AACE/AME Guidelines

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND ASSOCIAZIONE MEDICI ENDOCRINOLOGI MEDICAL GUIDELINES FOR CLINICAL PRACTICE FOR THE DIAGNOSIS AND MANAGEMENT OF THYROID NODULES

AACE/AME Task Force on Thyroid Nodules

American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice are systematically developed statements to assist health-care professionals in medical decision making for specific clinical conditions. Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment was applied.

These guidelines are a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual patient circumstances.

AACE/AME Task Force on Thyroid Nodules

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ABSTRACT

Thyroid nodules are common and are frequently benign. Current data suggest that the prevalence of palpable thyroid nodules is 3% to 7% in North America; the prevalence is as high as 50% based on ultrasonography (US) or autopsy data. The introduction of sensitive thyrotropin (thyroid-stimulating hormone or TSH) assays, the widespread application of fine-needle aspiration (FNA) biopsy, and the availability of high-resolution US have substantially improved the management of thyroid nodules.

This document was prepared as a collaborative effort between the American Association of Clinical Endocrinologists (AACE) and the Associazione Medici Endocrinologi (AME). Most Task Force members are members of AACE. We have used the AACE protocol for clinical practice guidelines, with rating of available evidence, linking the guidelines to the strength of recommendations.

Key observations include the following. Although most patients with thyroid nodules are asymptomatic, occasionally patients complain of dysphagia, dysphonia, pressure, pain, or symptoms of hyperthyroidism or hypothyroidism. Absence of symptoms does not rule out a malignant lesion; thus, it is important to review risk factors for malignant disease. Thyroid US should not be performed as a screening test. All patients with a palpable thyroid nodule, however, should undergo US examination. US-guided FNA (US-FNA) is recommended for nodules ≥10 mm; US-FNA is suggested for nodules <10 mm only if clinical information or US features are suspicious. Thyroid FNA is reliable and safe, and smears should be interpreted by an experienced pathologist. Patients with benign thyroid nodules should undergo follow-up, and malignant or suspicious nodules should be treated surgically. A radioisotope scan of the thyroid is useful if the TSH level is low or suppressed. Measurement of serum TSH is the best initial laboratory test of thyroid function and should be followed by measurement of free thyroxine if the TSH value is low and of thyroid peroxidase antibody if the TSH value is high. Percutaneous ethanol injection is useful in the treatment of cystic thyroid lesions; large, symptomatic goiters may be treated surgically or with radioiodine. Routine measurement of serum calcitonin is not recommended. Suggestions for thyroid nodule management during pregnancy are presented.

We believe that these guidelines will be useful to clinical endocrinologists, endocrine surgeons, pediatricians, and internists whose practices include management of patients with thyroid disorders. These guidelines are thorough and practical, and they offer reasoned and balanced recommendations based on the best available evidence. **(Endocr Pract. 2006;12:63-102)**

Abbreviations:
AFTN = autonomously functioning thyroid nodules; **CT** = computed tomography; **FNA** = fine-needle aspiration; **LOE** = level of evidence; **LT_4** = levothyroxine; **LTA** = laser thermal ablation; **MEN2** = multiple endocrine neoplasia type 2; **MeSH** = Medical Subject Headings; **MNG** = multinodular goiter; **MRI** = magnetic resonance imaging; **MTC** = medullary thyroid carcinoma; **PEI** = percutaneous ethanol injection; **PTC** = papillary thyroid carcinoma; **rhTSH** = recombinant human TSH; **T_3** = triiodothyronine; **T_4** = thyroxine; **TcTUs** = technetium thyroid uptake under suppression; **TPOAb** = thyroid peroxidase antibody; **TSH** = thyroid-stimulating hormone (thyrotropin); **US** = ultrasonography; **US-FNA** = US-guided FNA

1. INTRODUCTION

1.1. Development and Use of Guidelines: Methods of Bibliographic Research

We searched for the primary evidence to support the current guidelines by using a "clinical question" method. Each topic covered by the guidelines was translated to a related question. Each clinical question can be answered appropriately only by certain types of clinical studies and not by others. Accordingly, the bibliographic research was conducted by selecting the studies able to yield a methodologically reliable answer to each question.

The first step was to select pertinent published reports. The United States National Library of Medicine Medical Subject Headings (MeSH) database was used as a terminologic filter. Appropriate MeSH terms were identified, and care was exercised to select them on a sensitive rather than a specific basis. The MeSH terms and their proper combination enabled us to retrieve the reports pertinent to a specific issue.

The second step was to select relevant published studies. Beginning with the pertinent reports indexed with the appropriate MeSH terminologic filters, we applied the PubMed clinical queries methodologic filters. The clinical queries are grouped into 4 categories: diagnosis, etiology, prognosis, and therapy. For each clinical question, a proper complex search string is available (1). From the combination of terminologic (MeSH terms) and methodologic filters (clinical queries), the relevant studies, designed to provide a reliable answer to the question, were selected.

After the relevant published studies had been retrieved, the bibliographic research continued by looking for further evidence cited in the bibliography of each report and by following the Related Articles link listed next to each item in MEDLINE.

Meta-analyses were searched, both in MEDLINE and in the Cochrane Library. Three methods were used to search for meta-analyses in MEDLINE:

- Selection of "Meta-Analysis" from the "Publication Type" menu on the "Limits" tab of the PubMed main page
- Application of function "Find Systematic Reviews" on the "Clinical Queries" PubMed page
- Use of Hunt and McKibbon's complex string for systematic reviews (2):
  AND (meta-analysis [pt] OR meta-anal* [tw] OR metaanal* [tw] OR (quantitative* review* [tw] OR quantitative* overview* [tw]) OR (systematic* review* [tw] OR systematic* overview* [tw]) OR (methodologic* review* [tw] OR methodologic* overview* [tw]) OR (review [pt] AND medline [tw]))

The Cochrane Library was browsed by entering free terms in the search window.

Guidelines were searched in MEDLINE and in several guidelines databases. Two methods were used to search for guidelines in MEDLINE:

- Selection of "Practice Guidelines" from the "Publication Type" menu on the "Limits" tab of the PubMed main page
- Use of the following GIMBE-Gruppo Italiano Medicina Basata sulle Evidenze complex string for the guidelines:
  "guideline" [pt] OR "practice guideline" [pt] OR "health planning guidelines" [mh] OR "consensus development conference" [pt] OR "consensus development conference, nih" [pt] OR "consensus development conferences" [mh] OR "consensus development conferences, nih" [mh] OR "guidelines" [mh] OR "practice guidelines" [mh] OR (consensus [ti] AND statement [ti])

Guidelines were searched in the following databases: National Guideline Clearinghouse (USA); Agency for Healthcare Research and Quality (USA); Canadian Medical Association—Clinical Practice Guidelines; Canadian Task Force on Preventive Health Care; National Institutes of Health—National Heart, Lung, and Blood Institute (USA); National Health Service Research and Development Health Technology Assessment Programme (UK); National Institute of Clinical Excellence (UK); New Zealand Guidelines Group; PRODIGY Guidance—National Health Service (UK); and the Scottish Intercollegiate Guidelines Network.

1.2. Levels of Evidence and Grading of Recommendations

The American Association of Clinical Endocrinologists protocol for standardized production of clinical practice guidelines (3) was followed to rate the available evidence and to link the guidelines to the strength of recommendations, on the basis of the grade designations described in Table 1. All references involving clinical evidence used to support recommendation grades will have denotations regarding their level of evidence (LOE) in the reference list.

1.3. Thyroid Nodules: The Scope of the Problem

Thyroid nodules are a very common clinical finding, with an estimated prevalence on the basis of palpation that ranges from 3% to 7% (4). In a large population study (in Framingham, Massachusetts), clinically apparent thyroid nodules were present in 6.4% of women and 1.5% of men (5). During the past 2 decades, the widespread use of ultrasonography (US) for evaluation of thyroid and nonthyroid neck disease has resulted in a dramatic increase in the prevalence of clinically inapparent thyroid nodules, estimated at 20% to 76% in the general population. Moreover, 20% to 48% of patients with a single palpable thyroid nodule are found to have additional nodules when investigated by US (6,7). As a consequence, we are now facing an epidemic of thyroid nodules; the prevalence is similar to that reported in autopsy data, 50%, in patients with no history of thyroid disease (8-10).

Thyroid nodules are more common in elderly persons, in women, in those with iodine deficiency, and in those with a history of radiation exposure. The estimated annual incidence rate of 0.1% in the United States suggests that 300,000 new nodules were detected in this country in 2005

Table 1
Various Strength-of-Evidence Scales Reported in the Medical Literature

Level of evidence	Recommendation grade	Description
1		Well-controlled, generalizable, randomized trial Adequately powered Well-controlled multicenter trial Large meta-analysis with quality ratings All-or-none evidence
2		Randomized controlled trial—limited body of data Well-conducted prospective cohort study Well-conducted meta-analysis of cohort studies
3		Methodologically flawed randomized clinical trials Observational studies Case series or case reports Conflicting evidence with weight of evidence supporting the recommendation
4		Expert consensus Expert opinion based on experience "Theory-driven conclusions" "Unproven claims"
	A	Homogeneous evidence from multiple well-designed randomized controlled trials with sufficient statistical power Homogeneous evidence from multiple well-designed cohort controlled trials with sufficient statistical power ≥1 conclusive level 1 publications demonstrating benefit >> risk
	B	Evidence from at least one large well-designed clinical trial, cohort or case-controlled analytic study, or meta-analysis No conclusive level 1 publication; ≥1 conclusive level 2 publications demonstrating benefit >> risk
	C	Evidence based on clinical experience, descriptive studies, or expert consensus opinion No conclusive level 1 or 2 publication; ≥1 conclusive level 3 publications demonstrating benefit >> risk No conclusive risk at all and no conclusive benefit demonstrated by evidence
	D	Not rated No conclusive level 1, 2, or 3 publication demonstrating benefit >> risk Conclusive level 1, 2, or 3 publication demonstrating risk >> benefit

From the American Association of Clinical Endocrinologists Ad Hoc Task Force for Standardized Production of Clinical Practice Guidelines (3).

(10). In Italy, an area with mild to moderate iodine deficiency, several thousand new nodules will be diagnosed this year. The clinical implications of these data are overwhelming.

The clinical importance of thyroid nodules, besides the infrequent cases of local compressive symptoms or thyroid hyperfunction, is primarily the need to exclude the presence of a thyroid malignant lesion, which accounts for about 5% of all thyroid nodules, independent of their size (10,11). Because of the high prevalence of nodular thyroid disease, it is neither economically feasible nor necessary to submit all or even most thyroid nodules for a complete work-up for the assessment of their structure and function. Therefore, it is essential to develop and follow a reliable, cost-effective strategy for diagnosis and treatment of thyroid nodules.

2. DIAGNOSIS

2.1. History and Physical Examination

2.1.1. Clinical Evaluation

Many disorders, both malignant and benign, can cause thyroid nodules (Table 2) (4,9). The clinical importance of newly diagnosed thyroid nodules, as previously stated, is primarily the exclusion of thyroid malignant lesions (4,6,11). Hence, clinical evaluation should first be aimed at detecting symptoms or signs suggestive of malignant disease. Most patients with thyroid nodules have few or no symptoms, and usually no clear relationship exists between nodule histologic features or size and the reported symptoms. Thyroid nodules can grow insidiously for many years and are often discovered incidentally on physical examination, self-palpation, or imaging studies performed for unrelated reasons.

Patients should be asked about a family history of benign or malignant thyroid disease. Familial medullary thyroid carcinoma (MTC), multiple endocrine neoplasia type 2 (MEN2), familial papillary thyroid tumors, familial polyposis coli, Cowden disease, and Gardner's syndrome are rare disorders but should always be considered (12).

Previous disease or treatments involving the neck (history of head and neck irradiation during childhood), recent pregnancy, and rapidity of onset and rate of growth of the neck swelling should be documented. A slow but progressive growth (during weeks or months) is suggestive of malignant involvement and should prompt further evaluation.

Thyroid nodules during childhood and adolescence should induce caution; the malignancy rate for nodules occurring at a young age is 2-fold higher than in adult patients. The risk of thyroid cancer is also higher in older persons and in men; these patients require a more thorough diagnostic evaluation (4,9).

Symptoms such as a choking sensation, cervical tenderness or pain, dysphagia, or hoarseness may be perceived as attributable to thyroid disease, but in most patients, these symptoms are caused by nonthyroid disorders. In all symptomatic patients, evaluation should begin by obtaining a detailed history, performing a complete physical examination, and providing the information needed for the patient's reassurance and for the selection of appropriate clinical and laboratory investigations.

Sudden pain is commonly due to hemorrhage in a cystic nodule. In patients with rapid enlargement of a thyroid nodule, however, anaplastic carcinoma or primary lymphoma of the thyroid should always be considered.

The slow onset and progression of cervical symptoms and signs are caused by the compression of vital structures of the neck or upper thoracic cavity (trachea and esophagus), which usually occurs only if thyroid nodules are embedded within large goiters. Symptoms of compression are infrequent and are usually noted in a minority of middle-aged or elderly patients with long-standing multinodular goiter (MNG). The growth of the nodular goiter into the anterior mediastinum may cause partial occlusion of the thoracic inlet, occasionally leading to venous outflow obstruction. If the patient is asked to extend the arms over the head (Pemberton's sign), the further narrowing of the thoracic inlet is followed within a few minutes by the distention of the external jugular veins and by facial plethora (4).

When observed in the absence of large goiters, the symptoms of tracheal compression (cough and dysphonia) suggest an underlying malignant lesion. Patients with rapid growth of a large solid thyroid mass and vocal cord paresis should undergo surgical treatment even if cytologic results are benign (13; *grade C*). Differentiated thyroid carcinomas, however, rarely cause airway obstruction, vocal cord paralysis, or esophageal symptoms, and absence of symptoms does not rule out a malignant tumor (14; *grade C*).

Nodular thyroid disease may be associated with subclinical or overt hyperthyroidism. Hyperthyroidism is suggestive of a benign lesion because autonomously functioning nodules are almost always benign and need no further cytologic evaluation. Toxic MNGs, however, may harbor both hyperfunctioning (benign) areas and cold (potentially malignant) lesions, and thyroid nodules in patients with Graves' disease are reported to be malignant in about 9% of cases (15).

A firm or hard, solitary or dominant thyroid nodule that clearly differs from the rest of the gland suggests an increased risk of malignant involvement and warrants cytologic evaluation. The risk of cancer is not significantly higher in solitary nodules than in MNGs, and small differentiated thyroid cancers are frequently devoid of

Table 2
Causes of Thyroid Nodules

Benign
Multinodular goiter
Hashimoto's thyroiditis
Simple or hemorrhagic cysts
Follicular adenomas
Subacute thyroiditis
Malignant
Papillary carcinoma
Follicular carcinoma
Hürthle cell carcinoma
Medullary carcinoma
Anaplastic carcinoma
Primary thyroid lymphoma
Metastatic malignant lesion

alarming characteristics on clinical evaluation (16-18; *grade C*).

Despite the low predictive value of palpation and the high levels of intraobserver and interobserver variations (18,19), careful inspection and palpation of the thyroid as well as the anterior and lateral compartments of the neck should always be done.

2.1.2. Symptoms or Signs That Warrant Further Investigation

The following characteristics may increase the risk of thyroid cancer:

- Prior head and neck irradiation
- Family history of MTC or MEN2
- Age <20 years or >70 years
- Male sex
- Growing nodule
- Firm or hard consistency of nodule, ill-defined nodule margins on palpation
- Cervical adenopathy
- Fixed nodule on examination
- Dysphonia, dysphagia, and cough

2.1.3. Key Recommendations

The key recommendations regarding history and physical examination in patients with a thyroid nodule are outlined in Table 3.

2.2. US and Other Diagnostic Imaging Studies

2.2.1. When to Perform US Evaluation

High-resolution US is the most sensitive test available to detect thyroid lesions, measure their dimensions accurately, identify their structure, and evaluate diffuse changes in the thyroid gland. US can identify thyroid

Table 3
Key Recommendations
Regarding History and Physical Examination
in Patients With a Thyroid Nodule*

- Remember that the vast majority of nodules are asymptomatic, and absence of symptoms does not rule out a malignant lesion (*grade C*)†
- Always obtain a biopsy specimen from solitary, firm, or hard nodules. The risk of cancer is similar in a solitary nodule and MNG (*grade B*)
- Record the following information (*grade C*):
  - Family history of thyroid disease
  - Previous neck disease or treatment
  - Growth of the neck mass
  - Hoarseness, dysphonia, dysphagia, or dyspnea
  - Location, consistency, and size of the nodule
  - Neck tenderness or pain
  - Cervical adenopathy
  - Symptoms of hyperthyroidism or hypothyroidism
- Factors suggesting increased risk of malignant potential (*grade C*):
  - History of head and neck irradiation
  - Family history of MTC or MEN2
  - Age <20 or >70 years
  - Male sex
  - Growing nodule
  - Firm or hard consistency
  - Cervical adenopathy
  - Fixed nodule
  - Persistent hoarseness, dysphonia, dysphagia, or dyspnea

*MEN2 = multiple endocrine neoplasia type 2; MNG = multinodular goiter; MTC = medullary thyroid carcinoma.
†See Table 1 for explanation of grades.

nodules that have been missed on physical examination, isotope scanning, and other imaging techniques (20). This study, however, should not be performed on an otherwise normal thyroid gland nor used as a substitute for a physical examination. Because of the high prevalence of clinically inapparent, small thyroid nodules and the low-grade aggressiveness of most thyroid cancers, US should not be performed as a screening test in the general population unless well-known risk factors have been recognized.

US should be performed in all patients with a history of familial thyroid cancer, MEN2, or childhood cervical irradiation, even if palpation yields normal findings (20; *grade C*). The physical finding of adenopathy suspicious for malignant involvement in the anterior or lateral neck compartments warrants US examination of the lymph nodes and thyroid gland because of the risk of a lymph node metastatic lesion from an otherwise unrecognized papillary microcarcinoma.

In all patients with palpable thyroid nodules or MNG, US should be performed to accomplish the following:

- Help with the diagnosis in difficult cases (as in Hashimoto's thyroiditis)
- Look for coincidental thyroid nodules
- Detect US features suggestive of malignant growth and select the lesions to be recommended for fine-needle aspiration (FNA) biopsy (see Table 17)
- Choose the gauge and length of the biopsy needle
- Obtain an objective measure of the baseline volume and characteristics of the lesions that will be assigned to follow-up or medical therapy

In patients with nonspecific symptoms (cervical pain, dysphagia, persistent cough, voice changes), US evaluation of the thyroid gland should be performed only on the basis of findings on physical examination and the results of appropriate imaging and laboratory tests.

Standardized US reporting criteria should be followed, indicating position, shape, size, margins, content, echogenic pattern, and, whenever possible, the vascular pattern of the nodule (see Appendix 1). Nodules with malignant potential should be identified, and FNA biopsy should be suggested to the patient.

2.2.2. US as First Step for Routine Diagnosis of Thyroid Nodule

Widespread use of high-resolution US has led to the discovery of unsuspected small thyroid nodules of indeterminate significance (6,14). Clinically inapparent thyroid lesions (14% to 24% of those with a diameter >10 mm) are detected by US in about half (27% to 72%) of the women who undergo such assessment (6,21). Many of these nodules are further evaluated by US-guided FNA (US-FNA).

The prevalence of cancer reported in studies focused on the cytologic evaluation of nonpalpable thyroid lesions ranges from 5.4% to 7.7% and appears to be similar to that reported for palpable lesions (5.0% to 6.5%) (16,22-24; *grade C*). Clinical criteria for a malignant nodule are lacking in most cases of nonpalpable lesions, and only a few patients with palpable thyroid nodules present with a history or findings on physical examination suggestive of thyroid carcinoma (14; *grade C*). Hence, to avoid the inappropriate use of US-FNA in a large part of the general population, it is essential to determine, on the basis of their US features, which thyroid lesions have a high malignant potential (see Appendix 2).

2.2.3. US Criteria for US-FNA in Impalpable Nodules

Solitary Versus Multiple Nodules. The risk of cancer is not significantly higher in impalpable solitary thyroid nodules than in MNGs (16); this finding confirms what has been observed in palpable lesions (17,18; *grade C*).

Size. Malignant involvement is not less frequent in nodules <10 mm in diameter; thus, an arbitrary diameter cutoff of 10 or 15 mm for cancer risk is not justified (14). Both recent (16) and older data (25,26) suggest that some microcarcinomas can have an aggressive course; therefore, early diagnosis and treatment of small tumors are clinically important (*grade C*).

US Features and Color Doppler Findings. Among the diagnostic imaging techniques, high-resolution US is the most accurate for predicting the presence of malignant cells in thyroid lesions that cannot be palpated. The reported specificity for diagnosing cancer is 85.8% to 95.0% for microcalcifications (small intranodular punctate hyperechoic spots with scanty or no posterior acoustic shadowing), 83.0% to 85.0% for irregular or microlobulated margins, and 80.8% for chaotic arrangement of intranodular vascular images (16,21; *grade C*). For these characteristics, the predictive value for cancer is partially blunted by their low sensitivity (29.0% to 59.2%, 55.1% to 77.5%, and 74.2%, respectively), and no single US sign independently is fully predictive of a malignant lesion. Nevertheless, a hypoechoic appearance of a thyroid nodule (defined as a decreased echogenicity in comparison with the surrounding parenchyma, similar to that of the cervical strap muscles) in conjunction with one of the US patterns associated with malignant tumors effectively indicates a subset of impalpable thyroid nodules at high risk for cancer (16). 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 in comparison with the cervical muscles) are additional US patterns suggestive of malignant potential (27; *grade B*).

The presence of at least 2 suspicious sonographic criteria reliably identifies most neoplastic lesions of the thyroid gland (87% to 93% of cases). Thus, it is possible to restrict the number of US-FNA procedures to about a third of the impalpable thyroid nodules (16,27; *grade B*).

2.2.4. US Criteria for US-FNA in Palpable Nodules

Solitary Versus Multiple Nodules. The risk of cancer is not significantly higher in palpable solitary thyroid nodules than in multinodular lesions or in nodules embedded in diffuse goiters (17). Moreover, 50% of thyroid glands with a "solitary" nodule based on palpation have other small nodules disclosed by US (18). In multinodular thyroid glands, the cytologic sampling should be focused on lesions characterized by suspicious US features rather than on larger or clinically dominant nodules (28).

US Features and Color Doppler Findings. The US characteristics suggestive of malignant involvement in palpable thyroid nodules are the same as in impalpable nodules. On color Doppler examination, hypervascularity with chaotic arrangement of blood vessels (related to arteriovenous shunts and tortuosity of vessel course) is usually seen, whereas hypovascular lesions, sometimes observed in papillary microcarcinomas (because of their high fibrous component), are rare (29; *grade C*). In addition, large neoplastic lesions may be characterized by degenerative changes and multiple fluid areas, findings only exceptionally noted in microcarcinomas.

Extracapsular Growth. Extension of irregular hypoechoic lesions beyond the thyroid capsule, invasion of prethyroid muscles, posterior extracapsular growth, and infiltration of the recurrent laryngeal nerve are threatening US findings demanding immediate cytologic assessment (28).

Complex or Cystic Lesions. Most complex thyroid nodules with a dominant fluid component are benign. US-FNA, however, should always be performed because the rare papillary thyroid carcinoma (PTC) can be cystic (28).

Suspicious Cervical Adenopathy. The presence of enlarged lymph nodes with rounded appearance, no hilum, cystic changes, microcalcifications, or chaotic hypervascularity is highly suspicious. Such nodes and any coexistent thyroid nodules, whatever their size, always warrant US-FNA (28).

2.2.5. Other Diagnostic Imaging

Magnetic resonance imaging (MRI) and computed tomography (CT) should not be used routinely because they are rarely diagnostic for malignant lesions in nodular thyroid disease. MRI and CT may be of value, however, if assessment of size or substernal extension of a goiter is desired for clinical management. Remember that CT contrast medium usually contains iodine and reduces subsequent uptake of radioiodine (^{131}I).

2.2.6. Key Recommendations

The key recommendations pertaining to performance of US and other diagnostic imaging as well as US-FNA in patients with thyroid nodules are summarized in Table 4.

2.3. FNA Biopsy

Thyroid FNA biopsy is now established as reliable and safe and has become an integral part of thyroid nodule evaluation (10,30,31). The central role of the endocrinologist in thyroid nodule evaluation and FNA biopsy is clear, and recent surveys have emphasized that almost 100% of endocrinologists use FNA biopsies for diagnosis of thyroid nodules. It is axiomatic that thyroid nodules are common, thyroid glands frequently contain more than 1 nodule, and nodules are often benign. FNA is critical in establishing benignity (Fig. 1 and 2).

2.3.1. Procedure

Detailed reviews of aspiration biopsy of thyroid nodules have been published previously (30-33). Before FNA is performed, the thyroid gland should be palpated, and the nodule or nodules to be aspirated should be carefully identified. The procedure is explained to the patient, and the patient's questions and concerns should be satisfactorily answered. The patient then is placed supine on the examining table with the neck fully extended, supported by a pillow under the shoulders. Adequate lighting should be available. The skin is cleansed with alcohol, and the patient is asked not to swallow or talk during the needle placement. Local anesthesia is not required. An assistant or a nurse may be needed to help with the procedure, preparation and labeling of slides, and application of pressure over the puncture sites.

Commonly, a 27- or 25-gauge 1.5-inch (3.8-cm)-long needle attached to a 10-mL disposable plastic syringe is used. Some clinicians use a mechanical syringe holder, such as the Cameco syringe pistol (Precision Dynamics Corporation, Burbank, CA). The needle is inserted into the nodule without suction, and after the tip is in the nodule, suction is applied while the needle is moved back and forth within the nodule. This maneuver helps dislodge cellular material, which is then sucked into the needle; within a few seconds, the aspirate appears in the needle hub.

At that point, suction is released, the needle is withdrawn, and smears are prepared. The syringe is removed from the needle and filled with air by retracting the plunger. The needle is then reattached to the syringe, and with the bevel pointing down, one drop of aspirated material is placed on each of several glass slides. Smears are then prepared by using 2 glass slides, similar to those used to make blood smears. Prepared slides can be air-dried or wet-fixed by immediate submersion in 95% ethyl alcohol for Papanicolaou staining. Some facilities use automated cytology systems, such as Thin Prep, wherein the specimen is placed in the solution for the system and reviewed later in the laboratory. Usually, 2 to 4 aspirations are made from different sites in each nodule; for each aspiration, 2 to 4 slides are prepared. In general, 8 to 12 slides are prepared per biopsy (10,32-34).

Nonaspiration biopsy of a thyroid nodule can also be performed. In this technique, the hub of a 25-gauge needle is held in a pencil-grip fashion, the needle is inserted gently into the nodule, and, after aspirate flows into the hub, the needle is withdrawn. Cellular material in the needle shaft is expelled onto glass slides, and smears are prepared as described in the previous paragraph.

Table 4
Key Recommendations Regarding Ultrasonography and Other Diagnostic Imaging in Patients With a Thyroid Nodule*

- US evaluation
  - Not recommended (*grade C*†): as a screening test in the general population; in patients with normal thyroid on palpation and low risk for thyroid cancer
  - Recommended (*grade C*): for high-risk patients (history of familial thyroid cancer, MEN2, or external irradiation); for all patients with palpable thyroid nodules or MNG; for those with adenopathy suggestive of a malignant lesion
- US reporting criteria (*grade C*):
  - Describe position, shape, size, margins, content, echogenic pattern, and, whenever possible, the vascular pattern of the nodule
  - Identify the nodule at risk to be malignant, and stratify the nodule with a risk score based on the US findings
  - Identify the nodules for FNA biopsy
- No US-FNA of nodules <10 mm unless suspicious US findings or high-risk history (*grade C*)
- US-FNA of nodules of any size in patients with history of neck irradiation or family history of MTC or MEN2 (*grade C*)
- US-FNA should be based on US features (*grade B*)
- US-FNA should be performed on all hypoechoic nodules ≥10 mm with irregular margins, chaotic intranodular vascular spots, a more-tall-than-wide shape, or microcalcifications (*grade B*)
- US findings suggestive of extracapsular growth or metastatic cervical lymph nodes warrant an immediate cytologic evaluation, no matter the size of the lesions (*grade B*)
- In complex thyroid nodules, obtain US-FNA sampling of the solid component of the lesion before fluid drainage (*grade C*)
- Thyroid incidentalomas should be followed by US in 6-12 months and regularly thereafter (*grade D*)
- MRI and CT are not indicated in routine nodule evaluation (*grade C*)

*CT = computed tomography; FNA = fine-needle aspiration; MEN2 = multiple endocrine neoplasia type 2; MNG = multinodular goiter; MRI = magnetic resonance imaging; MTC = medullary thyroid carcinoma; US = ultrasonography; US-FNA = US-guided FNA.
†See Table 1 for explanation of grades.

Immediately after withdrawal of the needle, gentle pressure is applied to the aspiration site (or sites) to prevent hematoma formation. In the absence of problems and if the patient is comfortable, the patient is allowed to leave after a few minutes of observation.

2.3.2. Cytologic Diagnosis

FNA results may be diagnostic (satisfactory) or nondiagnostic (unsatisfactory), as outlined in Table 5. The specimen is labeled "diagnostic" or "adequate" if it contains a minimum of 6 groupings of well-preserved thyroid epithelial cells, consisting of at least 10 cells per group. Specimens labeled as "nondiagnostic" or "unsatisfactory" have an inadequate number of cells, which can be attributable to cystic fluid, bloody smears, or poor technique in preparing slides (10,32).

A benign (negative) cytodiagnosis is the most common finding, accounting for approximately 70% of results (32). Benign cytology includes benign colloid nodule, macrofollicular adenoma, lymphocytic thyroiditis, granulomatous thyroiditis, or benign cyst. The most common benign diagnosis is "colloid nodule," which may be found in the setting of a normal thyroid, a benign nodule, an MNG, or a macrofollicular adenoma.

Malignant (positive) results can be identified reliably by the cytopathologist (33; *grade C*). The most frequent malignant lesion encountered is PTC. Aspirates of PTC are characterized by increased cellularity; tumor cells arranged in sheets and papillary cell groups; and typical nuclear abnormalities, including intranuclear holes and grooves. Medullary carcinoma is characterized by hypercellularity, tumor cells that are notably noncohesive, and nuclei that are hyperchromatic and located at the end of an elongated cell body. Amyloid may be found in 50% to 60% of cases, appearing as amorphous background material that is readily stained with Congo red. Immuno-

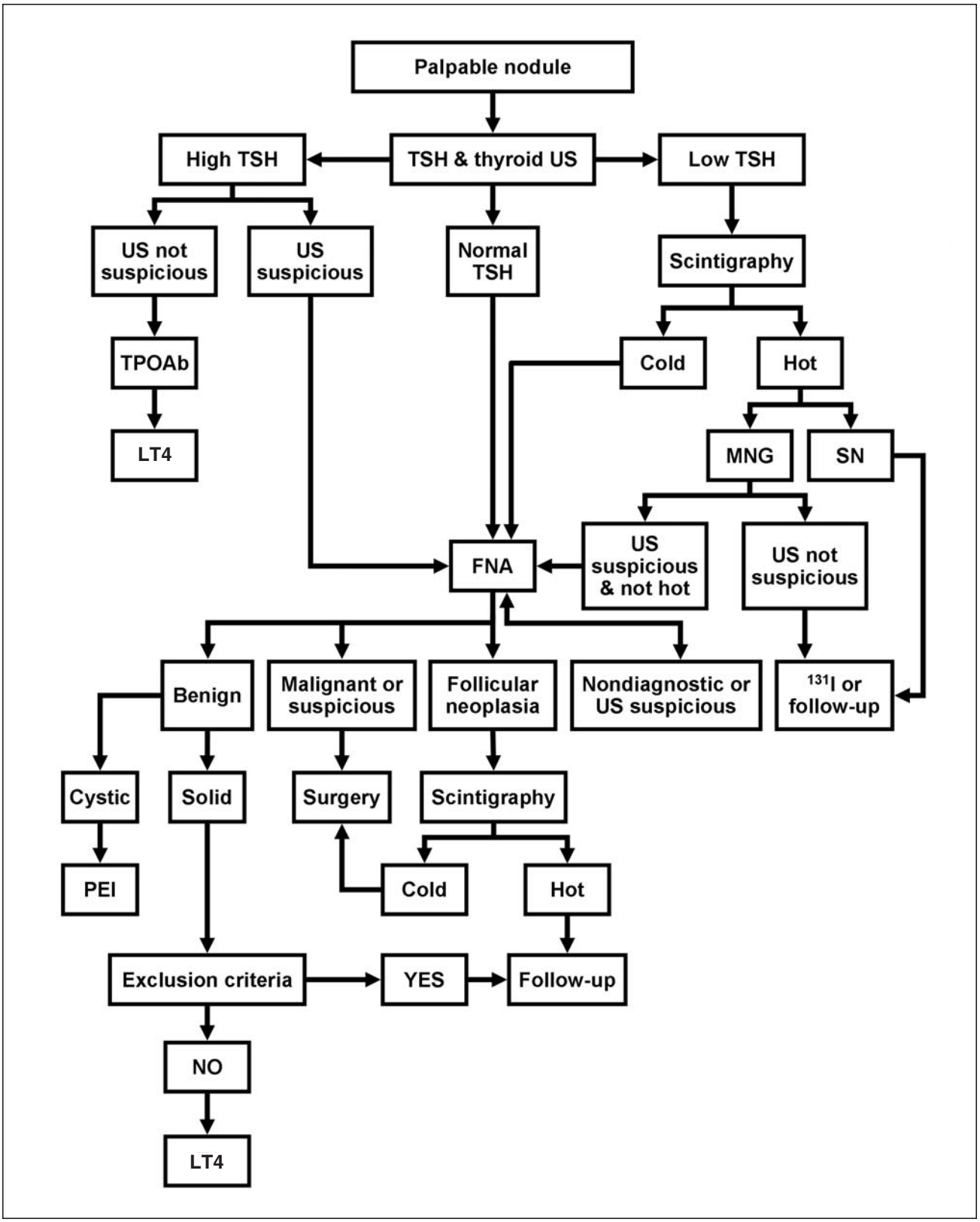

Fig. 1. Flowchart, indicating scheme for the diagnosis and management of palpable thyroid nodules. *FNA* = fine-needle aspiration; LT_4 = levothyroxine; *MNG* = multinodular goiter; *PEI* = percutaneous ethanol injection; *SN* = single nodule; *TPOAb* = thyroid peroxidase antibody; *TSH* = thyroid-stimulating hormone (thyrotropin); *US* = ultrasonography.

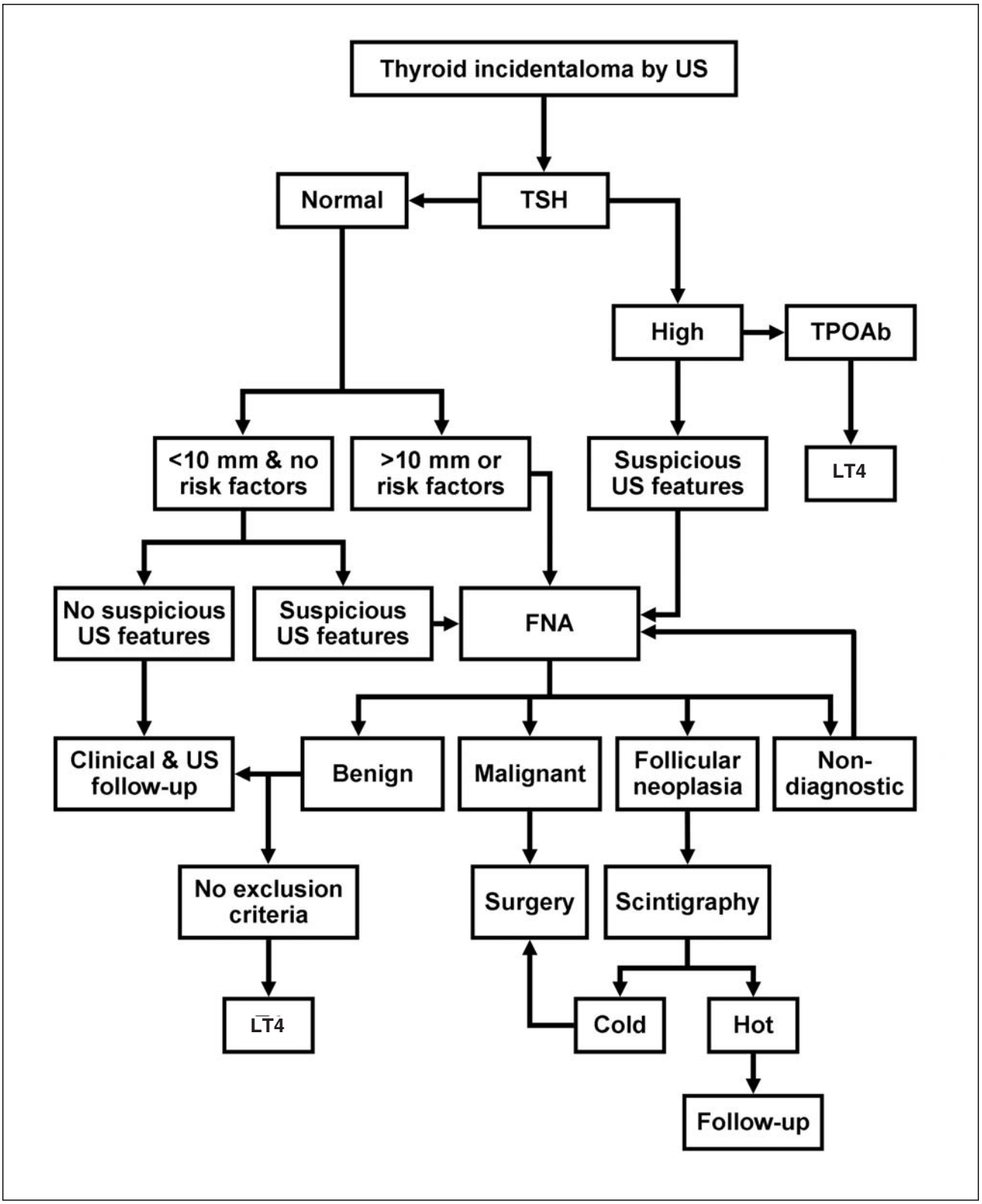

Fig. 2. Flowchart, showing recommended scheme for the diagnosis and management of ultrasonography-determined thyroid incidentalomas. *FNA* = fine-needle aspiration; LT_4 = levothyroxine; *TPOAb* = thyroid peroxidase antibody; *TSH* = thyroid-stimulating hormone (thyrotropin); *US* = ultrasonography.

Table 5
Fine-Needle Aspiration Cytologic Diagnosis

Diagnostic (satisfactory specimen)
Benign (negative)
Malignant (positive)
Suspicious (indeterminate)
Nondiagnostic (unsatisfactory specimen)
Foam cells
Cyst fluid
Blood

staining with calcitonin can sometimes be helpful in difficult cases. Other malignant lesions include primary anaplastic carcinoma and high-grade metastatic cancers (33).

Suspicious (indeterminate) results include specimens for which a definite cytologic diagnosis cannot be made (33-35). Often these include follicular neoplasms, Hürthle cell neoplasms, papillary cancer, or lymphoma. Follicular neoplasms appear as hypercellular specimens with monotony of cells, microfollicular arrangement, and diminished or absent colloid. Hürthle cell neoplasm is diagnosed in an aspirate that is almost entirely Hürthle cells, usually with absent or scanty colloid that lacks a lymphoid cell population, as found in Hashimoto's thyroiditis.

Nondiagnostic (unsatisfactory) aspirates are those with too few epithelial cells, accounting for 10% to 20% of specimens (30,36). The criteria for judging aspirates as inadequate or nondiagnostic are arbitrary and vary somewhat among laboratories. Commonly, inadequate smears are collected from cystic lesions that are leaking fluid and degenerative foam cells. Other causes of inadequate smears include too much blood, excessive air-drawing, and insufficient experience with FNA techniques.

Large-needle thyroid biopsy does not have a higher diagnostic accuracy than FNA, is cumbersome, and is associated with pain and, occasionally, severe bleeding. Currently, the use of large-needle biopsy in the routine management of thyroid nodules is not advised.

2.3.3. FNA Results

As already noted, about 70% of FNA specimens are classified as benign; in addition, 5% are malignant, 10% are suspicious, and 10% to 20% are nondiagnostic or unsatisfactory (30,33,37-39). The result of FNA is important in deciding whether to manage the patient medically or surgically. Some reviews and reports have indicated that the selection of patients for surgical treatment on the basis of FNA results has increased the yield of cancer from 15% to 50% (37,40; *grade C*). The sensitivity and specificity of FNA performed by experienced personnel are excellent, as shown in Table 6.

A major concern is the possibility of a false-negative FNA result—that is, a missed diagnosis of malignant disease (37,38,41; *grade C*). The false-negative rate is 1% to 11% (mean, 5%). Some methods for minimizing false-negative results are itemized in Table 7. Another concern is the false-positive FNA rate, defined as the percentage of patients with positive FNA results but negative histologic findings for cancer. This rate varies from less than 1% to 7%, as indicated in Table 6 (37,38; *grade C*).

2.3.4. Adverse Effects and Conclusions

FNA biopsy of a thyroid nodule often causes slight 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 (32,33; *grade C*). FNA is now considered safe, useful, and cost-effective. The accuracy of FNA is 95%.

2.3.5. Key Recommendations

The key recommendations regarding FNA biopsy procedures and pitfalls are presented in Table 8.

Table 6
Summary Characteristics for Thyroid Fine-Needle Aspiration: Results of Literature Survey

Feature	Mean (%)	Range (%)	Definition
Sensitivity	83	65-98	Likelihood that patient with disease has positive test results
Specificity	92	72-100	Likelihood that patient without disease has negative test results
Positive predictive value	75	50-96	Fraction of patients with positive test results who have disease
False-negative rate	5	1-11	Fine-needle aspiration negative; histology positive for cancer
False-positive rate	5	0-7	Fine-needle aspiration positive; histology negative for cancer

Data from Gharib (10), Castro and Gharib (30), Gharib and Goellner (33), and Jeffrey and Miller (39).

Table 7
Ways to Minimize False-Negative Results on Fine-Needle Aspiration of Thyroid Nodules

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

2.4. Radionuclide Scanning

2.4.1. Diagnostic Accuracy

Thyroid scintigraphy is the only technique that allows for assessment of thyroid regional function and detection of areas of autonomously functioning thyroid tissue. On the basis of the pattern of radionuclide uptake, nodules may be classified as hyperfunctioning ("hot") or hypofunctioning ("cold"). Hot nodules almost never represent clinically significant malignant lesions, whereas cold nodules have a reported malignant risk of about 5% to 8%. Because the vast majority (77% to 94%) of thyroid lesions are cold and only a small minority of these are malignant, the predictive value of hypofunctioning nodules for the presence of malignant involvement is low. The diagnostic specificity is further reduced in small lesions (<1 cm), which may not be identified by scintigraphy (42,43).

The role of scintigraphy in the diagnostic work-up of thyroid nodules is limited, especially in countries with iodine-rich diets, in which serum thyrotropin (thyroid-stimulating hormone or TSH) measurement *and* thyroid US can correctly diagnose autonomous nodules in most patients (42,43), and FNA facilitates accurate diagnosis of a malignant lesion (40). Moreover, because the resolution of US is considerably greater than that of scintigraphy, radionuclide scanning has little place in the topographic assessment of nodular goiter and no place in the measurement of thyroid nodules.

On the basis of these considerations, scintigraphy is generally not useful as a first-step diagnostic study in the

Table 8
Key Recommendations Relating to Thyroid Fine-Needle Aspiration Biopsy Procedures and Pitfalls*

- Thyroid FNA biopsy has been established as reliable and safe and has become an integral part of thyroid nodule evaluation
- Clinical management of thyroid nodules should be guided by the results of ultrasonographic evaluation and FNA biopsy
- Thyroid smears should be reviewed by a cytopathologist with a special interest in thyroid disease
- Diagnostic pitfalls:
  - False-negative results are usually due to inadequate sampling
  - False-positive results are usually due to "suspicious" findings
  - Gray zones in cytologic reports are follicular neoplasms, Hürthle cell neoplasms, and cytologic findings suggestive of but not diagnostic for papillary carcinoma
- Standardization of terminology will improve patient care. Cytologic diagnoses should be organized into 4 categories—inadequate material, benign, suspicious, and malignant tumors (see Table 5)
  - Inadequate, unsatisfactory, or nondiagnostic: smears with few or no follicular cells
  - Benign or negative: group including colloid nodule, Hashimoto's thyroiditis, cyst, thyroiditis
  - Suspicious or indeterminate: cytologic results that suggest a malignant lesion but do not completely fulfill the criteria for a definitive diagnosis, including follicular neoplasms, Hürthle cell tumors, and atypical papillary tumors
  - Malignant or positive: group consisting of primary (thyroid) or secondary (metastatic) cancers

*FNA = fine-needle aspiration.

evaluation of thyroid nodules. In geographic regions with iodine deficiency, however, thyroid scintigraphy is still used as part of the evaluation of patients with thyroid nodules (44) because it provides useful information on the functional characterization of thyroid nodules. In patients in these regions, the serum TSH may remain unsuppressed even if autonomy is present because of the low synthesis rate of thyroid hormones by iodine-depleted thyroid glands (45). Moreover, in the early phases of autonomy, the bulk of autonomous tissue may be insufficient to suppress the TSH level (46,47), and the early recognition of autonomous nodules, before they induce the suppression of TSH, may be useful for planning the subsequent diagnostic and therapeutic management.

Quantitative pertechnetate scintigraphy (that is, calculation of technetium thyroid uptake under suppression [TcTUs]) is used primarily in Germany (48). TcTUs is a sensitive and specific technique for the diagnosis and quantitation of thyroid autonomy and is a reliable predictor of hyperthyroidism in the setting of euthyroid autonomy. A few reports suggest that patients with thyroid autonomy and TcTUs of 3% or more should be treated even if the serum TSH level is normal. Those patients with TcTUs between 2% and 3% should be considered for treatment if they have a high risk of developing overt hyperthyroidism. In patients with TcTUs less than 2%, there is no indication for radioiodine treatment (48).

Thyroid scintigraphy can be performed with $^{99m}TcO_4^-$ or ^{123}I. The advantages and disadvantages of each of these imaging agents are as follows:

$^{99m}TcO_4^-$ advantages:

- Less expensive; more readily available; more rapid examination

$^{99m}TcO_4^-$ disadvantages:

- Tc is trapped but not organified (risk of false-positive images); activity in esophagus or vascular structures can be misleading; poor image quality when uptake is low

^{123}I advantages:

- Better visualization of retrosternal thyroid tissue; better images when thyroid uptake is low

^{123}I disadvantages:

- Higher cost; less comfortable for the patient (delayed imaging at 24 hours is often used)
- Less readily available; imaging times usually longer

2.4.2. Indications for Thyroid Scintigraphy

Thyroid scintigraphy is indicated in the following settings:

- Single thyroid nodule or MNG and suppressed TSH level; FNA not necessary
- Large MNG, especially with substernal extension
- In search of ectopic thyroid tissue (for example, struma ovarii or sublingual thyroid)
- In subclinical hyperthyroidism to identify occult hyperfunctioning tissue
- Some investigators suggest evaluation of follicular neoplasms with a scintiscan to identify a functioning cellular adenoma that may be benign; however, most such nodules are cold on a scintiscan

2.4.3. Key Recommendations

The key recommendations for performance of thyroid scintigraphy are summarized in Table 9.

2.5. Laboratory Evaluation

2.5.1. Assessment of Thyroid Function

Measurement of the serum TSH concentration is the single most useful laboratory test in the initial evaluation of thyroid nodules because of the high sensitivity of the TSH assay in detecting even subtle thyroid dysfunction

Table 9
Key Recommendations for Performance of Thyroid Scintigraphy*

- Perform thyroid scintigraphy for a thyroid nodule or MNG if the TSH level is below the lower limit of the normal range or if ectopic thyroid tissue or a retrosternal goiter is suspected (*grade B*)†
- In iodine-deficient areas, perform thyroid scintigraphy for a thyroid nodule or MNG even if the TSH level is in the low-normal range (*grade C*)
- Use ^{123}I or $^{99m}TcO_4^-$ for thyroid scintigraphy (*grade B*)

*MNG = multinodular goiter; TSH = thyroid-stimulating hormone (thyrotropin).
†See Table 1 for explanation of grades.

(48,49; *grade C*). The measurement of serum free thyroid hormones and thyroid peroxidase antibody (TPOAb) levels should be the second diagnostic step, which is necessary for confirmation and definition of thyroid dysfunction if TSH levels are outside the normal range.

2.5.2. TSH Assay

First- and second-generation TSH assays did not have adequate sensitivity to detect minor thyroid dysfunction (50). Third-generation TSH chemiluminometric assays, with detection limits of about 0.01 μIU/mL, should be used in current clinical practice. They detect TSH levels even in cases of mild hyperthyroidism and make possible a reliable diagnosis of subclinical thyroid hyperfunction (51,52).

2.5.3. Serum Free Thyroxine and Free Triiodothyronine

If the serum TSH level is within the normal range, the measurement of free thyroid hormones adds no further relevant information. If TSH levels are low, however, measurement of free thyroxine (T_4) and free triiodothyronine (T_3) levels is necessary to confirm the presence of hyperthyroidism or consider central hypothyroidism, in which both TSH and free T_4 levels may be low.

In order to limit unnecessary laboratory testing, the following strategy should be followed for most patients with thyroid nodules (52,53; *grade C*):

- Serum TSH level within normal limits: no further testing
- High serum TSH: test free T_4 and TPOAb to evaluate for hypothyroidism
- Low serum TSH: test free T_4 and T_3 to evaluate for hyperthyroidism

2.5.4. Antibody Assays

TPOAb should be measured in patients with high levels of serum TSH (54). High levels of serum TPOAb and a firm, diffusely enlarged thyroid are very suggestive of autoimmune or Hashimoto's thyroiditis (54,55). Occasionally, a nodular goiter may represent Hashimoto's thyroiditis.

The utility of the antithyroglobulin antibody assay is controversial. Thyroglobulin antibody testing should be reserved for the few patients with US and clinical findings suggestive of chronic lymphocytic thyroiditis in conjunction with normal serum TPOAb levels (54).

2.5.5. Thyroglobulin Assay

Serum thyroglobulin correlates with the iodine status and the size of the thyroid gland rather than with the nature of a thyroid nodule and adds no further information to the aforementioned tests. Routine assessment of serum thyroglobulin in the diagnosis of thyroid nodules is not recommended (56; *grade C*).

2.5.6. Calcitonin Assay

Calcitonin is a useful serum marker of MTC and correlates well with tumor burden (57). Although routine measurement of calcitonin in patients with thyroid nodules has been recommended (58), this practice remains controversial (59-61). MTC is reported to be present in less than 0.5% of the population with thyroid nodules, and large-scale studies of nodular thyroid disease have reported a prevalence of MTC ranging from 0.4% to 1.4% of patients (54,62,63). In addition, the risk of false-positive results should be considered; high levels of serum calcitonin can be present in patients with conditions such as impaired renal function or gastroenteric diseases treated with proton pump inhibitors (64,65).

Calcitonin testing is imperative in those patients with a history of familial MTC or MEN2, but routine testing of serum calcitonin in all patients with unselected thyroid nodules does not seem to be cost-effective. A baseline serum calcitonin value of 10 to 100 pg/mL is abnormal (normal baseline, <10 pg/mL) and should be followed by further investigations; values that exceed 100 pg/mL are highly suggestive of MTC.

The pentagastrin-stimulated calcitonin assay is used in Europe to screen family members of patients with MTC. In the United States, pentagastrin is no longer available, and calcium is used to stimulate calcitonin, although family screening should be done by genetic testing. A blood test for germline mutations of the *RET* proto-oncogene should be done for diagnosis or screening of at-risk family members (66,67).

2.5.7. Key Recommendations

The key recommendations for laboratory evaluation of patients with thyroid nodules are shown in Table 10.

3. MANAGEMENT AND THERAPY

Clinical management of thyroid nodules should be guided by the results of US evaluation and FNA biopsy (Fig. 1 and 2; see Appendix 3).

3.1. FNA-Positive Thyroid Nodule

3.1.1. Interventional Strategies

If cytologic results are positive (consistent with a primary thyroid malignant lesion), surgical intervention is almost always necessary (59,68). If cancer is due to metastatic disease, efforts should be directed toward finding the primary lesion, which often precludes a thyroid surgical procedure. The extent of thyroidectomy is a matter of controversy. Currently (in 2006), if preoperative FNA suggests PTC, near-total or total thyroidectomy is the preferred approach (59,68-71). The surgical procedure should be performed by an experienced thyroid surgeon, and lymph nodes within the central compartment of the

Table 10
Key Recommendations for Laboratory Evaluation of Thyroid Nodules*

- Serum TSH should be tested first, with a third-generation assay (*grade B*)†
- If TSH level is low (<0.5 μIU/mL), measure free T_4 and T_3; if TSH level is high (>5.0 μIU/mL), measure free T_4 and TPOAb (*grade C*)
- Routine assessment of serum thyroglobulin is not recommended for the diagnosis of thyroid nodules or nodular goiter (*grade C*)
- Serum calcitonin should be measured if FNA or family history suggests MTC (*grade B*)

*FNA = fine-needle aspiration; MTC = medullary thyroid carcinoma; T_3 = triiodothyronine; T_4 = thyroxine; TPOAb = thyroid peroxidase antibody; TSH = thyroid-stimulating hormone (thyrotropin).
†See Table 1 for explanation of grades.

neck (level 6) should be removed (68,71). Cervical lymph nodes in levels 2, 3, and 4 should be evaluated preoperatively by palpation and US. Suspicious lymph nodes identified preoperatively by US or discovered intraoperatively should be removed and sent for frozen section. Histologic confirmation of metastatic disease should be followed by selective (modified) ipsilateral neck dissection (59,68-71).

Patients with a diagnosis of PTC by FNA or confirmed at surgical intervention, with a nodule <1 cm in diameter and no evidence of lymph node involvement, *may* be treated by lobectomy plus isthmectomy alone (59,69-71). Therefore, we recommend that all patients undergoing thyroid surgical treatment be evaluated by US preoperatively.

Advanced, poorly differentiated follicular carcinomas, Hürthle cell tumors, and medullary carcinomas should be managed more aggressively. The therapeutic decisions for such lesions should be formulated by a multidisciplinary team (69).

3.1.2. Key Recommendations

The key recommendations for management of FNA-positive thyroid nodules are outlined in Table 11.

3.2. FNA-Negative Thyroid Nodule

3.2.1. Levothyroxine Suppressive Therapy

Efficacy. Suppression of serum TSH (<0.1 μIU/mL) with levothyroxine (LT_4), a controversial therapeutic practice, is aimed at shrinking palpable thyroid nodules and preventing the appearance of new nodules or the growth of the smaller ones coexistent with a dominant mass (60,61,72).

Table 11
Key Recommendations for Management of Thyroid Nodules That Are Positive by Fine-Needle Aspiration*

- For a thyroid nodule with positive (malignant) FNA results, surgical treatment is recommended (*grade B*)†
- Review US and cytologic results with the patient and family; discuss treatment options; answer all questions and concerns; recommend surgical excision and discuss potential complications; obtain surgical consultation, preferably with a surgeon experienced in endocrine surgical procedures (*grade D*)
- For most patients, especially those with differentiated cancers >1 cm, familial disease, and clinical or US evidence of multifocal disease, capsular invasion, or involved nodules, total or near-total thyroidectomy is indicated. Lymph nodes within the central compartment of the neck (level 6) should be removed, especially if the surgeon has specific training for and experience with thyroid surgical techniques (*grade C*)

*FNA = fine-needle aspiration; US = ultrasonography.
†See Table 1 for explanation of grades.

Several reports have shown that shrinkage of thyroid nodules occurs more frequently in patients with long-term TSH suppression than in untreated patients (73-76; *grade A*). A clinically significant (>50%) decrease in nodule volume, however, is obtained with LT_4 therapy in only a minority of patients—20% of those with palpable thyroid nodules (77,78; *grade A*). The growth of many thyroid nodules seems to be minimally dependent on TSH levels; part of the observed beneficial effect of LT_4 therapy on pressure symptoms or cosmetic complaints is probably because of the decrease in volume of the still-TSH-dependent perinodular thyroid tissue. Reduction of nodule volume seems to be more effective in small, recently diagnosed thyroid nodules, in lesions with colloid features at FNA evaluation, and in geographic regions with borderline iodine deficiency (79).

Further nodule growth and appearance of new nodules, however, may be impeded by LT_4 suppressive therapy. A 5-year prospective randomized study and a few meta-analyses have suggested that nodule growth, new nodule appearance, and the growth of the thyroid gland as a whole may be decreased in patients treated with LT_4 in comparison with a control group (80,81; *grade A*).

Adverse Effects. LT_4 treatment should not be targeted toward complete TSH suppression. Indeed, sustained subclinical hyperthyroidism is associated with a significant decrease in bone density in postmenopausal women, although no available evidence has indicated an increase in the rate of bone fractures (72,82,83; *grade A*). Moreover, in elderly patients with suppressed levels of serum TSH, a 3-fold increase in atrial fibrillation and increased mortality attributable to cardiovascular diseases have been reported (72,84,85; *grade B*).

Candidates for LT_4 Treatment. Currently, routine LT_4 treatment in patients with nodular thyroid disease is not recommended (72). LT_4 therapy may be considered in patients from iodine-deficient geographic areas, in young patients with small thyroid nodules and colloid features at cytologic sampling, and in those who have nodular goiters with no evidence of functional autonomy. The use of LT_4 should be avoided in patients with large thyroid nodules or long-standing goiters, if the TSH level is <1 μIU/mL, in postmenopausal women or in men older than 60 years, and in patients with osteoporosis, cardiovascular disease, or systemic illnesses.

The physician and the patient should be aware of the following:

- LT_4 treatment induces a clinically significant reduction of thyroid nodule volume in only a minority of patients; the variables of response are not known (*grade A*)
- Long-term TSH suppression may prevent an increase in size of a thyroid nodule and of the thyroid itself, but nodule regrowth occurs after cessation of therapy; thus, commitment to long-term therapy seems inevitable (*grade A*)
- LT_4 treatment should never be fully suppressive because of the adverse effects associated with prolonged subclinical hyperthyroidism (*grade A*)
- If a thyroid nodule does not shrink or grows while the patient is receiving LT_4 therapy, reaspiration is indicated (*grade C*)
- LT_4 suppressive therapy is not useful for prevention of goiter recurrence after lobectomy (*grade B*)

Key Recommendations. The key recommendations regarding LT_4 therapy in patients with FNA-negative thyroid nodules are presented in Table 12.

3.2.2. Surgical Treatment

Surgical Indications. The following situations are indications for surgical treatment in a patient with a thyroid nodule.

Symptoms. Patients may report dysphagia, a choking sensation, shortness of breath (especially when supine), dyspnea on exertion, hoarseness, neck pressure, or pain. These symptoms often occur if a thyroid nodule is large or has a substernal component. It is important to verify that the symptoms are associated with the nodule or goiter and not with other disease processes, such as pulmonary or cardiac disease, esophageal disorders, or other head and neck tumors (*grade C*).

Associated Hyperthyroidism. A large toxic uninodular goiter or MNG may be treated surgically or with radioiodine. A patient with a toxic nodule can be treated with thyroid lobectomy only, whereas a patient with multinodular hyperthyroidism should undergo near-total thyroidectomy (*grade C*).

Nodular Growth. Should a thyroid nodule increase in size despite benign findings on FNA, surgical resection should be considered. The risk of malignant involvement in this situation, however, is quite low.

Suspicious or Malignant FNA Results. Patients with suspicious thyroid nodules can be treated with thyroid lobectomy and isthmectomy or total thyroidectomy, depending on whether the patient already has hypothyroidism, a history of irradiation, or multiple thyroid nodules or has a treatment preference. At the time of the surgical procedure, frozen section should be performed to help guide the surgical decision making; often, however, it is not useful in distinguishing benign from malignant nodules (86). In the future, molecular markers may be helpful as an adjunct to FNA in the distinction of these lesions (see section 4.4) (87).

Most patients with a substantiated well-differentiated thyroid malignant lesion on FNA are treated with total or near-total thyroidectomy followed by radioiodine therapy. Patients with MTC should also undergo, at a minimum, concomitant central lymph node dissection and, in some cases, either ipsilateral or bilateral modified radical neck dissection (88).

Table 12
Key Recommendations Regarding Levothyroxine Therapy for Thyroid Nodules That Are Negative by Fine-Needle Aspiration*

- Use of LT_4 therapy may be considered in the following (*grade C*†):
  - Patients from geographic areas with iodine deficiency
  - Young patients with small thyroid nodules
  - Nodular goiters with no evidence of functional autonomy
- Use of LT_4 therapy should be avoided in most cases and especially in the following (*grade C*):
  - Large thyroid nodules and goiters, particularly in the presence of symptoms or signs of functional autonomy
  - Clinically suspicious lesions or lesions with an inadequate cytologic sample
  - Postmenopausal women and men older than 60 years
  - Patients with osteoporosis or systemic illnesses
  - Patients with cardiovascular disease
- Facts to remember:
  - LT_4 treatment induces a clinically significant reduction of thyroid nodule volume in only a minority of patients (*grade B*)
  - Long-term TSH suppression may be associated with bone loss and arrhythmia in elderly patients and menopausal women (*grade B*)
  - LT_4 treatment should never be fully suppressive (TSH <0.1 μIU/mL) (*grade C*)
  - Nodule regrowth is usually observed after cessation of LT_4 therapy (*grade C*)
  - If nodule size decreases, LT_4 therapy should be continued long term (*grade D*)
  - If thyroid nodule grows during LT_4 treatment, reaspiration and possibly surgical treatment should be considered (*grade D*)

*LT_4 = levothyroxine; TSH = thyroid-stimulating hormone (thyrotropin).
†See Table 1 for explanation of grades.

Preoperative Management. Preoperatively, in addition to standard evaluation by the anesthesia department, patients with documented thyroid cancer should have an US examination of the neck, vocal cord assessment, and chest radiography to ensure that they do not have evidence of pulmonary metastatic disease, although such lesions are rare.

Surgical Approach. Thyroid lobectomy includes total or near-total lobectomy, with or without isthmectomy. Should the patient require a completion thyroidectomy, it is usually technically easier to perform if the isthmus has previously been resected; this setting would lessen the need for dissection along the anterior aspect of the trachea.

Total thyroidectomy differs from near-total thyroidectomy in that a small rim of thyroid tissue is left along the cricopharyngeal muscle, where insertion of the recurrent laryngeal nerve occurs. During the surgical procedure, meticulous care must be exercised by the surgeon to identify and preserve all 4 parathyroid glands and to avoid injury to the recurrent laryngeal nerve.

A thyroid gland that extends substernally can almost always be resected through a cervical approach. In this setting, only rarely is a median sternotomy necessary to accomplish thyroid lobectomy or total thyroidectomy.

The surgical procedure is usually performed with the patient under general anesthesia, although a few surgeons operate with use of local anesthesia only (89). Some surgeons perform this operation by using a video-assisted technique; thus, the length of the neck incision can be shortened (90).

Postoperative Complications. As is the case with all operations, bleeding or infection can occur, but these complications are rare. Permanent hypoparathyroidism or injury to the recurrent laryngeal nerve should occur in less than 1% of the cases when the surgical procedure is performed by experienced surgeons.

Key Recommendations. In Table 13, the key recommendations for surgical treatment of thyroid nodules are summarized.

Table 13
Key Recommendations Regarding Surgical Treatment of Patients With Thyroid Nodules*

- Surgical indications in a patient with a thyroid nodule include the following:
  - Associated local symptoms
  - Hyperthyroidism from a large toxic nodule, or hyperthyroidism and concomitant MNG
  - Growth of the nodule
  - Suspicious or malignant FNA results
- Thyroid lobectomy includes total or near-total lobectomy, with or without isthmectomy. Should the patient require completion thyroidectomy, it is technically easier to perform if the isthmus has previously been resected
- For a solitary benign nodule, lobectomy plus isthmectomy is sufficient; for bilateral nodules, a near-total thyroidectomy is appropriate
- The surgical procedure is usually performed with use of general anesthesia; however, some surgeons operate with use of local anesthesia only
- A thyroid gland that extends substernally can almost always be resected through a cervical approach. Only rarely is median sternotomy necessary to accomplish thyroid lobectomy or total thyroidectomy
- With experienced surgeons, associated complications are rare

*FNA = fine-needle aspiration; MNG = multinodular goiter.

3.2.3. US-Guided Percutaneous Ethanol Injection

Percutaneous ethanol injection (PEI) is a US-guided, mini-invasive therapeutic procedure for the nonsurgical management of thyroid nodules (91,92).

Efficacy. In the management of *thyroid cysts*, PEI is highly effective in the treatment of complex nodules with a dominant fluid component. Aspiration may cure thyroid cysts; however, recurrences are common, and surgical resection is often the final treatment of large relapsing lesions. Prospective randomized trials showed that PEI is significantly superior to aspiration alone in inducing reduction of nodule volume (93-95; *grade C*). A reduction of >50% of the baseline volume is obtained in almost 90% of the treated cases (95-100; *grade A*).

The recurrence rate of cystic lesions of the thyroid is very low. In a 6-month survey, fluid refilling was reported in 5% of the treated nodules, and in a 12-month prospective study, only 1 of 38 complex (predominantly cystic) thyroid nodules recurred (95; *grade A*). In other published series, volume reduction was followed by the disappearance of compressive and cosmetic symptoms in 74.8% and 80.0% of patients treated with PEI but in only 24.4% and 37.4% of patients treated with simple drainage (94-97,99,100). In large or multilocular thyroid cysts, several injections may be necessary (95).

For *autonomously functioning thyroid nodules* (AFTN), the reported short-term rate of therapeutic response in toxic cases ranges from 64% to more than 95% (101-104; *grade C*), but 5 years after PEI, serum TSH is detectable in only 35.3% of the treated cases (95). PEI is reported to induce a volume decrease of 60% to 75%, but a small residual amount of tissue persists and accounts for the high relapse rate (95). Hence, PEI is not indicated for the treatment of toxic AFTN or hyperfunctioning nodular goiters with multiple foci of functional autonomy because of a high recurrence rate and the availability of alternative effective treatment options.

A clinically significant decrease in nodule size after PEI has been reported in patients with *solitary solid, benign thyroid nodules that were cold* on scintigraphy (105,106; *grade B*). In comparison with LT_4 treatment, PEI is more effective in inducing the reduction of nodule

volume and alleviating local symptoms (107; *grade A*). The response, however, is much less impressive than in cysts, and adverse effects are more frequent (95).

Indications. PEI should be the first line of treatment for recurrent cystic nodules of the thyroid gland after FNA has ruled out a malignant lesion (13,21,23). PEI may be considered only in AFTN with a large fluid component for a preliminary debulking before radioiodine treatment and in small AFTN with incomplete inhibition of the surrounding parenchyma, especially if a fluid component is present (108). The absence of associated scarring, exposure to irradiation, and late hypothyroidism may make this procedure appealing to young patients. PEI is not indicated in cold thyroid nodules because it necessitates repeated treatments, induces unpleasant adverse effects (transient cervical pain), can be complicated by dysphonia attributable to recurrent laryngeal nerve damage, and carries the risk of overlooking thyroid neoplasms.

Key Recommendations. The key recommendations for use and avoidance of PEI in patients with thyroid nodules are outlined in Table 14.

3.2.4. Radioiodine

Radioiodine is indicated for the treatment of hyperthyroidism attributable to hyperfunctioning adenoma or to toxic nodular goiter. The aims of radioiodine treatment are the ablation of the autonomously functioning areas and the achievement of euthyroidism (109,110). Autonomous thyroid nodules are usually more radioresistant than are toxic diffuse goiters, and higher radiation doses may be needed for successful treatment (111).

Efficacy and Adverse Effects. Radioiodine therapy is successful in 85% to 100% of patients with hyperfunctioning thyroid nodules or toxic MNGs (111; *grade C*). After treatment with ablative doses, the thyroid volume may decrease substantially (median decrease, 35% at 3

Table 14
Key Recommendations Regarding Performance of Percutaneous Ethanol Injection in Patients With Thyroid Nodules*

- PEI should be performed:
  - Only by personnel familiar with US-FNA (*grade D*)†
  - On cystic thyroid lesions. PEI is highly effective in the treatment of thyroid cysts and complex nodules with a large fluid component (*grade B*). Because the only alternative to PEI for recurrent and enlarging cysts is surgical resection, PEI is the first-line nonsurgical treatment for recurrent cystic nodules if US-FNA has ruled out a malignant lesion
- PEI should not be performed:
  - On solid, cold nodules, unless surgical treatment is contraindicated (*grade D*)
  - On large or toxic AFTN (nodule volume >5 mL)—the rate of cure is too low and relapse is frequent (*grade B*)
  - On toxic MNGs (*grade B*)
- PEI may be considered:
  - In some small AFTN (nodule volume <5 mL), with a relevant fluid component and not yet completely suppressing the surrounding thyroid parenchyma, if patients are concerned about late hypothyroidism (*grade C*)
- What to do before PEI:
  - If the nodule is considered suitable for PEI, malignant involvement should be ruled out by US-FNA. Multiple cytologic examinations of the cystic wall should be performed (*grade C*)
  - A thorough US examination should evaluate the position, shape, size, margins, and vascular pattern of the nodule (*grade C*)
- What to do during PEI (*grade D*):
  - Continuously monitor the position of the needle tip in the nodule and of ethanol diffusion within the nodule
  - Stop the procedure immediately if the patient reports severe pain, begins to cough, or has a change in voice

*AFTN = autonomously functioning thyroid nodules; MNGs = multinodular goiters; PEI = percutaneous ethanol injection; US = ultrasonography; US-FNA = US-guided fine-needle aspiration.
†See Table 1 for explanation of grades.

months and 45% at 24 months) (112). Radioiodine treatment is effective and safe. Although investigators have indicated that high doses of radioiodine may induce thyroid cancer, other solid tumors, or leukemia, large epidemiologic studies have not shown a clinically significant effect (113,114; *grade C*).

After ablation of the autonomous tissue, 80% to 90% of patients have euthyroidism because of residual normal thyroid function. Nevertheless, hypothyroidism may follow radioiodine treatment if the mass of normal thyroid tissue is too small or if its function is decreased from coexistent autoimmune thyroiditis (115) or from damage consequent to contiguity cross-irradiation from hot nodules. In less than 1% of patients, immunogenic hyperthyroidism may result from radioiodine treatment of toxic nodular goiter because of induction of TSH receptor autoantibodies (116).

Ingestion of high-iodine-content drugs (such as amiodarone or a saturated solution of potassium iodide) should be avoided before administration of radioiodine, so as not to impair thyroid radioiodine uptake. If possible, antithyroid drugs should be withdrawn at least 3 weeks before treatment, in an effort to prevent radioiodine uptake by normal thyroid tissue, and they should not be administered for 3 to 5 days after treatment, to avoid decreasing the effectiveness of therapy.

The amount of radioiodine to be administered can be fixed (300 to 1,800 MBq), without any dose calculation or adjustment on the basis of clinical and goiter size and uptake. This approach is simple, minimizes costs, and yields good results.

Alternatively, an individual computation of the desired concentration of radioiodine (2.96 to 7.4 MBq/g) or of radiation absorbed dose (300 to 400 Gy) at the target (that is, autonomous tissue) can be performed (111). For absorbed dose estimation, Marinelli's formula can be used:

$$A_0 = 5{,}829 \cdot \frac{D_T \cdot m}{U_{\max} \cdot T_{1/2eff}}$$

in which A_0 = administered activity of ^{131}I (MBq); D_T = prescribed absorbed dose (cGy); m = autonomous tissue mass (g); U_{max} = maximal thyroid uptake (%); and $T_{1/2eff}$ = ^{131}I effective half-life in target tissue (h). Maximal thyroid uptake and effective half-life are measured as tracer activity after administration of ^{131}I, and the target volume can be estimated by US or thyroid scan. In cases of multifocal autonomy, the thyroid gland as a whole can be used as the target volume, and the desired absorbed dose is decreased to 150 to 200 Gy.

Individualized approaches can decrease ineffective treatments or help to avoid administration of too much radioiodine, but individualizing therapy is more complex and expensive. Neither approach has been proved definitively superior to the other. Radioiodine therapy is usually defined as successful when the TSH value exceeds 0.5 μIU/mL. TcTUs can also be used to evaluate the success of radioiodine treatment. If thyrotoxicosis is not definitively cured, radioiodine treatment can be repeated after 3 to 6 months.

Indications. Radioiodine treatment is indicated for small goiters (volume <100 mL) without suspected thyroid malignant involvement or in patients previously treated surgically or at risk for surgical intervention. Radioiodine therapy, however, is not the first-line treatment if compressive symptoms are present, if the patient has large nodules that require high amounts of radioiodine and may be resistant to treatment, or if an immediate resolution of thyrotoxicosis is desired (109,110). The only absolute contraindications to radioiodine treatment are pregnancy and lactation, which should be excluded by performance of a pregnancy test (117).

Key Recommendations. In Table 15, the key recommendations pertaining to radioiodine therapy in patients with thyroid nodules are presented.

3.3. Suspicious (Indeterminate) Thyroid Nodule by FNA

3.3.1. Contributing Factors

Indeterminate FNA results are due to poorly defined morphologic criteria to distinguish benign from malignant lesions. Currently, no clear-cut cytologic criteria are available to help the clinician in decision making. If the cytologic appearance is equivocal, the specimen is labeled "suspicious for malignancy" or "indeterminate." At surgical intervention, about 20% of such indeterminate specimens are found to be malignant lesions (30,35,118; *grade C*). Repeated biopsy of these nodules is not recommended because it creates confusion and does not provide additional useful information for management. Some studies have suggested that clinical criteria such as nodule size (>4 cm), fixation, and age of the patient may be associated with increased risk for malignant potential (119), whereas others have not confirmed these observations (118).

Results indicating a suspicious cytodiagnosis include follicular neoplasms, Hürthle cell tumors, and specimens that show atypical but not classic features of PTC (34). In a large series at the Mayo Clinic, 15% of follicular neoplasms, 14% of Hürthle cell tumors, and 65% of atypical lesions had histologic confirmation of malignant involvement (30). It is generally agreed that cytologically suspicious lesions should be treated surgically.

3.3.2. Key Recommendations

The key recommendations regarding indeterminate FNA results of thyroid nodule biopsy are shown in Table 16.

Table 15
Key Recommendations Regarding Radioiodine Therapy in Patients With Thyroid Nodules*

- Consider radioiodine treatment for small goiters (volume <100 mL), in those without suspected malignant potential, in patients with a history of previous thyroidectomy, and in those at risk for surgical intervention (*grade B*)†
- Radioiodine treatment is not the first-line therapy if compressive symptoms are present, if patients have large nodules that require high amounts of radioiodine and may be resistant to treatment, or if immediate resolution of thyrotoxicosis is desired (*grade C*)
- Radioiodine treatment is effective and safe. Large epidemiologic studies have shown no associated clinically significant increase in the risk of cancers or leukemia (*grade B*)
- Give radioiodine therapy cautiously in elderly patients, especially those with heart disease (*grade C*)
- Radioiodine is contraindicated in pregnant or lactating women; always perform a pregnancy test before administration of radioiodine in women of childbearing age (*grade A*)
- Avoid use of iodine contrast agents or iodinated drugs before administration of radioiodine; withdraw antithyroid drugs at least 3 weeks before treatment and resume such regimens 3 to 5 days after radioiodine therapy (*grade C*)
- Follow-up of patients should include monitoring of serum levels of TSH, free T_4, and free T_3; consider repeating treatment in 3 to 6 months if TSH is still <0.1 μIU/mL (*grade C*)

*T_3 = triiodothyronine; T_4 = thyroxine; TSH = thyroid-stimulating hormone (thyrotropin).
†See Table 1 for explanation of grades.

3.4. Nondiagnostic Cytologic Specimen by FNA

3.4.1. Contributing Factors and Suggested Approach

US-FNA is indicated if the thyroid nodule is smaller than 1 cm or impalpable by examination or if the initial palpation-guided FNA was nondiagnostic (Table 17) (14,19). Additionally, for PEI or laser ablative treatment, US guidance is essential.

An unsatisfactory (nondiagnostic) specimen usually results from a cystic nodule that yields few or no follicular cells (120-122). Reaspiration yields satisfactory results in 50% of cases (33). Despite good initial technique, repeated biopsy, and US-FNA, approximately 5% of nodules still remain nondiagnostic. Such thyroid nodules should be surgically excised (*grade D*).

Several recent reports indicated that the application of US-FNA improves results. For example, 2 European studies showed that nondiagnostic rates of 8.7% and 16% were decreased to 3.5% and 7%, respectively, with the application of US-FNA (123,124; *grade C*). Additionally, the surgical yield of cancer increased by 20% in both series with use of US-FNA. Similar data have been reported by other medical centers. Clearly, the application of US-FNA, with indications as outlined in Table 17, improves results.

3.4.2. Key Recommendations

The key recommendations regarding nondiagnostic FNA cytologic specimens from thyroid nodules are summarized in Table 18.

3.5. Repeated Biopsy

Indications for reaspiration of a thyroid nodule are listed in Table 19. Whether routine rebiopsy is necessary is unclear. For physicians or clinics beginning to perform FNA, reaspiration provides reassurance with the procedure and may decrease false-negative rates. We recommend reaspiration if a nodule enlarges, a cyst reappears, a nodule is larger than 4 to 5 cm, or no shrinkage of the nodule occurs after LT_4 therapy (Table 19).

4. OTHER ISSUES AND FUTURE PERSPECTIVES

4.1. Thyroid Nodule During Pregnancy

Most cases of thyroid nodules during pregnancy are in patients with preexisting nodules who then become pregnant; occasionally, however, a thyroid nodule is detected for the first time during pregnancy. A thyroid nodule in a

Table 16
Key Recommendations Regarding Suspicious (Indeterminate) Fine-Needle Aspiration Biopsy of Thyroid Nodules*

- Indeterminate FNA results are due to poorly defined morphologic criteria for distinguishing benign from malignant lesions. No clear-cut cytologic criteria are available to aid in decision making. At surgical intervention, about 20% of indeterminate FNA specimens are malignant lesions
- Repeated biopsy of these nodules is not recommended because it creates confusion and does not provide additional useful information for management
- Because large-needle thyroid biopsy is not more accurate than FNA, is more cumbersome, and is associated with pain and occasional severe bleeding, it is currently not recommended in the management of thyroid nodules
- Clinical criteria such as nodule size (>4 cm), fixation, and age of the patient may suggest increasing risk for malignant potential
- Currently, we recommend surgical excision of all indeterminate thyroid nodules

*FNA = fine-needle aspiration.

pregnant woman should be managed in the same way as in nonpregnant women, except for the avoidance of use of radioactive agents for both diagnostic and therapeutic purposes. Thyroid nodule diagnosis during pregnancy necessitates FNA, regardless of the gestational age of the fetus.

Sharing of findings on the patient assessment among endocrinologist, obstetrician, thyroid surgeon, pathologist, and anesthesiologist is recommended. Furthermore, the patient's preferences should also be appropriately considered.

4.1.1. Effects of Pregnancy on Nodular Thyroid Disease

In a recently published series, thyroid nodules were diagnosed in 34 of 221 pregnant patients, and they underwent follow-up for 3 months after delivery (125). The mean volume of the single or dominant thyroid nodule increased from 60 mm^3 at the beginning of pregnancy to 65 mm^3 at the third trimester and to 103 mm^3 at 6 weeks after delivery. At the 3-month postpartum follow-up, the volume was still increased (73 mm^3). New thyroid nodules developed in 11.3% of women during pregnancy; this circumstance led to an increase in the incidence of thyroid nodular disease from 15.3% at baseline to 24.4% 3 months after delivery. No ultrasonographically discovered new thyroid nodules were palpable. These data indicate that pregnancy is associated with an increase in the size of preexisting nodules and with the appearance of newly developed thyroid nodules, possibly because of the negative iodine balance that frequently occurs during pregnancy (126; *grade C*).

4.1.2. LT_4 Suppressive Therapy

Although pregnancy is a risk factor for progression of nodular thyroid disease, no available evidence indicates that LT_4 is effective in reducing the size or arresting the growth of thyroid nodules during pregnancy. Hence, LT_4 therapy for thyroid nodules is not advisable during pregnancy (*grade C*).

4.1.3. FNA-Malignant Thyroid Nodule

Thyroid cancer is rarely diagnosed during pregnancy. If cancer is diagnosed during the first or second trimester, the patient should undergo surgical treatment during the second trimester, when anesthesia risks are minimal. If the cytologic diagnosis is made during the third trimester, the surgical procedure can be postponed until the immediate postpartum period (*grade C*).

4.1.4. FNA-Suspicious Thyroid Nodule

Suspicious cytologic findings pose a difficult problem during pregnancy. Although pregnancy may cause a misleading diagnosis of follicular neoplasm because of a physiologic increase in follicular epithelium, the malig-

Table 17
Indications for Ultrasonography-Guided Fine-Needle Aspiration of Thyroid Nodule*

Nondiagnostic palpation-guided FNA
Impalpable nodule
Thyroid nodule <1 cm
Neck node
Ablative therapy

*FNA = fine-needle aspiration.

Table 18
Key Recommendations Regarding Nondiagnostic Fine-Needle Aspiration Cytologic Specimens From Thyroid Nodules*

- An unsatisfactory (nondiagnostic) FNA specimen usually results from a cystic nodule that yields few or no follicular cells
- US-FNA directed at the peripheral portion of the lesion is indicated if initial palpation-guided FNA was nondiagnostic
- Reaspiration yields satisfactory results in 50% of cases
- Despite good initial technique, rebiopsy, and US-FNA, approximately 5% of thyroid nodules remain nondiagnostic. Such nodules should be surgically excised (*grade D*)†

*FNA = fine-needle aspiration; US-FNA = ultrasonography-guided FNA.
†See Table 1 for explanation of grades.

nancy rate of follicular neoplasm in pregnant women is similar to that in nonpregnant women—about 14%. Therefore, deferring surgical treatment to the postpartum period seems reasonable (*grade C*).

4.1.5. Key Recommendations

The key recommendations pertaining to thyroid nodules during pregnancy are outlined in Table 20.

4.2. Radioiodine Treatment of Nodular Goiter

As discussed earlier, the use of radioiodine for the treatment of toxic nodular goiter is well established. Its use in nontoxic nodular goiter has been reported in numerous studies from geographic areas with relatively low dietary intake of iodine (127-131). In these reports, patients with MNG had elevated or high-normal 24-hour radioiodine uptake in comparison with that in similar patients with MNG in the United States. In geographic areas of high dietary intake of iodine, patients with MNG usually have low radioiodine uptake accompanied by low-normal or suppressed levels of TSH in the circulation.

4.2.1. Use of Recombinant Human TSH

When patients with low-uptake MNG are given small doses (0.1 mg) of recombinant human TSH (rhTSH), their radioiodine uptake increases more than 4-fold within 72 hours—the time it takes to activate the sodium-iodine symporter (132-134). This scenario allows delivery of sufficient radiation therapy to the thyroid to cause a decrease in size and amelioration of compressive symptoms within 2 months. As in patients with high-uptake MNG, the average decrease in goiter size is 40% during the first year and 60% by the end of the second year. In patients with a suppressed TSH level, the TSH returns to normal or increases within 3 to 6 months.

Free T_4 and total T_3 levels increase approximately 50% over baseline within 72 hours after injection of the rhTSH. Patients are prescribed a β-adrenergic blocking agent or calcium channel blocker at the time of therapy to avoid any potential thyroid hormone-mediated adverse effects. The standard dose (30 mCi) of ^{131}I is given orally 72 hours after the rhTSH, and typically no substantial radioiodine-induced sequelae occur in the immediate post-treatment period. Rarely, immunogenic hyperthyroidism attributable to induction of TSH receptor antibodies has been reported to occur several months after treatment.

Patients should undergo US-FNA to rule out the presence of a malignant lesion before treatment. Currently, rhTSH is approved only for scanning and thyroglobulin stimulation in patients with postoperative thyroid cancer, and its use to augment radioiodine treatment is considered "off-label." Clinical trials are now under way, however, to obtain United States Food and Drug Administration approval for its use. In elderly patients or patients with comorbid conditions that preclude anesthesia or surgical treatment, rhTSH-augmented radioiodine treatment has proved to be effective for MNG (131).

4.2.2. Key Recommendations

In Table 21, the key recommendations for radioiodine treatment of nodular goiter are presented.

Table 19
Indications for Repeated Biopsy of Thyroid Nodule

Follow-up of benign nodule
Enlarging nodule
Recurrent cyst
Thyroid nodule >4 cm
Initial fine-needle aspiration biopsy nondiagnostic
No shrinkage of nodule after levothyroxine therapy

Table 20
Key Recommendations Relative to Thyroid Nodules During Pregnancy*

- No evidence indicates that administration of LT_4 is effective in reducing the size or arresting the growth of thyroid nodules during pregnancy; thus, LT_4 therapy during pregnancy is not advisable (*grade C*)†
- For a growing thyroid nodule during pregnancy, follow-up studies should include FNA and US (*grade C*)
- With a cytologic diagnosis of thyroid cancer during the first or second trimester in a pregnant woman, surgical intervention should be undertaken during the second trimester, when anesthesia risks are minimal. If this cytologic diagnosis is made during the third trimester, postpone surgical treatment until the immediate postpartum period (*grade C*)
- Pregnancy may cause a misleading diagnosis of follicular neoplasm. The malignancy rate of follicular neoplasm during pregnancy is about 14%. Therefore, defer surgical treatment to the postpartum period (*grade C*)

*FNA = fine-needle aspiration; LT_4 = levothyroxine; US = ultrasonography.
†See Table 1 for explanation of grades.

Table 21
Key Recommendations Regarding Radioiodine Treatment of Nodular Goiter*

- In patients with low-uptake MNG given small doses of rhTSH, radioiodine uptake increases >4-fold within 72 hours. Sufficient radiation therapy is delivered to the thyroid to decrease the size and to ameliorate compressive symptoms rapidly
- Average decrease in goiter size is 40% during the first year and 60% by the end of the second year. In patients with suppressed TSH levels, the TSH value returns to normal or increases within 3 to 6 months
- Free T_4 and total T_3 levels increase approximately 50% over baseline within 72 hours after injection of rhTSH. β-Adrenergic or calcium channel blockers are given to avoid thyroid hormone-mediated adverse effects
- ^{131}I (30 mCi) is given orally 72 hours after rhTSH. No significant radioiodine-induced sequelae occur immediately. Rarely, immunogenic hyperthyroidism occurs several months after treatment
- Before treatment, US-FNA should be performed to rule out a malignant lesion
- Currently, use of rhTSH to augment radioiodine treatment is considered "off-label." In elderly patients or patients with comorbid disorders that preclude anesthesia or surgical intervention, however, rhTSH-augmented radioiodine treatment is effective in management of MNG

*MNG = multinodular goiter; rhTSH = recombinant human TSH; T_3 = triiodothyronine; T_4 = thyroxine; TSH = thyroid-stimulating hormone (thyrotropin); US-FNA = ultrasonography-guided fine-needle aspiration.

Table 22
Key Recommendations Regarding Laser Thermal Ablation in Patients With Thyroid Nodules*

- LTA is a low-cost, rapid, and effective mini-invasive technique for the treatment of benign thyroid nodules causing pressure symptoms or cosmetic complaints
- The procedure should be performed only in carefully selected cases (high-surgical-risk patients). In most patients, 1 to 3 sessions of LTA or a single treatment with multiple fibers induces a nearly 50% decrease in nodule volume and the amelioration of local symptoms (*grade C*)†
- LTA should be restricted to specialized centers, in light of the need for skilled operators to avoid the risk of major complications (*grade D*)

*LTA = laser thermal ablation.
†See Table 1 for explanation of grades.

4.3. Laser Thermal Ablation

4.3.1. Technique and Outcome

Laser thermal ablation (LTA) is a mini-invasive procedure proposed as an alternative to surgical ablation of benign thyroid lesions causing compressive symptoms or cosmetic complaints (135,136; *grade C*). Under US guidance, a 21-gauge needle is inserted into the thyroid lesion, and a thin (300-μm) optical fiber is advanced into the needle sheath. With US monitoring, the needle and fiber tips are visualized as hyperechoic spots, and during laser irradiation, the site under treatment shows an echogenic area enlarging over time. The echogenic zone does not reflect the actual extent of thermal necrosis, and US and color Doppler evaluations provide a precise delineation of the laser-induced damage only after the conclusion of the procedure (136).

LTA induces a burning cervical pain, which rapidly decreases when the energy is turned off. In the few patients treated by this technique to date, no permanent dysphonia, cutaneous burning, or damage to the vital structures of the neck have been reported (137,138).

The treatment is performed on an outpatient basis, is inexpensive, and is not a time-consuming procedure (30 minutes). After LTA, the patients may return home; the persistence of cervical pain can be controlled by a 2-day course of orally administered analgesics or corticosteroids.

In most patients with large thyroid nodules, 1 to 3 sessions of LTA or a single treatment with multiple fibers has been reported to induce an almost 50% decrease in nodule volume and the amelioration of local symptoms (137,138). Because of the risk of major complications and the lack of large prospective trials and long-term follow-up, LTA should be restricted to specialized centers and should still be considered an experimental procedure.

4.3.2. Key Recommendations

The key recommendations relative to the use of LTA in patients with thyroid nodules are summarized in Table 22.

4.4. Histochemical Markers

Several laboratories are now developing molecular assays aimed at clarifying suspicious (indeterminate) FNA results. For example, HBME-1 (human bone marrow endothelial cell) is a monoclonal antibody that stains positively for papillary cancer but not for benign follicular tumors (118,139). In addition, one of the galectins (a calcium-independent class of lectins), galectin-3, which acts as a cell-death suppressor, has been reported to distinguish benign from malignant thyroid follicular tumors (118,140). Other markers being investigated, including thyroid peroxidase, telomerase, and others, have been used with variable success (141). Most studies show, however, that the markers have high sensitivity or specificity, but not both, in diagnosing thyroid cancer. Therefore, at this time, no specific tumor marker is available that will regularly and reliably distinguish benign from malignant thyroid cellular tumors.

4.5. Ultrasonographic Media

First- and second-generation contrast agents seem to provide only ancillary data for the diagnosis of malignant thyroid nodules. The variation of time-intensity curves during the transit times of the injected microbubbles offers a modest improvement over the information obtainable with traditional color Doppler or power Doppler examinations (142). New specifically designed microbubbles and new models of US equipment with specific software are needed to improve the predictive value of contrast-enhanced US for small-parts applications.

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APPENDIX 1: PRACTICAL TIPS

The following are suggestions for care of patients with nodular thyroid disease, based on Task Force consensus and other expert opinions (grade D).

Minimal Requirements for US Equipment

Overall

Advances in electronics and US technology have decreased the cost of US equipment and made it possible to have dedicated instruments for thyroid evaluation. Phased-array transducers have made mechanical transducers obsolete. The type of equipment required depends on its use.

Thyroid US and US-FNA

A 7.5- to 10.0-MHz transducer is sufficient to detect and measure thyroid nodules and to perform US-FNA. Such a transducer allows identification of microcalcifications in real time and usually affords adequate resolution to define the borders of nodules. A linear transducer is generally best for US-FNA. Doppler capability is necessary for determining the vascularity of nodules and sometimes aids in defining the borders of nodules. This level of resolution will allow identification of moderately enlarged lymph nodes (>0.5 cm) in the lateral areas of the neck but may not allow adequate evaluation of lymph node characteristics (hilar line, microcalcifications, cystic necrosis).

For lymph node surveillance in the postoperative thyroid cancer patient, for parathyroid identification, and for performance of PEI, a 10- to 14-MHz transducer is recommended. Power Doppler US is imperative to determine the vascularity of lymph nodes and accelerates the examination by quickly identifying small vessels that may resemble lymph nodes. It also will identify the polar artery in some parathyroid adenomas. The higher resolution allows detection of lymph nodes ≤0.5 cm and evaluation of the aforementioned characteristics. A needle guide attachment is necessary for PEI or LTA, to keep the needle under constant observation during the procedure.

Recommendations for US Evaluation and Reporting

The report of US examination of the thyroid is the main method of sharing information with the referring physician, the general practitioner, and the patient. The description of the US characteristics of the thyroid should provide all the information useful for clinical purposes. A definite diagnosis is not possible with US, but a mere descriptive report is inappropriate if it does not include clinically useful details. Hence, an US report should enable the reader to stratify the nodule under examination on a malignancy risk scale.

In light of the facts that US is a considerably operator-dependent imaging technique and that static images are always unsatisfactory, we recommend paying specific attention to several aspects of the US report.

- Aims of the US report:
  - Describe the US elements useful for making a correct diagnosis
  - Describe to the patient his or her own situation; make it possible for the patient to follow the nodule over time
- Content requirements:
  - Position within the thyroid
  - Size—at least the maximal diameter, specifying whether it is longitudinal, anteroposterior, or laterolateral with respect to the lobe anatomy
  - Echogenicity (anechoic, hypoechoic, isoechoic, or hyperechoic)
  - Presence of a fluid component (mixed nodules)
  - Characteristics of the borders
  - Presence of peripheral halo
  - Internal calcifications (microcalcifications or macrocalcifications)
  - If possible, vascular pattern

If the nodule is solitary or only a few well-separated nodules are present, each nodule should be described analytically. If multiple nodules are present, a general description of the thyroid size and structure may be advisable, pointing out with detail the nodule (or nodules) bearing the US characteristics associated with malignant potential (see text section 2.2), rather than describing only the largest (dominant) nodule.

The report should be typewritten and should indicate clearly the name of the operator and the clinic or hospital. It should be stored in an archive or saved on informatic databases; it should be retrievable.

Static pictures do not provide adequate information for a typically dynamic examination, and their usefulness is limited in US. Nevertheless, inclusion of some images in the report is recommended, especially if particularly important details are detected (suspicious nodules).

- Stylistic suggestions for writing the US report:
  Be concise
  Point out the pathologic aspects; avoid writing too much about normal findings. Describe normality only if a previous pathologic detail is no longer present (such as a cyst that disappeared) or if a normal report is clinically unexpected (for example, a thyroid nodule suspected by palpation but not shown with US)
  Do not use acronyms, or cite only widely known acronyms
  Use technical or easily understandable terms, avoiding words with uncertain or multiple meanings

Recommendations for US-FNA Procedure and Slide Preparation

FNA is the most important diagnostic procedure in the initial evaluation of thyroid nodules, and its accuracy influences subsequent clinical management. The use of US-FNA has increased during the past few years because its accuracy in diagnosing thyroid nodules exceeds that of conventional direct FNA. Proper FNA technique and smear preparation are critical to ensure good results (see text section 2.3).

Discuss the procedure with the patients to reassure them that serious complications are unlikely. US-FNA is not essential if the nodule is palpable, although US-FNA will be necessary if the initial report is unsatisfactory (nondiagnostic). FNA is safe with use of aspirin or anticoagulants.

US-FNA should be performed by physicians with expertise and interest in thyroid disease. Requisites are experience with palpation of thyroid nodules and with US evaluation of the thyroid, good training, and performance of several US-guided aspirations sufficient to attain expertise.

Commercially available US devices equipped with 7.5- to 10.0-MHz transducers provide a clear and continuous visualization of the thyroid gland and the needle tip on the monitor. Small transducers are especially convenient for US-FNA. After the biopsy sites have been determined, the needle should be inserted through a steering device (US-guided FNA) or just above the center of the transducer (US-assisted FNA). This positioning allows the needle to be inserted nearly perpendicular to the neck, and the tip of the needle (clearly visible as a bright spot on the screen) is observed on the monitor until it reaches the biopsy target. Because of the direct visualization of the needle, accidental damage to the trachea, carotid artery, jugular vein, or recurrent laryngeal nerve can be avoided. US-guided aspirations require a single operator and a shorter training program than conventional direct FNA, but the flexibility of the procedure is limited by the steering device.

Large needles may produce blood contamination of the aspirated sample. A 25- or 27-gauge needle is suitable for most palpable thyroid nodules, and its use is suggested for the first sampling of the lesion. Aspiration should be ceased as soon as sample appears in the hub of the needle, and smears are then prepared (see text section 2.3).

With US-FNA, the operator is able to choose the biopsy site after a careful US evaluation. The recommended biopsy sites are as follows:

- *In large nodules*, the peripheral part of the lesion rather than the central area, because of frequent degenerative changes
- *In entirely cystic areas*, the center of the lesion should be reached in order to drain the fluid content completely. Cystic fluids should be submitted to the laboratory for evaluation. Most colloid fluids are clear yellow; clear-colorless fluid suggests parathyroid origin, and material should be submitted for measurement of parathyroid hormone. Hemorrhagic fluid suggests a high malignant potential
- *In mixed or mostly fluid complex lesions*, the needle should be addressed 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, both the solid areas and the peripheral borders of the lesion should be sampled

A definite cytologic diagnosis should always be obtained before PEI treatment of cystic or complex lesions is performed.

Recommendations for Cytologic Reporting

The diagnostic accuracy of FNA is increased with communication between the clinician and the cytopathologist. Thyroid smears should be reviewed by a cytopathologist who has a special interest in thyroid disease.

- Diagnostic pitfalls:
  - False-negative results are usually due to inadequate sampling
  - False-positive results are usually due to "suspicious" (indeterminate) findings
  - Gray zones in cytologic reports are follicular neoplasms, Hürthle cell neoplasms, and cytologic findings suggestive of but not diagnostic for papillary carcinoma

The cytologic diagnosis should be clear to help the clinician manage the condition. Thus, standardization of terminology will improve patient care. Cytologic diagnoses should be organized into 4 categories—inadequate material, benign, suspicious, and malignant tumors (see text Table 5).

- Inadequate, unsatisfactory, or nondiagnostic: smears with few or no follicular cells. Action: repeat FNA
- Benign or negative: group including colloid nodule, Hashimoto's thyroiditis, cyst, thyroiditis. Action: observation and follow-up. Cytologically benign but clinically suspicious lesions should be excised
- Suspicious or indeterminate: cytologic results that suggest a malignant lesion but do not completely fulfill the criteria for a definitive diagnosis, including follicular neoplasms, Hürthle cell tumors, and atypical papillary tumors. Action: surgical intervention for definitive diagnosis
- Malignant or positive: group consisting of primary (thyroid) or secondary (metastatic) cancers. Action: surgical consultation and thyroidectomy for primary tumors; search for origin of metastatic disease

Recommendations for ^{131}I Treatment of MNG

- Until approval by the United States Food and Drug Administration, the use of rhTSH to augment radioiodine treatment of MNG is considered "off-label." Its use should be considered in elderly patients or in those with comorbid conditions that preclude anesthesia and surgical treatment
- Should not be used if the presence of a malignant lesion is suspected, and US-FNA should precede treatment
- Treat patient with a β-adrenergic blocking agent or calcium channel blocker during ^{131}I treatment
- After treatment, patient should undergo follow-up for the development of hypothyroidism or hyperthyroidism

Recommendations for PEI of Cystic Lesions

Equipment and Procedure

A real-time US system with a 7.5- to 10.0-MHz probe, 95% sterile ethanol, a spinal needle, and a disposable plastic syringe are needed. A 22-gauge, 75-mm spinal needle is used because it is a flexible needle, fitted with a mandrel and long enough to cross the steering device and reach deep thyroid nodules. Near-complete fluid removal is performed to facilitate clear visualization of the needle in the cavity. Without removal of the needle, a syringe containing ethanol is then substituted for the aspirating syringe. The ethanol is slowly injected in amounts of 1 to 10 mL, depending on the volume of the aspirated fluid. It may be useful to ask the patient to talk at regular intervals during the PEI procedure to ensure that the recurrent laryngeal nerves are intact. PEI can be performed by 1 operator, inserting the needle through a guiding device connected to the probe, or by 2 operators, one handling the probe and the other the needle.

- PEI is performed on outpatients; the procedure is rapid (not exceeding 10 minutes); no local or general anesthesia is needed
- There is no evidence that the serum ethanol level increases after PEI; a limited amount of ethanol is injected into the nodule
- This procedure must be performed by experienced operators with adequate training, to avoid damage to the recurrent laryngeal nerve or other neck structures

Avoidance of Adverse Effects

Adverse effects of PEI are generally mild and transient. Their occurrence depends on the experience of the center.

Mild local pain is common but is rapidly self-resolving or can be controlled with low doses of nonsteroidal anti-inflammatory drugs for 1 to 2 days.

Transient dysphonia is rare after PEI treatment of cystic lesions. Special care must be taken to avoid seepage of ethanol outside the nodule. Real-time US monitoring during PEI allows verification of the correct position of the needle tip within the nodule and assessment of the distribution of the injected ethanol, which should be recognizable as an expanding hyperechoic area within the cystic cavity. Ethanol seeping outside the cystic nodule is always attributable to incorrect procedure (usually the displacement of the needle tip) and induces chemical damage to the recurrent laryngeal nerve. After confirmation with laryngoscopy of unilateral vocal cord paresis, corticosteroid therapy (betamethasone, 1.5 mg daily) can be administered for a few days. The patients should be reassured that, in most cases, a complete recovery from vocal cord paresis usually occurs within a few weeks.

In a few patients with severe thyrotoxicosis (rare in cystic AFTN), the procedure may be followed by transient exacerbation of thyrotoxic symptoms. In most cases, only a slight, transient and asymptomatic increase in serum thyroid hormone levels is observed.

Subcutaneous and intracapsular hematomas are rare and self-resolving complications, provided the patient is not taking anticoagulants (which should be withdrawn at least 48 hours before PEI).

Serial Assessment of PEI-Treated Nodules

- Thyroid cysts: US of the neck should be performed every 6 months for 2 years and yearly thereafter
- Nontoxic AFTN: US evaluation as for thyroid cysts. Assess serum TSH and T_4 every 3 months after PEI

APPENDIX 2: SUMMARY OF RECOMMENDATIONS FOR DIAGNOSIS OF THYROID NODULES

History and Physical Examination

- The vast majority of nodules are asymptomatic, and absence of symptoms does not rule out a malignant lesion (*grade C*)
- Always obtain a biopsy specimen from solitary, firm, or hard nodules. The risk of cancer is similar in a solitary nodule and MNG (*grade B*)
- Record the following information (*grade C*):
  - Family history of thyroid disease
  - Previous neck disease or treatment
  - Growth of the neck mass
  - Hoarseness, dysphonia, dysphagia, or dyspnea
  - Location, consistency, and size of the nodule
  - Neck tenderness or pain
  - Cervical adenopathy
  - Symptoms of hyperthyroidism or hypothyroidism
- Factors suggesting increased risk of malignant potential (*grade C*):
  - History of head and neck irradiation
  - Family history of MTC or MEN2
  - Age <20 or >70 years
  - Male sex
  - Growing nodule
  - Firm or hard consistency
  - Cervical adenopathy
  - Fixed nodule
  - Persistent hoarseness, dysphonia, dysphagia, or dyspnea

US and Other Diagnostic Imaging

- US evaluation
  - Not recommended (*grade C*): as a screening test in the general population; in patients with normal thyroid on palpation and low risk for thyroid cancer
  - Recommended (*grade C*): for high-risk patients (history of familial thyroid cancer, MEN2, or external irradiation); for all patients with palpable thyroid nodules or MNG; for those with adenopathy suggestive of a malignant lesion
- US reporting criteria (*grade C*):
  - Describe position, shape, size, margins, content, echogenic pattern, and, whenever possible, the vascular pattern of the nodule
  - Identify the nodule at risk to be malignant, and stratify the nodule with a risk score based on the US findings
  - Identify the nodules for FNA biopsy
- No FNA of nodules <10 mm unless suspicious US findings or high-risk history (*grade C*)
- US-FNA of nodules of any size in patients with history of neck irradiation or family history of MTC or MEN2 (*grade C*)
- US-FNA should be based on US features (*grade B*)
- US-FNA should be performed on all hypoechoic nodules ≥10 mm with irregular margins, chaotic intranodular vascular spots, a more-tall-than-wide shape, or microcalcifications (*grade B*)
- US findings suggestive of extracapsular growth or metastatic cervical lymph nodes warrant an immediate cytologic evaluation, no matter the size of the lesions (*grade B*)
- In Hashimoto's thyroiditis, the presence of hypoechoic areas due to lymphocytic infiltration should be ruled out before performance of US-FNA on hypoechoic nodules with ill-defined margins (*grade C*)
- In complex thyroid nodules, obtain US-FNA sampling of the solid component of the lesion before fluid drainage (*grade C*)
- Thyroid incidentalomas should be followed by US in 6 to 12 months and regularly thereafter (*grade D*)
- MRI and CT are not indicated in routine nodule evaluation (*grade C*)

FNA Biopsy

- Thyroid FNA biopsy has been established as reliable and safe and has become an integral part of thyroid nodule evaluation
- Clinical management of thyroid nodules should be guided by the results of ultrasonographic evaluation and FNA biopsy
- Thyroid smears should be reviewed by a cytopathologist with a special interest in thyroid disease
- Diagnostic pitfalls:
  False-negative results are usually due to inadequate sampling
  False-positive results are usually due to "suspicious" findings
  Gray zones in cytologic reports are follicular neoplasms, Hürthle cell neoplasms, and cytologic findings suggestive of but not diagnostic for papillary carcinoma
- Standardization of terminology will improve patient care. Cytologic diagnoses should be organized into 4 categories—inadequate material, benign, suspicious, and malignant tumors
  Inadequate, unsatisfactory, or nondiagnostic: smears with few or no follicular cells
  Benign or negative: group including colloid nodule, Hashimoto's thyroiditis, cyst, thyroiditis
  Suspicious or indeterminate: cytologic results that suggest a malignant lesion but do not completely fulfill the criteria for a definitive diagnosis, including follicular neoplasms, Hürthle cell tumors, and atypical papillary tumors
  Malignant or positive: group consisting of primary (thyroid) or secondary (metastatic) cancers

Radionuclide Scanning

- Perform thyroid scintigraphy for a thyroid nodule or MNG if the TSH level is below the lower limit of the normal range or if ectopic thyroid tissue or a retrosternal goiter is suspected (*grade B*)
- In iodine-deficient areas, perform thyroid scintigraphy for a thyroid nodule or MNG even if the TSH level is in the low-normal range (*grade C*)
- Use ^{123}I or $^{99m}TcO_4^-$ for thyroid scintigraphy (*grade B*)

Laboratory Evaluation

- Serum TSH should be tested first, with a third-generation assay (*grade B*)
- If TSH level is low (<0.5 μIU/mL), measure free T_4 and T_3; if TSH level is high (>5.0 μIU/mL), measure free T_4 and TPOAb (*grade C*)
- Routine assessment of serum thyroglobulin is not recommended for the diagnosis of thyroid nodules or nodular goiter (*grade C*)
- Serum calcitonin should be measured if FNA or family history suggests MTC (*grade B*)

APPENDIX 3: SUMMARY OF RECOMMENDATIONS FOR MANAGEMENT AND TREATMENT OF THYROID NODULES

Clinical management of thyroid nodules should be guided by the results of US evaluation and FNA biopsy (*grade B*).

FNA-Positive Thyroid Nodule

- For a thyroid nodule with positive (malignant) FNA results, surgical treatment is recommended (*grade B*)
- Review US and cytologic results with the patient and family; discuss treatment options; answer all questions and concerns; recommend surgical excision and discuss potential complications; obtain surgical consultation, preferably with a surgeon experienced in endocrine surgical procedures (*grade D*)
- For most patients, especially those with differentiated cancers >1 cm, familial disease, and clinical or US evidence of multifocal disease, capsular invasion, or involved nodules, total or near-total thyroidectomy is indicated. Lymph nodes within the central compartment of the neck (level 6) should be removed, especially if the surgeon has specific training for and experience with thyroid surgical techniques (*grade C*)

FNA-Negative Thyroid Nodule

- Use of suppressive therapy with LT_4 may be considered in the following (*grade C*):
  - Patients from geographic areas with iodine deficiency
  - Young patients with small thyroid nodules
  - Nodular goiters with no evidence of functional autonomy
- Use of LT_4 therapy should be avoided in most cases and especially in the following (*grade C*):
  - Large thyroid nodules and goiters, particularly in the presence of symptoms or signs of functional autonomy
  - Clinically suspicious lesions or lesions with an inadequate cytologic sample
  - Postmenopausal women and men older than 60 years
  - Patients with osteoporosis or systemic illnesses
  - Patients with cardiovascular disease
- Facts to remember:
  - LT_4 treatment induces a clinically significant reduction of thyroid nodule volume in only a minority of patients (*grade B*)
  - Long-term TSH suppression may be associated with bone loss and arrhythmia in elderly patients and menopausal women (*grade B*)
  - LT_4 treatment should never be fully suppressive (TSH <0.1 μIU/mL) (*grade C*)
  - Nodule regrowth is usually observed after cessation of LT_4 therapy (*grade C*)
  - If nodule size decreases, LT_4 therapy should be continued long term (*grade D*)
  - If thyroid nodule grows during LT_4 treatment, reaspiration and possibly surgical treatment should be considered (*grade D*)

Surgical Treatment

- Surgical indications in a patient with a thyroid nodule include the following:
  - Associated local symptoms
  - Hyperthyroidism from a large toxic nodule, or hyperthyroidism and concomitant MNG
  - Growth of the nodule
  - Suspicious or malignant FNA results
- Thyroid lobectomy includes total or near-total lobectomy, with or without isthmectomy. Should the patient require completion thyroidectomy, it is technically easier to perform if the isthmus has previously been resected
- For a solitary benign nodule, lobectomy plus isthmectomy is sufficient; for bilateral nodules, a near-total thyroidectomy is appropriate
- The surgical procedure is usually performed with use of general anesthesia; however, some surgeons operate with use of local anesthesia only
- A thyroid gland that extends substernally can almost always be resected through a cervical approach. Only rarely is median sternotomy necessary to accomplish thyroid lobectomy or total thyroidectomy
- With experienced surgeons, associated complications are rare

Percutaneous Ethanol Injection

- PEI should be performed:
  - Only by personnel familiar with US-FNA (*grade D*)

On cystic thyroid lesions. PEI is highly effective in the treatment of thyroid cysts and complex nodules with a large fluid component (*grade B*). Because the only alternative to PEI for recurrent and enlarging cysts is surgical resection, PEI is the first-line nonsurgical treatment for recurrent cystic nodules if US-FNA has ruled out a malignant lesion

- PEI should not be performed:
  On solid, cold nodules, unless surgical treatment is contraindicated (*grade D*)
  On large or toxic AFTN (nodule volume >5 mL)—the rate of cure is too low and relapse is frequent (*grade B*)
  On toxic MNGs (*grade B*)
- PEI may be considered:
  In some small AFTN (nodule volume <5 mL), with a relevant fluid component and not yet completely suppressing the surrounding thyroid parenchyma, if patients are concerned about late hypothyroidism (*grade C*)
- What to do before PEI:
  If the nodule is considered suitable for PEI, malignant involvement should be ruled out by US-FNA. Multiple cytologic examinations of the cystic wall should be performed (*grade C*)
  A thorough US examination should evaluate the position, shape, size, margins, and vascular pattern of the nodule (*grade C*)
- What to do during PEI (*grade D*):
  Continuously monitor the position of the needle tip in the nodule and of ethanol diffusion within the nodule
  Stop the procedure immediately if the patient reports severe pain, begins to cough, or has a change in voice

Radioiodine

- Consider radioiodine treatment for small goiters (volume <100 mL), in those without suspected malignant potential, in patients with a history of previous thyroidectomy, and in those at risk for surgical intervention (*grade B*)
- Radioiodine treatment is not the first-line therapy if compressive symptoms are present, if patients have large nodules that require high amounts of radioiodine and may be resistant to treatment, or if immediate resolution of thyrotoxicosis is desired (*grade C*)
- Radioiodine treatment is effective and safe. Large epidemiologic studies have shown no associated clinically significant increase in the risk of thyroid cancers or leukemia (*grade B*)
- Give radioiodine therapy cautiously in elderly patients, especially those with heart disease (*grade C*)
- Radioiodine is contraindicated in pregnant or lactating women. Always perform a pregnancy test before administration of radioiodine in women of childbearing age (*grade A*)
- Avoid use of iodine contrast agents or iodinated drugs before administration of radioiodine; withdraw antithyroid drugs at least 3 weeks before treatment and resume such regimens 3 to 5 days after radioiodine therapy (*grade C*)
- Follow-up of patients should include monitoring of serum levels of TSH, free T_4, and free T_3; consider repeating treatment in 3 to 6 months if TSH is still <0.1 μIU/mL (*grade C*)

Nodules With Indeterminate FNA

- Indeterminate FNA results are due to poorly defined morphologic criteria for distinguishing benign from malignant lesions. No clear-cut cytologic criteria are available to aid in decision making. At surgical intervention, about 20% of indeterminate FNA specimens are malignant lesions
- Repeated biopsy of these nodules is not recommended because it creates confusion and does not provide additional useful information for management
- Because large-needle thyroid biopsy is not more accurate than FNA, is more cumbersome, and is associated with pain and occasional severe bleeding, it is currently not recommended in the management of thyroid nodules
- Clinical criteria such as nodule size (>4 cm), fixation, and age of the patient may suggest increasing risk for malignant potential
- Currently, we recommend surgical excision of all indeterminate thyroid nodules

Nodules With Nondiagnostic FNA

- An unsatisfactory (nondiagnostic) FNA specimen usually results from a cystic nodule that yields few or no follicular cells
- US-FNA directed at the peripheral portion of the lesion is indicated if initial palpation-guided FNA was nondiagnostic
- Reaspiration yields satisfactory results in 50% of cases
- Despite good initial technique, rebiopsy, and US-FNA, approximately 5% of thyroid nodules remain nondiagnostic. Such nodules should be surgically excised (*grade D*)

- Whether routine rebiopsy is necessary is unclear. For physicians or clinics beginning to perform FNA, reaspiration provides reassurance with the procedure. We recommend reaspiration if a nodule enlarges, a cyst reappears, a nodule is larger than 4 to 5 cm, or no shrinkage of the nodule occurs after LT_4 therapy (see text Table 19)

Thyroid Nodule During Pregnancy

- No evidence indicates that administration of LT_4 is effective in reducing the size or arresting the growth of thyroid nodules during pregnancy; thus, LT_4 therapy during pregnancy is not advisable (*grade C*)
- For a growing thyroid nodule during pregnancy, follow-up studies should include FNA and US (*grade C*)
- With a cytologic diagnosis of thyroid cancer during the first or second trimester in a pregnant woman, surgical intervention should be undertaken during the second trimester, when anesthesia risks are minimal. If this cytologic diagnosis is made during the third trimester, postpone surgical treatment until the immediate postpartum period (*grade C*)
- Pregnancy may cause a misleading diagnosis of follicular neoplasm. The malignancy rate of follicular neoplasm during pregnancy is about 14%. Therefore, defer surgical treatment to the postpartum period (*grade C*)

Radioiodine Treatment of Nodular Goiter

- In patients with low-uptake MNG given small doses of rhTSH, radioiodine uptake increases >4-fold within 72 hours. Sufficient radiation therapy is delivered to the thyroid to decrease the size and to ameliorate compressive symptoms rapidly
- Average decrease in goiter size is 40% during the first year and 60% by the end of the second year. In patients with suppressed TSH levels, the TSH value returns to normal or increases within 3 to 6 months
- Free T_4 and total T_3 levels increase approximately 50% over baseline within 72 hours after injection of rhTSH. β-Adrenergic or calcium channel blockers are given to avoid thyroid hormone-mediated adverse effects
- ^{131}I (30 mCi) is given orally 72 hours after rhTSH. No significant radioiodine-induced sequelae occur immediately. Rarely, immunogenic hyperthyroidism occurs several months after treatment
- Before treatment, US-FNA should be performed to rule out a malignant lesion
- Currently, use of rhTSH to augment radioiodine treatment is considered "off-label." In elderly patients or patients with comorbid disorders that preclude anesthesia or surgical intervention, however, rhTSH-augmented radioiodine treatment is effective in management of MNG

Laser Thermal Ablation

- LTA is a low-cost, rapid, and effective mini-invasive technique for the treatment of benign thyroid nodules causing pressure symptoms or cosmetic complaints
- The procedure should be performed only in carefully selected cases (high-surgical-risk patients). In most patients, 1 to 3 sessions of LTA or a single treatment with multiple fibers induces a nearly 50% decrease in nodule volume and the amelioration of local symptoms (*grade C*)
- LTA should be restricted to specialized centers, in light of the need for skilled operators to avoid the risk of major complications (*grade D*)

Histochemical Markers

- Several laboratories are developing molecular assays to clarify suspicious (indeterminate) FNA results: HBME-1, galectin-3, thyroid peroxidase antibodies
- Most markers show either high sensitivity or high specificity, but not both, for diagnosing thyroid cancer
- No specific tumor marker is available that will regularly and reliably distinguish benign from malignant thyroid cellular tumors

Ultrasonographic Media

- First- and second-generation contrast agents provide only ancillary data for diagnosis of malignant thyroid nodules. The variation of time-intensity curves during the transit times of the injected microbubbles offers a modest improvement over the information obtainable with traditional color Doppler or power Doppler examinations (*grade D*)
- New specifically designed microbubbles and new models of US equipment with specific software are needed to improve the predictive value of contrast-enhanced US for small-parts applications (*grade D*)