Current Best Practices in the Management of Thyroid Nodules and Cancer

Clinical Practice Today CME

Co-provided by

DukeHealth MedIQ

Learning Objectives

Upon completion, participants should be able to:

- Explain the diagnostic strategies and proper evaluation in patients presenting with thyroid nodules or thyroid cancer
- Discuss the recent advances in surgical and targeted treatment approaches for thyroid cancer

Introduction

Thyroid nodules are a common finding in clinical practice and can be palpated in 4% to 7% of adults on physical examination.[1-3] However, most thyroid nodules are not clinically recognized—an estimated 20% to 76% of the general population have at least 1 nonpalpable thyroid nodule, with similar percentages discovered at autopsy.[1-3] Nonpalpable thyroid nodules are discovered incidentally in approximately 50% of patients who undergo neck and carotid imaging, such as ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET).[4]

The incidence of thyroid nodules increases with age, and women are 4 times more likely than men to develop thyroid nodules.[5] Graves' disease and pregnancy are also associated with increasing numbers and size of thyroid nodules, and low iodine intake is linked to an increased incidence of hyperfunctioning nodules (toxic adenomas) and goiter formation.[1]

Introduction (cont.)

Thyroid Cancer

Thyroid cancer is relatively rare, representing 3.8% of all new malignancies.[6] Approximately 1.1% of adults will be diagnosed with thyroid cancer at some point during their lifetime.[6] However, the incidence of thyroid cancer is increasing worldwide and has been rising on average 5.5% annually in the United States over the last 10 years.[6,7] In developed countries, this dramatic increase has been attributed in part to the improved diagnosis of small papillary cancers that previously would have gone undiagnosed and would not have required treatment.[8] However, the rise has been observed across the globe and has been seen in larger-sized tumors as well; therefore, increased screening cannot account fully for the increased incidence.[7] Generally, survival rates for thyroid cancer patients are high, with more than 97% of persons diagnosed surviving 5 or more years, but disease recurrence is common.[5,6]

Introduction (cont.)

Thyroid Cancer (cont.)

Differentiated thyroid carcinomas (DTCs) account for more than 90% of all thyroid cancers.[9] In the United States, overall direct and indirect medical costs for DTC have been estimated at $1.6 billion annually and are projected to exceed $3.5 billion by 2030.[10] Diagnosis, surgery, and adjuvant therapy for newly diagnosed patients constitutes the greatest proportion of costs.[10]

Diagnosis of Thyroid Nodules

Presenting Symptoms

Most patients with thyroid nodules have few or no symptoms. Thyroid nodules are typically discovered by a clinician during a routine physical examination or imaging procedure or by the patient during routine self-care.[1] They may be soft or firm on palpation, although some nodules may be painful when palpated.[1] Sudden pain associated with a thyroid mass may indicate hemorrhage of a nodule.[2] Anaplastic carcinoma or primary lymphoma of the thyroid may also cause rapidly progressive and sometimes painful enlargement of a thyroid nodule.[2]

Diagnosis of Thyroid Nodules (cont.)

Presenting Symptoms (cont.)

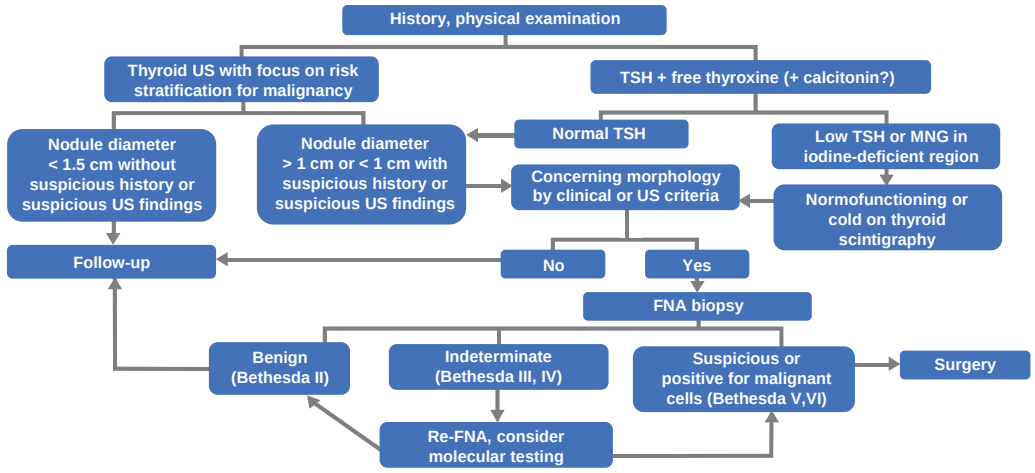
Small differentiated thyroid tumors usually do not cause any symptoms on initial physical examination and rarely cause esophageal symptoms, vocal cord paralysis, or airway obstruction at clinical presentation. Thus, a lack of local symptoms does not rule out malignancy.[1,2] Some thyroid tumors, however, may be embedded within large goiters and may cause a slowly progressive compression of vital structures of the neck; in the absence of a multinodular goiter (MNG), cough and dysphonia associated with tracheal compression also suggest a malignant lesion.[2] Additionally, slow but progressive growth of a nodule over weeks or months may be associated with malignancy.[2]

Diagnosis of Thyroid Nodules (cont.)

Thyroid Nodule Evaluation in the Primary Care Setting

Primary care clinicians are usually the first to recognize a thyroid mass. The primary goal of thyroid nodule evaluation is to determine whether the nodule is benign or malignant.[1] Figure 1 is an algorithm for the diagnosis and management of palpable thyroid nodules.[2] Patients should be queried about a family history of thyroid disease or thyroid cancer, previous head and neck irradiation (eg, in childhood), or recent pregnancy.[2,9] Physical findings suggesting possible malignancy include vocal cord paralysis, lateral cervical lymphadenopathy, and fixation of the nodule to surrounding tissue.[9]

Figure 1. Algorithm for the Diagnosis and Management of Palpable Thyroid Nodules



FNA = fine needle aspiration; MNG = multinodular goiter; TSH = thyroid stimulating hormone; US = ultrasound.
Adapted from Gharib H, Papini E, Paschke R, et al. American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. *Endocr Pract*. 2010;16(Suppl 1):1-43; Copyright 2010, with permission from the American Association of Clinical Endocrinologists; Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016;26(1):1-133.

Diagnosis of Thyroid Nodules (cont.)

Thyroid Nodule Evaluation in the Primary Care Setting (cont.)

Elevated serum TSH in the presence of a thyroid nodule is associated with an increased risk of malignancy, whereas low TSH levels are associated with a decreased probability of malignancy.[2,9] In adults with autonomously functioning (toxic or "hot") thyroid nodules, the incidence of malignancy is low. Hyperfunctioning MNGs may have both "cold" (potentially malignant) and hyperfunctioning areas.[2] Nodules discovered in patients with Hashimoto thyroiditis or Graves' disease should be evaluated in the same way as in other cases.[2]

Diagnosis of Thyroid Nodules (cont.)

Thyroid Nodule Evaluation in the Primary Care Setting (cont.)

High-resolution US is the most sensitive test available to evaluate a palpable nodule, determine its structure, measure its dimensions, and identify other nodules or changes in the thyroid gland.[2] Current guidelines from the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists/Italian Association of Clinical Endocrinologists/European Thyroid Association (AACE/AME/ETA) recommend that all patients with palpable thyroid nodules, MNGs, or nodules found incidentally on CT, MRI, or PET undergo thyroid US.[2,9] US is not recommended for general screening or in patients with a normal thyroid gland on palpation and low risk of thyroid cancer.[2] Although no US finding is fully predictive of malignancy, the following characteristics have been associated with cancerous nodules[2,9]:

- Marked hypoechogenicity
- Microcalcifications
- Irregular or microlobulated margins
- Extension of lesions beyond the thyroid capsule
- Chaotic arrangement or intranodular vascularity
- "More tall than wide" shape of the nodule

Diagnosis of Thyroid Nodules (cont.)

Thyroid Nodule Evaluation in the Primary Care Setting (cont.)

Although most thyroid nodules containing fluid are benign, papillary thyroid carcinoma (PTC) may present with cystic changes, and degenerative changes with fluid-filled areas may be noted in larger neoplastic lesions.[2] The presence of two or more suspicious US criteria substantially increases the risk of malignancy.[2]

Imaging studies other than US are generally not useful. Radioisotope imaging has largely been abandoned in the initial workup of a thyroid nodule because serum TSH, thyroid US, and fine needle aspiration (FNA) biopsy can accurately diagnose a majority of nodules.[2,11] CT and MRI play almost no role in the initial evaluation of a thyroid nodule, although CT may be of value in the assessment of size or substernal extension of a nodular goiter.[2,11]

Diagnosis of Thyroid Nodules (cont.)

When to Refer

Primary care physicians should consider timely referral to an endocrinologist or endocrine surgeon for any patient with US results suggestive of thyroid cancer. Patients with a higher risk of thyroid cancer based on age (> 65 years), past personal history of neck irradiation, or a strong family history of an endocrine tumor should receive immediate referral. Nonurgent referral is acceptable in patients who have a bland thyroid nodule and abnormal thyroid function because these nodules are rarely cancerous.[12] Nonurgent referral is also recommended if the nodule has been increasing in size slowly over months to years.[12,13]

Diagnosis of Thyroid Nodules (cont.)

When to Refer (cont.)

However, immediate referral (even before US is obtained) is warranted in patients presenting with any of the following symptoms or characteristics[12,13]:

- Tracheal compression/stridor due to thyroid swelling
- Unexplained hoarseness or voice changes
- Rapidly growing solitary nodule
- Palpable cervical lymphadenopathy

Diagnosis of Thyroid Nodules (cont.)

Fine Needle Aspiration Biopsy

FNA biopsy with a 25- or 27-gauge needle is the most accurate and cost-effective tool for evaluating thyroid nodules in euthyroid patients.[2,14,15] Its key benefits are in identifying benign nodules that might otherwise be surgically removed and differentiating types of neoplastic nodules.[15] Before the widespread use of FNA, only 14% of surgically resected thyroid nodules were found to be malignant. Current FNA use has increased that to more than 50%, indicating that far fewer patients with thyroid nodules are undergoing unnecessary surgeries.[15,16]

Diagnosis of Thyroid Nodules (cont.)

Fine Needle Aspiration Biopsy (cont.)

FNA can diagnose many thyroid cancers with certainty, especially PTC.[15] However, up to 30% of FNAs yield indeterminate cytologic findings.[17] For some, repeat FNA can be helpful; however, these patients should be referred to an endocrinologist or an endocrine surgeon for a clear discussion of all available diagnostic options and risks involved. When removed at surgery, 2% to 35% of nodules with indeterminate FNA results are found to be malignant.[17] In FNA-identified, follicular-patterned lesions, approximately 20% to 35% are determined to be cancerous.[14] FNA biopsies characterized by cytologic features that are suspicious of malignancy are confirmed to be malignant in 60% to 75% of lesions.[15]

Diagnosis of Thyroid Nodules (cont.)

Fine Needle Aspiration Biopsy (cont.)

The Bethesda System for reporting thyroid cytopathology was developed with the goal of standardizing terminology related to thyroid FNA. According to this system, FNA results fall into 1 of 6 categories[15]:

I. Nondiagnostic or unsatisfactory
II. Benign
III. Atypia of undetermined significance or follicular lesion of undetermined significance
IV. Follicular neoplasm or suspicious for a follicular neoplasm
V. Suspicious for malignancy
VI. Malignant

Diagnosis of Thyroid Nodules (cont.)

Fine Needle Aspiration Biopsy (cont.)

Patients in whom FNA-biopsied thyroid nodules are found to be benign should undergo periodic clinical and US monitoring.[2] Current guidelines recommend that nonpalpable nodules (≤ 1 cm) do not need to be biopsied unless suspicious characteristics are identified on US.[2,9] Otherwise, small nodules can be followed with serial US evaluation.[2]

Diagnosis of Thyroid Nodules (cont.)

Molecular Markers

In recent years, molecular markers have been identified that may help differentiate indeterminate nodules, thus preventing unnecessary surgeries.[11] Genetic mutations specific to PTC include alterations to the *BRAF*, *RAS*, or *RET/PTC* genes, whereas mutations in *RAS* proto-oncogenes or *PAX-8-PPAR* gamma rearrangements are found in approximately 70% of follicular cancers.[11] Finding these mutations in an indeterminate cytologic sample is strongly predictive of thyroid cancer; however, a negative result decreases but does not eliminate the risk of cancer.[11,18] Currently, *BRAF* and *RAS* are the most widely studied mutations used for clinical decision making in indeterminate FNA thyroid nodule biopsies.[11] Gene expression classifiers, which measure the expression of at least 140 genes, have also been developed that can aid in identifying both benign and malignant nodules.[5] These technologies have not yet been widely incorporated into clinical practice, but it is likely that they will eventually become integral diagnostic tools.[5,18,19]

Thyroid Cancers

Differentiated Thyroid Carcinomas

DTCs account for more than 90% of thyroid cancer cases and include PTC, follicular thyroid carcinoma (FTC), and Hürthle cell carcinoma.[20] Surgery, radioactive iodine (RAI), and TSH suppression are curative in more than 85% of patients with DTC, and the majority have a good prognosis.[20] In patients with localized disease, 5-year survival rates are approximately 98%.[6] In widely metastatic disease, however, the 10-year survival rate drops to 42%.[20]

Thyroid Cancers (cont.)

Papillary thyroid carcinoma. PTC, accounting for the vast majority (80% to 85%) of all thyroid cancers, is a slow-growing tumor that arises from the thyroxine (T4)- and thyroglobulin-producing follicular cells of the thyroid.[21] Its development is strongly associated with childhood exposure to ionizing radiation.[21] PTC usually presents as a solitary asymptomatic thyroid nodule.[5] The lesions may appear anywhere within the gland and average 2 to 3 cm, although carcinomas measuring less than 1 cm are also commonly identified.[21] The lesions are usually firm with an invasive appearance, resembling scar tissue; lesional calcification and cyst formation may also be observed. Microscopically, lesions consist of papillary fronds and psammoma bodies. Psammoma bodies are rarely found in benign tumors, and their presence in cervical lymph nodes is indicative of papillary carcinoma.[21] Regional lymph node metastases occur in more than 50% of cases, but this finding does not markedly affect survival, particularly in patients younger than 45 years of age. Lung and bone metastases occur in 5% to 7% of patients, but even in these situations, survival may be prolonged with RAI therapy.[21] Factors associated with more aggressive PTC variants and poorer prognosis include older age at diagnosis, male sex, larger tumor size, and extrathyroidal growth. Pathologic variables indicating a more guarded prognosis include tall cell, diffuse sclerosing, insular, solid, and columnar variants.[5,21]

Thyroid Cancers (cont.)

Follicular thyroid carcinoma. FTC, accounting for 11% of thyroid cancers, is generally a single encapsulated tumor with a microfollicular histologic pattern.[5] It is typically more aggressive than PTC and is characterized by follicular cell invasion of the tumor capsule and/or blood vessels. An FTC diagnosis can be assigned only after diagnostic thyroidectomy or lobectomy with histologic analysis demonstrating tumor capsule invasion by follicular cells.[5] In some instances, FTC can be highly invasive, with up to 80% metastasizing; these cases have a poorer prognosis, with 20% of patients dying within a few years of diagnosis. Older age at diagnosis, larger tumor size, and advanced tumor stage confer a poorer prognosis. The 10-year survival rate for FTC is 85%.[5]

Thyroid Cancers (cont.)

Hürthle cell carcinomas. Hürthle cell carcinomas, accounting for 3% of thyroid cancers, are sometimes considered a variant of FTC; however, they also share similarities with PTC.[5] As with FTC, diagnosis is made based on histopathology after diagnostic lobectomy or thyroidectomy. Pulmonary metastases may occur in up to 35% of patients, and Hürthle cell carcinomas may be more aggressive in older patients. Ten-year survival rates have been reported to be approximately 76%.[5]

Thyroid Cancers (cont.)

Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) represents 4% of thyroid cancers and arises from calcitonin-producing parafollicular C cells of the thyroid.[5] Tumors may arise either sporadically or as an inherited tumor syndrome. In sporadic disease, patients are usually diagnosed in the 5th or 6th decade, whereas inherited disease generally presents at a younger age.[5] All patients who are diagnosed with MTC should undergo genetic testing for multiple endocrine neoplasia syndromes.[22] Approximately 50% of patients have metastases to cervical lymph nodes, and up to 10% may have metastases to lungs or bones.[5] At initial presentation, up to 15% have symptoms of local compression or invasion of the trachea and/or esophagus. The 10-year survival rate is 75%.[5]

Thyroid Cancers (cont.)

Anaplastic Thyroid Carcinomas

Anaplastic thyroid carcinomas are rare, accounting for 2% of all thyroid cancers. They represent the most lethal solid tumor in humans, with mean survival times of only several weeks to months and mortality approaching 100%. Mean age at diagnosis is 71 years, and 60% to 70% of affected patients are women. Approximately 50% have a history of or coexistent DTC.[5] Diagnosis is usually made by core or surgical biopsy. Most patients have extensive local invasion, and as many as 50% of patients have distant metastases at presentation.[5]

Treatment Options

Current ATA guidelines offer the following treatment goals in thyroid cancer[9]:

- Removal of the primary tumor and involved cervical lymph nodes
- Minimization of treatment-related morbidity
- Accurate staging of the tumor
- Postoperative treatment with RAI when appropriate
- Accurate long-term surveillance for disease recurrence
- Minimization of risk of disease recurrence and spread of metastases

Treatment Options (cont.)

Surgery is the mainstay of treatment for thyroid cancer. The goal of primary surgery for thyroid carcinoma is to detect and remove all locoregional metastases because reoperative surgery and neck dissection present substantial challenges, greatly increasing the risk of complications.[23] Options include total thyroidectomy or lobectomy with isthmus resection.[24]

Treatment Options (cont.)

Some prominent thyroid specialists advocate unilateral lobectomy for most patients with PTC and FTC based on the fact that for patients with low-risk tumors up to 4 cm and no extrathyroidal extension or lymph node metastases, there is no survival difference between thyroid lobectomy and a total thyroidectomy.[25] Additionally, life-long levothyroxine replacement therapy may be avoided in certain patients.[5,24] Also, extensive thyroidectomy can have significant complication rates even in the hands of experienced surgeons. However, total thyroidectomy is theoretically more likely to remove all disease foci and allows for RAI remnant ablation and long-term thyroglobulin monitoring to detect recurrence more easily.[24] Total thyroidectomy may also result in a lower overall recurrence rate than lobectomy.[24]

Treatment Options (cont.)

Guidelines offer somewhat differing recommendations regarding the surgical treatment of PTC.[5,9] Current ATA guidelines indicate that total or near-total thyroidectomy is warranted in all patients with thyroid cancers larger than 1 cm, although lobectomy is considered a reasonable option for low-risk intrathyroid PTC if the patient has no history of head or neck irradiation or cervical node metastases.[9] In low-risk PTC, however, the extent of primary surgery required has been a subject of debate.[5,24] Based on new national data that demonstrated equivalent overall survival for patients with low-risk PTC (< 4 cm) who underwent thyroid lobectomy versus total thyroidectomy, current ATA guidelines support thyroid lobectomy as a viable surgical option for these tumors.[9,25]

Treatment Options (cont.)

Presurgical evaluation is critically important in determining the extent of disease and aiding in the surgical decision-making process.[5] Cervical US of the thyroid and central and lateral neck compartments to evaluate cervical lymph nodes is important and recommended.[23,26] In 20% to 33% of patients, cervical US performed before initial surgery can identify nonpalpable nodal metastases that would not otherwise be found.[27,28] Identification of any documented lateral cervical lymph node metastases will help plan the extent of surgery to include resection of these lateral compartments, thus allowing for a more complete upfront treatment. If the lateral cervical lymph nodes are not worrisome for metastatic disease, then the thyroid resection should be undertaken. Prophylactic lateral lymph node dissection for DTC is not indicated.[29]

Treatment Options (cont.)

Surgeon experience has been shown to be an important variable in successful outcomes in thyroid cancer treatment. Evidence suggests that length of hospital stay and rate of complications are lower when high-volume surgeons with more experience treating thyroid cancer perform the surgery.[30] A recent study found that patients who underwent thyroid cancer surgery performed by high-volume surgeons had a 30% lower incidence of recurrent laryngeal nerve injury (P = .024) and hypocalcemia (P = .002) and a 70% reduction in the risk of in-hospital death (P = .004) when compared with patients who underwent surgery performed by low-volume surgeons.[31]

Treatment Options (cont.)

Multidisciplinary Care

At all stages in the management of thyroid cancer, care should be coordinated by members of an experienced multidisciplinary team.[13,32] This team normally comprises clinicians with expertise in thyroid cancer, including a surgeon, medical endocrinologist, medical oncologist, nuclear medicine specialist, radiologist, and pathologist.[13,32] One option is to refer all patients with thyroid cancer to a multidisciplinary thyroid cancer or endocrine tumor center, as coordination and “real-time” communication among the team members are paramount to success.[32] Patients should be educated about diagnosis, prognosis, and treatment strategies to allow them to make informed contributions to care decisions.[33]

Postoperative Considerations

Tumor Staging

Postoperative staging is useful for estimating prognosis, tailoring postoperative treatment decisions, and determining follow-up.[9] The American Joint Committee on Cancer/Union for International Cancer Control's TNM 8th edition parameters are recommended for describing the extent of the tumor.[9a] This is the most commonly used and most useful staging system currently in use. One risk-stratification approach combines standard clinical factors from the patient's initial evaluation with response-to-therapy variables to improve staging accuracy and predict the patient's risk of death from thyroid cancer, risk of recurrence, and risk of failing initial therapy.[34] Another ATA-developed staging system was recently validated and categorizes patients into low, intermediate, or high risk of recurrence.[35] Recurrence of disease (rather than mortality) is one of the most common oncologic problems with DTC; therefore, determining the risk of recurrence is particularly important in patients with this type of cancer.

Postoperative Considerations (cont.)

Diagnostic and Therapeutic Radioactive Iodine

Normal thyroid tissue and DTC are sensitive to TSH and will take up RAI. Thus, RAI can be used diagnostically after thyroidectomy to detect residual thyroid tissue and/or cancer and therapeutically ablate residual tissue and/or micrometastases.[5,24] ATA and National Comprehensive Cancer Network (NCCN) guidelines recommend the selective use of RAI remnant ablation in patients with tumors larger than 1 cm.[5,9] Postoperative RAI is also recommended for patients who have a high risk of persistent disease after total thyroidectomy, such as patients with a primary tumor larger than 4 cm, gross extrathyroidal extension, lymph node metastases, and/or distant metastases.[5] Medullary and anaplastic carcinomas do not take up RAI; thus, RAI administration is not indicated in patients with these tumors.[5]

Postoperative Considerations (cont.)

Thyroid Hormone Replacement

All patients who have undergone a total thyroidectomy require life-long thyroid hormone replacement.[24] Treatment consists of levothyroxine in a dosage of 2.5 to 3.5 mcg/kg daily. High doses of levothyroxine also suppress TSH concentrations; the suppressive effect is important because TSH can stimulate cells derived from thyroid follicular epithelium, including DTC cells. Studies support the concept that TSH concentrations are associated with aggressiveness in thyroid cancer tumors.[5,36] The extent to which TSH should be suppressed is controversial, but in patients with a high risk of recurrence or with known residual carcinoma, TSH levels of less than 0.1 mU/L are recommended.[5,24] Because supraphysiologic levels of levothyroxine can cause symptoms of thyrotoxicosis, risks and benefits of TSH suppression must be weighed for individual patients.[24]

Postoperative Considerations (cont.)

Chemotherapy

Chemotherapy is generally a poor treatment option for patients with DTC but may be considered for patients who have unresectable, metastatic, RAI-resistant disease.[5] Doxorubicin is a cytotoxic agent approved by the United States Food and Drug Administration (FDA) for use in DTC, but it offers minimal survival benefit.[37] However, in one study of a combined doxorubicin protocol in anaplastic thyroid carcinoma that included hyperfractionated radiotherapy and surgery, 9% of patients survived at least 2 years.[38] Overall, conventional cytotoxic chemotherapy produces partial response rates in 5% to 17% of patients and is associated with significant toxicity.[39]

Postoperative Considerations (cont.)

Multitargeted Kinase Inhibitors

Until recently, few treatment options have been available for patients with RAI-resistant or metastatic DTC.[40] Improved understanding of oncogenic pathways has led to the recent development of a number of agents that target angiogenesis and tumor signaling pathways. Like many other cancers, thyroid malignancies are often highly vascularized.[39] Elevated serum vascular endothelial growth factor (VEGF) is a major promoter of tumor vascularization and is associated with tumor growth and poorer prognosis.[39]

Postoperative Considerations (cont.)

Multitargeted Kinase Inhibitors (cont.)

The RAS/RAF/MEK/ERK (MAPK) signaling pathway has been implicated in thyroid cancer.[41] Mutations that activate the *RET* proto-oncogene occur in the majority of patients with hereditary MTC syndromes and result in the activation of the MAPK pathway and promotion of tumorigenesis. Evidence also suggests that *RET* is involved in the pathogenesis of DTC. Additionally, mutations in the *BRAF* gene are observed in up to 69% of DTC cases. Mutations in Ras proteins are also well documented in thyroid cancer, and *RAS* activation has been associated with MTC and a more aggressive form of DTC.[41]

Postoperative Considerations (cont.)

Multitargeted Kinase Inhibitors (cont.)

Several targeted kinase therapies, including vandetanib, cabozantinib, lenvatinib, and sorafenib, have recently received FDA approval for the treatment of advanced or metastatic DTC or MTC (Table 1). Randomized clinical trials enrolling patients with locally recurrent unresectable and metastatic MTC and RAI-refractory DTC suggest that kinase inhibitors have a clinical benefit with a partial response in 50% to 60% of patients, typically for a period of 1 to 2 years.[5] Although kinase inhibitor therapies are not curative and their effects on overall survival are not known, they can confer a variable period of progression-free survival.[42] Systemic therapy with kinase inhibitors is most appropriate in patients with rapidly progressing disease or with advanced symptomatic disease.[42]

Table 1. Multitargeted Kinase Inhibitors Approved for Use in Thyroid Cancer

DRUG	FDA-APPROVED INDICATION	TARGET	KEY PHASE 3 TRIAL RESULTS	ADVERSE EFFECTS
Cabozantinib	Progressive metastatic MTC	VEGFR, MET, RET	• EXAM trial (metastatic MTC): Median PFS 11.2 months vs 4 months for placebo ($P < .001$) • 47.3% of cabozantinib-treated patients alive and progression free at 1 year vs 7.2% in placebo ($P < .001$)	Diarrhea, hand-foot skin reaction, weight loss, anorexia, nausea, fatigue Black-box warning: perforations, fistulas, and hemorrhage
Lenvatinib	Locally recurrent or metastatic, progressive, RAI-refractory DTC	VEGFR, FGFR, RET	• SELECT trial (RAI-resistant DTC): Median PFS in the lenvatinib group was 18.3 months vs 3.6 months in the placebo group ($P < .001$)	Hypertension, diarrhea, anorexia, weight loss, nausea
Sorafenib	Locally recurrent or metastatic, progressive, RAI-refractory DTC	BRAF,VEGFR, PDGFR, RET	• DECISION trial (locally advanced or metastatic RAI-resistant DTC): Median PFS was 10.8 months in the sorafenib group vs 5.8 months in the placebo group ($P < .0001$)	Diarrhea, fatigue, hand-foot skin reaction, alopecia, rash, hypertension, weight loss
Vandetanib	Symptomatic or progressive MTC with unresectable locally advanced or metastatic disease	VEGFR, EGFR, RET	• ZETA trial (locally advanced or metastatic MTC): Median PFS of at least 22.6 months in the vandetanib group vs 16.4 months for patients randomized to placebo ($P < .0001$)	Diarrhea, rash, acne, nausea, hypertension, headache, fatigue, anorexia, abdominal pain Black-box warning: QT prolongation, Torsades de pointes, and sudden death

DTC = differentiated thyroid cancer; MTC = medullary thyroid carcinoma; PFS = progression-free survival; RAI = radioactive iodine.

Derived from Liebner DA, et al. *Ther Adv Endocrinol Metab*. 2011;2(5):173-195; Elisei R, et al. *J Clin Oncol.* 2013;31(29):3639-3646; Schlumberger MJ, et al. *J Clin Oncol*. 2014;32(June 20 Supplement):LBA6008; Brose MS, et al; DECISION investigators. *Lancet*. 2014;384(9940):319-328; Wells SA, et al. *J Clin Oncol*. 2010;28(May 20 Supplement):5503; Wells SA, et al. *J Clin Oncol*. 2012;30(2):134-141.

Postoperative Considerations (cont.)

Multitargeted Kinase Inhibitors (cont.)

Although kinase inhibitors may cause severe or fatal adverse effects, including liver toxicity, hypertension, stroke, or bleeding, most side effects are reversible with drug discontinuation or can be successfully managed.[42]

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Sorafenib	Locally recurrent or metastatic, progressive, RAI-refractory DTC	BRAF,VEGFR, PDGFR, RET	• DECISION trial (locally advanced or metastatic RAI-resistant DTC): Median PFS was 10.8 months in the sorafenib group vs 5.8 months in the placebo group ($P < .0001$)	Diarrhea, fatigue, hand-foot skin reaction, alopecia, rash, hypertension, weight loss
Vandetanib	Symptomatic or progressive MTC with unresectable locally advanced or metastatic disease	VEGFR, EGFR, RET	• ZETA trial (locally advanced or metastatic MTC): Median PFS of at least 22.6 months in the vandetanib group vs 16.4 months for patients randomized to placebo ($P < .0001$)	Diarrhea, rash, acne, nausea, hypertension, headache, fatigue, anorexia, abdominal pain Black-box warning: QT prolongation, Torsades de pointes, and sudden death

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Postoperative Considerations (cont.)

Long-Term Patient Management

Patients treated for DTC require ongoing monitoring for possible recurrence.[9] Measuring serum thyroglobulin is an important part of follow-up because it can identify patients with residual disease.[5,9] A rise in the thyroglobulin level is consistent with thyroid cancer recurrence and can predict long-term recurrence.[9] Guidelines indicate that at 6 and 12 months after treatment for DTC, patients should undergo a complete physical examination and measurements of TSH, thyroglobulin, and an antithyroglobulin antibodies titer.[5] Periodic neck US is also warranted to assess for local recurrence.[9] In patients found to be disease free, these tests can then be conducted annually.[5] In RAI ablation–treated patients with negative US findings, a stimulated (increasing TSH levels by stopping thyroid hormone or by treating with recombinant TSH) thyroglobulin level of less than 2 ng/mL, negative antithyroglobulin antibodies, and negative RAI imaging may be followed annually with an unstimulated thyroglobulin and periodic US.[5] In patients with negative RAI imaging but a thyroglobulin level of 2 to 5 ng/mL, neck and/or chest CT or PET may be warranted to detect any metastases.[5] In patients with MTC, basal calcitonin should be measured at 2 to 3 months postoperatively to assess for disease persistence or metastases, then every 6 months for the first year, then annually if undetectable.[5] Neck imaging and additional tests are warranted in patients with detectable calcitonin to assess for disease recurrence.[5]

Postoperative Considerations (cont.)

Recurrent Disease

In patients with locoregional recurrence of DTC, surgery is generally recommended.

Postoperative repeat RAI therapy may also be recommended.[5,9] If locoregional disease is unresectable, treatment choices include external beam radiation (EBRT) or a kinase inhibitor.[5] Additionally, watchful waiting is a reasonable approach in patients with stable or slowly progressive asymptomatic disease.[5,9] In patients with symptomatic distant metastases, regional palliative resection, ablation, or kinase inhibitors are options.[5,43,44] Enrollment in a clinical trial should also be considered in patients with progressive refractory disease.[5,9]

Postoperative Considerations (cont.)

Recurrent Disease (cont.)

When recurrent disease is expected based on elevated thyroglobulin but imaging studies are negative, empiric RAI treatment is an option; however, this recommendation is controversial because no study has demonstrated a decrease in morbidity or mortality when RAI treatment is given in this circumstance.[5] Additionally, RAI is associated with potentially serious long-term side effects, including xerostomia, bone marrow compromise, and a risk of other malignancies.[45]

Postoperative Considerations (cont.)

Recurrent Disease (cont.)

In patients with locoregional recurrence of MTC, surgical resection is recommended, possibly combined with EBRT.[5] In metastatic or inoperable locoregional MTC, cabozantinib and vandetanib have been shown to improve progression-free survival.[46-48] However, in patients with indolent or asymptomatic metastatic disease, observation is acceptable because there is little evidence to suggest alteration in outcome in this patient population, and the toxic effects of systemic treatments may not outweigh the benefits.[5]

Conclusion

Thyroid nodules are an extremely common finding on physical examination and incidentally on imaging. Although the majority of thyroid nodules are benign and can be managed in primary care, clinicians must be able to properly assess and refer patients for US or timely evaluation to an experienced thyroid surgeon when appropriate. FNA biopsy is diagnostic in many cases, and most DTCs have an excellent prognosis. After surgery, long-term follow-up care is a critical aspect of successful outcomes. For the minority of patients with more aggressive thyroid cancers or with inoperable or RAI-resistant metastases, newly available treatments with targeted kinase inhibitors offer the potential for increased disease-free survival over traditional cytotoxic chemotherapy regimens.

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