Thyroid and Parathyroid Cancers

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Overview

Endocrine malignancies, although relatively uncommon, are often difficult to diagnose and treat effectively. This chapter will focus on thyroid and parathyroid cancers. (A discussion of carcinoid tumors, insulinomas, gastrinomas, and other gastrointestinal neuroendocrine tumors, as well as adrenocortical cancer, can be found in the «Pancreatic, Neuroendocrine GI, and Adrenal Cancers» chapter.)

FDA Approvals

In November 2012, the US Food and Drug Administration (FDA) approved the tyrosine kinase inhibitor cabozantinib (Cometriq) for the treatment of metastatic medullary thyroid cancer. The EXAM trial, a 330-patient clinical trial that led to its approval, randomized patients in a 2:1 ratio to cabozantinib at 140 mg daily (n = 219) or to placebo (n = 111). The study found that cabozantinib increased progression-free survival compared with placebo, 11.2 months vs 4 months, respectively (hazard ratio [HR] = 0.28; 95% confidence interval [CI], 0.19–0.40; $P < .001$). Reductions in tumor size lasting an average of nearly 15 months were seen in 27% of patients treated with cabozantinib.

Thyroid Cancer

Thyroid cancer is the most common endocrine cancer. For 2012, the estimated number of new cases of thyroid cancer in the United States is 56,460 (13,250 males and 43,210 females), with an estimated 1,780 deaths (780 male and 1,000 females). In women, thyroid cancer is the fifth most common cancer, accounting for 5% of all new cancer diagnosed in 2012.

The prevalence rate for occult thyroid cancers found at autopsy is 5% to 10%, except in Japan and Hawaii, where the rate can be as high as 28%. Autopsy rates do not correlate with clinical incidence.

The prevalence of thyroid nodules in the general population is 4% to 7%, with nodules more common in females than in males. The prevalence of thyroid cancer in a solitary nodule or in multinodular thyroid glands is 10% to 20%; this increases with irradiation of the neck in children and older men (see section on «Etiology and risk factors»).

Tumor Types

Thyroid cancer is classified into four main types according to its morphology and biologic characteristics. Differentiated (papillary and follicular) thyroid cancers account for more than 90% of thyroid malignancies and constitute approximately 0.8% of all human malignancies. Medullary thyroid cancers represent 3% to 5% of all thyroid neoplasms. About 75% of patients with medullary cancer have a sporadic form of the disease; the remaining 25% have inherited disease. Anaplastic carcinoma represents less than 3% of all thyroid carcinomas.

Papillary thyroid carcinoma

Papillary thyroid carcinoma is the most common subtype, and it has an excellent prognosis. Most papillary carcinomas contain varying amounts of follicular tissue. When the predominant histology is papillary, the tumor is considered to be a papillary carcinoma. Because the mixed papillary-follicular variant tends to behave like a pure papillary cancer, it is treated in the same manner and has a similar prognosis.

Papillary tumors arise from thyroid follicular cells, are unilateral in most cases, and are often multifocal within a single thyroid lobe. They vary in size from microscopic to large cancers that may invade the thyroid capsule and infiltrate into contiguous structures. Papillary tumors tend to invade the lymphatics, but vascular invasion (and hematogenous spread) is uncommon.

Up to 40% of adults with papillary thyroid cancer may present with regional lymph node metastases, usually ipsilateral. Distant metastases occur, in decreasing order of frequency, in the lungs, bones, and other soft tissues. Older patients have a higher risk of locally invasive tumors and of distant metastases. Children may present with a solitary thyroid nodule, but cervical node involvement is common in this age group; up to 10% of children and adolescents may have lung involvement at the time of diagnosis.

Follicular thyroid carcinoma

Follicular thyroid carcinoma is less common than papillary thyroid cancer, occurs in older age groups, and has a slightly worse prognosis. Follicular thyroid cancer can metastasize to the lungs and bones, often retaining the ability to accumulate radioactive iodine (RAI) (which can be used for therapy). Metastases may be appreciated many years after the initial diagnosis.

Follicular tumors, although frequently encapsulated, commonly exhibit microscopic vascular and capsular invasion. Microscopically, the nuclei tend to be large and have atypical mitotic figures. There is usually no lymph node involvement.

Follicular carcinoma can be difficult to distinguish from its benign counterpart, follicular adenoma. This distinction is based on the presence or absence of capsular or vascular invasion, which can be evaluated after surgical excision but not by fine-needle aspiration (FNA).

Thyroglobulin, normally synthesized in the follicular epithelium of the thyroid, is present in well-differentiated papillary and follicular carcinomas, infrequently in

anaplastic carcinomas, but not in medullary carcinomas. Therefore, thyroglobulin immunoreactivity is considered to be indicative of a follicular epithelial origin.

Hürthle cell, or oxyphil cell, carcinoma is a variant of follicular carcinoma. Hürthle cell carcinoma is composed of sheets of Hürthle cells and has the same criteria for malignancy as does follicular carcinoma. Hürthle cell carcinoma is thought to have a worse outcome than follicular carcinoma and is less likely to concentrate RAI.

Medullary thyroid carcinoma

Medullary thyroid carcinoma originates from the C cells (parafollicular cells) of the thyroid and secretes calcitonin. Secretory diarrhea and flushing, related to calcitonin secretion, can be clinical features of advanced medullary thyroid carcinoma. On gross examination, most tumors are firm, grayish, and gritty.

Sporadic medullary thyroid cancer usually presents as a solitary thyroid mass; metastases to cervical and mediastinal lymph nodes are found in half of patients and may be present at the time of initial presentation. Distant metastases to the lungs, liver, bones, and adrenal glands most commonly occur late in the course of the disease.

Hereditary medullary thyroid carcinoma typically presents as a bilateral, multifocal process. Histologically, hereditary medullary carcinoma of the thyroid does not differ from the sporadic form. However, the hereditary form is frequently multifocal, and it is common to find areas of C-cell hyperplasia in areas distant from the primary carcinoma. Another characteristic feature of hereditary medullary carcinoma is the presence of amyloid deposits.

There are three hereditary forms: familial medullary thyroid carcinoma; multiple endocrine neoplasia type 2A (MEN-2A), characterized by medullary thyroid cancer, pheochromocytomas, and hyperparathyroidism; and multiple endocrine neoplasia type 2B (MEN-2B), characterized by medullary thyroid cancer, marfanoid habitus, pheochromocytomas, and neuromas. These syndromes are associated with germ-line mutations of the *RET* proto-oncogene, which codes for a receptor tyrosine kinase. Hereditary medullary thyroid cancer is inherited as an autosomal dominant trait with high penetrance and variable expression. In addition, approximately 40% of sporadic medullary thyroid carcinomas contain somatic *RET* mutations, which may represent potential therapeutic targets. (For a discussion of genetic testing to screen for *RET* mutations in MEN kindreds, see section on «Diagnostic workup.»)

Anaplastic carcinoma

Anaplastic tumors are high-grade neoplasms characterized histologically by a high mitotic rate and lymphovascular invasion. Aggressive invasion of local structures is common, as are lymph node metastases. Distant metastases tend to occur in patients who do not succumb early to regional disease. Occasional cases of anaplastic carcinoma have been shown to arise from preexisting differentiated thyroid carcinoma or in a preexisting goiter.

Other tumor types

Lymphomas of the thyroid account for less than 5% of primary thyroid carcinomas. Other tumor types, such as teratomas, squamous cell carcinomas, and sarcomas, may also rarely cause primary thyroid cancers.

Sidebar: *Renal cell carcinoma is the most common extra-thyroidal tumor to metastasize to the thyroid. It accounts for almost half (42%) of patients with this condition. Colorectal cancer, lung cancer, breast cancer, and sarcomas account for 26%, 19%, 11%, and 6%, respectively, of metastases to the thyroid. Females show a slight predilection for metastases to the thyroid from nonthyroidal tumors. Of metastases to the thyroid gland, 44.2% occur in glands with abnormalities such as primary thyroid neoplasms and benign thyroid conditions. The interval between diagnosing the primary tumors and their metastases to the thyroid gland is 4.5 to 75 months (Chung AY et al:* Thyroid *22:258–268, 2012).*

Epidemiology

Age and gender

Most patients are between the ages of 25 and 65 years at the time of diagnosis of thyroid carcinoma. Women are affected more often than men (2:1 ratio for the development of both naturally occurring and radiation-induced thyroid cancer).

Etiology and Risk Factors

Differentiated thyroid cancer

Therapeutic Radiation-induced thyroid cancer. Radiation exposure of the thyroid during childhood is the most clearly defined environmental factor associated with benign and malignant thyroid tumors. The predominant types of radiation are therapeutic external radiation for the treatment of cancer, historical use of external radiation to treat a wide variety of nonmalignant conditions, and exposure to nuclear fallout (from testing or accidents or in Japanese survivors of atomic bombing and children living in the area of Chernobyl). External low-dose radiation therapy to the head and neck during infancy and childhood, frequently used between the 1940s and 1960s for the treatment of a variety of benign diseases, has been shown to predispose an individual to thyroid cancer. The younger a patient is at the time of radiation exposure, the higher is the subsequent risk of developing thyroid carcinoma. Also, as mentioned previously, women are at increased risk for radiation-induced thyroid cancer. There is a latency period ranging from 10 to 30 years from the time of low-dose irradiation to the development of thyroid cancer.

As little as 11 cGy and as much as 2,000 cGy of external radiation to the head and neck have been associated with a number of benign and malignant diseases. It was once thought that high-dose irradiation (> 2,000 cGy) to the head and neck did not increase the risk of neoplasia. However, it has been shown that patients treated with mantle-field irradiation for Hodgkin lymphoma are at increased risk for thyroid carcinoma compared with the general population, although they are more likely to develop hypothyroidism than thyroid cancer.

Radiation-associated thyroid cancer has a natural history and prognosis identical to that for sporadic thyroid cancer.

Non-therapeutic radiation exposure. Besides radiation-induced thyroid cancer, there are only sparse data on the etiology of differentiated thyroid cancer. There has been intensive research on distinguishing molecular factors important for cell differentiation, growth, and motility. Considerable attention has focused on BRAF, a member of the RAF family of serine/threonine kinases that mediates cellular responses to growth-promoting signals via the RAS-RAF-MEK-MAPK signaling pathway. *BRAF* mutations so far have only been documented in papillary thyroid carcinoma (45%) and papillary thyroid carcinoma–derived anaplastic thyroid carcinoma (25%). Patients with *BRAF* mutations have higher rates of mortality and are typically less responsive to therapy. Because of this, *BRAF* mutations have been implicated as potential prognostic factors and therapeutic targets. In addition, because angiogenesis is critical for survival of tumors, vascular endothelial growth factor (VEGF) expression in papillary thyroid carcinoma correlates with decreased disease-free survival, and presence of *BRAF* mutation is associated with a higher risk of metastasis and recurrence.

Medullary thyroid cancer

The notable risk factor is having a germ-line mutation of the *RET* proto-oncogene (see genetic testing). Approximately 25% of cases of medullary thyroid cancer are associated with heritable syndromes due to a *RET* mutation, MEN-2A and MEN-2B.

Anaplastic thyroid cancer

Approximately 20% of patients with anaplastic thyroid cancer have a history of differentiated thyroid cancer. The majority of synchronous thyroid tumors are papillary cancers, but coexisting follicular cancers have also been reported. Anaplastic thyroid cancer develops from more differentiated tumors as a result of one or more dedifferentiating events. Since activating mutations in *BRAF* and *RAS* are seen in both well-differentiated thyroid malignancies and anaplastic thyroid cancer, these are presumed to be early events in the progression pathway. Late events that are seen more commonly in the anaplastic tumor, rather than the precursor well-differentiated tumor, include mutations in p53 tumor suppressor protein, 16p, catenin, beta-1, and PIK3CA.

Signs and Symptoms

Most thyroid cancers present as asymptomatic thyroid nodules. Patients may feel pressure symptoms from nodules as they begin to increase in size. A change in the voice can be caused by a thyroid cancer or benign goiter. The voice change usually occurs when there is compression of the larynx or invasion of the recurrent laryngeal nerve. Secretory diarrhea and flushing can be symptoms suggestive of advanced medullary thyroid cancer.

On physical examination, a thyroid nodule that is hard or firm and fixed may represent a cancer. The presence of palpable enlarged nodes in the lateral neck, even

in the absence of a palpable nodule in the thyroid gland, could represent metastases to the lymph nodes.

Diagnostic Workup

As mentioned previously, thyroid nodules are present in 4% to 7% of the general population and in a higher percentage of individuals who have had irradiation to the head and neck region. Most thyroid nodules are benign (colloid nodules or adenomas); therefore, it is important for the workup to lead to surgical resection for malignant nodules and to avoid unnecessary surgery for benign lesions. Although most solid nodules are benign, thyroid carcinomas usually present as solid nodules. A cystic nodule or a «mixed» (cystic-solid) lesion is less likely to represent a carcinoma and more likely to be a degenerated colloid nodule. Molecular testing of a nodule for specific mutations (*BRAF, RAS, RET/PTC,* and *PAC8/PPAR-gamma)* can be useful in the analysis of an indeterminate FNA cytology. Standard molecular testing is not yet recommended.

History and physical examination

With the discovery of a thyroid nodule, a complete history and physical examination focusing on the thyroid gland and adjacent cervical lymph nodes should be performed. Pertinent historical factors include a history of childhood head and neck irradiation, total body irradiation for bone marrow transplant, family history of thyroid carcinoma or thyroid cancer syndrome in a first-degree relative, exposure to ionizing radiation from fallout in childhood or adolescence, and rapid growth of the nodule and hoarseness. In patients with a history of irradiation to the head and neck, the risk of cancer is higher (as great as 50%) than in nonirradiated patients (10% to 20%). Nodules that occur in either the very young or the very old are likely to be cancerous, particularly in men. Also, a new nodule or a nodule that suddenly begins to grow is worrisome. Pertinent physical findings suggesting possible malignancy include vocal cord paralysis, lateral cervical lymphadenopathy, and fixation of the nodule to surrounding tissues.

Imaging modalities. Ultrasonographic and radionuclide (radioiodine and technetium) scans are also used in the evaluation of thyroid nodules.

• *Ultrasonography*—Ultrasonography is now widely considered an essential tool in the assessment of thyroid nodules. Thyroid ultrasonography should be performed in all patients with known or suspected thyroid nodules. Certain features are associated with malignancy and can guide physicians in deciding which nodules should be biopsied. A consensus statement from the Society of Radiologists in Ultrasound outlined various features of solitary nodules associated with thyroid cancer: microcalcifications, hypoechogenicity, irregular margins or no halo, solid composition, intranodule vascularity, and more tall than wide dimensions. No single feature has both high sensitivity and specificity; however, the combination of two or more factors can increase the likelihood of cancer. Certain ultrasonographic appearances may also be highly predictive of a benign nodule—a pure cystic nodule is highly unlikely to be malignant. A spongiform appearance, defined as an aggregation of multiple microcystic components in more than 50% of the nodule

volume, is 99.7% specific for identification of a benign thyroid nodule. Although there is a decrease in cancer rate per nodule in patients with multiple nodules, the overall rate of thyroid cancer per patient is similar to that seen in patients with a solitary nodule.

Thyroid cancer is most often found in the dominant, or largest, nodule in multinodular glands; however, approximately one-third of the cases of cancer are found in nondominant nodules. Nodule size is a poor predictor of malignancy, because the likelihood of cancer has been shown to be the same regardless of nodule size. Multiple ultrasonographic features other than size need to be considered in determining which nodules are more likely to be malignant and thus should be biopsied, including increased intranodular vascularity, hypoechogenicity of a solid nodule, microcalcifications, or presence of abnormal cervical lymph nodes. Patients with multiple thyroid nodules have the same risk of malignancy as those with solitary nodules, and selective FNA biopsy based on suspicious ultrasonographic findings is performed for further diagnosis.

• *Radioactive iodine uptake and scan*—If the serum thyroid-stimulating hormone (TSH) level is subnormal, a radioiodine thyroid scan should be obtained to document whether the nodule is hyperfunctioning, or «hot» (ie, tracer uptake is greater than the surrounding normal thyroid); isofunctioning, or «warm» (ie, tracer uptake is equal to the surrounding thyroid); or nonfunctioning, or «cold» (ie, tracer uptake is less than the surrounding thyroid tissue). Thyroid isotope scans cannot differentiate absolutely a benign from a malignant nodule but can, based on the functional status of the nodule, assign a probability of malignancy. Most thyroid carcinomas occur in cold nodules, but only 10% of cold nodules are carcinomas. If the cytology reading reports a follicular neoplasm, an I-123 thyroid scan may be considered if it has not already been done, especially if the serum TSH level is in the low-normal range. If a concordant autonomously functioning nodule is absent on the radionuclide scan, lobectomy should be considered.

Computed tomography (CT) or magnetic resonance imaging (MRI) scans of the neck may be appropriate in some cases.

Sidebar: *A fluorodeoxyglucose positron emission tomography (FDG-PET) scan is shown to improve diagnostic accuracy of indeterminate thyroid nodules, but results vary among studies. A meta-analysis found that the incidence of thyroid «incidentalomas» on FDG-PET or PET/CT was 2.46%. For solitary nodules with FDG-avidity, a malignancy ratio was found to be 34.6%. Diffuse uptake in the thyroid is commonly due to benign disease, such as thyroiditis (Bertagna F et al:* J Clin Endocrinol Metab *97: 3866-3875, 2012).*

FNA. FNA has become the most accurate and cost-effective initial diagnostic test for the evaluation of thyroid nodules, and it is the procedure of choice. The 2009 guidelines by the American Thyroid Association (ATA) recommend ultrasound-guided FNA for evaluating thyroid nodules; this can determine whether the lesion is cystic or solid. Ultrasound guidance is preferred over palpation to localized nodules and leads to a higher likelihood of diagnostic cytology (> 25% to 50% cystic component) or sampling error (difficult to palpate or posteriorly located nodules). A

prospective study showed that ultrasound-guided FNA was more cost-effective than FNA by palpation. For solid lesions, cytology can yield one of three results: benign, malignant, or indeterminate. The accuracy of cytologic diagnosis from FNA is 70% to 80%, depending on the experience of the person performing the aspiration and the pathologist interpreting the cytologic specimen. FNA biopsy results are divided into four categories: nondiagnostic, malignant, indeterminate or suspicious for neoplasm, and benign. In a series of 98 «suspicious» FNA biopsies, findings of cellular atypia (pleomorphism, enlarged nuclei, nuclear grooves, coarse or irregular chromatin, prominent or multiple nucleoli, or atypical or numerous mitotic figures) or follicular lesions with atypia were associated with malignancy 20% and 44% of the time, respectively. Follicular lesions without atypia have a 6.7% risk of malignancy. Use of the Bethesda System recommended by the National Cancer Institute for reporting thyroid cytopathology allows for more systematic assessment of risk of malignancy and helps in determining follow-up and further course of management.

Core needle biopsy has been used as an alternative method for diagnosis. Some studies have shown that the adequacy of sample may be greater with core needle biopsy than with FNA. However, there are conflicting reports as to whether a core needle biopsy offers greater accuracy in the diagnosis of a thyroid nodule.

Molecular markers. Five percent to 30% of aspirations yield indeterminate cytologic findings, which include three subtypes: atypia (or follicular lesion) of undetermined significance, follicular neoplasm or suspicious for follicular neoplasm, and suspicious for malignancy. Improvement in the assessment of indeterminate FNA biopsy results may allow better risk stratification. Certain clinical features can improve the diagnostic accuracy for malignancy in patients with indeterminate cytology, but overall predictive values are still low. These include male sex, nodule size (> 4 cm), older patient age, and cytologic features such as presence of atypia.

In the United States, there are two commercially available approaches to the molecular characterization of FNA aspirates: molecular markers of malignancy and high-density genomic data for molecular classification.

The use of molecular markers (eg, *BRAF*, *RAS*, *RET/PTC*, *Pax8-PPARγ*) may be considered for patients with indeterminate cytology on FNA to help guide management. These genetic markers have high specificity and a high positive predictive value and therefore identify which indeterminate nodules are malignant. However, they fail to rule out cancer with sufficient certainty to avoid surgery in most patients with indeterminate nodules.

Recent studies have described the development of gene-expression classifiers that better distinguish benign from malignant thyroid nodules. With the use of the gene-expression classifier, the negative predictive value was 95% for aspirates classified as atypia (or follicular lesions) of undetermined significance and 94% for aspirates classified as follicular neoplasms or lesions suspicious for follicular neoplasm. These data suggest consideration of a more conservative approach for most patients with thyroid nodules that are cytologically indeterminate on FNA and benign according to gene-expression classifier results.

Laboratory evaluation

Thyroglobulin. Thyroglobulin (Tg) is synthesized only by thyroid follicular cells and is released into serum along with the thyroid hormones. Routine measurement of serum Tg for initial evaluation of thyroid nodules is not recommended by the 2009 ATA guidelines. Measurements of serum Tg provide important information about the presence or absence of residual, recurrent, or metastatic disease in patients with differentiated thyroid cancer. Limitations of serum Tg assays include interassay variability and the high prevalence of anti-Tg antibodies, which may interfere with Tg assay results. Testing should be done using a sensitive assay, ideally using the same assay for each sample. Thyroglobulin antibodies should be measured with each sample. In the absence of antibody interference, serum Tg has a high degree of sensitivity and specificity to detect thyroid cancer, especially after total thyroidectomy and remnant ablation, with the highest degrees of sensitivity noted following thyroid hormone withdrawal or stimulation using recombinant human TSH (rhTSH). A single rhTSH-stimulated serum Tg level less than 0.5 ng/mL in the absence of anti-Tg antibody has an approximately 98% to 99.5% likelihood of identifying patients who are completely free of tumor on follow-up.

Calcitonin level. Calcitonin is a specific product of thyroid C cells (parafollicular cells). The routine measurement of serum calcitonin in patients with thyroid nodules is controversial and is not currently recommended in the United States, given the rarity of the disease. However, if obtained, a basal or stimulated serum calcitonin level of 100 pg/mL or greater should be interpreted as suspicious for medullary thyroid carcinoma and further evaluation and treatment should ensue.

The serum calcitonin concentration should be measured preoperatively in patients with medullary thyroid cancer and in carriers of an *RET* mutation for comparison with postoperative values. It is a sensitive marker of residual medullary thyroid carcinoma. When the postoperative basal serum calcitonin is undetectable, the risk of persistent or recurrent residual disease is low. In patients who have clinically palpable medullary carcinoma , the basal calcitonin level is almost always elevated. In patients with smaller tumors or C-cell hyperplasia, the basal calcitonin level may be normal, but administration of synthetic gastrin (pentagastrin) or calcium results in marked elevation of calcitonin levels. The use of calcitonin levels as a tumor marker and stimulation screening in hereditary forms of medullary cancers has been largely replaced by genetic testing (see below).

Carcinoembryonic antigen (CEA). Serum CEA levels may be elevated in patients with medullary thyroid cancer. The serum markers (calcitonin and CEA) are important in the follow-up of patients with medullary thyroid cancer, and they should be measured 2 to 3 months postoperatively.

Ruling out pheochromocytoma and hyperparathyroidism. Medullary thyroid carcinoma can be associated with MEN-2A, MEN-2B, or familial non-MEN. Both the MEN-2A and MEN-2B syndromes are characterized by medullary thyroid cancer and pheochromocytoma. Thus, in any patient with hereditary medullary thyroid cancer, it is imperative that the preoperative workup include a determination of 24-hour urinary catecholamine and metanephrine levels to rule out the presence of a

pheochromocytoma. Fractionated plasma metanephrine levels have been demonstrated to have a high sensitivity and may be included in the initial assessment. According to the ATA 2009 guidelines, exclusion of a pheochromocytoma may include any of the following tests: (1) negative *RET* proto-oncogene analysis and family history; (2) negative plasma free metanephrines and normetanephrines, or negative 24-hour urinary metanephrines and normetanephrines; (3) negative findings on adrenal CT or MRI scans. Given the possibility that any patient with medullary thyroid cancer may have MEN-2, preoperative testing must also include measurement of serum calcium to rule out primary hyperparathyroidism, which requires concomitant surgical intervention.

Genetic testing. Germ-line mutations in the *RET* proto-oncogene are responsible for familial non-MEN medullary thyroid cancer, in addition to MEN-2A and MEN-2B. DNA analysis performed on a peripheral blood sample is a highly reliable method for identifying the presence of an *RET* mutation. The 2009 management guidelines of the ATA regarding medullary thyroid cancer recommend that all patients with FNA or calcitonin diagnostic or suspicious for medullary thyroid cancer undergo *RET* mutation analysis, ideally performed with genetics counseling and completed preoperatively. Approximately 95% of patients with an *RET* mutation will eventually develop medullary thyroid cancer; thus, prophylactic surgical treatment is recommended. The specific mutated codon of *RET* may correlate with the aggressiveness of medullary carcinoma of the thyroid. This should be considered when counseling affected individuals and their families regarding prophylactic thyroidectomy and the age at which to perform such surgery. Long-term data regarding the effectiveness of prophylactic thyroidectomy based on *RET* testing are scarce at this time. In a recent report of 50 patients (19 years and younger) treated surgically after positive *RET* mutation analysis, 33 had carcinoma identified in the surgical specimen. At the time of the publication, 44 patients were found to be free of disease more than 5 years after surgery.

Recommended ages for prophylactic surgery range from within the first 6 months of life to 10 years of age, depending on the mutation. The prophylactic surgical procedure of choice is total thyroidectomy with or without central lymph node dissection.

Periodic determinations of stimulated calcitonin levels may help establish the early diagnosis of medullary thyroid cancer in those who do not undergo surgery but will not always prevent the development of metastatic medullary thyroid carcinoma.

Screening

At this time, no organization recommends periodic screening for thyroid cancer using neck palpation or ultrasonography in average-risk, asymptomatic adults. However, the American Cancer Society recommends examination of the thyroid during a routine checkup, since this surveillance can result in case findings.

Staging and Prognosis

TABLE 1: AJCC/UICC staging of thyroid cancer

Primary tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤ 2 cm in greatest dimension limited to the thyroid
T1a	Tumor ≤ 1 cm, limited to the thyroid
T1b	Tumor > 1 cm but ≤ 2 cm in greatest dimension, limited to the thyroid
T2	Tumor 2 cm to 4 cm in greatest dimension, limited to the thyroid
T3	Tumor > 4 cm in greatest dimension limited to the thyroid, or any tumor wit minimal extrathyroid extension (eg, extension to sternothyroid muscle or perithyroid soft tissues)
T4	All anaplastic carcinomas are considered T4 tumors
T4a	Moderately advanced. Intrathyroidal anaplastic carcinoma. Tumor of any siz extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4b	Very advanced. Anaplastic carcinoma with gross extrathyroid extension. Tu invades prevertebral fascia or encases carotid artery or mediastinal vessel

Note: All categories may be subdivided: (s) solitary tumor, (m) multifocal tumor (the largest determines the classification).

Regional lymph nodes (N)

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

Distant metastasis (M)

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

Stage grouping:

	Papillary or follicular < 45 years old			Papillary or follicular (≥ 45 years or medullary (any age patie			
Stage I	Any T	Any N	M0	Stage I	T1	N0	M
Stage II	Any T	Any N	M1	Stage II	T2	N0	M
Stage III				Stage III	T3	N0	M
					T1	N1a	M
					T2	N1a	M
					T3	N1a	M
Stage IVA				Stage IVA	T4a	N0	M
					T4a	N1a	M
					T1	N1b	M
					T2	N1b	M
					T3	N1b	M
					T4a	N1b	M
					T4a	Any N	M

Table 1: AJCC/UICC staging of thyroid cancer
Unlike most other cancers, in which staging is based on the anatomic extent of disease, the American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC) staging of thyroid cancer also takes into consideration patient age at the time of diagnosis and tumor histology (Table 1).

Differentiated thyroid cancers

Recurrence and death following initial treatment of differentiated thyroid cancer can be predicted using a number of risk-classification schemes. The most commonly used systems are the AMES (age, metastases, extent, and size) and AGES (age, grade, extent, and size) classifications.

Low-risk patients are generally those younger than 45 years with low-grade nonmetastatic tumors that are confined to the thyroid gland and are less than 1 to 5 cm. Low-risk patients enjoy a 20-year survival rate of 97% to 100% after surgery alone.

High-risk patients are those 45 years and older with a high-grade, metastatic, locally invasive tumor in the neck or with a large tumor. Large size is defined by some authors as more than 1 cm and by others as more than 2 or more than 5 cm. The 20-year survival rate in the high-risk group drops to between 54% and 57%.

Intermediate-risk patients include young patients with a high-risk tumor (metastatic, large, locally invasive, or high grade) or older patients with a low-risk tumor. The 20-year survival rate in this group of patients is approximately 85%.

Medullary thyroid carcinoma

Medullary thyroid carcinoma is associated with an overall 10-year survival rate of 40% to 60%. When medullary carcinoma is discovered before it becomes palpable, the prognosis is much better: patients with stage I medullary tumors (ie, tumors ≤ 2 cm or nonpalpable lesions detected by screening and provocative testing) have a 10-year survival rate of 95%.

Stage II medullary cancers (tumors > 2 but < 4 cm) are associated with a survival rate of 50% to 90% at 10 years. Patients who have lymph node involvement (stages III and IVA disease) have a 10-year survival rate of 15% to 50%. Unfortunately, approximately 50% of patients have lymph node involvement at the time of diagnosis.

When there are distant metastases (stages IVB and IVC), the long-term survival rate is compromised. In patients with metastatic medullary thyroid cancer, the disease often progresses at a very slow rate, and patients may remain alive with disease for many years. Doubling time of calcitonin and CEA are predictive of prognosis. In a 2005 study by Barbet et al of patients with medullary thyroid cancer, those with a calcitonin doubling time of less than 6 months had a survival of 25% at 5 years and 8% at 10 years vs 100% survival among patients with a calcitonin doubling time of more than 2 years. The 2009 ATA management guidelines for medullary thyroid cancer recommend monitoring of doubling time of CEA and calcitonin. Frequency of

surveillance has been recommended on the basis of the doubling time calculation for calcitonin and CEA. Patients with calcitonin or CEA doubling times of more than 2 years typically do not require systemic therapy, and such treatment should only be initiated after thorough discussion with the patient. Patients with rapidly progressing disease with a doubling time of less than 2 years should be considered for treatment.

The ATA website has a calculator for CEA and calcitonin doubling time.

Anaplastic thyroid cancer

Anaplastic thyroid cancer does not have a generally accepted staging system, and all patients are classified as having stage IV disease. Anaplastic carcinoma is highly malignant and has a poor 5-year survival rate (0% to 25%). Most patients die of uncontrolled local disease within several months of diagnosis.

Treatment of Thyroid Cancer

Because most thyroid nodules are not malignant, it is important to differentiate malignant from benign lesions to determine which patients should undergo surgery. If the cytologic result from FNA biopsy indicates that the nodule is benign, which is the case most of the time, the nodule can be safely monitored.

Surgery
Malignant or indeterminate cytologic features are the main indications for surgery.

Malignant nodule

Differentiated thyroid cancer. If the cytologic result shows a malignant lesion, a total or near-total thyroidectomy should be performed if any of the following are present: a primary lesion larger than 1 cm, contralateral thyroid nodules, regional or distant metastases, personal history of radiation therapy to the head or neck, or a first-degree family history of differentiated thyroid cancer. There is significant debate in the literature regarding the extent of thyroid surgery for primary tumors confined to one lobe and for tumors that are small and of low-risk potential for recurrence. The surgical options include total lobectomy, total lobectomy with contralateral subtotal lobectomy (subtotal thyroidectomy), or total thyroidectomy. The decision about which procedure to perform should be based on the risk of local recurrence and the anticipated use of radioactive iodine (see section on «Radioactive I-131»).

Most authorities agree that a low-risk patient (age < 45 years) with a 1-cm or smaller papillary thyroid cancer should undergo ipsilateral total lobectomy alone. Most experts also agree that total thyroidectomy (or at least subtotal thyroidectomy) is appropriate for high-risk patients with high-risk tumors. Intermediate-risk patients are treated with total lobectomy alone or total (or subtotal) thyroidectomy plus postoperative radioactive iodine. Preoperative neck imaging may be helpful in planning the surgery. Patients with radiation-induced thyroid malignancies can be treated similarly, because their cancers have a similar prognosis; however, a total thyroidectomy may be preferable in these patients because of the increased risk of multicentric tumors.

For multinodular glands with a single nodule positive for differentiated thyroid cancer, the surgical approach would include total thyroidectomy. A lobectomy may be considered in some instances if other nodules are benign or if it is the patient's preference.

The neck should be palpated intraoperatively. If positive nodes are found, a regional lymph node dissection should be performed.

Medullary carcinoma. Patients with medullary thyroid cancer should be treated with total thyroidectomy and central neck dissection. If there is involvement of the lateral neck nodes found on imaging or on clinical examination, a modified neck dissection should be performed (see section on «Lymph node dissection»). If the cancer is confined to the thyroid gland, the patient is usually cured. Postoperative adjuvant external irradiation may be used in certain circumstances (see section on «External radiation therapy»).

Anaplastic carcinoma. A tracheostomy often is required in patients with anaplastic thyroid cancer because of compression of the trachea. If the tumor is confined to the local area, total thyroidectomy may be indicated to reduce local symptoms produced by the tumor mass. Radiation therapy is used to improve locoregional tumor control, often together with radiosensitizing chemotherapy.

Indeterminate or suspicious nodule

Indeterminate and suspicious FNA samples should be treated as possible cancers and should be histologically evaluated. The initial operation performed in most patients should be total lobectomy, which entails removal of the suspicious nodule, hemithyroid, and isthmus. There is no role for nodulectomy or enucleation of thyroid nodules. The specimen can be sent for frozen-section analysis during surgery. If the frozen section is clearly benign, no further resection is required.

Follicular lesion. If frozen-section biopsy results indicate a follicular lesion in a patient who is a candidate for total thyroidectomy and a decision cannot be made as to whether the lesion is benign or malignant, two options are available: (1) stop and wait for final confirmation of the diagnosis, which may require a future operation; or (2) proceed with subtotal or total thyroidectomy, which obviates the need for a later operation. The diagnosis of follicular carcinoma requires identification of vascular or capsular invasion, which may not be evident on frozen-section biopsy.

Hürthle cell carcinoma. If the nodule is diagnosed as a Hürthle cell carcinoma, total thyroidectomy is generally recommended for all large (> 4 cm) invasive lesions. Small lesions can be managed with total lobectomy. However, controversy remains over the optimal treatment approach for this cancer.

Lymph node dissection

Therapeutic dissection. Therapeutic central neck node dissection should be performed for medullary carcinomas and other thyroid neoplasms with nodal involvement by palpation or preoperative imaging. The dissection should include all

the lymphatic tissue in the pretracheal area and along the recurrent laryngeal nerve and anterior mediastinum. If there are clinically palpable nodes in the lateral neck, a modified neck dissection is performed.

Prophylactic dissection. There is no evidence that performing prophylactic neck dissection improves survival. Therefore, aside from patients with medullary thyroid cancer, who have a high incidence of involved nodes, only therapeutic neck dissection is indicated.

Removal of individual abnormal nodes. «Berry picking» is not advised when lateral neck nodes are palpable because of the likelihood of missing involved nodes and disrupting involved lymphatic channels.

Metastatic or recurrent disease

Survival rates from the time of the discovery of metastases (lung and bone) from differentiated thyroid cancer are less favorable than those associated with local recurrence (5-year survival rates of 38% and 50%, respectively). Survival also depends on whether the metastatic lesions take up I-131.

Surgery, with or without I-131 ablation (discussed below), can be useful for controlling localized sites of recurrence. Approximately half of patients who undergo surgery for recurrent disease can be rendered free of disease with a second operation.

Radioactive I-131

Uses in papillary or follicular thyroid carcinoma

There are two basic uses for I-131 in patients with papillary or follicular thyroid carcinoma: ablation of normal residual thyroid tissue after thyroid surgery and treatment of thyroid cancer, either residual disease in the neck or metastasis to other sites in the body. It should be emphasized that patients with medullary (in the absence of a concomitant epithelial cell-derived differentiated thyroid cancer), anaplastic, and most Hürthle cell cancers do not benefit from I-131 therapy.

Postoperative ablation. Postoperative ablation of residual thyroid tissue should be considered in high-risk patients and patients with high-risk tumors. Ablation of residual normal thyroid tissue allows for the use of I-131 scans to monitor for future recurrence, possibly destroys microscopic foci of metastatic cancer within the remnant, and improves the accuracy of thyroglobulin monitoring.

Ablation must also be accomplished in patients with regional or metastatic disease before the use of I-131 for treatment, because the normal thyroid tissue will preferentially take up iodine compared with the cancer. Some states permit the use of I-131 for ablation and treatment on an outpatient basis, but administration is strictly governed by national guidelines, which minimize the risk of radiation exposure to the public.

Following surgery, the patient can be treated with liothyronine (Cytomel) for 2 weeks. The TSH level should be determined approximately 4 to 6 weeks after surgery; in patients who undergo total or subtotal thyroidectomy, TSH levels will generally be greater than 50 μU/mL. A postoperative iodine scan can then be performed. If this scan documents residual thyroid tissue, an ablative dose of I-131 should be given. The patient should be advised not to undergo any radiographic studies with iodine during ablation therapy and to avoid seafood and vitamins or cough syrups containing iodine. Patients are prepared with a specific diet before the I-131 therapy. Iodine-123 may also be used in the postoperative setting. It may produce a better-quality image than I-131 scans.

For patients who have contraindications for thyroid hormone withdrawal, administration of rhTSH is an alternative for preparation for radioiodine ablation of a post-surgical thyroid remnant. Currently, there are no long-term data ascertaining the maintenance of a low tumor recurrence rate using rhTSH, which may have a quality-of-life advantage compared with thyroid hormone withdrawal and is the subject of a clinical trial.

In general, doses of I-131 up to 75 to 100 mCi will ablate residual thyroid tissue within 6 months following ingestion. In some patients, it may take up to 1 year for complete ablation to occur. Patients should be monitored following ablation, and when they become hypothyroid, hormone replacement therapy should be given until they are clinically euthyroid and TSH is suppressed. Recently, lower doses have been found to be effective, and some authors have recommended doses between 25 and 50 mCi, assuming they achieve euthyroid levels with TSH suppression to less than 0.1 μU/mL.

Approximately 6 to 12 months after ablation of the thyroid remnant, a follow-up I-131 scan should be performed. Recombinant human thyrotropin alfa (Thyrogen) is now available. Patients may continue on thyroid replacement and receive two doses of thyrotropin before I-131 scanning; this approach can prevent the symptoms of hypothyroidism.

Sidebar: *A large, multicenter, 2-by-2, randomized, noninferiority trial that compared low-dose radioiodine (30 mCi, 1.1GBq) and high-dose radioiodine (100 mCi, 3.7 GBq) as well as thyrotropin alfa administration versus thyroid hormone withdrawal for patients with differentiated thyroid cancer (excluding extracervical metastatic disease) was recently published. Noninferiority in successful ablation, as measured by negative scan and thyrotropin level, was found, demonstrating less toxicity with the lower doses of radioiodine (Mallick U et al:* N Engl J Med *366:1674–1685, 2012). At the same time, another randomized, 2-by-2 phase III trial in a similar group of differentiated thyroid cancers showed similar results (Schlumberger M et al:* N Engl J Med *366:1663–1673, 2012). This also raises the issues of whether any radioiodine therapy is required for low-risk patients, as noted in the accompanying editorial (Alexander EK et al:* N Engl J Med *366:1732–1733, 2012).*

Treatment of residual cancer. For disease in the tumor bed or lymph nodes that was not surgically resectable, an I-131 dose of 100 to 150 mCi is given. For disease in the lungs or bone, the I-131 dose is 200 to 250 mCi. Following this therapy, the patient is

again given thyroid hormone replacement, and adequate suppression is maintained by monitoring TSH levels.

Some clinicians advocate obtaining a repeat scan in 1 year, along with a chest x-ray film, and repeating this procedure yearly until a normal scan is obtained. However, the frequency of repeated scans and the dose of I-131 are rather controversial and should be guided by the individual's risk profile.

Following thyroid remnant ablation, serum Tg measurements are useful in monitoring for recurrence. Since Tg in a patient receiving thyroid hormone replacement may be suppressed, a normal test result may be incorrect about 10% of the time. In general, the presence of disease is accurately predicted by a Tg value of greater than 5 ng/mL while the patient is in the suppressed state and by a value of greater than 10 ng/mL in the hypothyroid state. However, measurable disease may not be identified in many patients. Whether or not they should be treated on the basis of the Tg value if the I-131 scan is normal is a subject of current debate. Any rise in the Tg level from the previous value should increase the suspicion of recurrent disease.

Neck ultrasonography is useful to evaluate locoregional tumor recurrence and should be performed at yearly intervals for 5 to 10 years after initial therapy, depending on the stage of disease. Continued monitoring is necessary, because late recurrence can occur. It should be pointed out that certain aggressive tumors may neither be RAI-avid nor synthesize Tg. PET scanning may contribute to localization of disease in some cases and may even carry prognostic value. PET/CT may be more useful than other imaging techniques; in a recent study, additional information was obtained with PET/CT in up to 67% of cases.

Side effects and complications

Acute effects. The acute side effects of I-131 therapy include painful swelling of the salivary glands and nausea. Ibuprofen or other pain relievers are usually used to decrease salivary gland discomfort. Nausea may be treated with standard antiemetics.

Rarely, in patients with significant residual thyroid tissue, radioactive iodine may cause acute thyroiditis, with a rapid release of thyroid hormone. This problem can be treated with steroids and beta-blockers.

Patients must also be cautioned not to wear contact lenses for at least 3 weeks following ingestion of I-131, because the tears are radioactive and will contaminate the lenses and possibly lead to corneal ulceration.

Long-term complications. Long-term risks of are not well understood. They can include effects on the salivary glands consisting of sialadenitis and xerostomia, and possible increased risk of bladder tumors and colon cancers with repeated administrations.

Bone marrow suppression and leukemia are potential long-term complications of I-131 therapy but are poorly documented and appear to be extremely rare. Patients

should have a complete blood cell count performed prior to ingestion of an I-131 dose to ensure adequate bone marrow reserve. They should also have blood counts measured yearly. Leukemia occurs rarely with doses of I-131 lower than 1,000 mCi.

Pulmonary fibrosis. Pulmonary fibrosis may be seen in patients with pulmonary metastases from papillary or follicular thyroid cancer who are treated with I-131. Those with a miliary or micronodular pattern are at greater risk, because a portion of normal lung around each lesion may receive radiation, leading to diffuse fibrosis.

Effects on fertility. Data have documented an increase in follicle-stimulating hormone (FSH) levels in one-third of male patients treated with I-131. Changes in FSH levels after one or two doses of I-131 are generally transitory, but repeated doses may lead to lasting damage to the germinal epithelium. Sperm banking should be considered in male patients likely to receive cumulative doses of I-131 higher than 500 mCi.

The effects of I-131 on female fertility have been investigated. A published article showed no significant difference in the fertility rate in women receiving RAI. Exposure to more than 100 mCi of I-131 was also not associated with increased miscarriages, congenital malformations, or thyroid disease or cancer in offspring. However, it is generally recommended to avoid pregnancy for 1 year after therapeutic I-131 administration.

External Radiation Therapy

Papillary or follicular thyroid cancer

There are a number of indications for external irradiation of papillary or follicular thyroid carcinoma. Surgery followed by RAI may be used for disease that extends beyond the capsule. However, if all gross disease cannot be resected, or if residual disease is not RAI-avid, external irradiation is used as part of the initial approach for locally advanced disease in older patients. The benefit of adjuvant external irradiation for cause-specific survival is inferred from institutional series. Intensity-modulated radiation therapy is associated with decreased severe late toxicities in an institutional series and provides the best target coverage in dosimetric studies.

Unresectable disease. External irradiation is useful for unresectable disease extending into the connective tissue, trachea, esophagus, great vessels, and anterior mediastinum. For unresected disease, doses of 6,000 to 6,500 cGy are recommended. The patient should then undergo I-131 scanning, and if uptake is detected, a dose of I-131 should be administered.

Recurrence after resection. External irradiation may also be used after resection of recurrent papillary or follicular thyroid carcinoma that no longer shows uptake of I-131, or for gross unresectable disease. In this situation, doses of 5,000 to 6,600 cGy are delivered to the tumor bed to prevent local recurrence. Multiple-field techniques and extensive treatment planning are necessary to deliver high doses to the target volume to minimize the risk of significant complications.

Recurrences to regional lymph nodes that are not resectable can be salvaged with regional external radiation therapy. In either situation, the radiation fields extend from cervical lymph node stations to the superior mediastinum, with esophageal stricture reported as a common long-term morbidity of treatment.

Palliation of bone metastases. External radiation therapy is useful in relieving pain from bone metastasis. If the metastasis shows evidence of I-131 uptake, the patient should be given a therapeutic dose of I-131 followed by local external radiation therapy to the lesion of up to 4,000 to 5,000 cGy. The use of intravenous bisphosphonate therapy has been shown to decrease the pain of bone metastasis and improve reported quality of life.

Anaplastic thyroid carcinoma

Anaplastic carcinoma of the thyroid is an exceptionally aggressive disease, with few long-term survivors. It often presents as a rapidly expanding mass in the neck and may not be completely resected. External irradiation to full dose (6,000 to 6,500 cGy) may slow the progress of this disease but rarely controls it.

Chemoradiation therapy. There are reports of the use of accelerated fractionation regimens of external irradiation (160 cGy twice daily to 5,700 cGy) with weekly doxorubicin in patients with anaplastic thyroid cancer, as well as reports of the combination of doxorubicin and cisplatin with external irradiation. These regimens have improved local tumor control but at the expense of increased toxicity. Unfortunately, the majority of patients die of local and/or distant recurrence.

Medullary thyroid carcinoma

External irradiation has been used for medullary thyroid cancer in the postoperative setting, but only retrospective series are available. Therefore, this technique is controversial. However, much of the available literature has indicated that indications would include positive surgical margins, gross residual disease, or extensive lymph node metastasis. Further controversy exists in the setting of elevated postoperative calcitonin levels in patients who have undergone macroscopically complete resection, without radiographic evidence of distant disease. The recommended dose is 5,000 to 7,000 cGy in 5 to 7 weeks. Radiation is also used for palliation of different sites of metastatic disease.

Role of Medical Therapy

Differentiated thyroid cancer

Thyroid hormone suppression. As mentioned previously, thyroid hormone is used to suppress TSH in most patients with differentiated thyroid cancer after surgery and I-131 (as appropriate) treatment. Greater TSH suppression has been associated with improved progression-free survival in patients with high-risk papillary thyroid carcinoma. Modest TSH suppression in patients with stage II disease yields similar results. Patients with stage I disease do not appear to have any change in outcomes based on the degree of TSH suppression. ATA and National Comprehensive Cancer Network (NCCN) guidelines recommend that initial TSH suppression should be

below 0.1 mU/L for high-risk and intermediate-risk thyroid cancer patients, while maintenance of the TSH at or slightly below the lower limit of normal (0.1 to 0.5 mU/L) is appropriate for low-risk patients. Patients who remain disease-free for several years can probably have their TSH levels maintained within the reference range.

Systemic therapy. Eighty-five percent of patients with differentiated thyroid carcinomas are cured with surgery, , and TSH suppression. A small percentage of patients will develop or present with metastases and are more difficult to treat. When metastases have radioiodine avidity, prognosis is better and further may be used. However, when multiple doses of have been tried or the patient has non-RAI–avid disease, other options need to be considered. Although it is the most effective medical treatment for differentiated thyroid carcinoma, only about 50% to 80% of primary tumors and their metastases take up . Metastatic differentiated thyroid cancer can be stable for many years, a reason why patients with progressive or symptomatic disease should be referred for consideration of systemic treatments. Systemic therapy through a clinical trial is the treatment of choice for RAI-refractory, progressive distant metastatic disease.

Systemic cytotoxic chemotherapy. The more frequently used agent in thyroid cancer studies was doxorubicin, either alone or in combination with cisplatin. The responses were limited and only lasted a few months. Newer cytotoxic drugs (eg, taxanes, gemcitabine, and irinotecan) have not been reported in a significant number of patients with differentiated thyroid cancer. Because of toxic side effects, short duration of responses, and low response rates, cytotoxic chemotherapy agents are not recommended.

Systemic cytotoxic chemotherapy has been evaluated for widespread disease, although reproducibly effective regimens have not been identified to date.

Newer molecular-targeted therapy. Within the past decade, molecularly targeted treatments have been studied in patients with advanced thyroid carcinoma no longer responsive to and not amenable to surgery. These agents are still being investigated in clinical trials. The most promising results in clinical trials have been seen with antiangiogenic therapies.

Several phase II trials have evaluated novel treatments with good response in patients with differentiated thyroid cancer that is refractory to traditional treatments. The recognition of the presence of oncogenic mutations such as *BRAF*, *RAS*, and *RET/PTC* in papillary thyroid carcinoma has prognostic implications and guides therapeutic effect in patients with advanced cancer. Because the vascular endothelial growth factor receptor (VEGFR) is also up-regulated in patients with differentiated thyroid carcinoma, drugs that target VEGFR and/or inhibit BRAF are currently under investigation. According to the 2011 NCCN guidelines, patients with metastatic differentiated thyroid carcinoma that is not amenable to surgery or radioiodine therapy should be referred to a clinical trial investigating targeted therapies or considered for treatment with other small molecule tyrosine kinase inhibitors (ie, sorafenib [Nexavar], axitinib [AG-013736]. sunitinib [Sutent], or pazopanib [Votrient]) if a clinical trial is not recommended or feasible (www.nccn.org, Thyroid

Carcinoma, v.2.2011). Sorafenib, sunitinib, and pazopanib are oral antiangiogenics and are commercially available and approved for other indications in the United States. These drugs have been used in phase II trials and are promising agents for patients with progressive, RAI-refractory differentiated thyroid carcinoma. Two phase II trials with sorafenib have been performed in patients with differentiated thyroid carcinoma, and both have shown favorable results. A phase III international randomized controlled trial is currently under way.

Several molecular-targeted tyrosine kinase inhibitors, such as sorafenib and sunitinib, have shown promising results for patients with RAI-resistant thyroid cancer with partial response ranging from 13% to 20%, and stable disease in 60% to 68% of treated patients.

Once differentiated thyroid carcinoma is found to be refractory to radioiodine, patients should have full staging examinations to determine the extent of disease and rate of progression. Diagnostic procedures should include neck ultrasonography; CT scan of the neck, chest, and abdomen; and CT scan or MRI of the brain. MRI of the spine and pelvis should be considered to evaluate fore bone metastases. A baseline PET scan may complete the workup. Progression rate is assessed using response evaluation criteria in solid tumors (RECIST).

Patients with RAI-refractory differentiated thyroid carcinoma enjoy a long indolent phase, when the tumor is stable or slowly progressive and asymptomatic. In such patients, the benefits of novel therapies may be outweighed by drug toxicities, and a «watchful waiting» approach is a valid strategy. Patients with measurable lesions and documented progression should be considered candidates for systemic treatment.

Sidebar: *A study of cabozantinib, an oral, potent inhibitor of MET, VEGFR2, and RET enrolled 15 patients with metastatic differentiated thyroid cancer. Participants were required to have RAI-refractory disease, to have progressed on standard therapies, and to have measurable disease. Eight of the 15 patients (53%) had confirmed partial responses (PRs), including 1 patient with marked improvement of a bone infiltrating lesion. Six patients (40%) had stable disease (SD); all 14 patients who had 1 or more post-baseline scans experienced tumor regression (range: -9% to -55%). The disease control rate (PR + SD) was 80% at 16 weeks. Ten of the 15 patients (67%) remain on cabozantinib with a median follow-up of 7.3 months. Median progression-free survival and overall survival have not been reached. Most common grade 3/4 adverse effects were diarrhea (20%), elevated lipase level (20%), hypertension (13%), and palmar-plantar erythrodyesthesia (13%); one related grade 5 event reported was hemoptysis due to aorto-tracheal fistula in a patient with a history of prior mediastinal radiation therapy and extensive neck surgeries (*J Clin Oncol *30(s), abstract 5547, 2012).*

Sidebar: *In a recent study of selumetinib (AZD6244, ARRY-142866), an MEK1/2 inhibitor, changes in tumor iodine uptake and RECIST response after RAI therapy were evaluated. In this study, 24 patients were enrolled, 22 were eligible, and 20 were evaluable. For the 20 evaluable patients, median age was 61 (range: 44 to 77 years) and 11 were men. Nineteen patients had tumors analyzed for* BRAF *and* N-,K-RAS *mutations. Eight patients had* BRAF *mutant (MUT) and 11 had* BRAF *wild-type*

tumors; 1 patient was to be analyzed. Selumetinib increased I-124 uptake in 12 of the 20 patients (4 of 8 with BRAF *MUT; 8 of the 12 other patients). Eight of the 12 patients who achieved sufficient iodine avidity to warrant RAI therapy included all 5 patients known to be* NRAS *MUT to date and 1* BRAF *MUT patient. Of the 7 patients who have received RAI, 5 had PRs; 2 had SD. Mean percent reduction in thyroglobulin level in this group (pre-RAI vs 2 months post-RAI) was 91%. No Common Terminology Criteria for Adverse Events toxicities greater than grade 2 attributable to selumetinib were observed. One patient received a diagnosis of myelodysplastic syndrome more than 51 weeks after RAI (unrelated to selumetinib;* J Clin Oncol *30(s), abstract 5509, 2012).*

Medullary thyroid carcinoma

In patients with medullary thyroid carcinoma, the usual treatment is surgery. Various oral, small molecule tyrosine kinase inhibitors have been investigated in patients with locally advanced, metastatic, or progressive hereditary and sporadic medullary thyroid carcinomas. The responses have been variable among agents and have consisted of partial response as the best outcome. However, the development of these novel agents and others offers much promise in the targeted treatment of metastatic medullary thyroid carcinoma, which currently has no cure. In patients with hereditary medullary carcinoma who have a coexisting pheochromocytoma, appropriate control of catecholamine hypersecretion should precede thyroid surgery.

In April 2011, the FDA approved vandetanib for treatment of medullary thyroid carcinoma in patients with progressive locoregional and metastatic disease under a restricted prescription program, REMS. Approval was based on two pivotal trials of vandetanib. An open-label phase II trial of patients with locally advanced or metastatic hereditary medullary thyroid carcinoma showed partial response in 20%, stable disease at 24 weeks or more in 53%, calcitonin levels decreased by 50% in 80%, and CEA levels decreased by 50% in 53%. In addition, vandetanib exhibited a significant objective response rate compared with placebo. Vandetanib's safety and efficacy were established in an international phase III randomized, double-blind, placebo-controlled study that showed median progression-free survival of 16.4 months in the placebo group vs 22.6 months in the vandetanib arm (HR = 0.35). In clinical trials of vandetanib, QT interval prolongation, torsade de pointes, and sudden death have been reported; thus, prescribers must be properly educated about these risks and should participate in the REMS program.

Cabozantinib, also known as XL-184 (a c-MET, VEGFR2, and RET kinase inhibitor), has shown robust antiangiogenic and antitumor effects in patients with medullary thyroid cancer in phase I trials. A phase I dose escalation study of XL-184 that included 37 patients with medullary thyroid cancer showed partial response in 68% of patients, stable disease in 41% of patients, and tumor shrinkage of 30% or more in 49% of patients. Dose-limiting toxicities included grade 3 palmar-plantar erythrodysesthesia, mucositis, and elevations in liver enyzme levels.

Sidebar: *Cabozantinib is an oral inhibitor of MET, VEGFR2, and RET. A phase III randomized study of cabozantinib vs placebo in 330 patients with progressive, unresectable, locally advanced or metastatic medullary thyroid cancer is under way.*

The median patient age is 55 years; 67% are male; 96% have measurable disease. RET *mutation status is positive in 48%, negative in 12%, and unknown 39%. Prior exposure to tyrosine kinase inhibitor was found in 21%; 78% had no prior exposure, and in 2% exposure history is unknown). As of June 15, 2011, 44.7% of patients receiving cabozantinib and 13.5% receiving placebo remained on the study treatment. Statistically significant progression-free survival prolongation of 7.2 months was observed; median progression-free survival for cabozantinib was 11.2 months vs 4 months for placebo (HR = 0.28; 95% CI, 0.19–0.40;* P < *.001). Progression-free survival results favored the cabozantinib group across subset analyses, including* RET *status and prior tyrosine kinase inhibitor use. Overall response rate was 28% for cabozantinib vs 0% for placebo (*P < *.001). An interim analysis of overall survival (44% of the 217 required events) did not show a difference between cabozantinib and placebo. The most frequent grade 3 or higher adverse events (cabozantinib vs placebo) were diarrhea (15.9% vs 1.8%), palmar-plantar erythrodysesthesia (12.6% vs 0%), fatigue (9.3% vs 2.8%), hypocalcemia (9.3% vs 0%), and hypertension (7.9% vs 0%;* J Clin Oncol *30(s), abstract 5508, 2012).*

Sidebar: *Fifty-nine patients were enrolled in a phase II trial of lenvatinib, an oral tyrosine kinase inhibitor targeting VEGFR1-3, FGFR1-4, RET, KIT, and PDGFRβ. A dose reduction for management of toxicity was needed in 54% of patients, and 22% were withdrawn from therapy because of toxicity. The most common treatment-related adverse events were proteinuria (58%), diarrhea (56%), hypertension (48%), fatigue (44%), decreased appetite (41%), nausea (34%), and decreased weight (32%). Independent imaging review (IIR) confirmed partial responses in 21 patients (relative risk [RR] = 36%; 95% CI, 24–49) and investigator assessment confirmed partial responses in 29 patients (RR = 49%; 95% CI, 36–62). For patients who received prior VEGFR-directed treatment (n = 26), RR was 35% (IIR); with no prior VEGFR-directed treatment (n = 33), RR was 36% (IIR). Median progression-free survival by IIR was 9 months (95% CI, 7; based on minimum 8 months' follow-up, 46% events observed). There was no clear difference in treatment response between* RET*-mutant and* RET*–wild type patients. Low baseline levels of angioprotein-2, sTie-2, hepatocyte growth factor, and interleukin-8 were associated with greater tumor shrinkage and prolonged progression-free survival, whereas high baseline levels of VEGF and sVEGFR3 were associated with greater tumor shrinkage (*J Clin Oncol *30(s), abstract 5591, 2012).*

Anaplastic thyroid carcinoma

As mentioned previously, the usual treatment for patients with resectable or localized anaplastic thyroid cancer is surgery. Like radiotherapy, chemotherapy is an important alternative approach, but further evaluation is needed to optimize its effectiveness. Patients with unresectable local tumors should be referred to clinical trials, treated with radiotherapy and chemotherapy, or maintained with best supportive care. Imatinib (Gleevec, a Bcr-Abl and PDGF inhibitor) and sorafenib (Nexavar) are currently being studied in phase II trials in patients with anaplastic thyroid carcinoma, with preliminary data showing partial response in 13% to 25%, and stable disease in 27% to 50% of patients. Further investigation is needed to identify better therapeutic options for patients with this aggressive form of thyroid carcionma.

Parathyroid Carcinoma

Parathyroid carcinoma is a rare cause of hypercalcemia, accounting for more than 2% of cases with primary hyperparathyroidism.

Epidemiology and Etiology

The disease presents in midlife and occurs with similar frequency in both sexes. The etiology of parathyroid carcinoma is obscure; an association with prior neck irradiation is not apparent. Parathyroid carcinoma can be associated with the hereditary hyperparathyroidism–jaw tumor syndrome, which is due to an inactivating mutation of the *HRPT2* gene that encodes the parafibromin protein. In addition, somatic mutations of the *HRPT2* gene have been demonstrated in sporadic parathyroid carcinomas (66% to 100%) but have not been seen with sporadic adenomas.

Signs and Symptoms

Most patients with parathyroid cancer have symptomatic moderate to severe hypercalcemia (mean serum calcium level, 15 mg/dL) and high parathyroid hormone levels. They often present with a palpable neck mass. Unlike benign hyperparathyroidism, renal and bone abnormalities are more common in patients with parathyroid cancer.

Rarely, nonfunctioning tumors may present as neck masses; their clinical course is similar to that of functioning tumors. Clinical concern about parathyroid cancer should be raised in the presence of a palpable neck mass and severe hypercalcemia, recurrent hyperparathyroidism, or associated vocal cord paralysis.

Pathology

The principal features of parathyroid cancer include a trabecular pattern, mitotic figures, thick fibrous bands, and capsular or vascular invasion of disease. Other important features include lymphatic or hematogenous metastases and histologic evidence of tumor infiltration into the surrounding tissues (including macroscopic adherence or vocal cord paralysis).

Although cytologic evidence of mitoses is necessary to establish the diagnosis of carcinoma, mitotic activity alone is an unreliable indicator of malignancy. The only reliable microscopic finding of malignancy is invasion of surrounding structures or metastasis to lymph nodes or other organs.

Treatment

Surgical treatment of primary hyperparathyroidism

The diagnosis of parathyroid carcinoma is sometimes made during surgical exploration for primary hyperparathyroidism. Most surgeons advocate identification of all four parathyroid glands. In most cases, the upper glands can be found on the posterior aspect of the upper third of the thyroid lobe, just cephalad to the inferior thyroid artery and adjacent to the recurrent laryngeal nerve as it enters the larynx.

The inferior parathyroid glands are more variable in location. Most are found on the posterior or lateral aspect of the lower pole of the thyroid gland, but the inferior parathyroid glands may be ectopically placed in the superior or true mediastinum, often within the thymus.

The inferior and, less commonly, superior glands can be found in an ectopic location in the upper or lateral neck, adjacent to the esophagus, or within the carotid sheath.

Surgical exploration for primary hyperparathyroidism. Most cases of primary hyperparathyroidism are caused by a single hyperfunctioning parathyroid adenoma. If the surgeon finds one (or occasionally two) enlarged abnormal gland(s) and the remaining glands are normal, the enlarged gland should be removed.

If four enlarged glands are found, indicating the rare case of primary parathyroid hyperplasia, subtotal parathyroidectomy including 3.5 glands should be performed. Consideration should be given to transplanting the remaining gland remnant to an ectopic location that would be easily accessible to the surgeon if hyperparathyroidism recurs.

If only normal glands are found at exploration, a missed adenoma in an ectopic location should be suspected. Thorough intraoperative neck and superior mediastinal exploration should be performed, and if the missing gland cannot be found, thymectomy and hemithyroidectomy should be performed to exclude an intrathymic or intrathyroidal adenoma. Localization studies, including CT/MRI or radionuclide imaging, should precede reexploration for a missed adenoma.

Intraoperative parathyroid hormone (ioPTH) levels are increasingly used to guide surgery for primary hyperparathyroidism. A 50% or greater decrease in the ioPTH level from the preexcision value to the 10-minute postexcision value is used as a predictor of successful surgery. The advent of ioPTH monitoring, coupled with preoperative localization studies (sestamibi scanning), has facilitated less invasive surgical techniques, such as minimally invasive parathyroidectomy. This has resulted in shorter average hospitalization stays and reduced postoperative recovery times. Loss of parafibromin and *Rb* expression and overexpression of *galectin-3* can be distinguishing features of parathyroid carcinoma vs other parathyroid tumors.

The use of ioPTH with parathyroid hyperplasia requires more strict evaluation of ioPTH levels. Siperstein et al performed a prospective evaluation of ioPTH and bilateral neck exploration and found that up to 15% of cases will have additional «abnormal» glands that were not predicted by ioPTH or preoperative imaging. This study demonstrates the need for long-term follow-up of patients undergoing focused parathyroid surgery.

If parathyroid carcinoma is suspected, based on the severity of hyperparathyroidism or invasion of surrounding tissues by a firm parathyroid tumor, aggressive wide excision is indicated. This procedure should include ipsilateral thyroidectomy and en bloc excision of surrounding tissues as necessary.

Patterns of recurrence of cancer. The average time from initial surgery to the first recurrence of cancer is approximately 3 years but may be as long as 10 years. The thyroid gland is the usual site of involvement, with disease «seeding» in the neck a common pattern. Other sites of involvement include the recurrent nerve, strap muscles, esophagus, and trachea.

Distant metastases can be present at the time of initial surgery, or local spread to contiguous structures in the neck may be followed subsequently by distant metastases to the lungs, bone, and liver.

In a recent analysis, 85% of patients with parathyroid carcinoma were alive 5 years after diagnosis; death usually results from complications of the hypercalcemia rather than from the tumor burden.

Treatment of isolated metastases. Isolated metastases should be aggressively resected to enhance survival and control hypercalcemia. Liver-directed therapies can be considered to reduce tumor/hormonal burden.

Medical therapy

Morbidity and mortality are generally caused by the effects of unremitting hypercalcemia rather than tumor growth. Medical treatment provides temporary palliation of hypercalcemia. Drugs used include bisphosphonates, such as pamidronate (60 to 80 mg every 4 to 6 days) or zoledronic acid (Zometa); calcitonin, at 4 to 8 IU/kg every 6 to 12 hours; mithramycin (plicamycin [Mithracin]), at 25 µg/kg every 4 to 6 days; and gallium nitrate (Ganite), at 100 to 200 mg/m²/d IV for 5 days. Cinacalcet (Sensipar), a calcimimetic that targets the calcium-sensing receptor on parathyroid cells and reduces parathyroid hormone secretion, is an FDA-approved oral treatment of hypercalcemia associated with parathyroid carcinoma (up to 90 mg bid) in patients who do not respond to surgery or other medical treatments.

Sidebar: *A proof-of-concept study using denosumab (Xgeva) to treat hypercalcemia of malignancy is ongoing and may provide potential therapeutic options for hypercalcemia in patients with parathyroid carcinoma that do not respond to standard therapy (Hu et al: ASCO 2011; available at www.asco.org in the trials in progress section).*

Radiation therapy

There is little evidence for an effect of adjuvant radiation therapy in achieving locoregional control. Some institutions have used surgical margin status to determine whether patients receive adjuvant radiation therapy including elective nodal irradiation.

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