ABSTRACT

Thyroid nodules are common and are being more commonly identified with improvement in imaging modalities. Because thyroid nodules are frequently found incidentally during routine physical examination or imaging performed for another reason, physicians from a diverse range of specialties encounter thyroid nodules. Clinical decision making depends on proper evaluation of the thyroid nodule. Diagnosis and treatment selection require a risk stratification by history, physical examination, and ancillary tests. Nodules causing airway compression or those at high risk for carcinoma should prompt evaluation for surgical treatment. In nodules larger than 1 cm, fine-needle aspiration biopsy is central to the evaluation as it is accurate, low risk, and cost effective. Subcentimeter nodules, often found incidentally on imaging obtained for another purpose, can usually be evaluated by ultrasonography. Other laboratory and imaging evaluations have specific and more limited roles. The treatment modalities range from observation to surgical resection in a small percentage of thyroid nodules. A number of non-surgical modalities are being explored with variable success rates.

Thyroid nodules are common. They are discovered by palpation in 3% to 7%, by Ultrasonography in 20% to 76%, and by autopsy in approximately 50%. Prevalence increases linearly with age, exposure to ionizing radiation, and iodine deficiency. Thyroid nodules are more common in women than in men. In the Framingham population study, follow-up indicated new nodules in 1.3% in 15 years, calculated as an annual incidence of 100 cases per 100,000 persons per year. The clinical importance of thyroid nodules, besides the infrequent local compressive symptoms or thyroid dysfunction, is primarily the possibility of thyroid cancer, which occurs in about 5% of all thyroid nodules regardless of their size. Clinical evaluation begins with a detailed patient history and careful thyroid palpation. (Table 1 lists the various causes of thyroid nodules)

An inquiry should be made about family history of benign or malignant thyroid disease. The malignancy rate for nodules in young persons is 2-fold higher than in adult patients. Previous disease or treatments concerning the neck (history of childhood head/neck radiation), rapidity of onset, and rate of growth of the neck swelling should be enquired. Appearance of a new mass, progressive nodule growth, a firm or hard solitary or dominant nodule, or the presence of adjacent cervical adenopathy, symptoms of invasion such as airway compression, hoarseness and dysphagia are suspicious for malignancy and should prompt further evaluation.

A thorough physical examination of the head and neck should be conducted. The thyroid gland and nodules within it move with swallowing while masses external to the thyroid do not. The size of the nodule, its consistency (firm, cystic or rubbery) should be noted as firmer the nodule the greater is the chance for malignancy. Fixation of the nodule also suggests cellular invasion and malignancy. Pemberton’s sign should be evaluated to assess the degree of substernal extension, careful palpation for cervical lymph nodes, assessment of mobility of vocal cords are other important points to be noted in the physical examination.

Table 1 lists the clinical features indicating a higher risk for malignancy in a thyroid nodule

ULTRASONOGRAPHY (US):

Thyroid ultrasonography is emerging as a very useful noninvasive tool in the evaluation of thyroid nodules. When examined by ultrasound, thyroid nodules are commonly detected with a prevalence of 40% to 50% in the general population. The ultrasound

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**Table 1: Common causes of thyroid nodules**

<table>
<thead>
<tr>
<th>Category</th>
<th>Cause</th>
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<tbody>
<tr>
<td>Benign</td>
<td>Colloid nodule</td>
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<tr>
<td></td>
<td>Hashimoto thyroiditis</td>
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<tr>
<td></td>
<td>Simple or hemorrhagic cyst</td>
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<tr>
<td></td>
<td>Follicular adenoma</td>
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<td></td>
<td>Subacute thyroiditis</td>
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<tr>
<td>Malignant</td>
<td>Primary</td>
</tr>
<tr>
<td></td>
<td>Follicular cell-derived carcinoma:</td>
</tr>
<tr>
<td></td>
<td>PTC, follicular thyroid carcinoma, anaplastic thyroid carcinoma</td>
</tr>
<tr>
<td></td>
<td>C-cell–derived carcinoma:</td>
</tr>
<tr>
<td></td>
<td>MTC</td>
</tr>
<tr>
<td></td>
<td>Thyroid lymphoma</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
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</tbody>
</table>

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features that are consistently associated with malignancy are: i) Hypoechoogenicity, ii) Increased vascularity, iii) Microcalcifications, iv) Irregular margins, v) Absence of a halo.

The vascularity of a thyroid nodule is demonstrated with color flow Doppler (CFD) or power Doppler (PD) imaging. Nodule vascularity is categorized as absent, perinodular, or intranodular. Increased intranodular flow is associated with malignancy and has good interobserver variability.

Microcalcifications image as echogenic foci smaller than 2 mm and are associated with malignancy. Microcalcifications are thought to represent aggregates of psammoma bodies characteristic of many papillary cancers, and are rarely found in benign nodules or follicular neoplastic lesions.

Coarse calcifications may be associated with malignancy when they appear with microcalcifications or in the center of a hypoechoic nodule. Peripheral calcifications can be seen in malignant nodules, sometimes with interruption of the circumferential calcific rim that suggests malignant invasion of thyroid parenchyma.

Irregular margins are seen with invasion of a malignant nodule into the surrounding thyroid parenchyma, e.g., an encapsulated papillary cancer. The irregular margin is less commonly observed with encapsulated follicular or Hurthle cell cancers. A halo is described as a thin hypoechoic rim that surrounds a nodule and is thought to represent compression of the extranodular blood vessels as a benign nodule slowly grows.

An invasive malignancy, such as unencapsulated papillary cancer or medullary cancer, lacks a halo. However, follicular and Hurthle cell adenomas and cancers are generally surrounded by a fibrous avascular capsule. This capsule images sonographically as a thick, irregular hypoechoic rim, which is now recognized as a more dangerous second type of halo.

### ADDITIONAL SONOGRAPHIC FEATURES

1. Shape of the nodule: A/T ratio greater than 1.0, indicating a spherical nodule this detected thyroid cancer with a sensitivity of 84% and a specificity of 82%.
2. Extrathyroidal invasion may be occasionally seen when the tumor growth extends through either the anterior or posterior thyroid capsule, which normally appears as a bright white outline surrounding the thyroid.

Some series have explored the association of combinations of features with cancer risk. In most series, as the specificity of a combination increases, the sensitivity decreases. Papillary thyroid cancers are more likely to be solid, hypoechoic, and lack a halo compared with follicular thyroid cancers. Follicular cancers most commonly have a halo (90%), which is irregular (60%) and are iso- to hyperechoic. Therefore, it is critical to recognize that ultrasound does not replace FNA cytology, rather the two modalities are complementary.

### CLINICAL SITUATIONS

For nodules smaller than 1.5 cm where the cost-benefit analysis of FNAC is unclear, decision making for FNAC based on suspicious sonographic features of hypoechogenicity, microcalcifications, irregular margins, or increased vascularity is superior to using an arbitrary size cut-off of larger than 1 cm². If multiple thyroid nodules are present as potential candidates for FNAC, sonographic appearance can assist in nodule selection.

Lymph nodes High frequency (10 to 14 MHz) ultrasound transducers allow for high-resolution imaging of cervical lymph nodes. For DTC patients, ultrasound provides an inexpensive and available means both to evaluate the lateral cervical lymph nodes before thyroidectomy and to monitor for recurrence in the central and lateral compartment lymph nodes and in the thyroid bed. In addition, ultrasound can also be a complementary modality in the surveillance of medullary thyroid cancer.

### ULTRASOUND IMAGING OF METASTATIC LYMPH NODES

It is essential to appreciate the different imaging characteristics of benign and malignant lymph nodes. The evaluated parameters should include size, shape, presence of an echogenic hilus and a hypoechoic cortex, vascularity, and other aspects of echogenicity, including cystic change and calcifications.

No single sonographic feature is adequately sensitive for detection of lymph nodes with metastatic thyroid cancer. Some of the most specific criteria are presence of cystic areas (100%), presence of hyperechoic punctations representing either colloid or microcalcifications (100%), and peripheral vascularity (82%).

A reasonable approach to identify suspicious lymph nodes for further investigation would be to submit those without a fatty hilus to a careful Doppler examination for evaluation of vascularity. Peripheral or diffuse vascularization is worrisome. However, a rounded shape, an absent hilus, and heterogeneous echogenicity raise the suspicion of malignancy, especially when they coexist in the same lymph node. Last, lymph nodes with cystic change or microcalcifications should be considered as metastatic thyroid cancer.
THYROID ELASTOGRAPHY

Thyroid elastography is a newer technique advocated to evaluate a thyroid nodule. US elastography was developed to determine tissue stiffness and strain information non invasively. Strain represents the amount of deformation; thus, stiff tissue shows less strain than softer tissue. The strain images or elastograms are displayed with a color map. Elastography was initially used in breast and prostate tumors.

A thyroid lesion can have varying levels of stiffness within it, depending on the cellularity and composition of the nodule. Elastograms help to assess the relative stiffness of the lesion compared with its surrounding tissues and within itself. This information cannot be used to compare the stiffness of thyroid lesions from different patients because strain changes with applied compression. If pulsation of the carotid artery is used as the compression source, strain near the carotid artery can indicate the amount of compression applied by carotid arterial pulsation. Because the thyroid gland is located between the trachea and the carotid artery, lateral expansion of the carotid artery during systole compresses the thyroid gland against the trachea. As a result, the thyroid gland expands in the anteroposterior direction, that is, in the direction of the US probe (beam axis). Because US is sensitive to detecting motion along the beam axis, deformation of the thyroid gland in this direction can be readily detected. Because the thyroid stiffness index is a ratio between the carotid strain and the strain in the thyroid nodule, the varying strain from change in the blood pressure does not affect the ratio.

Of all the elastographic techniques, tissue strain imaging under a quasistatic compression load is the simplest to use and results are very encouraging. Here, strain images are constructed by using measurements of the local displacements induced by a compressive force applied to the tissue surface. The displacement fields are estimated by using correlation techniques that track the echo delays in segmented waveforms that are recorded before and after the quasistatic compression. The results of the tissue compression are displayed as an image called an elastogram, on which hard areas appear dark and soft areas appear bright.

Lyshchik et al. concluded that elastography is a promising imaging technique that can assist in differential diagnosis of thyroid nodules. Among the criteria evaluated at off-line elastography, only a tumor–to–normal tissue strain ratio greater than 4 was strongly associated with thyroid cancer (P < .001), with a specificity of 96% and a sensitivity of 82%.

Papillary carcinoma can be non-invasively differentiated with elastography by using the thyroid stiffness index. Multiple nodules in a patient can be evaluated with elastography to select probable papillary carcinoma.

FINE NEEDLE ASPIRATION CYTOLOGY (FNAC):

FNAC is the single most important diagnostic test which is the safest, most cost-effective, and most reliable technique available to differentiate between benign and malignant diseases of the thyroid. It is highly accurate, inexpensive and has low morbidity. Processing time is usually only a few days. It is estimated that its use reduces the number of thyroidectomies by half and the overall cost of thyroid nodule medical care by one quarter while doubling the surgical confirmation of carcinoma. Cytologic evaluation has improved significantly over the past two decades, but good aspiration technique and an experienced cytopathologist are necessary to reach the modern high standards. Immediate on-site evaluation of FNA specimens dramatically increases the adequacy of specimens compared with specimens not evaluated immediately. Current characteristics of FNAC are shown in table 3. With use of small needles (21 to 24 gauge), earlier concerns for needle-track seeding of malignancy have not materialized. The false-negative rate varies from 1% to 5% and is associated with cysts or nodules smaller than 1 cm or masses greater than 3 cm.

In general, FNABs are reported as clearly malignant, clearly benign, suspicious, or nondiagnostic. A nondiagnostic result should never be interpreted as benign; rather, it represents a lack of diagnosis, usually due to insufficient cells for evaluation. Papillary thyroid carcinoma is the easiest to diagnose microscopically with evidence of papillary fronds and fibrovascular cores. The nuclei are grooved and have eccentric nucleoli. Anaplastic carcinoma is also easy to identify due to its high degree of cellular atypia. Lymphoma can be suggested by FNAC, but formulating a diagnosis often requires greater amounts of tissue via open biopsy for evaluation of cytoarchitecture and flow cytometry studies. MTC is also easily identified by calcitonin immunohistochemistry performed on the aspirate. The difficulty with thyroid FNACs occurs in reports categorized as suspicious. Usually, this represents a follicular neoplasm that is indeterminate for adenoma vs carcinoma — a diagnosis requiring identification of tumor invading the thyroid capsule or blood vessel lumens. This is impossible with an FNAC specimen. However, an FNAC specimen that is densely cellular, lacks colloid, and has a microfollicular pattern suggests follicular carcinoma over adenoma. Microfollicular aspirates harbor carcinoma up to 25% of the time. Benign masses typically have an abundance of colloid, small numbers of follicular cells in a macrofollicular pattern, and abundant macrophages. Follicular neoplasms are generally treated with hemithyroidectomy and isthmusectomy, a conservative procedure that may be followed by completion thyroidectomy if the final pathology confirms...
carcinoma.

Because recent guidelines recommend that all patients with palpable nodules undergo ultrasound examination\(^1\) an increasing number of biopsies are now being performed with ultrasound guidance.

**PALPATION-GUIDED FINE-NEEDLE ASPIRATION**

For each nodule, two to four aspirations should be attempted from different areas of the nodule. Although major complications of FNA biopsy are rare, proper cytologic interpretation necessitates special expertise. Cytologic diagnoses are usually categorized as diagnostic or nondiagnostic, and the diagnostic specimens are classified as benign, “suspicious,” or malignant. Rebiopsy is indicated for enlarging nodules, recurrent cysts, and nondiagnostic cytologic findings.

**ULTRASOUND-GUIDED FINE-NEEDLE ASPIRATION**

Commercially available US machines equipped with 7.5- to 10.0-MHz transducers give a clear, concise, and continuous visualization of the thyroid gland and permit real-time visualization of the needle tip during the procedure to ensure accurate sampling of the desired area. Because of the direct visualization of the needle, accidental damage to vital neck structures, such as the trachea, carotid artery, jugular vein, or laryngeal nerve, is easily avoided. The needle should be directed to the peripheral rather than the central part of the nodule to avoid cystic degenerative areas in the nodule center, whereas in pure cysts, the center of the lesion should be reached first to completely drain the fluid. Cystic fluid should be submitted to the laboratory for cytologic analysis. Colloid fluids are clear-yellow; watery, clear-colorless fluid is likely of parathyroid origin and should have parathyroid hormone measurement. Hemorrhagic fluid carries a higher risk of malignancy.

Overall, 70% of FNAC specimens are benign, 5% malignant, 10% suspicious, and 15% unsatisfactory\(^4\). The final FNAC report is critical in dictating whether the patient’s management should be medical or surgical.

Thyroglobulin in fine-needle aspiration of cervical lymph nodes: Thyroglobulin (Tg) can be measured in lymph node or nodule aspirates (FNAC-Tg). Cytologic examination and measurement of Tg can be performed on the same specimen. In one report\(^4\), FNAC-Tg levels were markedly elevated in metastatic lymph nodes in patients awaiting thyroidectomy and in patients postthyroidectomy. FNAC-Tg sensitivity, evaluated through histologic examination, was 84.0%, and the combination of cytology plus FNAC-Tg increased FNAC sensitivity from 76% to 92.0%\(^5\).

**OTHER RADIOLOGICAL INVESTIGATIONS**

MRI and CT are not recommended for routine use because they are costly and rarely diagnostic for malignancy in nodular thyroid disease.

**IMMUNOHISTOCHEMICAL MARKERS**

HBME-1 is a monoclonal antibody that reportedly stains papillary cancer positively but does not stain benign follicular tumors\(^4\). In addition, galectin-3, which acts as a cell-death suppressor, is reported to distinguish benign from malignant thyroid follicular tumors\(^4\). Other markers, such as thyroid peroxidase and telomerase, have been reported to identify or exclude malignancy with variable success. Therefore, no single specific tumor marker is available to regularly and reliably distinguish benign from malignant thyroid cellular tumors.

**BIOCHEMICAL EVALUATION**

Measurement of serum TSH is the most useful test in the initial evaluation of thyroid nodules because of the high sensitivity of the TSH assay in detecting early or subtle thyroid dysfunction\(^6\). The measurement of serum free thyroid hormones and thyroid peroxidase antibody (TPOAb) levels should be the second diagnostic step, which is needed for confirmation and definition of thyroid dysfunction if TSH levels are outside the normal range.

The following practical strategy is suggested by the American Association of Clinical Endocrinologists guidelines for most patients with thyroid nodules\(^7\):

a. Normal serum TSH, no further testing.

b. High serum TSH, measure free T4 and TPOAb to evaluate hypothyroidism;

c. Low serum TSH, measure free T4 and free triiodothyronine to evaluate hyperthyroidism.

High levels of serum TPOAb associated with a firm, diffusely enlarged thyroid is highly suggestive of autoimmune disease (Hashimoto thyroiditis).

Serum calcitonin is a good marker for C-cell disease and correlates well with tumor burden. Calcitonin should be measured in patients who have a family history of MTC, multiple endocrine neoplasia type 2, or pheochromocytoma, or when FNAC results suggest MTC. A baseline serum calcitonin value of 10 to 100 pg/mL is considered abnormal (normal, 10 pg/mL) and should be followed by pentagastrin stimulation.

**RADIOISOTOPE SCANNING**

Based on the pattern of radioisotope uptake, nodules may be classified as hyperfunctioning (“hot”) or hypofunctioning (“cold”). Hot nodules are seldom, if ever, malignant, whereas cold ones have a reported cancer risk between 5% and 15%. Thyroid scintigraphy can be performed with \(^99\)TcO\(_4\) or \(^123\)I, although the latter is preferred. The role of scintigraphy in the diagnostic work-up of thyroid nodules is generally limited to:

1. A single nodule with suppressed TSH, in which case no FNAC is necessary.
2. A large toxic or nontoxic MNG, especially with substernal extension and
3. When searching for ectopic thyroid tissue, such as struma ovarii or sublingual thyroid.

**MANAGEMENT**

Clinical management of thyroid nodules is influenced by the combined results of TSH measurement, FNAC biopsy, and US and depends primarily on cytologic diagnosis.

**FINE-NEEDLE ASPIRATION–POSITIVE NODULE**

If cytologic results are positive for primary thyroid malignancy, surgery is almost always needed. Cancer due to metastasis requires further investigations aimed at finding the primary lesion, which often precludes thyroid surgery. If preoperative FNAC results suggest PTC, a near-total or total thyroidectomy is preferred. With the exception of intrathyroidal microcarcinomas with no evidence of nodal involvement, lymph nodes within the central compartment of the neck (level 6) should be removed. If central compartment (level 6) nodes are positive for cancer, ipsilateral modified neck dissection may be needed. In patients who have a solitary, small (1 cm) nodule (without lymph node involvement) proved to be PTC by preoperative FNAC or by frozen section at surgery, lobectomy plus isthmectomy may be sufficient treatment.

**FINE-NEEDLE ASPIRATION–NEGATIVE NODULE**

Routine use of T4 suppressive therapy in nodular thyroid disease is not recommended. Most thyroid nodules do not need specific treatment if malignancy and abnormal thyroid function have been excluded. Unless the nodule (or nodules) is causing local symptoms or the patient's concerns are excessive, treatment aimed at volume debulking or growth prevention is unnecessary on the basis of the usually slow growth rate of benign thyroid lesions. Clinical and US follow-up should be performed every 1 to 2 years.

Fine-needle aspiration–suspicious nodule: Cytologically suspicious lesions are best surgically excised.

Fine-needle aspiration–nondiagnostic nodule: Despite advance techniques, repeat biopsy, and US-FNAC, a residual 5% of nodules remain nondiagnostic, which creates a management dilemma for the clinician. Nondiagnostic, large (O3–4 cm), recurrent cysts or solid nodules should be treated surgically.

**THERAPEUTIC TECHNIQUES**

**Surgery**

Presence or persistence of dysphagia, choking, shortness of breath (especially when supine), hoarseness, and neck pressure or pain are indications for thyroidectomy. Patients who have cytologically suspicious nodules can be treated with thyroid lobectomy plus isthmectomy or total thyroidectomy; the latter is preferred if the patient is hyperthyroid, has a history of radiation, or has bilateral nodules.

**RADIOIODINE THERAPY**

Toxic nodular goiters are usually more radioresistant than toxic diffuse goiters, and higher 131I doses (30–100 mCi) may be needed for successful treatment. 131I therapy is successful in more than 85% of patients who have hyperfunctioning nodules or toxic MNGs. Hypothyroidism may develop after radioiodine treatment if the mass of normal thyroid tissue is too small, if its function is decreased because of concomitant autoimmune thyroiditis, or if there is damage to the thyroid consequent to contiguous cross-radiation from hot nodules. 131I therapy can be repeated after 6 months if thyrotoxicosis is not cured, as documented by persistent low TSH levels.

131I is preferred over thyroidectomy for small, nontoxic goiters (volume 100 mL) without suspected thyroid malignancy, in patients previously treated with surgery, or in those at risk for surgical intervention. 131I is not the treatment of choice if compressive symptoms are present, in larger nodules requiring high doses of 131I (which may be resistant to treatment), or if an immediate resolution of hyperthyroidism is medically indicated.

The only absolute contraindications to 131I treatment are pregnancy (which should be excluded by a pregnancy test) and breast feeding; treatment should be avoided for an arbitrary period of 3 to 6 months.

The administration of small doses (0.1–0.3 mg) of recombinant human TSH (rhTSH) to patients who have low-uptake MNG increases 131I uptake by more than 4-fold in 24 to 72 hours. rhTSH is approved only for scanning and Tg stimulation in patients who have thyroid cancer; its use to augment 131I treatment is considered “off-label”.

**NONSURGICAL MINIMALLY INVASIVE PROCEDURES:**

Percutaneous ethanol injection (PEI): PEI is an effective alternative to surgery in the treatment of complex nodules with a dominant fluid component. Aspiration of thyroid cysts decreases the volume, but recurrences are common, and surgery is often required to remove large, relapsing lesions. PEI is not recommended for treatment of toxic solitary or multinodular goiters, in part because of a high recurrence rate and in part because 131I and surgery are effective and safe. PEI is not suitable for cold thyroid nodules because it requires repeated treatments, induces unpleasant adverse effects (eg, transient cervical pain), and can be complicated by recurrent laryngeal nerve damage.

Percutaneous Laser thermal ablation (PLA): PLA is a minimally invasive procedure that is proposed as an alternative to surgery for thyroid nodules causing local symptoms or cosmetic concerns. In patients who have large nodules, one to three sessions of PLA or a single treatment with multiple fibers induces a nearly 50% decrease in nodule volume and alleviation of local symptoms. Despite its apparent efficacy, because of the potential for major
complications, PLA use should be restricted to specialized centers. Radiofrequency ablation (RF): RF ablation is under evaluation as a nonsurgical therapeutic modality for the ablation of benign and malignant thyroid lesions. RF ablation induces substantial volume reduction, but a few relevant complications have been reported: cervical hematoma, burn at the puncture site, and vocal cord palsy due to recurrent laryngeal nerve damage.

REFERENCES