ARTICLE TITLE: New Developments in the Diagnosis and Treatment of Thyroid Cancer

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2. Summarize current recommendations for the evaluation of thyroid nodules.
3. Summarize current recommendations for the diagnosis and management of thyroid cancer.

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New Developments in the Diagnosis and Treatment of Thyroid Cancer

David F. Schneider, MD, MS; Herbert Chen, MD

Thyroid cancer exists in several forms. Differentiated thyroid cancers include those with papillary and follicular histologies. These tumors exist along a spectrum of differentiation, and their incidence continues to climb. A number of advances in the diagnosis and treatment of differentiated thyroid cancers now exist. These include molecular diagnostics and more advanced strategies for risk stratification. Medullary cancer arises from the parafollicular cells and not the follicular cells. Therefore, diagnosis and treatment differs from those of differentiated thyroid tumors. Genetic testing and newer adjuvant therapies have changed the diagnosis and treatment of medullary thyroid cancer. This review will focus on the epidemiology, diagnosis, workup, and treatment of both differentiated and medullary thyroid cancers, focusing specifically on newer developments in the field.

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Keywords: thyroid cancer, papillary thyroid cancer, follicular thyroid cancer, medullary thyroid cancer, diagnosis, treatment, epidemiology

Introduction

Thyroid cancers exist in several forms. Providers caring for patients with thyroid cancer must tailor the evaluation, treatment, and surveillance to the specific type of tumor and each individual patient’s risk factors for recurrence and mortality. Newer molecular diagnostics and targeted therapies offer patients the potential for tailored, or personalized, thyroid cancer therapy. However, the risk of complications versus any potential benefit must be weighed carefully since most thyroid cancers behave indolently, and complications could be lifelong.1,2

The most common type of thyroid cancer is papillary thyroid cancer (PTC), comprising 80% of all cases. The second most common type is follicular thyroid cancer (FTC), which accounts for 10% to 20% of all cases. Together, PTC and FTC are termed differentiated thyroid cancer (DTC), and both arise from the thyroid follicular cells. Medullary thyroid cancer (MTC), however, arises from the parafollicular C cells. This neuroendocrine thyroid tumor represents 6% to 8% of all thyroid cancer cases and occurs in both familial and sporadic forms. Finally, anaplastic thyroid cancer (ATC) is one of the most aggressive and rapidly fatal cancers. It can develop from DTC that dedifferentiates over time or it also arises de novo.3-6 The first part of this review will consider the spectrum of DTC, and the second section will cover MTC.

Differentiated Thyroid Cancer

Epidemiology

Thyroid cancer is the most rapidly increasing malignancy in the United States for both men and women. Although the incidence of DTC has increased worldwide, there was a 2.4-fold increase in its incidence in the United States between 1973 and 2002, and the incidence has continued to rise over the last decade.7,8 This increasing incidence is attributed to the improved detection of smaller (<2 cm) tumors via more frequent and better ultrasound detection and fine-needle aspiration...
(FNA) biopsies.9 Another theory with which to explain the increasing incidence of DTC is the increased pathologic reporting of incidental microcarcinomas (tumors measuring < 1 cm) in thyroids removed for benign disease. Autopsy studies support this notion, since incidental microcarcinomas are discovered in 10% to 30% of the population.10–12 Further analysis of the increasing incidence of thyroid cancers revealed that although the incidence of microcarcinomas increased by 19.3% per year between 1983 and 2006, the incidence of tumors measuring 1 cm to 2 cm, 2 cm to 5 cm, and greater than 5 cm in size increased by 12.3%, 10.3%, and 12.0% per year, respectively, over that same period.13 This suggests that the better detection of smaller tumors does not fully account for the overall increasing incidence of DTC. Possible explanations for the rising incidence include increased iatrogenic, or “diagnostic,” radiation exposure; changes in the population’s body mass index; fertility drugs; or changes in menstrual cycles.14–17 These potential causative factors need further exploration in the US population. Regardless of the reason behind the rising incidence of DTC, the mortality rate remains largely unchanged at 0.5 per 100,000 population.8,18

Etiology

External radiation exposure to the head and neck region is one of the most well-known causes of thyroid cancer. Historically, patients received radiation treatments for enlarged tonsils or acne. Today, patients with cancer such as Hodgkin disease might still receive mantle radiation. In addition, children exposed to radioactive fallout from the Chernobyl nuclear accident have demonstrated an increased incidence of thyroid cancer.19,20 Children, especially females, are particularly sensitive to external radiation, with the greatest risk for exposures before adolescence. This occurs with exposure to either radioactive isotopes, as in nuclear accidents, or external-beam radiation used for medical diagnostics or treatment. Originally, radiation doses of 1 to 10 gray (Gy) were considered causative, but further evaluation of patients exposed to the Chernobyl fallout demonstrated a linear dose-response relationship. Several studies have demonstrated an exposure odds ratio of 5.2 per Gy, even with lower doses.21–23 Epidemiologic studies report that 7% to 9% of patients who received 5 Gy to 10 Gy of external-beam radiation develop thyroid cancer.24 A lag time of 10 to 20 years usually exists between exposure and the diagnosis of thyroid cancer, although much shorter periods have been reported.24

Another environmental etiology for thyroid cancer is dietary iodine content. PTC occurs with a higher frequency in regions with a high dietary iodine content such as Iceland and the Pacific Rim.25 Iodine-deficient countries, in contrast, have a higher incidence of FTC. Many factors confound these studies linking changes in DTC frequencies to iodine intake. Other dietary factors such as selenium, goitrogen, and carcinogen intake likely play causative roles.26 However, it is difficult to isolate these factors from genetic and environmental factors that also likely contribute to thyroid carcinogenesis. Finally, the thyroid-stimulating hormone (TSH) level has also been identified as a cancer risk. A higher TSH level in patients with thyroid nodular disease is associated with both a greater risk of DTC and advanced tumor stage.27

In the last 10 to 15 years, the information on genetic etiologies of DTC has seen an exponential growth. Both inherited and acquired genetic lesions have been studied. DTC occurs in inherited syndromes such as Gardner, Cowden, and Werner syndromes.28,29 Familial nonmedullary thyroid cancer (FNMTCT) is defined when 2 or more first-degree relatives are diagnosed with DTC in the absence of another syndrome. It exhibits autosomal dominant behavior with incomplete penetrance and variable expressivity.29–31 Several candidate genes for FNMTCT have been studied, including thyroid tumors with cell oxyphilia 1 (TCO1), multinodular goiter 1 (MNG1), familial papillary thyroid cancer/papillary renal neoplasia (fPTC)/PRN, and nonmedullary thyroid carcinoma 1 (NMTC1), but a single responsible gene has yet to be definitively identified.32–35 Compared with sporadic DTC, FNMTCT is more aggressive, with increased recurrence, local invasion, multcentricity, and lymph node metastases. FNMTCT should be suspected in the setting of 2 or more family members with DTC and/or younger family members (those in their 20s to 30s) with more advanced cancers (ie, lymph node metastases). More recently, Mazeh et al demonstrated that even patients with just one family member affected by DTC were similar to patients with FNMTCT in terms of age, tumor size, tumor multicentricity, lymph node metastases, local invasiveness, and disease recurrence.36 Hence, inherited forms of DTC may prove more common than previously thought, and current definitions may change with further study. Currently, FNMTCT remains difficult to distinguish from sporadic DTC in the absence of a validated genetic test and therefore no screening recommendations exist.36

Increasing investigation into acquired genetic lesions that can distinguish carcinoma from benign nodules has greatly expanded our knowledge of the molecular pathogenesis of DTC. A number of different molecular markers have been identified in DTC. Here, 4 molecular markers with the most literature in human studies will be discussed. Some centers are beginning to use these markers in clinical practice, as we will discuss in the section regarding diagnosis. One such marker is the RET and PTC (RET/PTC) rearrangement. For example, 70% of cancers found in Chernobyl survivors carried a RET/PTC rearrangement. The fusion of the
tyrosine kinase–encoding domain of the RET protein with a heterologous group of genes occurs in 20% to 40% cases. RET/PTC rearrangements are common in small, multifocal PTCs accompanied by an inflammatory infiltrate, and often are seen in individuals exposed to ionizing radiation.38

BRAF is a member of the RAF-MEK-ERK (extracellular signal–related kinase) serine/threonine kinase signaling cascade, and a BRAF mutation is found in 40% of PTC cases.39 The BRAF point mutation, or mutations in another member of this signaling pathway, RAS, are frequent in cases of poorly differentiated PTC or ATC.40 Most BRAF mutations keep the protein in its active form, resulting in constitutive activation of the RAF-MEK-ERK signaling cascade and continued mitogenic activity. The Ras proteins are plasma membrane GTPases activated by growth factor receptors. Mutations that result in constitutive activation of RAS lead to oncogenesis. RAS mutations occur in 20% to 50% of follicular cancers.

Similar to the RET/PTC rearrangement, another chromosomal translocation occurs in FTC. The promoter region of the gene encoding paired box 8 (PAX8) fuses with the coding sequence of the peroxisome proliferator-activated receptor-γ (PPARγ) gene in 35% of FTC cases.40–42 The intracellular signaling consequences of the PAX8-PPARγ rearrangement remain unclear. RAS mutations are also highly prevalent in FTC, but Nikiforova et al found that RAS and PAX8-PPARγ rearrangements are mutually exclusive, suggesting that these are 2 distinct molecular pathways for FTC development.40

Classification and Prognosis

DTCs are broadly categorized as papillary or follicular. In general, well-differentiated PTC has an excellent prognosis, with a 5-year survival rate of greater than 97%.8 Smaller tumors carry a better prognosis than larger tumors. PTCs measuring less than 1 cm in size are called papillary microcarcinomas, and have been reported in 10% to 30% of autopsy studies.10,43,44 In the past, these tumors were incidentally detected in thyroidectomy specimens, but they are now detected with increasing frequency by high-resolution ultrasound. They are believed to have an excellent prognosis, but some may behave more aggressively than previously appreciated, and management remains controversial.45,46 In general, however, microcarcinomas hold an excellent prognosis with 10-year and even 15-year disease–specific survival rates exceeding 99%.45 Risk factors of mortality from a microcarcinoma include age older than 45 years, male sex, minority racial group, lymph node metastases, extrathyroidal extension or superficial location, intraglandular spread or multifocality, peritumoral fibrosis, and BRAF positivity. Several scoring systems that incorporate these factors have been developed to risk-stratify patients with microcarcinomas.35,47

In addition to tumor size, age is another important determinant of prognosis in patients with DTC. Older patients tend to have more poorly differentiated, aggressive variants. In these cases, death results from local invasion and extensive metastases. Therefore, age, the completeness of resection, and extrathyroidal extension also are prognostic indicators that are used in many staging systems for DTC.48,49

One of the greatest risk factors for disease–specific mortality is the presence of distant metastases.50–52 While the significance of distant metastases is rarely disputed, the importance of lymph node metastases in determining DTC-specific survival remains controversial. Lymph node involvement is common in patients with PTC, but the precise incidence of lymph node metastases depends on how it is defined. Palpable disease in the lymph nodes is present in 5% to 10% of patients with PTC, but ultrasound detects pathologic lymph nodes in 30% of patients. Only 2% of patients with FTC have lymph node metastases because the route of spread is hematogenous rather than lymphatic, but treatment guidelines and retrospective studies frequently consider PTC and FTC together. Routine histologic examination of lymph nodes detects DTC in 20% to 50% of patients, but when polymerase chain reaction is performed, up to 90% of patients with DTC will be found to have lymph nodes with microscopic disease. Historically, lymph node involvement was believed to increase the rate of local recurrence without affecting survival, and therefore surgeons took a conservative approach to lymph node dissection for DTC. Wada et al demonstrated that patients with pathologically positive lymph nodes had a recurrence rate of 16.3% compared with 0% in patients without pathologic lymph nodes.53 Whether metastatic lymph nodes are clinically evident preoperatively appears to be an important factor in determining recurrence. For example, Ito et al found that if metastatic lymph nodes were not seen preoperatively, then the risk of lymph node recurrence was only 1.5%.54 Of note, in this study of 590 patients with microcarcinomas, 40% of patients had lateral neck lymph node metastases identified histologically after prophylactic neck dissection.54 Hence, lymph node metastases do affect recurrence, and clinically apparent lymph nodes are more important than pathologically positive ones. The impact of lymph node involvement on survival is less clear. Large series and population-based studies suggest that there is a small but significant affect on survival.55–57

Most current staging systems consider lymph node metastases as a binary factor, classifying patients by the presence or absence of diseased lymph nodes, or the anatomic location of these lymph nodes (Tables 1 and 2).58 The lymph node ratio (number of metastatic lymph nodes divided by the total number of lymph nodes harvested) is a
method with which to further risk-stratify patients with lymph node disease. The lymph node ratio is helpful for clinicians caring for patients with PTC because it indicates the adequacy of lymph node dissection and the extent of disease. Although the lymph node ratio does independently impact disease-specific survival, it is probably most helpful in assessing recurrence risk and tailoring postoperative treatment and follow-up accordingly.

PTC Subtypes

PTC has several subtypes spanning the spectrum of well-differentiated, classical papillary cancers to the most aggressive, anaplastic tumors. Well-differentiated tumors can be subdivided by their aggressiveness. Less aggressive variants include follicular, oxyphilic, and cribriform-morular. The most common subtype is follicular variant PTC (FVPTC), which has features of both PTC and FTC but is classified as a PTC subtype. This subtype exhibits the overall follicular structure but with the nuclear features of PTC. Often FVPTC is mistaken for follicular neoplasms or carcinomas. Overall, the prognosis is intermediate between classical PTC and FTC. The prognosis also hinges on whether the tumors are completely encapsulated or invasive. Since FVPTC histologically resembles follicular adenomas or carcinomas, immunohistochemical stains such as HBME-1 have proven particularly useful in making the pathologic diagnosis.

It is important to recognize more aggressive variants of well-differentiated tumors. These include tall-cell, columnar-cell, solid, and diffuse-sclerosing variants. The tall-cell variant of PTC, commonly encountered in older patients, is larger and more invasive with extrathyroidal extension and metastatic disease. While tall-cell variant PTC is less iodine-avid than classical PTC, these tumors are typically positive on positron emission tomography (PET). Histologically, these tumors have cells whose height is at least 2 to 3 times as tall as they are wide. Traditionally, criteria require at least 50% of the cells to exhibit these tall features. Necrosis, a high mitotic index, and nuclear pseudoinclusions are also prominent in these tumors. Recently, several different centers have noted that tall-cell variant PTCs often harbor BRAF mutations, and molecular markers can be used to identify this subtype preoperatively. Such molecular diagnostics may become helpful since this subtype is believed to be underdiagnosed.

In addition to tall-cell variant, columnar-cell, solid, and diffuse-sclerosing types also exhibit more aggressive behavior than classical PTC.

As follicular or papillary cancers progress or dedifferentiate, their prognosis becomes much worse. Anaplastic cancers are at the least-differentiated side of the spectrum, and represent one of the most aggressive cancers, with a 5-year disease-free survival rate and cause-specific survival rate approaching 0%. ATC can arise from well-differentiated tumors that dedifferentiate or it can also develop de novo. A group of tumors falls in between well-differentiated...
thyroid cancers and ATCs. These cancers, called poorly differentiated thyroid cancers, have a histologic appearance and behavior that is intermediate between well-differentiated PTC and ATC.\(^3\) Although the literature remains inconsistent regarding what constitutes poorly differentiated cancer, the best definition comes from Burman et al that “poorly differentiated thyroid carcinoma is a concept proposed to include carcinomas of follicular thyroid epithelium that retain sufficient differentiation to produce scattered small follicular structures and some thyroglobulin, but generally lack the usual morphologic characteristics of papillary and follicular carcinoma.”\(^71\) These tumors include insular and large-cell variants.\(^3\,\,^71\) Patients with these types of tumors tend toward locally advanced disease with recurrence and metastases. Furthermore, dedifferentiation of thyroid cancers leads to underexpression or disordered assembly of the sodium-iodide symporter, thereby decreasing the usefulness of radioactive iodine for treating or detecting metastatic disease.\(^72\)

| Primary Tumor (T) | AJCC TNM Staging for Thyroid Cancer\(^a\) |
|-------------------|------------------------------------------|
| TX                | Primary tumor cannot be assessed          |
| T0                | No evidence of primary tumor              |
| T1                | Tumor ≤ 2 cm, limited to the thyroid      |
| T1a               | Tumor ≤ 1 cm, limited to the thyroid      |
| T1b               | Tumor >1 cm but <2 cm, limited to the thyroid |
| T2                | Tumor >2 cm but <4 cm, limited to the thyroid |
| T3                | Tumor >4 cm, limited to the thyroid or minimal extrathyroid extension (sternothyroid or perithyroidal soft tissues) |
| T4a\(^b\)         | Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve |
| T4b               | Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels |

| Regional Lymph Nodes (N) | AJCC TNM Staging for Thyroid Cancer\(^a\) |
|--------------------------|------------------------------------------|
| NX                       | Regional lymph nodes cannot be assessed  |
| N0                       | No regional lymph node metastasis        |
| N1                       | Regional lymph node metastasis           |
| N1a                      | Metastasis to level VI lymph nodes       |
| N1b                      | Metastasis to unilateral, bilateral, or contralateral cervical (levels II, III, IV, or V) or superior mediastinal (level VII) lymph nodes |

| Distant Metastasis (M) | AJCC TNM Staging for Thyroid Cancer\(^a\) |
|-----------------------|------------------------------------------|
| M0                    | No distant metastasis                     |
| M1                    | Distant metastasis                        |

**STAGE GROUPING**

| Differentiated Cancer in Those Aged <45 y | AJCC TNM Staging for Thyroid Cancer\(^a\) |
|------------------------------------------|------------------------------------------|
| Stage I                                  | Any T any N M0                           |
| Stage II                                 | Any T any N M1                           |
| Differentiated Cancer in Those Aged ≥45 y | AJCC TNM Staging for Thyroid Cancer\(^a\) |
| Stage I                                  | T1 N0 M0                                 |
| Stage II                                 | T2 N0 M0                                 |
| Stage III                                | T3 N0 M0                                 |
| Stage IVA                                | T4a N0 M0                                |
| Stage IVB                                | T4b any N M0                             |
| Stage IVC                                | Any T any N M1                           |

| Anaplastic Carcinomas\(^d\) | AJCC TNM Staging for Thyroid Cancer\(^a\) |
|-----------------------------|------------------------------------------|
| Stage IVA                   | T4a any N M0                             |
| Stage IVB                   | T4b any N M0                             |
| Stage IVC                   | Any T any N M1                           |

AJCC indicates American Joint Committee on Cancer.

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**TABLE 2. Continued**

| Medullary Carcinoma | AJCC TNM Staging for Thyroid Cancer\(^a\) |
|---------------------|------------------------------------------|
| Stage I             | T1 N0 M0                                 |
| Stage II            | T2 N0 M0                                 |
| Stage III           | T3 N0 M0                                 |
| Stage IVA           | T4a N1a M0                               |
| Stage IVB           | T4b any N M0                             |
| Stage IVC           | Any T any N M1                           |

| Papillary and follicular carcinomas are considered to be differentiated thyroid cancers. |

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| Anaplastic Carcinomas\(^d\) | AJCC TNM Staging for Thyroid Cancer\(^a\) |
|-----------------------------|------------------------------------------|
| Stage IVA                   | T4a any N M0                             |
| Stage IVB                   | T4b any N M0                             |
| Stage IVC                   | Any T any N M1                           |

AJCC indicates American Joint Committee on Cancer.

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| According to Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Troatti A, eds. American Joint Committee on Cancer Staging Manual. 7th ed. New York, NY: Springer; 2010.58 |

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| All anaplastic tumors are considered to be T4 tumors. |

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| Papillary and follicular carcinomas are considered to be differentiated thyroid cancers. |

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| All anaplastic carcinomas are considered to be stage IV. |
For these reasons, poorly differentiated thyroid cancers have a 51% disease-free survival rate and a 70% cause-specific survival rate at 5 years.3,70

Figure 1 provides an organizational scheme for classifying tumors of follicular cell origin by differentiation status.

**FTC and Variants**

It is worth noting some important ways in which FTC differs from PTC. Pure FTC carries a worse prognosis compared with PTC. Even when the disease is confined to the thyroid, mortality rates range from 5% to 15%, although survival time still extends decades as in PTC.73 In addition to the prognostic factors common to DTC staging systems (discussed below), the prognosis in patients with FTC especially depends on the degree of capsular and vascular invasion. Minimally invasive tumors are macroscopically contained within the thyroid, but have microscopic foci of invasion into the capsule. Invasive tumors carry a worse prognosis and invade the capsule and vasculature.74–76 For these reasons, FNA biopsy cannot distinguish a follicular adenoma from carcinoma.74,77 As with follicular lesions, the adequacy of surgical treatment is determined to be cancer on final pathology.80

Hurthle cell or oncocytic tumors of the thyroid are often classified with follicular cancer as they are derived from the follicular cell. Hurthle cells arise from the follicular epithelium. Histologically, these cells feature large size, distinct cellular borders, plentiful granular cytoplasm, a large nucleus, and a prominent nucleolus. Hurthle cells are found in a variety of conditions including nodular goiter, chronic lymphocytic (Hashimoto) thyroiditis, and long-standing hyperthyroidism.78,79 Both adenomas and carcinomas of the Hurthle cell can occur, and differentiating them by cytology is as difficult as it is with follicular lesions.76,80 As with follicular tumors, capsular and vascular invasion distinguish carcinoma from adenomas. Large Hurthle cell cancers (those measuring > 2 cm) have a higher recurrence rate, ranging from 21% to 59%.80,81 Furthermore, Hurthle cell cancers do not always concentrate iodine. For these reasons, Hurthle cell carcinoma carries a worse prognosis compared with other DTCs. Adenomas carry an excellent prognosis after resection and less than 2.5% demonstrate malignant behavior, but resection is recommended for larger adenomas since size is a major predictor of malignancy.81,82 In one series, 65% of Hurthle cell neoplasms measuring 4 cm or greater were determined to be cancer on final pathology.80

**Thyroid Lymphoma**

Primary lymphoma of the thyroid is not as common as DTC. Older females or patients with Hashimoto thyroiditis are at highest risk for developing thyroid lymphoma.83,84 These tumors typically present as a rapidly expanding mass causing pain and compressive symptoms. Flow cytometry of cytologic specimens can sometimes make the diagnosis, but it might also be difficult to distinguish from advanced Hashimoto thyroiditis. A core needle biopsy may therefore become necessary when this diagnosis is suspected to obtain enough tissue for flow cytometric analysis and/or analysis of antigen receptor gene rearrangements. Most are B-cell lymphomas treated with chemotherapy and radiation. Surgery is occasionally necessary for palliation.84 Prognosis depends on the histologic subtype. Of note, up to 20% of patients diagnosed with generalized lymphoma can also have secondary involvement of the thyroid.85

**Staging Systems**

Because of its unique extended survival period and the spectrum of disease behavior, a number of different staging or prognostic scoring systems have been developed for DTC.48,86,87 Table 1 summarizes these various staging systems.

Classical prognostic indicators for DTC include age and sex. Age is such an important factor in determining a patient’s survival from DTC that it is included in many of the staging systems for thyroid cancer. As with most other solid tumors, the tumor size also has prognostic significance, and most of the prognostic schemes also include this measure (Table 1).

Because of its questionable effect on mortality, lymph node status is not included in all of the staging systems available for DTC. For example, the AGES system (patient age, histologic grade of the tumor, tumor extent [extrathyroidal extension], and size of primary tumor) considers age, grade, extrathyroidal extension, and size.88 The AMES system (patient age, presence of distant metastases, extent and size of primary tumor) uses age, distant (non-lymph node) metastases, extent of primary tumor, and size.89 Some, like the MACIS system (metastasis, patient age, completeness of resection, local invasion, and tumor size) also account for the adequacy of surgical treatment.90 Alternatively, staging systems developed by the Ohio State University,91 the European Organization for Research and Treatment of Cancer,92 the National Thyroid Cancer Treatment Cooperative Study,93 Clinical Class,49 and the American Joint Committee on Cancer98 all do consider lymph node status.

The American Joint Committee on Cancer is the most widely used staging system (Table 2).58 It also is known as the TNM system since it considers tumor size and local extent (T), lymph node metastases (N), and distant metastases (M). Similar to many of the other thyroid cancer staging systems, it also considers age, with 2
FIGURE 1. Classification of Follicular Cell-Derived Tumors by Differentiation Status. Adapted from Patel KN, Shaha AR. Poorly differentiated and anaplastic thyroid cancer. Cancer Control. 2006;13:119–128.3

different classifications for those individuals aged younger and those aged older than 45 years. In those aged younger than 45 years, patients with lymph node metastases are classified as having stage I disease unless they have distant metastases (stage II).58

**Diagnosis**

Like any newly discovered mass elsewhere in the body, the workup of a thyroid nodule begins with a thorough history and physical examination. A strong family history of thyroid cancer or prior radiation exposure to the head and neck should raise the suspicion of thyroid cancer. Rapid growth with compressive symptoms may indicate that the thyroid nodule is thyroid lymphoma or a poorly differentiated thyroid cancer.3,4,24

On physical examination, malignant nodules are harder and fixed while a nodule that is rubbery or soft and moves easily with deglutition suggests a benign nodule. Physical examination features alone do not ensure a benign diagnosis. Cervical lymphadenopathy also increases the likelihood that a thyroid nodule is malignant.4,94

Since the management of patients with hyperthyroidism differs from those with nonfunctional nodules, obtaining a TSH measurement early in the workup of a thyroid nodule can efficiently identify patients with a nodule and hyperthyroidism. In the subset of patients with a suppressed TSH (hyperthyroid), a radioactive iodine-123 (123I) scan can distinguish a solitary toxic nodule from a toxic multinodular goiter and Graves disease. A solitary hyperfunctioning nodule is rarely malignant, and FNA biopsy or further cancer workup is rarely necessary. Hyperfunctioning nodules are usually hypercellular, and may confuse the provider since cytology may suggest neoplasia, when the cellularity only reflects benign hyperplasia associated with excessive stimulation. The one exception is that functioning nodules in children do carry a higher risk of malignancy.95

If thyroid radionuclide scanning is undertaken, “cold” nodules should undergo FNA biopsy because 10% to 20% are malignant.96,97 Nevertheless, thyroid radionuclide scanning is not recommended as part of the initial workup of adult patients with thyroid nodules as it generally does not alter the management.

Other laboratory tests can be helpful once the diagnosis of a certain type of thyroid cancer is made. For example, measuring serum thyroglobulin (Tg) in patients with DTC can assist with the long-term follow-up of patients treated for DTC.98–100 Although Tg can be elevated in patients with DTC, the test is not specific for diagnosing cancer. Elevations in Tg can occur in patients with benign thyroid disorders, and the American Thyroid Association guidelines do not recommend routine preoperative Tg measurement for patients with DTC. After a total thyroidectomy, however, elevations in Tg can reliably indicate recurrent or metastatic disease.99 Different threshold Tg levels can indicate recurrence depending on the concomitant TSH level.

FNA biopsy remains the gold standard for evaluating thyroid nodules. Most clinical practice guidelines recommend FNA biopsy for nodules measuring greater than 1 cm in largest dimension.96,99,101 When the FNA result is clearly benign or malignant, the decision for further treatment including thyroidectomy then becomes evident. The false-negative rate for FNA biopsy is 1% to 3% (Table 3). The false-negative rate increases to 10% to 15% when the
nodule is large (>4 cm).\textsuperscript{101–103} Other clinical scenarios where the clinician should not always trust a benign FNA result include patients with a family history of thyroid cancer, patients with a history of radiation exposure, and those with cystic nodules.\textsuperscript{104} Ultrasound guidance can improve the accuracy of FNA biopsy because ultrasound can confirm that the nodule is actually being sampled and target the most suspicious portions of the nodule (ie, the wall of a cyst). This is especially true for nonpalpable or posteriorly located nodules.\textsuperscript{105}

FNA results are classified according to the Bethesda criteria that indicate the risk of malignancy (Table 3). One of the limitations of cytology in evaluating thyroid nodules is that it cannot distinguish between adenoma and carcinoma for follicular lesions.\textsuperscript{96,102,103} Therefore, lobectomy with permanent histology may be the best way to make a definitive diagnosis in patients with follicular or indeterminate lesions. Many centers have turned to the molecular analysis of FNA specimens to help distinguish follicular lesions. Cytology specimens are analyzed for a panel of mutations including BRAF, RAS, RET/PTC, and PAX8-PPAR\textsubscript{c} rearrangements.\textsuperscript{39–41,70,106} This will be discussed further in subsequent sections.

Not only can ultrasound improve the accuracy of FNA biopsy, but it is also an important tool for evaluating thyroid nodules as it is used to measure the size and features of the nodule such as its borders, echogenicity, and vascularity. It can also identify additional nonpalpable nodules. Ultrasound alone can increase the clinician’s suspicion for malignancy if the nodule has fine microcalcifications, irregular borders, or chaotic vascular patterns. In addition, ultrasound evaluates the lymph nodes in both the central and lateral neck compartments, which may prompt additional FNA biopsy of suspicious lymph nodes or alter the surgical plan (Fig. 2). Small metastatic central compartment lymph nodes may not be seen on ultrasound because they are obscured by the overlying thyroid. Although ultrasound is highly operator-dependent, it is noninvasive and does not involve any radiation or contrast risk to the patient. High-resolution ultrasound can also demonstrate extracapsular invasion and subtle lymph node involvement.\textsuperscript{2,105,107–111} Therefore, ultrasound is the preferred method with which to evaluate the thyroid and cervical lymph nodes.

Very aggressive cancers that may invade local structures, extend into the chest, or demonstrate poorly differentiated cytology require careful preoperative planning. In this situation, computed tomography (CT) becomes a helpful preoperative imaging study for helping to plan en bloc resection of other organs aside from the thyroid, understand the extent of vascular involvement, determine if a thoracic incision is necessary, and plan for reconstruction.\textsuperscript{2,3,112,113} When using CT, it is best to avoid the administration of iodinated contrast as this will reduce the ability of residual thyroid tissue or thyroid cancer to take up subsequent radioactive iodine for many months.

\textbf{FIGURE 2. Lymph Node Compartments of the Neck.} Adapted from Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules. Thyroid. 2009;19:1–48.

\begin{table}
\centering
\begin{tabular}{|l|c|c|}
\hline
\textbf{CATEGORY} & \textbf{RISK OF MALIGNANCY, %} & \textbf{RECOMMENDED MANAGEMENT} \\
\hline
Nondiagnostic or unsatisfactory & 1-4 & Repeat FNA with US guidance \\
Benign & 0-3 & Clinical follow-up \\
Atypia of undetermined significance or follicular lesion of undetermined significance & 5-15 & Repeat FNA\textsuperscript{a} \\
Follicular neoplasm or suspicious for follicular neoplasm & 15-30 & Lobectomy \\
Suspicious for malignancy & 60-75 & Lobectomy ± frozen section or total thyroidectomy \\
Malignant & 97-99 & Total thyroidectomy \\
\hline
\end{tabular}
\caption{The Bethesda System for Thyroid Cytopathology}
\end{table}

\textsuperscript{a}Lobectomy can also be considered depending on clinical or sonographic characteristics.

FNA indicates fine-needle aspiration; US, ultrasound.
Imaging studies often identify thyroid nodules incidentally. PET scans detect thyroid masses during the workup and staging of other cancers. This subset of incidentally discovered thyroid nodules deserves special attention because up to 50% of $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG)-avid thyroid nodules will contain thyroid cancer. Therefore, PET-positive thyroid nodules should be biopsied by FNA. PET and/or CT scans are helpful for identifying lung or bone tumors in patients at risk for metastases, and this is especially true for patients with tumors that are not iodine-avid.$^{2,112}$

Role of Molecular Markers
As discussed above, the identification of molecular markers associated with either PTC or FTC has led to the development of several assays to improve upon FNA biopsy results. Specifically, these assays or gene panels target nodules with indeterminate cytology (follicular neoplasm, atypia, etc) to determine whether they are benign or malignant without the need for diagnostic surgery. For example, Nikiforov et al recently developed a panel of mutations including BRAF, NRAS, HRAS, KRAS, and 2 different RET/PTC rearrangements.$^{114}$ The detection of any one of these mutations was associated with a final histopathologic diagnosis of cancer in 88% of cases with a cytologic diagnosis of atypia and 87% of cases with cytologic diagnoses of follicular neoplasm/suspicious for a follicular neoplasm. The risk of cancer in nodules without any mutation was as high as 28% in patients with a cytologic diagnosis suspicious for malignancy, 14% of patients with follicular cytology, and 6% of patients with atypia.$^{114}$ While these results are quite encouraging, the sensitivity of the molecular panel still leaves room for uncertainty and has not negated the need for diagnostic surgery to make a definitive diagnosis.

Rather than identifying the molecular signature of malignancy, another group has developed a different molecular test designed to identify the gene expression profile of a benign nodule. In a multicenter study, this test had a sensitivity of 92% and a specificity of 52%. The negative predictive value (predicts truly benign lesions) was 95%, 94%, and 85%, respectively, for the cytologic diagnoses of atypia, follicular neoplasm/suspicious for follicular neoplasm, and suspicious.$^{115}$ This testing may be helpful for patients who wish to avoid surgery because of excessive surgical risk, but still leaves at least a 7% chance that a benign result truly is a cancer. At this point, it remains unclear how patients who avoid surgery because of a molecular profile should be followed. Furthermore, the natural history of follicular lesions is unknown. Until these questions are clarified, these molecular tests will play a limited role in clinical decision-making for most patients.

Treatment
The treatment of DTC is multidisciplinary and involves a surgeon, endocrinologist, nuclear medicine specialist, and, occasionally, a radiation oncologist. This approach best serves patients with DTC and will be highlighted in the sections that follow.

Surgery
The extent of surgery for DTC remains controversial. This is especially true for small, encapsulated, well-differentiated tumors, and tumors measuring less than 1 cm in size (microcarcinomas). The approach to microcarcinomas will be discussed further below, but for the majority of DTCs measuring 1 cm or more and diagnosed preoperatively, most clinicians recommend a total thyroidectomy.$^{99}$ The rationale for total thyroidectomy is based on tumor biology and current treatment modalities. DTC, especially PTC, tends to be multicentric, with up to 80% of patients having multiple tumor foci and bilateral disease detected in 60% when a thorough pathologic examination of the contralateral lobe is performed.$^{2,6,45}$ A total thyroidectomy as the initial procedure negates the need for reoperative surgery to remove the contralateral lobe should a recurrence become detected. Second, experienced thyroid surgeons can safely perform a total thyroidectomy, with permanent complications such as recurrent laryngeal nerve injury and hypoparathyroidism occurring at a rate of less than 2%.$^{46,113}$ Radioactive iodine therapy for ablating microscopic disease becomes most effective when the thyroid remnant is small or absent. Tg measurement and radioiodine whole-body scanning are highly sensitive modalities for detecting recurrent or metastatic disease, but these 2 methods are most effective when all thyroid tissue has been removed.$^{2,4}$

Most low-risk cancers carry an excellent prognosis regardless of the extent of thyroidectomy, and there are no randomized prospective trials comparing total thyroidectomy with thyroid lobectomy in this group of patients. In addition, radioiodine may have limited usefulness in low-risk patients.$^{6,45}$ For these reasons, some favor thyroid lobectomy in low-risk patients. For example, Shaha et al have reported a 20-year follow-up of 465 patients with low-risk DTC. Although the lobectomy group had more local recurrence compared with the group undergoing total thyroidectomy (4% vs 1%), this was not statistically significant.$^{116}$ Similarly, other groups have also failed to demonstrate any significant effect on survival.$^{117–119}$ In contrast, large retrospective series have demonstrated improvement in recurrence for total thyroidectomy compared with less extensive resections.$^{91,120–122}$ In a frequently cited study, Mazzaferr et al reported on 1355 patients with a mean follow-up of 15.7 years.$^{91}$ Patients treated with total thyroidectomy experienced significant improvements in the recurrence rate (26% vs 40%; $P < .02$) and mortality rate (6% vs 9%; $P = .02$) compared with those undergoing lesser resections.$^{91}$ While some have questioned the accuracy of risk stratification and accounting for complications in these
retrospective studies, current guidelines still recommend a total or near-total thyroidectomy for small (those measuring <4 cm), unifocal, well-differentiated tumors with no lymph node metastases or extrathyroidal extension.99

Another hotly debated topic related to the extent of initial surgery for DTC is the role of prophylactic central neck dissection. Although the 2006 American Thyroid Association guidelines stated that routine prophylactic central neck dissection should be considered for patients with DTC,123 the most recent guidelines have been revised to recommend that “prophylactic central neck dissection may be performed, especially in patients with advanced primary tumors” and “total thyroidectomy without prophylactic central neck dissection may be appropriate for small (T1 or T2), non-invasive, clinically node negative patients.”99

The central neck lymph nodes are also classified as level VI lymph nodes and include the paratracheal, perithyroidal, and pretracheal lymph nodes. These lymph nodes are found along and behind the recurrent laryngeal nerve and frequently surround the lower parathyroid gland (Fig. 2). Although the level VI lymph nodes contain macroscopic disease in 10% of cases, when they are removed prophylactically, 32% to 69% of patients will have microscopic metastases.52,124,125

Proponents of prophylactic central neck dissection argue that the initial operation is the safest time to remove central neck lymph nodes to prevent local recurrences and the complications associated with reoperative surgery in the central neck. Furthermore, the central neck lymph nodes are difficult to evaluate with preoperative ultrasound when the thyroid remains in place. Wada et al found the recurrence rate in patients treated with therapeutic lymph node dissection to be 21%, while patients who underwent prophylactic neck dissection experienced a recurrence rate of only 0.43%. Importantly, those patients without clinically overt lymph node disease who did not undergo prophylactic central neck dissection also experienced a very low recurrence rate of 0.65%. Hence, the absolute differences in recurrence are miniscule.53 Several other studies also support the concept that microscopically positive lymph nodes rarely progress to recurrence, especially after postoperative radioactive iodine ablation.126–128 Therefore, the debate regarding prophylactic central neck dissection is closely tied to the usefulness of radioactive iodine.

Clinically evident lymph node metastases place patients at higher risk of recurrence, and these patients benefit from therapeutic lymph node dissection. Prophylactic central neck dissection modestly reduces an already low recurrence rate and potentially eliminates or reduces the need for radioactive iodine, but is also associated with its own risks such as hypoparathyroidism. The risk-benefit ratio may favor prophylactic central neck dissection in a subset of patients, but the putative risk factors that define such a subset remains unknown.2,61,129,130

Some groups are currently using molecular markers to preoperatively risk-stratify patients, and decide who might benefit from more aggressive surgery up front.131,132

Thyroidectomy still involves the same basic steps historically described, but newer technology and attention to cosmesis account for some more recent modifications of the basic technique. Traditionally, a Kocher collar incision was used, but this requires a very large dissection superiorly to reach the upper pole of the thyroid, thereby placing the patient at risk for postoperative seroma. Intraoperative ultrasound can help assess the upper extent of the gland and place the incision appropriately. Often, the incision can be placed higher in the neck but hidden in a neck crease to allow a smaller but still cosmetically pleasing incision. Superior and inferior platysmal flaps are raised to create a working space around the thyroid. Instead of traditional clamps and ties, most of the vasculature feeding the thyroid can now be managed using energy devices such as the Harmonic scalpel or LigaSure device,133,134 but larger vessels still may require clips and/or ties. Before dividing any structures along the medial border of the gland, the recurrent laryngeal nerve must be identified and its course dissected. The nerve is found medial to the upper parathyroid gland and lateral to the lower parathyroid. The parathyroid glands must also be identified and dissected free from the thyroid on an intact vascular pedicle. Once the recurrent laryngeal nerve is identified, the branches of the inferior thyroid artery can be divided along the thyroid capsule.

In recent years, nerve monitoring devices have enabled surgeons to test the functionality of the recurrent laryngeal nerve intraoperatively. Reported rates of permanent recurrent laryngeal nerve injury when the surgeon visually identifies the nerve is less than 2%.135,136 Even the largest trials have failed to show any significant prevention of nerve injury.137,138 A multiinstitutional, prospective, nonrandomized study of 16,448 patients (29,998 nerves at risk) found no statistical difference in nerve injury rates when comparing patients treated with visual identification of the nerve alone with those treated with a combination of visual identification and nerve monitoring.139 In one of the few prospective studies, Thomusch et al reported on 8534 patients (15,403 nerves at risk). They compared direct stimulation of the recurrent laryngeal nerve with indirect stimulation of the vagus nerve (the recurrent nerve is a distal branch of the vagus), and found that direct stimulation had a much lower sensitivity for predicting nerve palsy compared with indirect stimulation (45.9% vs 99.6%).140 Although nerve monitoring does not prevent nerve injury, many surgeons still use this technology to identify nerve palsies when they do occur. This last study suggests that when nerve monitoring is used in this fashion, it should not simply be used to stimulate the recurrent laryngeal nerve directly. The use of nerve monitoring remains quite controversial. Many experts believe that nerve
stimulation is generally not necessary for the primary surgery on the thyroid, and may be more useful for reoperations.

Before passing the specimen off the field, the surgeon should examine it to make sure that there is no parathyroid tissue adherent to the gland. Any inadvertently removed parathyroid tissue can be finely minced and reimplanted into either the sternocleidomastoid or the strap muscles. Frozen section of a biopsy of this tissue can distinguish between fat, parathyroid, or lymph node; this will also avoid autotransplanting cancer-bearing lymph nodes back into the patient. Two to 3 pockets are created within the muscle, and the minced parathyroid tissue is divided between these pockets. Each pocket should be marked with a permanent suture so that it can easily be found in a reoperative setting.

Preoperative FNA or intraoperative frozen section can confirm that enlarged lymph nodes seen on ultrasound harbor metastatic disease. Cytologic or pathologic confirmation of lymph node metastases should prompt the surgeon to perform a compartment-oriented lymph node dissection. Lymph node sampling or “berry picking” should be avoided as this leaves behind lymph nodes that likely contain microscopic disease that then become more difficult to excise in a reoperative setting. Although “skip” metastases directly to the lateral compartment can occur in patients with PTC, the central neck lymph nodes (level VI) are usually the first to receive drainage from the thyroid (Fig. 2). The boundaries of the central neck are the carotid sheathes laterally, the hyoid bone superiorly, and the innominate artery inferiorly. Lymphadenectomy in this area requires skeletonizing the recurrent laryngeal nerve along its entire cervical course, and removing all the fibrofatty tissue along the trachea. Frequently, the lower parathyroid is invested in this tissue and becomes devascularized with this dissection.

A lateral neck dissection usually involves dissection of levels II, III, and IV (Fig. 2). This dissection puts the spinal accessory, phrenic, vagus, cervical sensory, sympathetic trunk, hypoglossal, greater auricular, and the marginal mandibular branch of the facial nerves at risk. The extent of lymph node dissection should be guided by preoperative and intraoperative ultrasound findings. Usually, the great vessels can be preserved, but more aggressive tumors can invade the internal jugular vein, and it should be sacrificed in this scenario. In addition to nerve injury, chyle leak is another complication of performing a lateral neck dissection.

In recent years, transaxillary approaches to thyroidectomy have been developed. There are several variations of these techniques including transaxillary endoscopic, robotic, and axillo-breast techniques. All of these techniques avoid a neck incision, and instead hide the incision in the crease between the axilla and the breast. Long-term data on the adequacy of resection using these approaches are lacking, and these techniques come with added complication risks such as brachial plexus injury.

Radioactive Iodine

Remnant ablation with radioactive iodine is the standard adjuvant treatment in selected patients with DTC. It can only be administered after a total or near-total thyroidectomy, or otherwise the radioactive isotope will be absorbed by the remnant thyroid and will not destroy any micrometastatic disease as intended. Radioactive iodine is administered 1 to 3 months postoperatively as iodine-131 ($^{131}$I) in an oral form whose half-life is 7 to 8 days. Consensus guidelines recommend a dose of 30 to 100 mCi for patients with low-risk tumors and higher doses (100-200 mCi) for patients with residual disease, suspected microscopic disease, or more aggressive histologic subtypes (ie, tall-cell, columnar-cell, or insular variants). To stimulate intracellular uptake of the isotope, the TSH concentration should be at least as high as 30 mU/L.

There are 2 methods for achieving such an elevation in TSH. The traditional method requires the patient to withdraw from thyroid hormone replacement over 4 to 6 weeks. A newer method is to administer recombinant human TSH (rhTSH). rhTSH is administered in the form of intramuscular injections on 2 consecutive days followed by radioactive iodine on the third day. The advantage of this method is that the patient does not experience an extended period of hypothyroidism as with hormone withdrawal. However, long-term data on the effectiveness of rhTSH compared with traditional withdrawal are not established, although it appears effective for patients considered to be at low risk. The US Food and Drug Administration approved rhTSH for thyroid remnant ablation in patients who do not have evidence of metastatic disease. In addition to making the TSH rise, clinicians should also prepare patients by instructing them to follow a low-iodine diet for 1 to 2 weeks prior to radioactive iodine treatment. This diet requires patients to avoid foods that contain iodized salt, dairy products, eggs, seafood, soybeans or soy-containing products, and foods colored with red dye #3. Its important to note that rhTSH is not approved for use in children.

While some studies show no benefit to radioactive iodine therapy, other studies have demonstrated a reduction in locoregional recurrences and distant metastases. As with the controversy over the extent of thyroidectomy, the benefit of radioactive iodine for low-risk patients remains unclear. The most recent American Thyroid Association guidelines recommend remnant ablation for patients with T3 tumors or lymph node disease. Selective use is recommended for intrathyroidal tumors measuring 1 cm to 2 cm in size or T2 tumors. It is not recommended for intrathyroidal tumors less than or equal to 1 cm in size.
The National Comprehensive Cancer Network guidelines require a more thorough evaluation for the extent of remaining disease after thyroidectomy with a radioiodine scan 1 to 12 weeks postoperatively. Radioactive iodine ablation is not recommended if the stimulated Tg is less than 1 ng/mL and the radioiodine scan is negative.148

Recently, some studies have shown an increase in the risk of developing secondary malignancies after radioactive iodine therapy. This has been examined using the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) database. Brown et al found that patients treated for DTC had significantly higher rates of nonthyroid second primary malignancies than expected in the general population. Although the excess risk was relatively small, it was greater in the subset of patients who were treated with radioactive iodine.156 Iyer et al specifically examined low-risk patients (T1N0 disease) treated with radioactive iodine and found that their excess absolute risk was 4.6 excess cases per 10,000 person-years at risk.157 As discussed above, radioactive iodine clearly benefits patients with larger tumors and metastatic disease, but the increased risk of secondary malignancies in low-risk patients, in whom the long-term benefit of radioactive iodine is questionable, means that careful patient selection is necessary.

Hematologic malignancies are the most common secondary malignancies after radioactive iodine, but there is also an association with kidney, breast, bladder, skin, and salivary gland cancers.158–160 The more commonly noted side effects after radioiodine treatment include dry mouth, mouth pain, salivary gland swelling (sialadenitis), altered smell and taste, conjunctivitis, and fatigue. Women should not be pregnant at the time of treatment nor should they become pregnant for at least 6 months following treatment. Similarly, men should avoid conception for at least 6 months following treatment.150,159,161,162

**Thyroxine Suppression**

Since all cells of follicular origin depend on TSH for growth, TSH suppression through the administration of supraphysiologic doses of levothyroxine (T4) remains an important strategy for maintaining disease-free survival and overall survival.163,164 For high-risk patients with incomplete resection, tumor invasion into adjacent structures, or distant metastases, their physician should initially titrate levothyroxine dosing to a TSH of less than 0.1 mU/L. Patients at lower risk should be dosed to a TSH at or slightly below the lower limit of normal (0.1 mU/L–0.5 mU/L).99,148 Once patients remain disease free for at least 2 years, their TSH suppression can be liberalized to within the reference range. Patients with persistent disease should be kept at a TSH of less than 0.1 mU/L indefinitely. TSH suppression carries risks of arrhythmias, anxiety, and osteoporosis. The risks and benefits should be carefully considered, particularly in older patients. Due to the risk of bone loss, the National Comprehensive Cancer Network guidelines recommend daily calcium and vitamin D supplementation for patients receiving treatment with TSH suppression.148

**External-Beam Radiation**

Although 131I is the preferred adjuvant therapy for thyroid carcinoma, external-beam radiation sometimes plays a role in treating this disease. Persistent, recurrent, anaplastic, or poorly differentiated tumors may fail to take up 131I. Treatment of ATCs almost always includes external-beam radiation since these tumors often cannot be completely resected and do not concentrate iodine. Although no improvement in overall survival has ever been documented, external-beam radiation is often administered after resection of poorly differentiated tumors to reduce the risk of local recurrence.165 The group at Memorial Sloan-Kettering Cancer Center has found that up to 85% of poorly differentiated tumors display some iodine avidity, and therefore treatment with radioactive iodine may remain worthwhile.3 Patients with incompletely resected tumors, unresectable disease, and locoregional recurrence in a previously operated field may benefit from external-beam radiation.3,165,166 External-beam radiation is typically reserved as a last resort, after surgery and radioactive iodine have been exhausted.

**Chemotherapy**

Since radioactive iodine often can be effective for the treatment of well-differentiated tumors that have metastasized, cytotoxic chemotherapy has not been extensively evaluated for metastatic thyroid cancers. For patients with a large burden of disease, anaplastic cancers, or poorly differentiated tumors that are not iodine-avid, chemotherapy becomes an important treatment component after surgery or if the tumor is not resectable. In these rare situations, chemotherapy confers minimal effects as these tumors hold a very poor prognosis. Historically, doxorubicin was the most effective single agent. Combination therapy with doxorubicin and cisplatin resulted in modest objective response rates.167,168 Newer, targeted therapies have shown some promise. Small molecule tyrosine kinase inhibitors (such as sorafenib or sunitinib) and antibodies (anti-vascular endothelial growth factor [VEGF]) should be considered in the context of ongoing clinical trials.148,169–171

Mitogen-activated protein kinase (MAPK) inhibitors target specific oncogenic pathways in DTC progression. These small molecules are generally well tolerated with low toxicity profiles. As discussed above, the BRAF gene is commonly mutated in thyroid cancer, and therefore many of the targeted MAPK drugs block the Raf kinases in patients with RET or BRAF mutations.172,173 Sorafenib is an orally administered multikinase inhibitor targeting BRAF, VEGF, RET, and c-Kit. Two different phase 2 clinical trials...
enrolled patients with radioiodine-resistant metastatic DTC and reported that sorafenib stabilized disease progression and lowered serum Tg with minimal toxicity.\textsuperscript{174,175}

Emerging therapies specifically target angiogenesis because DTC tumors express high levels of VEGF receptors.\textsuperscript{176,177} Multikinase inhibitors such as motesanib, vandetanib, sunitinib, and axitinib have shown early promise in patients with DTC.\textsuperscript{170,178,179} These drugs often target multiple VEGF receptors in addition to other signaling pathways such as c-Kit, RET, and platelet-derived growth factor.

Another mechanism targeted in anticancer therapy is the acetylation of N-terminal lysine residues on histones. Histone acetylation results in a more open chromatin configuration and gene transcription. Many different types of cancer cells have been found to have dysregulated histone acetyltransferase or histone deacetylase enzymes.\textsuperscript{180–182} Several histone deacetylase inhibitors, including vorinostat, depsipeptide, and valproic acid, have been shown to have an effect on thyroid cancer cells.\textsuperscript{183–185} For example, in thyroid carcinoma cell lines, valproic acid increased expression of the sodium-iodide symporter and radioiodine uptake.\textsuperscript{186–188} Although many of these results come from in vitro studies or early-phase clinical trials, they do represent promising novel therapies with much lower toxicity than traditional chemotherapeutic agents.

### Medullary Thyroid Cancer

MTC accounts for 6% to 8% of all thyroid cancers. Unlike DTC, MTC arises from the parafollicular C cells instead of the follicular epithelial cells. Hence, MTC is a neuroendocrine tumor and shares some properties common among neuroendocrine cancers, including secretion of peptide hormones such as calcitonin, serotonin, or vasoactive intestinal peptide. Approximately 25% of cases are due to germline genetic mutations, but most cases of MTC are sporadic. Hereditary cases occur either in isolation (familial MTC [FMTC]) or as part of the multiple endocrine neoplasia syndrome type 2 (MEN 2A or MEN 2B).\textsuperscript{189–191}

### Diagnosis

Although any thyroid nodule could potentially harbor MTC, historical features that may alert the physician to the potential for MTC include a family history of MTC, pheochromocytoma, hyperparathyroidism, or other manifestations of MEN 2 syndromes.\textsuperscript{5} Similar to the evaluation of all thyroid nodules, neck ultrasound and FNA play a major role in diagnosing MTC. Hereditary cases are often detected through genetic screening to identify germline mutations in the \textit{RET} gene. Almost all patients with sporadic disease present with a palpable neck mass and this could be either in the thyroid or a metastatic lymph node. Lymph node metastases occur in 35% to 50% of patients at the time of initial diagnosis.\textsuperscript{192} Therefore, ultrasound evaluation of the central and lateral neck compartments for suspicious lymph nodes becomes a crucial component of the initial diagnosis.\textsuperscript{193}

Since the parafollicular C cells are concentrated in the upper posterior portion of each thyroid lobe, many MTCs arise in a posterior location, causing symptoms such as hoarseness or dysphagia due to compression of local structures. If there is any concern for vocal cord function, then direct laryngoscopy should be performed preoperatively.\textsuperscript{192} MTCs secrete cytokines and other peptides that can cause symptoms such as flushing, diarrhea, and weight loss.\textsuperscript{194}

FNA characteristics of MTC include the presence of stromal amyloid without thyroid follicles. Spindle-shaped cells may be seen, and therefore MTC can be mistaken for parathyroid carcinoma or ATC unless the specimen is stained for calcitonin, chromogranin A, or carcinoembryonic antigen (CEA), substances produced by MTC that confirm the diagnosis. A more sensitive technique than immunohistochemistry on cytology specimens is to measure the calcitonin level in the washout fluid from an FNA.\textsuperscript{195} In addition, the presence of calcitonin messenger RNA has been performed when the cytologic or histologic diagnosis remains unclear.\textsuperscript{196} Histologically, MTCs form nests of cells with deposition of stromal amyloid that stains positively with Congo red stain.\textsuperscript{192} Staining for chromogranin A can also help to confirm the diagnosis.

Several serum markers can aid in the diagnosis of MTC, and are useful in following patients for recurrence and metastases. Calcitonin is commonly elevated in patients with MTC. Although a small percentage of healthy patients will have some elevation in calcitonin, patients with a diagnosis of MTC usually exhibit levels greater than 100 pg/mL. In borderline cases, the diagnosis can be clarified by stimulating the calcitonin with either intravenous calcium gluconate or pentagastrin. Before the advent of genetic testing, these stimulated measurements were used to screen patients at high risk for MTC.\textsuperscript{197} The degree of calcitonin elevation correlates with tumor burden, with lymph node metastases found at basal calcitonin levels of 10 pg/mL to 40 pg/mL, and distant metastases found with calcitonin levels greater than 150 pg/mL. Patients with calcitonin levels over 3000 pg/mL are likely to have widely metastatic disease, and are unlikely to be cured despite aggressive surgery.\textsuperscript{198}

Preoperative measurement of serum (CEA can also help risk-stratify patients. Overall, CEA elevations occur in more than 50% of patients with MTC, but a preoperative serum CEA level of greater than 30 ng/mL highly predicts the inability to cure the patient with surgery.\textsuperscript{199} CEA levels above 100 ng/mL may signify extensive lymph node and distant metastases. Following CEA levels postoperatively
can also monitor disease progression. An increasing CEA level in the presence of a stable calcitonin level is associated with a worse prognosis as it may indicate tumor dedifferentiation and distant metastases. Other markers such as chromogranin A or serotonin can be elevated in patients with MTC as with many other neuroendocrine tumors, but calcitonin, chromogranin A, and CEA are the most useful for following MTC patients in the long term.192,200,201

Genetic testing plays an important role in the initial management because it identifies familial disease and risk-stratifies patients with hereditary forms. Familial disease is characterized by germline mutations in the RET gene.202 A small percentage of patients with apparently “sporadic” disease will also carry germline RET mutations, but truly sporadic cases frequently harbor somatic RET mutations. Commercial testing is performed through polymerase chain reaction amplification of the patient’s germline DNA obtained from the white blood cells.

A spectrum of tumor aggressiveness exists among the various RET mutations, and the timing of prophylactic thyroidectomy is based on the specific mutation. Table 4 lists each mutation by codon and phenotype.203 Once a patient tests positive for a germline RET mutation, they should be carefully counseled regarding the risk to other family members and their children. At-risk family members should be identified and also tested so that prophylactic thyroidectomy can be offered at the appropriate time (Table 5).203 While some overlap exists for genetic mutations associated with MEN 2A and familial MTC, distinct mutations are usually associated with MEN 2B.204,205

### Treatment

Complete surgical excision is the treatment of choice for patients with MTC. The minimum extent of surgery for patients with clinically apparent disease is a total thyroidectomy with bilateral central neck dissection. Approximately 81% of patients with palpable disease have central neck lymph node metastases, and the addition of central neck dissection improves cure rates over thyroidectomy alone in patients with clinically evident disease at the time of presentation.206,207 The initial approach to lateral neck lymph nodes continues to evolve. Historically, the initial surgical treatment included an ipsilateral lateral compartment neck dissection because up to 80% of patients will have ipsilateral lymph node metastases.208 However, current guidelines recommend performing an ipsilateral lateral neck dissection if ultrasound or physical examination detects lymphadenopathy in the lateral neck, if central compartment lymph nodes are involved, or when the primary tumor measures greater than 1 cm.193 Contralateral lateral neck dissection is added when patients have bilateral tumors or there is extensive lymph node disease on the ipsilateral side. Because some patients often require extensive neck dissection, these procedures are often staged.192,193 Unlike DTC, where micrometastatic disease can be effectively treated with radioactive iodine ablation, the only effective treatment in patients with MTC is complete surgical resection. Therefore, all evident disease must be resected for the best long-term cure.

Prophylactic thyroidectomy is recommended for at-risk family members in hereditary MTC. Current recommendations for the timing of prophylactic thyroidectomy balance the need to remove the at-risk organ prior to it developing clinically apparent disease with the risks of surgery. In patients with hereditary MTC, an age-related progression exists from C-cell hyperplasia to carcinoma, and ultimately lymph node metastases. The optimal timing of prophylactic thyroidectomy depends on the risk level of the RET mutation (Table 5).203 In general, current guidelines recommend operating on children with MEN 2A and FMTC by age 5 years, while those with MEN 2B should undergo surgery before 6 months of age.209,210 Prophylactic surgery should consist of at least a total thyroidectomy. The role of prophylactic lymph node dissection in familial disease remains controversial. Lymph node metastases are present in 6% of screened patients,211 and therefore some argue that prophylactic central lymph node dissection should be performed. Opponents of this approach state that with a normal preoperative ultrasound, a normal calcitonin (basal and/or stimulated) level, and a normal CEA level, the risk of occult lymph node disease is very low and does not outweigh the risks of a central neck dissection such as permanent hypoparathyroidism.5,206,211 Because any complications resulting from a prophylactic surgery become lifelong problems for the patient, experienced surgeons should perform prophylactic surgery for patients with MTC.

In general, prophylactic thyroidectomy does not need to include a central neck dissection for patients with MEN 2A and FMTC as long as surgery is performed prophylactically, before disease is clinically apparent. Because of the more aggressive nature of MTCs associated with MEN 2B, the performance of a central neck dissection with prophylactic thyroidectomy is optional, depending on the timing and the specific codon mutated.192,193

Prior to proceeding with surgery, the surgeon should screen patients with hereditary disease for associated conditions such as pheochromocytoma (MEN 2A and MEN 2B) and hyperparathyroidism (MEN 2A).205,210,211

All patients will require thyroid hormone replacement once the thyroid is removed, but TSH suppression is not required because the parafollicular C cells are not under TSH growth control. After surgery, the next phase of treatment is surveillance. This begins 2 to 3 months postoperatively with new baseline calcitonin and CEA levels. If the calcitonin level is undetectable, these patients can then be
### TABLE 4. Frequency of RET Mutations Associated With Familial RET Syndromes

| EXON | CODON   | AMINO ACID (WILD-TYPE–MUTANT) | PHENOTYPE       | FREQUENCY OF MEN 2 CASES, % |
|------|---------|-------------------------------|-----------------|-----------------------------|
| 8    | 532, 533, 534 | Ins-Glu-Glu-Cys               | FMTC            | Rare                        |
|      | 533     | Gly-Cys                       | FMTC            |                             |
| 10   | 609     | Cys-Arg                       | MEN 2A/FMTC     | 0-1                         |
|      |         | Cys-Gly                       |                 |                             |
|      |         | Cys-Tyr                       |                 |                             |
|      | 611     | Cys-Ser                       | MEN 2A/FMTC     | 2-3                         |
|      |         | Cys-Arg                       |                 |                             |
|      |         | Cys-Tyr                       |                 |                             |
|      |         | Cys-Phe                       |                 |                             |
|      |         | Cys-Trp                       |                 |                             |
|      | 618     | Cys-Ser                       | MEN 2A/FMTC     | 3-5                         |
|      |         | Cys-Arg                       |                 |                             |
|      |         | Cys-Gly                       |                 |                             |
|      |         | Cys-Tyr                       |                 |                             |
|      | 620     | Cys-Ser                       | MEN 2A/FMTC     | 6-8                         |
|      |         | Cys-Arg                       |                 |                             |
|      |         | Cys-Gly                       |                 |                             |
|      |         | Cys-Tyr                       |                 |                             |
|      |         | Cys-Ser                       |                 |                             |
| 11   | 630     | Cys-Tyr                       | MEN 2A/FMTC     | 0-1                         |
|      |         | Cys-Ser                       |                 |                             |
|      |         | Cys-Phe                       |                 |                             |
|      | 634     | Cys-Ser                       | MEN 2A           | 80-90                       |
|      |         | Cys-Arg                       | MEN 2A/FMTC     |                             |
|      |         | Cys-Gly                       | MEN 2A/FMTC     | 80-90                       |
|      |         | Cys-Tyr                       | MEN 2A/FMTC     |                             |
|      |         | Cys-Ser                       | MEN 2A/FMTC     |                             |
|      |         | Cys-Phe                       | MEN 2A/FMTC     |                             |
|      |         | Cys-Trp                       | MEN 2A/FMTC     |                             |
|      | 635, 636, 637, 638 | Ins-Thr-Ser-Cys-Ala         | MEN 2A/FMTC     | Rare                       |
|      | 637-638-639 | Ins-Cys-Arg-Thr              | MEN 2A          |                             |
| 13   | 648     | Val-Ile                       | MEN 2A           |                             |
| 14   | 768     | Glu-Asp                       | MEN 2A/FMTC     | Rare                       |
|      | 790     | Leu-Phe                       | MEN 2A/FMTC     |                             |
|      | 791     | Tyr-Phe                       | MEN 2A/FMTC     |                             |
| 15   | 804     | Val-Met                       | MEN 2A/FMTC     | 0-1                        |
|      |         | Val-Leu                       | MEN 2A           |                             |
| 16   | 883     | Ala-Phe                       | MEN 2B           | Rare                       |
|      | 891     | Ser-Ala                       | MEN 2A/FMTC     |                             |
|      | 918     | Met-Thr                       | MEN 2B           | 3-5                        |
|      | 922     | Ser-Tyr                       | MEN 2B           | Rare                       |

MEN 2 indicates multiple endocrine neoplasia type 2; FMTC, familial medullary thyroid carcinoma.

Adapted from Pinchot SN, Sippel RS. Management of medullary thyroid cancer. In: Sippel RS, Chen H, eds. The Handbook of Endocrine Surgery. Hackensack, NJ: World Scientific Publishing Company; 2011:63-78.203
followed with yearly calcitonin measurements. Imaging is undertaken when the calcitonin level rises.

A spectrum of disease severity exists for patients with both hereditary and sporadic MTC, and therefore the natural history of MTC varies widely. Distant metastases in the lung, liver, or bone can arise and quickly lead to death. Conversely, many patients live with a large tumor burden and very high calcitonin levels with few symptoms. Others develop intractable diarrhea. In this case, cytoreductive surgery or somatostatin analogs such as octreotide can palliate severe symptoms. Conventional chemotherapy regimens with doxorubicin, dacarbazine, capecitabine, and fluorouracil have demonstrated only limited efficacy in patients with MTC. Newer, targeted therapies block the RET receptor tyrosine kinase or its multiple downstream pathways such as the ERK, phosphoinositide 3-kinase (PI3K)/Akt, p38 mitogen-activated protein kinase (MAPK), and c-Jun N-terminal kinase pathways. Some of these tyrosine kinase inhibitors inhibit multiple signaling pathways simultaneously. These targeted therapies are currently being evaluated in multicenter trials.

Recently, the US Food and Drug Administration approved one of these targeted therapies, vandetanib, for the treatment of metastatic MTC. Vandetanib is a small molecule inhibitor of the VEGF receptor, epidermal growth factor receptor, and the RET tyrosine kinase. In a randomized controlled clinical trial, patients treated with vandetanib experienced a median progression-free survival of 22.6 months compared with 16.4 months in patients treated with placebo.

| RISK LEVEL FOR MTC | ATA RISK LEVEL | CODON MUTATION | AGE AT PROPHYLACTIC SURGERY |
|--------------------|---------------|----------------|-----------------------------|
| Level 3 (highest)  | D             | 883            | Within the first 6 mo of life (preferably within the first y) |
|                    | D             | 918            |                             |
|                    | D             | 922            |                             |
| Level 2 (higher)   | B             | 611            | By age 5 y                  |
|                    | B             | 618            |                             |
|                    | B             | 620            |                             |
|                    | B/C           | 634            |                             |
| Level 1 (high)     | B             | 609            | By age 5 y to 10 y          |
|                    | B             | 630            |                             |
|                    | A             | 768            |                             |
|                    | A             | 790            |                             |
|                    | A             | 791            |                             |
|                    | A             | 804            |                             |
|                    | A             | 891            |                             |

MTC indicates medullary thyroid cancer; ATA, American Thyroid Association.

The ATA medullary thyroid cancer guidelines risk stratify the RET codon mutations by risk of malignancy with category A being the least high risk and category D representing the highest risk.

Adapted from Pinchot SN, Sippel RS. Management of medullary thyroid cancer. In: Sippel RS, Chen H, eds. The Handbook of Endocrine Surgery. Hackensack, NJ: World Scientific Publishing Company; 2011:63-78.
940 cancer patients. J Am Geriatr Soc. 1979;27:307-313.

12. Bisi H, Fernandes VS, de Camargo RO, Koch L, Abdo AH, de Brito T. The prevalence of unsuspected thyroid pathology in 300 sequential autopsies, with special reference to the incidental carcinoma. Cancer. 1989;64:1888-1893.

13. Cramer JD, Fu P, Harth KC, Margevicius S, Wilhelm SM. Analysis of the rising incidence of thyroid cancer using the Surveillance, Epidemiology and End Results (SEER) thyroid cancer data registry. Surgery. 2010;148:1147-1152; discussion 1152-1153.

14. Baker SR, Bhatti WA. The thyroid cancer epidemic: is it the dark side of the CT revolution? Eur J Radiol. 2006;60:67-69.

15. Engeland A, Tretli S, Akslen LA, Bjorge T. Body size and thyroid cancer in two million Norwegian men and women. Br J Cancer. 2006;95:366-370.

16. Hannibal CG, Jensen A, Sharif H, Kjaer lion Norwegian men and women. Eur J Radiol. 2010;148:1147-1152; discussion 1152-1153.

17. Brindel P, Doyon F, Rachedi F, et al. Men-

18. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA. 2006;295:2164-2167.

19. Tuttle RM, Becker DV. The Chernobyl accident and its consequences: update at the millennium. Semin Nucl Med. 2000;30:133-140.

20. J Team. 2009;27:307-313.

21. Cetra F. Montalto G, Petracchi M, Fusco A. Thyroid cancer and the Chernobyl accident. Are long-term and long distance side effects of fall-out radiation greater than estimated? J Clin Endocrinol Metab. 1997;82:2105-2017.

22. Cardis E, Kesminiene A, Ivanov V, et al. Risk of thyroid cancer after exposure to fertility drugs: results from a large Danish cohort study. Hum Reprod. 2008;23:451-456.

23. Bevan S, Pal T, Greenberg CR, et al. Familial non-toxic multinodular thyroid goiter locus maps to chromosome 1q44 but does not account for familial nonmendul-

24. Bignell GR, Canzian F, Shayeghi M, et al. Familial non-toxic multinodular thyroid cancer: clinical and research applications. J Clin Endocrinol Metab. 2006;86:3701-3704.

25. McKay JD, Lesueur F, Jonard L, et al. Localization of a susceptibility gene for familial non-endocrine thyroid cancer to chromosome 2q21. Int J Cancer. 2001;89:440-446.

26. Mazeh H, Benavidez J, Poehls JL, Young-wirth L, Chen H, Sippel RS. In patients with thyroid cancer of follicular cell origin, a family history of nonendocrine thyroid cancer in one first-degree relative is associated with more aggressive disease. Thyroid. 2001;11:697-700.

27. Alberti L, Carniti M, Miranda C, Roccat E, Piroli MA. RET and NTRK1 proto-oncogenes in human diseases. J Cell Physiol. 2003;195:168-186.

28. Fusco A, Chiappetta G, Hui P, et al. Assessment of RET/PTC oncogene activation and clonality in thyroid nodules with incomplete morphological evidence of papillary carcinoma: a search for the early precursors of papillary cancer. J Pathol. 2002;196:251-260.

29. Horn-Ross PL, Morris JS, Lee M, et al. Iodine and thyroid cancer risk among women in a multiethnic population: the Bay Area Thyroid Cancer Study. Cancer Epidemiol Biomarkers Prev. 2001;10:979-985.

30. Knobel M, Medeiros-Neto G. Relevance of iodine intake as a reputed predisposing factor for thyroid cancer. Adv Bras Endocrino Metab. 2007;51:701-712.

31. Haymart MR, Reppinger DJ, Leverston GE, et al. Higher serum thyroid stimulating hormone level in thyroid nodule patients is associated with greater risks of differentiated thyroid cancer and advanced tumor stage. J Clin Endocrinol Metab. 2008;93:809-814.

32. Lee S, Hong SW, Shin SJ, et al. Papillary thyroid carcinoma associated with familial adenomatous polyposis: molecular analysis of pathogenesis in a family and review of the literature. Endocr J. 2004;51:317-323.

33. Cardis E, Akslen LA, Bjorge T. Body size and thyroid cancer in two million Norwegian men and women. Br J Cancer. 2006;95:366-370.
metastasis on survival in patients with well-differentiated thyroid cancer. Am Surg. 2005;71:731-734.

57. Schneider DF, Chen H, Sippel RS. Impact of lymph node ratio on survival in papillary thyroid cancer [published online ahead of print December 23, 2012]. Ann Surg Oncol.

58. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. American Joint Committee on Cancer Staging Manual. 7th ed. New York, NY: Springer; 2010.

59. Schneider DF, Mazeh H, Chen H, Sippel RS. Lymph node ratio predicts recurrence in papillary thyroid cancer. Oncologist. 2013;18:157-162.

60. Beal SH, Chen SL, Schneider PD, Martinez SR. An evaluation of lymph node yield and lymph node ratio in well-differentiated thyroid carcinoma. Am Surg. 2010; 76:28-32.

61. Lang BH, Wong KP, Wan KY, Lo CY. Significance of metastatic lymph node ratio on survival and thyroglobulin levels in papillary thyroid carcinoma after prophylactic unilateral central neck dissection. Ann Surg Oncol. 2012;19:1257-1263.

62. Lloyd RV, Buehler D, Kahanafshar E. Papillary thyroid carcinoma variants. Head Neck Pathol. 2011;5:51-56.

63. LiVolsi VA. Papillary thyroid carcinoma: an update. Mod Pathol. 2011;24(suppl 2):S1-S9.

64. Rivera M, Ricarte-Filho J, Patel S, et al. Encapsulated thyroid tumors of follicular cell origin with high grade features (high mitotic rate/tumor necrosis): a clinicopathologic and molecular study. Hum Pathol. 2010;41:172-180.

65. Lloyd RV, Erickson LA, Casey MB, et al. Observer variation in the diagnosis of follicular variant of papillary thyroid carcinoma. Am J Surg Pathol. 2004;28:1336-1340.

66. Scognamiglio T, Hyjek E, Kao J, Chen YT. Diagnostic usefulness of HBME1, galectin-3, CK19, and CITED1 and evaluation of their expression in encapsulated lesions with questionable features of papillary thyroid carcinoma. Am J Clin Pathol. 2006;126:700-708.

67. Nikiforova MN, Kimura ET, Gandhi M, et al. BRAF mutations in thyroid tumors are restricted to papillary carcinomas and anaplastic or poorly differentiated carcinomas arising from papillary carcinomas. J Clin Endocrinol Metab. 2003;88:5399-5404.

68. Tetzlaff MT, LiVolsi V, Baloch ZW. Assessing the utility of a mutational assay for BRAF as an adjunct to conventional fine needle aspiration of the thyroid gland. Adv Anat Pathol. 2006;13:228-237.

69. Elisei R, Ugolini C, Viola D, et al. BRAF(V600E) mutation and outcome of patients with papillary thyroid carcinoma: a 15-year median follow-up study. J Clin Endocrinol Metab. 2008;93:3943-3949.

70. Wreesmann VB, Ghosein RA, Patel SG, et al. Genome-wide appraisal of thyroid cancer progression. Am J Surg Pathol. 2002;161:1549-1556.

71. Burman KD, Ringel MD, Wartofsky L. Unusual types of thyroid neoplasms. Endocrinol Metab Clin North Am. 1996;25:49-68.

72. Wang W, Macapinlac H, Larson SM, et al. [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography localizes residual thyroid cancer in patients with negative diagnostic 131I whole body scans and elevated serum thyroglobulin levels. J Clin Endocrinol Metab. 1999;84:2291-2302.

73. Schlumberger MJ. Papillary and follicular thyroid carcinoma. N Engl J Med. 1998;338:297-306.

74. Brennan MD, Bergstralh EJ, van Heerden JA, McConahey WM. Follicular thyroid cancer treated at the Mayo Clinic, 1946 through 1970: initial manifestations, pathologic findings, therapy, and outcome. Mayo Clin Proc. 1991;66:11-22.

75. Thompson LD, Wieneke JA, Paal E, Fromelt RA, Adair CF, Heffess CS. A clinicopathologic study of minimally invasive thyroid carcinoma of the gland with a review of the English literature. Cancer. 2001;91:505-524.

76. Harrick JK, Thompson NW, McLeod MK, Eckhauser FE, Lloyd RV. Follicular carcinoma of the thyroid gland: trends and changes in surgical management. Surgery. 1984;96:972-986.

77. Grebe SK, Hay ID. Follicular thyroid cancer. Endocrinol Metab Clin North Am. 1995;24:761-801.

78. Nesland JM, Sobrinho-Simoes MA, Holm SR, Privat A, Johannessen JV. Hurthle-cell lesions of the thyroid: a combined study using transmission electron microscopy, scanning electron microscopy, and immunocytochemistry. Ultrastruct Pathol. 1985;8:269-290.

79. Gonzalez-Campora R, Herrera-Zapatero A, Lerma E, Sanchez F, Galera H. Hurthle cell and mitochondiron-rich cell tumors. A clinicopathologic study. Cancer. 1986;57:1154-1163.

80. Chen H, Nicol TL, Zeiger MA, et al. Hurthle-cell neoplasms of the thyroid: are there factors predictive of malignancy? Ann Surg. 1998;227:542-546.

81. Phitayakorn R, McHenry CR. Follicular and Hurthle-cell carcinoma of the thyroid gland. Surg Oncol Clin N Am. 2000;15:2842-2846.

82. Zhang YW, Greenblatt DY, Repplinger D, et al. A comparison of recombinant human thyrotropin with recombinant human choriogonadotropin as a monitoring method for low-risk patients with papillary thyroid carcinoma. J Clin Endocrinol Metab. 2003;88:1433-1441.

83. Haugen BR, Grant CS, Taylor WF, McConahey WM. Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid carcinoma: a retrospective analysis of surgical outcome using a novel prognostic scoring system. Surgery. 1987;102:1088-1095.

84. Cady B, Rossi R. An expanded view of risk-group definition in differentiated thyroid carcinoma. Surgery. 1988;104:947-953.

85. Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery. 1993;114:1050-1057; discussion 1057-1058.

86. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med. 1994;97:418-428.

87. Byar DP, Green SB, Dor P, et al. A prognostic index for thyroid carcinoma. A study of the E.O.R.T.C. Thyroid Cancer Cooperative Group. Eur J Cancer. 1979;15:1033-1041.

88. Sherman SI, Brierley JD, Spirling M, et al. Prospective multicenter study of thyroid carcinoma treatment: initial analysis of staging and outcome. National Thyroid Cancer Treatment Cooperative Study Registry Group. Cancer. 1998;83:1012-1021.

89. Scheumann GF, Gimm O, Wegener G, Hundeshagen H, Dralle H. Prognostic significance and surgical management of locoregional lymph node metastases in papillary thyroid cancer. World J Surg. 1994;18:559-567.

90. Belfiore A, Carofalo MR, Giusfreda D, et al. Increased aggressiveness of thyroid cancer in patients with Graves’ disease. J Clin Endocrinol Metab. 1990;70:830-835.

91. Mazzaferri EL. Management of a solitary thyroid nodule. N Engl J Med. 1993;328:553-559.

92. Nagai GR, Pitts WC, Basso L, Cisco JA, McDougall IR. Scintigraphic hot nodules and thyroid carcinoma. Clin Nucl Med. 1987;12:123-127.

93. Haugen BR, Ridgway EC, McLaughlin BA, McDermott MT. Clinical comparison of recombinant human thyrotropin with recombinant human thyrotropin after stimulation with recombinant human thyrotropin. Thyroid. 2002;12:37-43.

94. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19:1167-1214.

95. Mazzaferri EL, Robbins RJ, Spencer CA, et al. A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. J Clin Endocrinol Metab. 2003;88:1433-1441.

96. Chobar H, Papini E, Valcavi R, et al; AACE/AME Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists and American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and monitoring of thyroid nodules. Endocrinol Metab Clin North Am. 2009;38:53-83.
management of thyroid nodules. *Endocr Pract.* 2006;12:63-102.

102. Lowhagen T, Granberg PO, Lundell G, Skinnari P, Sundblad R, Willems JS. Aspiration biopsy cytology (ABC) in nodules of the thyroid gland suspected to be malignant. *Surg Clin North Am.* 1979;59:3-18.

103. Crippa S, Mazzucchelli L, Cibas ES, Ali SZ. The Bethesda System for reporting thyroid fine-needle aspiration specimens. *Am J Clin Pathol.* 2010;134:343-344; author reply 345.

104. Vriens MR, Sabanci U, Epstein HD, et al. Reliability of fine-needle aspiration in patients with familial nonmedullary thyroid cancer. *Thyroid.* 1999;9:1011-1016.

105. Carmeci C, Jeffrey RB, McDougall IR, Novels KW, Weigel RJ. Ultrasound-guided fine-needle aspiration biopsy of thyroid masses. *Thyroid.* 1998;8:283-289.

106. Nikiforov YE. Thyroid carcinoma: molecular pathways and therapeutic targets. *Mod Pathol.* 2008;21(suppl 2):S37-543.

107. Poehls JL, Chen H, Sippel RS. Preoperative ultrasonography findings predict the need for repeated surgery in papillary thyroid cancer. *Endocr Pract.* 2012;18:403-409.

108. Luo J, McManus C, Chen H, Sippel RS. Age and sex predictors of malignancy in patients with multinodular goiter. *J Clin Surg.* 2012;174:207-210.

109. Sippel RS, Elaraj DM, Poder L, Duh QY, Luo J, McManus C, Chen H, Sippel RS. Tru-Cut biopsy: clinical use for focal lesion biopsy in patients with thyroid nodules. *World J Surg.* 2009;33:434-439.

110. Al-Azawi D, Mann GB, Judson RT, Miller JA. Endocrine surgeon-performed US guided thyroid FNAC is accurate and efficient. *World J Surg.* 2012;36:1947-1952.

111. Goldfarb M, Gondek SS, Sanchez Y, Lew JH. Clinic-based ultrasound can predict malignancy in pediatric thyroid nodules. *Thyroid.* 2012;22:827-831.

112. Kim MH, O JH, Ko SH, et al. Role of [(18)F]-fluorodeoxy-D-glucose positron emission tomography and computed tomography in the early detection of persistent/recurrent thyroid carcinoma in initial-to-high-risk patients following initial radioactive iodine ablation therapy. *Thyroid.* 2012;22:157-164.

113. Yip L, Stang MT, Carty SE. Thyroid carcinoma: the surgeon’s perspective. *Radial Clin North Am.* 2011;49:463-471, vi.

114. Nikiforov YE, Ohori NP, Hodak SP, et al. Impact of mutational testing on the diagnosis and management of patients with thyroid neoplasms. *Thyroid:* a systematic review. *Endocr Pract.* 2010;16:458-469.

115. Alexander EK, Kennedy GC, Baloch ZW, et al. Preoperative diagnosis of benign thyroid nodules with indeterminate cytology. *N Engl J Med.* 2012;367:705-715.

116. Shahar AR, Shah JP, Loree TR. Low-risk differentiated thyroid cancer: the need for selective treatment. *Ann Surg Oncol.* 1997;4:328-333.

117. Wanebo H, Coburn M, Teates D, Cole B. Total thyroidectomy does not enhance disease control or survival even in high-risk patients with differentiated thyroid cancer. *Ann Surg.* 1998;227:912-921.

118. Sanders LE, Cady B. Differentiated thyroid cancer: reevaluation of risk groups and outcome of treatment. *Arch Surg.* 1998;133:419-425.

119. Van Nguyen K, Dilawari RA. Predictive value of AMES scoring system in selection of extent of surgery in well differentiated carcinomas of thyroid. *Am Surg.* 1995;61:151-155.

120. Mazzaferrli EL, Young RL. Papillary thyroid carcinoma: a 10 year follow-up report of the impact of therapy in 576 patients. *Am J Med.* 1981;70:511-518.

121. Samaan NA, Schultz PN, Hickey RC, et al. The results of various modalities of treatment of well differentiated thyroid carcinoma: a retrospective review of 1599 patients. *J Clin Endocrinol Metab.* 1992;75:714-720.

122. Loh KC, Greenspan FS, Lee L, Miller TR, Yeo PP. Pathological tumor-node-metastasis (pTNM) staging for papillary and follicular thyroid carcinomas: a retrospective analysis of 700 patients. *J Clin Endocrinol Metab.* 1997;82:3553-3562.

123. Cooper DS, Doherty GM, Haugen BR, et al; American Thyroid Association Guidelines Taskforce. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid.* 2006;16:109-142.

124. Shindo M, Wu JC, Park EE, Tanzella F, Lang BH, Lo CY. Technological innovation and preservation in thyroid and parathyroid operations. *Surg Endosc.* 2010;24:3186-3194.

125. Wagner HE, Seiler C. Recurrent laryngeal nerve palsy after thyroid gland surgery. *Br J Surg.* 1994;81:226-228.

126. Dackiw AP, Rotstein LE, Clark OH. Computer-assisted evoked electromyography with stimulating surgical instruments for recurrent/external laryngeal nerve identification and preservation in thyroid and parathyroid operations. *Surg Endosc.* 2010;24:3186-3194.

127. Bardet S, Malville E, Rame JP, et al. Macrosopic lymph-node involvement and neck dissection predict lymph-node recurrence in papillary thyroid carcinoma. *Arch Otolaryngol Head Neck Surg.* 2006;132:650-654.

128. Wada N, Duh QY, Sugino K, et al. Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection. *Ann Surg.* 2003;237:399-407.

129. Gensenjager E, Perren A, Seifert B, Schul G, Schweizer I, Heitz PU. Lymph node metastases in papillary carcinoma. *J Am Coll Surg.* 2003;197:182-190.

130. Mazzaferri EL, Doherty GM, Steward DL. The pros and cons of prophylactic central compartment lymph node dissection for papillary thyroid cancer. *Cancer Control.* 2009;16:131-135.

131. Melck AL, Yip L, Carty SE, Cooper DS, Doherty GM, et al. Consensus statement on the terminology and classification of recurrence, and postoperative levels of serum parathyroid hormone. *Ann Surg.* 2007;245:604-610.

132. Xing M. Prognostic utility of BRAF mutation in papillary thyroid carcinoma. *Mol Cell Endocrinol.* 2010;321:86-93.

133. Zarebaczan B, Mohanty D, Chen H. A comparison of the LigaSure and harmonic scalpel in thyroid surgery: a single institution review. *Ann Surg Oncol.* 2011;18:214-218.

134. Musenuru S, Schaefer S, Chen H. The use of the Ligasure for hemostasis during thyroid lobectomy. *Am J Surg.* 2008;195:382-384; discussion 384-385.

135. Bolt GR, McMurray GT, Joseph DJ. Recurrent laryngeal nerve injury following thyroid operations. *Surg Gynecol Obstet.* 1977;144:567-570.

136. Wagner HE, Seiler C. Recurrent laryngeal nerve palsy after thyroid gland surgery. *Br J Surg.* 1994;81:226-228.
radioactive iodine on salivary gland function in patients with thyroid cancer. Head Neck. 2011;33:686-690.

163. Cady B, Sedgwicke CE, Meisssner WA, Bookwalter JR, Romagosa V, Werber J. Changing clinical, pathologic, therapeutic, and survival patterns in differentiated thyroid carcinoma. Ann Surg. 1976;184:541-553.

164. McGriff NJ, Csako G,ourgiotis L, Lori CG, Pucino F, Sarlis NJ. Effects of thyroid hormone suppression therapy on adverse clinical outcomes in differentiated thyroid cancer. Ann Med. 2002;34:554-564.

165. Brierley JD, Tsang RW. External-beam radiation therapy in the treatment of differentiated thyroid cancer. Semin Surg Oncol. 1999;16:42-49.

166. Tennvall J, Lundell G, Hallquist A, Wahlberg P, Wallin G, Tibblin S. Combined doxorubicin, hyperfractionated radiotherapy, and surgery in anaplastic thyroid carcinoma. Report on two protocols. The Swedish Anaplastic Thyroid Cancer Group. Cancer. 1994;74:1348-1354.

167. Shimaaoka K, Schoenfeld DA, DeWys WD, Creech RH, DeConti R. A randomized trial of doxorubicin versus doxorubicin plus cisplatin in patients with advanced thyroid carcinoma. Cancer. 1985;56:2155-2160.

168. Williams SD, Birch R, Einhorn LH. Phase II evaluation of doxorubicin plus cisplatin in advanced thyroid cancer: a Southeastern Cancer Study Group Trial. Cancer Treat Rep. 1986;70:405-407.

169. Higgins MJ, Forastiere A, Marur S. New directions in the systemic treatment of metastatic thyroid cancer. Oncology (Williston Park). 2009;23:768-775.

170. Kim DW, Jo YS, Jung HS, et al. An orally administered multitarget tyrosine kinase inhibitor, SU11248, is a novel potent inhibitor of thyroid oncogenic RET/papillary thyroid cancer kinases. J Clin Endocrinol Metab. 2006;91:4070-4076.

171. Haugen BR, Kane MA. Approach to the thyroid cancer patient with extracervical metastases. J Clin Endocrinol Metab. 2010;95:987-993.

172. Xing M, Westra WH, Tufano RP, et al. BRAF mutation predicts a poorer clinical outcome in human thyroid cancer cells. J Cell Physiol. 2005;209:637-639.

173. Ouyang B, Knauf JA, Smith EP, et al. Novel histone deacetylase inhibitors in cancer: causes and therapies. Nat Rev Cancer. 2002;1:194-202.

174. Gupta-Abramson V, Troxel AB, Nellore A, et al. Phase II trial of sorafenib in metastatic thyroid cancer. J Clin Endocrinol Metab. 2006;91:4070-4076.

175. Mitjaiades CS, Poukali V, McMullan C, et al. Novel histone deacetylase inhibitors in the treatment of thyroid cancer. Clin Cancer Res. 2005;11:3958-3965.

176. Luong QT, O’Kelly J, Braunstein GD, Hershman JM, Koefler HP. Antitumor activity of suberoylanilide hydroxamic acid against thyroid cancer cell lines in vitro and in vivo. Cancer Res. 2006;62:5570-5577.

177. Petrie SR, Bhandari D, Rakha EA, et al. A phase II trial of the histone deacetylase inhibitor, depsipeptide (FR901228, NSC 630176), in patients with refractory neoplasms. Cancer. 2006;10:597-605.

178. Fortunati N, Catalano MG, Arena K, Brignardello E, Povesan A, Boccuzzi G. Valproic acid induces the expression of the Nalpha-/beta-sympporter and iodine uptake in poorly differentiated thyroid cancer cells. J Endocrinol Metab. 2004;89:1006-1009.

179. Xiao X, Ning L, Chen H. Notch1 mediates growth suppression of papillary and follicular thyroid cancer cells by histone deacetylase inhibitors. Mol Cancer Ther. 2009;8:350-356.

180. Shen WT, Kong T, Wu SY, et al. Valproic acid inhibits growth, induces apoptosis, and modulates transcriptional regulation and differentiation gene expression in human thyroid cancer cells. Cancer. 2005;105:979-984; discussion 984-985.

181. Pinchot SN, Kunimaiyaia M, Sippel RS, Chen H. Medullary thyroid carcinoma: targeted therapies and future directions. J Clin Oncol. 2009;27:183031.

182. Williams ED. Histogenesis of medullary carcinoma of the thyroid. J Clin Pathol. 1966:19:114-118.

183. Hill CS Jr, Ibanez ML, Samaan NA, Ahearn MJ, Clark RL. Medullary (solid) carcinoma of the thyroid gland: an analysis of the M. D. Anderson hospital experience with patients with the tumor, its special features, and its histogenesis. Medicine (Baltimore). 1973;52:141-171.

184. Sippel RS, Kunimaiyaia M, Chen H. Current management of medullary thyroid cancer. Oncologist. 2008:13:539-547.

185. Chen H, Sippel RS, O’Dorisio MS, Vinik AI, Lloyd RV, Pacak K. North American Neuroendocrine Tumor Society.
194. Williams ED, Brown CL, Doniach I. Pathological and clinical findings in a series of 67 cases of medullary carcinoma of the thyroid. J Clin Pathol. 1966;19:103-113.

195. Boi F, Maurelli I, Pinna G, et al. Calcitonin measurement in wash-out fluid from fine needle aspiration of neck masses in patients with primary and metastatic medullary thyroid carcinoma. J Clin Endocrinol Metab. 2007;92:2115-2118.

196. Chin WW, Goodman RH, Jacobs JW, Wolfe HJ, Daniels GH, Habener JF. Medullary thyroid carcinoma identified by cell-free translation of tumor messenger ribonucleic acid in a patient with a neck mass and the syndrome of ectopic adrenocorticotropin. J Clin Endocrinol Metab. 1981;52:572-575.

197. Costante G, Meringolo D, Durante C, et al. Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules. J Clin Endocrinol Metab. 2007;92:450-455.

198. Machens A, Schneyer U, Holzhausen HJ, Dralle H. Prospects of remission in medullary thyroid carcinoma according to basal calcitonin level. J Clin Endocrinol Metab. 2005;90:2029-2034.

199. Machens A, Dralle H. Pretargeted anti-carcinomembranic-antigen radioimmunotherapy for medullary thyroid carcinoma. J Clin Oncol. 2006;24:e37; author reply e38.

200. de Groot JW, Kema IP, Breukelman H, et al. Biochemical markers in the follow-up of medullary thyroid cancer. Thyroid. 2006;16:1163-1170.

201. Roman S, Lin R, Sosa JA. Prognosis of medullary thyroid carcinoma: demographic, clinical, and pathologic predictors of survival in 1252 cases. Cancer. 2006;107:2134-2142.

202. Wells SA Jr, Chi DD, Toshima K, et al. Predictive DNA testing and prophylactic thyroidectomy in patients at risk for multiple endocrine neoplasia type 2A. Ann Surg. 1994;220:237-247; discussion 247-250.

203. Pinchot SN, Sippel RS. Management of medullary thyroid cancer. In: Sippel RS, Chen H, eds. The Handbook of Endocrine Surgery. Hackensack, NJ: World Scientific Publishing Company; 2011:63-78.

204. Kouvaraki MA, Shapiro SE, Perrier ND, et al. RET proto-oncogene: a review and update of genotype-phenotype correlations in hereditary medullary thyroid cancer and associated endocrine tumors. Thyroid. 2005;15:531-544.

205. Ogilvie JB, Kebebew E. Indication and timing of thyroid surgery for patients with hereditary medullary thyroid cancer syndromes. J Natl Compr Canc Netw. 2006;4:139-147.

206. Moley JF, DeBenedetti MK. Patterns of nodal metastases in palpable medullary thyroid carcinoma: recommendations for extent of node dissection. Ann Surg. 1999;229:880-887; discussion 887-888.

207. Greenblatt DY, Elson D, Mack E, Chen H. Initial lymph node dissection increases cure rates in patients with medullary thyroid cancer. Asian J Surg. 2007;30:108-112.

208. Machens A, Hauptmann S, Dralle H. Increased risk of lymph node metastasis in multifocal hereditary and sporadic medullary thyroid cancer. World J Surg. 2007;31:1960-1965.

209. Machens A, Dralle H. Genotype-phenotype based surgical concept of hereditary medullary thyroid carcinoma. World J Surg. 2007;31:957-968.

210. American Thyroid Association Guidelines Task Force, Kloos RT, Eng C, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid. 2009;19:565-612.

211. Tischler AS, Khan A, DeLellis RA. Prophylactic thyroidectomy in multiple endocrine neoplasia type 2A. N Engl J Med. 2005;353:2817-2818; author reply 2817-2818.

212. Chen H, Roberts JR, Ball DW, et al. Effective long-term palliation of symptomatic, incurable metastatic medullary thyroid cancer by operative resection. Ann Surg. 1998;227:857-895.

213. Ball DW. Medullary thyroid cancer: therapeutic targets and molecular markers. Curr Opin Oncol. 2007;19:18-23.

214. Wells SA Jr, Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol. 2012;30:134-141.

215. de Groot JW, Zonnenberg BA, van Ufford-Mannesse PQ, et al. A phase II trial of imatinib therapy for metastatic medullary thyroid carcinoma. J Clin Endocrinol Metab. 2007;92:3466-3469.

216. Langmuir PB, Yver A. Vandetanib for the treatment of thyroid cancer. Clin Pharmacol Ther. 2012;91:71-80.