Thyroid Nodules: Clinical Importance, Assessment, and Treatment

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Since the previous publication on thyroid nodule diagnosis and treatment in Endocrinology and Metabolism Clinics of North America a decade ago [1], many advances have occurred in the diagnosis and management of thyroid nodular disease. The introduction of new thyroid-stimulating hormone (TSH) assays, widespread application of fine-needle aspiration (FNA) biopsy, and the increasing availability and use of high-resolution ultrasonography (US) have facilitated, modified, and improved the management of thyroid nodules.

Although these new techniques have vastly improved patient care, controversy continues in some areas, including the evaluation of thyroid micro-nodules discovered incidentally on US, the use of US-guided FNA, management of nodules with cytologically suspicious FNA results, thyroxine (T4) therapy for benign nodules, and routine serum calcitonin measurement in patients presenting with a nodular thyroid. This article reviews many of these issues, focusing on advances and controversies. Recent practice management guidelines published by the American Association of Clinical Endocrinologists in collaboration with Associazione Medici Endocrinologi [2] and by the American Thyroid Association [3] are the main sources of the evidence-based recommendations. Published data are categorized using recent criteria suggested for grading, and the level of evidence is noted for all references in the bibliography [4].
Clinical importance

Thyroid nodules are common. They are discovered by palpation in 3% to 7% [5,6], by US in 20% to 76% in the general population [7,8], and by autopsy in approximately 50% [9,10]. 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 [6]. With an incidence of 0.1% per year, an estimated 300,000 new nodules will be identified in the United States in 2007, with a 10% lifetime probability of a nodule developing [7,10,11]. The clinical significance of these data cannot be overstated.

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 [7,11,12]. Because of the high prevalence of nodular thyroid disease, it is not economically feasible or clinically necessary to perform a complete structural and functional assessment for all or even most thyroid nodules. Therefore, it is essential to develop and follow a systematic, cost-effective strategy for diagnosis and treatment of thyroid nodules and to avoid unnecessary, potentially harmful surgery.

Diagnosis

History and physical examination

Clinical evaluation begins with a detailed patient history and careful thyroid palpation. Most patients present with an asymptomatic mass discovered by a physician on routine neck palpation or by the patient during self-examination. Many disorders, benign and malignant, can cause thyroid nodules (Box 1) [5,10]. Newly diagnosed thyroid nodules should be evaluated primarily to rule out thyroid malignancy [5,7,10]. An inquiry should be made about family history of benign or malignant thyroid disease. Thyroid cancer (medullary thyroid carcinoma [MTC] or papillary thyroid carcinoma [PTC]), multiple endocrine neoplasia type 2, familial polyposis coli, Cowden disease, and Gardner syndrome are rare disorders but should be considered [13]. Presentation of nodules during childhood and adolescence should induce caution; 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 documented. Appearance of a new mass, slow but progressive nodule growth, a firm or hard solitary or dominant nodule, or the presence of adjacent cervical adenopathy is suspicious for malignancy and should prompt further evaluation.
Box 1. Common causes of thyroid nodules

Benign
- Colloid nodule
- Hashimoto thyroiditis
- Simple or hemorrhagic cyst
- Follicular adenoma
- Subacute thyroiditis

Malignant
- Primary
  - Follicular cell-derived carcinoma:
    - PTC, follicular thyroid carcinoma, anaplastic thyroid carcinoma
  - C-cell–derived carcinoma:
    - MTC
- Secondary
  - Thyroid lymphoma

Box 2. Increased risk of malignancy in thyroid nodule

- History of childhood head/neck irradiation
- Family history of PTC, MTC, or multiple endocrine neoplasia type 2 (MEN2)
- Age <20 or >70 years
- Male sex
- Enlarging nodule
- Abnormal cervical adenopathy
- Fixed nodule
- Vocal cord paralysis

[5,10,11]. Box 2 highlights features associated with increased risk of cancer in thyroid nodules.

**Ultrasonography**

Brightness-mode US is the most sensitive test to detect lesions in the thyroid. It accurately measures the dimensions, identifies the structure, and evaluates diffuse changes in the thyroid parenchyma. US is noninvasive, relatively inexpensive, and can identify nodules not apparent on physical examination, isotope scanning, or other imaging techniques (Fig. 1) [14].
should not be a substitute for a physical examination or be performed on an otherwise normal thyroid gland or as a screening test in the general population. Because of the high prevalence of small, clinically inapparent thyroid nodules and the minimal aggressiveness of most thyroid cancers, US should be used as a screening test only if well-known risk factors are present (Box 3).

Sonographic examination should be ordered for all patients who have a history of familial thyroid cancer, multiple endocrine neoplasia type 2, or childhood head/neck irradiation, even if the thyroid appears normal by palpation [2,14]. The finding of adenopathy suspicious for malignancy in the anterior or lateral neck compartments warrants US examination of the lymph nodes and thyroid because of the risk of nodal metastasis from an otherwise unrecognized papillary microcarcinoma.

It is recommended that all patients who have a nodular thyroid, with a palpable solitary nodule or a multinodular goiter (MNG), be evaluated by US [2,3]. US examination should search for additional, unsuspected nodules; measure nodule number and size; record sonographic appearances to assess risk of malignancy; and select lesions that require US-guided FNA (US-FNA) biopsy [7,14]. A recent report showed that using thyroid US can result in an improved and important management change for many patients who have “presumed” thyroid nodules: 44% of patients had no nodule or had unsuspected but clinically important nodules that warranted further evaluation [15].

Ultrasound-guided fine-needle aspiration

In recent years, US-FNA has become increasingly popular because of increased precision and the ability to guide the biopsy needle to the desired location in real time (Fig. 2) [14]. The cardinal indications for US-FNA, listed in Box 4, include nondiagnostic results by palpation-guided FNA, impalpable or small (<1.5 cm) nodules, a nodule with solid and cystic

![Fig. 1. Transverse ultrasonographic view of the right thyroid lobe showing a 1.2-cm hypoechoic nodule (N), which was benign by fine-needle aspiration biopsy. C, carotid artery; T, trachea.](image)
components, and abnormal cervical adenopathy. Recent studies show that US-FNA decreases nondiagnostic rates from 15% to between 3.5% and 7% [16,17].

Thyroid micronodules that are not clinically apparent (14%–24% of those with a diameter $\leq 10$ mm) are detected by US in about half (27%–72%) of the women evaluated [5,7,10,11]. The prevalence of cancer ranges from 5.4% to 7.7% in studies regarding the cytologic evaluation of nonpalpable thyroid lesions and seems to be similar to that reported for palpable lesions (5.0%–6.5%) [18,19]. Few clinical criteria for malignancy exist for most nonpalpable lesions, and patients who have palpable thyroid nodules seldom present with history or physical examination findings suggestive of thyroid carcinoma [20]. Therefore, to avoid the inappropriate use of US-FNA, it is essential to determine which thyroid lesions are at risk of malignancy on the basis of US characteristics.

**Box 3. Thyroid ultrasonographic examination**

Not indicated
- As screening test in general population
- In patient who has low risk for thyroid cancer and normal thyroid on palpation

Indicated
- In a patient who has a palpable nodule
- In a patient who has history of neck irradiation
- In a patient who has family history of MTC, MEN2, or PTC
- If unexplained cervical adenopathy is present

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**Fig. 2.** A 50-year-old woman had multiple small thyroid nodules. US showed the largest nodule to be a complex, predominantly cystic mass in the right lobe measuring 2.6 $\times$ 1.7 cm. The nodule was benign by US-FNA. Arrow illustrates needle tip (circled) accurately placed in the nodule.
Ultrasound prediction of malignancy

Although no single US characteristic can unequivocally distinguish benign and malignant nodules, several US features and, more importantly, a combination of features, have been evaluated as predictors of malignancy [18,21].

**Solitary versus multiple nodules.** The risk of cancer is not significantly higher for solitary nodules than for glands with several nodules, whether the nodules are palpable or impalpable [18–25]. In glands with multiple nodules, selection for FNA should be based on US features rather than on size or clinically “dominant” nodules [18,23,25]. Although criteria for selection of 1 or more nodules for US-FNA is a matter of debate, Table 1 summarizes recent recommendations from three different professional societies (Fig. 3) [2,3,25].

**Size.** Nodule size is not predictive of malignancy. Cancer is not less frequent in small nodules (diameter <10 mm); thus, an arbitrary diameter cutoff of 10 or 15 mm for cancer risk should be discouraged in clinical practice [2,18]. The lower size limit of a micronodule that should be chosen for biopsy is also controversial. US-FNA should be considered for nodules smaller

<table>
<thead>
<tr>
<th>Box 4. Indications for ultrasonography fine-needle aspiration</th>
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<tbody>
<tr>
<td>- Palpation-guided FNA nondiagnostic</td>
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<tr>
<td>- Complex (solid/cystic) nodule</td>
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<tr>
<td>- Palpable small nodule (&lt;1.5 cm)</td>
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<tr>
<td>- Impalpable incidentaloma</td>
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<tr>
<td>- Abnormal cervical nodes</td>
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<td>- Nodule with suspicious US features</td>
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**Table 1**

<table>
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<th>Biopsy recommendations for multiple nodules</th>
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<td>Guidelines</td>
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<td>ACE [2]</td>
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<td>ATA [3]</td>
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<td>SRU [25]</td>
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**Abbreviations:** AACE, American Association of Clinical Endocrinologists; ATA, American Thyroid Association; SRU, Society of Radiologists in Ultrasound; US, ultrasonographic.
than 10 mm if associated with punctate microcalcifications, if a history of neck irradiation is present, or in a young patient (see Box 2). Because some microcarcinomas can have aggressive clinical behavior, early diagnosis by FNA of a small (<10 mm) PTC followed by immediate thyroidectomy may not only decrease morbidity but also be curative [18,26].

**Ultrasound features and color Doppler findings.** The specificity of US features for diagnosing cancer varies from 85% to 95% for microcalcifications (small intranodular punctate hyperechoic spots, with scanty or no posterior acoustic shadowing) (Fig. 4), from 83% to 85% for irregular or indistinct nodule margins, and about 81% for chaotic appearance of intranodular vascular images [18,21,25]. The predictive value of these US features for cancer is in part diminished by their low sensitivity (29.0%–59.2%, 55.1%–77.5%, and 74.2%, respectively), and no US sign by itself can reliably predict malignancy. The association of hypoechoic appearance of the nodule with at least one or more US features suggestive of malignancy effectively indicates a subset of nonpalpable thyroid nodules at high risk for malignancy [18,21]. The presence of at least two suspicious sonographic criteria reliably identifies 85% to 93% of thyroid gland neoplastic lesions, thus decreasing the number of US-FNA procedures to about one third of the nonpalpable nodules (Table 2) [18,23,27].

Color Doppler US evaluates nodule vascularity. The assumption is that hypervascularity with chaotic arrangement of blood vessels favors malignancy, whereas peripheral flow indicates a benign nodule. Reports have failed to consistently identify cancer on color Doppler alone (Fig. 5) [25].

**Extracapsular growth.** Hypoechoic nodules with irregular borders, extension beyond the thyroid capsule, invasion into perithyroid muscles, and
infiltration of the recurrent laryngeal nerve are sonographic features that warrant cytologic evaluation [23,27,28].

**Complex or cystic lesions.** Complex thyroid nodules have solid and cystic components, often with a dominant cystic part, and are frequently benign. These lesions are common, frequently smaller than 3 or 4 cm in diameter, and asymptomatic. US-FNA is necessary to document the morphology because some PTCs may be cystic (Fig. 6) [25,28].

### Table 2

<table>
<thead>
<tr>
<th>US feature</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Positive predictive value, %</th>
<th>Negative predictive value, %</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcalcifications</td>
<td>26.1–59.1</td>
<td>85.8–95.0</td>
<td>24.3–70.7</td>
<td>41.8–94.2</td>
<td>4.97</td>
</tr>
<tr>
<td>Hypoechoogenicity</td>
<td>26.5–87.1</td>
<td>43.4–94.3</td>
<td>11.4–68.4</td>
<td>73.5–93.8</td>
<td>1.92</td>
</tr>
<tr>
<td>Irregular margins or no halo</td>
<td>17.4–77.5</td>
<td>38.9–85.0</td>
<td>9.3–60.0</td>
<td>38.9–97.8</td>
<td>16.83</td>
</tr>
<tr>
<td>Solid</td>
<td>69.0–75.0</td>
<td>52.5–55.9</td>
<td>15.6–27.0</td>
<td>88.0–92.1</td>
<td>4.2a</td>
</tr>
<tr>
<td>Intranodule vascularity</td>
<td>54.3–74.2</td>
<td>78.6–80.8</td>
<td>24.0–41.9</td>
<td>85.7–97.4</td>
<td>14.29</td>
</tr>
<tr>
<td>More tall than wide</td>
<td>32.7</td>
<td>92.5</td>
<td>66.7</td>
<td>74.8</td>
<td>10.5a</td>
</tr>
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</table>

*Abbreviation:* US, ultrasonography.

*a Unpublished data from a series of 400 patients undergoing surgery for thyroid nodular disease. Regina Apostolorum Hospital, Albano, Rome. Courtesy of Papini E and Guglielmi R.

Nodule shape. A rounded appearance or a “more tall (anteroposterior) than wide (transverse)” shape of the nodule and a “marked hypoechogenicity” of a solid lesion (hypoechoic even compared with the cervical muscles) are newly described US patterns suggestive of malignancy [29].

Suspicious cervical adenopathy. Enlarged cervical lymph nodes that have a rounded appearance by US, no hilus, cystic changes, microcalcifications, or chaotic hypervascularity have a high probability for malignancy. These nodes and any coexistent, especially ipsilateral, thyroid nodules, whatever their size, always warrant US-FNA biopsy [25,26,28].

Other imaging techniques

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

Fig. 5. US images of a left lobe thyroid nodule. (A) The 1.7 × 1.4-cm solid left lobe thyroid nodule was hypoechoic. (B) Color Doppler flow imaging shows hypervascularity. FNA biopsy showed papillary thyroid carcinoma, which was confirmed at surgery.

Fig. 6. Transverse US images of two mostly cystic thyroid nodules. The similarity between the cysts mandates US-FNA biopsy to accurately distinguish a benign (A) from a malignant (B) nodule.
MRI and CT are of value to assess size, substernal extension, and positional relationship of the goiter to surrounding structures (Fig. 7). Caution should be used with CT contrast medium that contains iodine because it decreases subsequent iodine 131 (\(^{131}\text{I}\)) uptake. Positron emission tomography with \([^{18}\text{F}]\) fluorodeoxyglucose may add functional information to anatomic visualization provided by US [30]. The high cost of these procedures makes them impractical for routine clinical assessment of thyroid nodules.

**Fine-needle aspiration biopsy**

Thyroid FNA biopsy is the most accurate test for determining malignancy and is an integral part of thyroid nodule evaluation [2,31–42].

**Palpation-guided fine-needle aspiration**

Detailed descriptions of the palpation-guided FNA procedure, its problems, and progress to date have been published elsewhere [31–33,36–40,42].

**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 FNA procedure to ensure accurate sampling of the desired area (see Fig. 2). The small-sized transducers currently in use are especially convenient for US-FNA. After the biopsy sites are identified, the needle is inserted through a steering device (US-guided FNA) or just above the center of the

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**Fig. 7.** Images of a large, asymmetric multinodular goiter. (A) Chest radiography shows marked tracheal deviation to the right (arrow). (B) Chest CT confirmed the presence of a large substernal goiter on the left to the level of tracheal bifurcation.
transducer (US-assisted FNA). 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 [43]. 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. Most 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. In mixed or mostly fluid complex lesions, the needle should be directed to the root of hubs or pedicles growing into the cystic lumen (the inner area of the pedicle facing the lumen usually contains necrotic debris and cells with degenerative changes). After complete drainage of the fluid, the solid areas and the peripheral borders of the lesion should be carefully sampled.

Cytologic diagnosis

FNA results are categorized as diagnostic (satisfactory) or nondiagnostic (unsatisfactory). The specimen is “diagnostic,” “adequate,” or “satisfactory” if it contains no less than six groups of well-preserved thyroid epithelial cells consisting of at least 10 cells in each group. Nondiagnostic or unsatisfactory smears with an inadequate number of cells result from acellular cystic fluid, bloody smears, or poor techniques in preparing slides [32,34]. Benign (negative) cytology, the most common finding, is indicative of a colloid nodule, macrofollicular adenoma, lymphocytic thyroiditis, granulomatous thyroiditis, or benign cyst [32]. The most common benign diagnosis is “colloid nodule,” which may come from a normal thyroid gland, a benign nodule, an MNG, or a macrofollicular adenoma (Fig. 8).

Malignant (positive) results are reliably identified by an experienced cytopathologist; the cytopathologist’s expertise in thyroid cytology is crucial in ensuring proper interpretation of smears [31,33,37]. PTC is the most common malignancy; aspirates are characterized by increased cellularity, tumor cells arranged in sheets and papillary cell groups, and typical nuclear abnormalities, which include intranuclear holes and grooves. Other malignant lesions include MTC, anaplastic carcinoma, and high-grade metastatic cancers [33]. Suspicious (indeterminate) specimens are those for which a clear cytologic diagnosis cannot be made [31,33,35] and include follicular neoplasms, Hürthle cell neoplasms, atypical PTC, or lymphoma. Follicular neoplasms are the most common and are hypercellular with microfollicular arrangement and decreased or absent colloid. Hürthle cell neoplasm is diagnosed if the aspirate contains almost exclusively Hürthle cells, usually with absent or scanty colloid lacking a lymphoid cell population, similar to what is usually found in Hashimoto thyroiditis. Nondiagnostic (unsatisfactory)
aspirates have few or no epithelial cells for proper cytodiagnosis and account for up to 20% of all specimens [36,44,45]. The criteria for judging aspirates as inadequate are somewhat arbitrary and are influenced by the standards of a given laboratory, the nature of the cystic nodule, and the expertise of the cytopathologist.

Overall, 70% of FNA specimens are benign, 5% malignant, 10% suspicious, and 15% unsatisfactory [2,31–33,37]. The final FNA report is critical in dictating whether the patient’s management should be medical or surgical. According to recent reviews and reports, FNA has improved patient selection for thyroidectomy, such that cancer yield at surgery has increased from 15% before the use of FNA to 50% with FNA use [39,46]. The sensitivity and specificity of FNA in experienced hands are excellent (Table 3).

A major concern with FNA is the possibility of a false-negative result (ie, a missed malignancy) [37,39]. Although the false-negative rate ranges from 1% to 11%, it is less than 2% in most clinics with adequate FNA experience. Box 5 illustrates some suggestions for minimizing false-negative results.

Biopsy often causes mild temporary pain and is occasionally associated with a minor hematoma. No serious adverse effects and no seeding of tumor cells in the needle track have been reported [37,42]. The consensus is that FNA is a safe, useful, and cost-effective procedure [2,3,37,39].

Some clinicians have debated whether routine rebiopsy is necessary after benign cytologic results [2,47]. For physicians or clinics just beginning to perform FNA, routine rebiopsy may provide reassurance with the procedure.
and decrease false-negative rates; however, we believe that successive FNA biopsies do not change nodule management and suggest rebiopsy only of an enlarging nodule, a recurrent cyst, a large (>4–5 cm) nodule, or demonstrated lack of shrinkage on T4 therapy (Box 6) [2,39].

Thyroglobulin in fine-needle aspiration of cervical lymph nodes

An important recent advance in thyroid cancer practice is the demonstration that thyroglobulin (Tg) can be measured in lymph node or nodule aspirates (FNA-Tg) [48]. The appearance of cervical adenopathy in patients who have thyroid cancer requires diagnostic US-FNA for confirmation of metastasis and appropriate management.

Cytologic examination and measurement of Tg can be performed on the same specimen. To measure Tg, the needle is rinsed with 1 mL of normal saline solution immediately after FNA biopsy, and Tg levels are measured on the needle washout by immunoradiometric or chemiluminescence assays. The procedure does not require an additional puncture (washout is

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<td><strong>Summary characteristics for thyroid fine-needle aspiration: results of literature survey</strong></td>
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<table>
<thead>
<tr>
<th>Feature</th>
<th>Mean</th>
<th>Range</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Sensitivity, %</td>
<td>83</td>
<td>65–98</td>
<td>Likelihood that patient who has disease has positive test results</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>92</td>
<td>72–100</td>
<td>Likelihood that patient without disease has negative test results</td>
</tr>
<tr>
<td>Positive predictive value, %</td>
<td>75</td>
<td>50–96</td>
<td>Fraction of patients who have positive test who have disease</td>
</tr>
<tr>
<td>False-negative rate, %</td>
<td>5</td>
<td>1–11</td>
<td>FNA negative; histology positive for cancer</td>
</tr>
<tr>
<td>False-positive rate, %</td>
<td>5</td>
<td>0–7</td>
<td>FNA positive; histology negative for cancer</td>
</tr>
</tbody>
</table>

*Abbreviation:* FNA, fine-needle aspiration.


**Box 5. Ways to minimize false-negative results**

- Follow-up cytologically benign nodules
- Aspirate multiple nodule sites
- Aspirate multiple nodules in MNG
- Submit cyst fluid for examination
- Review slides with experienced cytopathologist

performed after smear preparation), requires little extra time, and is easy to do. In one report [48], FNA-Tg levels were markedly elevated in metastatic lymph nodes in patients awaiting thyroidectomy and in patients postthyroidectomy. FNA-Tg sensitivity, evaluated through histologic examination, was 84.0%, and the combination of cytology plus FNA-Tg increased FNA sensitivity from 76% to 92.0% [48]. This test is attractive because the clinical performance of FNA-Tg is unaffected by the presence of Tg antibodies in the serum [49].

**Immunohistochemical markers**

Several molecular markers and assays have shown promise in clarifying suspicious FNA results. For example, HBME-1 is a monoclonal antibody that reportedly stains papillary cancer positively but does not stain benign follicular tumors [46,50]. In addition, galectin-3, which acts as a cell-death suppressor, is reported to distinguish benign from malignant thyroid follicular tumors [51]. Other markers, such as thyroid peroxidase and telomerase, have been reported to identify or exclude malignancy with variable success [52]. Despite most studies showing markers to have high sensitivity or specificity, no markers have high sensitivity and specificity for correctly diagnosing thyroid cancer. Therefore, no single specific tumor marker is available to regularly and reliably distinguish benign from malignant thyroid cellular tumors [2,46].

**Laboratory 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 [53,54]. The measurement of serum free thyroid hormones and thyroid peroxidase antibody (TPOAb) levels should be the second diagnostic step, which is needed for confirmation

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**Box 6. Indications for repeat biopsy**

- Follow-up of benign nodule
- Enlarging nodule
- Recurrent cyst
- Nodule >4 cm
- Initial FNA nondiagnostic
- No nodule shrinkage after T4 therapy

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and definition of thyroid dysfunction if TSH levels are outside the normal range [55].

Third-generation TSH assays, with detection limits of about 0.01 mIU/mL, should be used in clinical practice. These assays detect TSH levels even in cases of mild hypo- or hyperthyroidism and make possible a reliable diagnosis of subclinical disease [55–57]. If serum TSH is within the normal range, determination of free thyroid hormones adds no further relevant information. If TSH levels are low, measurement of free T4 and free triiodothyronine is required to confirm hyperthyroidism. To limit unnecessary laboratory testing, the following practical strategy is suggested by the American Association of Clinical Endocrinologists guidelines for most patients with thyroid nodules [2]: normal serum TSH—no further testing; high serum TSH—measure free T4 and TPOAb to evaluate hypothyroidism; low serum TSH—measure free T4 and free triiodothyronine to evaluate hyperthyroidism.

TPOAb should be measured in patients who have increased levels of serum TSH [57]. High levels of serum TPOAb associated with a firm, diffusely enlarged thyroid is highly suggestive of autoimmune disease (Hashimoto thyroiditis). Occasionally, a nodular goiter may represent Hashimoto thyroiditis [57]. Anti-Tg antibody assays are not routinely used and should be reserved for the few patients who have sonographic and clinical findings suggestive of chronic lymphocytic thyroiditis with normal or negative serum TPOAb titers [58].

Serum Tg concentration correlates with iodine intake and the size of the thyroid gland rather than with the nature or function of the nodule. Because Tg concentration does not influence management, measurement of Tg is seldom used in nodule diagnosis [2,59].

Serum calcitonin is a good marker for C-cell disease and correlates well with tumor burden [60]. Although MTC accounts for only 5% of thyroid cancers, several prospective studies show a prevalence of MTC ranging from 0.4% to 1.4% in patients who have nodular thyroid disease [61,62]. Therefore, to detect and treat early unsuspected C-cell disease, routine calcitonin measurement in all patients who have a nodular thyroid has been recommended by European studies [63–65]. There is no consensus on this issue because of the unproven clinical significance of C-cell hyperplasia or medullary microcarcinoma in studied patients, the possibility of false-positive results that necessitate further unnecessary work-up, and lack of data that this practice is cost-effective [46,61,62,66,67].

Two recent thyroid practice guidelines have not endorsed routine calcitonin determination [2,3]. Calcitonin should be measured in patients who have a family history of MTC, multiple endocrine neoplasia type 2, or pheochromocytoma, or when FNA 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. If a patient has a marked response to pentagastrin, thyroidectomy frequently reveals microscopic
MTC [61,62,65]. Pentagastrin is no longer available for clinical use in the United States.

Radioisotope scanning

Thyroid scanning is the only technique that allows for assessment of thyroid nodular function and detects areas of autonomy within the thyroid gland. Based on the pattern of radioisotope uptake, nodules may be classified as hyperfunctioning ("hot") or hypofunctioning ("cold") (Fig. 9). Hot nodules are seldom, if ever, malignant, whereas cold ones have a reported cancer risk between 5% and 15%. Because the vast majority (80%–90%) of thyroid lesions are cold and only a small minority of these are malignant, the predictive value of hypofunctioning nodules for malignancy is low. The diagnostic specificity is further decreased in small lesions (<1 cm), which may not be identified by scanning [68–70].

Thyroid scintigraphy can be performed with $^{99m}$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 FNA is necessary; (2) a large toxic or non-toxic 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, FNA 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 [2,3,71,72]. Cancer due to metastasis requires further investigations aimed at finding the primary lesion, which often precludes thyroid surgery. If preoperative FNA results suggest PTC, a near-total or total thyroidectomy is preferred [2,3,73,74]. 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 [2,3,71].

It is recommended that all patients undergoing thyroid surgery be evaluated by US preoperatively [2]. Abnormal lymph nodes identified by US should be removed and sent for pathologic examination at cervical exploration. If central compartment (level 6) nodes are positive for cancer, ipsilateral modified neck dissection should follow [71–74]. In patients who have a solitary, small (<1 cm) nodule (without lymph node involvement) proved to be PTC by preoperative FNA or by frozen section at surgery, lobectomy plus isthmectomy may be sufficient treatment. This issue continues to be debated [3,71,72,74].
Fine-needle aspiration–negative nodule

Administration of T4 with TSH suppression is aimed at shrinking nodule size, arresting further nodule growth, and preventing the appearance of new nodules [2,3,46,75–80]. Although some reports show that nodule shrinkage is more frequent in patients who have long-term TSH suppression than in untreated patients [76–78], a clinically significant (>$50\%$) decrease in nodule volume is obtained with T4 only in a minority of patients (ie, 20\% of those who have palpable thyroid nodules) [46,75,79]. The growth of most thyroid nodules seems to be minimally dependent on TSH levels, and the

Fig. 9. Four different iodine 123 ($^{123}$I) thyroid scintigraphy patterns. (A) Normal thyroid showing homogeneous function in both lobes. (B) Nonfunctioning “cold” nodule in the right thyroid lobe. (C) Hyperfunctioning “hot” right thyroid nodule, with suppressed serum thyroid-stimulating hormone level and suppressed uptake of $^{123}$I in the rest of the thyroid gland. (D) Typical pattern of a multinodular goiter with irregular, patchy uptake of an enlarged thyroid gland, including areas of normal, decreased, and increased $^{123}$I uptake.

Fine-needle aspiration–negative nodule
observed beneficial effect of T4 may be explained by a decrease in volume of the still-TSH–dependent perinodular thyroid tissue. Nodule volume reduction is more likely in small, recently diagnosed nodules, in lesions with colloid features at FNA evaluation, and in geographic regions with borderline iodine deficiency [76,80].

T4 treatment is not free of adverse effects, and therapy should be targeted toward partial TSH suppression. Sustained subclinical hyperthyroidism is associated with a substantial decrease in bone density in postmenopausal women [81–83] and a 3-fold increase in atrial fibrillation, with increased morbidity and mortality from cardiovascular diseases [84–86].

Routine use of T4 suppressive therapy in nodular thyroid disease is not recommended [2,3,5,75]. The use of T4 may be considered in patients from iodine-deficient areas, in younger patients who have small nodules and colloid features on cytology, and in small MNGs with no evidence of functional autonomy [2]. The use of T4 should be avoided for large thyroid nodules or long-standing goiters, particularly if the TSH value is less than 0.5 mIU/mL; in postmenopausal women or persons older than 60 years; and in patients who have osteoporosis, cardiovascular disease, or systemic illnesses (Box 7). T4 treatment induces a clinically significant volume reduction only in a minority of patients, and the parameters of such a response are not known. Often, commitment to chronic therapy seems inevitable, but therapy should never be fully TSH suppressive because of the adverse effects of prolonged subclinical hyperthyroidism. If the nodule does not shrink or grows during the course of T4 therapy, US-FNA and possible surgery may be necessary.

Most thyroid nodules do not need specific treatment if malignancy and abnormal thyroid function have been excluded [2,3,5]. 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 [87,88]. Clinical and US follow-up should be performed every 1 to 2 years.

**Fine-needle aspiration–suspicious nodule**

Indeterminate FNA results occur because the morphologic criteria used to distinguish benign from malignant lesions are poorly defined. No clear-cut

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**Box 7. Thyroxine-suppressive therapy for benign nodules**

Not recommended:
- As routine treatment
- If TSH <0.5 mIU/mL
- In large nodule or MNG
- For postmenopausal women
- In patients with cardiac disease
cytologic criteria are available to help the clinician with the diagnosis. Overall, about 20% of indeterminate specimens are malignant, but cancer risk varies from 15% for “follicular neoplasm” to 60% for “atypical PTC” specimens [31,33,39]. It has been suggested that patients who have follicular neoplasm nodules undergo radioisotope scanning to rule out a hyperfunctioning, and therefore benign, process that may not require surgery. Because most follicular neoplasms are nonfunctional on these scans, this suggestion may not be cost-effective [31]. Reaspiration is not helpful; it typically creates confusion and does not provide useful information for management [35]. Clinical criteria such as sex, age, nodule size (<4 cm), and nodule consistency have been reported to favor [89] and not favor malignancy [46]. It is generally agreed that cytologically suspicious lesions are best surgically excised [2,3,39]. Current immunohistochemical or molecular markers do not reliably or regularly separate benign from malignant follicular neoplasms [46], and their application in clinical practice is not endorsed [2,3].

Fine-needle aspiration–nondiagnostic nodule

An unsatisfactory specimen usually results from a cystic nodule that yields few or no follicular cells; reaspiration yields satisfactory smears in about 50% of cases [36]. US-FNA improves FNA accuracy and decreases the rates of nondiagnostic specimens. Two recent European studies showed that rates of nondiagnostic specimens (8.7% and 16%) decreased (to 3.5% and 7%, respectively) with the use of US-FNA [16,17]. Despite experienced centers, repeat biopsy, and US-FNA, a residual 5% of nodules remain nondiagnostic, which creates a management dilemma for the clinician [44,45,90]. Nondiagnostic, large (>3–4 cm), recurrent cysts or solid nodules should be treated surgically.

Therapeutic techniques

Surgery

Surgical options include lobectomy plus isthmectomy for a benign nodule, less-than-total thyroidectomy for MNG, and near-total or total thyroidectomy for malignant disease [3,71,72]. When established to be caused by thyroid enlargement, the presence or persistence of dysphagia, choking, shortness of breath (especially when supine), hoarseness, and neck pressure or pain are indications for thyroidectomy. A single toxic nodule or a toxic MNG may be treated surgically [2]. 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. Frozen section should be performed at the time of surgery to help guide surgical decision making but may be of limited use in distinguishing benign from malignant follicular lesions [91].
Radioiodine

The aim of radioiodine (\(^{131}\)I) treatment is the ablation of thyroid autonomy, restoration of normal thyroid function, and reduction of thyroid mass (Box 8) [92,93]. Toxic nodular goiters are usually more radioresistant than toxic diffuse goiters, and higher \(^{131}\)I doses (30–100 mCi) may be needed for successful treatment [94]. \(^{131}\)I therapy is successful in more than 85% of patients who have hyperfunctioning nodules or toxic MNGs [95]. After treatment with ablative doses of \(^{131}\)I, thyroid volume can decrease considerably (median decrease, 35% at 3 months and 45% at 24 months); 80% to 90% of patients become euthyroid. 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 [96]. Although rare (occurring in <1% of patients), immunogenic hyperthyroidism may occur due to induction of TSH receptor autoantibodies after \(^{131}\)I treatment of toxic nodular goiter [97]. \(^{131}\)I therapy can be repeated after 6 months if thyrotoxicosis is not cured, as documented by persistent low TSH levels.

\(^{131}\)I 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. \(^{131}\)I is not the treatment of choice if compressive symptoms are present, in larger nodules requiring high doses of \(^{131}\)I (which may be resistant to treatment), or if an immediate resolution of hyperthyroidism is medically indicated [92,93]. High doses of \(^{131}\)I may increase cancer risk in the residual goiter, a consideration that disfavors its use in younger patients [92]. The only absolute contraindications to \(^{131}\)I treatment are pregnancy (which should be excluded by a pregnancy test) and breast feeding [98]; treatment should be avoided for an arbitrary period of 3 to 6 months.

Recombinant human thyroid-stimulating hormone

The use of \(^{131}\)I for nontoxic nodular goiter has been more successful in areas with mild iodine deficiency, in which 24-hour \(^{131}\)I uptake is greater than in patients in the United States who have higher iodine intake [99–102]. In areas of high iodine intake, many patients who have MNG have low or low-normal \(^{131}\)I uptake, which is often accompanied by partial or

Box 8. \(^{131}\)I therapy for nodular thyroid

- An effective alternative to surgery for patients with high-risk or previous thyroidectomy
- Can be effective in toxic and nontoxic MNG
- Risk of malignancy in residual thyroid tissue unknown
- Contraindicated in pregnancy and lactation
complete suppression of serum TSH levels, thus rendering $^{131}$I likely ineffective as a treatment option. The administration of small doses (0.1–0.3 mg) of recombinant human TSH (rhTSH) to patients who have low-uptake MNG increases $^{131}$I uptake by more than 4-fold in 24 to 72 hours [103,104]. This allows for delivery of sufficient radiation to the thyroid to cause a decrease in size and amelioration of compressive symptoms within 2 months. As in patients who have high-uptake MNG, the average decrease in goiter size is 40% and 60% by the end of the first and second years, respectively [105,106].

rhTSH may cause a transient but clinically significant and symptomatic goiter enlargement of up to 24% and increased posttherapy hypothyroidism [107]. All patients should undergo US-FNA to rule out malignancy before $^{131}$I treatment. rhTSH is approved only for scanning and Tg stimulation in patients who have thyroid cancer; its use to augment $^{131}$I treatment is considered “off-label.”

Nonsurgical minimally invasive procedures

Percutaneous ethanol injection

Percutaneous ethanol injection (PEI) is a US-guided, mini-invasive procedure that has been used for the nonsurgical management of some thyroid nodules [108–116].

Thyroid cysts. 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. Prospective randomized studies have shown that PEI is significantly superior to aspiration alone in reducing nodule volume [113,114]. A reduction of greater than 50% of the baseline size is obtained in nearly 90% of cases treated with PEI [111,114].

The recurrence rate of cysts after PEI is low, with the best results reported in large or symptomatic cystic lesions [11]. In one report, fluid reaccumulation was noted in only 5% of the treated nodules, and in two thirds of patients, one injection was curative [112]. In another randomized study comparing T4 suppression with PEI, the investigators found greater nodule shrinkage with PEI, and only 1 of 38 complex (predominantly cystic) nodules recurred after a 12-month follow-up [114]. Moreover, PEI reduced symptoms in 75% of treated patients, whereas simple fluid aspiration reduced symptoms in only 24% of treated patients. PEI seems to be safe in experienced hands; adverse effects of pain and dysphonia are reportedly transient and mild. Frequently, a single injection results in complete disappearance or significant size reduction of the treated cyst [2]. Only occasionally does a large or multilobulated cystic nodule require several injections.

Autonomously functioning thyroid nodules. Short-term successful results of PEI for toxic autonomously functioning thyroid nodules range from 64%
to more than 95% [115,117], but after 5 years, serum TSH is detectable in only 35% of those treated [113]. PEI reportedly induces a decrease in volume of 60% to 75%, but a small residual amount of tissue persists, which accounts for the high rate of relapse [113]. PEI is not recommended for treatment of toxic solitary or multinodular goiters, in part because of a high recurrence rate and in part because $^{131}$I and surgery are effective and safe.

Cold solid nodules. A clinically significant decrease in nodule size after PEI has been reported in patients who have benign, solitary, solid nodules that are cold on scintigraphy [116,118]. The procedure seems to be more effective than T4 therapy in decreasing nodule volume and in relieving local pressure symptoms. The response is much less impressive and adverse effects are more common than in treatment of cysts [113].

In summary, PEI is an appropriate treatment for recurrent thyroid cysts if FNA has excluded the possibility of malignancy. PEI may be considered for autonomously functioning thyroid nodules with a large fluid component for preliminary drainage and debulking before radioiodine treatment [119]. 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.

Laser thermal ablation

Although percutaneous laser thermal ablation (PLA) has been used for many years to treat advanced cancer, it has been applied to the thyroid only recently. PLA is a minimally invasive procedure that is proposed as an alternative to surgery for thyroid nodules causing local symptoms or cosmetic concerns [120–123]. With US guidance and after local anesthesia, a 21-gauge needle is carefully inserted into the thyroid mass, and a thin optical fiber is advanced into the needle sheath. The fiber tips are seen as hyperechoic spots, and the area to be treated appears as an echogenic area enlarging over time on US [122]. The echogenic zone on US correlates poorly with the actual extent of thermal necrosis. US and color Doppler studies offer a precise definition of the laser-induced damage only a few hours after the procedure.

Adverse effects of PLA include burning cervical pain, which decreases rapidly as the energy is turned off. Localized pain can be treated with oral analgesics. Other problems, such as permanent dysphonia, skin burning, or damage to neck structures, have not been observed [120,121]. PLA is an outpatient procedure that lasts about 30 minutes, and patients can be dismissed shortly after the treatment.

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 [122–124]. Despite its apparent efficacy and because of the potential for major complications, PLA use should be restricted to specialized centers and is considered an experimental procedure.
Radiofrequency ablation

Radiofrequency (RF) ablation is a relatively novel procedure that is used widely for inoperable liver tumors [125]. On the basis of experience in animal models [126], RF is under evaluation as a nonsurgical therapeutic modality for the ablation of benign and malignant thyroid lesions [127].

Treatment is performed with an RF generator and an internally cooled electrode. After local anesthesia, a small skin incision is made, and a 17-gauge straight needle with a 1-cm active tip is inserted into the lesion along its longest axis. The RF energy is applied for at least 12 minutes with progressive increase of power output. Pain can be controlled during the procedure with conscious sedation and after treatment with oral analgesics. 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. RF ablation is considered an experimental procedure.

Summary

Thyroid nodules are common and carry a 5% risk of malignancy. The challenge of management is to identify benign nodules and to accurately diagnose and treat malignant thyroid disease early. The current treatment plan—using TSH measurement, US, and FNA as initial tests, followed by US-FNA whenever necessary—seems to be practical, efficient, and cost-effective. US-FNA is gaining popularity because of its increased diagnostic accuracy and because new US machines are easy to operate and less costly. An ever-increasing number of practicing endocrinologists are using US in the office. The smallest size of a micronodule and the number of nodules in the thyroid gland that should undergo US-FNA are matters of debate. Routine T4 therapy for cytologically benign nodules and routine measurement of serum calcitonin are not recommended. New treatment options include the use of $^{131}$I for large symptomatic MNGs; rhTSH to increase the efficacy of $^{131}$I therapy; and PEI for benign, large, or recurrent cysts.

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