Diagnosis and Evaluation of Thyroid Nodules-the Clinician's Perspective

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KEYWORDS

• Thyroid nodules • Thyroid incidentaloma • Fine needle aspiration • Thyroid cancer
• Thyroid ultrasound • Thyroid imaging

KEY POINTS

- Thyroid nodules are a common clinical problem, and the increased use of imaging techniques has led to increased diagnosis of thyroid incidentalomas and low-risk thyroid cancers.
- Greater emphasis is being placed on risk assessment and sonographic features to avoid unnecessary evaluation and therapy.
- Ultrasound-guided fine need aspiration cytology remains the gold standard test to evaluate thyroid nodules.
- Molecular diagnostics are being widely used for further risk assessment and characterization of indeterminate thyroid nodules.

INTRODUCTION

Epidemiologic studies show that about 5% women and 1% men have palpable nodules in the iodine-sufficient areas of the world.[1] With the advent of high-quality imaging techniques and more patients undergoing radiological imaging for a myriad of clinical problems, thyroid nodules have become a common clinical issue. Most of these nodules are benign; however, the clinical importance lies in the need to exclude cancer.

As per the Surveillance, Epidemiology and End Results (SEER) data, thyroid cancer constitutes 3.0% of all newly diagnosed cancers, and there were an estimated 52,070 new cases diagnosed in 2019. However, the prognosis is excellent, with an overall 5-year survival of 98.2%.[2]

Greater use of thyroid ultrasound has led to an increased diagnosis of low-risk thyroid cancer.[3] Thus, there is a greater emphasis on risk assessment and outcome prediction to minimize morbidity and unnecessary therapy. This strategy led to the changing paradigm in thyroid cancer management from the traditional model of one size fits all to a risk adapted paradigm that involves management based on individualized risk assessment.

THYROID NODULES

A thyroid nodule is a discrete lesion within the thyroid gland that is radiologically and histologically different from the surrounding thyroid parenchyma. Both benign and malignant thyroid disease can cause thyroid nodules. Thyroid cancer occurs in 7% to 15% of any thyroid nodule.[4,5]

PALPABLE AND NONPALPABLE NODULES

The estimated annual incidence rate of thyroid nodules is 0.1% in the United States.[6] The

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frequency of thyroid nodules, about half of which are solitary on physical examination, increases throughout life.[7] Thyroid nodules are more common in elderly persons, females, people from iodine-deficient geographic areas, and in those with a history of radiation exposure. Single nodules are about 4 times more common in women than in men. Nodules are 10 times more frequent when the gland is examined at autopsy, during surgery, or by ultrasonography. Clinically unrecognized thyroid nodules are common and can be found in up to 50% to 60% of patients at autopsy.[6]

DETECTION

Thyroid nodules can be detected during palpation by the patient or on physical examination by a physician. They are often diagnosed during work-up for hypothyroidism or hyperthyroidism. They are also commonly noted incidentally on imaging studies performed for an unrelated condition. A thyroid nodule discovered during either imaging study or surgery performed because of an unrelated thyroid gland pathology is known as a thyroid incidentaloma. The prevalence rate of a thyroid incidentaloma is 67% with thyroid ultrasound imaging,[8] 16% with computed tomography (CT) or MR imaging,[9] 9.4% by carotid duplex ultrasound,[10] and 2% to 3% with fluorodeoxyglucose (FDG) positron emission tomography (PET).[11] Thyroid incidentalomas, thus, represents a large proportion of patients seen for evaluation of thyroid nodules in an endocrine practice.

INITIAL EVALUATION

History and Physical Examination

The initial evaluation for thyroid nodule(s) is comprised of a thorough history and physical examination. Any personal or family history of benign or malignant thyroid disease should be obtained. The patient should be evaluated for symptoms of hypothyroidism or hyperthyroidism. Pertinent history that increases the risk of malignancy includes a history of head or neck radiation, presentation at extremes of age (less than 14 or more than 70 years), history of rapid growth of the nodule, persistent dysphonia, male gender,[6] and significant family history of differentiated thyroid cancer, medullary thyroid cancer, or multiple endocrine neoplasia (MEN), Type 2.

A complete thyroid examination with palpation of the thyroid gland should be performed. The location, size, and consistency of any palpable nodules should be assessed. Any neck tenderness or cervical adenopathy should also be noted. A complete review of systems for any signs and symptoms of hypothyroidism and hyperthyroidism should also be performed (**Table 1**).

DIAGNOSIS

Laboratory Studies

The initial laboratory step in the work-up to evaluate a thyroid nodule is obtaining a TSH (thyroid-stimulating hormone) level. A suppressed or low TSH, which signifies a hyperthyroid state, is associated with a decreased probability of malignancy.[12] The management of patients with a low serum TSH is described later in this article. On the other hand, an increased level of serum TSH, even when the level is still within reference limits, is statistically associated with an increased risk of cancer in thyroid nodular disease.[13] Routine measurement of serum thyroglobulin and serum calcitonin is not recommended in the initial evaluation of thyroid nodules.[14]

Imaging

Thyroid ultrasound

All patients with a suspected thyroid nodule, a known nodular goiter, or a thyroid nodule incidentally diagnosed on any other imaging study should undergo a diagnostic thyroid ultrasound**.** High-resolution ultrasound is the most sensitive imaging technique to detect thyroid nodules, and it is well-suited to evaluate the gland architecture.[15] Thyroid ultrasound should be used to determine the size and number of nodules and provide a description of any abnormal lymphadenopathy in the neck. The size and sonographic features of the nodules (eg, composition, echogenicity, shape, margins, and echogenic foci) are taken into consideration while deciding the need for fine needle aspiration (FNA) as described later in this article.[16,17]

Table 1
Shows the symptoms associated with a hypothyroid and hyperthyroid state

Hyperthyroidism	Hypothyroidism
Palpitations	Dry skin and hair
Heat intolerance	Cold intolerance
Weight loss	Weight gain
Frequent bowel movements	Constipation
Anxiety	Fatigue
Oligomenorrhea	Menorrhagia
Increased appetite	Decreased appetite

Thyroid ultrasound is not indicated in patients with medical thyroid disease if the gland is normal in size without evidence of a palpable nodule on physical examination. It is also not indicated as a screening test except in patients with high genetic risk or possibly in those with history of radiation to the head or neck region.

Ultrasound elastography, which uses both sonography and a computational module to measure tissue stiffness, has been used in some institutions to assess cancer risk. Recently, larger clinical trials show that ultrasound elastography has been inferior to gray scale sonography, especially with partially cystic or cystic nodules.[18] Patients with multinodular goiter, coalescence of nodules, obese patients, or those with nodules that are inferior or posterior are not candidates for ultrasound elastography.[19]

Other imaging modalities

A chest radiograph is not useful and therefore not recommended for evaluation of the thyroid gland, although it may indicate a substernal goiter, which typically presents as a mass associated with tracheal narrowing, tracheal stenosis, and mediastinal widening causing shortness of breath.

Cross-sectional imaging with CT scan is recommended to evaluate and confirm substernal extension and tracheal compression. It is also recommended in suspected advanced thyroid cancer to assess for nodal disease and widespread metastases.[14] Iodinated contrast administration should be avoided in patients with suspected thyroid cancer, as it will delay therapy with radioactive iodine (RAI).

FDG-PET imaging is not recommended for the evaluation of patients with newly detected thyroid nodules or thyroid disease. Incidental FDG-PET uptake in the thyroid gland is seen in 2% to 3% patients and can be either focal or diffuse.[11] Focal FDG-PET uptake in the thyroid is associated with an approximately 35% risk of being cancerous.[20] For PET-positive nodules greater than 1 cm diameter, a dedicated ultrasound and FNA are recommended. However, diffuse FDG uptake in conjunction with sonographic and clinical evidence of chronic lymphocytic thyroiditis does not require further imaging or FNA.

MULTINODULAR GOITER AND TOXIC NODULES

A radioactive iodine uptake and scan should be obtained if the TSH is low to assess whether the nodule is hyperfunctioning.[21] The pattern of uptake in a patient with a single hyperfunctioning nodule generally shows focal uptake in the adenoma with suppressed uptake in the surrounding and contralateral thyroid tissue (**Fig. 1**).

No further cytology evaluation is generally recommended for a hyperfunctioning nodule, as these nodules rarely harbor malignancy. However, the prevalence of thyroid cancer in hyperfunctioning nodules is approximately 3%.[22] Therefore, in clinical practice, FNA of a hyperfunctioning nodule should be considered in patients with risk factors for thyroid cancer, any nodules with suspicious sonographic features, and those that show growth on surveillance.

Patients with a suppressed TSH who are noted to have one or more hyperfunctioning nodules on uptake and scan should also undergo thyroid ultrasound to evaluate the presence of nodules concordant with the hyperfunctioning areas on the scan and other nonfunctioning nodules that might be present (**Fig. 2**).

A multicenter study looked at association of thyroid cancer in patients with nodular Graves' disease and found the rate of carcinoma in a cold nodule was 15% (n = 140 patients). In patients with nodular Graves' disease, ultrasound-guided FNA is useful before radioiodine therapy or surgery.[23]

The risk of thyroid cancer in patients with a multinodular goiter is the same as in those with a solitary nodule.[24,25] Therefore, all nodules within a multinodular goiter that meet sonographic and size criteria concerning for malignancy should undergo biopsy.[14]

Fine Needle Aspiration

FNA is the procedure of choice in the histologic evaluation of thyroid nodules. The nodule size at initial ultrasound, the ultrasound characteristics, and definite increase in size during follow-up are generally considered as reasonable criteria for deciding whether to proceed with FNA. FNA should be performed under ultrasound guidance to ensure optimal placement of the needle tip for nodule sampling.

In the United States, the two commonly used guidelines to estimate risk of malignancy, and thus assess a need for FNA, are the ATA (American Thyroid Association) guidelines[14] and the ACR TI-RADS (American College of Radiology Thyroid Imaging Reporting and Data System).[16,26]

Table 2 shows the ATA ultrasound features and criteria for biopsy as per the guidelines.[14] In comparison, **Fig. 3** shows thyroid nodule imaging features and guidelines for biopsy as recommended by the ACR TI-RADS reporting system.[16]

Both guidelines recommend biopsy if size of the thyroid nodule is over 1 cm and there are high-suspicion sonographic features. For intermediate-

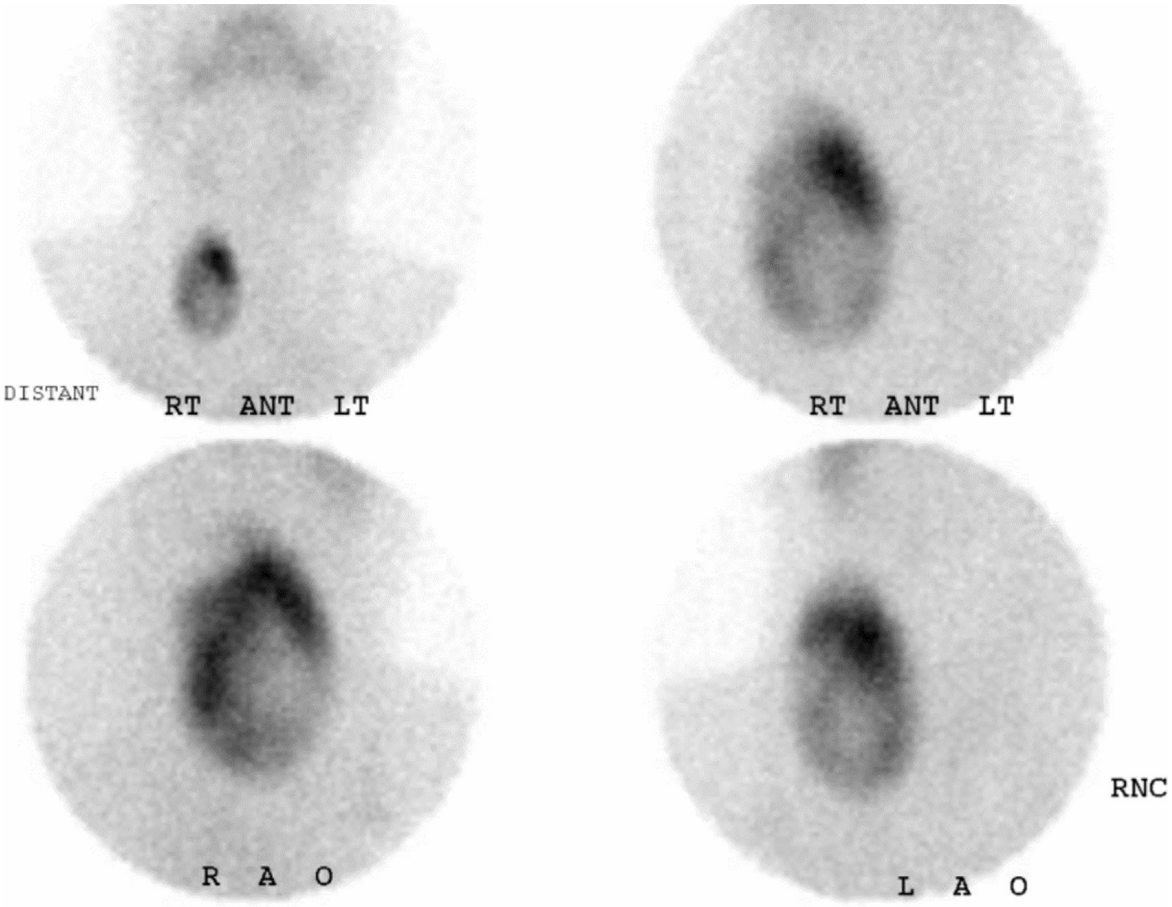

Fig. 1. Thyroid scan with I-131 of a solitary functioning nodule in the right thyroid lobe in a 22-year-old woman noted to have a suppressed TSH. A functioning nodule is nearly always benign, whereas, a nonfunctioning nodule (approximately 90% of nodules) has a 5% to 15% risk of being malignant.

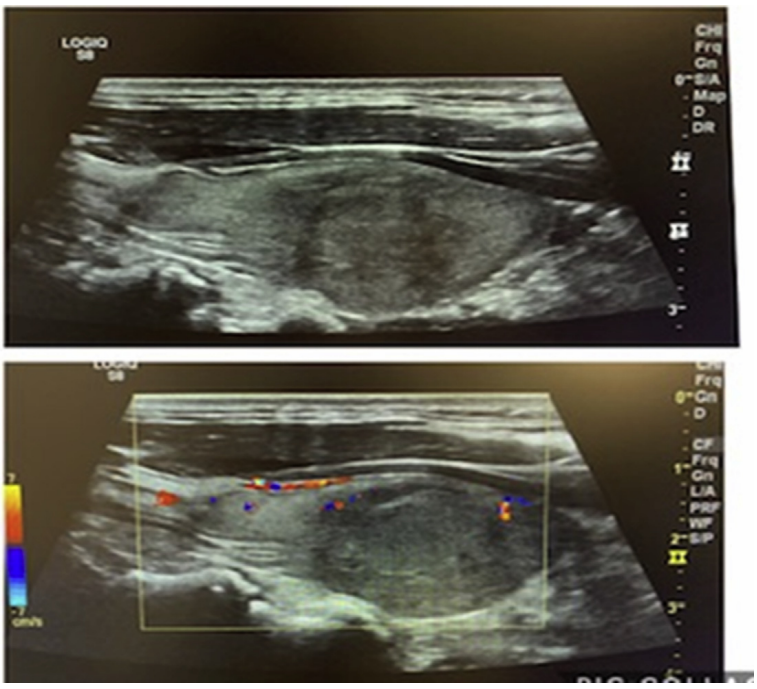

Fig. 2. A 62-year-old man presented with thyrotoxicosis from Graves' disease. Thyroid ultrasound showed a left thyroid lobe solid nodule 2.3 × 1.9 cm (ACR TI-RADS 4). A nuclear uptake scan reported this nodule to be cold, and biopsy proved to be medullary thyroid cancer.

Table 2
Ultrasound features and criteria for fine need aspiration

High Risk of Malignancy (70%–90%)	Intermediate Risk of Malignancy (10%–20%)	Low Risk of Malignancy (5%–10%)	Very Low Risk of Malignancy (<3%)	Benign(<1%)
Hypoechoic nodule with • Microcalcifications • Taller than wide • Irregular margins • Evidence of extrathyroidal extension	Hypoechoic nodule with regular margins	Hyperechoic nodule Isoechoic nodule Partially cystic nodule with eccentric solid component	Spongiform nodule Partially cystic nodule with no concerning features	Purely cystic nodule
FNA at greater than equal to 1 cm	FNA at greater than equal to 1 cm	FNA at greater than equal to 1.5 cm	FNA at greater than equal to 2 cm or observation without FNA	No biopsy

and low- suspicion nodules, there is some variability in the size criteria when the 2 guidelines are compared. FNA can be performed based on patient and clinician preference, availability of high-resolution ultrasound, and a high-volume skilled radiologist. There is currently an ongoing international effort to harmonize recommendations on the management of thyroid nodules based on ultrasound.

CYTOLOGY

Bethesda Classification

Recent efforts to standardize the reporting of thyroid nodule cytology have improved the consistency of this aspect of thyroid disease diagnosis. The Bethesda classification was developed to maintain consistency in reporting and classification of cytology of thyroid nodules.[27,28] The categories can be described as

Composition	Echogenic	Margins	Shape	Foci
Cystic - 0 Spongiform - 0 Mixed cystic/solid -1 Completely solid - 2	Anechoic - 0 Hyperechoic/isoechoic - 1 Hypoechoic - 2 Very hypoechoic - 3	Wider than tall - 0 Taller than wide - 3	Smooth - 0 Ill-defined - 0 Lobulated/irregular - 2 Extra-thyroidal extension - 3	None/comet tail - 0 Macro-calcifications - 1 Peripheral (rim) calcifications - 2 Punctate echogenic foci - 3
Add points from all above categories ↓				
0 points	2 points	3 points	4–6 points	>7 points
TR1	**TR2**	**TR3**	**TR4**	**TR5**
Benign	Not suspicious	Mildly suspicious	Moderately suspicious	Highly suspicious
No FNA	No FNA	FNA >2.5 cm Follow if >1.5 cm	FNA >1.5 cm Follow >1 cm	FNA >1 cm Follow >0.5 cm

Fig. 3. Imaging features of thyroid nodules based on ACR TI-RADS reporting system. The total score is determined by adding the number of points assigned to each feature including composition, echogenicity, margins, shape, and the presence of calcifications in the nodule.

Category 1 - nondiagnostic; the estimated risk of malignancy is 1% to 4%
Category 2 - benign cytology implies a less than 3% likelihood of cancer
Category 3 – follicular lesion of undetermined significance (FLUS) or atypia of undetermined significance (AUS); the risk for malignancy is 5% to 15%
Category 4 – follicular neoplasm/suspicious for follicular neoplasm (FN/SFN), Hurthle cell neoplasm or suspicious for Hurthle cell neoplasm; risk for malignancy is 15% to 30%
Category 5 – suspicious for malignancy; there is a 60% to 75% chance of papillary thyroid cancer
Category 6 – malignant

Role of Molecular Markers

FNA cytology is the reference standard test to distinguish benign versus malignant thyroid nodule, but it is not without limitations. Cibas and colleagues evaluated 635 patients with 776 surgically resected nodules and found substantial inter- and intraobserver variability in the cytopathologic and histopathologic evaluation of thyroid nodules. This variability was higher for AUS and FLUS (atypia and follicular lesions) using the Bethesda criteria.[29]

These nodules are indeterminate on FNA cytology and need to be further characterized to help clinicians decide the best course of action and avoid unnecessary diagnostic thyroid surgeries. Therein arises the application of molecular markers in the management of thyroid nodules. The two commonly used molecular tests to better characterize indeterminate nodules are the Gene Expression Classifier (GEC) and Next Generation Sequencing[30]

GEC was developed to rule out malignancy and thereby decrease the rate of surgeries for indeterminate cytology. GEC was proposed as a rule-out test because of its relatively high sensitivity (92%) and negative predictive value (93%). GEC tests for a panel of mRNAs that assigns a low risk of malignancy similar to a benign FNA.[31]

Mutational testing was proposed for use as a rule-in test because of relatively high reported specificity (86%–100%) and positive predictive value (84%–100%). **Table 3** shows a panel of common mutations in differentiated thyroid cancer.

The Cancer Genome Atlas project mapped mutations to various forms of differentiated thyroid cancer. This subsequently led to development of Next Generation Sequencing (ThyroSeq) to improve the sensitivity and negative predictive value with mild reduction in specificity and thereby identify benign versus malignant cytology.[32] Both these tests are being optimized for Hurthle cell and follicular tumors. Another approach to molecular testing with high sensitivity and specificity is microRNA testing. Patients should be counseled regarding the potential benefits and limitations of the testing, and about the possible uncertainties in the therapeutic and long-term clinical implications of the results.

Table 3
The common mutations seen in papillary and follicular thyroid cancer

Papillary	Follicular
BRAF (40%–50%)	RAS (40%–50%)
RAS (7%–20%)	PAX8/PPAR(30%–35%)
RET/PTC(10%–20%)	TP53(21%)
EGFR (5%)	PTEN(8%)
TRK(<5%)	PIK3CA(7%)
PIK3CA(2%)	BRAF(2%)

Data from Roth MY, Witt RL, Steward DL. Molecular testing for thyroid nodules: Review and current state. Cancer. 2018;124(5):888-98.

Medical Management

Historically, TSH suppression with levothyroxine has been practiced in an effort to decrease the size and prevent growth of existing or new thyroid nodules. The data regarding this practice, however, show modest clinical efficacy while increasing the risk of adverse effects from iatrogenic thyrotoxicosis, which include atrial fibrillation and reduced bone density.[33,34] Therefore, routine TSH suppression for benign thyroid nodules is not recommended.[14] An adequate dietary iodine intake (150 μg daily) has shown some benefit in reducing nodule size.[35] However, it has not been shown whether dietary modification can affect risk of thyroid malignancy.

Surgical Management

Surgery should be considered for benign nodules (Bethseda Category 2) that are large (>4 cm), continue to grow and/or are causing compressive symptoms including dysphonia, dysphagia, or dyspnea.[36,37] (**Fig. 4**).

A single-center study evaluated the FNA results and ultrasound features in patients with nodules over 4 cm. Of the subset of 125 nodules that were identified as benign in preoperative FNA, 10.4% were malignant on postoperative pathology.[38] Another retrospective study confirmed

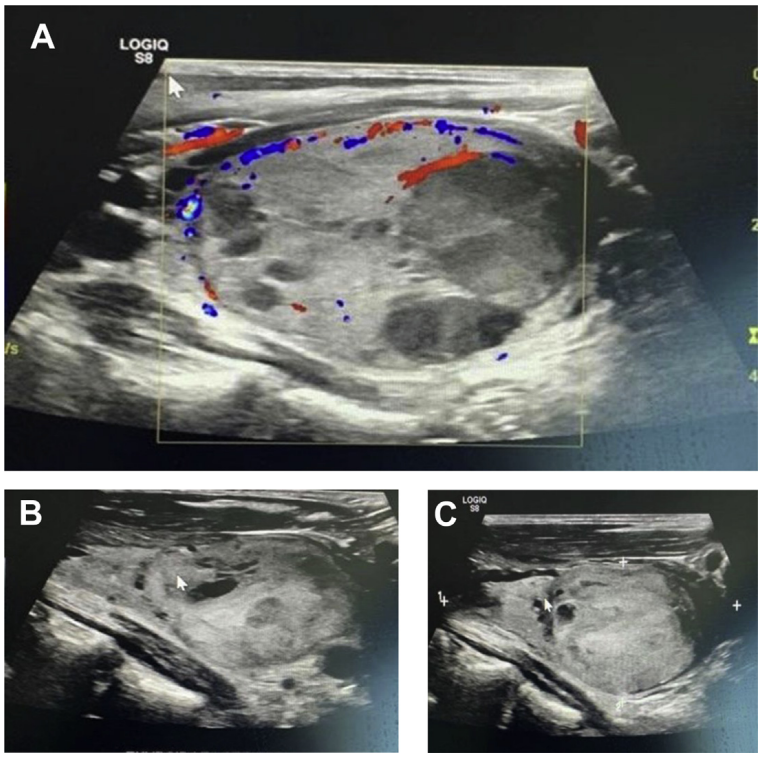

Fig. 4. A 50-year-old man followed for an incidentally found multinodular goiter. Image A shows solid left thyroid nodule 5 × 3.5 cm with some cystic content. Biopsy at that time was benign. Images B and C show follow-up demonstrating more solid sonographic features 2 years later. Considering the size of the nodule and patient and clinician preference, a partial thyroidectomy was performed. Surgical pathology showed a 4 cm papillary thyroid cancer. Patient subsequently underwent a completion thyroidectomy.

that patients with initially benign FNA had a low mortality risk during long-term follow-up even though they had a low, but real risk of false negatives.[39]

Surgical excision of indeterminate thyroid nodules (AUS/FLUS-Bethesda Category 3) should be considered if repeat biopsy or molecular testing or both is either not performed or is conclusive or suspicious.

Surgical excision is also recommended for follicular neoplasms (FN/SFN-Bethesda Category 4). In these patients, thyroid lobectomy is the initial procedure of choice. Total thyroidectomy, however, should be considered in patients with high clinical suspicion, presence of high-risk sonographic features, suspicious molecular diagnostics, presence of risk factors, presence of multiple nodules, and patient preference.

Surgical management is similar to that of a malignant nodule for lesions classified Suspicious for Malignancy (Bethesda Category 5). Historically, total thyroidectomy has been the recommended approach to a patient with biopsy-proven malignant disease (Bethesda Category 6). However, recent data have suggested similar outcomes in patients with unilateral or bilateral thyroid surgery in appropriately chosen patients with low-risk disease.[40,41] Total thyroidectomy is recommended for patients with large tumors (>4 cm), gross extrathyroidal extension, and either regional nodal or distant metastasis. For patients with tumors greater than 1 cm but less than 4 cm with no evidence of extrathyroidal spread or metastatic disease, the initial procedure of choice can be a lobectomy versus total thyroidectomy based on clinical concern and patient preference. Thyroid lobectomy is the procedure of choice for patients with tumors less than 1 cm and no evidence of extrathyroidal extension, nodal, or distant metastatic disease.[42]

For patients with a nondiagnostic cytology (Bethesda Category 1), FNA should be repeated, preferably with onsite cytologic evaluation.[43] Surgery should be considered in nondiagnostic nodules with high-suspicion sonographic features, growth during surveillance, or presence of clinical risk factors for malignancy.

Toxic Nodules

Radioactive iodine therapy and surgery are the recommended treatment modalities for patients with toxic multinodular goiter and toxic adenomas. The size and number of nodules, sonographic features, other comorbidities, and patient preference should be taken into consideration when deciding on the treatment. For patients with hyperfunction, surgery is usually recommended for patients with large multiple nodules, presence of compressive symptoms, substernal or retrosternal extension,

concern for thyroid cancer, or need for rapid correction of hyperthyroid state. RAI therapy should be considered for patients with contraindications to surgery, advanced age, and prior surgery or other comorbidities. FNA biopsy should be performed for any nodules with suspicious sonographic features before radioactive iodine therapy, if chosen. Antithyroid drugs may be considered for patients with small nodules and mild hyperthyroidism, in those with advanced age, and patients with contraindications to both surgery and radioactive iodine therapy.

Nodules in Pregnancy

Clinically relevant nodules in a pregnant patient are evaluated the same as in nonpregnant adults. However, radioactive diagnostic scanning is contraindicated in pregnancy. Patients with nodules diagnosed as differentiated thyroid cancer during the course of pregnancy should be monitored sonographically; delaying surgery until after delivery has not been shown to affect outcome.[44] Surgery should be considered in the second trimester if there is evidence of growth of the nodule, cervical lymphadenopathy, or distant metastasis.

FOLLOW-UP

Thyroid ultrasound is used for follow-up over time to assess for changes in nodule size and characteristics. A significant increase in nodule size, defined as increase in size of nodule by 20% in 2 dimensions or a 50% increase in volume is an indication for repeat sampling/FNA.[14] As described elsewhere, the possibility of malignancy is best judged by the ultrasound characteristics, rather than growth. As per the ATA 2015 guidelines, any thyroid nodule with high-suspicion sonographic features and benign FNA cytology should be followed with a repeat ultrasound or FNA in 12 months. For the nodules with intermediate suspicion, the recommended interval of follow-up is typically 12 to 24 months. For a low-suspicion nodule, ultrasound can be repeated in more than 24 months. During the course of surveillance, if the nodule shows any growth or change in characteristic or development of high-risk sonographic features, a repeat FNA should be performed.

The ACR TI-RADS system guidelines have similar recommendations as the ATA 2015 with regards to long-term follow-up of benign thyroid nodules. ACR TI-RADS recommends following nodules up to 5 years and discontinuing surveillance if stable. However, repeat imaging or continued surveillance should be done if there is increase in ACR TI-RADS score or increase in nodule size.

SUMMARY

Thyroid nodules are a common clinical problem encountered in an endocrine practice. Increasingly, thyroid nodules are being detected incidentally, leading to an increased diagnosis of low-risk thyroid cancers. There is, therefore, a greater emphasis on risk assessment based on clinical and sonographic features to avoid morbidity secondary to unnecessary therapy. Molecular diagnostics are also being widely used to further characterize indeterminate nodules. The ATA and ACR TI-RADS guidelines are the most used in clinical practice for risk assessment. Ultimately, it is important to take into consideration a patient's risk factors, clinical findings, comorbidities, life expectancy, and preference prior to making management decisions.

DISCLOSURE

The authors have nothing to disclose.

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