Introduction

In this monograph, a comprehensive review of thyroid cancer is presented. This represents the work of 4 endocrine surgeons all of whom have been or are currently affiliated with Case Western Reserve University School of Medicine and have important roots in Cleveland, Ohio. This monograph is a case-based review of primary malignancies of the thyroid gland, in which the clinical presentation, diagnosis, treatment, follow-up, outcome, and new advancements are emphasized.

Epidemiology of differentiated thyroid cancer (DTC)

DTC accounts for approximately 2% of all malignancies in the United States. The incidence of thyroid cancer for all racial and ethnic groups in the United States from 2004-2008 was 5.5 per 100,000 in men and 16.3 per 100,000 in women. The American Cancer Society has reported a dramatic increase in the incidence of thyroid cancer since the mid-1990s. Since 2004, the incidence has increased 5.5% per year in men and 6.6% per year in women, which represents the largest annual percentage increase of any cancer in both men and women.

The American Cancer Society estimated that 56,460 new cases of thyroid cancer would be diagnosed in the United States in 2012; this includes 43,210 women and 13,250 men. It is estimated that there would be 1780 thyroid cancer-related deaths, for an overall 3% mortality from thyroid cancer. From 2004-2008, there has also been a small increase in death rate from thyroid cancer from 0.47-0.50 per 100,000 in men and from 0.47-0.52 in women, in contrast to a reduction in mortality for most other solid tumors.

Thyroid cancer has become the fifth most common cancer in women in the United States. Thyroid cancer is the second most common cause of cancer in women in the Gulf Cooperation Council countries of Saudi Arabia, Kuwait, Qatar, and United Arab Emirates and the most common cause of cancer in women in Korea. The increased incidence in thyroid cancer has also been observed elsewhere including Europe, Asia, South America, and Australia. These statistics are a reflection of the dramatic increase in the incidence of thyroid cancer that has been observed for the last 4 decades.

The incidence has increased for tumors of all sizes and for all stages. The largest increase in incidence, however, has been in cancers smaller than 1 cm and it has been suggested that the increased incidence in thyroid cancer is related to the increased use of office-based ultrasound and detection of smaller cancers. Additionally, ultrasound-guided
fine-needle aspiration (FNA) biopsy of nonpalpable nodules, more frequent use of total thyroidectomy for treatment of benign disease, and increased pathologic scrutiny with more extensive thyroid sectioning and histologic examination are likely contributory factors. However, the increased incidence cannot solely be attributed to increased detection because the incidence rates of larger and more advanced tumors would be expected to decrease if cancers were being detected earlier.\textsuperscript{6} Radiation exposure, from the increased use of computed tomography (CT) and other diagnostic x-rays, may also be an important contributor to the increased incidence in thyroid cancer. Obesity, dietary nitrosamines, polybrominated diphenyl ethers, or flame retardants found in plastics, electrical appliances, carpets, and upholstery have also been suggested as potential contributory factors in the increased incidence of thyroid cancer.\textsuperscript{9,10}

DTC occurs more commonly in women. It is estimated that 3 out of every 4 cases of thyroid cancer occur in women.\textsuperscript{2} The lifetime risk of developing thyroid cancer in the United States has been reported to be 0.84\% in women and 0.30\% in men.\textsuperscript{11} Most women who develop DTC are 40-50 years of age and most men are 50-60 years of age.

**Papillary thyroid cancer (PTC)**

**Case**

A 23-year-old woman was incidentally found to have enlarged thyroid gland on a work-related physical examination. She denied any symptoms of hypothyroidism or hyperthyroidism. She had no compressive symptoms, prior history of head or neck radiation, or family medical history of thyroid cancer or other endocrinopathies. She had no active medical problems and was taking no medications. She smoked 3 cigarettes per day.

On physical examination she was noted to have a 3 cm hard mass in the left lobe of the thyroid gland. She had no palpable dominant nodule in the right lobe of her thyroid gland. Her trachea was midline. She was noted to have large bulky lymphadenopathy involving the left lateral neck, corresponding to lymph nodes in levels II-IV. The rest of her physical examination was normal.

She had a serum thyroid-stimulating hormone (TSH) level of 2.08 $\mu$IU/mL. An ultrasound examination revealed a heterogeneous solid nodule in the left lobe of the thyroid gland with ill-defined margins and increased vascular flow (Fig 1). The right lobe of the thyroid gland was normal. Adjacent to the left lobe of the thyroid gland were multiple enlarged heterogeneous lymph nodes in the left internal jugular chain that demonstrated a rounded appearance with microcalcifications and absence of normal echogenic hilum (Fig 2). An FNA

![Fig. 1. (A) Large heterogeneous, hypoechoic nodule with irregular borders that is taller than it is wide. Final pathology revealed a papillary thyroid cancer. (B) Doppler ultrasound study demonstrating increased intranodular vascularity. T, trachea; IJV, internal jugular vein; CA, carotid artery. (Color version of figure is available online.)](image-url)
biopsy of the nodule in the left lobe of thyroid gland and one of the large lymph nodes in the lateral neck was completed. Cytologic analysis of both FNA biopsy specimens revealed PTC. The patient underwent a total thyroidectomy with a central compartment neck dissection, bilateral transcervical thymectomy, autotransplantation of the right and left inferior parathyroid glands into the right sternocleidomastoid muscle, and a left lateral compartment neck dissection with removal of lymph nodes from level IIA, III, IV, and VB. The final pathology revealed a 3.9-cm well-differentiated, encapsulated, classic PTC involving the left lobe of the thyroid gland with 11 of 16 lymph nodes from the central neck and 20 of 30 lymph nodes from the lateral neck positive for metastatic PTC (level IIA, 5/8; level III, 9/10; level IV, 5/8; and level VB, 2/4). On the first postoperative day, her serum calcium level was 7.8 mg/dL and intact parathyroid hormone level was 16.7 pg/mL. She was treated with calcium carbonate and calcitriol for 2 weeks, after which her serum calcium normalized. She was started on a suppressive dose of levothyroxine with plans to keep her serum TSH level less than 0.1 µIU/mL. Her serum calcium level normalized and calcium carbonate and calcitriol were discontinued.

**Introduction**

The increase in incidence of thyroid cancer is attributed primarily to an increase in incidence of PTC, whereas the incidences of follicular, Hurthle cell, anaplastic, and medullary cancers have remained stable. PTC is the most common type of thyroid cancer, accounting for approximately 85% of all thyroid cancers. In a 2010 study by Cramer and colleagues, analysis of thyroid cancer incidence using Surveillance, Epidemiology, and End Results data showed that papillary microcarcinoma (<1 cm) increased 19.3% per year from 1973-2006. Although this was the highest increase among all PTCs, there was also an increase in incidence of tumors larger than 1 cm: 12.3% per year for tumors 1-2 cm; 10.3% per year for tumors 2.1-5 cm; and 12.0% per year for tumors larger than 5 cm.

**Risk factors**

In patients who present with a thyroid nodule, multiple factors are associated with an increased likelihood of malignancy: age less than 15 or older than 45 years, male gender, a history of head or neck irradiation, and a family history of thyroid cancer in a first-degree relative. In patients with a thyroid nodule that is firm and fixed on physical examination or associated with cervical or supraclavicular lymphadenopathy or vocal cord paralysis, it is more likely to be cancer. Higher serum TSH levels have also been associated with a greater risk of malignancy.
Radiation exposure

The most important risk factor for the development of DTC is a history of radiation exposure during childhood and adolescence. This includes radiation treatment for benign diseases such as facial acne or hirsutism, thymic enlargement, enlarged tonsils and adenoids, tinea capitus, and tuberculous cervical adenitis. Treatment of childhood malignancies including leukemia, Hodgkin's and non-Hodgkin's lymphoma, and central nervous system cancer, as well radiation exposure from atomic bombings and radioactive fallout from atomic weapons testing and nuclear power accidents, have been associated with thyroid cancer. Children who survived the atomic bombings of Hiroshima and Nagasaki continue to have a higher-than-normal risk of thyroid cancer more than 50 years after radiation exposure.

The practice of using ionizing radiation for treatment for benign head and neck disease ended in the late 1950s and early 1960s because of the recognition of its carcinogenic effect on the thyroid. The latency period for development of thyroid cancer varies from 20-50 years and PTC is the predominant histologic type. Patients with a thyroid nodule and a history of head or neck irradiation have an approximate 40% incidence of carcinoma and the cancer may be found outside of the index nodule. In a Childhood Cancer Survivor Study, 12,547 survivors of childhood cancer who received head and neck radiation as part of cancer treatment between 1970 and 1986 were followed up until 2005 and 119 survivors were found to have thyroid cancer. The thyroid cancer risk increased linearly with radiation dose up to approximately 20 Gy, where the relative risk peaked at 15-fold. Radiation exposure in younger patients (<5 years), females, and time since exposure (≥25 years) were found to be significant modifiers for radiation associated thyroid cancer.

Family history of thyroid cancer

Patients with a family history of thyroid cancer have a higher incidence of thyroid cancer. Familial nonmedullary thyroid cancer (FNMTCL) accounts for approximately 5% of all thyroid cancers. FNMTCL is defined as DTC occurring in 2 or more first-degree relatives. PTC is the most common histologic type of FNMTCL; Hurthle cell and follicular types are much less common. Compared with sporadic PTC, patients with FNMTCL are younger at presentation and are more likely to have multicentric disease, extrathyroidal tumor invasion, and lymph node metastases. They are also more likely to develop recurrent disease and have a lower disease-free survival. However, not all studies have found FNMTCL to be more aggressive than sporadic PTC.

PTC may occur as part of a familial cancer syndrome (Table 1). Patients with one of the familial cancer syndromes have a significantly increased risk of developing DTC. A neck ultrasound screening program instituted at the Cleveland Clinic Foundation for patients diagnosed with familial adenomatous polyposis (FAP) demonstrated a 5% incidence of thyroid cancer compared with a 0.2% incidence in the general population, resulting in the recommendation for routine thyroid surveillance of patients with FAP. Approximately two-thirds of patients with Cowden disease (PTEN hamartoma tumor syndrome) would develop a thyroid neoplasm, which is most commonly a follicular tumor. The lifetime risk of developing thyroid cancer is 35% and follicular cancer is the most common histologic type. Patients with the PTEN mutation and thyroid cancer are younger, with a mean age of 30 years. Patients with Werner syndrome primarily develop follicular cancer, but PTC may also occur. Approximately 15% of patients with Carney complex develop PTC or follicular thyroid cancer (FC).

The causative gene for nonsyndromic FNMTCL has not been identified. Its mode of inheritance is autosomal dominant with incomplete penetrance. In patients without a known familial syndrome, the risk of thyroid cancer risk is increased 10-fold when a first-degree relative has thyroid cancer. Hemminki and colleagues documented a standard incidence ratio of 3.2 for PTC when a parent had PTC, 6.2 with an affected sibling, and 11.9 when the affected sibling is a sister.
Clinical presentation and diagnosis

In the past, thyroid cancer was most commonly diagnosed as a result of palpable thyroid nodule detected by the patient or on physical examination performed by a healthcare provider. However, with increased recognition of risk factors for thyroid cancer as well as technologic advancements in ultrasonography and FNA biopsy technique, thyroid cancers are being detected even when they are not palpable. Clinically unsuspected thyroid nodules and cancers are being detected on imaging studies or during operations for reasons unrelated to the thyroid gland.

The typical patient with PTC is a 40- to 50-year-old woman. Male patients and patients at the extremes of age are less likely to be affected, and may have more aggressive histologic variants of PTC. Incidentally discovered PTC, found on imaging studies obtained for reasons other than thyroid disease, is increasing.

Thyroid nodules with focal increase in 18F-fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET) imaging have a 33% risk of thyroid cancer.28 A firm, fixed, or rapidly enlarging thyroid nodule, hoarseness or vocal cord paralysis, and associated cervical lymphadenopathy are clinical features raising suspicion for thyroid cancer. Various sonographic characteristics of a thyroid nodule have been associated with high likelihood of thyroid cancer (Fig 1), including hypoechogenicity, increased intranodular vascularity, irregular infiltrative borders, microcalcifications, and an absent halo sign. Thyroid nodules larger than 1 cm in size or smaller nodules with suspicious sonographic features should be evaluated with FNA biopsy.

FNA biopsy is the gold standard for diagnostic evaluation of a patient with a thyroid nodule. Cytologic features of PTC include large monolayer sheets of follicular epithelial cells in a papillary configuration with large irregular nuclei containing fine, powdery chromatin and nuclear inclusions and grooves (Fig 3). Psammoma bodies may be present, and when seen on cytologic examination of a thyroid nodule, are highly suggestive of PTC. The false-positive rate for an FNA biopsy diagnosis of PTC is 1%-2%.29 As a result, definitive surgical therapy is recommended for patients with an FNA biopsy diagnosis of PTC. Patients with PTC may also have an FNA biopsy that is interpreted as suspicious for PTC, for which rates of PTC have been reported to vary from 40%-82%,30 and are best managed with thyroid lobectomy, isthmusectomy, frozen section examination, and total thyroidectomy when a diagnosis of PTC is confirmed histologically.30-32 Patients with a follicular variant (FV) of PTC may have an FNA biopsy consistent with a follicular neoplasm. A thyroid lobectomy and isthmusectomy is recommended for patients with a thyroid nodule and an FNA biopsy diagnosis of follicular neoplasm and completion thyroidectomy for a final diagnosis of PTC.
The evaluation of patients with a thyroid nodule includes a screening of the serum TSH level to evaluate the functional status of the thyroid gland. Higher serum TSH levels have been shown to be associated with a higher risk of thyroid cancer.\(^{13,33-35}\) It has also been proposed that higher serum TSH levels may be associated with a worse prognosis\(^{36,37}\) in patients with thyroid cancer, but this would require further investigation using longitudinal studies.

Once a diagnosis of PTC is made, an ultrasound of the neck is obtained to evaluate the central and lateral neck for abnormal lymph nodes. Lymph node metastases from PTC can be detected on ultrasound in up to 50% of patients.\(^{38,39}\) Microcalcifications, cystic change, loss of the fatty hilum, and a rounded rather than an oval contour are all features seen on ultrasound that raise suspicion for a metastatic lymph node (Table 2). An abnormal lymph node should be biopsied for appropriate surgical planning.

Preoperative laryngoscopic examination is important in patients with a diagnosis of thyroid cancer because the status of the vocal cords affects how a cancer that is invading the recurrent laryngeal nerve is managed. Besides the strap muscles, the recurrent laryngeal nerve is the most common site involved in local invasion from DTC. Resection of the recurrent laryngeal nerve is recommended when there is tumor invasion and a documented paralysis of the vocal cord. When the vocal cord is functioning, the tumor should be shaved from the recurrent laryngeal nerve to preserve its function.

**Surgical therapy**

There are no prospective randomized studies evaluating the appropriate extent of thyroidectomy for PTC. Most recommendations for the extent of thyroidectomy for PTC are

---

**Table 2**

Sonographic features raising suspicion for a metastatic lymph node.

<table>
<thead>
<tr>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter (&gt; 1) cm</td>
</tr>
<tr>
<td>Loss of the normal fatty hilum</td>
</tr>
<tr>
<td>Irregular, rounded contour with long axis to short axis ratio (&lt; 1.5)</td>
</tr>
<tr>
<td>Heterogeneous echogenicity</td>
</tr>
<tr>
<td>Microcalcifications</td>
</tr>
<tr>
<td>Hypervascularity</td>
</tr>
</tbody>
</table>
based on expert opinion or large patient cohorts that have been treated in a nonrandomized fashion. One of the major advances in the management of PTC has been the categorization of patients into low- and high-risk groups based on well-defined prognostic factors, including age, tumor size, tumor differentiation, local invasion, and distant metastases (Table 3). Shaha and colleagues further refined the risk group definition by identifying an intermediate-risk group consisting of patients younger than 45 years of age with high-risk tumors and patients older than 45 years of age with low-risk tumors. Risk group definition is important for estimation of recurrence and mortality from DTC and for determining the extent of thyroidectomy. Approximately 10%-20% of patients with PTC are at a high risk for recurrence and mortality. Cady reported a 59% recurrence rate and 46% mortality rate for high-risk DTC.41 Because of the high risk of recurrence and mortality, total thyroidectomy is a uniformly accepted therapy for high-risk PTC. The treatment of low-risk PTC is more controversial. The National Comprehensive Cancer Network guidelines have proposed thyroid lobectomy as an alternative to total thyroidectomy for low-risk PTC, but this may not be the optimal therapy.42

Most experts and published guidelines recommend total thyroidectomy for all patients with PTC greater than or equal to 1 cm in size.43,44 Total thyroidectomy is also recommended for patients with PTC smaller than 1 cm in size when there is nodular disease involving the contralateral lobe, regional, or distant metastases, a personal history of head and neck radiation, or a family history of thyroid cancer. The rationale for total thyroidectomy in patients with PTC is to remove multicentric disease, which is present in 30%-80% of patients. Total thyroidectomy is associated with the lowest incidence of local and regional recurrence.45

Bilimora and colleagues reviewed the data from more than 52,000 patients with PTC from the National Cancer Data Base and, adjusting for age, lymph node status, distant metastases, radioiodine use, and year of diagnosis, reported a significantly lower recurrence rate and a higher survival rate for patients with PTC who underwent total thyroidectomy vs less than total thyroidectomy.47 Improved survival and lower recurrence rates with total or near-total thyroidectomy have also been demonstrated in other centers.46,48,49 Other advantages of total thyroidectomy are that it optimizes the use of serum thyroglobulin (Tg) for detection of recurrent cancer and the use of radioiodine for imaging and treatment of metastatic disease and it eliminates anaplastic dedifferentiation, which may occur in up to 1% of DTCs. Thyroid lobectomy is best reserved for PTC smaller than 1 cm when it is unifocal without metastasis or aggressive histologic features.

Cady, using the “age, metastases, extent, and size (AMES)” prognostic scheme for classification of DTC, reported 89% of patients with DTC were in a low-risk group and after a mean 20-year follow-up had a 7.7% recurrence rate and a 1.8% mortality rate compared with 11% in the high-risk group who had a 59% recurrence rate and 46% mortality rate.41 Shaha and colleagues, in a review of 1038 patients with DTC treated at Memorial Sloan Kettering Cancer Center with a mean 20-year follow-up, reported that 39% of patients were in the low-risk group and that they had a 13% recurrence rate, a 2% rate of distant metastases, and mortality of 1% compared with 22% of patients in the high-risk group who had a recurrence rate of 50%, a 34%

<table>
<thead>
<tr>
<th>Low risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women &lt; 50 y</td>
<td>Women ≥ 50 y</td>
</tr>
<tr>
<td>Men &lt; 40 y</td>
<td>Men ≥ 40 y</td>
</tr>
<tr>
<td>Well-differentiated tumor</td>
<td>Poorly differentiated or aggressive variants (tall cell columnar and oxyphilic)</td>
</tr>
<tr>
<td>Tumor &lt; 4 cm</td>
<td>Tumor ≥ 4 cm</td>
</tr>
<tr>
<td>Tumor confined to thyroid</td>
<td>Local invasion</td>
</tr>
<tr>
<td>No distant metastases</td>
<td>Distant metastases</td>
</tr>
</tbody>
</table>

AMES, age, metastases, extent, and size.
rate of distant metastases, and a mortality rate of 33%. With only 2% of patients in the low-risk group developing distant metastases, the authors questioned the necessity for total thyroidectomy.40

Cady, Shaha, and Shah have been among the leading proponents for conservative therapy for patients with DTC in the low-risk group because most patients with low-risk DTC have an excellent long-term prognosis and the rate of complications is lower than that for total thyroidectomy. However, when total thyroidectomy can be performed with a complication rate comparable to thyroid lobectomy, it is the preferred approach for low-risk PTC. Although it may or may not be associated with an improvement in overall survival, it has been shown to substantially reduce local and regional recurrence rates. Hay and colleagues reported a reduction in local recurrence from 14%-2% and regional recurrence from 19%-6% and Mazzaferri reported a reduction in overall recurrence from 18.4%-7.1% with near-total or total thyroidectomy vs thyroid lobectomy.50

In Japan, some clinicians have opted to observe patients with papillary microcarcinoma without surgical intervention, a practice that is extremely controversial. Ito and colleagues from Japan reported their observation trial for papillary microcarcinoma in 2010 and suggested that papillary microcarcinoma without unfavorable features can be safely monitored without significant disease progression.51 In their study, papillary microcarcinoma was termed unfavorable when there was concern for invasion of the recurrent laryngeal nerve, cytologic features indicative of a tall cell, diffuse sclerosing, or poorly differentiated variant of PTC or lymph node metastases.

When a diagnosis of PTC is made after an initial thyroid lobectomy for an indeterminate, benign, or nondiagnostic FNA biopsy, the decision for a completion thyroidectomy should follow the same management principles used for patients whose diagnosis of cancer was made prior to operation. Once a decision for completion thyroidectomy is made, patients should undergo the procedure within 6 months from the diagnosis of thyroid cancer. Scheumann demonstrated that patients who were operated on within the 6-month period had significantly fewer recurrences, fewer lymph node and hematogenous metastases, and survived significantly longer than those in whom the second operation was delayed for longer than 6 months.52

Extrathyroidal tumor spread occurs in approximately 15% of patients with PTC. It is associated with higher rates of local recurrence and systemic metastases and significant reduction in survival.53,54 The strap muscles, recurrent laryngeal nerve, and trachea are the most common sites of local invasion. The esophagus and larynx are rare sites of local invasion. Patients with strap muscle invasion should be treated with an en bloc resection of the thyroid gland and the involved strap muscles. Resection of a recurrent laryngeal nerve that is invaded by tumor is performed when the nerve is nonfunctioning, as determined by laryngoscopic examination. Otherwise, the tumor should be shaved off the recurrent laryngeal nerve to preserve its function. There has been no documented case of vocal cord recovery in a patient with a paralyzed vocal cord from tumor invasion treated with incomplete tumor excision and nerve preservation.55

For patients with tracheal invasion without intraluminal involvement, removal of all gross disease by tangential shaving of the tumor from the trachea is recommended. Alternatively, a wedge of trachea may be resected en bloc when only a small segment of the anterior or lateral wall of the trachea is involved. Complete tracheal resection is reserved for patients with tumor invasion through the entire wall of the trachea with mucosal involvement.56

Similar to the management of tracheal invasion, patients with esophageal invasion confined to the muscle layers are treated with a tangential partial resection of the esophageal wall or a small full-thickness resection of the esophageal wall. The defect is closed with sutures and with or without a muscle, myofascial, or myocutaneous flap. For patients with laryngeal invasion that can be completely resected, a partial laryngectomy is performed. Total laryngectomy or laryngopharyngectomy is recommended when partial laryngectomy cannot remove all gross disease or when more than one-third of the circumference of the cricoid cartilage must be removed to achieve tumor-free margins.57
Management of lymph node metastases

Approximately 35% of patients with PTC would have macroscopic lymph node metastases and up to 80% would have microscopic lymph node metastases at the time of initial surgery.\(^{58,59}\) It is standard practice to perform an ultrasound examination of the neck for all patients with malignant cytology prior to thyroideectomy.\(^ {43}\) Identification of lymph node metastases preoperatively may result in the addition of a central and lateral compartment neck dissection at the time of thyroideectomy or both.

Clinically unsuspected lymph node and soft tissue metastases have been identified in 14%-20% of patients with DTC prior to initial surgical therapy.\(^ {60,61}\) FNA biopsy of clinically or sonographically suspicious (Table 2) lymph nodes should be performed preoperatively. Tg washings of fine-needle aspirates from suspicious lymph nodes may be helpful when a cytologic diagnosis cannot be made, particularly when there is scant cellular material.

Lymph node metastases in patients with PTC most commonly involve the lymph nodes in the central compartment of the neck (level VI). When the lateral neck is involved, it is the middle (level III) and lower (level IV) jugular lymph nodes that most commonly have metastatic disease. Younger patients and men are more likely to have cervical lymph node metastases.\(^ {62}\) The lateral neck is more likely to be involved with metastatic disease, the greater the number of central neck nodes that are involved.\(^ {63,64}\)

Patients with PTC and macroscopic lymph node metastases have higher recurrence rates.\(^ {39}\) It has also been shown that patients over 45 years of age with PTC and regional lymph node metastases have an increased mortality rate.\(^ {65,66}\) There is evidence that lymphadenectomy in patients with PTC and macroscopic lymph node metastases are associated with reduced rates of recurrence and improved survival.\(^ {39,67,68}\) The clinical significance of microscopic metastases is less clear. Routine prophylactic central compartment or lateral neck dissection for PTC has not been shown to improve survival.

Patients with macroscopic lymph node metastases in the central neck should undergo a therapeutic central compartment neck dissection. Patients with microscopic lymph node metastases are treated with radioiodine. It is important to confirm that an enlarged or abnormal lymph node contains metastatic disease either with a preoperative FNA biopsy or with an intraoperative frozen section examination. Patients with PTC and concomitant Hashimoto thyroiditis may have benign reactive lymph nodes, which may be mistaken for metastatic disease, underscoring the importance of confirming metastatic disease prior to performing a compartment-oriented neck dissection.

A central compartment neck dissection consists of removal of all nodal and fibrofatty tissue between the common carotid arteries from the hyoid bone superiorly to the innominate artery inferiorly. The level VI (prelaryngeal, pretracheal, and paratracheal) and level VII (anterior mediastinal) lymph nodes are removed in a central compartment neck dissection (Fig 4). It is difficult to preserve the blood supply to the inferior parathyroid glands when performing a central compartment neck dissection. As a result, it is a good routine practice to autotransplant the inferior parathyroid glands into the sternocleidomastoid muscle to reduce the risk of permanent hypoparathyroidism.

Whether or not to perform a prophylactic central compartment neck dissection for patients with PTC is controversial. A prophylactic central compartment neck dissection is defined as a compartment-oriented level VI dissection performed in a patient without evidence of lymph node metastases on preoperative physical examination, imaging studies, or intraoperative evaluation. Occult micrometastases occur in 31%-62% of patients with PTC,\(^ {59,70}\) yet most micrometastases remain dormant and rarely become clinically significant. Recurrence in the central neck occurs in approximately 2%-3% of patients with clinically node-negative PTC larger than 1 cm who underwent thyroidectomy alone or thyroidectomy and prophylactic central compartment neck dissection.\(^ {71}\) Locoregional recurrence has been reported to be equivalent in patients with or without microscopic lymph node metastases.\(^ {69}\)

A meta-analysis of retrospective studies examining the outcome of treatment of 1264 patients with PTC found no significant difference in overall locoregional recurrence rates (2% vs
3.9%), central neck recurrence (1.9% vs 1.7%), or recurrence in the lateral neck (3.7% vs 3.8%), whether or not a prophylactic central compartment neck dissection was performed. Prophylactic central compartment neck dissection has been advocated for accurate staging of patients and more selective use of adjuvant radioiodine. This must be balanced with the potential increased risk of permanent hypoparathyroidism that may occur as a result of the addition of a central compartment neck dissection.

For patients with thyroid cancer and macroscopic lymph node metastases in the lateral neck, a selective compartment-oriented neck dissection is the preferred approach. In the past, a modified neck dissection, defined as removal of all lymph nodes from levels I-V, with preservation of the sternocleidomastoid muscle, internal jugular vein, and spinal accessory nerve, was advocated. However, it has subsequently been shown that there is no survival advantage to performing a classic modified neck dissection vs a selective neck dissection. A selective neck dissection is defined as removal of fewer than all the nodal basins from levels I-V. We recommend performing a selective compartment-oriented neck dissection, consisting of removal of lymph nodes from levels IIA, III, IV, and VB, for patients with DTC and macroscopic lymph node metastases in the lateral neck (Fig 5). Modification of the extent of dissection is based on preoperative ultrasound findings. Excision of enlarged lymph nodes only, known as “berry picking,” is not advocated because of a higher recurrence rate.

Level I lymph nodes, which consist of the submental (IA) and submandibular (IB) lymph nodes, are rarely involved with metastatic thyroid cancer and are not routinely removed. Because of the lower risk for metastases, lymph nodes superior to the spinal accessory nerve in level IIB and lymph nodes in the posterior cervical triangle along the spinal accessory nerve superior to the horizontal plane extending from the cricoid cartilage to the convergence of the trapezius and sternocleidomastoid muscle (level VA) are also not routinely removed unless they are identified as abnormal by ultrasound or intraoperative evaluation. Avoiding
The dissection of level IIA and VB compartments helps to reduce injury to the spinal accessory nerve. Level IIA is bounded superiorly by the base of the skull, inferiorly by a horizontal plane defined by the hyoid bone, anteriorly by the posterior edge of the submandibular gland, and posteriorly by the spinal accessory nerve. The lymph nodes in level IIA correspond to lymph nodes along the upper third of the internal jugular vein. Level III and IV lymph nodes correspond to the lymph nodes along the middle and lower thirds of the internal jugular vein. The boundaries of level III are a horizontal plane corresponding to the hyoid bone superiorly, a horizontal plane defined by the cricoid cartilage inferiorly, anteriorly by the medial border of the carotid artery, and posteriorly by the posterior border of the sternocleidomastoid muscle. Level IV is bounded superiorly by the horizontal plane defined by the cricoid cartilage, inferiorly by the clavicle, anteriorly by the medial border of the carotid artery, and posteriorly by the posterior border of the sternocleidomastoid muscle. Level VB corresponds to the inferior aspect of the posterior cervical triangle and contains the transverse cervical and supraclavicular lymph nodes. Level VB is bounded superiorly by a horizontal plane extending from the cricoid cartilage to the trapezius muscle, inferiorly to the clavicle, anteriorly by the posterior border of the sternocleidomastoid muscle, and posteriorly by the anterior border of the trapezius muscle (Fig 5).
Surgical site infection
Bleeding
Chylous fistula
Nerve injury:
  Dissection level I: hypoglossal, lingual, and marginal mandibular
  Dissection levels II-V: spinal accessory, greater auricular, cervical sensory roots, phrenic, cervical sympathetic trunk, vagus, and brachial plexus

Significant complications may occur from a lateral neck dissection (Table 4). Nerve injury is the most important complication. The spinal accessory nerve may be transected or injured from traction or cautery. Patients may experience shoulder pain and weakness with difficulty in raising their arm, a shoulder droop, or a winged scapula. The most common complication from a lateral neck dissection is numbness of the lateral neck and ear resulting from injury to the greater auricular nerve and sacrifice of the sensory nerve roots.

Horner syndrome, manifested by ipsilateral ptosis, miosis, and anhidrosis, may result from injury to the cervical sympathetic chain with dissection posteriomedial to the carotid artery. Phrenic nerve injury may result in paresis or paralysis of the hemidiaphragm and reduction in lung capacity. Hypoglossal, lingual, and marginal mandibular nerve injury may occur with dissection of level I lymph nodes in the submandibular and submental triangles. Injury to the vagus nerve and brachial plexus are uncommon. Injury to the vagus nerve may affect the recurrent laryngeal nerve and result in vocal cord paralysis, or the superior laryngeal nerve and result in loss of supraglottic sensation with aspiration. Injury to the brachial plexus results in pain, numbness, and weakness that can involve the shoulder, arm, or hand. Chylous fistula may occur with interruption of the thoracic duct, which empties into the internal jugular vein at its junction with the subclavian vein in the left neck. It also may occur from interruption of the lymphatic duct in the right neck.

Surgical pathology and histologic variants of PTC

Most often PTC is a well-circumscribed, unencapsulated solid gray-white mass with irregular and infiltrative borders. Architectural features that are characteristic of PTC include a papillary growth pattern, elongated-appearing follicles, psammoma bodies, and intratumoral fibrosis. “Orphan Annie eyes” or nuclear clearing, a classic cytomorphologic change associated with PTC, occurs as a result of fixation artifact.

Several histologic variants of PTC are recognized based on distinct architectural and cytomorphologic features. Architectural subtypes of PTC include classic, follicular, diffuse sclerosing, and cribiform-morular; whereas cytomorphologic subtypes include classic, tall cell, columnar, clear cell, and oncocytic. Tall cell, diffuse sclerosing, and cribiform-morular are more aggressive variants of PTC.

The FV of PTC is second only to the classic variant of PTC, accounting for approximately 15%-35% of cases. It is characterized by an almost exclusive follicular pattern of growth with many of the features of classic PTC, including oval nuclei, nuclear crowding with a lack of follicular polarity, clear or pale nuclear chromatin, prominent nuclear grooves, and psammoma bodies. However, there is no consensus on the exact histologic characterization of FV PTC. There has been an increase in the incidence of the FV of PTC as a result of reclassification of lesions once felt to be FC.

Lin and colleagues reported similar 10- and 15-year survival for classic and FV PTC. FV PTC has a significantly lower rate of nodal involvement than the classic type. Most patients with FV PTC have a well-encapsulated tumor. Nonencapsulated, diffuse, infiltrative FV PTC is less common and is more likely to have nodal metastases, extrathyroidal extension, positive margins, and marked intratumoral fibrosis.
The tall cell variant (TCV) of PTC accounts for approximately 7%-14% of all PTCs.\textsuperscript{80} The TCV consists of follicular epithelial cells whose height is twice their width with nuclear features characteristic of PTC and eosinophilic cytoplasm owing to the presence of increased mitochondria.\textsuperscript{77,81} Tall cells account for more than 50% of tumor cells. Compared with classic PTC, the TCV is more often associated with metastases, is less likely to concentrate radioiodine, and has a higher rate of recurrence and mortality. Factors that may contribute to a worse prognosis include older age at presentation, larger tumor size, and a higher incidence of extrathyroidal extension.\textsuperscript{82} Approximately 80% of patients with the TCV of PTC have BRAF mutations.\textsuperscript{83-85}

Diffuse sclerosing variant (DSV) of PTC is rare with an estimated incidence of 0.75%-5.3%.\textsuperscript{86} Clinically, DSV of PTC can be confused with Hashimoto thyroiditis because of the diffuse thyroid involvement and the presence of serum anti-Tg antibody. Pathologically, it is characterized by diffuse involvement of the thyroid parenchyma, sclerosis, abundant psammoma bodies, prominent squamous metaplasia, and extensive lymphatic permeation. Patients with DSV are usually younger at presentation, have larger tumor size, and higher incidence of lymph node metastases. In a case series of 22 patients with DSV of PTC, 82% had extrathyroidal extension and lymph node metastases. Although biologically more aggressive, the overall survival is not significantly different compared with classic PTC.\textsuperscript{86} This result was reflected similarly in other studies.\textsuperscript{87,88}

The cribiform-morular variant accounts for less than 0.1% of all PTC. It can be seen in sporadic cases but most often occurs in patients with FAP syndrome. It occurs predominantly in women in their twenties, and can precede the diagnosis of FAP. Histologically, this variant is characterized by a combination of cribiform, follicular, papillary, trabecular, solid, and spindle cell growth patterns with morular areas.\textsuperscript{89} Its peculiar morphologic features are related to the permanent activation of the WNT (wingless type) signaling pathway, with nuclear and cytoplasmic accumulation of beta-catenin.\textsuperscript{90} Because of the low number of reported cases, it is difficult to ascertain whether this variant harbors a significantly worse prognosis compared with classic PTC.

Molecular pathogenesis

Biomarkers specific for thyroid cancer have been identified that have diagnostic, therapeutic, and prognostic implications and that have advanced our understanding of the genetic basis of thyroid cancer. Activating alterations in several genes within the mitogen-activating protein kinase pathway have been identified in the majority of patients with PTC. REarranged during Transfection (RET) oncogene activation in PTC occurs by RET rearrangements when the intracellular tyrosine kinase domain of RET is coupled to the N-terminal fragment of different heterologous genes.

RET/PTC1 and RET/PTC3 are the most common gene rearrangements identified in PTC. RET rearrangements occur in 70% of radiation-induced PTC and 40% of sporadic PTC.\textsuperscript{91} The reported incidence of RET mutations in patients with PTC has decreased from 33% during the period from 1996-2000 to 17% from 2001-2005 to 9.8% from 2006-2010.\textsuperscript{92} The higher incidence found in 1996-2000 may have been related to the post-Chernobyl radioactive fallout. The decrease in incidence in RET mutations over time may be because of better education about radiation exposure and its associated risks.

A point mutation in the BRAF gene at codon 600 is the most common genetic alteration found in sporadic PTC.\textsuperscript{93} This point mutation results in a valine to glutamate alteration, leading to constitutive mitogen-activating protein kinase pathway stimulation. The BRAF V600E mutation has been detected in approximately 45% of PTC and ranges from 23%-83% depending on different cohorts.\textsuperscript{94-96} The prevalence of the BRAF V600E mutation in PTC has been documented to have progressively increased over time from 28% in 1996-2000 to 49% in 2001-2005 and 58% in 2006-2010.\textsuperscript{92} The BRAF mutation is most commonly present in the classic and TCVs of PTC. It is rarely seen in the FV of PTC, nor is it very common in radiation-induced PTC.
The BRAF mutation can also occur in thyroid lymphoma, poorly differentiated and anaplastic thyroid cancers (ATCs), and has also been identified in rare cases of benign hyperplastic nodules. It has not been identified in FC or MTC. The overall increase in the incidence of BRAF mutation may be the result of environmental factors that cause DNA point mutations. High iodine intake and air pollutants have been identified as potential sources.

Molecular testing for gene mutations has been increasingly used for diagnostic purposes, especially in the case of the patient with a thyroid nodule and an indeterminate FNA biopsy result. In a study by Nikiforov and colleagues, 470 nodules were sampled with FNA from 328 consecutive patients and were tested for BRAF, RAS, PAX8-PPARγ, and RET/PTC mutations. Thirty-two of the 470 (7%) FNA samples were positive for one of the mutations, 31 of which were confirmed to be malignant on pathologic examination. Molecular testing had a sensitivity of 62%, but when combined with cytology, the sensitivity increased to 80% with a PPV of 98%. In the 10 prospective studies performed since 2004 to test for BRAF mutations in the FNA samples, the sensitivity of BRAF in detection of malignancy ranged from 27%-83%, but the specificity was nearly 100%. Because of the high specificity, some centers have advocated initial definitive total thyroidectomy for patients with nodular thyroid disease and an indeterminate FNA biopsy when genetic testing is positive. The cost associated with molecular testing has yet to be elucidated, and whether routine molecular testing will become a routine adjunct diagnostic tool to FNA biopsy remains to be seen.

Molecular markers also have significant prognostic implications in the management of patients with PTC. The BRAF V600E mutation has been reported to be associated with a higher incidence of extrathyroidal tumor spread, lymph node and systemic metastases, and recurrence. In a study of 500 patients with PTC conducted by Lupi and colleagues, 43% of the patients tested positive for BRAF mutation. The BRAF-positive patients were older and had a higher incidence of extrathyroidal extension, nodal metastases, and multicentricity. Using multivariate analysis, Kebebew found that the BRAF mutation was independently associated with persistent and recurrent PTC. Patients with papillary microcarcinoma and a BRAF mutation had an incidence of extrathyroidal extension and lymph node metastases similar to that in patients with larger PTCs, suggesting that BRAF mutation positivity may be associated with a worse prognosis regardless of tumor size.

Not all studies have found the BRAF mutation to be a marker of more aggressive disease. Two recent reports have demonstrated a significant increase in the frequency of the BRAF mutation in patients with PTC over time without an increase in the incidence of extrathyroidal tumor spread, lymph node metastases, and node or systemic metastases. Sancisi and colleagues and others have suggested that the BRAF mutation may not be an initiating event in BRAF-positive tumors and that BRAF status alone cannot be an independent predictor of aggressive disease.

Staging, recurrence, survival, and prognosis

Postoperative staging of PTC is important for determining the need for adjuvant radioactive iodine (RAI) therapy, the degree of TSH-suppressive therapy with levothyroxine, the methods and intensity of follow-up, and prognosis. Thyroid cancer staging is based on the American Joint Committee on Cancer (AJCC) TNM staging system (Fig 6). The AJCC TNM staging is intended for prediction of death, and not for recurrence.

In a study by Hundahl and colleagues, the outcome of 42,687 patients who underwent thyroidectomy for thyroid cancer between 1985 and 1995 was determined. The majority of the patients had stage I (56.9%) or stage II disease (14.4%). Overall, patients with PTC had the best 10-year survival rate (93%) when compared with follicular (85%), Hurthle cell (76%), medullary (75%), and anaplastic (10%) cancers. Based on the seventh edition AJCC Cancer Staging system, the 5-year disease-specific survival rates for PTC are 100% for stages I and II, 93% for stage III, and 51% for stage IV.

The incorporation of patient age into the AJCC system favors patients younger than 45 years of age. Even in the presence of systemic metastases, patients younger than 45 years are
classified under stage II disease. The 1986 study of National Cancer Data Base on PTC showed a 10-year disease-specific survival of 95% for patient age less than 45 years, 85% for age 45-59 years, 65% for age 60-69 years and 47% in patients older than 70 years. However, the AJCC system appears to understage younger patients. In a recent study by Tran and colleagues, the mortality rate for patients younger than 45 years of age with stage II PTC was 11 times greater than that for patients with stage I disease. The survival of patients with stage II PTC in the less

### Regional Lymph Nodes (N)

- **NX**: Regional lymph nodes cannot be assessed.
- **N0**: No regional lymph node metastasis.
- **N1**: Regional lymph node metastasis.
  - N1a: Metastases to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes).
  - N1b: Metastases to unilateral, bilateral, or contralateral cervical (Levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (Level VII).

### Distant Metastases (M)

- **M0**: No distant metastasis.
- **M1**: Distant metastasis.

### Stage T N M

#### Medullary carcinoma (all age groups)

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T1</td>
<td>N1a</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1a</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1a</td>
<td>M0</td>
</tr>
<tr>
<td>IVA</td>
<td>T4a</td>
<td>N1a</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4b</td>
<td>Any</td>
<td>N0</td>
</tr>
<tr>
<td>IVC</td>
<td>Any</td>
<td>T</td>
<td>Any</td>
</tr>
</tbody>
</table>

#### Anaplastic carcinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVA</td>
<td>T4a</td>
<td>Any</td>
<td>N0</td>
</tr>
<tr>
<td>IVC</td>
<td>Any</td>
<td>T</td>
<td>Any</td>
</tr>
</tbody>
</table>

### Fig. 6.

Seventh edition American Joint Committee on Cancer (AJCC) tumor, lymph node, and metastases (TNM) staging system. (A) TNM staging, and (B) staging for differentiated, medullary, and anaplastic thyroid cancer (http://www.cancer.gov/cancertopics/pdq/treatment/thyroid/HealthProfessional/page3).
than 45 years old age group was less than that for older stage II patients, raising concern that the AJCC should be revised.\textsuperscript{105}

Although the long-term survival of patients with PTC is generally excellent, the recurrence rate is significant. In a 40-year follow-up study of patients with PTC, Mazzaferreri and colleagues\textsuperscript{50} reported a 35% recurrence rate. This may be an underestimation of the true rate of recurrence because only patients with positive imaging findings or a positive biopsy were included. Those with an elevated serum Tg level but no evidence of disease recurrence on imaging studies were not included. In a follow-up study, Mazzaferreri demonstrated that 50% of all recurrences occurred during the first 5 years following definitive surgical therapy and 75% within the first 10 years.\textsuperscript{50} Seventy percent of the recurrences occurred in the neck whereas the other 30% occurred in distant sites. Patients at the extremes of age had higher disease-specific recurrence rates. Patients younger than age 15 years had a recurrence rate of 50% and patients older than the age of 60 had a recurrence rate of approximately 40%.

Once distant metastases are detected in patients with PTC, approximately 50% of patients would die within 5 years. Younger patients with systemic metastases survive longer.\textsuperscript{106} Forty-nine percent of systemic metastases are to the lung, 25% to the bones, 15% to both the lung and bones, and the remaining are to miscellaneous sites, including the central nervous system, liver, adrenal glands, and skin.

The significance of gender in predicting thyroid cancer prognosis is not completely clear. Men typically present at an older age than women do. The peak age at the time of cancer diagnosis is 10-20 years later in men than in women. Men have more than twice the frequency of distant metastases and approximately 30% more regional metastases at the time of diagnosis. These differences have been largely attributed to how men and women access the healthcare systems, with men presenting at a later age and with more advanced stage tumors. So, male gender when corrected for age may not be an independent predictor of outcome for patients with PTC.

\textit{Follicular and Hurthle cell carcinoma (HCC)}

\textbf{Case}

A 58-year-old healthy woman was referred for evaluation of a right-sided thyroid nodule that was felt on routine physical examination by her primary care physician. She was asymptomatic, denied a history of head or neck irradiation and had no family history of thyroid cancer or other endocrinopathies. On physical examination, she had a firm, mobile 2-cm nodule palpable in the right lobe of the thyroid gland. Her trachea was midline and she had no abnormal cervical lymphadenopathy. The remainder of her physical examination was normal.

An ultrasound examination demonstrated a well-circumscribed, 2-cm hypoechoic nodule with smooth borders in the right lobe of the thyroid gland that was hypervascular on Doppler examination. There were no additional thyroid nodules. Cytologic analysis of an ultrasound-guided FNA biopsy was interpreted as a follicular neoplasm. Her serum TSH level was 1.50 $\mu$IU/mL.

A right thyroid lobectomy and isthmusectomy was performed. There were no abnormal lymph nodes in the central neck. The final pathology revealed a 2-cm follicular carcinoma of the thyroid gland with both capsular and vascular invasion. She underwent a completion thyroidectomy 3 months later. Pathology revealed no residual cancer. She subsequently underwent radioiodine ablation with 30 mCi of $^{131}$I. A follow-up whole-body scan (WBS) was negative. She is on levothyroxine therapy to maintain her serum TSH level between 0.1 and 0.5 $\mu$IU/mL. Twelve months after her radioiodine ablation, a TSH-stimulated Tg was less than 2.0 ng/mL.

\textit{Follicular thyroid cancer (FC)}

FC of the thyroid gland accounts for approximately 11% of all thyroid malignancies in iodine-sufficient countries and 25%-40% of thyroid malignancies in areas of
iodine deficiency. FC is the second most common form of DTC. However, the incidence of FC has decreased in the United States in relation to the elimination of iodine deficiency and the more accurate diagnosis of FV of PTC. FC occurs most commonly in the sixth decade of life, and as with all thyroid malignancies, it is more common in women than in men.

FC is usually a unifocal tumor. It more commonly spreads hematogenously. Systemic metastases are present in 10%-15% of patients at the time of diagnosis of FC. Lymph node metastases occur in fewer than 10% of patients. Overall 10-year survival for FC is 85%. In patients with distant metastases, the survival rate drops to 38%-50% at 5 years.

Diagnosis

Histologically, FC consists of a microfollicular architecture with follicles lined by cuboidal epithelial cells. A benign follicular adenoma has the same architecture. FC tends to be more cellular than a follicular adenoma with more frequent mitoses and a thicker and often irregular capsule. However, the primary features that distinguish an FC from a follicular adenoma are capsular and vascular invasion, which cannot be determined based on examination of cells from an FNA biopsy.

Most patients with FC present with a solitary thyroid nodule and the diagnostic evaluation consists of an ultrasound of the neck, a screening of serum TSH level, and a routine FNA biopsy. Patients with a thyroid nodule and an FNA biopsy interpreted as a follicular neoplasm, as in our case, have an approximately 20% likelihood of malignancy, which on final pathology can be FC, FV of PTC, or classic PTC. Although it has been suggested that age greater than 50 years, nodule size greater than 3 cm, and male gender may be associated with a higher likelihood of FC in patients with a follicular neoplasm, we and others have not found these to be independent predictors of malignancy. Ultrasound is important to characterize the nodule and also to evaluate the opposite lobe of the thyroid gland for nodular disease. In one study, the absence of intranodular blood flow using duplex Doppler ultrasonography in a follicular neoplasm was shown to have a 96% negative predictive value, making it unlikely to be FC. Patients with a low serum TSH level should undergo 123I thyroid scintigraphy to exclude a hyperfunctioning nodule, which is much less likely to be malignant, with a reported rate of malignancy of 1% or less.

Oncogene activation has been demonstrated to play an important role in the pathogenesis of FC. Point mutations in the rat sarcoma (RAS) genes, N-RAS, H-RAS, and K-RAS, occur in approximately 40% of patients with FC and are responsible for uncontrolled growth. Paired box gene 8/peroxisome proliferator–activated receptor γ (PAX8-PPARγ) gene rearrangement has been found in 29%-56% of FC and is a cause for loss of inhibitory control of growth. MicroRNAs (miR-192, miR-197, miR-328, and miR-346), which alter gene transcription and affect apoptosis and cell proliferation, have been shown to have greater expression in FC. Genetic mutations in p53, c-myc, c-fos, the TSH receptor, and the PTEN suppressor gene have also been identified as potential factors involved in the pathogenesis of FC.

Molecular profiling is being used in the diagnostic evaluation of patients with an indeterminate FNA biopsy, which include cytologic interpretations consistent with follicular or Hurthle cell neoplasm and suspicious for PTC. Recently, several mutational panels have been developed that combine multiple genetic markers to help better define the risk of malignancy for a thyroid nodule based on FNA biopsy. Nikiforov and colleagues, using a molecular profiling panel, analyzed more than 1000 patients with thyroid nodules and indeterminate cytology for BRAF V600E, N-RAS, H-RAS, K-RAS, RET/PTC 1,3, and PAX8/PPARγ mutations in FNA biopsy samples. The detection of any mutation conferred a risk of malignancy of 87%-95% whereas the risk of cancer in a mutation negative nodule was only 6%-28%. The negative predictive value in this and other studies for the absence of genetic mutations is not high enough to forgo proceeding with a diagnostic thyroid lobectomy and isthmusection.
Other investigators have used mRNA expression analysis to measure almost 250,000 transcripts in FNA samples and surgical tissues from thyroid nodules and have created a molecular classifier, known as the Veracyte Afirma, gene expression classifier. A prospective, multicenter validation of the novel molecular classifier was completed utilizing the Veracyte gene expression classifier data analysis of 167 genes in 265 indeterminate thyroid FNA biopsy samples and demonstrated a 92% sensitivity and 52% specificity based on surgical pathology. The negative predictive values for follicular lesion of undetermined significance and follicular neoplasms were 95% and 94%, respectively. The results of this study emphasize the potential of molecular classification of thyroid nodules using FNA biopsy specimens to reduce the performance of unnecessary thyroidectomy in patients with benign disease.

Another strategy has been to look for blood-based markers of malignancy that could be used preoperatively to assess the risk of malignancy in a thyroid nodule or postoperatively to assess for recurrence of cancer. TSH receptor and Tg mRNA transcripts identified in the blood have been reported to be sensitive and specific for thyroid cancer. A TSH receptor messenger RNA level greater than 1 mg/μg in the blood of a patient with a follicular neoplasm has been reported to have a 96% predictive value for cancer and an undetectable level in a patient with no abnormal sonographic findings has been reported to have a 95% predictive value for benign disease. Molecular profiling holds great promise, but will need further refinement to exclude surgery.

Because clinical factors, cytomorphologic criteria, and sonographic features cannot definitively distinguish a follicular adenoma from FC, a diagnostic thyroid lobectomy and isthmusectomy is necessary to evaluate for capsular and vascular invasion and make a definitive diagnosis of FC. Capsular invasion is defined as tumor invasion through the entire capsule of the tumor. Vascular invasion is a more reliable sign of FC and is defined as tumor penetration of a large caliber vessel within or immediately outside the capsule of the tumor. An FC may also be distinguished from a follicular adenoma on the basis of extrathyroidal tumor spread, lymph node metastases, or systemic metastases.

Pathologic evaluation is important to classify FC as minimally invasive or invasive. Minimally invasive FC has traditionally been described as an encapsulated tumor of the thyroid that exhibits microscopic penetration of the tumor capsule without evidence of vascular invasion. Invasive FC has been defined as a tumor with either gross capsular invasion, extension beyond capsule into the surrounding thyroid parenchyma or vascular invasion.

The distinction between minimally invasive and invasive FC is important because minimally invasive FC is a much less aggressive tumor with overall survival rates of 98% or greater compared with invasive FC, which has a 10-year disease-specific mortality rate of 15%-28%. D’Avanzo and colleagues classified FC into minimally invasive, moderately invasive, and widely invasive variants and reviewed the outcome after a mean 7-year follow-up in 132 patients who underwent total thyroidectomy with or without radiiodine treatment. Minimally invasive FC was defined as microscopic capsular invasion only. Moderately invasive FC was defined by the presence of angioinvasion with or without capsular invasion, and widely invasive FC was defined by extensive tumor invasion into the surrounding muscle, fat, or other structures. Twelve of the 132 patients had synchronous distant metastases and were excluded from the survival analysis. Kaplan-Meier survival curves were dramatically different for the 3 histologic variants of FC. Recurrence and death occurred in 13% and 11% of patients, respectively, with minimally invasive FC; 20% and 14% of patients, respectively, with moderately invasive FC; and 38% and 62% of patients, respectively with widely invasive FC.

In contrast to D’Avanzo and colleagues, other large centers have had no mortality from minimally invasive FC. van Heerden and colleagues followed 20 patients with minimally invasive FC for 20 years after surgical therapy and no patient developed systemic metastases or died from FC and only 1 patient developed recurrence. Sanders and Silverman followed 80 patients with minimally invasive FC for a mean period of 14 years and no patient developed a recurrence or died from FC.
Surgical therapy

Patients who present with a solitary thyroid nodule that yields a diagnosis of follicular neoplasm on FNA biopsy should undergo a thyroid lobectomy and isthmusectomy. Clinical factors, with the exception of a history of head or neck irradiation or disease involving both lobes of the thyroid gland, do not affect intraoperative decision making regarding the extent of thyroidectomy. Patients with a history of head or neck irradiation or nodular disease involving the contralateral lobe of the thyroid gland should undergo a total thyroidectomy. At operation, the opposite lobe of the thyroid gland should be palpated for concomitant nodular disease and the central neck examined for abnormal lymph nodes. Patients with FV of PTC and classic PTC may present with a follicular neoplasm and are more likely to have lymph node metastases. A central neck dissection is rarely necessary because lymph node metastases are present in fewer than 10% of patients with FC.

Intraoperative frozen section examination of a follicular neoplasm is rarely valuable because a single pathologic section has a high likelihood of missing a solitary focus of capsular or vascular invasion. Multiple sections of the nodule capsule interface are usually required to make a diagnosis of FC. In addition to sampling error, the assessment of capsular or vascular invasion by frozen section examination is limited by the variable thickness and irregularity of the capsule, blood vessel distortion, and collapse and sectioning artifact. Frozen section examination has been shown to have a high false-negative rate and is not cost effective.

If the final pathologic examination reveals a true microinvasive lesion with a solitary area of capsular invasion without angioinvasion or gross extrathyroidal extension, then no additional therapy is necessary. Because minimally invasive FC has been shown to be very indolent in its behavior, with a disease-free survival similar to that in patients with a follicular adenoma, most experts agree that thyroid lobectomy and isthmusectomy is definitive therapy. Patients can be followed up with ultrasound or physical examination or both for the development of a nodule in the remaining lobe of the thyroid gland. Patients diagnosed with invasive FC should undergo completion thyroidectomy and radioiodine ablation to optimize the use of serum Tg and whole-body scanning for detection of residual or recurrent disease. In contrast to patients with minimally invasive FC, patients with invasive FC have a 10-year disease-specific mortality rate of 15%-28%.

HCC

HCC, first described by Ewing in 1928, is the least common type of DTC, accounting for approximately 3% of all thyroid cancers. It is a follicular cell–derived tumor with TSH receptors, a functioning TSH adenylate cyclase system, and Tg immunoreactivity. HCC is composed of more than 75% Hurthle cells arranged in a follicular or trabecular pattern with capsular or vascular invasion. Hurthle cells are large polygonal cells that have pleomorphic hyperchromatic nuclei and a distinctive eosinophilic granular cytoplasm demonstrated on Hematoxylin and Eosin staining, which corresponds to an abundance of mitochondria on electron microscopy. HCC, like FC, produces Tg. In contrast to FC, HCC is a more aggressive tumor. It is more often multifocal and bilateral, more likely to have lymph node metastases and extrathyroidal tumor spread, and is less likely to concentrate radioiodine. Of all DTCs, HCC is the most likely to have metastases and has the lowest 10-year survival rate: 76%, compared with 85% for FC and 93% for PTC.

HCC generally manifests in the fifth and sixth decades. Patients with HCC most commonly present with a palpable thyroid nodule. They may also present with cervical lymphadenopathy and rarely pulmonary nodules. Approximately 10%-20% of patients would present with systemic metastases most commonly involving the lung or bones. Only 10%-25% of patients with HCC and metastases concentrate radioiodine, compared with 75% or more of patients with FC.
Diagnosis

If FNA biopsy of the thyroid nodule reveals a Hurthle cell neoplasm several potential diagnoses can be entertained, including Hashimoto thyroiditis, adenomatous hyperplasia, benign Hurthle cell nodules, Graves disease, oxyphillic variant of PTC and benign Hurthle cell adenoma, and HCC. Neoplastic disease accounts for two-thirds of the pathology in patients with an FNA biopsy consistent with a Hurthle cell neoplasm. Hurthle cell neoplasms, also known as oncocytic thyroid neoplasms, are defined as encapsulated tumors composed of at least 75% Hurthle cells. Hurthle cell neoplasms are similar to follicular neoplasms in that 20% are malignant. A benign Hurthle cell adenoma is distinguished from a HCC based on the presence of capsular or vascular invasion, lymph node metastases, and systemic metastases.

HCC, like FC, is defined by the presence of capsular or vascular invasion, and thus a diagnosis of HCC cannot be made by FNA biopsy alone. There are some data suggesting that the rate of cancer found in a Hurthle neoplasm increases with increasing age, male gender, and increasing tumor size. In one study, 70% of Hurthle neoplasms which were larger than 5 cm were malignant and all Hurthle cell neoplasms which were larger than 10 cm were malignant. Most studies that have evaluated clinical factors for their potential value in predicting carcinoma and helping to determine the extent of thyroidectomy for patients with Hurthle cell and follicular neoplasms have been retrospective studies of patients with a final pathologic diagnosis of Hurthle cell or follicular adenoma, FC, and HCC as opposed to an analysis of all patients with an FNA diagnosis of follicular and Hurthle cell neoplasm. They are also surgical series with selection bias. In our experience, clinical and cytomorphologic features have not been helpful in predicting carcinoma in patients with thyroid nodules and an FNA biopsy consistent with either a Hurthle cell neoplasm or follicular cell neoplasm. As a result, we continue to recommend thyroidectomy in all patients with thyroid nodules and an FNA biopsy consistent with a Hurthle cell or follicular neoplasm and clinical factors are not used to determine the extent of thyroidectomy.

Surgical therapy

If an FNA biopsy of a solitary thyroid nodule yields a diagnosis of Hurthle cell neoplasm, a thyroid lobectomy with isthmusectomy should be performed to distinguish nonneoplastic nodules and benign Hurthle adenoma from a HCC. Patients with a history of head or neck irradiation or nodular disease involving the contralateral lobe of the thyroid gland should undergo a total thyroidectomy. Similar to follicular neoplasms, intraoperative frozen section examination has not been shown to be useful in distinguishing a Hurthle cell adenoma from a HCC. In one study, frozen section examination was helpful in determining the extent of thyroidectomy in only 3.3% of cases and in 5% of cases frozen section examination led to additional unnecessary resection. If final pathology reveals a diagnosis of HCC, completion thyroidectomy should be performed in all patients because of its more aggressive behavior and a higher rate of multicentric and bilateral disease.

At the time of surgical resection, the central neck should be examined for abnormal lymph nodes. An abnormal lymph node should be excised and submitted for frozen section examination. This is important because patients with Hashimoto thyroiditis may have nonneoplastic Hurthle cell nodules and abnormally enlarged central neck lymph nodes that may be confused with HCC. A central neck dissection should be performed for macroscopic lymph node metastases.

Because of the more aggressive behavior of HCC, we advocate routine radioiodine ablation. Despite the fact that HCC is less likely to concentrate radioiodine, radioiodine ablation will destroy residual normal cells, which optimizes the value of serum Tg for detection of recurrent disease. Ten percent to 35% of metastases in patients with HCC will concentrate radioiodine. If the patient has evidence of residual disease based on high Tg levels or
radiographic evidence of metastatic disease without uptake of $^{131}$I on whole-body scanning or both, additional dosing is not clinically valuable. Tyrosine kinase inhibitors (TKI) are being used in limited clinical trials for metastatic or locally recurrent radioresistant HCC.

**Postoperative treatment and follow-up of patients with DTC**

*Thyroid hormone therapy*

Postoperatively, patients with DTC are treated with levothyroxine (LT4) to reduce serum TSH, which has been shown to stimulate tumor growth, invasion, and angiogenesis. TSH, produced in the anterior pituitary gland, is a 28-kD glycoprotein that is involved in thyroid growth and hormone regulation. $^{138}$ TSH has been shown to upregulate follicular cell growth and is thought to increase follicular cell mitosis by a cyclic adenosine monophosphate mechanism via its interaction with the TSH receptor on the cell surface of follicular cells. $^{139}$ TSH suppression is important in the long-term management of patients with DTC to prevent the growth or dedifferentiation of residual tumor cells.

TSH suppression has become a routine component in the treatment of DTC. Pujol and colleagues in a study of 141 patients found that TSH suppression to undetectable levels (TSH < 0.05 mU/L) resulted in a longer disease-free survival and lower recurrence rate when compared with patients with serum TSH levels greater than 1 mU/L. $^{140}$ A larger cohort analysis of 683 patients with DTC followed up for a median of 4.5 years (range 1–8.5 years) after thyroid resection was performed by Cooper and colleagues with the National Thyroid Cancer Cooperative Study Group Registry. $^{141}$ This retrospective study examined patients by cancer type (papillary = 617 and follicular = 66), stage (I and II = low risk, and III and IV = high risk), and the extent of TSH suppression. The extent of serum TSH suppression was an independent predictor of disease progression only in high-risk patients. Mazzaferrri and colleagues in a 30-year retrospective analysis of patients with DTC reported that patients treated with LT4 had 25% fewer recurrences and 50% fewer cancer-related deaths than those without adequate LT4 therapy and elevated serum TSH levels. Other studies have also shown a survival benefit from TSH suppression. $^{49}$

Biondi and colleagues $^{143}$ agree that LT4 suppression is warranted in patients with high-risk disease, but question if long-term TSH suppression is necessary in patients who have an undetectable TSH-stimulated Tg level and a negative radioiodine WBS. TSH-suppressive doses of thyroid hormone are a known cause for atrial fibrillation and other cardiac arrhythmias, spontaneous postmenopausal bone loss, osteoporosis, and exacerbation of underlying ischemic heart disease. Approximately 80% of patients treated for DTC would ultimately have no demonstrable disease and as a result, replacement rather than suppressive doses of LT4 are preferable to avoid the potential complications of TSH-suppressive doses. The American Thyroid Association Guidelines Taskforce recommends maintaining serum TSH between 0.1 and 0.5 mU/L in patients with high-risk DTC who are free of disease, between 0.3 and 2.0 mU/L for patients with low-risk DTC, and less than 0.1 mU/L for patients with metastatic disease. $^{43}$

*Radioiodine remnant ablation*

Postoperative radioiodine ablation is advocated for destruction of residual normal or malignant thyroid cells. $^{43,44,144}$ It helps facilitate the most effective use of Tg and radioiodine whole-body scanning for early detection of persistent or recurrent disease. A 30-mCi dose of $^{131}$I given as an outpatient procedure is recommended and is successful in 80% or more of patients who have undergone total thyroidectomy. $^{133}$ Results of remnant ablation with 50-100 mCi of $^{131}$I have been shown to be equivalent after thyroid hormone withdrawal or administration of recombinant human (rhTSH) but may be lower with a 30-mCi dose of $^{131}$I. $^{145-147}$
There is good evidence that radioiodine ablation is valuable in patients with distant metastases, extrathyroidal tumor spread, and tumor size greater than 4 cm. Based on expert opinion, the American Thyroid Association management guidelines for DTC also recommend postoperative $^{131}$I ablation for patients with DTC 1-4 cm in size for aggressive histologic subtypes, lymph node metastases, lymphovascular invasion, and multifocality. $^{131}$I ablation is also recommended for patients with DTC smaller than 1 cm with associated high-risk features. A WBS is obtained 3-7 days after radioiodine administration to evaluate for residual uptake in the thyroid bed and regional lymph node or systemic metastases.

Follow-up

In general, patients with DTC are followed up every 6 months for the first 2 years because this is the time when recurrence is highest. Follow-up consists of clinical examination for local recurrence in the thyroid bed and abnormal cervical or supraclavicular lymphadenopathy and laboratory studies, including serum levels of TSH, Tg, and anti-Tg antibody (TgAb).

Twelve months after thyroidectomy and radioiodine ablation, an ultrasound of the neck is obtained and serum Tg is measured after thyroid hormone withdrawal or rhTSH administration. A serum TSH level of greater than 30 mU/L indicates adequate stimulation. A stimulated Tg level greater than 2 ng/mL is highly sensitive in identifying patients with persistent tumor. In the absence of increased Tg level after TSH stimulation and a negative ultrasound examination, no additional diagnostic testing is needed.

Approximately 25% of patients with DTC will have TgAb, which is a cause for both false-positive and false-negative Tg levels, compromising the clinical utility of Tg monitoring for disease recurrence. TgAb positivity interferes with Tg measurement, causing underestimation of Tg when measured by immunometric assay, and either underestimation or overestimation when measured by radioimmunoassay. Assay methods performed on different analytical machines may yield different results and therefore it is best to follow the changes in the Tg and TgAb levels using the same analytical machine and method.

Low-risk patients with an undetectable TSH-suppressed Tg less than 0.1 ng/mL and a negative neck ultrasound are followed with clinical examination, TSH-suppressed Tg and anti-Tg antibody levels, and periodic neck ultrasound. It is estimated that only 0.3%-2.5% of patients with a TSH-suppressed Tg level less than 0.1 ng/mL would have a rhTSH-stimulated level greater than 2 ng/mL. Ultrasound remains important because there is no absolute level of Tg below which recurrent disease can be completely excluded. Ultrasound is used for examination of the thyroid bed for local recurrence, and both the central and lateral compartments of the neck for regional lymph node recurrence. Suspicious lymph nodes are biopsied. Measurement of Tg in the FNA fluid can enhance the sensitivity of diagnosis of metastatic disease. Isolated small abnormal lymph nodes smaller than 5 mm seen on ultrasound are preferably followed up with serial ultrasound examinations because of the difficulty finding them during operation and the potential morbidity associated with resection. Biopsy and resection are reserved for patients with a lymph node that continues to grow. Routine use of WBS is not recommended for surveillance in this low-risk group.

In low-risk patients who have undergone near-total or total thyroidectomy without postoperative RAI, interpretation of the Tg and TgAb can be challenging. A detectable Tg may be indicative of normal remnant thyroid tissue or persistent or recurrent disease. In a group of 50 patients with papillary microcarcinoma who underwent total thyroidectomy without RAI, 44% had a stimulated Tg level greater than 1 ng/mL. $^{131}$I WBSs revealed uptake only in the thyroid bed. Durante and colleagues demonstrated that Tg levels in patients who did not undergo RAI fell over time. An undetectable Tg level was present in 60% and 80% of patients...
within 1 and 5 years after operation respectively, underscoring the importance of following the trend in serum Tg and recognizing the value of Tg monitoring in patients who do not undergo radioiodine therapy.

During surveillance, an increase in the previously undetectable Tg level is an indicator of disease recurrence. Monitoring TgAb as a surrogate tumor marker is appropriate for patients with positive TgAb. The de novo appearance, persistence, or increase in TgAb concentration in the postoperative period represents a significant risk factor for persistent or recurrent disease. During the first year, not all patients will achieve a negative TgAb status. It is normal to see an initial rise in TgAb after RAI therapy when there is a release of Tg antigen secondary to radioiodine-induced lytic damage of the thyroid cells. What is important is to observe a gradual decrease of the TgAb level over time. Kim and colleagues found that fewer than 1% of patients with more than a 50% drop in TgAb level after 6-12 months of radioiodine treatment had disease recurrence whereas 19% of patients in whom TgAb declined less than 50% were diagnosed with recurrence.

In patients with intermediate- or high-risk PTC and an increasing TSH-suppressed Tg or a TSH-stimulated Tg greater than 2 ng/dL and no evidence of disease on neck ultrasonography, a diagnostic 131I WBS should be performed. A 1-2-mCi dose of 131I should be used to minimize stunning, a phenomenon whereby the pretreatment scanning dose reduces the subsequent uptake of the 131I therapy dose. If the WBS identifies persistent or recurrent disease, a therapeutic dose of 131I is administered.

In patients with negative WBS and mildly elevated stimulated Tg level (< 5-10 ng/mL), the American Thyroid Association management guidelines recommend continued surveillance with TSH-suppressed Tg and neck US at regular intervals. If serum Tg continues to rise in the absence of ultrasonographic findings, further imaging and empiric 131I therapy should be considered. CT of the neck, chest, and abdomen, magnetic resonance imaging (MRI) of the brain, and PET/CT are reserved for patients with an elevated Tg level and a negative ultrasound of the neck and 131I WBS. The administration of oral or intravenous contrast for CT imaging or both reduces iodine uptake of metastatic disease, interfering with subsequent RAI scanning and treatment.

Empiric 131I therapy is controversial. The goals of empiric, high-dose 131I therapy are for treatment of metastatic disease and for identifying disease foci on a posttreatment WBS that may be amenable to further therapy. Pacini and colleagues found that empiric high-dose 131I therapy was only effective in identification and treatment of lung metastases. Others have failed to show any benefit in the rate of disease remission.

In patients with a negative WBS and a TSH-stimulated Tg level greater than 5-10 ng/mL, FDG-PET scanning is recommended. DTC that loses its iodine avidity is usually metabolically active and hence would be visualized on PET imaging. PET imaging has a 92% positive predictive value for patients with negative WBS and elevated stimulated Tg level and a 93% negative predictive value for negative WBS and low Tg level. The majority of cases that are missed with PET imaging are small-volume cervical lymph nodes that can often be detected with neck ultrasonography. The sensitivity of FDG-PET scanning may be improved with simultaneous TSH stimulation. However, the clinical benefit of identifying these additional small foci is not clear. Patients with metastases that are FDG avid on PET scan are known to have a worse prognosis.

With improvement in imaging technology, PET imaging with CT or MRI co-localization has gained popularity over PET imaging alone. The combination of functional and anatomical imaging allows for better visualization of suspected thyroid cancer metastases. PET/CT scanning has been able to improve the diagnostic accuracy of lymph node and lung metastases. The recent development of PET/MRI fusion technology has the potential of replacing PET/CT imaging for detection of metastatic thyroid disease. In a study by Seiboth and colleagues, one-third of patients had a change in management based on the PET/MRI results. Nagaiah and colleagues examined PET/MRI vs PET/CT imaging for identification of remnant thyroid tissue and lymph node metastases prior to patients undergoing RAI therapy for the treatment of high-risk DTC. PET/MRI was superior to PET/CT in differentiating
lymph node metastases and was especially effective for identifying lesions that were smaller than 1 cm.171

Treatment of systemic metastases

DTC is known to result in distant systemic metastases in approximately 5%-23% of cases.172,173 The 5-year survival rate in patients with DTC and distant metastases is approximately 56%.104 Younger patients (age < 45 years), solitary distant organ spread, lower tumor burden, radioiodine concentration, and treatment of metastases with $^{131}$I are associated with better treatment outcomes.172,173 An $^{131}$I WBS after withdrawal of thyroid hormone or rhTSH stimulation is the best initial localization test to evaluate for distant metastases. When metastatic DTC maintains its ability to concentrate iodine, high doses of $^{131}$I may be used for treatment of metastatic disease. Tala and colleagues reported no difference in the response rate or 5-year survival rate in patients with metastatic DTC who were treated with $^{131}$I following thyroid hormone withdrawal or TSH stimulation.174

Pulmonary metastases

Pulmonary metastases are the most common site of distant spread for DTC and can occur as diffuse micrometastases or macronodular disease defined as tumor nodules larger than 1 cm in size. Patients with micrometastases have a more favorable outcome.175 In a study of 394 patients with systemic metastases, 241 patients were found to have isolated pulmonary metastases, 108 had bone metastases, and 72 had combined lung and bone metastases.172 In the 241 patients with isolated lung metastases, postoperative CXR revealed micronodules in 30%, macronodules (> 1 cm) in 34%, and was normal in 36%. All patients were treated with $^{131}$I, 100 mCi in adults and 1 mCi/kg in children. Multivariate analysis revealed that the risk of death was highest in patients with macronodular lung disease or multiple bone metastases, intermediate in patients with micronodular lung disease or bone disease visible on plain CXR or skeletal survey, and lowest in patients with lung or bone metastases only seen on radioiodine WBS. In patients with a negative WBS after $^{131}$I treatment, 10- to 15-year survival rates have been reported to be as high as 89%-92% vs 8%-19% in patients with persistent disease demonstrable on $^{131}$I WBS despite multiple doses of RAI.172,176

Treatment of pulmonary metastases consists of $^{131}$I treatment followed by suppressive doses of LT4. Empiric dosing of $^{131}$I with a 100-200 mCi of $^{131}$I or a dosimetric approach to try and maximize the therapeutic effect and minimize the potential harm to the normal lung parenchyma and bone marrow are utilized. Dosimetry is more complicated, expensive, time consuming, and labor intensive. There are, however, some studies which have shown that dosimetry may help achieve remission in patients when empiric dosing is unsuccessful and may be safer in pediatric or elderly patients.177,178 Surgical resection is indicated for the solitary pulmonary metastasis.179

Bone metastases

The second most common site of distant metastases from DTC is bone. The vertebrae, ribs, and pelvis are the most common sites of bone metastases. Bone metastases can be seen in 2%-13% of patients with DTC, occurring in 7%-20% of patients with follicular cancer and 1%-7% of patients with PTC.144,176 The increased rate of bone metastases seen in follicular cancer is likely due to its higher rate of vascular invasion. Overall 10-year survival in patients with bone metastases is 0%-34% with a mean survival time of only 4 years.176,180 The risk of death increases with multiple bony metastases and with increasing age greater than 45 years.173

Patients with bone metastases present with pain from tumor replacement of the marrow cavity or pathologic fracture. Patients may be asymptomatic if the metastases are small. Diagnosis can often be made on a radioiodine WBS. Bone MRI is the most definitive diagnostic
test, with an overall diagnostic accuracy of 91% as compared with a 78% accuracy for an FDG-PET scan.\textsuperscript{181}

Treatment of bone metastases is based on the extent of tumor infiltration as well as patient symptoms. Most patients are initially treated with TSH-suppressive doses of thyroid hormone and empiric doses of radioiodine ranging from 100-200 mCi. However, unlike patients with micronodular lung metastases, patients with bone metastases are rarely cured.

If patients have symptomatic bone metastases other strategies may be employed. Pathologic fractures or vertebral metastases with instability may benefit from bone stabilization in combination with adjuvant radioiodine therapy. An isolated bone metastasis may benefit from surgical resection and adjuvant radioiodine treatment. If complete resection can be obtained there has been an improved survival seen in some studies.\textsuperscript{181} External beam irradiation, radiofrequency ablation, intra-arterial embolization, vertebroplasty, kyphoplasty, and bisphosphonates, alone or in combination, may have a role in palliation of patients with painful bone metastases that are unable to be resected.\textsuperscript{182}

\textbf{Central nervous system metastases}

Brain and spinal cord metastases from DTC are rare. Surgical resection, external beam radiotherapy, and radioiodine are used for treatment of central nervous system metastases. Surgical resection should be considered for lesions that can be completely excised because this may improve survival. A retrospective analysis of patients with DTC and brain metastases treated at the M.D. Anderson Cancer Center demonstrated a significantly longer survival time for patients who underwent surgical resection compared with patients who did not undergo resection (16.7 months vs 3.4 months).\textsuperscript{183} Patients were not matched for tumor size, age, comorbidities, or other factors, and as a result this study may reflect a bias toward resection of smaller, less complicated lesions. However it still demonstrates a role for surgical resection in selected patients with brain metastases. When patients are not amenable to surgical resection, targeted radiotherapy therapy should be considered to minimize the radiation effects to the normal brain. Radioiodine can be used to treat iodine-avid metastases, but should be preceded by external radiation and glucocorticoid administration to reduce the likelihood of central nervous system edema and increase in tumor that may occur as a result of increased serum TSH levels.

\textbf{Clinical trials for }\textsuperscript{131}\text{I}-\text{resistant metastatic disease}

Metastases that fail to concentrate radioiodine are associated with a worse prognosis. In a study by Schlumberger and colleagues,\textsuperscript{172} patients with iodine-avid metastases had a highly significant reduction in relative risk of death compared with patients with metastases that did not concentrate radioiodine. Ronga and colleagues reported an overall 10-year survival rate of 76% for patients with iodine-avid lung metastases compared with 25% in patients with lung metastases that did not concentrate iodine.\textsuperscript{184} Alternative therapeutic strategies are necessary for improving patient outcomes in patients with DTC and iodine-resistant metastases.

\textbf{BRAF, Ras, and RET-PTC mutations in patients with DTC} lead to downstream alterations in the genes encoding for the transmembrane tyrosine kinase receptors. This has led to the use of TKI as a novel treatment regimen. TKI competitively binds to the ATP portion of the tyrosine kinase receptor. Sorafenib, sunitinib, and pazopanib are commercially available TKI that are being investigated for treatment of radioiodine-resistant metastases. Axitinib, gefitinib, and mosafenib are TKI that are only available as part of a clinical trial. TKI have been shown to variably inhibit BRAF receptor, RET/PTC receptor, vascular endothelial growth factor receptor (VEGFR), and platelet-derived growth factor receptor (PDGFR). Each TKI has a different binding site to the tyrosine kinase receptor, which has clinical relevance because many tumors become resistant to these drugs by the activation of new tyrosine kinases.
The largest clinical trials to date have employed either sorafenib or mosafenib. In 2009, Kloos and colleagues\textsuperscript{185} reported the results of a phase II trial using sorafenib to treat 56 patients with metastatic thyroid cancer not responsive to standard therapeutic regimens. Sorafenib inhibits BRAF, RET, and VEGFR subtypes 2 and 3. In this phase II trial, there were 41 patients with PTC, 11 FC/HCC, and 4 ATC. With the exception of patients with ATC, all patients had undergone thyroidectomy and prior RAI treatment and were not candidates for additional\textsuperscript{131}I therapy; 95\% had lung, 10\% had bone, and 10 \% had other sites of metastases. Tumor burden was assessed by CT, MRI, and PET scans and Response Evaluation Criteria in Solid Tumors was used to assess the objective responses. Thirty-two patients were alive at the end of the 3-year study and 24 had died of which 20 died because of disease progression. Further analysis was mostly limited to patients with PTC because they had the best overall survival. No patients achieved a complete tumor response, 15\% had a partial response, 56 \% had stable disease with no further progression as measured by scans or serum Tg levels for at least 6 months with a median progression-free survival of 15 months. The therapy was well tolerated in most patients but dose reductions were required because of adverse events such as fatigue, arthralgia, diarrhea, and musculoskeletal pain. Rare side effects were pericardial effusion and reversible neutropenia.

In a large phase II trial utilizing motesanib to treat 93 patients with progressive locally advanced or metastatic DTC that was refractory to standard therapy, similar results were reported. Motesanib inhibits VEGFR subtypes 1-3, PDGFR, and RET. Of the 93 patients, only 32 completed the 48-week treatment protocol; 5 died before completing the therapy and treatment was discontinued because of disease progression in 35 and adverse events in 12 patients. A partial response occurred in 14\% of patients as assessed by Response Evaluation Criteria in Solid Tumors and a decrease in serum Tg levels. Disease was stable at 6 and 12 months in 67\% and 35\% of patients, respectively, and overall survival at 1 year was 73\%. In selected patients with aggressive DTC, TKI hold promise for stabilizing disease and extending overall length of survival. TKI have significant toxicities and their use should be restricted to centers with ongoing trials or experience treating patients with aggressive thyroid cancer.\textsuperscript{186,187}

Other strategies for treatment of refractory metastatic DTC are being directed at reversing iodine resistance.\textsuperscript{188} Many of these tumors have downregulation of the sodium-iodide symporter (NIS) rendering the tumor unable to take up and concentrate iodine. Agents such as retinoic acid, rosiglitazone, trichostatin-A, and lithium are being trialed to either increase NIS activity or reduce iodine excretion from tumor cells in the hope of restoring sensitivity to\textsuperscript{131}I therapy.

Other alternative pathways have been discovered that may allow tumors to continue to upregulate growth and differentiation in a TSH-independent pathway utilizing the insulin growth factor receptor. Studies both in vitro and in vivo show that insulin growth factor-I receptor activation can lead to papillary thyroid hyperplasia in mice and that some of these receptor subtypes exist in both normal human thyroid follicular cells and in PTC.\textsuperscript{189,190} This may lead to alternative strategies to inhibit tumor growth.

**ATC**

**Case no. 1**

A 71-year-old white woman presented with a chief complaint of difficulty swallowing and pressure sensation in her neck that was worse when she laid flat or when her arms were up over her head. She also had hoarseness and difficulty expectorating mucus. She was first diagnosed with a “goiter” 21 years prior to her presentation and was started on thyroid hormone. Over the past year she reported that her goiter had increased in size. She denied any prior history of head or neck radiation. Both her mother and sister had undergone surgery for benign thyroid disease. Her other medical problems were hypertension and hypercholesterolemia.
The patient was referred for definitive management after having undergone an extensive evaluation. An ultrasound of the thyroid gland demonstrated diffuse heterogeneity with multiple bilateral nodules. There was marked enlargement of the left lobe of the thyroid gland with interval increase in size and additional nodules throughout both lobes of the thyroid gland compared with an ultrasound exam from 1 year prior. A 24-hour $^{131}$I uptake was measured and was only 1.7% and a thyroid scintiscan demonstrated very little uptake by the thyroid gland. A chest radiograph revealed tracheal impingement and displacement to the right due to the enlarged left lobe of thyroid gland. She had an FNA biopsy of the large neck mass, which was nondiagnostic. No follicular epithelial cells were identified. There was extensive cellular degeneration and this was felt to be consistent with a cyst.

On physical examination she had a 6-cm mass involving most of the left lobe of the thyroid gland, the isthmus, and the medial portion of the right lobe of the thyroid gland. The mass was tender to palpation. She had no cervical or supraclavicular adenopathy. Her trachea was displaced to the right.

A total thyroidectomy was performed for a presumed multinodular goiter with a cystic degeneration that was causing compressive symptoms and tracheal impingement and displacement. At operation the patient was noted to have a huge mass involving the entire isthmus and both lobes of the thyroid gland. The mass was adherent to the left sternothyroid muscle, but there was no obvious invasion. The mass extended substernally and was filled with a thick amorphous material. The mass was entered during delivery from its retrosternal location resulting in some spillage of the amorphous debris into the wound.

The weight of the excised thyroid gland was 67 g. There was a large complex cystic-solid nodule that was 5 cm in greatest dimension and was full of necrotic tissue and amorphous debris. The final pathology revealed anaplastic large cell carcinoma, spindle cell type, with extensive necrosis and chronic inflammation within an adenomatous goiter. The margins of resection were free of tumor. Immunohistochemical stains confirmed the diagnosis of ATC. Postoperatively, the patient developed transient asymptomatic hypocalcemia with a serum calcium level of 7.6 mg/dL on the first postoperative day. This was treated with calcium supplementation. Her serum calcium level was normal at her 2-week follow-up visit and her calcium supplementation was discontinued.

Although the tumor was completely resected, there was some spillage of the cyst contents intraoperatively. As a result, the patient was referred for evaluation for adjuvant radiotherapy. The patient had additional staging evaluation, which included a CT scan of the chest, abdomen, and pelvis and a bone scan, all of which were negative. She was treated with 6000 cGy in 30 fractions to her neck. After 15 years of follow-up, she has no evidence for recurrent disease.

Case no. 2

A 52-year-old white man presented to the emergency department with progressive bilateral lower extremity weakness, inability to walk, and difficulty urinating. CT of the thoracic spine revealed osteolytic lesions of the fifth, sixth, and eighth thoracic vertebral bodies. There was collapse of the fifth vertebral body with a large associated epidural mass (Fig 7). MRI of the thoracic spine demonstrated enhancement of the marrow with infiltrative lesions involving the fifth, sixth, and eighth vertebral bodies which were extending into the epidural space at the T5-6 level. It also demonstrated marked compression of the thoracic spinal cord by an enhancing epidural mass at the T5-6 level (Fig 7). An incidental 4.6-cm mass with course calcifications involving the left lobe of the thyroid gland was also noted (Fig 7).

The patient underwent emergency T5 and T6 laminectomies and corpectomies with interbody and posterior arthrodesis. A large epidural tumor was also resected. The pathology revealed poorly differentiated carcinoma from an unknown primary tumor. Additional history was obtained and additional physical examination was performed. The patient reported no
prior head or neck radiation or family history of thyroid cancer or other endocrinopathies. He had no prior history of malignancy. He denied any compressive symptoms.

On physical examination, the patient had displacement of his trachea and thyroid cartilage to the right. He had a large hard mass in the left lobe of the thyroid gland that was extending substernally. The right lobe of the thyroid gland was palpable and was firm in character. He had no associated cervical or supraclavicular adenopathy.

An ultrasound of the thyroid gland revealed a large heterogeneous mass occupying most of the left lobe of the thyroid gland measuring $5.8 \times 4.7 \times 4.4$ cm. The mass had cystic and solid components, calcifications, and increased vascularity. His serum TSH level was 3.60 mIU/mL. An FNA biopsy of the left neck mass was interpreted as poorly differentiated carcinoma. The cytomorphologic features were similar to the malignant cells that were seen from the epidural mass. The cytopathologist could not give a definitive diagnosis but suggested that the differential diagnosis included medullary thyroid cancer, Hurthle cell cancer, and ATC.

The patient underwent an en bloc resection of the mass, which included a total thyroidectomy with a segment of the muscle layer of the esophagus. The pathology revealed ATC involving the posterior-medial and posterior-inferior margins. There was perithyroidal extension, vascular invasion, and extensive necrosis. Immunohistochemical studies supported the diagnosis of ATC.

The patient's postoperative course was unremarkable. He was started on thyroid hormone therapy. He subsequently underwent radiation treatment, which consisted of 3000 cGy in 10 fractions to T3 to T10 followed by 3000 cGy in 10 fractions to the neck. Six months following his original surgery he died as a consequence of metastatic disease.
Background

ATC is one of the most aggressive solid human cancers with a median survival of 5 months after diagnosis.\(^\text{191}\) It is the least common type of thyroid cancer, but it carries the highest mortality rate. Less than 3% of all thyroid cancers diagnosed each year are ATC.\(^\text{192-194}\) The overall incidence of ATC worldwide is 1-2 cases for every 1 million individuals. The incidence of ATC is decreasing likely because of increased dietary iodine supplementation and a decrease in endemic goiter, earlier diagnosis, and treatment of DTC before anaplastic dedifferentiation occurs and better distinction of ATC from poorly differentiated thyroid carcinoma, insular thyroid carcinoma, lymphoma, and undifferentiated MTC.\(^\text{195,196}\)

Presentation

Patients with ATC are older than patients with DTC, typically 60-70 years of age. ATC occurs more often in women. Patients with ATC usually present with a rapidly enlarging tender, painful, firm, and fixed neck mass that on average is greater than 6 cm in size. They commonly have compressive symptoms as a result of invasion of the aerodigestive tract. Signs and symptoms include a rapidly growing central (77%) or lateral (54%) neck mass, dysphagia (40%), voice change or hoarseness (40%), neck pain (26%), and stridor or dyspnea (24%). Patients may also present with anorexia, weight loss, fatigue, cough, and hemoptysis. Patients often have a long history of a stable goiter that suddenly and rapidly increases in size as was true in our first case. Rarely, ATC has been reported to present with superior vena cava syndrome and Horner syndrome.\(^\text{197}\) Ninety percent of patients with ATC will present with regional or systemic metastases.

On physical examination, patients usually have marked bilateral enlargement of the thyroid gland, frequently with substernal extension. The thyroid gland is hard with indistinct borders. The trachea is most often not palpable because of the extent of thyroid enlargement and the firm character of the gland. Cervical lymph node enlargement is common. Patients may have vocal cord paralysis, facial edema, and venous engorgement.

Distant metastases are present at the time of diagnosis in 25%-66% of patients.\(^\text{198}\) The lung is the most common site of distant metastatic spread. ATC also metastasizes to the mediastinum, liver, bones, kidneys, heart, adrenal glands, brain, skin, and the abdominal cavity.\(^\text{198,199}\) ATC is usually a systemic disease at the time of diagnosis, and as a result all patients with ATC are considered to have stage IV disease by the American Joint Commission on Cancer TNM staging system (Fig 6).

Histopathology and diagnosis

ATC is a follicular cell–derived tumor that arises from dedifferentiation of DTC or de novo from normal thyroid tissue, which rapidly loses its normal differentiation. ATC does not retain any of the functional characteristics of the follicular cell, including synthesis of Tg and radioiodine uptake. Mutations in genes encoding for p53, RAS, BRAF, MIB-1, PIK3CA, Axin 1, and β-catenin may be associated with anaplastic transformation (Fig 8). Mutations in oncogenes and tumor suppressor genes result in underexpression and overexpression of proteins that are vital for cell function.\(^\text{200}\)

ATC cells typically have large, bizarre-shaped nuclei with numerous atypical mitotic structures that resemble polymorphic mesenchymal sarcoma. This “dedifferentiation” of ATC can make histologic diagnosis difficult. PAX8 is a transcription factor expressed in the nuclei of normal and abnormal thyroid, the kidneys, and the female genital tract tissue. Expression of PAX8 appears to be preserved in ATC and may help differentiate ATC from head and neck squamous cell carcinomas.\(^\text{201}\) ATC usually has numerous areas of hemorrhage and necrosis along with several different histologic patterns, which frequently coexist and do not affect the
already poor prognosis. These patterns include spindle cell, giant cell, squamoid, paucicellular, and carcinosarcoma.

ATC may be diagnosed by an FNA biopsy. However, extensive cellular degeneration or tumor necrosis or both may make it difficult to make an FNA biopsy diagnosis of ATC, which was true in both the cases that are presented. Ultrasound may be helpful to identify a nonnecrotic area of the thyroid gland to biopsy. A core needle biopsy or incisional biopsy may be needed to obtain enough tissue for immunohistochemical testing. Useful markers that may distinguish ATC from other thyroid tumors or sarcomas include cytokeratin, carcinoembryonic antigen (CEA), epithelial membrane antigen, α-1-chymotrypsin, desmin, vimentin, and anticytokeratin antibodies.

Imaging

Imaging is important to determine if the ATC is resectable and to evaluate for metastatic disease. CT of the neck and chest is recommended to assess for tracheal, esophageal, and major vascular invasion and retrosternal extension. CT of the chest and abdomen, bone scintigraphy, and MRI of the brain are useful to evaluate for distant metastases. FDG-PET imaging may also be useful for staging patients with ATC. Poisson and colleagues imaged 20 consecutive patients with biopsy-proven ATC with FDG-PET combined with CT and noted that ATC cells have a high uptake of FDG. The high level of FDG uptake resulted in a higher sensitivity for detection of cervical and mediastinal lymph node and bone metastases than CT or bone scintigraphy. The sensitivity of FDG-PET imaging for detection of lung masses was comparable to CT.

Treatment

The optimal treatment strategy for patients with ATC has yet to be determined. The results of various treatment strategies come from small retrospective studies that suffer from selection...
bias. In many early series of ATC, poorly differentiated thyroid carcinoma, metastases, sarcoma, and primary thyroid lymphoma (PTL) were often incorrectly reported as ATC and reports of long-term survival were flawed because of misdiagnosis. In general, the management of ATC includes locoregional control and preemptive treatment of gross or occult metastatic disease.

The vast majority of patients with ATC present with locally invasive disease that is unresectable. In the rare patient with ATC that is confined to the thyroid gland, there is a role for surgical resection and it may be curative (as was true in our first patient). In all patients who may have resectable disease, an en bloc resection and total thyroidectomy should be considered. Attempts at segmental resection of the carotid artery, trachea, esophagus, pharynx, or larynx should not be performed because this significantly exacerbates the morbidity of the operation with no clear survival advantage. It is unnecessary to perform a prophylactic tracheostomy in the absence of impending airway obstruction as this increases the complexity of care postoperatively and reduces the patient’s overall quality of life.

Radiotherapy is recommended for locoregional control in all patients with ATC, preferably intensity-modulated radiotherapy. External beam radiotherapy reduces the morbidity and mortality from local invasion. High-dose external beam therapy has also been shown to improve the length of survival. Neoadjuvant therapy has been advocated to convert an unresectable ATC to a resectable one.

Stage IVA ATC, defined as ATC confined to the thyroid gland, with or without nodal metastases, is rarely encountered in clinical practice. Stage IVB, defined as ATC with gross extrathyroidal extension, with or without lymph node metastases, and no distant metastases, account for approximately 40%-60% of patients. Patients with stage IVA or IVB are candidates for multimodal treatment with some combination of complete surgical resection, radiation therapy, and chemotherapy to improve overall survival. However, in most patients, the ATC is not amenable to curative surgical resection. Patients with stage IVC ATC, defined by the presence of distant metastases have the shortest survival. The combination of intensity-modulated radiation therapy and chemotherapy has been shown to improve survival in patients with stage IVA and stage IVB ATC. Neoadjuvant chemotherapy and radiotherapy do not improve overall survival in patients with stage IVC disease.

Consideration should be given to enrolling patients with ATC and gross or occult metastatic disease in a clinical trial (www.clinicaltrials.gov).

Radiation therapy

Traditional external beam radiation therapy delivers a targeted dosage of radiation to a specific anatomical site. In patients with ATC, high-energy photons result in DNA fragmentation and ultimately cell death through a proposed necroptosis cellular pathway. However, it is unclear what the optimal radiotherapy regimen or schedule should be. Dose-related effects of radiation include skin changes, pharyngoesophagitis, tracheitis, and myelopathy.

Hyperfractionation of external beam radiotherapy is the process whereby multiple small dosages of radiation are given daily. This process allows for less overall toxicity and the completion of an entire radiation therapy course over a shorter time. The theoretical benefit of this shortened time is the prevention of accelerated repopulation of ATC cells and an increase in overall tissue repair. Unfortunately, the recent Hyperfractionated Accelerated Radiotherapy trial for patients with ATC was stopped early because 56% of the patients suffered grade 3 or 4 toxicity (erythema, desquamation, dysphagia, and esophagitis) from the radiation.

The neck is a difficult “target” for external beam radiation because of its natural curvature as well as interference from the vertebral bodies and trachea. Three-dimensional planning using CT images helps direct radiation dosages. Intensity-modulated radiation therapy uses sophisticated computer algorithms and linear accelerators to shape radiation dosage fields to more closely align with a patient’s neck anatomy. Images taken during the day of radiation treatment allow for image-guided radiation therapy, which accounts for any change in tumor.
size from the last time the patient was seen by a radiation oncologist. Intensity-modulated and image-guided radiation therapy may result in less radiation-related toxicity with better local control.212

Chemotherapy

In general, patients with ATC have a poor response to chemotherapy alone, which necessitates combination therapy with radiation and, when possible, surgery. Chemotherapeutic agents that have been used to treat ATC include taxanes or platins and doxorubicin. Taxanes (docetaxel or paclitaxel) are radiosensitizing agents and seem to improve overall response to external beam radiation therapy, especially in stage IVB patients.213 Doxorubicin has known activity against ATC and works in synergy with taxanes.205,209 In general, there are too few studies of too few patients with ATC to determine definitively the optimum chemotherapy regimen.

Future targeted therapies

Clinical trials have been initiated to examine various targeted therapies for ATC including histone deacetylase inhibitors to induce redifferentiation and restore iodine uptake in ATC cells, monoclonal antibodies to block growth factor receptors, and proteasome inhibitors to stimulate apoptosis.214-216 Other promising targeted therapies include small molecule TKI and antiangiogenesis agents.

Human ATC trials with small molecule TKI include imatinib and sorafenib. Imatinib is a selective c-abl TKI and appears to trigger apoptosis in ATC cells when combined with docetaxel in mice.217 Sorafenib acts on the raf-1 serine/tyrosine kinase and also blocks VEGFR2 and PDGFR-β. Small human trials with these agents have not demonstrated any measurable improvement in survival, but more research is ongoing.

Several antiangiogenesis and vascular-disrupting agents, including axitinib, fosbretabulin, and combretastatin, are also being tested in ATC patients. Axitinib is an oral, selective inhibitor of VEGFRs 1-3. Fosbretabulin is a tubulin-binding agent that disrupts established tumor vasculature by binding to the colchicine-binding site to inhibit microtubule assembly and destabilize the cytoskeleton. Finally, combretastatin A4 phosphate is a tubulin-binding vascular-disrupting agent that inhibits tumor blood flow, blocks the development of new blood vessels, and occludes existing vasculature in ATC cell lines.218

Prognosis

The prognosis of ATC is poor, with a 1-year survival rate of 20% and a 5-year survival rate of 5%.219-222 The Surveillance, Epidemiology, and End Results data from 1983-2002 indicate a 2-year survival rate of 33% and a 5-year survival rate of 23% if the ATC is confined to the thyroid and completely resected.219 Age less than 60 years, female gender, and tumor confined to the thyroid gland are associated with increased length of survival.220-222 Higher dose radiation therapy and greater extent of surgery are also predictive of longer survival and distant metastases are predictive of higher mortality.200

Sugitani and colleagues developed a prognostic index based on the presence of acute symptoms or progression of tumor within 1 month, tumor size greater than 5 cm, presence of distant metastases at diagnosis, and a WBC count greater than 10,000 μL⁻¹. If prognostic score was ≤ 1 there was a 62% survival rate at 6 months vs 0% survival rate at 6 months if the score was more than 3.223 They applied this prognostic index prospectively and found that patients with stage IVA or IVB and a prognostic index score greater than 3 should not receive chemotherapy or EBRT as their disease-specific survival was very low and efforts should be made to maximize their overall quality of life.224
Death from ATC is most often related to distant metastases (as was true for our second case) or airway obstruction. Kitamura and colleagues reviewed 62 fatal cases of ATC and confirmed that most common cause of death is severe hypoxia from replacement of lung tissue with pulmonary metastases or airway obstruction.\textsuperscript{225} Other causes of death in ATC patients include tumor hemorrhage and circulatory failure from sepsis, cardiac metastases, disseminated intravascular coagulation, hypercalcemia, and vena cava stenosis. All patients with ATC should have a consultation from a palliative care team if possible prior to initiating treatments to ensure the patient’s quality of life is given the highest priority.

In summary, ATC remains a challenging clinical problem with low overall patient survival. Our case no. 1 represents the rare exception, a long-term survivor from ATC as a result of incidental detection of a small clinically occult tumor that was confined to the thyroid gland in a patient with a large multinodular goiter. Multimodality therapy that includes resection of all gross disease if feasible, radiosensitizing and adjuvant chemotherapy, and intensity-modulated and image-guided radiotherapy produces the best results. New therapies for ATC will probably come from targeted therapies that directly address the multiple genetic derangements of ATC.

**MTC**

Case

A 30-year-old healthy woman with no significant medical history presented with a right-sided thyroid nodule. She was asymptomatic. She had no prior history of head or neck irradiation and there was no family history of thyroid cancer or known endocrinopathies, sudden death, or thyroid, parathyroid, or adrenal surgery. On physical examination, she had a 2.0-cm firm nodule in the right lobe of the thyroid gland. There was no cervical or supraclavicular lymphadenopathy. Her trachea was midline. The rest of her physical examination was normal.

An ultrasound examination demonstrated a 1.8 × 2.9 × 1.3-cm complex, hypoechoic nodule in the right lobe of the thyroid gland. The left lobe and isthmus were normal. There was no central or lateral compartment lymphadenopathy. An ultrasound-guided FNA biopsy of the thyroid nodule was positive for MTC with positive immunostaining for calcitonin. Serum calcitonin and calcium levels were 300 pg/mL and 9.5 mg/dL, respectively. A CEA level and plasma metanephrines were all within normal ranges. CT imaging of the neck, chest, and abdomen was normal. RET proto-oncogene testing was negative.

A total thyroidectomy with bilateral central compartment neck dissection was completed. The final pathology revealed a single focus of medullary carcinoma, 1.8 cm in size, that was confined to the thyroid gland. There was an incidental 0.2-cm papillary microcarcinoma in the left lobe of the thyroid gland and a 0.1 cm focus of metastatic MTC in a lymph node that was attached to lower pole of the right thyroid lobe. The remaining 12 central compartment lymph nodes were negative for metastatic disease.

Postoperatively, her voice was normal. She had no symptoms of hypocalcemia and she was normocalcemic. Her serum calcitonin level was undetectable and has remained so at the 3-years follow-up.

**Background**

MTC accounts for approximately 4% of all thyroid malignancies.\textsuperscript{103} MTC was initially described by Hazard and colleagues.\textsuperscript{226} In 1966, Williams discovered that MTC originated from the parafollicular or “C” cells of the thyroid gland.\textsuperscript{227} C cells comprise 1% of all cells in the thyroid gland and are primarily concentrated in the upper posterior one-third of each lobe of the thyroid gland. Embryologically, the C cells are associated with the ultimobranchial bodies and migrate from the neural crest to the thyroid gland. The neural crest origin is responsible for the amine precursor uptake and decarboxylating activity of MTC and its ability to secrete neurohumoral peptides, including calcitonin, CEA, serotonin, adrenocortotropic stimulating...
hormone, chromogranin A, somatostatin, neurotensin, proopiomelanocortin, prostaglandins, kinins, histaminase, and vasoactive intestinal peptide.\textsuperscript{228}

In contrast to DTC, MTC does not produce Tg and it does not respond to TSH suppression. C cells do not express the sodium-iodide symporter and thus do not concentrate radioiodine. MTC is more aggressive than DTC with a higher rate of recurrence and mortality. MTC commonly metastasizes to cervical lymph nodes and cure of the disease is dependent on resection of lymph node metastases. MTC is sporadic in 70%-80% of patients and an autosomal dominant inherited disease in 20%-30% of patients, which occurs as a result of germline activating missense mutations in the RET proto-oncogene. The RET proto-oncogene is found on chromosome 10q.11.2 and is a 21-exon gene that encodes for a transmembrane tyrosine kinase receptor.

Patients with sporadic MTC are typically diagnosed later in life with a peak incidence between 40 and 60 years of age. These patients usually present with a solitary thyroid nodule or palpable cervical lymphadenopathy and may present with neck pain, dysphagia, dyspnea, cough, choking, and hoarseness with impingement or invasion of the aerodigestive tract or recurrent laryngeal nerve. Up to 75% of patients with a palpable MTC would have cervical lymph node metastases.\textsuperscript{182} Patients may present with diarrhea, flushing or Cushing syndrome, which usually occurs in patients with marked hypercalcitoninemia and advanced disease and is related to the vasoactive amines that are secreted by the tumor cells. Approximately 5% of patients would present with systemic metastases most commonly involving the lungs, liver, and bone.

Sporadic MTC is most often solitary, but up to 30% of patients may have bilateral disease.\textsuperscript{229} Approximately 10% of patients with sporadic MTCs have a de novo RET germline mutation.\textsuperscript{230} Somatic mutations or rearrangements involving RET that occur later in life and are limited to C cells have been identified in 40%-50% of patients with sporadic MTC, which are associated with lymph node metastases, more advanced disease, persistent disease, and lower overall survival.\textsuperscript{228}

Patients with hereditary MTC may present as early as the first decade of life and typically have bilateral or multicentric tumors or both. Hereditary MTC is caused by germline gain-of-function mutations in the RET proto-oncogene and is believed to start with C-cell hyperplasia, which progresses to medullary microcarcinoma, macroscopic MTC, and then eventually to lymph node or distant metastases. Somatic mutations are thought to be involved in the progression to malignancy in an individual with a germline mutation in the RET proto-oncogene. There are 3 distinct hereditary forms of MTC: multiple endocrine neoplasia (MEN) 2A (Sipple Syndrome), MEN 2B (Wagenmann-Froboese Syndrome), and familial MTC (FMTC).

MEN 2A is the most common subtype of hereditary MTC accounting for almost 80% of hereditary MTC. Features of MEN 2A vary with the affected RET codon and include MTC (95% penetrance), unilateral or bilateral pheochromocytoma (~60% penetrance), and primary hyperparathyroidism (~20% penetrance), which is typically mild and can result from multiglandular disease or a single adenoma. Less common features include Hirschsprung disease and cutaneous lichen planus amyloidosis, which can occur, respectively, in 6%-16% and 9% of families with MEN 2A.\textsuperscript{231,232} Patients usually present in the third or fourth decade of life.

FMTC is felt to be a variant of MEN 2A. Patients with FMTC have MTC without other endocrinopathies are typically older than patients with MEN 2A at the time of diagnosis of MTC. FMTC is defined as MTC in 4 or more family members without pheochromocytoma or hyperparathyroidism.\textsuperscript{233} Patients with isolated MTC but less than 4 affected family members should be considered as “unclassified MTC.”\textsuperscript{234} Many of these patients would eventually be diagnosed with MEN 2A and as a result, should be appropriately screened until the criteria for MEN 2A or FMTC are met.\textsuperscript{182,234}

MEN 2B is the least common form of hereditary MTC. Patients with MEN 2B have MTC (100% penetrance), unilateral or bilateral pheochromocytoma (> 50% penetrance), a thin, lanky, Marfanoid habitus with joint laxity, musculoskeletal abnormalities, including pescavus and pectus excavatum, multiple mucosal neuromas, medullated corneal nerve fibers, enlarged lips, eversion of the eyelids, and ganglioneuromas in the gastrointestinal tract and megacolon.
All patients have ganglioneuromas, two-thirds of patients have megacolon and, in contrast to MEN 2A, hyperparathyroidism is not part of the syndrome. The stigmata of MEN 2B precede the onset of MTC. However, in most patients there is a delay in diagnosis until the MTC becomes palpable. MTC occurs at an average age of 10 years and most patients develop metastases in childhood or adolescence. In at least 50% of patients, MEN 2B occurs as a result of a de novo germline mutation in the RET proto-oncogene. It is rare to make a diagnosis of MEN 2B based on screening because most patients are index cases resulting from de novo mutations and most patients with MEN 2B do not have offsprings.

Diagnosis

Although most patients with MTC present with a thyroid nodule, less than 1% of patients with a thyroid nodule would have MTC. The diagnosis of MTC should be considered in patients with a family history of MTC, hyperparathyroidism, pheochromocytoma, severe hypertension, sudden death, and Hirschsprung disease. Physical examination should include palpation for unilateral or bilateral disease nodular disease and cervical lymphadenopathy as well as inspection of the tongue, lips, and conjunctivae for mucosal neuromas and evaluation for musculoskeletal abnormalities and other developmental defects. Patients should be examined for pruritic skin lesions on the upper back indicative of cutaneous lichen planus amyloidosis.

Immunohistochemical staining of FNA biopsy specimens for calcitonin is performed when the cytologic evaluation is consistent with MTC. Cytologically, MTC is characterized by pleomorphic cells that present singly or in loosely cohesive groups. The cells can be small and round, cuboidal, polygonal, or spindle-shaped with a plasmacytoid appearance containing fine cytoplasmic granules that stain positive for calcitonin. Amyloid deposits may be present (presumably derived from transformed calcitonin polypeptides) and are difficult or impossible to distinguish from colloid on Papanicolau staining and are confirmed by positive Congo red staining. FNA cytology in patients with MTC may be difficult to distinguish from Hurthle cell neoplasms and ATC emphasizing the importance of immunohistochemical staining and measurement of serum calcitonin.

Patients with an FNA biopsy consistent with MTC should have a basal serum calcitonin level, CEA, calcium and plasma metanephrine levels measured. It is important to exclude a pheochromocytoma prior to operation for MTC. If a patient has hypercalcemia, a serum parathyroid hormone level should be measured to establish the diagnosis of primary hyperparathyroidism. Mildly elevated calcitonin levels can be seen in patients with C-cell hyperplasia, renal disease, hypergastrinemia secondary to proton pump inhibitor use, tobacco use, advanced age, and in patients with neuroendocrine tumors from lung, pancreas, or prostate. Patients with mildly elevated levels should undergo repeat testing. Calcium-stimulated serum calcitonin levels may be used to further evaluate patients with mildly elevated calcitonin levels. A calcitonin level in the 20-40 pg/mL range suggests lymph node involvement and a calcitonin level greater than 150 pg/mL is associated with distant metastases. CEA is predominantly expressed in less differentiated cancers and serum levels greater than 30 ng/mL suggest extrathyroidal disease.

A neck ultrasound with lymph node mapping of both central and lateral neck compartments is obtained in all patients with MTC, although it may be falsely negative in up to one-third of patients with central compartment lymph node metastases. Additional imaging for metastatic disease is reserved for patients with basal serum calcitonin levels greater than 150 pg/mL. Up to 15% of patients with MTC have distant metastases at the time of diagnosis, most frequently in the mediastinum, liver, lungs, or bone. CT imaging of the neck, chest, and abdomen is obtained to evaluate for local tumor invasion and lung, lymph node, and liver metastases. FDG-PET may be more sensitive for the identification of neck and mediastinal disease. MRI is the most sensitive modality for detection of liver metastases. MRI, in combination with bone scintigraphy, is used to evaluate for bone metastases. Diagnostic
laparoscopy may have a role for diagnosis of occult liver metastases prior to initial operation in patients with serum calcitonin levels greater than 1000 pg/mL. All patients with MTC should be offered genetic counseling and screening for germline RET mutations. RET proto-oncogene testing provides important risk information for family members and helps estimate a patient’s risk for developing pheochromocytoma and hyperparathyroidism.

**Treatment**

Surgery is the mainstay of therapy for MTC and consists of 3 separate strategies: prophylactic surgery for hereditary MTC, surgery for clinically apparent MTC, and palliative surgery for widely metastatic MTC. Strong correlation exists between the RET codon mutation, the age of onset, and the risk for aggressive MTC that can be used as a guide to help determine the timing of prophylactic thyroidectomy (Table 5). The goal of prophylactic thyroidectomy is to treat the patient before serum basal calcitonin levels increase and before lymph node and systemic metastases develop so that the patient can be cured of their disease.

RET proto-oncogene carriers with normal basal calcitonin levels are treated with total thyroidectomy alone without a central neck dissection. This has important implications for reducing morbidity, related to the minimal working space and the more delicate anatomical structures of the infant and child. The predominant complication is permanent hypoparathyroidism. Waiting until the patient is older may reduce the morbidity of operation. The development of MTC is age-dependent and varies with the RET codon. Therefore, as long as basal calcitonin levels are normal, consideration may be given to postponing prophylactic surgery in patients with American Thyroid Association low-risk (A and B) mutations until the stimulated calcitonin levels begin to rise. Most patients with MEN 2B have increased basal calcitonin levels at the time of diagnosis and are treated with total thyroidectomy and a central compartment neck dissection. Patients with hereditary MTC and a pheochromocytoma should undergo preoperative alpha blockade and adrenalectomy prior to thyroidectomy.

Surgery for clinically apparent MTC, whether sporadic or familial, should include a total thyroidectomy and a complete central compartment neck dissection. Total thyroidectomy is advocated because most patients with hereditary MTC and approximately 30% of patients with sporadic MTC would have bilateral disease. Routine bilateral central compartment neck dissection is performed because of the high incidence of lymph node metastases in patients with clinically apparent MTC. In patients with an incidentally discovered medullary microcarcinoma, a central compartment neck dissection may not be necessary. Because the inferior parathyroid glands are at risk for devascularization or removal during a central compartment neck dissection, consideration should be given to autotransplantation of the inferior parathyroid glands into the sternocleidomastoid muscle in patients with sporadic MTC, FMTC, MEN 2B, or in the nondominant forearm in patients with MEN 2A, when there is a risk for development of hyperparathyroidism.

The role of lateral neck dissection at the time of the initial operation is more controversial. Ipsilateral and contralateral cervical lymph node metastases are present in 14%-80% and

### Table 5

<table>
<thead>
<tr>
<th>Codons</th>
<th>Association</th>
<th>Recommended management</th>
</tr>
</thead>
<tbody>
<tr>
<td>883, 918, and 922</td>
<td>MEN 2B</td>
<td>Prophylactic total thyroidectomy as soon as it is feasible and within the first 6-12 mo of life.</td>
</tr>
<tr>
<td>609, 611, 618, 620, 634, and 819</td>
<td>MEN 2A and FMTC</td>
<td>Prophylactic total thyroidectomy by 5 y of age.</td>
</tr>
<tr>
<td>768, 790, 791, 804, and 891</td>
<td>MEN 2A and FMTC</td>
<td>Prophylactic total thyroidectomy may be delayed until stimulated calcitonin levels increase or before 10 y of age.</td>
</tr>
</tbody>
</table>

MTC, medullary thyroid cancer; RET, Re-arranged during transfection; MEN, multiple endocrine neoplasia; FTMC, familial medullary thyroid cancer.
19%-49% of patients with MTC, respectively.\textsuperscript{242} Therefore, some surgeons have advocated bilateral lateral neck dissection for all patients with palpable MTC.\textsuperscript{243} Other surgeons recommend an ipsilateral lateral neck dissection for patients with a palpable MTC, positive central compartment lymph nodes, serum calcitonin levels greater than 200 pg/mL, and MTC greater than 1.0 cm in size.\textsuperscript{242,244} \textsuperscript{242} It is our practice, as well as the practice of other surgeons, to perform a compartment-oriented lateral neck dissection only if there are abnormal lymph nodes present on physical examination, or identified on imaging studies.\textsuperscript{228,245}

Palliative or cytoreductive surgery should be offered to patients who present with advanced MTC. A unilateral thyroidectomy may be the most appropriate therapy for patients with MTC and distant metastases to prevent future airway compromise. Also, patients with diffusely metastatic disease may develop flushing, weight loss, and diarrhea, which may improve with cytoreductive surgery.

**Prognosis and follow-up**

Postoperatively, all patients are started on replacement doses of thyroid hormone. In contrast to patients with follicular cell–derived cancers, the C cells do not respond to TSH suppression. A physical examination is performed and serum calcitonin and CEA levels are measured at 6-month intervals to evaluate for persistent or recurrent disease. Patients with normalization of their serum calcitonin levels postoperatively are less likely to develop recurrent disease. Patients with persistent calcitonin elevation postoperatively should undergo further imaging evaluation if it has not already been done. Patients with a persistent, stable serum calcitonin elevation less than 150 pg/mL and a negative imaging evaluation may be followed with ultrasound of the neck alone and most do well without evidence for clinical or radiographic evidence of recurrence.

Although the risk of recurrence after prophylactic total thyroidectomy is low, patients with hereditary MTC should have a plasma calcitonin and CEA levels monitored annually. Patients with “unclassified MTC,” or suspected MEN 2A should be screened for hyperparathyroidism and patients with “unclassified MTC,” suspected MEN 2A, or MEN 2B should be screened for the development of pheochromocytoma. The 10-year cause-specific survival with MTC is approximately 75% but decreases to 45% in patients with lymph node metastases.\textsuperscript{246} Prognosis most closely correlates with stage of disease (Fig 6) and postoperative serum calcitonin and CEA levels. After adjusting for stage of disease, there is no difference in survival between hereditary and sporadic MTC.\textsuperscript{237,247} Ten-year survival rates for stages I through IV are 100%, 93%, 71%, and 21%, respectively.\textsuperscript{246}

Calcitonin levels largely correlate with tumor burden and a decrease in postoperative calcitonin levels to a normal level typically indicates successful removal of all MTC. It may take several months to reach a nadir in the decline of calcitonin, but most patients reach a stable level by 72 hours. Mildly elevated, but stable, serum calcitonin levels (< 150 pg/mL) can be safely observed. Increased CEA levels combined with stable calcitonin levels may indicate progressive dedifferentiation of remaining MTC cells and is associated with a worse prognosis.

Rapid calcitonin doubling times, new elevation of serum calcitonin levels, or the development of palpable disease necessitates a neck ultrasound with FNA biopsy of any suspicious masses. Evaluation for distant metastases should include a CT scan of the neck, chest, and abdomen, MRI of the liver and bone, bone scintigraphy, and FDG-PET imaging. Liver micrometastases may have a hypervascular, miliary pattern that is too small to be seen on CT imaging and may be best visualized on MRI. FDG-PET and FDG-PET/CT provide both functional and anatomic information and have a sensitivity of 68% for detection of recurrent or metastatic MTC.\textsuperscript{248} The sensitivity of FDG-PET/CT increases to 78%-80% if used selectively in patients with a serum calcitonin greater than 1000 pg/mL.\textsuperscript{249}

**Treatment of persistent or recurrent MTC**

In patients with an elevated serum calcitonin level after total thyroidectomy and a properly completed central compartment neck dissection, a lateral neck dissection is performed when
abnormal lymph nodes are identified on ultrasound, CT, or FDG-PET scanning. In the absence of imageable disease, patients with hypercalcitoninemia are followed. Approximately 50% of patients with MTC develop recurrent disease. Repeat neck operations are indicated for disease limited to the neck when all the disease can be removed, surgical palliation of compressive symptoms or impending asphyxiation, cytoreductive therapy for palliation of diarrhea or flushing, and for patients who underwent an inadequate initial operation. Repeat central neck dissection may be facilitated by using a lateral approach where the space between the common carotid artery and trachea is entered through undissected tissue planes lateral to the strap muscles.

The role of radiation therapy in the treatment of MTC is limited. The C cells of the thyroid gland do not concentrate radioiodine. As a result, $^{131}$I therapy is not utilized. External beam radiation and bisphosphonates have a role in helping to alleviate symptoms secondary to bone metastases. External beam radiation therapy may also have a palliative role in patients with extensive local disease and involvement of the aerodigestive tract and major vessels. External beam therapy can help achieve locoregional control in patients with high-risk MTC with gross or microscopic residual disease, soft tissue extension, nodal metastases, or mediastinal disease. However, it results in no survival benefit and it is associated with significant morbidity, including severe postradiation fibrosis, mucositis, esophagitis, and dysphagia. As a result, the risks and benefits must always be considered before recommending radiation therapy. Conventional chemotherapy has limited efficacy in patients with metastatic MTC. Targeted molecular therapies, most of which are TKI that target RET, VEGF, and epidermal growth factor receptors, are being investigated and currently appear to be the best available treatment option for locally advanced and metastatic MTC. Vandetanib has been recently approved by the Food and Drug Administration for symptomatic or progressive MTC. Vandetanib administration in patients with locally advanced, unresectable, or metastatic MTC has been shown to produce partial response in 30% and stable disease in 30% of patients and a 50% reduction in calcitonin levels. Other multikinase inhibitors such as sorafenib, axitinib, motesanib, and cabozantinib are also being investigated. New National Institutes of Health–funded trials are currently recruiting patients to examine the effects of panobinostat, a histone deacetylase inhibitor, pasireotide, a somatostatinpeptidomimetic, lithium, and everolimus, an inhibitor of the mammalian target of rapamycin (www.clinicaltrials.gov).

**PTL case**

A 66-year-old woman reported the sudden appearance of a large right-sided neck mass that was rapidly increasing in size. She complained of neck pressure, cough, and dyspnea that was worse when she lay flat. She had a known history of hypothyroidism and was on levothyroxine therapy. She had no prior history of head or neck radiation. She had a cousin who was treated for thyroid cancer.

On physical examination, she had an 8-cm mass in the right lobe of the thyroid gland that was extending substernally and was displacing her trachea to the left. She had no cervical or supraclavicular adenopathy. The rest of her physical examination was normal.

An ultrasound examination of the neck demonstrated a large heterogeneous mass measuring $8 \times 2.9 \times 2.9$ cm in dimensions that was completely replacing the right lobe and isthmus of the thyroid gland. The left lobe of the thyroid gland was enlarged but there was no definite dominant nodule appreciated. There were 2 abnormal-appearing right lower cervical lymph nodes with loss of the normal fatty hila. Laboratory evaluation revealed a serum TSH level of 4.88 $\mu$IU/mL, an antimicrosomal antibody titer of 805.7 IU/mL, and an anti-Tg antibody of 242.2 IU/mL.

An FNA biopsy of the mass in the right lobe of the thyroid gland revealed an atypical lymphoid cell population that was highly suspicious for a lymphoproliferative disorder. The patient underwent an incisional biopsy, which revealed a diffuse large B-cell lymphoma that was infiltrating the skeletal muscle. Postoperatively, the patient underwent a staging evaluation that included a PET-CT scan which demonstrated a large intensely hypermetabolic
mass in the right neck surrounding the carotid artery, internal jugular vein, and the trachea with extension into the right superior mediastinum consistent with the patient’s known lymphoma. There were also 4 separate hypermetabolic skeletal foci 2 in the thoracic spine and 2 in the pelvis consistent with bony metastases. A bone marrow biopsy was negative.

The patient was treated with a standard regimen of chemotherapy consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for stage IV diffuse B-cell lymphoma. She was also given prophylactic intrathecal methotrexate. With initiation of the prednisone therapy the patient experienced a rapid reduction in the size of the right-sided neck mass with significant improvement in her compressive symptoms. She completed 6 cycles of R-CHOP, the first 4 with intrathecal methotrexate. She refused radiation consolidation. At her 3-year follow-up she had no evidence for recurrent disease.

Background

PTL is a rare form of thyroid malignancy making up less than 1% of all thyroid malignancies with an annual incidence rate of 2.1 cases per 1 million persons. It accounts for only 2% of extranodal lymphomas. Like many other thyroid diseases, it has a female predominance with a female:male ratio of 3:1-4:1, and generally occurs later in life, between the ages of 50 and 80, with a peak incidence in females in their 60s.

Most thyroid lymphomas are derived from a non-Hodgkin’s B-cell lineage (70%-80%) with diffuse large B cell being the predominant form. Other rare B-cell subtypes include follicular lymphoma, Hodgkin’s lymphoma, small lymphocytic lymphoma, and Burkitt lymphoma. The remaining 20%-30% of thyroid lymphomas are derived from mucosa-associated lymphoid tissues (MALT) tumors. Since the mid-1990s, making the diagnosis of a B cell vs MALT-derived thyroid lymphoma has become important in determining treatment options and prognosis.

Clinical presentation and diagnosis

The most common presentation of PTL is a rapidly enlarging thyroid or neck mass often over the course of only 2-3 weeks. Although the acute thyromegaly is generally a painless mass, up to 30%-40% of patients complain of local compressive symptoms, including cough, dysphagia, dyspnea, hoarseness, and stridor. These symptoms are usually due to local compression by the tumor on the esophagus and trachea and by involvement of the recurrent laryngeal nerve(s). This clinical presentation is similar to patients with ATC or poorly differentiated thyroid carcinoma. Patients may have a history of hypothyroidism and a preexisting goiter that suddenly and rapidly increases in size. The “B symptoms” of lymphoma (fever, night sweats, anorexia, and weight loss) are not typical of PTL unless there is concomitant widespread nodal involvement.

Patients with PTL may have a history of Hashimoto thyroiditis that predates the development of their lymphoma by 20-30 years. Holm and colleagues have documented that Hashimoto thyroiditis increases the relative risk of developing thyroid lymphoma by a factor of 67. The exact mechanism of this is not known, but may be similar to other cancers caused by a chronic inflammatory process such as chronic erosive esophagitis leading to Barrett esophagus and esophageal adenocarcinoma. Another theory is that the lymphocytic infiltration seen in Hashimoto thyroiditis provides a lymphocyte population in the thyroid that can later undergo malignant transformation. Nevertheless, a diagnosis of PTL should be considered in any patient with Hashimoto thyroiditis and enlarging goiter.

On physical examination, patients usually have marked, firm, bilateral thyroid enlargement, often with substernal extension. The thyroid gland may be fixed to surrounding structures. They may have associated cervical lymphadenopathy.

When PTL is suspected, a serum TSH and antimicrosomal antibody levels are obtained and an FNA or core needle biopsy with flow cytometry is performed. An open biopsy with
immunohistochemical studies may be necessary to determine the specific type of lymphoma. The typical morphologic findings of high-grade B-cell lymphomas are large cells with basophilic cytoplasm and coarse nuclear chromatin, which can usually be identified with simple Hematoxylin and Eosin staining. There are scant to absent follicular cells. However, MALT tumors and some of the less well-characterized B-cell lymphomas may require immunohistochemistry and flow cytometry for identification of typical B-cell markers such as CD19-, CD20-, and CD45-positive cells, and MALT markers such as CD5-, CD10-, and CD23-negative cells. Some institutions have shown the ability to establish these diagnoses on FNA biopsy in up to 88% of cases, but emphasize that core needle biopsy or open incisional biopsy may be necessary to determine the specific cell type of lymphoma.

Once a diagnosis of PTL is made, a CT scan of the neck, chest, abdomen, and pelvis, FDG-PET scan, and bone marrow biopsy are recommended to determine the stage of the disease. Takashima and colleagues found CT scan to be superior to ultrasound in determining the local extent of disease and lymph node involvement in both the neck and in other lymph node basins. The most widely used staging system of PTL is the Ann Arbor Stage classification system (Table 6). Staging is important and plays a role in determining both overall prognosis as well as treatment recommendations. Overall 5-year survival by stage is as follows: stage IE, 80%; stage IIE, 50%; and stage III and IVE, <36%. Other prognostic factors include tumor size (>10 cm, worse prognosis), presence of local compressive symptoms, which are indicative of local invasion, rapid tumor growth, and histologic subtype. MALT lymphomas tend to be much more indolent than their B-cell counterparts. In a large case series by Derringer and colleagues 30 patients with MALT lymphomas had a 100% 5-year survival rate whereas B-cell tumors had an approximate 80% 5-year survival rate.

Treatment

PTL, like other non-solid organ lymphomas, is both radiosensitive and highly responsive to chemotherapy. However, because of the rarity of this malignancy, there are no randomized controlled studies to help guide therapeutic decision making for thyroid lymphoma. Most patients with diffuse B-cell lymphoma are treated with a standard regimen of chemotherapy consisting of rituximab, a monoclonal antibody directed against CD20 generally present on the cell surface of most B-cell lymphomas, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in combination with external radiation. Patients experience rapid and dramatic reduction in size of the thyroid lymphoma usually within hours after initiation of prednisone therapy.

The original mainstay for the treatment of PTL was surgical resection or debulking with or without radiotherapy. However, the outcomes for this approach were uniformly poor, with mortality rates of 50%-70%, and recurrence rates of at least 50% outside the treated area of the neck and upper mediastinum. As a result, in the 1980s chemotherapy was added to radiotherapy and the use of surgery was for the most part relegated for diagnosis and palliative treatment of patients with acute compressive symptoms. In a meta-analysis of more than 200 patients with PTL treated with combined chemoradiation, Doria and colleagues demonstrated a dramatic reduction in relapse rates from 43% and 37%, respectively, for chemotherapy or radiation therapy alone to 7.7% for combined chemoradiation. Similar studies from M.D. Anderson, and Matsuzuka and colleagues have documented relapse rates of 9% and 0%

Table 6

Ann Arbor staging classification of primary thyroid lymphoma (PTL).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IE</td>
<td>PTL with or without extension into the perithyroidal soft tissues.</td>
</tr>
<tr>
<td>IIE</td>
<td>PTL with involvement of lymph nodes on the same side of the diaphragm.</td>
</tr>
<tr>
<td>IIIIE</td>
<td>PTL with involvement of lymph nodes on both sides of the diaphragm.</td>
</tr>
<tr>
<td>IVE</td>
<td>PTL with dissemination to other extranodal sites such as liver, spleen, or bone marrow.</td>
</tr>
</tbody>
</table>
with overall 5-year survival rates of 80%-100% using combined chemoradiation. Most patients had a predominance of B-cell lymphomas.

Up to 80% of patients with MALT of the thyroid gland present with stage I E disease and are treated with radiation or surgical resection alone. Chemotherapy is used for patients with more advanced disease. Some small retrospective studies have borne out this concept. Derringer and colleagues reported that 30 of their 108 patients with PTL had MALT, 16 were treated with surgery alone, and 14 had combined radiation and chemotherapy. The average 5-year survival rate was 79% and there was no difference in overall survival in either treatment arm. Laing and colleagues reported a 70% disease-free survival in 31 patients with stage I or IIE MALT of the thyroid gland treated with radiation alone. As a result, the National Comprehensive Cancer Network recommends radiation or surgery alone for treatment of stage IE MALT of the thyroid gland, with chemotherapy and radiation reserved for more advanced disease.

Sippel and colleagues have reported that there may still be a role for palliative surgical resection of PTL. In this retrospective study, 27 patients underwent surgical resection or debulking of their PTL for acute airway obstruction. One patient died on the tenth postoperative day from a myocardial infarction and 5 patients required tracheostomy, but the remaining 21 patients had minimal operative morbidity. There was no comparison with patients who underwent medical therapy alone.

In summary, PTL remains a rare form of thyroid malignancy that precludes formal randomized studies of treatment protocols, but the existing literature does provide us with some general guidelines. A rapidly enlarging neck mass of thyroid origin should certainly prompt a differential diagnosis of PTL vs ATC. Recent advances in cytopathology have allowed accurate diagnosis of these tumors with the use of fine-needle biopsy and flow cytometry. Core needle biopsy and open biopsy may also be necessary for definitive diagnosis. Distinguishing a primary B-cell lymphoma from MALT should be a priority as it affects treatment and prognosis. Once a diagnosis of PTL is made, CT scan with FDG-PET remains the mainstay of appropriate staging treated with combined chemotherapy and radiation therapy with surgery reserved for patients with acute airway obstruction. Surgical intervention for this complex and rare malignancy should be carried out in experienced centers. Surgery or radiation therapy alone or in combination may be considered for early stage MALT lymphomas.

References


146. Pilli T, Brianzoni E, Capocchetti F, et al. A comparison of 1850 (50 mCi) and 3700 MBq (100 mCi) 131-Iodine administered doses for recombinant thyrotropin-stimulated postoperative thyroid remnant ablation in differentiated thyroid cancer. *J Clin Endocrinol Metab.* 2007;92:3542–3546.


152. Chindris AM, Diehl NN, Crook JE, Fatourechi V, Smallridge RC. Undetectable sensitive serum thyroglobulin (<0.1 ng/ml) in 163 patients with follicular cell-derived thyroid cancer: results of RHTSH stimulation and neck ultrasonography and long-term biochemical and clinical follow-up. *J Clin Endocrinol Metab.* 2012;97:2714–2723.


