tumor, the frequency of the tumor being malignant, and the relative efficacy of medical management to control the associated endocrinopathy (Table 20-1).

Nonfunctional PNETs represent approximately 30% of pancreatic endocrine tumors. Because these tumors do not have a clinically detectable endocrinopathy, they are often diagnosed at a late stage.[3] The tumors are often large and located in the head of the pancreas. The majority are sporadic tumors and are malignant. In fact, nearly 80% of these tumors have locoregional or distant metastases present at the time of diagnosis. Glucagonomas are rare tumors that predominantly arise in the body and tail of the pancreas.[4] They often present late, and most are solitary and large (>4 cm). Nearly 75% of glucagonomas are malignant.

Somatostatinomas are among the rarest endocrine neoplasms, with an estimated annual incidence of only one case in 40 million.[5] The mean age at presentation is 50 years, and there does not appear to be any gender predilection. Nearly 75% of these tumors are malignant, and regional lymph node, hepatic, or bone metastases at the time of diagnosis are common. Roughly 30% of somatostatinomas are located outside the pancreatic parenchyma. Common sites include the duodenum, small bowel, and ampulla of Vater.

VIPomas are also rare PNETs.[6,7] Extrapancreatic sites of disease include the bronchi, colon, adrenal glands, liver, and sympathetic ganglia. Most of these tumors are solitary and located in the body or tail of the pancreas. About 60%to 80% of VIPomas are malignant, and 75% have metastasized by the time of surgical exploration.

TABLE 20-1. Other Functional and Nonfunctional Neuroendocrine Tumors

Tumor Type	*Location (Prevalence)*	*Medical Therapy*	*% Malignant*	*% Associated with MEN1*
Nonfunctional	Pancreas (100%)	None	> 60	Frequent
Glucagonoma	Pancreas (100%)	Octreotide, TPN	60–70	3
Somatostatinoma	Pancreas (85%) Duodenum, (15%)	IFN-α	90	1
VIPoma	Pancreas (85%) Duodenum, (15%)	Octreotide, glucocorticoids	60–80	1
GRFoma	Pancreas (90%) Duodenum, (10%)	Octreotide	30	30
ACTHoma	Pancreas (100%)	Octreotide	100	—

ACTH = adrenocorticotropic hormone; GRF = growth hormone–releasing factor; IFN-α = interferon-α; MEN1 = multiple endocrine neoplasia type 1; TPN = total parenteral nutrition; VIP = vasoactive intestinal peptide.

RISK FACTORS

PNETs may arise in an isolated, sporadic fashion or as a manifestation of a more systemic, inherited predisposition to tumor formation. After a diagnosis of a PNET is confirmed, it is imperative to assess the possibility that the patient has a familial cause for the tumor. The presence of an endocrine neoplasia syndrome often guides the overall treatment planning.

The most frequent inherited endocrinopathy associated with PNETs is multiple endocrine neoplasia type 1 (MEN1). This is an autosomal dominant syndrome classically characterized by anterior pituitary micro- and macroadenomas, multiglandular parathyroid adenomas, and PNETs. More detailed studies, however, reveal an increased incidence of benign and malignant tumors of other tissues such as the subcutaneous fat (lipomas), thymus and bronchi (carcinoids), thyroid gland, adrenal glands, and skin. The syndrome has nearly 100% penetrance but variable expressivity. The etiologic genetic mutation for MEN1 has been identified to be the *menin* tumor suppressor gene on the long arm of chromosome 13.[8] The *menin* gene product is a 610 amino acid nuclear protein thought to repress JUN-D–mediated RNA transcription. This gene product has also been found to be altered in some cases of apparently sporadic cases of PNETs. Direct DNA testing for *menin* is now available but should be accompanied by qualified genetic counseling to interpret the results and plan for screening and intervention for the proband and family members.[9]

Another less common inherited tumor syndrome that should be considered when evaluating a PNET is von Hippel-Lindau (VHL) syndrome. This diagnosis should especially be considered if the pancreatic tumors are cystic. VHL is an autosomal dominant condition caused by a mutation on the short arm of chromosome 3 that leads to angiomatous tumors of the central nervous system (specifically, the internal auditory canal and retina) as well as cystic tumors of the pancreas, adrenals, and kidneys. These patients carry an increased risk of developing renal cell carcinoma.

CLINICAL PRESENTATION

Because of the remote location of the pancreas, PNETs do not produce symptoms from mass effect until later stages. However, the symptoms associated with hormone overproduction often bring these tumors to clinical attention. Each functional PNET has a unique endocrinopathy, and although subtle and nonspecific, attentive and suspecting clinicians can use these signs and symptoms together to arrive at an accurate diagnosis.

Glucagon is a peptide produced by the α cells of pancreatic islets. Tumors that produce excessive glucagon may lead to altered glucose tolerance and

frank diabetes mellitus. In fact, new-onset type II diabetes in a thin patient older than age 60 years should prompt investigation into the presence of a pancreatic glucagonoma. If present, a characteristic skin rash, named *necrolytic migratory erythema*, is pathognomonic for glucagonoma[4] and is present in two thirds of patients with glucagonomas. The rash consists of painful, pruritic lesions that begin as blistering, erythematous plaques and slowly spread outward. The edges appear to erode and then crust over. Hyperpigmentation may be seen at the location of a prior lesion. These lesions generally appear in areas subject to great friction and pressure, such as the perineum, lower abdomen, buttocks, and groin. Patients with glucagonomas often have other signs of nutritional deficiencies, such as hypoaminoacidemia and zinc deficiency. They may present with stomatitis, glossitis, cheilosis, and vulvovaginitis. Other symptoms may include weight loss, depression, and anemia that is normochromic and normocytic. Finally, patients with a glucagonoma may have a marked risk of hypercoagulability and deep venous thrombosis.

The endocrine syndrome produced by excess somatostatin release is quite subtle.[5] Patients may present with weight loss, diarrhea, and steatorrhea. These symptoms are partly caused by impaired secretion of cholecystokinin and pancreatic exocrine enzymes. Furthermore, one may find cholelithiasis upon workup for a somatostatinoma, or conversely, may discover a pancreatic or duodenal somatostatinoma upon evaluation of a patient with gallstones. On detailed gastric acid analysis, one may find patients with a somatostatinoma to have hypochlorhydria. Finally, excess somatostatin release may impair glucose tolerance and lead to both fasting and postprandial hyperglycemia. This "classic" syndrome, however, is typically absent in patients with duodenal somatostatinomas.[10]

Tumors of the pancreas producing excess VIP demonstrate a distinctive endocrine syndrome. This has been termed the *Verner Morrison syndrome* after the physicians who first described this entity originally called *pancreatic cholera*. The syndrome also has the associated acronym WDHA (water diarrhea, hypokalemia, achlorhydria) for its component signs and symptoms. Patients with VIPomas have profuse watery diarrhea leading to dehydration. This diarrhea persists even during fasting. These patients have hypokalemia as well as a metabolic acidosis from the loss of bicarbonate and potassium in the stool. Finally, excess VIP may directly inhibit gastric acid secretion, leading to achlorhydria. Dehydration and hypokalemia often leave these patients with extreme weakness.[7]

Nonfunctional PNETs often present later in life than their functional counterparts.[11] They are most frequently diagnosed in the fifth or sixth decade of life. The presenting signs and symptoms relate to local enlargement or infiltration. These may include (but are not limited to) an abdominal mass, abdominal pain, early satiety, weight loss, jaundice, nausea and

vomiting, back pain, left-sided hypertension with associated gastric variceal bleeding, and metastatic disease (cachexia and hepatosplenomegaly). A pancreatic tumor is often discovered with a cross-sectional imaging modality performed in search of the cause of one of these aforementioned signs or symptoms.

DIAGNOSTIC EVALUATION

The diagnostic evaluation of a patient suspected to harbor a PNET must proceed in a stepwise, organized approach to avoid major missteps in diagnosis and therapeutic intervention planning (Table 20-2). Although patients occasionally present for evaluation after a cross-sectional imaging test reveals a pancreatic tumor, it is important to ensure the accuracy and completeness of the biochemical diagnosis.

Whenever a PNET is considered, it is advisable to obtain a serum level of chromogranin A and pancreatic polypeptide. The former is a general marker for cells of neuroendocrine lineage. When the level is elevated, it may suggest the diagnosis of a NET, and it is a useful tumor marker to follow in the postoperative surveillance setting. Although elevated levels of pancreatic polypeptide are not associated with any clinically detectable endocrinopathy, it is found in association with as many as 75% of all nonfunctional PNETs.

The remainder of the biochemical evaluation is tailored to the individual patient and his or her presenting symptoms. An elevated fasting serum glucagon level (>1000 pg/mL) is diagnostic of a glucagonoma. Associated laboratory findings may include an elevated blood glucose level. The suspicion of a somatostatinoma may be confirmed with an elevated fasting serum somatostatin level (50-fold higher than normal). Evaluation of a VIPoma should include measurement of stool volume. This may be 3 to 5 L/day during acute episodes and is not resolved by discontinuing oral intake. An elevated fasting serum VIP level (>190 pg/mL) is virtually diagnostic of

TABLE 20-2. Principles in the Evaluation and Management of Enteropancreatic Neuroendocrine Tumors

1. Accurately and completely establish a biochemical diagnosis.
2. Assess the possibility of an inherited familial syndrome.
3. Obtain medical control of any syndrome of hormone excess.
4. Localize the tumor(s).
5. Prepare for operative resection.

a VIPoma. Confirmatory electrolyte testing in the case of a VIPoma reveals a significant metabolic acidosis with decreased serum bicarbonate levels.

After the biochemical diagnosis has been established, a careful family history should be undertaken with specific attention given to evaluating for an inherited familial syndrome. Screening laboratory tests for MEN1 should include serum levels of calcium and prolactin. If there is doubt, one may choose to investigate first-degree relatives in whom the syndrome is suspected. With a suspicious family history or an unusually early age at diagnosis of a PNET (e.g., <40 years of age), consultation with a medical geneticist is indicated to explore with the patient the idea of genetic testing for MEN1 or vHL.[9]

Treatment planning commences with tumor localization.[12] Not only does this guide the choice of operative procedure and the extent of resection necessitated, but it may also reveal the presence of metastatic disease that may need to be considered at the time of initial operation or render a patient a non-operative candidate. The most widely used cross-sectional imaging modality to view the pancreas and any associated tumors is computed tomography (CT). With different phases of imaging, one can view the tumor accurately in relation to the surrounding vascular structures. Neuroendocrine tumors typically appear as hypervascular tumors on the arterial phase of the scan (Figure 20-1). The presence of lymphatic metastases as well as hepatic metastases can also be well visualized with this modality. Magnetic resonance imaging (MRI) is an acceptable alternative for pancreatic imaging. Abdominal ultrasonography may reveal gallbladder dilatation and cholelithiasis in the setting of a somatostatinoma.[5]

Somatostatin receptor scintigraphy (SRS), or octreotide scanning, is an adjunctive test useful for neuroendocrine tumors. This study provides functional data to complement the anatomic abnormalities visualized on CT or MRI. Octreoscanning is useful to identify multifocal disease.[13] Endoscopic ultrasonography (EUS) is a highly sensitive and specific modality for imaging these hypoechoic lesions in the pancreas. EUS may also be useful in identifying enlarged locoregional lymph nodes as well as vascular encroachment by these tumors. EUS requires an experienced practitioner who can perform and interpret this technically demanding study. Along with CT, EUS provides an excellent modality for obtaining a tissue biopsy of a potential PNET. Finally, intraoperative ultrasonography done by the surgeon at the time of exploration is extremely sensitive.[14]

MANAGEMENT

After a diagnosis of a PNET is secured, medical control of any syndrome of hormone excess should be achieved before operative resection is contemplated. In other words, the control of the hormonal syndrome should be separated from the control of the potential malignancy. This normalization

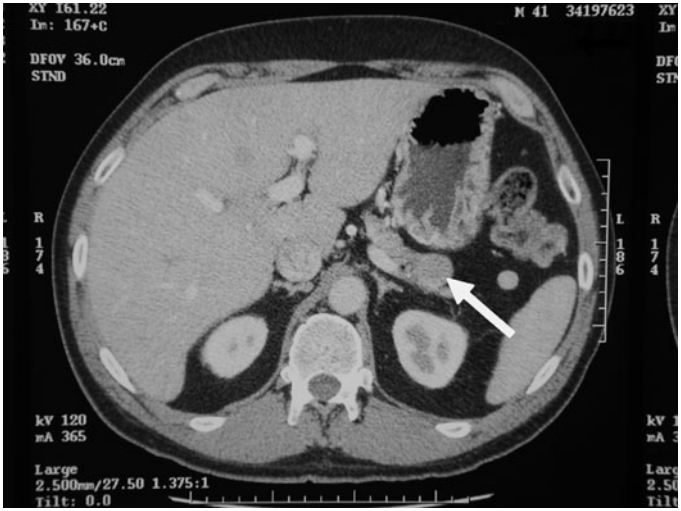

Figure 20-1. Representative computed tomography scan of a 54-year-old woman found incidentally to have a pancreatic body tumor. Note the hypervascular nature characteristic of a neuroendocrine tumor. Biopsy was consistent with a nonfunctional neuroendocrine tumor, and immunohistochemical staining was positive for chromogranin A.

of physiology often improves patient outcomes because the metabolic and nutritional status of the patient is restored. All too often, the endocrinopathy itself is more life threatening than the tumor.

Nonfunctional PNETs, by definition, do not exhibit any associated hormonal syndrome that requires medical control. Somatostatinomas exhibit a very subtle endocrine syndrome that often does not warrant medical management. Unlike with other syndromes, octreotide is ineffective for symptoms associated with somatostatinomas. Trials of interferon-α have shown promising results in its ability to stabilize somatostatinoma-induced endocrinopathy.

Patients with the hormonal syndrome associated with glucagon excess respond very well to treatment with octreotide. The characteristic rash, necrolytic migratory erythema, almost universally resolves with octreotide therapy. Patients with this syndrome also require nutritional supplementation, often in the form of total parenteral nutrition. Finally, glucagonoma-associated thrombophilia is significant in these patients, so great

consideration should be given to prophylactic anticoagulation and the placement of a retrievable or permanent inferior vena cava filter.

With the exception of gastrinomas, medical control of endocrinopathy associated with VIPomas is possibly the best of all PNETs. Somatostatin analogs, especially the long-acting depot formulations, provide highly effective control against the debilitating diarrhea and the associated volume and bicarbonate losses. The addition of oral potassium supplementation may greatly help to correct the patient's electrolyte balance and acid–base status.

An intimate knowledge of the biologic behavior of these rare neoplasms is imperative for the proper selection of operative resection. Although often discussed and written about as one group, each PNET is unique. The findings on preoperative imaging may guide the planned resection and inform the surgeon of the need to perform therapeutic locoregional lymphadenectomy, metastasectomy, or both. The combination of the relative indolent nature of these malignancies and morbidity of the associated syndromes of hormone excess argue for palliative debulking in the setting of unresectable disease or bulky metastases.

A liberal use of intraoperative ultrasonography may complement preoperative imaging.[14] PNETs of the head of the gland often require a pancreaticoduodenectomy (Whipple procedure) to completely extirpate. Tumors of the body and tail of the pancreas may be removed with a distal pancreatectomy.[15,16] It is often difficult to spare the spleen in these situations, especially if the tumor is bulky and resulting in any degree of splenic vein occlusion. Pneumococcal vaccination should be administered preoperatively if splenectomy is potentially necessary.

The operative management of patients with glucagonoma is attempted complete resection, which includes resection of the primary disease, regional lymph nodes, and metastatic sites. These tumors are typically malignant; however, even with unresectable metastatic disease, the progression of the tumor is slow and may allow the patient to live for years. Resectional planning for somatostatinomas is dictated by the extent of the tumor. Surgery varies from a distal pancreatectomy to pancreaticoduodenectomy. Enucleation is inappropriate for these tumors. Debulking of hepatic somatostatinoma metastases is indicated for relief of symptoms. The only potential curative option for the treatment of VIPomas is complete resection. All patients who are fit for surgery and whose imaged disease appears to be resectable should undergo abdominal exploration with resection of the appropriate portion of the pancreas, regional lymph node dissection, and resection of any metastatic disease. All patients undergoing operation for PNETs should have a cholecystectomy, regardless of their disease stage, to facilitate later treatment with a somatostatin analog. As a side effect, somatostatin analogs can promote the development of gallstones.

There is little evidence to guide decision making on the application of laparoscopic techniques for the operative management of patients with malignant PNETs because of the rarity of these tumors. Although the feasibility of minimally invasive approaches has been demonstrated for both formal pancreatic resections and enucleation, the long-term oncologic outcomes have not. Sound surgical judgment, the laparoscopic skill of the individual surgeon, and the anatomic details of the individual case should be considered to ensure adequate resection for the greatest chance of cure for these patients.

The major perioperative morbidity and mortality rates for pancreatic surgery in treatment of patients with neuroendocrine tumors are similar to those seen in pancreatic surgery performed for pancreatic ductal adenocarcinoma. One must inform the patient of the risk of postoperative bleeding, superficial or deep space infections, failure of wound healing, pancreatic fistula, biliary fistula, gastric outlet obstruction or delayed gastric emptying, overwhelming postsplenectomy sepsis, impaired glucose tolerance, pancreatic exocrine insufficiency, and venous thromboembolism.

Few nonsurgical options remain for PNETs. Consideration may be given to external-beam radiotherapy for improved locoregional control if there is uncertainty as to the completeness of resection. Patients with unresectable or metastatic disease often has some response to chemotherapy regimens, including streptozocin, dacarbazine, or doxorubicin.[17] Octreotide and other somatostatin analogs are useful for symptomatic relief in patients with metastatic disease and have been shown by some investigators to have some effect on tumor growth.[18,19] Still, the 5-year disease-free survival rate of nonfunctional PNETs is 44%. The 1-year survival in patients with unresectable VIPomas is only 40%, and the 5-year survival is 15%.[20] The 5-year survival for patients with glucagonoma is believed to be 50%. The 1-year survival for somatostatinoma is 48%, and the 5-year survival is only 13%.

Long-term survival from PNETs is possible. Surveillance for these patients requires a combination of biochemical screening and imaging. The choice of surveillance blood tests is largely guided by elevated laboratory values in the preoperative state. At a minimum, chromogranin A can be used as a tumor marker for neuroendocrine tumors. The hormonal evaluation should be performed annually. A negative biochemical evaluation result can reassure the patient and clinician and allow other examinations to be performed at a greater interval (every 2 to 3 years) but should not be solely relied upon. For imaging examinations, a combination of CT and SRS provides the best evaluation of the abdomen and thorax. EUS appears to be useful in providing a very sensitive assessment of the pancreas and may be especially useful in patients with biochemical evidence of tumor but no disease

imaged on CT or octreoscan. This modality may also be of particular value in patients who have had a previous partial pancreatectomy, which may complicate the interpretation of the CT scan.

PRACTICAL PEARLS

- The majority of clinically recognized PNETs are functional, producing clinically recognizable syndromes.
- Malignant PNETs are determined by the presence of local invasion and lymph node or hepatic metastases, not based on histologic examination.
- The biochemical diagnosis of a PNET must be established before any therapy, especially surgical, can be considered.
- The initial imaging technique for patients with PNETs is a high-quality spiral CT scan.
- The tumor syndrome should always be controlled before surgery.
- The characteristic severe dermatitis (necrolytic migratory erythema) associated with a glucagonoma is effectively treated with octreotide.
- Octreotide is ineffective at treating the somatostatinoma hormonal syndrome.
- Nonfunctional islet cell tumors of the pancreas, although often quite large at diagnosis, tend to grow slowly and have a more indolent course than pancreatic ductal cancer.
- Chromogranin A and pancreatic polypeptide are useful markers for follow-up of PNETs.

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SECTION V

Familial Endocrine Syndromes

Chapter 21

Multiple Endocrine Neoplasia Type 1

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DEFINITION

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant genetic predisposition to develop multiglandular parathyroid disease, benign and malignant neuroendocrine tumors (NET of the pancreas and duodenum, and adenomas of the anterior pituitary.[1,2] Benign and malignant tumors of these organs may develop, with multiple target organs affected and multifocal tumors within a target organ. Less often, carcinoid tumors (bronchial, gastrointestinal, or thymic), lipomas, cutaneous angiofibromas, or ependymomas of the central nervous system may be associated with this syndrome. The clinical definition of MEN1 includes a patient with tumor development in two associated endocrine tissues (parathyroid, pancreas, pituitary) and a first-degree relative with involvement of one of the three principal endocrine tissues. Direct genetic testing can detect disease-associated germline mutations in the *MEN1* gene and identify affected individuals.

EPIDEMIOLOGY

MEN1 has an estimated frequency of one in 30,000 people, with no apparent geographic or race predilection.[3] However, it has been noted that often the syndrome is not completely recognized, which may lead to a underestimation of the actual prevalence.[2] In patients presenting with early-onset hyperparathyroidism, multiple gland parathyroid disease, or rare neuroendocrine neoplasms, the diagnosis of MEN1 should be considered and specifically sought. The peak age of incidence in men and women may differ. Women most often present with clinical symptoms in the third decade of life, and men present in the fourth decade.[4] Systematic, prospective biochemical

screening in presymptomatic but known genetically affected patients may reveal evidence of endocrine neoplasia 5 to 10 years before the development of clinical manifestations.[5]

Genetics

The *MEN1* tumor suppressor gene is located on chromosome 11 and encodes for the protein menin. Menin is primarily an intranuclear protein whose functions are not yet clearly understood. However, menin does appear to participate in many different cellular processes, including transcription regulation, cell proliferation, genomic stability, and regulation of apoptosis.[3] As a tumor suppressor gene, development of MEN1 requires two genetic "hits" involving both allelic copies of the gene to result in loss of function. The first mutation is inherited in the germline and present in every cell; the second somatic mutation occurs in an individual cell of an involved target tissue and results in tumor formation. Various types of genetic alterations (frameshift, missense, or nonsense; RNA spicing defects; and large genomic deletions) of the menin gene and result in protein loss of function by subsequent truncation, absence, or point mutation and substitution of a single erroneous amino acid. More than 300 independent *MEN1* gene mutations have been described, almost as many unique mutations as families. Although the *MEN1* mutation has high penetrance, there is a great degree of variation in the expression of the syndrome in individual patients, specifically regarding chronology, type, course, and outcomes of the various clinical manifestations.

CLINICAL PRESENTATION

Parathyroid Tumors

Primary hyperparathyroidism (PHPT) is the most common clinical expression of MEN1, occurring in 95% of patients, and is the first manifestation in approximately 90% of patients. Patients present with symptoms that are similar to those of sporadic PHPT, including nephrolithiasis, abdominal pain, lethargy, psychiatric disturbances, and (if profound) osteoporosis, among others. In contrast to PHPT, which presents most often in the fifth decade of life, MEN1 patients present with hypercalcemia and related symptoms at an earlier age in the second or third decade of life and rarely as early as age 4 years.[1] The parathyroid tumors result from the chance occurrence of "two hits" in the *MEN1* tumor suppressor gene in a parathyroid cell, with subsequent clonal expansion of the tumor. Therefore, from a strict genetic standpoint, they are actually multiple adenomas rather than hyperplasia (polyclonal).[6]

Pancreaticoduodenal Tumors

Clinically manifested in nearly 40% of individuals with MEN1, pancreatic and duodenal neuroendocrine tumors are the second most frequent manifestations of MEN1. These tumors have a malignant potential, and along with the malignant intrathoracic tumors (thymic, bronchial carcinoid), they account for most of the disease-related morbidity and mortality. Diffuse, preneoplastic islet cell hyperplasia develops throughout the pancreas with subsequent development of multifocal functional and nonfunctional neuroendocrine tumors.

The two most common functional tumors are gastrinomas and insulinomas.[2] Patients with gastrinomas present with classic signs and symptoms of Zollinger-Ellison syndrome (i.e., abdominal pain, reflux, secretory diarrhea, and weight loss). Patients with insulinomas present clinically with Whipple's triad, which includes symptoms of neuroglycopenia (confusion, anxiety, tremor, and diaphoresis), fasting hypoglycemia, and reversal of the symptoms after glucose administration.

Nonfunctional tumors become symptomatic only as a result of their location or growth and mass effect on surrounding structures. They are, however, most often discovered incidentally. A recent study of the combined functional and nonfunctional neuroendocrine tumors that develop in patients with MEN1 was unable to demonstrate a correlation between maximum size of the largest tumor and regional or distant metastases.[7]

Pituitary Tumors

Anterior pituitary tumors have been reported in 30% of MEN1 patients. Clinical manifestations may be caused by mass effect or hormonal production. Local mass effects include visual field defects, blurred vision, and headaches. The most common pituitary adenoma is a prolactinoma, which may cause galactorrhea, amenorrhea, and infertility in women and hypogonadism in men.[2] Additionally, anterior pituitary tumors may also produce growth hormone, causing acromegaly or adrenocorticotropic hormone, resulting in Cushing's syndrome.[8,9]

DIAGNOSTIC EVALUATION

Genetic Testing

Because no correlation has been found between specific mutations in the *MEN1* gene and the phenotype of the affected patients, the use of genetic testing for prediction of malignant potential and prognosis is not possible at this time.[8,9] Additionally, widespread genetic screening is currently impractical; however, there are a few clear indications for testing for mutations in the *MEN1* gene. When an initial case is diagnosed clinically, DNA evaluation of

that patient and his or her presymptomatic first-degree relatives should be completed. Presymptomatic individuals who test positive for a *MEN1* mutation should then undergo more frequent and more intensive biochemical testing with special emphasis on the potentially malignant pancreaticoduodenal and intrathoracic tumors. Close observation and frequent surveillance of patients with *MEN1* mutations allows for much earlier detection of biochemical abnormalities associated with neoplasia.[3,5,10]

Conversely, a negative genetic screening result in a family in which the previous mutation is known obviates further lifelong screening or testing with the associated costs and psychological impact.[11] Because *MEN1* mutations are identified in only 85% to 90% of MEN1 families with standard genetic screening methods, failure to identify a disease-associated mutation in members at direct genetic risk from a new MEN1 family with a previously unknown specific genetic change does not exclude affected status.

Biochemical Tests

Parathyroid Tumors

The diagnosis of PHPT is based on an elevated serum calcium level in the presence of an elevated level of parathyroid hormone (PTH). Some have recommended that screening for these abnormalities should begin as early as age 8 years in *MEN1* mutation carriers,[3,12] but the peak incidence of clinically apparent hyperparathyroidism is in the late second or early third decade of life.

Pancreatic Tumors

Biochemical evidence of gastrinoma consists of an elevated fasting serum gastrin level (>100 pg/mL) and gastric acid hypersecretion (>15 mEq/hr with no previous gastric surgery or >5 mEq/hr with previous gastric surgery). Alternatively, a secretin stimulation test may be performed. Secretin is administered intravenously (2 U/kg); a subsequent increase in gastrin of more than 200 pg/mL is diagnostic of a gastrinoma.

Diagnosis of an insulinoma requires a closely monitored inpatient fast to eliminate the possibility of factitious hypoglycemia or exogenous insulin administration. During the inpatient fast, frequent blood samples are taken to measure levels of blood glucose and insulin. At the conclusion of the fast and before glucose administration, C-peptide, sulfonylureas, and anti-insulin antibodies should be measured. The diagnosis of an insulinoma is supported by neuroglycopenic symptoms associated with inappropriate hyperinsulinemia concomitant with profound hypoglycemia (blood glucose <40 mg/dL). C-peptide levels are also elevated in the presence of an insulinoma because this component of the insulin molecule is not present in the exogenously administered form of insulin.[1]

Other less common functional neuroendocrine tumors of the pancreas, such as glucagonomas, vasoactive intestinal peptide (VIP)-omas, and somatostatinomas, result in characteristic constellations of symptoms secondary to the specific hormone produced. Current recommendations indicate that annual biochemical testing, including pancreatic polypeptide, gastrin, glucagon, and chromogranin A, should begin at approximately age 15 to 20 years in presymptomatic affected individuals.[3,5,10,12]

Pituitary Tumors

Prolactinomas are the most common anterior pituitary tumors associated with MEN1. The diagnosis is based on an elevated prolactin level, often resulting in the symptoms previously mentioned. Hormonal products of other functional pituitary adenomas, namely somatotrophin or corticotrophin, may be measured as well. It is currently recommended to begin biochemical screening for pituitary adenomas in carriers of *MEN1* mutations at age 5 years.[3,12]

Radiographic Tests

Parathyroid Tumors

Although sestamibi scan may be used to localize hyperfunctioning parathyroid tissue, the hyperparathyroidism associated with MEN1 is commonly multiglandular, and sestamibi scanning has not been shown to accurately depict the distribution of multiply enlarged glands. The usefulness of routine preoperative imaging in patients with MEN1 is arguable because all four glands must be identified intraoperatively for effective surgical management. However, sestamibi and ultrasonography may be used for localization in patients with recurrent disease after a failed initial exploration or a missed or ectopic tumor. Computed tomography (CT) or magnetic resonance imaging (MRI), arteriography, and selective venous sampling may also be used to localize and resect the abnormal gland in these difficult cases.

Pancreatic Tumors

The optimal imaging method for pancreatic tumors is debated. Biphasic thin-slice CT has been reported to have a sensitivity of 94.4% for pancreatic neuroendocrine tumors (PNETs).[13,14] However, the sensitivity decreases with smaller tumors (<2 cm), multiple tumors (as is often the case with MEN1), tumors located in extrapancreatic locations (e.g., the duodenal wall), and tumors located in the distal tail of the pancreas.[14–16] MRI is advocated by some and is able to detect smaller tumors (even <1 cm in size). However, no clear advantage of MRI over CT imaging has been shown. A cross-sectional imaging test (CT or MRI) should be performed, however, as an initial test in essentially all patients to exclude a very large primary neoplasm or metastases.

An important modality that has emerged in the past 20 years is endoscopic ultrasonography (EUS). In 1992, Rosch et al.[17] published their results

using this technique. This study reported a sensitivity of 82% and specificity of 95% for EUS in detecting pancreatic islet cell tumors that had been non-localized by transabdominal ultrasonography or CT.[17,18] However, the detection rate decreases with distal progression along the pancreatic tail, likely owing to increased distance from the gastric or duodenal lumen. EUS is a very effective and relatively non-invasive localizing test (after initial CT), but it is dependent on the skill and experience of the operator and availability.

Somatostatin receptor scintigraphy (SRS) may also be used to localize these tumors.[19] In the subpopulation of MEN1 patients, the specificity and positive predictive value (PPV) of SRS for pancreatic tumors are 25% and 100%, respectively; the specificity and PPV of SRS for duodenal gastrinomas are 72% and 100%, respectively.[18,20] In the study that reported these results, all PNETs were detected by either EUS or SRS. This combination may be the most effective preoperative imaging strategy.

Selective pancreatic arteriography with provocative stimulation by selected secretagogues and measurement of increment hormone secretion in the hepatic vein is an invasive test available only in certain centers, but it may be the most accurate single localizing modality.[21,22] This test provides regional localization of functional tumors (insulinomas, gastrinomas) within the pancreas and is especially useful in patients with MEN1 who characteristically have multiple tumors.

Pituitary Tumors

Pituitary tumors are best imaged and diagnosed with MRI. This is the most sensitive method for diagnosis and evaluation of pituitary masses.[9] If MRI is contraindicated, CT may be used (Figure 21-1).

MANAGEMENT

Parathyroid Tumors

The primary modality for treatment of MEN1 patients with hyperparathyroidism is surgery. Because MEN1 is associated with multiglandular parathyroid disease, the surgical strategy must address all four glands. The options for surgical approach are a $3^1/_2$-gland parathyroidectomy or a total four-gland parathyroidectomy with heterotopic autotransplantation of parathyroid tissue to the forearm. Routine partial cervical thymectomy is also recommended in patients with MEN1 to address a possible supernumerary or ectopic parathyroid gland within the mediastinum. Although the value of routine preoperative imaging in patients with MEN1 and hyperparathyroidism has not been defined, diagnostic localization with sestamibi scanning, ultrasonography, CT, or MRI may be particularly helpful in reoperative cases and patients with missed ectopic glands.

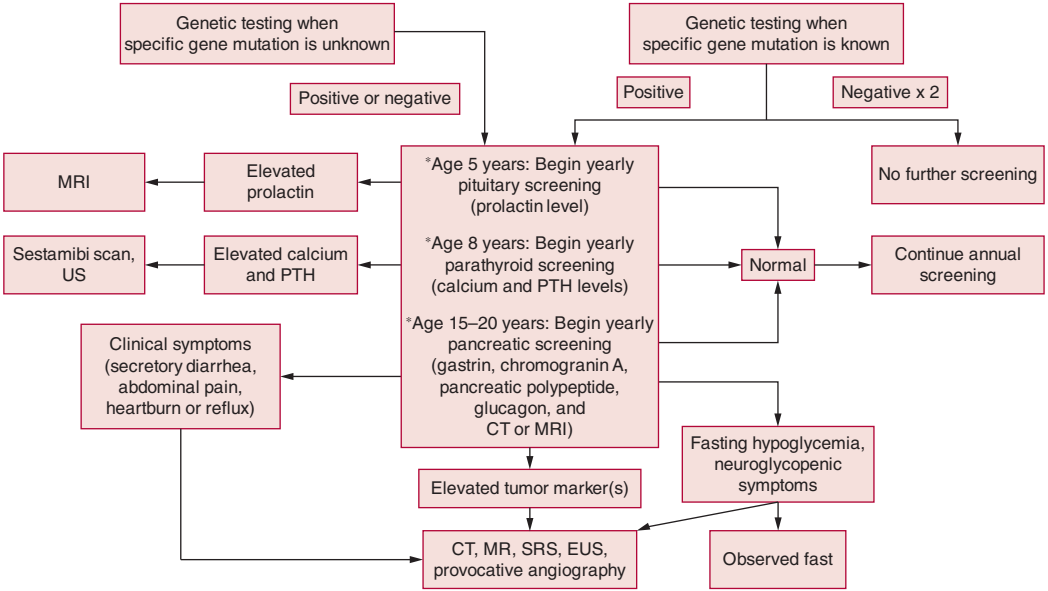

Figure 21-1. Algorithm for diagnosis and surveillance of multiple endocrine neoplasia type 1 patients, including relevant biochemical and radiographic studies. CT = computed tomography; EUS = endoscopic ultrasonography; MRI = magnetic resonance imaging; PTH = parathyroid hormone; SRS = somatostatin receptor scintigraphy; US = ultrasonography. (Data from Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrinol Metab* 2001;86:5658-5671.)

It is also important to remember that hypercalcemia aggravates hypergastrinemia, so patients with parathyroid disease should be treated surgically before or concomitant with gastrinoma resection. There is a much higher incidence of persistent or recurrent hyperparathyroidism (≤50% at 5 years) in patients after any appropriate surgical approach. MEN1 patients should optimally undergo their primary operation in centers of endocrine surgery excellence with availability of intraoperative PTH measurements, surgeon-directed ultrasonography, and capabilities for parathyroid cryopreservation.

Pancreatic Tumors

The management of patients with MEN1-associated PNET remains controversial. The primary reason for this is that the natural history of these tumors is not completely understood; prognostic indicators of malignancy or propensity to metastasize are unknown at this time. There is general consensus that functional tumors should be removed surgically. It can be argued that symptoms of gastrinomas may be effectively controlled with proton pump inhibitors; however, the progression of the tumoral process with potential for metastases remains with medical treatment alone. Although a correlation between the size of the primary gastrinoma and the frequency of metastases involving the lymph nodes and liver has been reported,[23] another study[7] including all MEN1-associated pancreaticoduodenal neuroendocrine tumors, both functional and nonfunctional, failed to show a correlation between size of the largest tumor and regional or distant metastases. Surgical resection of gastrinomas is complicated by the fact that tumors are small, often multiple, and may be extrapancreatic, within the duodenal wall or even possibly as lymph node primaries. Most large studies have shown that surgical treatment of patients with gastrinomas in MEN1 rarely have long-term normalization of their gastrin levels.[24] However, owing to the possibility of decreasing metastatic disease in these patients, we recommend surgical exploration; duodenal exploration with intraoperative ultrasonography of the duodenal wall and pancreas; resection of gastrinomas; and an aggressive, extended regional lymphadenectomy in otherwise low-risk surgical candidates. Pancreaticoduodenectomy is appropriate for extensive or malignant gastrinomas in the duodenum or head of the pancreas.

Insulinomas require surgical intervention resection after the biochemical diagnosis has been established. Preoperative imaging may or may not accurately localize these tumors, which may be small (1 to 2 cm) and occult. The surgical approach consists of full mobilization and evaluation of the entire pancreas by visualization, palpation, and intraoperative ultrasound examination by an experienced operator (radiologist or surgeon). Enucleation is often the approach for these tumors, which are typically small and usually benign. Alternatively, a distal pancreatectomy may be performed for tumors within the tail of the pancreas; limited evidence suggests that this may reduce the risk of recurrence.

Patients with asymptomatic or nonfunctional tumors of the pancreas associated with MEN1 present the most challenging question regarding surgical management. Two alternative strategies have been proposed. First, surgical exploration in young asymptomatic patients with biochemical evidence of MEN1 may be performed. This may provide the benefit of decreasing the risk of malignant transformation or metastatic disease and may identify and treat disease well before it is clinically apparent.[10] Alternatively, others advocate removal of PNETs that are functional, symptomatic, or large enough to be imaged with radiographic tests.

The operation for MEN1 PNET resection may be performed via a bilateral subcostal incision or an upper midline incision. An extended Kocher maneuver is performed to mobilize the duodenum and head of the pancreas, the greater omentum is taken down from the transverse colon, and the lesser sac is entered. To avoid bleeding, it is useful to ligate the middle colic vein at its origin in the superior mesenteric vein. The retroperitoneum is opened just below the inferior edge of the pancreas. Additionally, a medial rotation of the spleen and tail of pancreas may be performed for complete evaluation of the entire pancreas. Careful blunt dissection at each of these borders of the pancreas allows for palpation of the entire gland and surrounding lymphatic structures. Intraoperative ultrasonography is the gold standard localizing test and should be routinely used, preferably by an experienced operating surgeon. Smaller tumors of the pancreatic head are most commonly enucleated, and those of the body or tail may be managed with either enucleation or distal pancreatectomy. Splenic-preserving distal pancreatic is desirable when technically feasible. On the other hand, splenectomy may provide a more complete resection of lymph nodes along the splenic vessels in larger or malignant tumors of the pancreatic tail. Additionally, lymph nodes within the hepatoduodenal ligament, along the celiac axis, and posterior to the pancreatic head should be inspected and removed if suspicious.[25]

MEN1 neuroendocrine tumors located within the duodenum are removed surgically via longitudinal duodenotomy. After distending the duodenum with saline via the nasogastric tube, intraoperative ultrasonography and opening of the duodenum with digital palpation of the entire duodenal wall are performed. Enucleation of tumors smaller than 5 mm may be performed; the overlying mucosa is removed with the tumor. Full-thickness duodenal wall excision is required for tumors larger than this. The full-thickness excision site(s) and the duodenotomy are closed longitudinally in two layers.[25] Some argue for a routine extended regional lymphadenectomy for MEN1 gastrinomas because they are frequently (80%) malignant with early lymph node metastases from even small primary tumors. Additionally, intraoperative hepatic ultrasonography may be beneficial to further investigate for metastatic disease involving the liver.

Pituitary Tumors

The most common functional pituitary tumors in MEN1 patients are prolactinomas. These tumors are most often managed medically with administration of dopamine receptor agonists such as bromocriptine or pergolide. However, surgical resection with a transsphenoidal approach may rarely be used for certain tumors. Operative treatment is most commonly indicated in large or rapidly growing prolactinomas that are unresponsive to medical therapy and in the other less common functional pituitary tumors mentioned above[1] (Figure 21-2).

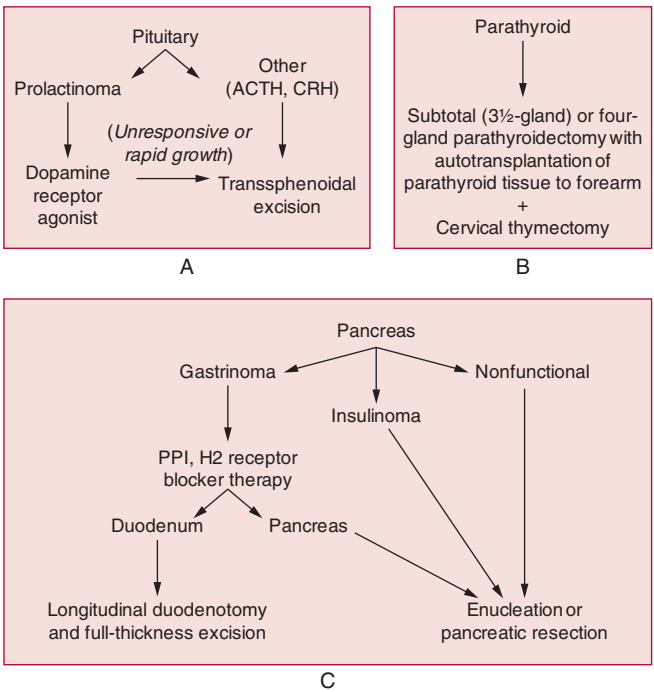

Figure 21-2. Algorithm for management of multiple endocrine neoplasia type 1 tumors by location: the pituitary (**A**), parathyroid (**B**), and pancreas (**C**). ACTH = adrenocorticotropic hormone; CRH = Corticotropin Releasing Hormone; PPI = proton pump inhibitor.

SURVEILLANCE AND FOLLOW-UP

Historically, recommended biochemical screening only included testing for hyperparathyroidism because it is the most common presenting abnormality in patients with MEN1. However, that strategy has been shown to miss the diagnosis of MEN1 in a significant number of patients. Family members at risk for familial MEN1 should undergo genetic testing. Subsequently, in the patients with positive genetic test results, the following recommendations have been proposed: (1) yearly physical examination; measurement of fasting glucose, gastrin, pancreatic polypeptide, calcium, albumin, and PTH levels; and abdominal imaging (CT or MRI), especially in patients with symptoms or positive biochemical markers, and (2) every-other-year head imaging (MRI) and measurement of the prolactin level.[2]

Continued yearly follow-up with physical examination and the above-referenced biochemical and imaging tests are indicated after surgery for neuroendocrine tumors of any organ in MEN1 patients. Patients with recurrent parathyroid disease and recurrent PNETs often require reoperation; those with recurrent or residual prolactinomas are often responsive to postoperative bromocriptine therapy.

PROGNOSIS

Overall life expectancy for patients with MEN1 is decreased; these individuals have a 50% probability of death by age 50 years. Approximately 50% of these deaths are secondary to malignancy or other sequelae directly related to MEN1.[4] Furthermore, mortality seems to be most often affected by pancreatic tumor presence, growth, malignant transformation, and metastasis.

PRACTICAL PEARLS

- Although direct genetic testing is clinically available, in newly detected families with an unknown specific mutation in MEN1, affected status cannot be excluded by a negative genetic screen result (only 85% to 90% of mutations are detected).
- A high index of suspicion for MEN1 should be maintained in patients presenting with hyperparathyroidism early in life, parathyroid disease involving multiple glands, and rare neuroendocrine tumors. The diagnosis of MEN1 should be investigated in these patients.

(*Continued*)

- In families with a known mutation, negative genetic testing results for first-degree relatives of MEN1 patients eliminates the need for repeated biochemical and radiographic testing.
- Yearly biochemical testing for hyperparathyroidism in MEN1 patients should begin at age 8 years.
- Yearly biochemical testing for functional neuroendocrine tumors of the pancreas should begin by age 15 to 20 years.
- Prospective, systematic biochemical surveillance for presymptomatic patients with a positive genetic diagnosis should emphasize early detection of the pancreaticoduodenal and intrathoracic neuroendocrine tumors that carry a significant malignant potential.
- The combination of EUS and SRS may be the most accurate means for localizing PNETs preoperatively.
- MEN1 patients with hyperparathyroidism develop multiglandular disease.
- Recurrent parathyroid or pancreatic disease after surgical treatment is more common in MEN1 patients than in patients with sporadic tumors.
- Surgical resection of small asymptomatic pancreaticoduodenal neuroendocrine tumors may prevent development of malignancy and metastatic disease.
- Full examination of the pancreas is required at the time of surgical exploration. Tumors may be enucleated or removed via pancreatic resection, depending on their size and location.
- MRI is the radiographic modality of choice for imaging pituitary tumors associated with MEN1.
- Prolactinomas, the most common pituitary adenomas, are usually effectively treated medically with dopamine receptor agonists and only rarely require surgical intervention.
- The majority of deaths from MEN1-related causes are secondary to malignant transformation or metastatic disease.

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Chapter 22

Multiple Endocrine Neoplasia Type 2

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EPIDEMIOLOGY AND RISK FACTORS

Sipple described pheochromocytoma associated with carcinoma of the thyroid gland in 1961.[1] Seven years later, multiple endocrine neoplasia type 2 (MEN2) was recognized as a distinct entity from MEN type 1 (MEN1) after analysis of a family with cases of pheochromocytoma, medullary thyroid carcinoma (MTC), and parathyroid hyperplasia.

MEN2 is an autosomal dominant tumor susceptibility syndrome. There are several variants of MEN2, but they are all caused by an activating mutation in the rearranged during transfection (*RET*) proto-oncogene. The two main variants are MEN2A and MEN2B. More rare variants of MEN2 include familial MTC (FMTC), MEN2A with cutaneous lichen amyloidosis, and MEN2A or FMTC with Hirschsprung's disease (Table 22-1).

MEN2 has been identified to date in about 500 to 1000 kindreds.[2,3] All variants of MEN2 show a high penetrance for MTC. In fact, more than 90% of MEN2 carriers eventually show evidence of MTC or its precursor, C-cell hyperplasia.[4,5] MEN2A, which accounts for 75% of MEN2 cases, is a syndrome of MTC in more than 90% of adult gene carriers, unilateral or bilateral pheochromocytoma in 50%, and multigland parathyroid tumors in 20% to 30%.[3–5] MTC is the first neoplastic manifestation in most MEN2 kindreds because of its earlier and overall higher penetrance. MEN2B is characterized by MTC and pheochromocytoma, decreased upper-to-lower body ratio, a marfanoid habitus, and mucosal and intestinal ganglioneuromatosis. Hyperparathyroidism (HPT) does not occur in individuals with MEN2B.[6] Patients with FMTC only develop MTC; they do not develop any of the other tumors associated with MEN2A and 2B.

TABLE 22-1. Multiple Endocrine Neoplasia Type 2 and Its Clinical Syndromes

Syndrome	*Characteristic Features*
MEN2A	MTC Pheochromocytoma Parathyroid neoplasia
FMTC	MTC
MEN2A or FMTC with Hirschsprung's disease	MEN2A or FMTC + Colonic aganglionosis
MEN2A with cutaneous lichen amyloidosis	MEN2A + Pruritic cutaneous lesions located over the upper back
MEN2B	MTC Pheochromocytoma Intestinal and mucosal ganglioneuromatosis Characteristic marfanoid body habitus

FMTC = familial MTC; MEN = multiple endocrine neoplasia; MTC = medullary thyroid carcinoma.

To be classified as having FMTC, a kindred must have more than 10 carriers displaying MTC; multiple affected members or carriers older than age 50 years; and an adequate medical history to exclude pheochromocytomas or HPT, especially in older members.[3] These rigorous criteria are used to avoid misclassifying small MEN2A kindreds whose members may not yet have developed pheochromocytomas or HPT. Ultimately, 20% to 25% of MTC cases are recognized as hereditary (see Chapter 6).

Mutations in the *RET* gene, located near the centromere on chromosome 10, cause MEN2, and the affected protein is a receptor tyrosine kinase.[7] Its extracellular portion contains four cadherin-like repeats, a calcium-binding site, and a cysteine-rich domain. The intracellular portion contains a typical tyrosine kinase domain. *RET* disruption by germline mutations in humans and mice causes congenital aganglionosis of the gastrointestinal (GI) tract, leading to Hirschsprung's disease. The RET protein is a subunit of a multimolecular complex that binds growth factors of the glial-derived neurotrophic factor family.[8] Approximately 98% of MEN2 patients carry germline point mutations in RET.[3,9] Most MEN2A mutations affect cysteines in the extracellular cysteine-rich domain of RET. MEN2A

is associated most frequently with mutations of codon 634 (85%), particularly C634R. Most MEN2B patients carry the M918T mutation in RET kinase domain, but only a small fraction of patients harbor the A883F substitution. The mechanisms leading to *RET* oncogenic conversion in individuals with MEN2 depend on the site of the amino acid change. RET cysteine mutants form covalent dimers that display constitutive kinase activity; cysteine removal is believed to prevent the formation of intramolecular disulfide bonds, allowing free cysteine residues to form intermolecular bonds.[8]

CLINICAL PRESENTATION

Patients either present as an index case or as a member of a known MEN2 kindred. Index cases are most likely to present with MTC (i.e., a thyroid nodule), and the age of onset depends on the underlying RET mutations (see below). Occasionally, an index case may present with signs and symptoms of pheochromocytoma. It is unusual for MEN2A patients to present primarily with HPT.

DIAGNOSTIC EVALUATION

MEN2 carrier determination may lead to highly effective clinical intervention and possible cure, particularly for MTC, by total thyroidectomy with possible lymphadenectomy.[4] Additionally, DNA-based testing is now widely available, and only a limited number of mutations have been identified.[3] Based on the specific *RET* mutation genotypes, many MEN2 carriers should undergo total thyroidectomy to prevent the expression of clinical MTC. In contrast to MEN1, phenotype–genotype correlations are seen in MEN2, which directs the management of these patients (see Management).[3,9,10] The results of a genetic test thus may dramatically alter treatment, especially in presymptomatic patients.

Genetic Testing

Currently, 15 clinical laboratory improvement amendments (CLIA)-certified laboratories in the United States offer genetic testing for *RET* mutation. The standard screening test involves direct germline DNA sequencing using polymerase chain reaction for mutations in exons 10, 11, and 13 to 16. An *RET* germline mutation can be identified in more than 88% of FMTC, 95% of MEN2B, and 98% of MEN2A kindreds. After a mutation is identified in a family, screening at-risk relatives involves targeted DNA sequencing. If a mutation is not identified, the remaining 15 exons should be sequenced. This latter analysis is currently available only in research laboratories. If the extended *RET* mutation testing results are negative in the index case of a family, the family pattern of MEN2 is suspicious for an

undiscovered *RET* mutation, then haplotype or genetic linkage testing of the *RET* locus should be considered.

Indications for RET Gene Mutational Analysis

Consensus guidelines for MEN2 genetic testing include confirmation of a clinical diagnosis in an index case, identification of asymptomatic at-risk relatives, and discontinuation of clinical screening in "at-risk" relatives with negative test results for a known mutation within the kindred.[2] All first-degree relatives should be screened, and screening for second-degree relatives should be considered if testing of the first-degree link is not possible. The likelihood of an *RET* germline mutation in a patient with apparently sporadic MTC is 1% to 7%.[11] An *RET* germline mutation is more likely to be identified in a patient with MTC diagnosed at an early age or with multifocal MTC. Given the critical implications of finding a *RET* mutation, all individuals with sporadic MTC should be tested for an *RET* germline mutation.[2] Genetic testing also is beneficial for all children who have apparently sporadic cases of Hirschsprung's disease and pheochromocytoma because of these disorders' known association with MEN2. Genetic counseling issues are similar among all familial cancer syndromes. Before giving or authorizing blood or other tissue for genetic testing, children, adults, or the parents of children at risk should be counseled about the implications of genetic testing.

Biochemical and Radiologic Evaluation

In addition to genetic testing, biochemical and radiographic evaluation are important both in screening MEN2 carriers and in surveillance. Basal serum calcitonin and carcinoembryonic antigen (CEA) levels are useful biochemical markers for MTC and are indicative of tumor mass. Calcitonin and CEA may be used in screening for MTC as well as in postoperative surveillance. Pheochromocytoma has been found in kindreds with all RET proto-oncogene mutations except in codons 609, 768, val804met, and 891. Pheochromocytomas have been identified with codon 634 mutations as early as age 5 to 10 years. Annual screening for pheochromocytoma with plasma metanephrines and normetanephrines may be initiated at age 5 to 7 years in these children. Patients who have mutations in lower risk codons may have screening initiated at a later age. After a patient reaches age 15 years, imaging studies should be conducted every 3 to 5 years, even with normal biochemical results. There is no consensus regarding the best imaging study for the detection or preoperative planning for pheochromocytoma in individuals with MEN2. Computed tomography (CT), magnetic resonance imaging (MRI), and iodine 131 meta-iodobenzylguanidine (MIBG) scans are all used. Measurements of serum calcium and parathyroid hormone (PTH) should occur annually to screening for HPT in patients who have codon 634 mutations.

Mutations in codons 609, 611, 618, 620, 790, and 791 less frequently cause HPT. These patients may have screening every 2 to 3 years unless family history dictates more frequent testing. Those who have codon 768, V804M, and 891 mutations rarely develop HPT. Patients who have mutations in codons 883 and 918, causing MEN2B, do not develop HPT.

MANAGEMENT

Medullary Thyroid Carcinoma

Multifocal C-cell hyperplasia is a precursor lesion to MTC in individuals with MEN2. The progression from hyperplasia to frank MTC is variable and may take many years. MTC often metastasizes to central and lateral, cervical, or mediastinal lymph nodes or more distantly to lung, liver, or bone. Surgery is the mainstay of treatment, both to prevent progression to MTC and to treat and potentially cure clinical disease. The adequacy of the extent of resection during the initial operation is paramount. Surgery for MTC (i.e., total thyroidectomy and node dissection of at least the central compartment) should ideally be performed before the age of possible malignant progression.[12] The thyroid C cells are preferentially located in the superior or lateral part of the thyroid lobe. During thyroidectomy, it is essential not to leave any thyroid tissue behind at the level of the insertion of the recurrent laryngeal nerve and the ligament of Berry to prevent recurrence. Histologically, MTC in MEN2 syndromes are usually multifocal. The aggressiveness of MTC correlates with the MEN2 variant syndromes and with the mutated *RET* codon, and several recent studies have tried to specify this genotype–phenotype relationship (Table 22-2).[3,4,9]

Children with MEN2B or *RET* codon 883, 918, or 922 mutations are classified as level 3, or as having the highest risk from aggressive MTC, and should be operated on within the first 6 months of life. Children with any *RET* codon 611, 618, 620, or 634 mutations are classified as level 2 and should have thyroidectomy performed before age 5 years. Children with *RET* codon 609, 768, 790, 791 804, and 891 mutations are classified as level 1 and may be operated on at a later stage (see Table 22-2). It should be noted that these are general recommendations, and MTC as well as nodal metastases have been reported with an earlier onset in certain families. For all groups, a more aggressive neck dissection (lateral compartment resection, modified radical neck dissection) should be performed if there is evidence of involved lymph nodes in the lateral neck[13] (see also Chapter 6).

There is currently no effective systemic therapy for patients with MTC, although promising therapies are in development. The majority of such drugs are tyrosine kinase inhibitors or monoclonal antibody based. Access of therapies for locally advanced, metastatic, or recurrent MTC associated with MEN2 are currently available through clinical trials only.[14]

TABLE 22-2. Relationship Between Risk Group, *RET* Codon Mutations, and Surgical Management in Multiple Endocrine Neoplasia Type 2 (Genotype–Phenotype Correlation)

MTC Risk Group	*Affected Codons*	*MTC Phenotypic Features*	*Surgical Management*
Low risk	609, 768, 790, 791, 804, 891	Node metastasis and mortality reported for all mutations except 790, 791	Total thyroidectomy before age 5 to 10 years
Intermediate risk	611, 618, 620, 634	MTC has been reported as early as age 2 years and node metastasis as early as age 5 years	Total thyroidectomy with CND before age 5 years
High risk	883, 918, 922	Includes MEN2B mutation Highest risk of MTC and node metastasis	Total thyroidectomy with CND before age 6 months

CND = central lymph node dissection; MEN = multiple endocrine neoplasia; MTC = medullary thyroid carcinoma.

Pheochromocytoma

Pheochromocytoma has been found in kindreds with all RET proto-oncogene mutations except those in codons 609, 768, val804met, and 891. The pheochromocytomas generally present in the second or third decade of life and are often bilateral. The size of the tumor is usually smaller than 3 cm in MEN2A patients but tends to be larger in those with MEN2B. Even in MEN2A patients with apparent unilateral disease, the contralateral adrenal gland almost always shows medullary hyperplasia. The pheochromocytomas associated with MEN2A and MEN2B are rarely malignant or extra-adrenal (i.e., paraganglioma). Histologically, they are indistinguishable from sporadic pheochromocytomas. The preoperative management with α-blockade and volume expansion is the same as for sporadic cases (see Chapter 15). There is no consensus regarding the best imaging study for the detection or preoperative planning for pheochromocytoma in patients with MEN2. However, CT, MRI (Figure 22-1), and MIBG scans are all

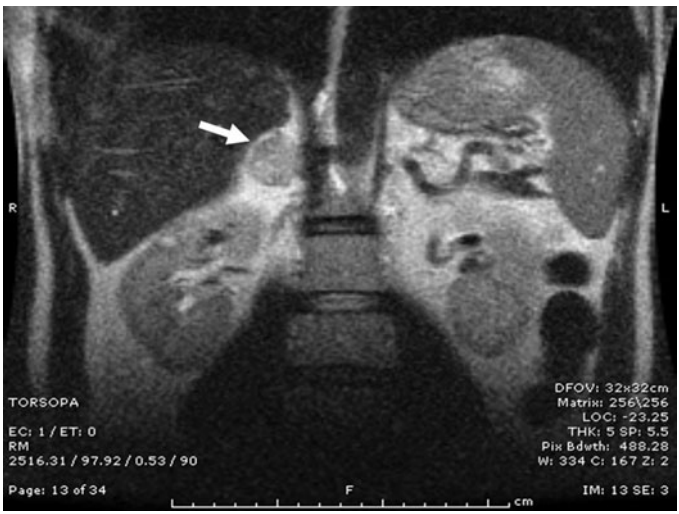

Figure 22-1. Magnetic resonance image of the abdomen in a 35-year-old man with multiple endocrine neoplasia type 2. The patient has undergone adrenalectomy for a left-sided pheochromocytoma. The *arrow* indicates a right adrenal mass. Subsequent laparoscopic adrenalectomy removed a right 3.5-cm pheochromocytoma.

being used successfully. Laparoscopic adrenalectomy is the procedure of choice for patients with unilateral and most bilateral lesions.

In bilateral disease, complete removal of all adrenal tissue commits a patient to lifelong steroid dependence and creates the risk of death from Addisonian crisis. Cortical-sparing adrenalectomy has been advocated by some surgeons to mitigate adrenal insufficiency. Encouraging results are reported with this technique. One group reported that 65% of patients were steroid independent after cortical-sparing adrenalectomy as part of a bilateral adrenal resection.[15] However, a risk of recurrence exists, and further long-term follow-up studies are warranted.

Parathyroid Tumors

Primary HPT in patients with MEN2A is less common than in those with MEN1, occurring in 20% to 30% of patients.[3] The presence of a germline mutation at codon 634 was found to be highly associated with the development of HPT in a given MEN2A family.[2] Although conflicting reports exist, the presence of a codon 634 mutation should alert the clinician to an increased risk of HPT as well as pheochromocytoma in a particular kindred. HPT in patients with MEN2A differs from that seen in patients with MEN1 by several important features. In those with MEN2A, MTC is the dominant feature, and HPT is generally diagnosed synchronously or after thyroidectomy. HPT tends to be milder, is more often asymptomatic, and is caused by a single enlarged parathyroid gland, although multiglandular neoplasia does occur and curative resection can be less aggressive.

Enlarged parathyroid glands encountered during thyroidectomy for MTC in eucalcemic patients should be resected. Many experienced endocrine surgeons leave normal-appearing parathyroid glands in situ during thyroid surgery for MEN2A, but autotransplantation to the forearm has been advocated by some. Subtotal or less than subtotal parathyroidectomy tends to be associated with less risk of hypoparathyroidism than total parathyroidectomy with autotransplantation without having a significantly higher rate or persistent or recurrent HPT. Overall, the risk of recurrent or persistent disease is 18% and postoperative hypoparathyroidism has been reported in 18% of patients.[16]

SURVEILLANCE

Surveillance is dependent on the underlying *RET* gene mutation, the level of disease involvement at the time of initial surgery (e.g., C-cell hyperplasia vs. MTC, lymph node metastases), and the type of operation performed (e.g., unilateral vs. bilateral adrenalectomy for pheochromocytoma). Serum calcitonin and CEA in patients with MTC, plasma meta- and normetanephrines

in those with pheochromocytoma, and serum calcium as well as PTH in those with HPT are all excellent biochemical markers of recurrent or metastatic disease and should be followed. An elevation in any of these tumor markers should prompt further investigation.

PROGNOSIS

The prognosis of patients with MEN2 has improved, mainly because of prophylactic thyroidectomy before the development of MTC. In older MEN2A series, MTC progressed and showed 15% to 20% cancer mortality. Early thyroidectomy has lowered the mortality from hereditary MTC to less than 5%. However, the longest follow-up period for prospective calcitonin screening is less than 25 years. Before the recognition of MEN2, sudden death from pheochromocytoma was frequent in these families, perhaps as frequent as death from progression of MTC. However, improved management of pheochromocytoma is likely to have decreased the rate of premature mortality in individuals with MEN2. The overall morbidity is more severe, and mortality is earlier in patients with MEN2B than in those with MEN2A. Recognition of the most highly aggressive MTC in patients with MEN2B and recognition of the possibility for early carrier detection have led to thyroidectomy in MEN2B far earlier than before. The two major comorbid MEN2B conditions are MTC and intestinal ganglioneuromatosis. Diarrhea from humoral factors and hypercalcitonemia produced by MTC combined with GI dysmotility from intestinal ganglioneuromatosis may significantly reduce the quality of life in these patients. Pheochromocytoma in patients with MEN2B has been virtually eliminated as a major cause of death because of improved and timely management.

PRACTICAL PEARLS

- *RET* gene mutational analysis is widely available and should be used in the workup of patients who may have any of the subtypes of MEN2.
- A genotype–phenotype correlation exists in individuals with MEN2; the management and treatment should be individualized based on which codon is mutated in a patient or family.
- In MEN2 carriers, prophylactic thyroidectomy before the development of MTC has become the standard of care.

(*Continued*)

- Pheochromocytoma needs to be ruled out before any invasive intervention is done in MEN2 carriers.
- Bilateral pheochromocytomas are common, and adrenalectomy is preferentially performed laparoscopically.
- Surveillance should be performed using biochemical analysis of serum calcitonin, CEA, calcium, PTH, and plasma meta- and normetanephrins as well as imaging on an individual basis.

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Chapter 23

von Hippel-Lindau Disease

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DEFINITION

von Hippel-Lindau (VHL) disease is an autosomal dominant syndrome that predisposes individuals to a variety of tumors. VHL is associated with tumors in a variety of organs, including the kidney, adrenal gland, central nervous system (CNS), eye, inner ear, epididymis, and pancreas. VHL is associated with renal cell carcinoma (RCC), pheochromocytoma, hemangioblastomas of the CNS, retinal angiomas, endolymphatic sac tumors, and pancreatic cysts and solid lesions.

EPIDEMIOLOGY

VHL occurs in one of every 36,000 live births[1] and has a penetrance in 90% of patients by age 65 years.[2] Before computed tomography (CT) and other imaging modalities were developed and before the advent of comprehensive screening in affected individuals, median survival in these patients was less than 50 years. The cause of death in these patients was typically either metastases from RCC or symptoms related to CNS hemangioblastomas.[3] Now with a multidisciplinary approach to these complex patients, survival rates have improved.

RISK FACTORS

There are no proven risk factors for VHL other than documented family history.

Genetics

VHL is an autosomal dominant disease resulting from a germline mutation in the *VHL* gene. The gene was first identified in 1993.[4] The gene is an RCC

tumor suppressor gene that has been shown to be involved in multiple functions, including regulation of angiogenesis, ubiquitination, and gatekeeper functions in mitosis.[5] The gene has been localized to chromosome 3p25.5.

CLINICAL PRESENTATION

VHL is associated with tumors in a multitude of organs, including the kidney, adrenal gland, CNS, eye, inner ear, epididymis, and pancreas. With current imaging modalities and genetic testing, many individuals are diagnosed while still asymptomatic. The diagnosis continues to be based on clinical criteria. Individuals with a family history are considered positive for the disease if screening tests diagnose a CNS hemangioblastoma (including retinal), pheochromocytoma, or renal manifestations. Patients who are diagnosed de novo without a family history must have evidence of two or more CNS hemangioblastomas or one CNS manifestation with a visceral tumor to meet diagnostic criteria.[3]

Because of the multiple organs involved in this disease process, this chapter separately describes the clinical presentation of each organ system.

Central Nervous System Lesions

Hemangioblastomas are the most common tumor found in VHL patients, affecting up to 80% of patients. The average age of presentation is 33 years.[6] These lesions are always benign but may cause significant morbidity because of volume effect. These lesions may occur anywhere along the craniospinal axis and may cause swelling and symptoms based on their location along this axis.

Retina

Retinal hemangioblastomas are very common in VHL patients, occurring in 60% of patients.[3] They may be multifocal or bilateral and occur early in life. The mean age of diagnosis of retinal hemangioblastomas is 25 years.[3] They are benign but symptomatic and may lead to vision loss.

Inner Ear

Occurring in 11% of VHL patients, endolymphatic sac tumors are not as common as other CNS manifestations of VHL. They may lead to hearing loss and problems with equilibrium.[7]

Visceral Lesions

Kidneys

VHL patients are prone to both renal cystic disease and solid lesions of the kidneys. RCC, which may be malignant, occurs in 25% to 45% of VHL patients.[3] VHL may also be associated with renal cysts that do not have a malignant potential but may cause local effects. Sixty percent of VHL patients have some renal manifestation.[3] Because of its malignant potential,

RCC is a significant cause of death in VHL patients, and when left untreated, it can lead to death from metastases in 13% to 42% of patients.[8,9] These renal manifestations may be multifocal and bilateral, including bilateral RCCs. The mean age of presentation for renal manifestations is 39 years.

Adrenal Glands

Pheochromocytomas occur in up to 20% of patients with VHL disease. These may be multiple as well as bilateral and may occur as extra-adrenal lesions as paragangliomas.[3] They occur at a mean age of 30 years.

Pancreas

Most of the pancreatic lesions associated with VHL are cystic and are classified histologically as serous cystadenomas. These cystic lesions may occur as a single lesion or as multiple lesions and occur in 17% to 56% of patients with VHL.[10,11] These lesions have no malignant potential but may replace enough of the pancreas to cause endocrine or exocrine insufficiency of the pancreas or compression of the intestine or the bile duct.

Solid lesions are also linked to VHL. Pancreatic neuroendocrinetumors (PNETs), which are always nonfunctional, have a malignant potential. PNETs have been previously reported to be present in 12% to 17% of patients with VHL, and these tumors behave in a malignant fashion in up to 17% of patients.[12,13] Despite their malignant potential, they remain an uncommon cause of death.[14] An association between PNETs and pheochromocytoma has been reported.[15]

Epididymis and Broad Ligament

Cystadenomas

Broad ligament cystadenomas have been reported in women with VHL. Epididymal cystadenomas are benign and typically asymptomatic but may occur in up to 60% of patients with VHL.

DIAGNOSTIC EVALUATION

VHL germline mutations can be detected by a variety of tests performed on DNA. These include quantitative Southern blotting to detect gene deletions or rearrangements and complete gene sequencing of peripheral blood lymphocytes.[16] Because of improvements in these genetic tests as well as a greater understanding of the different mutations present in affected individuals, detection rates are approaching 100%.[3]

Biochemical Tests

Pancreatic neuroendocrine tumors in patients with VHL are always nonfunctional. Biochemical testing does not help in these patients; however,

it is helpful in detecting pheochromocytomas. Before any intervention in these patients, 24-hour urinary metanephrines along with plasma levels should be tested to avoid missing an undiagnosed pheochromocytoma and possible hypertensive crisis.

Radiographic Tests

CNS Tumors

Magnetic resonance imaging (MRI) remains the most comprehensive test to identify and follow hemangioblastomas in the CNS.

Retinal Lesions

Retinal lesions can be seen on ophthalmoscopy, which should be performed at regular intervals in these patients.

Endolymphatic Sac Tumors

CT and MRI imaging of the internal auditory canals can identify and be used in follow-up of patients with these tumors.

Visceral Lesions

Contrast-enhanced abdominal CT is the gold standard modality used to screen for and follow visceral involvement of the disease. This screening modality has the benefit of being easy to perform and can be accessed in almost any hospital. It also has the benefit of being able to screen for all of the visceral manifestations of VHL with one screening test.

Although MRI is not commonly used as the primary screening modality in these lesions, it is useful for equivocal lesions seen on CT and in patients with CT contrast allergies.

Pancreatic Lesions

The majority of these lesions appear cystic on CT and MRI. These lesions are all benign. Histologically, they are serous cystadenomas. These cystic masses do not enhance on contrast CT or MRI studies. On T2-weighted MRI, pancreatic lesions have a high signal intensity consistent with their cystic nature.[17] Figure 23-1 shows a typical appearance of PNETs in a patient with VHL.

Comparatively, solid lesions of the pancreas in patients with VHL do have a malignant potential. In patients with VHL, these lesions represent neuroendocrine tumors. They enhance homogeneously on contrast CT and MRI studies. Most of these lesions are small and are typically located in the head of the pancreas, but they may occur anywhere in the pancreas.[17]

Renal Lesions

Pre- and postcontrast scans are compared to differentiate enhancing solid lesions of the kidney from hemorrhagic cysts. MRI is used as an adjunct, but CT remains the preferred method of screening.

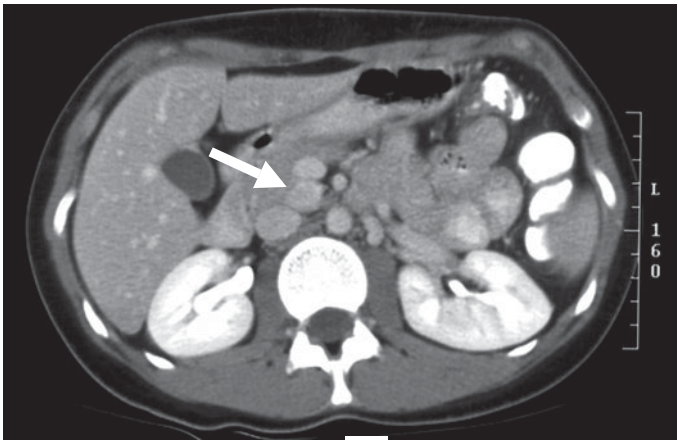

Figure 23-1. Intravenous contrasted computed tomography scan image of a pancreatic neuroendocrine tumor as shown at the tip of the *arrow* in the uncinate process of the pancreas between the portal vein and inferior vena cava.

Adrenal Lesions

CT is useful at identifying adrenal masses, especially in patients who have abnormal biochemical study results with elevated catecholamine levels. In patients with negative CT scan results but elevated catecholamine levels, iodine-131-meta-iodobenzylguanidine (MIBG) nuclear medicine scans are useful to look for extra-adrenal paragangliomas.

MANAGEMENT

Because of the number of organs involved and the number of lesions that may be present, the management of these patients can become quite complex and should be handled using a multidisciplinary team approach with neurosurgeons, urologists, ophthalmologists, and endocrine surgeons (Table 23-1).

Central Nervous System, Retinal, and Endolymphatic Manifestations

The management of these lesions is beyond the scope of this chapter and can be found elsewhere.

TABLE 23-1. Screening Intervals in At-Risk Individuals

Tumor	*Recommended Starting Age for Screening (Frequency)*	*Test*
CNS hemangioblastoma	11 years (yearly)	MRI
Retinal hemangioblastoma	Infancy (yearly)	Ophthalmoscopy
Endolymphatic sac tumor	Onset of symptoms	CT and MRI of the internal auditory canal Audiology testing
RCC or renal cysts	18 years (yearly)	CT of the abdomen
Pheochromocytoma	18 years (yearly)	Biochemical testing CT of the abdomen
Epididymal cystadenoma	N/A	N/A

CNS = central nervous system; CT = computed tomography; MRI = magnetic resonance imaging; N/A = not applicable; RCC = renal cell carcinoma.

Data from Lonser RR, Glenn GM, Walther M, et al. von Hippel-Lindau. *Lancet* 2003;361:2059-2067.

Visceral Lesions

Renal Cell Carcinoma and Renal Cysts

Renal tumors in patients with VHL may be multifocal and bilateral. A field defect is present in patients with VHL, which puts all kidney tissue at risk for tumors.[8] Because of this field defect, the primary goal of treating RCC in these patients is the prevention of metastases. Secondary goals include preserving renal function, maximizing quality of life, and minimizing morbidity and mortality from unnecessary surgical interventions.[8] To achieve these goals, observational strategies have been devised with interval CT imaging and specific size criteria leading to resection. Currently, a 3-cm tumor size threshold is used for recommendation of surgery using nephron-sparing surgery to preserve renal function in these patients.[8]

Pheochromocytoma

A complete assessment looking for hidden pheochromocytomas should be undertaken before any potential intervention is done. Doing so minimizes the risk of a hypertensive crisis in these patients. Laparoscopic adrenalectomy or partial adrenalectomy is the preferred treatment option in these

patients. Patients are treated with appropriate perioperative α- and β-blockade to prevent hypertensive crisis.

Treatment of Pancreatic Neuroendocrine Tumors

Lesions associated with the pancreas have traditionally been managed surgically because of their potential for malignancy. However, surgical management of these patients is not without morbidity and mortality because of the complex nature of pancreatic surgery. Because these lesions are nonfunctional, resection must be predicated on a potential benefit because of a reduction in the risk of metastasis and therefore a positive impact on survival (Table 23-2).

Currently, the management strategy of PNETs in patients with VHL is based on the size of the primary lesion, specific genetic mutations found in the tumors, and doubling time of the lesion. Each of these three criteria may be used as a prognostic indicator for metastatic disease in patients with VHL who present with PNETs.[14] Because functioning tumors are extremely rare to almost nonexistent, serum hormone level is not a good indicator for the presence of a PNET, and we recommend that patients undergo serum hormone testing only in the unlikely event that they have symptoms.

Based on prospective findings, our group has devised a rational management for the follow-up of these patients can be based on three criteria: tumor size greater than or equal to 3 cm, presence of a mutation in exon 3, and tumor doubling time less than 500 days. If the patient has none of these criteria, we believe the likelihood of the patient's lesion resulting in metastatic disease is

TABLE 23-2. Pancreatic Neuroendocrine Tumor Treatment Algorithm in Patients with von Hippel-Lindau Disease

Prognostic Factor	*Number of Factors Present*	*Metastatic Potential*	*Management*
Tumor size ≥3 cm	0	Low	History and physical examination CT or MRI every 2 to 3 years
Exon 3 mutation	1	Moderate	History and physical examination CT or MRI every 6 to 12 months
Tumor doubling time <500 days	2 or 3	High	Consider operative intervention

CT = computed tomography; MRI = magnetic resonance imaging.

very low, and the patient can be followed with a history and physical examination and radiologic scans on a 2- to 3-year cycle. If the patient has one criterion present, he or she should be followed more closely every 6 months to 1 year to detect the manifestation of a second criterion. If the patient has two or three criteria, he or she should be considered for surgical management of the lesion because of the higher likelihood of future malignancy from the PNET.

In patients who undergo surgical intervention for PNET, the type of surgery should be based on the position of the tumor and its relation to the main pancreatic duct. Intraoperative ultrasonography may be used to map the relation of the tumor to the duct. Surgical extirpation may be performed by enucleation or by formal pancreatic resection. Laparoscopic enucleation and distal pancreatectomy have been used in this patient population with good results.[12,14]

SURVEILLANCE AND FOLLOW-UP

For renal lesions, CT imaging along with history and physical examinations are typically performed at 6- to 12-month intervals, and operative intervention is undertaken with solid kidney lesions larger than 3 cm (see Table 23-1).

PROGNOSIS

Better imaging modalities, improved knowledge of the natural histories of the specific clinical manifestations, and better genetic testing have led to an improved quality of life in patients with VHL and their families. These improvements should also lead to an improvement in the overall survival in affected patients.

PRACTICAL PEARLS

- A multidisciplinary approach is paramount in patients with VHL.
- Pancreatic lesions are nonfunctional.
- Operative intervention should be undertaken for pancreatic lesions that are 3 cm in size, if the patient has an exon 3 mutation as part of the genetic analysis, or if the doubling time for the tumor is less than 500 days to prevent the possibility of metastases.
- Operative intervention should be undertaken for solid renal lesions larger than 3 cm.
- Before any intervention, biochemical studies should be undertaken to look for a pheochromocytoma so that potential hypertensive crisis is avoided.

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