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Section 2: Thyroid Tumors

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Tobias Carling

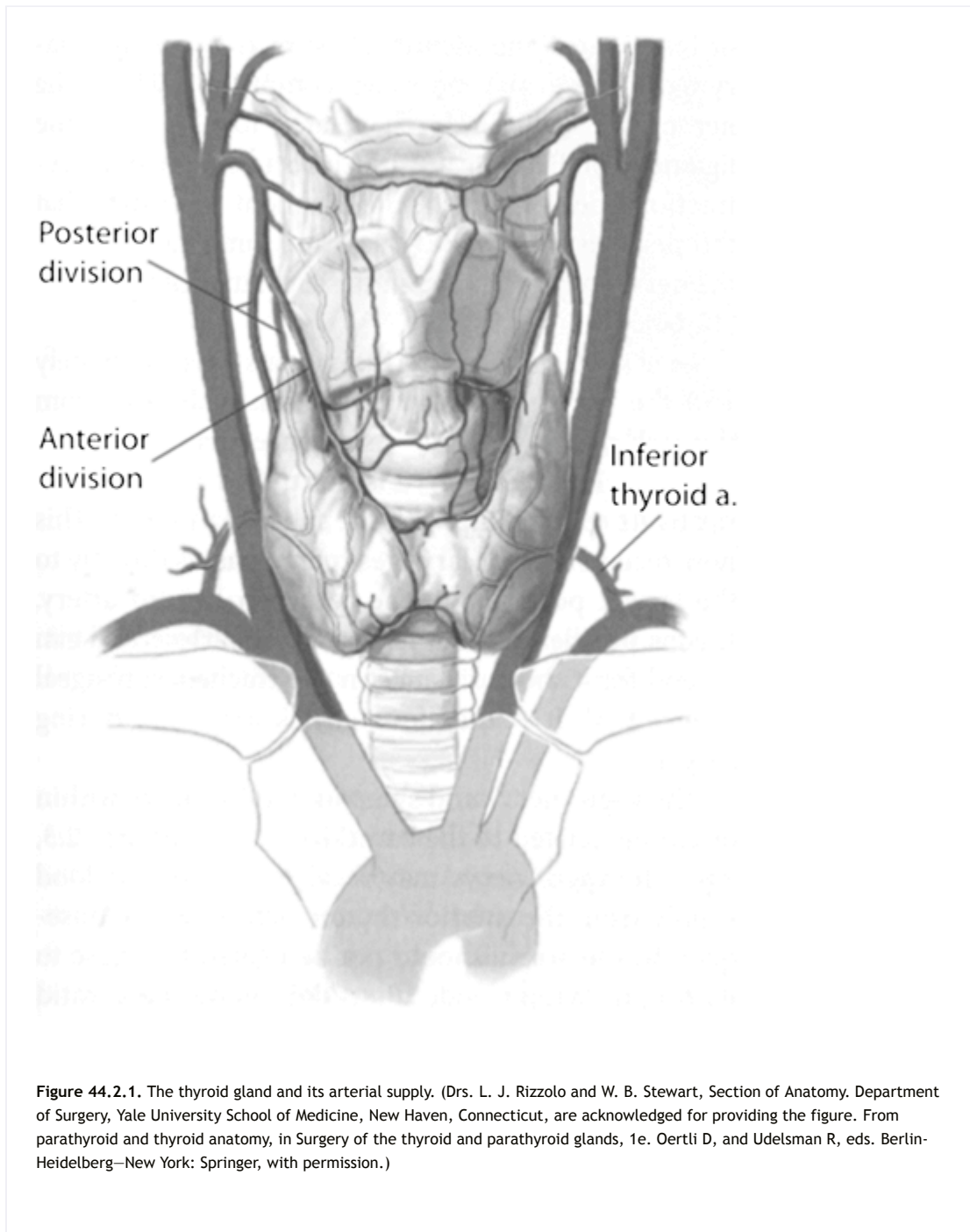
Robert Udelsman

Introduction

Goiter, or enlargement of the thyroid gland, has plagued humans since antiquity and was previously referred to as a *bronchocele* ("tracheal outpouch").¹ The modern name of the gland was introduced in 1656, when Thomas Wharton called it the thyroid gland, after the Greek for "shield-shaped," because of the configuration of the nearby thyroid cartilage. Theodor Kocher, professor from 1871 at Berne, markedly enhanced the surgical treatment for disorders of the thyroid gland and was

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awarded the Nobel Prize 1909 for his work on thyroid physiology, pathology, and surgery. Charles H. Mayo had a major interest in goiter as noted in a publication from 1904: "My first incursion into the field of thyroid surgery began on December 13, 1889, when a big Norwegian came in with an enormous goiter."² The Norwegian was operated on for obstruction of the trachea by the thyroid enlargement, and subsequently returned back to his farm. Mayo was not only joined in Rochester by Henry Plummer, who defined toxic multinodular goiter and was instrumental in the growth of the Mayo Clinic, but also by Edward Kendall, who succeeded in isolating bioactive crystalline material from the thyroid on Christmas Day 1914.² He and his associate A. E. Osterberg named it *thyroxin*. At Johns Hopkins University Hospital, William S. Halsted revolutionized surgical treatment and education and made an enormous contribution to the operative treatment of both the thyroid and parathyroid glands. Since then a number of important advances have been made in the diagnosis and management of patients with thyroid tumors, including the development of antithyroid drugs, fine needle aspiration biopsy, radioiodine treatment, and various imaging modalities. The anatomy of the thyroid gland and its arterial blood supply is depicted in Figure 44.2.1.



Thyroid Tumor Classification and Staging Systems

The normal thyroid is composed histologically of two main parenchymal cell types. *Follicular cells* line the colloid follicles, concentrate iodine, and produce thyroid hormone. These cells give rise to both well-differentiated cancers and anaplastic thyroid cancer. The second cell type, the C or *parafollicular cell*, produces the hormone calcitonin and is the cell of origin for medullary thyroid carcinoma. Immune cells and stromal cells of the thyroid are responsible for lymphoma and sarcoma, respectively. Of the 33,550 new cases of thyroid cancer diagnosed each year in the United States, approximately 90% are well-differentiated cancers, 5% to 9% are medullary, 1% to 2% are anaplastic, 1% to 3% are lymphoma, and fewer than 1% are sarcomas or other rare tumors.

Within the category of well-differentiated thyroid cancers various histologic subtypes have evolved

due to an improved understanding of their biology. Initial categories included papillary, follicular, and mixed tumor with variable areas of both papillary and follicular histology. Recent studies have established that these mixed tumors with areas of papillary features have a similar natural history and prognosis as papillary thyroid cancer without follicular features.³ Accordingly, mixed papillary and follicular carcinoma are now grouped with papillary carcinoma. Also, the follicular variant of papillary carcinoma has cytologic characteristics of a papillary carcinoma, but appears histologically to have a follicular architecture and behaves biologically as well-differentiated papillary carcinoma. The major cytologic feature shared by all members of this papillary group, regardless of the histologic pattern, is the characteristic nucleus containing Orphan-Annie nuclei, nuclear grooves, and intranuclear pseudoinclusions. Follicular carcinomas lack these cytologic characteristics but do demonstrate capsular and/or vascular invasion on histopathological examination. A third category of lesions grouped with differentiated thyroid carcinoma is Hürthle cell or oncocytic carcinoma. The distribution of well-differentiated thyroid cancer subgroups in some reports reveals that 80% to 85% are papillary, 10% to 15% are follicular, and 3% to 5% are Hürthle cell carcinomas.³ This distribution may not reflect adequate pathologic recognition of the recently appreciated follicular variant of papillary carcinoma. True follicular carcinoma now appears to represent 5% or fewer cases of well-differentiated thyroid cancers in countries with iodine-sufficient diets.

Thyroid carcinoma can be categorized by increasing clinical aggressiveness. The least aggressive are well differentiated (papillary carcinoma, follicular carcinoma), followed by intermediate forms (medullary thyroid carcinoma, Hürthle cell carcinoma, some rare variants of papillary carcinoma including the tall cell variant, columnar cell variant, diffuse sclerosing variant, and insular carcinoma or poorly differentiated),⁴ and the frequently incurable undifferentiated (anaplastic carcinoma). Since medullary thyroid carcinoma has unique inheritance, growth, and treatment options, it is reviewed in a independent section of this chapter (see Medullary Thyroid Carcinoma).

At least eight systems have been proposed and to a lesser or greater extent validated for staging thyroid cancer (Table 44.2.1). None has been universally adopted, and the lack of a common staging system has impeded the development of multicenter trials and cross-institutional comparisons of outcomes. In the absence of a universally accepted system, it is recommended that the TNM (tumor-node-metastasis) staging system, introduced by the International Union Against Cancer (UICC) and promoted by the American Joint Committee on Cancer (AJCC), the American Cancer Society, the National Cooperative Cancer

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Network, and the American College of Surgeons, be adopted as the international staging system.^{5,6} The TNM (or AJCC) classification system is outlined in Table 44.2.2.

Table 44.2.1 Comparison of Seven Different Prognostic Classification Systems in Well-Differentiated Thyroid Carcinoma

<i>System</i>	<i>Criteria</i>	<i>Reference</i>
AGES	Age, grade of tumor, extent, size	41
AMES	Age, metastases, extent, size	37
MACIS	Metastases, age, completeness of resection, invasion, size	51

Ohio State	Size, cervical metastases, multiplicity, invasion, distant metastases	36
Sloan-Kettering	Age, histology, size, extension, metastases	90
NTCTS	Size, multifocality, invasion, differentiation, cervical metastases, extracervical metastases	43
TNM	Size, extension, nodal metastases, distant metastases	5

NTCTS, National Thyroid Cancer Treatment Cooperative Society; TNM, tumor-node-metastasis.

Epidemiology and Demographics

Thyroid cancer is one of the fastest growing cancers in the United States, with a 240% increased incidence over the past three decades.⁷ It is the most common endocrine malignancy, accounting for 94.5% of the total new endocrine cancers, and 65.9% of the deaths due to endocrine cancers. Based on cancer statistics, 33,550 new cases of thyroid cancer will be diagnosed in 2007 with a total of 1,530 deaths due to the disease.⁸ The discrepancy between the total number of cases of all endocrine cancers arising in the thyroid (94.5%) and the total proportion of endocrine cancer deaths (65.9%) reflects the relatively indolent nature and long-term survival associated with thyroid malignancies.

Both papillary and follicular thyroid carcinomas are approximately 2.5 times more common in females.⁹ The median age at diagnosis is earlier in women than in men for both papillary and follicular subtypes and tends to be earlier for papillary cancer as compared to follicular cancer in either gender. Specifically, the median age at diagnosis in white women is between 40 and 41 years, whereas for white men, it is 44 to 45 years for papillary carcinoma.¹⁰ For follicular thyroid carcinoma, the median age at diagnosis is 48 for white women as compared to 53 for white men.¹⁰ Well-differentiated thyroid cancer has a greater incidence in whites than in blacks of both genders. The relative proportion of age-adjusted incidence rates is slightly more than twofold higher for whites. One significant difference in the incidence in terms of race is that the proportion of well-differentiated thyroid carcinomas that are follicular is increased greatly in blacks as compared to whites. It is reported that follicular carcinoma accounts for 15% of all well-differentiated tumors in whites as compared to 34% in blacks.¹⁰

Etiology and Risk Factors

Radiation exposure to the thyroid gland in childhood, age, female sex, and family history are risk factors known to increase the incidence of well-differentiated thyroid cancer. Exposure of radiation to the thyroid may occur either from external sources or from ingestion of radioactive material.

Several studies have shown an inverse relationship between increased risk of thyroid cancer and age of exposure to radiation.^{11,12,13} Relative risk is also linearly related to exposure dose, starting as low as 10 cGy and at least up to 30 Gy.¹⁴ The latency period after childhood exposure is at least 3 to 5 years, and there is no apparent drop off in the increased risk even 40 years after the radiation exposure.¹⁴ The majority of cases occurs between 20 and 40 years after exposure. However, even after 40 years, the relative risk as compared to a nonirradiated population is still increased. For these reasons, the large cohort of patients who underwent childhood irradiation for benign medical conditions such as thymic enlargement and acne between 1920 and 1960 are now between the ages of

45 and 85, and this population still has an increased risk of developing thyroid carcinoma.

Although the use of radiation for benign conditions has not been practiced since the 1960s, there is increased use of radiation treatments for neoplastic conditions, in infants, children, and young adults. The majority of this population have either Hodgkin's or non-Hodgkin's lymphoma but also includes long-term survivors of Wilms tumor or neuroblastoma in which there is some scatter to the thyroid gland.^{15,16} The young age at treatment for neuroblastoma and Wilms tumor (mean age, 2 and 3 years, respectively) and the relatively high dose of thyroid exposure have led to a dramatic increase in relative risk of 350 for neuroblastoma patients and 132 for survivors of Wilms tumors for the development of thyroid cancer.¹⁶ Relative risks between 16 and 80 have been reported in this patient population of adolescents and young adults treated for lymphoma.¹⁵ In the adult patient population treated with therapeutic radiation for malignancies, there is a drop off in risk, reflecting the importance of age at exposure. A large study of more than 150,000 women treated with radiation for cervical cancer had an estimated thyroid exposure of 11 cGy, with a relative risk of 2.35, compared to nonirradiated age-matched controls.¹⁷

Radiation exposure to the thyroid gland may also be due to iodine-133 (¹³¹I) administered for diagnostic thyroid scans. In a nationwide, population-based cohort study in Sweden, including all 36,792 individuals who received ¹³¹I for diagnostic purposes between 1952 to 1969, there was no evidence that the diagnostic scans increased the risk of thyroid cancer.¹⁸ Additionally, therapeutic ¹³¹I administered for ablation of thyroid tissue to treat hyperthyroidism seemed to be associated with, at most, a very modest increased incidence of thyroid cancer.¹⁹

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Table 44.2.2 American Joint Committee on Cancer Classification of Thyroid Cancer

PRIMARY TUMOR (T)^a

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤2 cm confined to the thyroid
T2	Tumor >2 cm and <4 cm confined to the thyroid
T3	Tumor >4 cm confined to the thyroid or tumor of any size with minimal extrathyroid extension
T4a	Tumor of any size with extrathyroid extension to subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve or Intrathyroidal anaplastic carcinoma ^b
T4b	Tumor invading prevertebral fascia or encases carotid artery or mediastinal vessels or Extrathyroidal anaplastic carcinoma ^b

REGIONAL LYMPH NODES (N)(central compartment, lateral cervical, and upper mediastinal)

- NX Regional lymph nodes cannot be assessed

- N0 No regional lymph node metastasis

- N1 Regional lymph node metastasis
 - N1a Metastasis to level VI (pre- or paratracheal, and prelaryngeal)
 - N1b Metastasis to uni-, bi-, 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 GROUPINGS
PAPILLARY AND FOLLICULAR**

Under 45 years of age

Stage I	Any T	Any N	M0
Stage II	Any T	Any N	M1

45 years of age and over

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1a	M0
	T2	N1a	M0
	T3	N1a	M0
Stage IVA	T4a	N0	M0
	T4a	N1a	M0

	T1	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4a	N1b	M0
	T4a	N1b	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1
<i>Medullary carcinoma</i>			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T3	N0	M0
Stage III	T1	N1a	M0
	T2	N1a	M0
	T3	N1a	M0
Stage IVA	T4a	N0	M0
	T4a	N1a	M0
	T1	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4a	N1b	M0
Stage IVB	T4b	Any N	M0

Stage IVC	Any T	Any N	M1
<i>Anaplastic carcinoma</i>			
Stage IVA	T4a	Any N	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

^aAll categories may be subdivided; (a) solitary tumor, (b) multifocal tumor (the largest determines the classification).
^bAll anaplastic carcinomas are considered T4 tumors.
 Modified from ref. 5, with permission.

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Table 44.2.3 Clinical and Genetic Characteristics of Familial Thyroid Follicular Cell Carcinoma Susceptibility Syndromes

<i>Syndrome</i>	<i>Chromosome Linkage/Gene</i>	<i>Characteristics</i>
Papillary thyroid carcinoma with papillary renal neoplasia (PTC-PRN)	1q21/?	Associated with papillary renal neoplasia Autosomal dominant with partial penetrance
Familial non-medullary thyroid carcinoma (fNMTC)	2q21/? and 19p13/?	Two genetic loci identified Autosomal dominant with partial penetrance
Familial thyroid tumors with cell oxyphilia (TCO)	19p13.2/?	Characteristic oxyphilic cells Autosomal dominant with partial penetrance
Familial adenomatous polyposis (FAP)	5q21-22/ <i>APC</i>	Papillary thyroid carcinoma with ~10 times increased prevalence Colorectal carcinoma, ampullary carcinoma, hepatoblastoma, medulloblastoma Autosomal dominant
Cowden disease (multiple hamartoma syndrome)	10q23.3/ <i>PTEN</i>	Follicular and papillary thyroid carcinoma Multiple hamartomas, breast, and endometrial cancer Autosomal dominant
Carney Complex 1	17q/ <i>PRKAR1A</i>	Follicular and papillary thyroid carcinoma Skin pigmentation, and cardiac, endocrine, cutaneous, and neural myxomatous tumors Autosomal dominant

A more harmful type of ingestion of radioisotopes of iodine comes from exposure to nuclear fallout. Data on the effect on thyroid cancer incidence come from populations exposed from the nuclear power station accident at Chernobyl and the results of atomic bomb development and testing at Hanford (Washington), the Nevada test site, and the Marshall Islands.²⁰ Within the first decade after the Chernobyl accident some regions of Belarus showed a 100-fold increase in thyroid cancer in individuals below the age of 15 at the time of exposure.²⁰ Essentially all of these radiation-induced tumors were shown to be papillary thyroid cancer, associated with more aggressive growth, a higher likelihood of local invasion and spread to regional lymph nodes, as well as a higher incidence of ret/PTC translocation (see Chapter 44.1).^{20,21} These data reflect the importance of age at exposure in the development of radiation-associated thyroid cancer.

Factors other than radiation exposure, including dietary influence, sex hormones, environmental exposures, or genetic susceptibility, have been studied, with mixed results and no clear associations. Dietary influences have primarily focused on the level of iodine in the diet. Iodine-deficient diets or diets that include a large intake of vegetables from the crucifer family (which block iodine uptake) may lead to increased thyroid-stimulating hormone (TSH) levels and are considered goitrogenic. Increased iodine intake due to shellfish occurs in the geographic areas with the highest incidence of predominantly papillary thyroid cancer, such as Iceland, Norway, and Hawaii. However, recent data suggest that relatively elevated levels of fish consumption does not appreciably increase thyroid cancer risk.²²

Epidemiological studies have demonstrated a four- to tenfold increased risk of well-differentiated thyroid cancer in first-degree relatives of subjects with this neoplasia.²³ In contrast to the well-described molecular pathology associated with medullary thyroid carcinoma, the molecular and clinical genetics of follicular cell-derived thyroid cancer have only recently been unveiled. Well-differentiated thyroid cancer can both be inherited in an autosomal dominant fashion as the main feature in some syndromes as well as having an increased incidence in other tumor susceptibility syndromes. The clinical and genetic characteristics of familial thyroid follicular cell carcinoma susceptibility syndromes are outlined in Table 44.2.3.^{24,25} For details related to the molecular biology of these disorders, see the Chapter 44.1.

Evaluation of the Thyroid Nodule

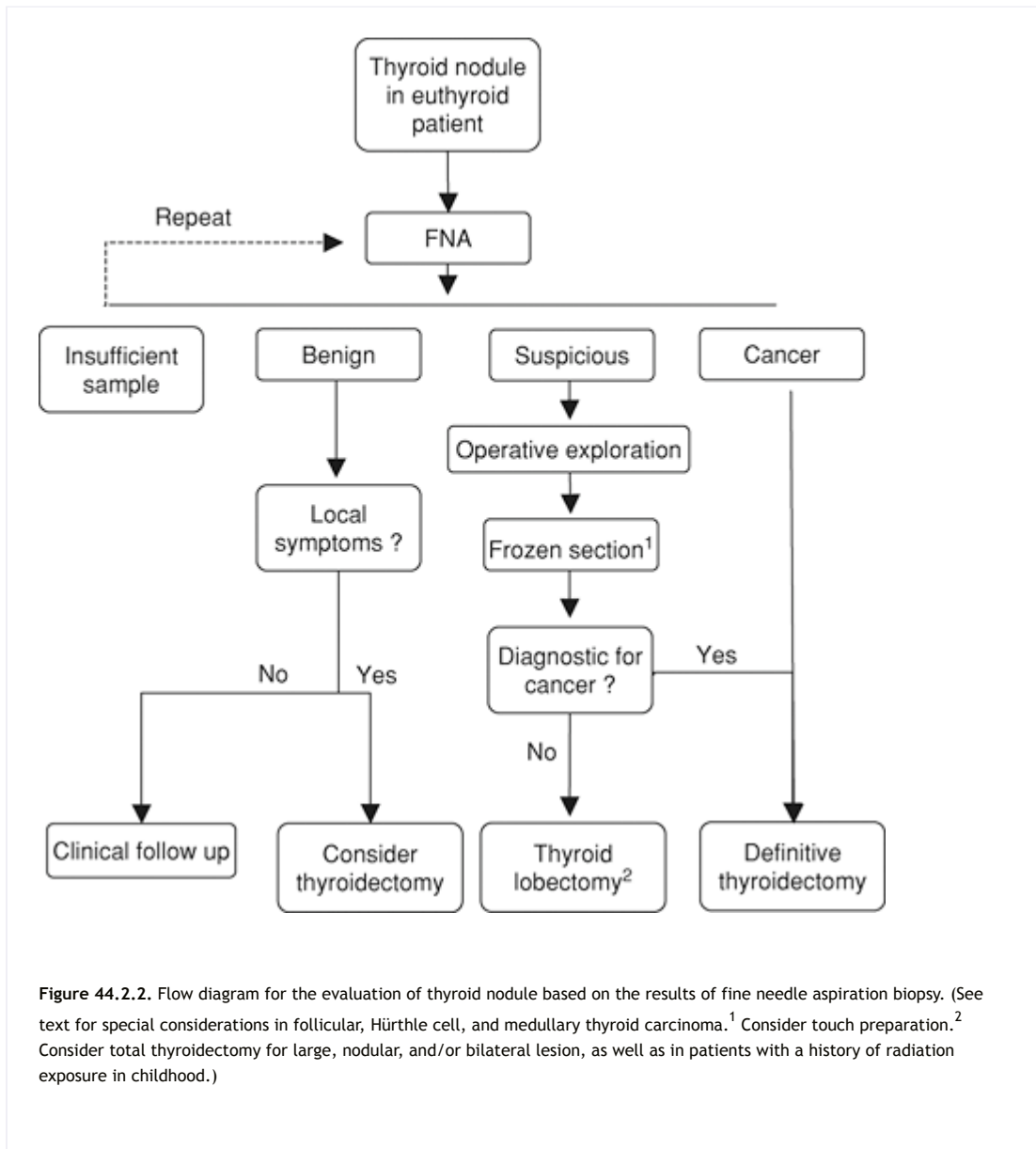
The vast majority of thyroid cancers presents as thyroid nodules detected either by the patient or by the clinician through physical examination or with imaging techniques of the neck for other disorders. As only a minority of thyroid nodules are malignant, a general review of the incidence, evaluation, and management of thyroid nodules precedes a detailed description of specific thyroid neoplasias (Fig. 44.2.2).

In iodine replete areas, thyroid nodules are clinically detectable by physical examination in at least 4% to 7 % of the general population. However, the prevalence of thyroid nodules depends on the population under study; gender, age, and history of exposure to ionizing radiation strongly influence the results of various large studies, as does the method by which nodules are detected, physical examination, intraoperative palpation, imaging techniques, histopathologically, or at autopsy. Thus, nodules are approximately ten times more frequent when examined at

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autopsy, during surgery, or by ultrasonography as compared to physical examination. There is an age-dependent increase in thyroid nodules, and in one histopathologic study, up to 90% of women older than 70 years and 60% of men older than 80 years had nodular goiter. All studies show that women develop nodules more frequently than men, although reports of the female to male ratio vary from 1.2:1 to 4.3:1.²⁶ An increased tendency to develop thyroid nodules is demonstrated in groups exposed to ionizing radiation, especially during childhood (see the section Etiology and Risk Factors

earlier in this chapter).



By obtaining information from the patient history and physical examination, the risk of malignancy in that individual can to a certain extent be assessed. In general, there is an approximately 5% to 10% chance of malignancy in all thyroid nodules for the total population, but men and patients at the extremes of age are at higher risk for malignancy. Nodules found in a patient with a history of childhood neck irradiation carry a 33% to 37% chance of malignancy.¹³ The presence of a solitary nodule is of greater concern than a thyroid with multiple nodules, but a dominant nodule or a nodule that grows in the setting of a multi-nodular goiter should be investigated to exclude carcinoma. Patients with Graves disease who develop a nodule may have a higher risk of cancer.^{9,26} However, the occurrence of carcinoma in autonomously functioning nodules is extremely rare.^{9,26}

A history of rapid increase in size, dyspnea, dysphagia, hoarseness, or the development of Horner's syndrome, albeit not specific for malignancy, are worrisome findings. Tender nodules are more often associated with thyroiditis and are likely to be benign. A family history of thyroid cancer or history, signs and symptoms consistent with any of the tumor susceptibility syndromes outlined in Tables 44.2.3 and 44.2.7 should prompt an extended investigation. (For details see the sections Etiology and

Risk Factors, Medullary Thyroid Carcinoma, and Molecular Biology of Endocrine Tumors.) On examination of the neck, attention to the firmness, mobility, and size of the nodules, their adherence to surrounding structures, and the presence of lymphadenopathy is important to determine the presence of carcinoma. However, these features lack specificity for malignancy. Routine indirect or direct laryngoscopy is important not only in the preoperative evaluation but also in the assessment of a thyroid nodule. Vocal cord paralysis is generally associated with advanced thyroid malignancy.

Thyroid function testing should be performed to identify underlying thyroid pathology and not to differentiate benign from malignant nodules. Subclinical hyperthyroidism, with a suppressed TSH, may be secondary to an autonomously functioning nodule. In this case, one can determine whether the nodule is functional with a radionuclide uptake scan. The majority of both benign and malignant thyroid nodules are hypofunctional when compared to normal thyroid tissue; thus, the finding of a "cold nodule" on iodine-123 (^{123}I) or technetium-99 (^{99}Tc) scanning is nonspecific. Radionuclide scans can be helpful in determining the functional status of nodules in patients with multinodular thyroid disease to focus a biopsy on cold nodules. However, routine thyroid scans in the initial evaluation of the thyroid nodule is not advocated since it is less cost effective, specific, and sensitive compared to fine-needle aspiration biopsy (FNA). Routine measurement of serum calcitonin has been advocated by some authors to identify patients with medullary carcinoma of the thyroid preoperatively, although the cost effectiveness of this procedure is unknown.²⁷ In any case, serum calcitonin levels should be determined in

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all patients with a thyroid nodule when either sporadic or familial medullary thyroid carcinoma is suspected.

Table 44.2.4 Fine-Needle Aspiration Diagnoses in Thyroid Nodules

<i>Benign</i>	<i>Suspicious</i>	<i>Malignant</i>
Acute suppurative thyroiditis	Follicular neoplasm	Papillary carcinoma
Subacute thyroiditis	Hürthle cell neoplasm	Follicular-variant of papillary carcinoma
Hashimoto's (lymphocytic) thyroiditis	Suspicious for papillary carcinoma	Medullary thyroid carcinoma
Nodular goiter		Anaplastic carcinoma
Adenomatoid nodule		Thyroid lymphoma
Colloid nodule		Metastatic carcinoma

High-resolution ultrasonography is a useful adjunct to the clinical examination for size assessment of nodules, for the detection of multiple nodules not discerned by palpation, and for assisting in FNA.²⁸ Several studies have aimed at identifying sonographic criteria in distinguishing benign from malignant thyroid nodules. Presence of microcalcification, irregular margins, spotty intranodular flow as well as hypervascularity is suggestive but not diagnostic of malignancy.²⁹ Ultrasonography can identify whether a lesion is cystic or solid, and the vast majority of purely cystic lesions are benign.

FNA has revolutionized the management of thyroid nodules, providing an extremely sensitive and cost-effective method of detecting thyroid malignancies.²⁸ The impact this procedure has had on clinical practice is reflected by a reduction of the total number of thyroid surgical procedures performed, a greater proportion of malignancies removed at surgery, and an overall reduction in the cost of managing patients with thyroid nodules.²⁶ The accuracy of cytologic diagnosis from FNA ranges from 70% to 97%²⁸ and is highly dependent on both the skill of the individual performing the biopsy and the cytopathologist interpreting it. If an adequate sample is obtained, the results of FNA are most commonly divided into the categories outlined in Table 44.2.4. Approximately 70% are classified as benign (range, 53% to 90%), 4.0% as malignant (range, 1% to 10%), 10% as suspicious or indeterminate (range, 5% to 23%), and 17% demonstrate an insufficient sample (range, 15% to 20%).²⁸ The insufficient sample rate can be improved by performing on-site cytologic assessment of the adequacy of the sample.²⁸

The malignant potential of follicular neoplasms can rarely be determined by cytologic evaluation; thus, the biopsies from such lesions are generally classified as suspicious or indeterminate, and most come to surgical resection. The cells from follicular adenomas and follicular carcinomas appear cytologically identical; only by identifying capsular or vascular invasion on histologic specimens can cancer be diagnosed. Specimens with predominantly Hürthle cells are treated in the same fashion; however, extensive Hürthle cell changes can be seen in Hashimoto's thyroiditis. Malignancy is found in approximately 20% of follicular nodules that are classified as indeterminate on FNA.³⁰

A variety of molecular markers have been assessed in FNA specimens in an attempt to develop more discriminating cytologic subclassifications to improve the yield of malignancy found at surgery. These markers include telomerase activity, loss of heterozygosity, as well as various pattern of protein expression by immunocytochemistry. Although there is little doubt that molecular markers will prove useful in the future, currently there is no single or group of markers that has been adopted in routine clinical practice.

Biopsies classified as benign or negative are safely followed nonoperatively with the caveat that false-negative results occur in 1% to 6% of cases.²⁸ Clinical judgment should dictate the course of action in these cases; if a large, hard nodule is fixed to surrounding tissue, surgery should be performed despite a negative aspirate. Sampling error can occur during biopsy of large, cystic hemorrhagic nodule. The cytologic features of Hashimoto's thyroiditis occasionally lead to these false-positive interpretations, but can be greatly reduced with experienced cytopathologists.

Benign thyroid nodules must be followed carefully by routine physical examination or, more precisely, by ultrasonography but do not generally require repeat biopsy. Thyroxine suppression therapy is widely used, although its efficacy is controversial. Multiple randomized controlled trials and meta-analyses show some decrement in nodule size in relatively iodine-replete populations, but seem to be of no or little value in the iodine-sufficient population. These findings in conjunction with the morbidities of exogenous thyroid hormone administration, including osteoporosis and cardiac side effects, suggest that routine suppression therapy for benign thyroid nodules is not warranted.³¹

Well-Differentiated Thyroid Carcinoma

Pathology

Thyroid malignancies are derived from either follicular cells (papillary, follicular, Hürthle cell, and anaplastic carcinomas) or parafollicular C cells (medullary carcinoma). A classification based on differentiation (i.e., well, intermediate, and poor) is of use both for clinicians and pathologists (Table 44.2.5).

Papillary thyroid carcinoma constitutes approximately 80% to 85% of malignant epithelial thyroid

tumors in developed countries where sufficient iodine is present in the diet. Grossly, papillary carcinomas have a variable appearance from minute subcapsular white scars to large tumors greater than 5 to 6 cm that grossly extend and invade contiguous structures outside

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the thyroid gland. Cystic change, calcification, and even ossification may be identified.

Table 44.2.5 Classification of Thyroid Follicular and Parafollicular Cell Carcinoma, Based on Differentiation

WELL DIFFERENTIATED (low-grade malignancy)
 Usual papillary thyroid carcinoma (PTC)
 Microcarcinoma (lesions <1 cm)
 Cystic
 Follicular variant of PTC (FVPTC)
 Usual follicular thyroid carcinoma (FTC)
 Hürthle cell (oxyphilic; oncocytic) carcinomas (HCC)
INTERMEDIATE DIFFERENTIATION
 Medullary thyroid carcinoma (MTC)
 Diffuse sclerosing variant of papillary carcinoma (DSV)
 Columnar cell variant of papillary carcinoma (CCV)
 Insular carcinoma (IC)
 Tall cell variant of papillary carcinoma (TCV)
POORLY DIFFERENTIATED (high-grade malignancy)
 Anaplastic (undifferentiated) carcinoma

Microscopically, papillary carcinomas are characterized by the presence of papillae, but some variants contain no papillary areas, are totally follicular in pattern, and are identified as a follicular variant.³² The terms *mixed papillary* and *follicular carcinoma* are no longer used because the great majority of papillary carcinomas of the thyroid do contain some follicular areas. Biologically, all these tumors, independent of their degree of follicular pattern, show similar clinical characteristics.³² The nuclei of papillary carcinoma are enlarged and ovoid and contain thick nuclear membranes, small nucleoli often pressed against the nuclear membrane, intranuclear grooves, and intranuclear cytoplasmic inclusions.³³ Because the nuclei are enlarged, they frequently overlap one another, which is a helpful clue in both the cytologic preparations and histologic slides. Papillary carcinoma has a propensity to invade lymphatic spaces and, therefore, leads to microscopic multimodal lesions in the gland as well as a high incidence of regional lymph node metastases. The latter may be the presenting symptom of a thyroid papillary carcinoma as, in some cases, a primary tumor is very small. Papillary thyroid carcinomas less than 1 cm are often referred to as *microcarcinomas*.

True follicular thyroid carcinoma is an unusual tumor comprising approximately 5% to 10% of thyroid malignancies in nonendemic goiter areas of the world.³⁴ Prior to the introduction of iodinated salt, follicular carcinoma was much more frequently diagnosed. In addition, the pathologic dictum—that any tumor with a pattern that is 50% or more characteristic of follicular carcinoma should be diagnostically placed in a follicular carcinoma category—has been shown to be incorrect. Indeed, most of the follicular pattern thyroid malignancies represent the follicular variant of papillary carcinoma and share the biological features, natural history, and prognosis of papillary thyroid carcinoma.³⁵ Follicular thyroid carcinoma is unifocal and thickly encapsulated and shows invasion of the capsule and/or vessels. Because of the diagnostic confusion, statistical data about the survival rate or the metastatic potential of true follicular carcinoma are not easily obtained. Most studies show that if capsular, but not vascular, invasion is present, the prognosis is excellent, with 85% to 100% of patients surviving at least 10 years of follow-up.³⁵

Natural History and Prognosis

The natural history and prognosis of well-differentiated thyroid cancer has been intensively studied since the 1980s. A clear definition of risk factors associated with poor outcome have allowed more selective and less aggressive treatment recommendations. In general, well-differentiated thyroid cancer is one of the least morbid solid carcinomas, with favorable long-term survival. However, a small proportion of patients with papillary cancer and a slightly larger proportion of patients with follicular thyroid cancer die from disease-related causes. As opposed to other solid neoplasms, one major difference is that regional lymph node metastases appear not to have a strong correlation with overall survival in most series, but do consistently correlate to local recurrence.³⁶

At presentation, approximately two thirds of patients have disease localized to the thyroid. The median size of tumors is between 2.0 and 2.5 cm in most large series.^{36,37} Patients with papillary carcinomas smaller than 1 cm are considered to have minimal or occult papillary thyroid cancer (papillary microcarcinoma). In North American studies, the incidence of occult papillary tumors ranges between 0.5% and 14%, with a greater proportional incidence in older age groups. It has been shown that a majority of such occult microcarcinomas are unlikely to ever lead to clinically significant disease.³⁸ For this reason, standard practice is not to investigate or submit to biopsy nodules that are smaller than 1 cm, except in the setting of familial thyroid carcinoma or a history of neck irradiation.

Approximately 33% to 61% of patients with papillary thyroid cancer will have involvement of clinically apparent cervical lymph nodes at the time of diagnosis.³⁶ The reported incidence of positive cervical lymph node metastases in follicular thyroid cancers is lower, ranging between 5% and 20%, with a median of approximately 10%.^{36,37} This is probably an overestimate, however, as many series of follicular thyroid carcinomas include follicular variants of papillary carcinoma that have the natural history of papillary thyroid cancer and metastasize to lymph nodes with a high incidence. Some argue that the frequency of true lymphatic metastases from follicular thyroid carcinoma to regional lymph nodes may be extremely unusual, less than 1%,³⁴ although one report demonstrated a 31% incidence of nodal metastases in follicular carcinoma.³⁹ If patients with papillary cancer have lymph nodes studied in great detail, the incidence of micrometastases in lymph nodes increases to 80%.³⁶ The clinical significance of these occult micrometastases parallels the significance of the microscopic foci of intrathyroidal disease, as it is very common but does not usually progress or change clinical outcome.

Only a small minority of patients have distant metastatic hematogenous disease at the time of diagnosis. In a large series 1% to 2% of papillary thyroid cancer patients and 2% to 5% of follicular thyroid cancer patients had metastases outside the neck or mediastinum at the time of diagnosis.³⁶ One series of 1,038 patients reported that 44 patients (4.2%) presented with metastases at diagnosis, including 2.3% of patients with papillary cancer and 11% with follicular cancer.⁴⁰ Having distant metastases at the time of presentation is a strong predictor of

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very poor outcome as 43% to 90% of these patients die secondary to their thyroid malignancy.^{36,40}

In the overall population with papillary thyroid cancer, there is a 90% to 95% long-term disease-free survival; there is a 70% to 80% long-term disease-free survival for patients with follicular cancers. The 20% of patients in this group who develop recurrent disease include a majority with local cervical recurrences either in lymph nodes or the thyroid bed and a minority of patients with distant metastases to the lung, bone, and liver.^{3,36}

Considerable databases exist that define prognostic risk factors for well-differentiated thyroid cancer.^{36,37,41} The two dominant factors in all series are the age at diagnosis and the presence of distant metastases. All systems also include some measurement of the size of the lesion and other

factors, such as local invasion or grade of the tumor, which have an impact on outcome. In general, younger patients do well with well-differentiated thyroid cancer. Cady and Rossi³⁷ defined low-risk categories as men younger than 40 and women younger than 50 years. Although historical data report follicular cancer as having a worse outcome than papillary thyroid cancer, Donohue et al.⁴² showed that if one corrects for age and other prognostic variables, the outcomes are similar within these two pathologic subcategories.

Patients who have distant metastatic disease either at presentation or at the time of recurrence do much worse.^{36,40} Similarly, patients with local invasion or high-grade lesions have a poorer prognosis. The risk categorization schema called AMES (*age, metastatic disease, extrathyroidal extension, size*) incorporated these components.³⁷ Using this system, low-risk patients can be identified as those who have a long-term overall survival rate of 98% and overall disease-free survival of 95% as compared to 54% and 45%, respectively, for high-risk patients. The initial system developed by the Mayo Clinic group carried the acronym AGES (*age, tumor grade, tumor extent, tumor size*). A mathematical formula based on weighted risk factors was developed to yield a prognostic score. The scoring system showed that patients with a prognostic score of less than 4 had a 99% 20-year survival rate, whereas, patients with a prognostic score greater than 6 had a 13% 20-year survival rate, with graded categories in between.⁴¹ Clearly, if subgroups of patients with 99% 20-year survivals can be prospectively identified, aggressive therapy with potential lifelong complications are difficult to justify in this subpopulation.

The importance of age, extrathyroidal extension, and distant metastases plays an important role in the AJCC staging of thyroid cancer.⁵ There is no large database that has verified this adaptation of the other staging system into the AJCC/UICC TNM classification.⁵ However, a very similar staging system was developed by the National Thyroid Cancer Treatment Cooperative Study registry, which initiated collection of data in 1987. A report of more than 1,500 patients analyzed by this staging system showed that 5-year disease-specific survivals for papillary thyroid cancer in stage I and II were 100%, 93.8% for stage III, and 78.5% for stage IV.⁴³ The disease-free survival rate similarly showed a high correlation with stages I through IV papillary carcinoma, with survivals of 94.4%, 92.5%, 82.7%, and 30%, respectively. Additionally, one recent study compared the fifth versus the most recent sixth edition of the AJCC/UICC TNM classification, and concluded that the sixth edition more accurately predicts outcomes in patients with extrathyroidal extension.⁴⁴

Apart from clinical indicators of prognosis, several molecular genetic alterations have been studied as putative predictive markers in thyroid cancer. Genes, encoding effectors in the mitogen-activated protein kinase pathway have been of particular interest. Mutations in one such gene, *BRAF*, has been shown in some, but not all, studies to be associated with increased likelihood of extrathyroidal extension, lymph node metastasis, and recurrence.⁴⁵ (For further discussion on the clinical and molecular genetics of endocrine tumorigenesis, see Chapter 44.1.)

Intermediately Differentiated Thyroid Tumors

Within the category of papillary and follicular thyroid cancer various histological subtypes have evolved due to an improved understanding of their biology. In contrast to the overall indolent behavior of the classical well-differentiated thyroid carcinomas, subtypes of these tumors have been identified as being more aggressive and thus have been labeled thyroid cancers with intermediate differentiation. These tumors comprise approximately 10% to 15% of all thyroid cancers.⁴ These include Hürthle cell (oncocytic, oxyphilic) carcinomas (HCC), as well as variants of papillary thyroid cancer such as the tall cell variant (TCV), columnar cell variant (CCV), diffuse sclerosing variant (DSV), and insular carcinoma (IC; Table 44.2.5).

The Hürthle cell neoplasm is considered a variant of follicular neoplasms. Historically, all such lesions, despite the histologic features, were considered to be malignant; hence, it was recommended that

they all be treated aggressively. However, many studies have evaluated the clinical pathologic features of thyroid Hürthle cell tumors and have shown that, on average, only 20% to 33% show histologic evidence of malignancy or invasive growth and may metastasize.³⁵ However, the size of the lesion is related to the risk of malignancy, and 65% of tumors over 4 cm are found to be malignant.³⁵ Hürthle cell tumors that do not demonstrate invasion microscopically behave as adenomas and may be treated conservatively.

The variants of papillary thyroid cancer, such as TCV, CCV, DSV, and IC, all exhibit unique histopathological features. However, these variants do share some commonalities, such as a high rate of extrathyroidal extension and nodal metastasis at diagnosis, as well as locoregional recurrence and development of synchronous and metachronous metastasis.⁴ The TCV is characterized by tumor cells being twice as tall as they are wide that need to be present in more than 50% of the lesion to make the diagnosis.⁴⁶ In contrast to usual papillary thyroid carcinoma (PTC), TCV often demonstrate strong immunoreactivity for antibodies against Leu M1 antigen. In a recent review of all reported cases until 2004, extrathyroidal extension of tumor at diagnosis was found in 67%, and cervical adenopathy in 57%.⁴⁷ During a mean follow-up period of 61 month, average rates of locoregional recurrence, distant metastasis, and tumor-related mortality were 25%, 22%, and 16%, respectively. The CCV is a rare tumor, accounting for only 0.15% to 0.2% of all PTCs.⁴⁸ The cell height in CCV is usually at least twice the width, greater than that seen in the TCV, and the presence of prominent nuclear stratification is the most distinctive histologic feature. Overall, CCV is associated with a poor prognosis. During a mean follow-up period of 43 months, average rates of locoregional recurrence, distant metastasis, and tumor-related mortality were 33%, 36%, and 29%, respectively.⁴ However, CCV on its own is not an independent poor prognostic factor. When the tumor is encapsulated or minimally infiltrative, all patients

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described in the literature remained free of disease at a mean follow-up of 5 years.^{48,49} Histologically, DSV is made up of numerous papillae alternating with areas of solid foci, with squamous metaplasia being a constant feature. Approximately, two thirds of cases with DSV have been described in the adults, whereas, the remaining one third were diagnosed in the pediatric population of Ukraine and Belarus following the Chernobyl nuclear disaster.⁴⁷ DSV tends to occur in younger patients, with a mean age of diagnosis at 27 years, and cervical adenopathy is present in approximately 70% of cases. Insular carcinoma displays small uniform neoplastic cells in a characteristic nesting pattern. In a review of more than 200 cases, extrathyroidal extension of tumor at diagnosis was found in 44%, and cervical adenopathy in 51%.⁴⁷ During a mean follow-up period of 72 months, average rates of locoregional recurrence and/or distant metastasis and tumor-related mortality were 64% and 32%, respectively. In summary, these variants of thyroid follicular cell carcinoma appear to exhibit an aggressive biology and are associated with significant mortality at 5 years, ranging between 25% and 90%.⁴

Treatment of Well- and Intermediately Differentiated Thyroid Carcinoma

Surgery

The key decisions in the surgical management of thyroid nodules or cancers (or both) is whom to operate on and how extensive a resection to perform. Before the development and widespread use of preoperative FNA of thyroid nodules, surgeons frequently relied on intraoperative frozen-section analysis to guide the extent of resection. The utility of frozen-section diagnosis for thyroid nodules is limited. The situations in which intraoperative frozen section may be useful is for patients who have suspicious but nondiagnostic FNA results in the setting of papillary thyroid cancer. The quality of both the cytologic specimen and its interpretation is paramount to modern thyroid surgery. If a high-quality

FNA specimen is diagnostic of malignancy a definitive procedure can be performed in the absence of intraoperative frozen-section analysis. If the FNA is highly suggestive, but not diagnostic of papillary thyroid carcinoma, frozen-section evaluation can be beneficial especially when touch preparation techniques are employed to assess cytologic features. Most of the lesions in the indeterminate FNA category are follicular neoplasms, the majority of which are benign. Capsular and vascular invasion determine malignancy, and the ability to render an accurate interpretation on frozen-section analysis is very limited. A randomized controlled trial demonstrated a very limited role of frozen-section analysis for the vast majority of patients with follicular neoplasms.³⁰ Thus, the recommended approach in this group of patients is to perform excision of the thyroid lobe harboring the nodule and wait for definitive pathologic analyses on paraffin-embedded histology. If the lesion turns out to be a follicular carcinoma with characteristics that place a patient at high risk, such as significant capsular invasion or angioinvasion, a completion total or near total thyroidectomy is performed during a second operation to remove the contralateral thyroid lobe.³⁵ In cases suspicious for the follicular variant of papillary carcinoma, the presence of specific nuclear features that define papillary thyroid cancer may be identifiable by employing touch preparations in addition to frozen-section analysis. For this reason, patients with FNA results that are read as follicular neoplasm with some features of papillary nuclei should undergo lobectomy and intraoperative assessment (frozen section, touch preparation) in an attempt to identify follicular variant of papillary thyroid cancer.

A long-standing controversy among endocrine surgeons has existed regarding the extent of surgical resection for well-differentiated thyroid cancer. This question is unlikely to be answered definitively even by a large clinical trial, since the expense and number of patients needed for trials of this indolent low-risk disease are overwhelming. Acceptable surgical procedures to remove a thyroid neoplasm include an ipsilateral lobectomy, a near-total thyroidectomy, and a total thyroidectomy. The entire thyroid lobe on the side of the primary cancer is taken out as completely as possible for any of these procedures. The difference in procedures relates to the management of the contralateral lobe and how this choice affects both the outcome and operative morbidity. In a thyroid lobectomy, the contralateral lobe is not dissected but is simply examined for abnormalities by palpation. A subtotal thyroidectomy leaves a rim of 2 to 4 g of tissue in the upper lateral portion of the contralateral thyroid lobe, whereas a near-total thyroidectomy leaves a much smaller amount of normal tissue (less than 1 g) immediately adjacent to the ligament of Berry. Both procedures may offer some protection to the recurrent laryngeal nerve, but a near-total thyroidectomy offers minimal benefit in terms of preserving the blood supply of the upper parathyroid. A total extracapsular thyroidectomy implies that every effort is made to excise all thyroid tissue, leaving no macroscopic residual thyroid in either lobe. The difference between a total thyroidectomy and a near-total thyroidectomy usually depends on the particular anatomy of the thyroid in any given patient. A small ledge of thyroid tissue, called the *tubercle of Zuckerkandl*, frequently exists near the ligament of Berry that often lies immediately superficial to the recurrent nerve. Some surgeons routinely leave this small remnant of normal thyroid tissue *in situ*.

The increased risk of performing a total thyroidectomy versus a lesser resection may be in the long-term incidence of hypocalcemia. A study from the Mayo Clinic spanning the years between 1946 and 1970 reported a 32% incidence of permanent hypocalcemia after total thyroidectomy versus only a 0.3% incidence after a subtotal procedure.⁴¹ More recent series report much less permanent morbidity and show variable results comparing the patients undergoing subtotal with those undergoing total thyroidectomy. Virtually all experienced surgeons should be able to perform total thyroidectomies with less than 1% recurrent nerve injuries, with the long-term risk of hypoparathyroidism of 2% to 9%. It should be mentioned, however, that surgeon experience is strongly related to lower complication rates, especially in total thyroidectomy, and when operating on malignant versus benign disease.⁵⁰ We advocate for a more aggressive (i.e., total thyroidectomy) for the vast majority of patients with well-differentiated thyroid carcinoma, and the reasons are outlined in Table 44.2.6. This recommendation is also shared with the recent American Thyroid Association

Guidelines.³¹

The data showing a 20-year survival of 99% with a 20-year disease-free survival of more than 95% in low-risk patients present

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a most compelling argument for performing a unilateral lobectomy or a subtotal thyroidectomy in a subset of thyroid cancer patients.³⁷ However, careful medical surveillance for cancer in the contralateral lobe as well as recurrence must be maintained. Furthermore, in situations in which a small thyroid remnant is left, the true morbidity of treating this patient with ablative doses of ¹³¹I (if indicated) is relatively minimal. In fact, it is typical for patients with a surgical report of a "total thyroidectomy" to detect normal residual thyroid tissue within the bed of the thyroid identified on the postresection diagnostic scan. This small thyroid remnant is readily ablated with postoperative ¹³¹I treatments, whereas successful ablation of an intact thyroid lobe is associated with considerably more difficulty.

Table 44.2.6 Arguments for Total Thyroidectomy in Well-Differentiated Thyroid Carcinoma

- Higher survival rate for lesions >1.5 cm in diameter
- Lowest recurrent rate in all patients
- Prevention of recurrence in the contralateral lobe
- Reduces the risk of developing pulmonary metastasis
- Can be performed with the same morbidity and mortality as thyroid lobectomy
- Improved sensitivity of serum thyroglobulin as a marker for persistent or recurrent disease
- Radioactive iodine can be used to detect and treat persistent or recurrent disease
- Reduces possibility of residual tumor in contralateral lobe undergoing transformation to anaplastic carcinoma

A large review from the Mayo Clinic of 1,685 patients with papillary thyroid cancer treated between 1940 and 1991 has been reported with a long-term follow-up.⁵¹ Based on surgeons' preference, 1,468 patients underwent a near-total or total thyroidectomy (87%), while 195 patients (12%) had a unilateral resection. With a 20-year follow-up, the incidence of local recurrence with unilateral resection was 14%, whereas, for bilateral resection, it was 2%.⁵¹ Similarly, the incidence of recurrent cervical lymph node metastases after unilateral resection was 19% as compared to 6% after bilateral resection. Despite this very clear difference in recurrence rates, there was no benefit in terms of disease-specific survival or distant metastases. The overall mortality at 30 years for patients with either unilateral resection or bilateral resection was approximately 2%. The authors concluded that although no survival benefit is gained from bilateral thyroid resection, the significant improvement in local recurrence with a minimal operative morbidity in the hands of experienced surgeons would lead to recommendation of near-total or total thyroidectomy for even this low-risk category of patients.

For patients in a high-risk category, there is much less disagreement regarding the extent of surgery. Due to the effectiveness of adjuvant postoperative radioiodine treatments and ease of follow-up with serum thyroglobulin (Tg) measurements, the vast majority of investigators agree that a total or near-total thyroidectomy is indicated for high-risk patients. For patients with extrathyroidal extension, *en bloc* resection of invaded structures should be performed. If the tumor is on the anterior thyroid, this causes minimal morbidity, as resection of the overlying strap muscles, causes no

symptoms postoperatively. For posterior tumors, the margins are either the trachea or esophagus. For the majority of well-differentiated thyroid cancers tracheal or esophageal resections are not indicated. However, for gross involvement of either of these structures, resection with reconstruction may be appropriate.⁵²

Gross cervical metastatic disease is treated by modified radical neck dissection, preserving the internal jugular vein, sternocleidomastoid muscle, and the accessory nerve, which results in excellent local control and minimal morbidity.⁵³ The lymph nodes typically involved are the level VI (central compartment) lymph nodes and the level II, III, and IV lymph nodes along the internal jugular vein corresponding to the upper, mid-, and lower neck, and level V (posterior neck; Fig. 44.2.3). During any thyroid resection, these lymph node areas should be palpated. Lymph nodes that are abnormal because they are firm or large should be subjected to biopsy with frozen-section pathologic evaluation. If positive for metastatic cancer, these lymph node areas should be completely dissected. Although lymph node metastases correlate with increased local recurrence, they do not carry a worse prognosis in several series.^{36,37}

Some investigators have noted a correlation of lymph node metastases and worse outcome and have argued for more routine formal dissections. Tisell et al.,⁵⁴ who have widely promoted microdissection of all cervical lymphatic tissue for medullary thyroid carcinoma, reported their results applying the same technique to papillary thyroid cancer. In their series of 195 patients, there was a 70% incidence of lymph node metastases in men and a 45% incidence of lymph node metastases in women. With long-term follow-up, only three patients (1.6%) died, partially due to locally recurrent thyroid cancer, all living more than 17 years after the initial surgery. The recent American Thyroid Association Guidelines suggest that routine level VI neck dissection should be considered for patients with papillary thyroid carcinoma and those that are suspicious for Hürthle cell carcinomas.³¹ Although, level VI node dissection can be achieved with low morbidity in experienced hands, routine dissection, which is, to date, of unproven benefit, is likely to lead to an increased rate of permanent hypoparathyroidism. The current practice by the vast majority of endocrine surgeons with regard to well-differentiated thyroid cancer (exclusive of medullary thyroid carcinoma, see the section Medullary Thyroid Carcinoma) is to perform formal node dissection in the setting of imagable or palpable nodal disease.

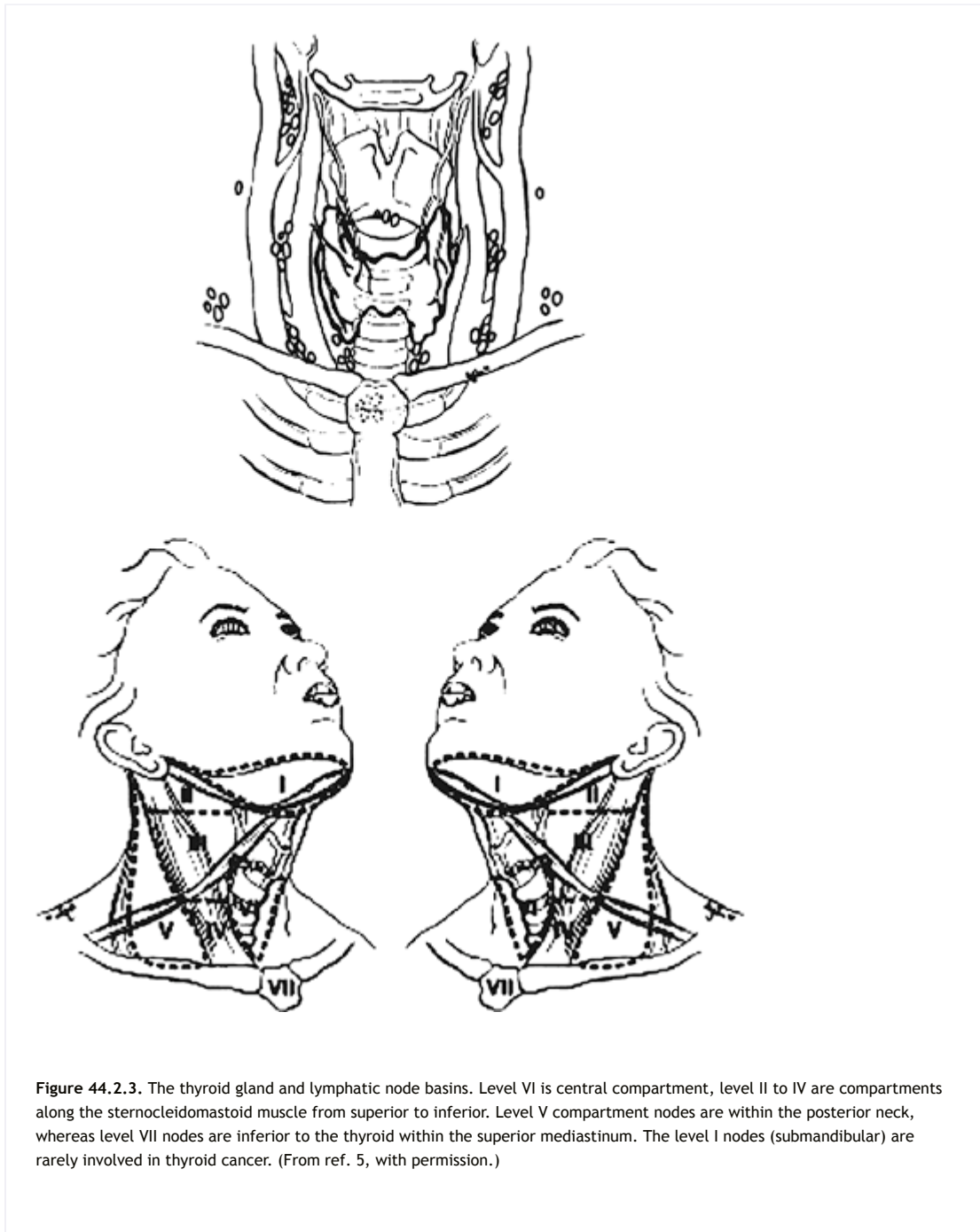
Radioiodine Therapy

Postoperative radioiodine ablation is increasingly being used in well-differentiated thyroid cancer. The lack of well-designed, randomized controlled studies and the low probability that any large multicenter treatment studies will ever come to fruition force the clinician to rely on retrospective studies, surveys of practice habits, and guidelines.³¹ The goals of the treatment are to destroy any residual thyroid tissue to prevent locoregional recurrence and to facilitate long-term surveillance with whole-body iodine scans and/or stimulated thyroglobulin measurements.

Several large retrospective studies demonstrate reductions in both recurrence and cause-specific mortality after ¹³¹I ablation.^{31,55} It should be noted, however, that other large studies fail to show such a relationship, especially in low-risk patients.⁵⁵ In studies showing a benefit with ¹³¹I ablation, patients with

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larger tumors (greater than 1.5 cm), multifocality, residual disease, and nodal metastasis seem to gain from the treatment. Thus, the recent American Thyroid Association Guidelines recommend radioiodine ablation for patients with stage III or IV disease, all patients with stage II disease younger than 45 years, and most of those older than 45 years, and selected patients with stage I disease, especially those with larger tumors (greater than 1.5 cm), multifocality, residual disease, nodal metastasis, vascular invasion, and intermediately differentiated histology.³¹



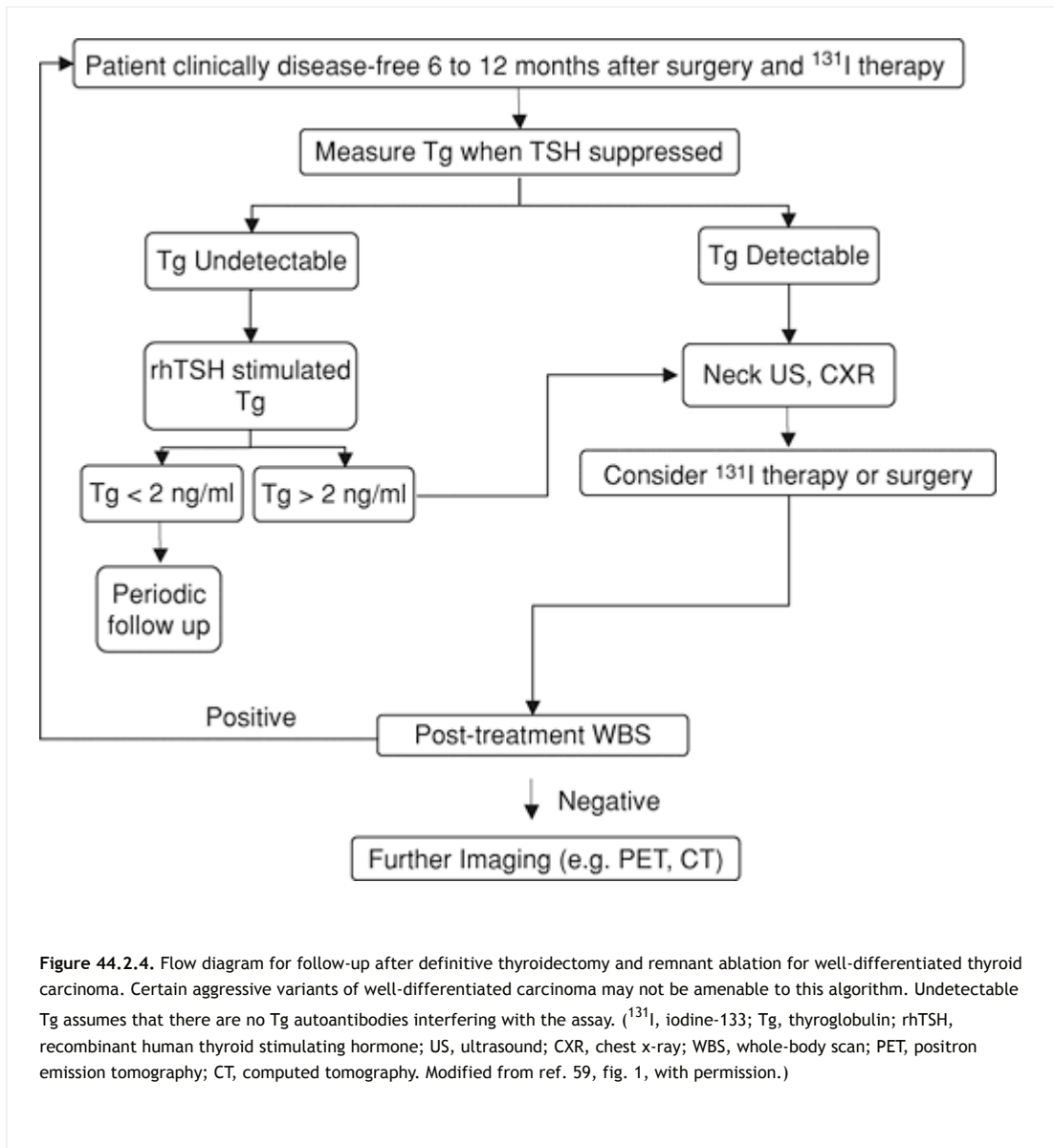
The dosing of ^{131}I for ablation is somewhat controversial. Some recommend low-dose ablation with less than 30 mCi administered on an outpatient basis. This approach should be reserved for low-risk young patients who may benefit from an overall lower radiation exposure and who accept the fact that several low radioiodine doses may be necessary before successful ablation. Activities between 30 and 100 mCi show similar rates of successful ablation, although there is a trend toward improved success rates with higher activities.³¹ Thus, higher ablative doses ranging from 100 to 200 mCi should be used preferentially for older, high-risk patients, particularly those known to have an incomplete resection of the primary tumor, an invasive primary tumor, tumors of intermediate differentiation, or metastases. Some authors advocate use of dosimetry with the goal to derive the dose of ^{131}I that will deliver no more than 200 cGy to the blood, with no more than 120 mCi retained at 48 hours or 80 mCi in the presence of pulmonary metastases. This decreases the risk of bone marrow damage and

radiation fibrosis in patients with metastatic lung disease. One recommended approach is for all patients with metastatic disease treated with repeated therapeutic doses of ^{131}I to undergo dosimetric quantification of the highest, safe dose, using a ceiling of 300 mCi. Other investigators recommend a standard fixed dose that may vary according to the site of uptake. For example, a dose of 150 mCi is given for residual or recurrent thyroid bed carcinoma with or without metastases, up to 200 mCi for bone metastases, and a reduced dose of 75 mCi for diffuse pulmonary metastases to prevent radiation pneumonitis and fibrosis. In spite of the theoretical advantage of formal dosimetry, its use has not been embraced by most centers.

Postoperative ablation is typically performed approximately 6 weeks after near-total or total thyroidectomy. Most, but not

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all, centers perform a pretherapy whole body iodine scan. Just as there is lack of consensus regarding ablation and therapeutic doses of ^{131}I , the diagnostic scanning dose is also controversial. The ideal dose achieves high sensitivity in detecting residual thyroid tissue, thyroid cancer, and metastatic foci and reduces the potential for sublethal radiation "stunning" of thyroid tissue that prevents optimal uptake of future ^{131}I therapy. Stunning is defined as a reduction in uptake of the ^{131}I therapy dose induced by a pretreatment diagnostic dose. Some authors suggest that diagnostic scanning with ^{123}I may prevent the stunning effect.⁵⁶ If performed, a pretherapy scan should use a low dose of ^{131}I (1 to 3 mCi) or ^{123}I . To optimize uptake by both normal residual thyroid and thyroid cancer, patients are rendered hypothyroid with a goal of increasing serum TSH. To accomplish this, thyroid replacement after thyroidectomy is often performed with the administration of tri-iodothyronine (T_3), as it has a much shorter half-life than thyroxine (T_4), and it is discontinued 2 weeks before treatment. In response to this hypothyroid state, TSH must achieve levels of greater than 30 mU/L to obtain optimal uptake of radioiodine. It is also recommended that a serum thyroglobulin level is obtained during this period of hypothyroid state (see the section Surveillance). A low-iodine diet is recommended 1 to 2 weeks before scanning and/or ablative ^{131}I therapy to enhance the uptake and retention of radioiodine.³¹ Posttherapy whole body iodine scanning is typically performed 1 week after ^{131}I treatment to identify metastases. Follow-up diagnostic scanning is performed and outlined in Figure 44.2.4.



Most, but not all, studies have demonstrated a role for TSH suppression therapy in the medical management of thyroid cancer after therapy. A recent meta-analysis supported the efficacy of TSH suppression in preventing adverse clinical effects.⁵⁷ However, such a benefit has not been substantiated in low-risk patients. Thus, it is recommended that high-risk patients are maintained at a TSH level below 0.1 mU/L, while TSH levels at or slightly below the normal range (i.e., 0.1 to 0.5 mU/L) seem appropriate for low-risk patients. It should be noted, however, that the degree of thyroid suppression is dictated by balancing the risk of recurrent thyroid cancer and the risks associated with subclinical thyrotoxicosis, particularly the cardiovascular risks.

The most common side effects from radioiodine therapy include sialadenitis, nausea, and temporary bone marrow suppression. Women undergoing ¹³¹I treatment should be advised to avoid pregnancy during and 6 to 12 months after treatment due to risk of miscarriage and fetal malformation. Temporary amenorrhea/oligomenorrhea occurs in about 25% of cases and typically lasts for 4 to 10 months. In men, testicular function and spermatogenesis may be transiently impaired but appear to recover with time. There is a weak, but dose-dependent relationship between ¹³¹I therapy and the development of second malignancies, such as bone and soft tissue tumors, colorectal cancer, salivary tumors, and leukemia.⁵⁸

Surveillance

The goal of long-term follow-up is to identify recurrence in patients thought to be free of disease. Tg, an important tumor marker in the surveillance of thyroid cancer patients, is the protein that provides a matrix for thyroid hormone synthesis within thyroid follicles and is critical in the storage of thyroid hormone within the thyroid gland. After successful thyroidectomy and ablation of residual normal or malignant thyroid tissue by radioiodine, the Tg should be in the athyreotic range. Levels above the athyreotic range are indicative of persistent, functioning thyroid tissue or carcinoma. Thyroxine may suppress Tg in patients with metastatic disease; therefore, the test is more sensitive in the setting of thyroid hormone suppressive therapy withdrawal and frank hypothyroidism documented by an elevated TSH.

Table 44.2.7 Clinical and Genetic Characteristics of Familial Medullary Thyroid Cancer Syndromes

<i>Syndrome</i>	<i>Characteristic Features</i>
FMTC	MTC
MEN2a	MTC Adrenal medulla (pheochromocytoma) Parathyroid hyperplasia
MEN2a with cutaneous lichen amyloidosis	MEN2a and a pruritic cutaneous lesion located over the upper back
MEN2a or FMTC with Hirschsprung's disease	MEN2a or FMTC with Hirschsprung's disease
MEN2b	MTC Adrenal medulla (pheochromocytoma) Intestinal and mucosal ganglioneuromatosis Characteristic Marfanoid habitus

FMTC, familial medullary thyroid carcinoma; MEN, multiple endocrine neoplasia; MTC, medullary thyroid carcinoma.

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At the time of thyroid hormone withdrawal or recombinant human TSH (rhTSH) stimulation for both initial postoperative scans and for subsequent follow-up scans, Tg is measured in conjunction with the diagnostic whole-body scan and may be more sensitive than the scan in detecting cancer.⁵⁹ There is good evidence that a Tg cutoff level above 2 ng/mL after TSH stimulation (either after thyroid hormone withdrawal or 72 hours after rhTSH administration) is highly sensitive in detecting patients with persistent or recurrent tumor.⁵⁹ Serum Tg levels should be measured every 6 to 12 months after definitive therapy, as outlined in Figure 44.2.4. The presence of autoantibodies to Tg, which occur in 25% of thyroid cancer patients and 10% of the general population, will falsely lower serum Tg levels. Thus, such antibodies should quantitatively be determined at every measurement of serum Tg levels. Routine use of diagnostic whole body scanning in the follow-up management of low-risk patients with negative TSH stimulated Tg and neck ultrasound is discouraged. When indicated, a scan should use

low-dose ^{131}I (1 to 3 mCi) or ^{123}I . Cervical ultrasonography, however, has become increasingly used in the follow-up management of patients with differentiated thyroid cancer. Cervical metastases may occasionally be detected by ultrasonography even when TSH stimulated Tg levels are negative. Thus, recent recommendations suggest that neck ultrasound should be performed 6 and 12 months after surgery, and then annually for 3 to 5 years depending on the patients risk for recurrence and Tg status.³¹ There has been a great deal of debate regarding the optimal management of patients who are Tg positive but negative on whole body iodine scans and ultrasonography. Computed tomography (CT), ^{18}F -FDG positron emission tomography (PET) scans, and ^{18}F -FDG PET/CT fusion imaging have been increasingly used in the surveillance and treatment planning of these patients with iodine-negative, differentiated thyroid carcinoma. Although, ^{18}F -FDG PET/CT show both false-negative and -positive results, its accuracy in selected patients may be as high as 93%.⁶⁰

Management of Local Recurrence and Distant Metastasis

Metastases discovered during surveillance are likely to be manifestations of persistent disease that survived ^{131}I therapy and thus are often incurable by additional such treatment. However, a reduction of the tumor burden with additional treatment may offer survival and/or palliative benefit. The preferred treatment, in hierarchical order, are surgical excision of locoregional disease in potentially curable patients, ^{131}I therapy, external beam irradiation therapy (EBRT), close surveillance in asymptomatic patients, and experimental chemotherapy trials.³¹

Patients with nodal locoregional recurrence in the neck should undergo modified radical neck dissection and/or central compartment (level VI) neck dissection depending on the location of the recurrence. More aggressive surgery may be warranted in selected patients with invasion into the aerodigestive tract.⁵² Tracheal stents and tracheotomy can be used as palliative measures. For regional lymph node metastasis not amenable to surgical therapy, or distant metastasis detected with whole body iodine scan ^{131}I therapy is usually employed, especially in lesions that are radioiodine avid. Similar to the discussion of initial treatment, no consensus exists with regards to dosing of ^{131}I , although most authors use a high dose ranging between 150 to 300 mCi. Pulmonary metastases are frequently detected exclusively on radioiodine scanning and tend to respond to ^{131}I treatment. Treatment can be performed every 6 to 12 months as long as the disease continues to respond. It should be noted, however, that pulmonary fibrosis may limit further ^{131}I treatment.⁶¹ For selected patients with incurable pulmonary disease, palliative treatments using metastasectomy, laser ablation, or EBRT may be considered. Complete surgical resection of isolated symptomatic bone metastases and ^{131}I treatment for radioiodine avid widespread disease have both been associated with an increased survival and are recommended especially in younger patients.⁶¹ A combination of treatments may be considered for symptomatic bone lesions when surgery or ^{131}I treatment is not possible or effective.³¹ Similarly, complete surgical resection of central nervous system (CNS) metastasis seems to be the most efficacious treatment, whereas EBRT may be considered in those not candidates for surgery.

Role of External Beam Radiation Therapy and Chemotherapy

The role of EBRT and chemotherapy in thyroid cancer is limited. EBRT should be considered in patients with unresectable gross residual cervical disease, painful bone metastases, and for metastases in critical locations that are not amenable to surgery and that would likely result in fracture, neurological, or compressive symptoms (such as metastases in the CNS, vertebral bodies, selected mediastinal lymph nodes, and pelvis). The best single chemotherapeutic agent for thyroid cancer is doxorubicin, with partial response rates of 30% and up to 45% in some series. Combination therapy with doxorubicin and cisplatin has produced disappointing results that were no better than single-agent trials, and the toxicity was worse. For surgically unresectable local disease that has not

responded to radioiodine, the best treatment may be a combination of hyperfractionated radiation treatments plus doxorubicin. Response rates of more than 80% have been reported using this regimen, although even in this situation, complete responses are rare and limited in duration.³¹

The management of patients with well-differentiated thyroid cancer that progresses despite current therapies represents a great challenge, and several novel agents are currently being tested *in vitro* and in clinical studies. Such agents include those targeting the Ras oncogenic pathway, various receptor tyrosine kinases, apoptotic pathways, as well as using gene therapy.⁶²

Poorly Differentiated Thyroid Carcinoma

Anaplastic thyroid carcinoma (ATC) is one of the most aggressive and difficult human malignancies to treat as well as one of the most lethal. As opposed to the excellent long-term survival for well-differentiated thyroid carcinoma, ATC in most series has a median survival of 4 to 5 months from the time of diagnosis, with rare long-term survivors.⁶³ The proportional incidence of ATC compared to the total number of thyroid carcinomas is variable but appears to be declining over time, and current epidemiologic studies indicate that this lethal form of thyroid cancer has decreased to between 1% and 3% of the total number of cases. Institutional reviews over a distinct period suggest a real decrease in the incidence of ATC.⁶³

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Patients with ATC differ epidemiologically from patients with well-differentiated thyroid neoplasms, with a median age two to three decades older and with a more equal gender distribution.⁶³ The median age at diagnosis ranges between 63 and 74 years. The largest series from the Mayo Clinic with 134 patients demonstrated a female-to-male ratio of 1.5:1 and a mean age of 67 years.⁶³ ATC is commonly related to a prior or a concurrent diagnosis of well-differentiated thyroid cancer or benign nodular thyroid disease.⁶³ This association of ATC with well-differentiated thyroid carcinoma suggests two features of the biology of this tumor. First, ATC may arise via the dedifferentiation of prior well-differentiated thyroid cancer, and the aggressive growth pattern of this anaplastic tumor may replace all previous evidence of well-differentiated tumor. Also, the close association between ATC and well-differentiated thyroid cancer suggests that the risk factors are similar.

The natural history, clinical presentation, and outcome of ATC reflect the biology of this tumor as an undifferentiated, rapidly growing neoplasm with invasive characteristics. The patients uniformly present with a palpable mass that is rapidly increasing in size. The median tumor size in patients with ATC was 8 to 9 cm, with a range of 3 to 20 cm as compared to the usual size of 2 to 3 cm for well-differentiated thyroid cancer. Invasion into the trachea, larynx, or recurrent laryngeal nerve leads to obstructive symptoms, hemoptysis, dysphagia, and hoarseness, which are often present at diagnosis.

The majority of patients with ATC die from aggressive local-regional disease, primarily with upper airway respiratory failure. At the time of diagnosis, 25% to 50% of patients have synchronous pulmonary metastases.^{63,64} However, it is usually the local growth causing obliteration of the airway that causes the patient's demise. For this reason, aggressive local therapy is indicated in all patients who can tolerate it and in whom it is technically possible. As opposed to well-differentiated thyroid cancer, ¹³¹I plays no role in the treatment of recurrent or metastatic disease for this tumor. Therefore, total or near-total thyroidectomy is not as important in ATC, except as needed to obtain local control.^{63,64}

Survival after the diagnosis of ATC is very poor. The median survival in most series is less than 5 months from the time of diagnosis. The majority of patients die due to local recurrence, although distant metastases occur primarily in lung, bone, and liver. External radiation has been used with limited success to treat locally recurrent ATC. Doxorubicin is the single most effective

chemotherapeutic for ATC, and it has been shown that doxorubicin plus platinum is more effective than doxorubicin alone. Early diagnosis with aggressive surgical therapy supplemented by EBRT and doxorubicin-based chemotherapy is regarded by many as the most appropriate treatment. However, a recent prospective phase II clinical trial demonstrated one complete response and nine partial responses in 19 patients after treatment with paclitaxel, suggesting its potential role in the treatment of anaplastic thyroid carcinoma.⁶⁵

Medullary Thyroid Carcinoma

Pathology

Medullary thyroid carcinoma (MTC) was recognized in the 1950s by Hazard et al.⁶⁶ as a distinct clinicopathologic entity. Over the next 10 years, investigators identified and described the parafollicular C cell that produces calcitonin and give rise to MTC. During the decade of the 1970s, Wells et al.⁶⁷ extended the measurement of calcitonin by defining a provocative test that rendered this hormonal tumor marker one of the most sensitive and specific in all of oncology. Understanding of the familial associations of MTC with corollary genetic studies reported in the 1980s and early 1990s have defined molecular changes responsible for familial forms of inherited MTC and with implications for sporadic MTC as well. The familial forms of MTC are outlined in Table 44.2.7. More recent research has identified genotype-phenotype relationships, leading to more individualized treatment of patients with inherited MTC.⁶⁸ For details on molecular pathogenesis of MTC see Chapter 44.7.

MTC constitutes between 3% and 12% of most institutional series of detectible thyroid cancers.³⁴ As opposed to well-differentiated thyroid cancer, MTC is not associated with radiation exposure, but it does occur in distinct familial syndromes. Sporadic or nonfamilial MTC accounts for 60% to 70% of cases, with three distinct familial syndromes accounting for the

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remainder. MTC is the most prominent clinical diagnosis in multiple endocrine neoplasia (MEN)2a and MEN2b. In 1986, familial MTC in the absence of the associated features of MEN2a or MEN2b, was described.⁶⁹ Appreciation of this syndrome has shifted the percentage of sporadic MTC as a function of the total number of cases from 80% to 60% and even lower in some series. In addition to the presence or absence of other associated endocrine abnormalities, each of these familial forms of MTC has a unique natural history and prognosis.⁷⁰

Parafollicular, or C cells, arise embryologically from the neural crest and are located primarily in the upper and middle thirds of the thyroid lobes, with a particular concentration posteriorly. This feature is important to surgical therapy, as this is in direct proximity to where the recurrent laryngeal nerve passes under the ligament of Berry and enters the larynx. Accordingly, performance of a near-total thyroidectomy is likely to leave remnant neoplastic disease in this location.

Grossly, MTC may be circumscribed or infiltrative and is usually white-yellow. Histologically, this tumor demonstrates a wide variety of patterns, including glandular, solid, spindle-cell, oncocytic, clear cell, papillary, small cell, and giant cell. The nuclei of MTC resemble those of neuroendocrine tumors in other areas of the body. They are usually round and have a stippled "pepper-and-salt" chromatin. Pathologic features associated with a poor prognosis include the presence of necrosis, a squamous pattern, oxyphil cells in the tumor and absence of cells with intermediate cytoplasm, and less than 50% calcitonin immunoreactivity.⁷¹

Clinical Presentation and Diagnosis

The clinical symptoms at the time of presentation vary. Patients with familial MTC who are identified by screening with stimulation tests or with molecular analysis (detection of *RET* gene mutation) are usually identified before the development of macroscopic disease. Patients with sporadic disease

typically present with an asymptomatic thyroid mass. Patients with bulky disease, local or metastatic, with extremely high levels of calcitonin may have severe secretory diarrhea as a principal symptom. Before the availability of genetic testing for familial MTC, basal and stimulated serum calcitonin levels were used to screen patients. Sequential calcitonin and carcinoembryonic antigen (CEA) measurements are still important as a tumor marker for surveillance of patients with MTC.

Various nuclear imaging studies have been evaluated in patients with MTC to identify gross and occult metastases. ¹³¹I thyroid scans are of no utility since MTC does not concentrate iodine. Similarly, thallium as well as technetium scans have been used with minimal efficacy. Several studies have used somatostatin receptor scintigraphy in the setting of MTC.⁷⁰ The results are promising for this imaging technique, but occult lesions smaller than 1 cm as well as liver lesions still are missed with this technique. Although not specific, ultrasound, MRI, CT, PET, and PET/CT imaging are increasingly being used in the management of patients with MTC.⁷⁰

Treatment

Chemotherapy and EBRT are, for the most part, ineffective against MTC, rendering surgical resection the only definitive therapy. For patients with sporadic MTC who are not identified by biochemical or genetic screening, the appropriate operation in most cases is total thyroidectomy, central node dissection, and ipsilateral modified radical neck dissection. Total thyroidectomy is indicated in this sporadic setting because a small proportion of lesions may be bilateral and because it may not be clear at the time of operation whether a patient is an index case of familial disease or the disorder is a true sporadic case. Because all familial syndromes have a high propensity for bilateral tumors, total thyroidectomy is always indicated. Combined with thyroid resection, a central lymph node dissection should be performed, removing lymphoid tissue from the level of the hyoid bone superiorly to the innominate vessels inferiorly and laterally to the jugular veins. Because of the high incidence of ipsilateral nodal metastasis at presentation, formal modified radical neck microdissections are ideally combined with the initial exploration.

The incidence of positive lymph nodes correlates with the size of the primary lesion at the time of diagnosis. It has been reported that for lesions smaller than 1 cm, there is an 11% incidence of nodal disease, whereas in patients with tumors larger than 2 cm, 60% will have positive cervical lymph nodes.⁷⁰ The incidence of distant metastases at the time of diagnosis varies with the clinical setting. Twelve percent of patients with sporadic MTC have distant metastases, whereas 20% of those with MEN2b have metastatic spread but only 3.3% of patients with MEN2a.⁷² Patients with familial non-MEN MTC tend to have even a less aggressive clinical course, and approximately 2% of these patients present with distant metastases. Patients with MTC are ideally treated immediately after the diagnosis has been established. Unfortunately, patients with sporadic disease are often explored without a clear diagnosis and/or by surgeons without experience in managing this malignancy. FNA specimens suggestive of MTC should be stained for calcitonin, which if positive is highly suggestive of MTC.²⁸ In addition, serum calcitonin and CEA levels in this setting are almost always elevated, thereby confirming the diagnosis. It is important to screen for catecholamine excess prior to surgical exploration as an apparent sporadic patient with MTC may in fact have a familial syndrome with an occult pheochromocytoma.

The outcome of treatment of patients with sporadic MTC has improved. Recent studies show a 5-year survival rate between 80% and 90% and 10-year survival rate between 70% and 80% for combined series of familial and sporadic MTC.⁷³ The natural history and prognosis for the various subtypes of MTC correlate with described genetic changes. The introduction of genetic testing and prophylactic surgery has improved the prognosis in cases of familial disease (see the section Treatment of Familial Medullary Thyroid Carcinoma).

One challenge in the surgical management of patients with MTC is the proper approach to patients

who have persistently elevated basal or stimulated calcitonin after resection of all gross disease. In many of these cases, imaging studies fail to demonstrate areas of disease. One strategy to identify the region from which elevated calcitonin is coming is to perform selected venous sampling. Excision attempts generally do not produce normalization of calcitonin levels. Tisell et al.⁷⁴ has advocated meticulous 12-hour neck dissections, often removing 40 to 60 additional cervical lymph nodes in patients with occult MTC. In a series of 11 patients, four demonstrated normalization of calcitonin levels, with another four that had dramatic improvement in their calcitonin levels. However, even these

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improvements in the calcitonin levels do not necessarily translate into improved survival. More recent data suggest that 28% of these patients can achieve eucalcitonemia following aggressive resection.⁷⁵

For patients with metastatic MTC, surgical resection may still offer the best chance of survival as well as long-term palliation. In 16 patients with metastatic MTC at Johns Hopkins, 21 palliative reoperations were performed. These procedures included neck reoperations in 11 cases but also removal of mediastinal masses and liver metastases as well as other miscellaneous lesions. All patients had clear relief of their index symptoms, typically diarrhea and fatigue, and had a median survival rate of 8.2 years.⁷⁶ In the setting of persistent hypercalcitonemia and negative imaging studies, remedial surgery with formal neck dissection is often indicated. However, prior to such an operation it is recommended to perform a laparoscopic evaluation of the liver to rule out superficial hepatic metastases.⁷⁰ If present, the enthusiasm for remedial neck dissection, especially in an asymptomatic patient, is markedly reduced.

The results of MTC treatment with EBRT or chemotherapeutic agents are disappointing. One study from France of 59 patients reported local recurrences within the radiation field in 30% of patients,⁷⁷ and the treatment may be associated with significant local toxicity such as dysphagia and dyspnea. Chemotherapeutic agents used in the treatment of MTC include doxorubicin, dacarbazine, streptozocin, and 5-fluorouracil. Single-agent response rates are poor, with aggressive doxorubicin regimens producing 20% to 30% objective responses, and combinations of chemotherapy have so far not been promising. The poor outcome of treatment of metastatic disease validates the treatment recommendation to diagnose patients with MTC early and treat with initial aggressive surgery. Recent data indicate that the tyrosine kinase inhibitor ZD6474 may be of benefit in the treatment of metastatic MTC.⁷⁸

Treatment of Familial Medullary Thyroid Carcinoma

An increasing number of patients are identified in one of the three familial settings of MTC that are diagnosed using biochemical or genetic screening for *RET* gene mutations. Routine use of screening to diagnose MTC led to significant decreases in both the age of diagnosis and the incidence of lymph node metastases, as well as a significant increase in the number of patients cured biochemically at these earlier operations. Wells et al.⁷⁹ used a molecular genetic screening technique to identify patients who are carriers of the MEN2a mutation as infants or young children. Before any abnormality in basal or stimulated calcitonin, these patients undergo a total thyroidectomy and central neck dissection. Pathologic evaluation of these children's thyroid glands identified C-cell hyperplasia and microscopic or macroscopic MTC. In the initial trial, no patients treated with this strategy had evidence of lymph node metastases, and this surgical strategy should be curative.

The genetic test for the mutations in the *RET* gene are commercially available, and many individuals are reporting series based on early operations for patients identified by *RET* mutation screening. A recent review noted that in a total of 209 patients treated in this manner, 3.4% had normal thyroid glands with no evidence of C-cell hyperplasia or MTC. It has also been noted in these patients

undergoing prophylactic operations that there was an 8.6% incidence of lymph node metastases.⁸⁰ Based on these results, it is thought that a prophylactic central neck dissection should be performed at the time of prophylactic thyroidectomy, based on genetic testing. Since different mutations in the *RET* gene are associated with variable disease aggressiveness, more recent research has attempted to correlate a certain mutation (genotype) with the patients clinical course (phenotype) in order to provide genotype-specific recommendations for treatment.⁶⁸ Thus, individuals with *RET* gene mutations associated with MEN2a and familial medullary thyroid carcinoma (FMTC) are advised to undergo prophylactic thyroidectomy at age 5 to 6 years, whereas affected individuals in kindreds with MEN2b should undergo thyroidectomy during infancy due to the aggressiveness and earlier age at onset of MTC in these patients.⁷⁰ At the M. D. Anderson Cancer Center, 86 patients with inherited MTC were stratified into three *RET* gene mutation risk groups; level 1, low risk for MTC (mutations in codons 609, 768, 790, 791, 804, and 891); level 2, intermediate risk (mutations in codons 611, 618, 620, and 634); and level 3, highest risk (mutations in codons 883 and 918).⁸¹ All patients in the level 3 group (all with MEN2b) had MTC present at initial thyroidectomy performed at a median age of 13.5 years. Similar, but not identical, findings were identified by the large European Multiple Endocrine Neoplasia study group.⁶⁸ With increased knowledge of genotype-phenotype correlations, it is likely that more individualized management can be used in the treatment of familial variants of MTC.

Thyroid Lymphoma

Thyroid lymphoma is a relatively rare disease constituting fewer than 1% of all lymphomas and accounting for 2% of extranodal non-Hodgkin's lymphoma.⁸² Almost all these thyroid lymphomas are non-Hodgkin's lymphoma, with the majority (70% to 90%) being intermediate grade and the remainder being high grade (see Chapter 51.2). Many are considered mucosa-associated lymphoid tissue lymphomas (MALTomas) that show plasmacytic differentiation and may be associated with similar lesions in extranodal sites especially in the gastrointestinal tract (see Chapter 51.2).

The majority of patients with thyroid lymphoma have disease on one side of the diaphragm with a proportion confined to the thyroid (stage IE). The majority have thyroid disease plus cervical or mediastinal lymph nodes (stage IIE).⁸² The incidence of this disease may be changing, primarily due to improved recognition and diagnosis of thyroid lymphoma. One hypothesis to explain the incidence increase is that these patients were previously diagnosed as having anaplastic thyroid carcinoma and, with better understanding and more sophisticated diagnostic tools, such as immunohistochemistry, these patients are being correctly categorized as having thyroid lymphoma.

In most series, there is a strong female predominance, ranging from 3:1 up to 8:1.⁸³ The median age in most series at diagnosis places patients in the seventh decade of life, similar to what is seen for ATC and much older than patients with well-differentiated thyroid cancer. Between 10% and 30% of patients report a symptom or combination of symptoms relating to local invasion, including hoarseness, dyspnea with stridor, or

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dysphagia. Patients with thyroid lymphoma virtually never have hyperthyroidism but frequently have hypothyroidism. These hypothyroid patients have evidence of autoimmune thyroiditis or Hashimoto's thyroiditis, either by FNA or from the pathologic specimen.⁸⁴

The optimal treatment for thyroid lymphoma has evolved with the success of combination chemotherapy used in the treatment of non-Hodgkin's lymphoma and with the ability to obtain an accurate diagnosis without invasive surgery by large-needle or core needle biopsy. Some argue that the role of surgery in this disease is simply to obtain adequate tissue for diagnosis, and that the primary treatment should be EBRT combined with a chemotherapy regimen based on the histopathological subtype of lymphoma.⁸³ Patients with extrathyroidal disease either by direct extension or lymph node involvement should be considered to have systemic disease. Although some

surgeons argue that attempts to clear the trachea to avoid airway obstruction should be performed if at all possible in all patients, others report that the rapid use of radiation therapy (starting the day after the diagnostic biopsy procedure) produces the same beneficial results. All would agree that the efficacy and long-term survival achieved using a combination of radiation therapy and chemotherapy render aggressive surgical resection with a sacrifice of recurrent laryngeal nerve or possibly resulting in hypoparathyroidism contraindicated for thyroid lymphoma.

Metastatic Disease of the Thyroid

Clinically significant involvement of the thyroid gland by metastases from other sites is rare, accounting for fewer than 1% of thyroid malignancies in most series involving surgical resection or FNA biopsies.^{85,86} On the other hand, the incidence of thyroid metastases identified in autopsy series is greater and can range between 2% and 26%, probably depending on the thoroughness of the examination by the pathologists.⁸⁵ From these autopsy series, the most predominant malignancies metastatic to the thyroid are breast and lung, each accounting for 25% of the total.⁸⁵ Melanoma, renal cell carcinoma, and gastrointestinal tract malignancies each account for approximately 10% of these secondary malignancies from autopsy studies. A variety of other miscellaneous diagnoses account for the remainder.

For the more clinically relevant situation in which the thyroid metastasis is detected pre-mortem, the most common primary site is renal cell carcinoma, accounting for 23% of 111 such cases combined from the literature.^{85,86} The next most common sites are breast (16%), lung (15%), melanoma (5%), and colon and larynx (4.5% each). Occasionally, thyroid metastasis may be the initial presentation of an occult primary from a gastrointestinal source or renal primary. Because FNA biopsy is the diagnostic tool used to evaluate thyroid nodules as the initial step, awareness of the potential of secondary metastases is important for interpretation of these biopsy results.

Dependent on the clinical situation, some of these patients may need thyroidectomy for palliation of local symptoms. Thyroid metastases may grow at a rapid rate and can cause airway obstruction.

Children with Thyroid Carcinoma

Well-Differentiated Thyroid Carcinoma

Well-differentiated thyroid carcinoma comprised only 1.4% of all newly diagnosed childhood carcinomas in the United States reported from 1975 to 1995.⁸⁷ Current treatment strategies for pediatric patients with well-differentiated thyroid carcinoma are derived from single-institution clinical cohorts, reports of extensive personal experience, and extrapolation of several common therapeutic practices in adults. Children with well-differentiated thyroid carcinoma more often than their adult counterparts have a history of external irradiation to the head and neck, although the majority present without such a history.⁸⁸ At presentation, pediatric patients tend to have a higher incidence of palpable cervical adenopathy, local infiltration of the primary cancer, and pulmonary metastases. The incidence of cervical nodal metastases in a series from the University of Michigan remained 88% from 1936 to 1990,⁸⁸ and the long-term mortality rate was 2.2%. Despite presenting with more advanced disease compared to adults, children tend to have a better prognosis.⁸⁷ Even in children with distant metastases, the survival rates are remarkably good. One study showed that at the end of a 15-year period only 14% had died from the disease.⁸⁹

Most authors agree that aggressive initial management with total thyroidectomy and cervical lymph node dissection should be performed in most children with well-differentiated thyroid carcinoma. This is commonly followed by administration of radioiodine therapy to destroy any residual normal thyroid remnant.⁸⁷ Finally, and importantly, because the duration of follow-up is lifelong, the care of children

with prior diagnosis of well-differentiated thyroid carcinoma should be transferred to an adult endocrinologist after they reach adulthood, even if they have no evidence of disease by that time.

Medullary Thyroid Carcinoma

With the introduction of genetic screening for *RET* gene mutations, an increasing number of patients are diagnosed with inherited forms of MTC during childhood or even infancy. The current recommendations advise that individuals with *RET* gene mutations associated with MEN2a and FMTC undergo prophylactic thyroidectomy between ages 5 to 6 years, whereas affected individuals in kindreds with MEN2b should undergo thyroidectomy during infancy due to the aggressiveness and earlier age at onset of MTC in these patients.⁷⁰ As more information about genotype-phenotype correlations are gathered, these recommendations may be altered, and thus more individual recommendations based on specific genetic information can be made.⁶⁸

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