



Published in final edited form as:

CA Cancer J Clin. 2013 November ; 63(6): 373–394. doi:10.3322/caac.21195.

NEW DEVELOPMENTS IN THE DIAGNOSIS AND TREATMENT OF THYROID CANCER

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Abstract

Thyroid cancer exists in several forms. Differentiated thyroid cancers include 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 differentiated thyroid tumors. Genetic testing and newer adjuvant therapies has changed the diagnosis and treatment of medullary thyroid cancer. This review will focus on the epidemiology, diagnosis, work-up, and treatment of both differentiated and medullary thyroid cancers, focusing specifically on newer developments in the field.

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 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 life-long (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) that accounts for 10–20% of all cases. Together, papillary and follicular cancers are termed differentiated thyroid cancer (DTC), and both arise from the thyroid follicular cells. Medullary thyroid cancer (MTC), on the other hand, arises from the parafollicular C cells. This neuroendocrine thyroid tumor represents 6–8% of all thyroid cancer cases and occurs in familial and sporadic forms. Finally, anaplastic thyroid cancer is one of the most aggressive and rapidly fatal cancers. It can develop from DTC that de-differentiates over time or it also arises de-

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No disclosures or conflicts of interest.

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 (DTC)

Epidemiology

Thyroid cancer is the most rapidly increasing malignancy in the U.S. for both men and women. Although the incidence has of DTC has increased worldwide, there was a 2.4-fold increase in DTC incidence in the U.S. between 1973 and 2002, and the incidence has continued to rise over the last decade (7, 8). This increasing incidence is attributed to improved detection of smaller (<2 cm) tumors via more frequent and better ultrasound detection and fine needle aspiration (FNA) biopsies (9). Another theory to explain the increasing incidence of DTC is the increased pathologic reporting of incidental microcarcinomas (tumors < 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 1–2 cm, 2–5 cm, and >5 cm in size increased by 12.3%, 10.3%, and 12.0% per year, respectively, over that same period (13). This suggests that better detection of smaller tumors does not fully account for the overall rising 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 U.S. population. Regardless of the reason behind the rising incidence of DTC, the mortality rate remains largely unchanged at 0.5 per 100,000 population despite greater increases in incidence (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's disease might still receive mantle radiation. In addition, children exposed to radioactive fallout from the Chernobyl 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 Gy were considered causative, but further evaluation of patients exposed to 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 7–9% of patients who received 5–10 Gy external beam radiation develop thyroid cancer (24). A lag time of 10 to 20 years usually exists between exposure and 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 higher frequency in regions with high dietary iodine content such as the 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 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's, Cowden's, and Werner's syndromes (28, 29). Familial non-medullary thyroid cancer (FNMTc) is defined when two 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 FNMTc have been studied, including TCO1, MNG1, fPTC/PRN, and NMTC1, but a single responsible gene has yet to be definitively identified (32–35). Compared to sporadic DTC, FNMTc is more aggressive with increased recurrence, local invasion, multicentricity, and lymph node metastases. FNMTc should be suspected in the setting of two or more family members with DTC and/or younger family members (20's – 30's) with more advanced cancers (i.e, lymph node metastases). More recently, Mazeh and colleagues demonstrated that even patients with just one family member affected by DTC were similar to FNMTc patients 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, FNMTc 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, four molecular markers with the most literature in human studies will be discussed. Some centers are beginning to utilize these markers in clinical practice as we will discuss in the diagnosis section. One such marker is the RET and papillary thyroid cancer (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 20–40% cases (37). RET/PTC rearrangements are common in small, multifocal PTCs accompanied by an inflammatory infiltrate, often seen in individuals exposed to ionizing radiation (38).

BRAF is a member of the RAF-MEK-ERK 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 anaplastic thyroid cancer (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 20–50% of follicular cancers.

Similar to the RET/PTC re-arrangement, 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 (PPAR γ) gene in 35% of FTCs (40–42). The intracellular signaling consequences of the PAX8-PPAR γ rearrangement remain unclear. RAS mutations are also highly prevalent in FTC, but Nikiforova et al found that RAS and PAX8-PPAR γ rearrangements are mutually exclusive, suggesting that these are two 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 five year survival greater than 97% (8). Smaller tumors carry a better prognosis than larger tumors. PTC less than 1 cm in size are called papillary microcarcinomas, and have been reported in 10–30% 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 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 (45, 47).

Aside from size, age is another important determinant of prognosis in 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 prognostic indicators employed 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 importance 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 PTC, but the precise incidence of lymph node metastases depends on how it is defined. Palpable disease in the lymph nodes is present in 5–10% 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 20–50% of patients, but when PCR is performed, up to 90% of patients with DTC will have lymph nodes with microscopic disease. Historically, lymph node involvement was felt to increase 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 to 0% in patients without pathologic lymph nodes (53). Whether metastatic lymph nodes are clinically evident preoperatively appears to be an important factor determining recurrence. For example, Ito and colleagues found that if metastatic lymph nodes were not seen preoperatively, then the risk of nodal recurrence was only 1.5%. 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 nodes are more important than pathologically positive nodes. 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 a binary factor, classifying patients by the presence or absence of diseased lymph nodes, or the anatomic location of these nodes (Table 1 and 2). The lymph node ratio (number of metastatic nodes divided by the total number of nodes harvested) is a method of further risk-stratifying patients with lymph node disease (57–60). 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 (57), it is probably most helpful in assessing recurrence risk and tailoring postoperative treatment and follow-up accordingly (58).

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) that has features of both PTC and FTC, but is classified as a PTC subtype. This subtype exhibits the overall follicular structure but with nuclear features of PTC. Often FVPTC is confused for follicular neoplasms or carcinomas (61, 62). Overall, the prognosis is intermediate between classical PTC and FTC. The prognosis also hinges upon whether the tumors are completely encapsulated or invasive (63). Since FVPTC histologically resembles follicular adenomas or carcinomas, immunohistochemical stains such as HBME-1 have proven particularly useful in making the pathologic diagnosis (64, 65).

It is important to recognize more aggressive variants of well-differentiated tumors. These include tall cell, columnar cell, solid, and diffuse-sclerosing variants. Tall cell variant of PTC, commonly encountered in older patients, are 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 PET positive. Histologically, these tumors have cells whose height is at least 2–3 times as tall as they are wide. Traditional criteria require at least 50% of the cells to exhibit these tall features (62). Necrosis, a high mitotic index, and nuclear pseudoinclusions are also prominent in these tumors (61). Recently, several different centers have noted that tall cell variant PTCs often harbor BRAF mutations, and molecular markers can be utilized to identify this subtype preoperatively (66–68). Such molecular diagnostics may become helpful since this subtype is believed to be under-diagnosed (62). 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 de-differentiate, 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 five year disease-free survival and cause-specific survival approaching zero (69). Anaplastic thyroid cancer can arise from well-differentiated tumors that de-differentiate or it can also develop de-novo(69). A group of tumors falls in between well-differentiated thyroid cancers and anaplastic cancers. These cancers, called poorly differentiated thyroid cancers, have a histologic appearance and behavior that is intermediate between well-differentiated PTC and anaplastic cancers (3). Although the literature remains inconsistent about 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” (70). These tumors include insular and large cell variants (3, 70). Patients with these types tend toward locally advanced disease with recurrence and metastases. Furthermore, de-differentiation of thyroid cancers leads to under expression or disordered assembly of the sodium-iodide symporter, decreasing the utility of radioactive iodine for treating or detecting metastatic disease (71). For these reasons, poorly differentiated thyroid cancers have a 51% disease-free survival and a 70% cause-specific survival at five years (3, 69).

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 to PTC. Even when the disease is confined to the thyroid, mortality rates range from 5–15%, although survival time still extends decades as in PTC (72). In addition to the prognostic factors common to DTC staging systems (discussed below), prognosis in FTC especially depends on the degree of capsular and vascular invasion. Minimally invasive tumors are grossly 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 (73–75). For these reasons, FNA biopsy cannot distinguish a follicular adenoma from a carcinoma, and this has led to the investigation of molecular markers that can make this diagnosis as will be discussed below. Until molecular diagnostics are perfected, the current standard of care is to perform a diagnostic lobectomy in order to distinguish follicular adenoma from carcinoma (73, 76).

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 prominent nucleolus. Hurthle cells are found in a variety of conditions including nodular goiter, chronic lymphocytic (Hashimoto's) thyroiditis, and long-standing hyperthyroidism (77, 78). Both adenomas and carcinomas of the Hurthle cell can occur, and differentiating them by cytology is difficult as it is with follicular lesions (75, 79). As with follicular tumors, capsular and vascular invasion distinguish carcinoma from adenomas. Large Hurthle cell cancers (>2 cm) have a higher recurrence rate, ranging from 21 to 59% (79, 80). Furthermore, Hurthle cell cancers do not always concentrate iodine. For these reasons, Hurthle cell carcinoma carries a worse prognosis compared to other DTC. 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 (80, 81). In one series, 65% of Hurthle cell neoplasms 4 cm or greater in size were cancer on final pathology (79).

Thyroid Lymphoma

Primary lymphoma of the thyroid is not as common as DTC. Older females or patients with Hashimoto's thyroiditis are at highest risk for developing thyroid lymphoma (82, 83). 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 might also be difficult to distinguish from advanced Hashimoto's thyroiditis. A core biopsy may therefore become necessary when this diagnosis is suspected in order 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 (83). Prognosis depends on the histologic subtype. Of note, up to 20% of patients suffering from generalized lymphoma can also have secondary involvement of the thyroid (84).

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, 85, 86). Table 1 summarizes the various staging systems for DTC.

Classical prognostic indicators for DTC include age and gender. 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 tumor size (Table 1)

Because of their questionable effect on mortality, lymph node status is not included in all of the staging systems available for DTC. For example, the AGES system considers age, grade, extrathyroidal extension, and size (87). The AMES system uses age, distant (non-lymph node) metastases, extent of primary tumor, and size (88). Some, like the MACIS (metastases, age, complete excision, invasion, and size) system also account for the adequacy of surgical treatment (89). Alternatively, staging systems developed by the Ohio State University (90), the European Organization for Research and Treatment of Cancer (EORTC) (91), the National Thyroid Cancer Treatment Cooperative Study (NTCTCS) (92), Clinical Class (49), and the American Joint Committee on Cancer (AJCC) (93) all do consider lymph node status.

The AJCC is the most widely utilized staging system (Table 2). Also known as the TNM system since it considers tumor size and local extent (T), lymph node metastases (N), and distant metastases (M). Like many of the other thyroid cancer staging systems, it also considers age, with two different classifications for those younger and older than 45 years of age. In those under 45, patients with lymph node metastases are classified as stage I unless they have distant metastases (stage II) (93).

Diagnosis

Like any newly discovered mass elsewhere in the body, the workup of a thyroid nodule begins with a thorough history and physical exam. 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 exam, malignant nodules are harder and fixed while a nodule that is rubbery or soft and moves easily with deglutition suggests a benign nodule. Physical exam 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 thyroid stimulating hormone (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), an ^{123}I scan can distinguish a solitary toxic nodule from a toxic multinodular goiter and Graves' Disease. A solitary hyper functioning nodule is rarely malignant, and FNA biopsy or further cancer workup is rarely necessary. Hyperfunctioning nodules are usually hypercellular, and will 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 10–20% of "cold" nodules 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 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 greater than 1 cm in largest dimension (96, 99, 101). When the FNA result is clearly benign or malignant, then the decision for further treatment including thyroidectomy becomes evident. The false-negative rate for FNA biopsy is 1–3% (Table 3). The false negative rate increases to 10–15% when the nodule is large (> 4 cm) (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 cystic nodules (104). Ultrasound-guidance can improve the accuracy of FNA biopsy because ultrasound can confirm the nodule is actually being sampled and target the most suspicious portions of the nodule (i.e., the wall of a cyst). This is especially true for non-palpable or posteriorly located nodules (105, 106).

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 (96, 102, 103). Therefore, lobectomy with permanent histology may be the best way to make a definitive diagnosis in follicular or indeterminate lesions. Many centers have turned to 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 γ rearrangements (39–41, 69, 107). 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 in evaluating thyroid nodules as it is used to measure size and features of the nodule such as its borders, echogenicity, and vascularity. It can also identify additional non-palpable 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 (Figure 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 non-invasive 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 (2, 105, 108–112). Therefore, ultrasound is the preferred method 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, CT becomes a helpful preoperative imaging study to help 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 (2, 3, 113, 114). 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.

Imaging studies often identify thyroid nodules incidentally. Positron emission tomography (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 FDG-avid thyroid nodules will contain thyroid cancer. Therefore, PET-positive thyroid nodules should be FNA biopsied. PET and/or CT scan 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, 113).

Role of Molecular Markers

As discussed above, the identification of several 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 these nodules are benign or malignant without the need for diagnostic surgery. For example, Nikiforov and colleagues recently developed a panel of mutations including BRAF, NRAS, HRAS, KRAS, and two different RET/PTC rearrangements. 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 (115). 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%, for the cytologic diagnoses of atypia, follicular neoplasm/suspicious for follicular neoplasm, and suspicious, respectively (116). 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

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 less than one centimeter in size (microcarcinomas). The approach to microcarcinomas will be discussed further below, but for most DTC \leq 1 cm 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 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 re-operative 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% (114, 117). 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 two methods are most effective when all the 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 to thyroid lobectomy in this group of patients. In addition, radioiodine may have limited utility in low-risk patients (6, 45). For these reasons, some favor thyroid lobectomy in low risk patients. For example, Shaha and associates have reported 20-year follow-up on 465 patients with low risk DTC. Although the lobectomy group had more local recurrence compared to the total thyroidectomy group (4% versus 1%), this was not statistically significant (118). Similarly, other groups have also failed to demonstrate any significant effect on survival (119–121). In contrast, large retrospective series have demonstrated improvement in recurrence for total thyroidectomy compared to lesser operations (122–125). In a frequently cited study, Mazzaferri and colleagues reported on 1355 patients with a mean follow-up of 15.7 years. Patients treated with total thyroidectomy experienced significant improvements in recurrence rate (26% vs. 40%, $p < 0.02$) and mortality rate (6% vs. 9%, $p = 0.02$) compared to lesser resections (122). 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 (< 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 (126), 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 6 lymph nodes and include the paratracheal, peri-thyroidal, and precricoid lymph nodes. These nodes are found along and behind the recurrent laryngeal nerve and frequently surround the lower parathyroid gland (Figure 2). Although the level 6 lymph nodes contain macroscopic disease in 10% of cases, when they are removed prophylactically, 32–69% of patients will have microscopic metastases (52, 127, 128).

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 re-operative surgery in the central neck. Furthermore, the central neck 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 nodal 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 (129–131). Therefore, the debate regarding prophylactic central neck dissection is closely tied to the utility of radioactive iodine.

Clinically evident lymph node metastases place patients at higher risk for recurrence, and these patients benefit from therapeutic lymph node dissection. Prophylactic central neck dissection modestly reduces an already low recurrence rate, 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, 60, 132, 133). Some groups are currently using molecular markers to preoperatively risk stratify patients, and decide who might benefit from more aggressive surgery up front (134, 135).

Thyroidectomy still involves the same basic steps historically described, but newer technology and attention to cosmetics account for some more recent modifications of the basic technique. Traditionally, a Kocher collar incision was utilized, but this requires a very large dissection superiorly to reach the upper pole of the thyroid, 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 sub-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® (136, 137), 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% (138, 139). Even the largest trials have failed to show any significant prevention of nerve injury (140, 141). A multi-institutional prospective non-randomized 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 compared to those treated with a combination of visual identification and nerve monitoring (142). One of the few prospective studies, Thomusch and colleagues reported on 8,534 patients (15,403 nerves at risk). They compared direct stimulation of the recurrent laryngeal nerve to 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 of predicting nerve palsy compared to indirect stimulation (45.9% vs. 99.6%) (143). 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 feel 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 re-implanted 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 auto-transplanting cancer-bearing lymph nodes back into the patient. Two to three pockets are created within the muscle, and the minced parathyroid

tissue is divided between these pockets. Each pocket should be marked with permanent suture so that it can easily be found in a re-operative 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 which then become more difficult to excise in a re-operative setting.

Although “skip” metastases directly to the lateral compartment can occur in PTC, the central neck nodes (level VI) are usually the first nodes to receive drainage from the thyroid (Figure 2). The boundaries of the central neck are the carotid sheathes laterally, the hyoid bone superiorly, and the innominate artery inferiorly (144). Lymphadenectomy in this area requires skeletonizing the recurrent laryngeal nerve along its entire cervical course, and removing all the fibro-fatty tissue along the trachea. Frequently the lower parathyroid is invested in this tissue and becomes devascularized with this dissection (132).

A lateral neck dissection usually involves dissection of levels II, III, and IV (Figure 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 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 from performing lateral neck dissection (2, 114).

In recent years, transaxillary approaches to thyroidectomy have been developed. There are several variations of these techniques including, trans-axillary endoscopic, robotic, and axillo-breast techniques (145–150). 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 is lacking, and these techniques come with added complication risk such as brachial plexus injury (149).

Radioactive Iodine—Remnant ablation with radioactive iodine is the standard adjuvant treatment for selected patients with DTC. It can only be administered after a total or near-total thyroidectomy, otherwise the radioactive isotope will be absorbed by the remnant thyroid and not destroy any micro-metastatic disease as intended. Radioactive iodine is administered 1–3 months postoperatively as ^{131}I as sodium iodide in an oral form whose half-life is 7–8 days. Consensus guidelines recommend a dose of 30–100 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 (i.e., tall cell, columnar cell, or insular variants) (99, 151–153). In order to stimulate intracellular uptake of the isotope, the TSH concentration should be at least as high as 30 mU/L.

There are two methods for achieving such an elevation in TSH. The traditional method requires the patient to withdraw from thyroid hormone replacement over 4–6 weeks (4, 154). A newer method is to administer recombinant human TSH (rhTSH). rhTSH is administered in the form of intramuscular injections on two 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 to traditional withdrawal are not established, although it appears effective for low-risk patients. The U.S. Food and Drug Administration

(FDA) approved rhTSH for thyroid remnant ablation in patients who do not have evidence of metastatic disease (155, 156). In addition to making the TSH rise, clinicians should also prepare patients by instructing them to follow a low-iodine diet for 1–2 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 (152, 153). It is important to note that rhTSH is not approved for use in children.

While some studies show no benefit to radioactive iodine therapy (157, 158), other studies demonstrate a reduction in locoregional recurrences and distant metastases (122, 123). As with the controversy over the extent of thyroidectomy, the benefit of radioactive iodine for low risk patients remains unclear (154). The most recent ATA guidelines recommend remnant ablation for patients with T3 tumors or nodal disease. Selective use is recommended for 1–2 cm intrathyroidal tumors or T2 tumors. It is not recommended for intrathyroidal tumors less than or equal to 1 cm in size (99). The National Comprehensive Cancer Network (NCCN) guidelines require a more thorough evaluation for the extent of remaining disease after thyroidectomy with a radioiodine scan 1–12 weeks postoperatively. Radioactive iodine ablation is not recommended if the stimulated Tg is less than 1 ng/mL and the radioiodine scan is negative (151).

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 and colleagues found that patients treated for DTC had significantly higher rates of non-thyroid 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 (159). Iyer and associates specifically examined low risk patients (T1N0) treated with radioactive iodine and found that their excess absolute risk was 4.6 excess cases per 10,000 person years at risk (160). 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 where 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 (161–163). 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 (153, 162, 164, 165).

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 (166, 167). 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 < 0.1 mU/L. Lower risk patients should be dosed to a TSH at or slightly below the lower limit of normal (0.1 – 0.5 mU/L) (99, 151). Once patients remain disease-free for at least two years, their TSH suppression can be liberalized to within the reference range. Patients with persistent disease should be kept at a TSH < 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 NCCN guidelines recommend daily calcium and vitamin D supplementation for patients on TSH suppression (151).

External-beam radiation—Although ^{131}I 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 ^{131}I . Treatment of anaplastic thyroid tumors 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 given after resection of poorly differentiated tumors to reduce the risk of local relapse (168). 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. Patients with incompletely resected tumors, unresectable disease, and locoregional recurrence in a previously operated field may benefit from external beam radiation (3, 168, 169). External beam radiation is typically reserved as a last resort, after surgery and RAI have been exhausted.

Chemotherapy—Since radioactive iodine often can be effective treatment for well-differentiated tumors that have metastasized, cytotoxic chemotherapy has not been extensively evaluated for metastatic thyroid cancers. For 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 (170, 171).

Newer, targeted therapies have shown some promise. Small molecule tyrosine kinase inhibitors (such as sorafenib or sunitinib) and antibodies (anti-VEGF) should be considered in the context of ongoing clinical trials (151, 172–174).

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 for patients with RET or BRAF mutations (175, 176). Sorafenib is an orally administered multi-kinase inhibitor targeting BRAF, VEGF, RET, and c-kit. Two different phase II clinical trials enrolled patients with radioiodine resistant metastatic DTC, and reported that sorafenib stabilized disease progression and lowered serum thyroglobulin with minimal toxicity (177, 178).

Emerging therapies specifically target angiogenesis because DTC tumors express high levels of vascular endothelial growth factor (VEGF) receptors (179, 180). Multi-kinase inhibitors such as motesanib, vandetanib, sunitinib, and axitinib have shown early promise in patients with DTC (173, 181, 182). These drugs often target multiple VEGF receptors in addition to other signaling pathways such as c-Kit, RET, and PDGF.

Another mechanism targeted in anti-cancer 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 (HDAC) enzymes (183–185). Several HDAC inhibitors including vorinostat, depsipeptide, and valproic acid have been shown to have an effect on thyroid cancer cells (186–188). For example, in thyroid carcinoma cell lines, valproic acid increased expression of the sodium-iodide symporter and

radioiodine uptake (189–191). Many of these results come from in-vitro studies or early phase clinical trials, but do represent promising novel therapies with much lower toxicity than traditional chemotherapeutic agents.

Medullary Thyroid Cancer (MTC)

Medullary thyroid carcinoma (MTC) accounts for 6–8% 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. 25% of cases are due to germline genetic mutations, but most cases of MTC are sporadic. Hereditary cases occur either in isolation (familial medullary thyroid cancer) or as part of the multiple endocrine neoplasia syndrome type 2 (2A or 2B) (192–194).

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 (5). As in evaluating 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 *RET* gene. Almost all sporadic cases present with a palpable neck mass and this could be either in the thyroid or a metastatic lymph node. Lymph nodes metastases occur in 35–50% of patients at initial diagnosis (195). Therefore ultrasound evaluation of the central and lateral neck compartments for suspicious lymph nodes becomes a crucial component to the initial diagnosis (196).

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 (195). MTCs secrete cytokines and other peptides that can cause symptoms such as flushing, diarrhea, and weight loss (197).

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 anaplastic thyroid cancer unless the specimen is stained for calcitonin, chromogranin A, or 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 (198). Additionally, the presence of calcitonin messenger RNA (mRNA) has been performed when the cytologic or histologic diagnosis remains unclear (199). Histologically, MTCs form nests of cells with deposition of stromal amyloid that stains positively with Congo Red stain (195). Staining for chromogranin A can also help 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 normal patients will have some elevation in calcitonin, patients with a diagnosis of MTC usually exhibit levels above 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 (200). The degree of calcitonin elevation correlates with tumor burden, with nodal metastases found at basal

calcitonin levels of 10–40 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 (201).

Preoperative measurement of serum Carcinoembryonic antigen (CEA) can also help risk stratify patients. Overall, CEA elevations occur in more than 50% of patients with MTC, but a preoperative serum CEA greater than 30 ng/ml highly predicts the inability to cure the patient with surgery (202). 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 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 long-term (195, 203, 204)

Genetic testing plays an important part of 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 (205). A small percentage of apparently “sporadic” disease will also carry germline RET mutations, but truly sporadic cases frequently harbor somatic RET mutations. Commercial testing is performed through PCR amplification of the patient's germline DNA obtained from the patients 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. 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). While some overlap exists for genetic mutations associated with MEN-2A and familial MTC, distinct mutations are usually associated with MEN-2B (206, 207).

Treatment

Complete surgical excision is the treatment of choice for MTC. The minimum extent of surgery for patients with clinically apparent disease is a total thyroidectomy with bilateral central neck dissection. Eighty-one percent of patients with palpable disease have central neck lymph node metastases, and the addition of central neck dissection improves cure rates over total thyroidectomy alone in patients with clinically evident disease at presentation (208, 209). 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 nodal metastases (210). However, current guidelines recommend performing an ipsilateral lateral neck dissection if ultrasound or physical exam detects lymphadenopathy in the lateral neck, central compartment lymph nodes are involved, or when the primary tumor is greater than 1 cm (196). 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 (195, 196). Unlike DTC where micro-metastatic disease can be effectively treated with radioactive iodine ablation, the only effective treatment for 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 hereditary MTC, an age-related progression exists from C-cell hyperplasia to carcinoma, and ultimately nodal metastases. The optimal timing of prophylactic thyroidectomy depends on the risk level of the RET mutation (Table 5). In general, current guidelines recommend operating on children with MEN-2A and familial MTC by age 5 while those with MEN-2B should be operated on before 6 months of age (211, 212). 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 (213), and therefore, some argue that prophylactic central lymph node dissection should be performed. Opponents to this approach state that with a normal preoperative ultrasound, normal calcitonin (basal and/or stimulated), and a normal CEA, the risk of occult nodal disease is very low and do not outweigh the risks of a central neck dissection such as permanent hypoparathyroidism (5, 208, 213). Because any complications resulting from a prophylactic surgery become lifelong problems for the patient, experienced surgeons should perform prophylactic surgery for MTC.

In general, prophylactic thyroidectomy does not need to include a central neck dissection for MEN-2A and FMTC as long as surgery is done prophylactically, before disease is clinically apparent. Because of the more aggressive nature of MTCs associated with MEN-2B, performance of a central neck dissection with prophylactic thyroidectomy is optional, depending on the timing, and the specific codon mutated (195, 196) Prior to proceeding with surgery, the surgeon should screen patients with hereditary disease for associated conditions such as pheochromocytoma (MEN-2A and B) and hyperparathyroidism (MEN-2A) (207, 212, 213).

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 2–3 months postoperatively with a new baseline calcitonin and CEA. If the calcitonin is undetectable, then these patients can be followed with yearly calcitonin measurements. Imaging is undertaken when the calcitonin level rises.

A spectrum of disease severity exists for 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 lead to death quite quickly. On the other hand, many patients live with a large tumor burden and very high calcitonin levels with few symptoms. Others suffer from intractable diarrhea. In this case, cytoreductive surgery or somatostatin analogs like octreotide can palliate severe symptoms (214).

Conventional chemotherapy regimens with doxorubicin, dacarbazine, capecitabine, and 5-fluorouracil only have demonstrated limited efficacy in patients with MTC. Newer, targeted therapies block the RET receptor tyrosine kinase or its multiple downstream pathways such as the extracellular signal-related kinase (ERK), phosphatidylinositol 3-kinase (PI3K)/Akt, p38 mitogen-activated protein kinase (MAPK), and c-Jun N-terminal kinase pathways (107, 195, 215). Some of these tyrosine kinase inhibitors inhibit multiple signaling pathways simultaneously (107, 216). These targeted therapies are currently being evaluated in multicenter trials (216, 217).

Recently, the U.S. Food and Drug Administration (FDA) approved one of these targeted therapies, vandetanib, for treatment of metastatic MTC. Vandetanib is a small molecule inhibitor of the vascular endothelial growth factor (VEGF) receptor, epidermal growth factor (EGF) receptor, and the RET tyrosine kinase (218). In a randomized controlled clinical trial,

patients treated with vandetanib experienced a median progression-free survival of 22.6 months compared to 16.4 months in patients treated with placebo (216).

Acknowledgments

This study was supported by NIH T32 CA009614-23.

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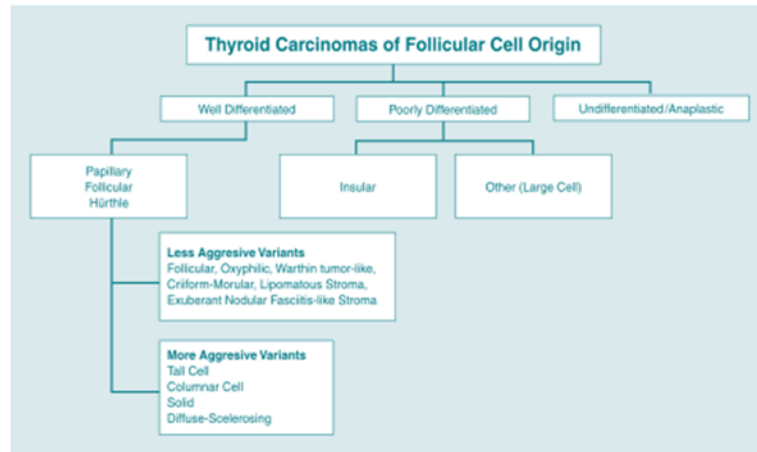


Figure 1.
Classification of Follicular Cell Derived Tumors

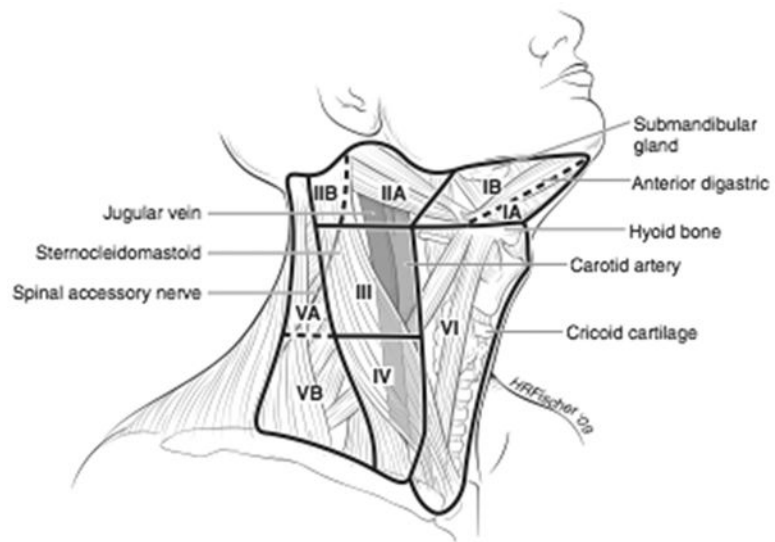


Figure 2.
Lymph Node Compartments of the Neck

Table 1

Prognostic Schemes for Differentiated Thyroid Cancer

Prognostic Variable	EORTC (1979)	AGES (1987)	AMES (1988)	MACIS (1993)	OSU (1994)	MSKCC (1995)	NTCTCS (1998)	Clinical Class (1990)
Patient Factors								
Age	X	X	X	X	-	X	X	
Sex	X	-	X	-	-	-	-	
Tumor Factors								
Size	-	X	X	X	X	X	X	
Multicentricity	-	X	-	-	X	-	X	
Grade	-	X	-	-	-	X	-	
Histology	X	Y	X	Y	-	X	X	X
ETE	X	X	X	X	X	X	X	
+ LN's	-	-	-	-	X	X	X	X
Distant mets	X	X	X	X	X	X	X	X
Operative Factors								
Incomplete Resection	-	-	-	X	-	-	-	

X = variable used in staging system

Y = variable used in staging system designed for PTC only

- = variable not used in staging system

EORTC = European Organization for Research on Treatment of Cancer

AGES = patient age, histologic grade of the tumor, tumor extent (extrathyroidal extension), and size of primary tumor

AMES = patient age, presence of distant metastases, extent and size of primary tumor

MACIS = metastasis, patient age, completeness of resection, local invasion, and tumor size

OSU = Ohio State University

MSKCC = Memorial Sloan-Kettering Cancer Center

NTCTCS = National Thyroid Cancer Treatment Cooperative Study

Table 2American Joint Committee on Cancer (AJCC) TNM Staging for Thyroid Cancer⁺

Primary Tumor (T)	
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 perithyroid soft tissues)
T4a *	Tumor of any size extending beyond thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4b	Tumor invades prevertebral fascia or incases carotid artery or mediastinal vessels
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph nodes metastasis
N1a	Metastasis to Level VI lymph nodes
N1b	Metastasis to unilateral, bilateral, or contralateral cervical [levels I, II, III, IV, or V] or superior mediastinal (level VII) lymph nodes
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
STAGE GROUPING:	
Differentiated Cancers^{&} < 45 years old	
Stage I	Any T Any N M0
Stage II	Any T Any N M1
Differentiated Cancer ≥ 45 years old	
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0
	T1 N1a M0
	T2 N1a M0
	T3 N1a M0
Stage IVA	T4a N0 M0
	T4a N1a M0
	T1 N1b M0
	T2 N1b M0
	T3 N1b M0
	T4a N1b M0

Stage IVB T4b Any N M0
Stage IVC Any T Any N M1

Medullary Carcinoma

Stage I T1 N0 M0
Stage II T2 N0 M0
 T3 N0 M0
Stage III T1 N1a M0
 T2 N1a M0
 T3 N1a M0
Stage IVA T4a N0 M0
 T4a N1a M0
 T1 N1b M0
 T2 N1b M0
 T3 N1b M0
 T4a N1b M0
Stage IVB T4b Any N M0
Stage IVC Any T Any N M1

Anaplastic Carcinomas[§]

Stage IVA T4a Any N M0
Stage IVB T4b Any N M0
Stage IVC Any T Any N M1

⁺ AJCC TNM Staging Manual, 7th ed., 2010

^{*} All anaplastic tumors are considered T4 tumors

[&] Papillary and follicular carcinomas are considered *differentiated thyroid cancers*

[§] All anaplastic carcinomas are considered Stage IV

Table 3

The Bethesda System for Thyroid Cytopathology

Category	Risk of Malignancy (%)	Recommended Management
Nondiagnostic or Unsatisfactory	1–4	Repeat FNA with U/S guidance
Benign	0–3	Clinical follow-up
Atypia of Undetermined Significance (AUS) or Follicular Lesion of Undetermined Significance (FLUS)	5–15	Repeat FNA *
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

FNA, fine needle aspiration

U/S, ultrasound

* Lobectomy can also be considered depending on clinical or sonographic characteristics

Table 4Frequency of *RET* mutations associated with familial *RET* syndromes

Exon	Codon	Amino Acid (wild type→mutant)	Phenotype	Frequency (%), MEN2 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			
	618	Cys-Trp	MEN 2A/FMTC	3–5	
		Cys-Ser			
		Cys-Arg			
		Cys-Gly			
	620	Cys-Tyr	MEN 2A/FMTC	6–8	
		Cys-Ser			
		Cys-Arg			
Cys-Gly					
Cys-Tyr					
Cys-Trp					
11	630	Cys-Tyr	MEN 2A/FMTC	0–1	
		Cys-Ser			
		Cys-Phe			
	634	Cys-Ser	MEN 2A	80–90	
		Cys-Arg			
		Cys-Gly	MEN 2A/FMTC	80–90	
		Cys-Tyr			
		Cys-Ser			
		Cys-Phe			
	635,636,637,638	Ins-Thr-Ser-Cys-Ala	MEN 2A/FMTC	Rare	
		637-638-639			Ins-Cys-Arg-Thr
		648			Val-Ile
	13	768	Glu-Asp	MEN 2A/FMTC	Rare
790		Leu-Phe			
791		Tyr-Phe			

Exon	Codon	Amino Acid (wild type→mutant)	Phenotype	Frequency (%), MEN2 cases
14	804	Val-Met	MEN 2A/FMTC	0-1
		Val-Leu		
15	883	Ala-Phe	MEN 2B	Rare
	891	Ser-Ala	MEN 2A/FMTC	
16	918	Met-Thr	MEN 2B	3-5
	922	Ser-Tyr	MEN 2B	Rare

Adapted from "Management of Medullary Thyroid Cancer" in *The Handbook of Endocrine Surgery* (RS Sippel, and H Chen, eds.)

Table 5

‘Codon-directed’ timing of surgery based on *ret* mutations associated with hereditary MTC

Risk level for MTC	ATA Risk level	Codon mutation	Age of prophylactic surgery
Level 3 (highest)	D	883	Within the first 6 months of life (preferably in the first year)
	D	918	
	D	922	
Level 2 (higher)	B	611	By age 5
	B	618	
	B	620	
	B/C	634	
Level 1 (high)	B	609	By age 5–10
	B	630	
	A	768	
	A	790	
	A	791	
	A	804	
	A	891	

Adapted from “Management of Medullary Thyroid Cancer” in *The Handbook of Endocrine Surgery* (RS Sippel, and H Chen, eds.)