Introduction To Guidelines

AACE Clinical Practice Guidelines for the Diagnosis and Management of Thyroid Nodules

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The Clinical Practice Guidelines for the Diagnosis and Management of Thyroid Nodules were developed by the Thyroid Nodule Task Force of the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE). The publication of these clinical practice consensus guidelines coincides with AACE's second Thyroid Disease Awareness Month in January 1996. The goal is to increase the understanding and awareness of the diagnosis and management of thyroid nodules for physicians and the public.

The guidelines are not meant to be complete, nor are they intended to be dogma. Achieving unanimous agreement by clinical endocrinologists on all aspects of this very complicated subject would be difficult. The committee was selected in an attempt to arrive at a consensus by a diversely opinionated group.

The purpose of the task force was to formulate a clear and concise state-of-the-art approach to thyroid nodules. These guidelines are not intended to be definitive because all knowledge is fluid and subject to change. Additionally, the guidelines clarify and emphasize the added value of the clinical endocrinologist in the diagnosis and management of thyroid nodules.

I thank Drs. Jack Baskin, Rhoda Cobin, Hossein Gharib, Ian Hay, Michael Kaplan, and Ernest Mazzaferri for their extraordinary effort in contributing to and shaping these guidelines. The process has been an invigorating experience for all participants.

Dr. Michael Garcia, my co-chairman, must be applauded independently for his tireless work in completing these guidelines.

The fellowship generated during the development of these guidelines is another memorable life experience for me personally that will never be forgotten.

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AACE CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF THYROID NODULES

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MISSION

Nodular thyroid disease is extremely common; a 5 to 10% lifetime risk exists for developing a palpable thyroid nodule. With sensitive imaging studies, more than a third of all women will be found to have at least one thyroid nodule. In contrast, 12,000 cases of thyroid cancer are diagnosed annually in the United States (0.004% of the population), and thyroid cancer-related deaths are rare.

How can the less common malignant thyroid nodule be distinguished from the much more common benign nodule? Moreover, how are patients with thyroid nodules to be managed with both cost and quality of care as codominant concerns? These issues are central to the purpose of these guidelines.

The criteria by which patients with thyroid nodules are selected for surgical treatment have been controversial. Thyroidectomy for diagnosis of a thyroid nodule has never been satisfactory and is costly. With technologic advances, many studies and procedures can be ordered for evaluation of thyroid nodules, but application of all these in all patients with nodules would also be an inordinate burden to the health-care system. Not all studies are necessary in most instances, and for some patients, only a limited evaluation is needed.

AACE believes that experienced clinical endocrinologists are most familiar with management of thyroid nodules and are most able to utilize each technique in its proper role in the diagnosis of thyroid nodules. With these guidelines, AACE hopes to provide a public service to decrease patient morbidity and increase the cost-effectiveness of care to the 30 million potential patients with thyroid nodules.

DIAGNOSIS OF THYROID NODULES

History and Physical Examination

A comprehensive history and physical examination are essential because elements therein can provide firm clues about the statistical probability of thyroid cancer.

Skill in palpation of the thyroid gland should not be dismissed. The experienced clinician can usually distinguish a normal from a goitrous or nodular thyroid. This distinction helps direct the investigation and may eliminate the need for some diagnostic tests. Physicians with little experience in thyroid examination should consider referring patients to an endocrinologist before scheduling any potentially unnecessary and expensive testing.

The following elements of the history and physical examination favor benign disease. These factors do not exclude the presence of thyroid cancer.

- Family history of Hashimoto's thyroiditis or autoimmune thyroid disease
- Family history of benign thyroid nodule or goiter
- Symptoms of hypothyroidism or hyperthyroidism
- Pain or tenderness associated with the nodule
- Soft, smooth, mobile nodule
- Multinodular goiter without a dominant nodule

The following are elements of the history and physical examination increasing the suspicion of malignant thyroid disease.

- Age-the young (<20 years old) and the old (>70 years old) have the highest incidence of thyroid cancer in a palpable nodule
- Gender-the proportion of nodules that are malignant in males is double that in females
- · Nodule plus dysphagia or hoarseness
- History of external neck irradiation during childhood or adolescence (this factor also increases the incidence of nonmalignant thyroid nodular disease)
- Firm, hard, irregular, and fixed nodule
- Presence of cervical lymphadenopathy
- Previous history of thyroid cancer

When nothing in the history favors a malignant nodule, a small but disturbing number of patients still have thyroid cancer. Thus, the history is useful mostly for identifying the presence of factors favoring malignancy. The examination is of more value. Although not definitive in the diagnosis of thyroid cancer, the findings on palpation can be strongly suggestive of thyroid cancer in exceptional cases. Findings from the history and physical examination should not be discounted and can be used as factors in the decision-making process and in directing the use of the available technical diagnostic studies.

Laboratory Evaluation

In patients with a thyroid nodule, a sensitive thyroidstimulating hormone (TSH) assay should be done, at a minimum, to determine the presence of hyperthyroidism or hypothyroidism. Measurement of the serum thyroxine and triiodothyronine levels may also be helpful. Only rarely do patients with solitary nodules that are malignant have hyperthyroidism or hypothyroidism. An abnormal TSH determination decreases the suspicion, but does not eliminate the possibility, of malignancy in a thyroid nodule.

With thyroid nodular disease, serum antithyroid peroxidase (formerly called antimicrosomal) antibody and antithyroglobulin antibody levels are helpful for diagnosing Hashimoto's disease (chronic thyroiditis), especially if the serum TSH level is increased. These antibodies are positive in more than 85% of adult patients with this disease. Often in Hashimoto's disease, the thyroid gland may have a size and consistency that simulate a solitary nodule or bilateral nodules. Evidence for Hashimoto's thyroiditis, however, does not preclude the presence of cancer in the thyroid gland.

A baseline serum thyroglobulin level in the evaluation of a solitary thyroid nodule is not a useful or cost-effective test. The value of the thyroglobulin level lies in serial determinations after thyroid cancer has been diagnosed and the patient has been treated by elimination of most or all of the thyroid gland.

In patients with a family history of medullary carcinoma of the thyroid, specific genetic testing and a calcitonin (or a stimulated calcitonin) level should be determined. In the absence of suspicion of medullary thyroid cancer or multiple endocrine neoplasia II syndrome, it is neither routinely necessary nor cost-effective to determine calcitonin levels in patients with a solitary thyroid nodule.

Radionuclide Scanning

Historically, the thyroid scan has been the foundation for assessment of the thyroid nodule. "Hot" or autonomously functioning thyroid nodules are identified visually when the area of the thyroid gland on the scan containing the nodule accumulates the isotope more than the normal thyroid tissue. The extranodular tissue can also take up the isotope or may be suppressed so that only the nodule is seen.

"Warm" or functionally nondelineated nodules have function equivalent to normal thyroid tissue. "Cold" nodules, either hypofunctioning or nonfunctioning, are seen as defects on the scan. The approximately 10% of nodules that are functioning are exceedingly unlikely to be malignant. "Warm" and "cold" nodules can be malignant in approximately 5 to 8% of cases. Thus, the limitation of the nuclear thyroid scan is that only about 10% of nodules are delineated as benign; hence, results are uncertain in the remaining 90%.

The isotopes commonly available for thyroid imaging include 131I, 99m Tc, and 123I. Technetium scanning is quick and convenient, but results may be misleading in a small number of patients. The shortcoming is that a few technetium-identified "warm" or "hot" nodules may be hypofunctional on iodine scanning, and a few of these nodules with discordant technetium and iodine scans are malignant. 131I is clearly the most effective isotope for thyroid cancer follow-up evaluation, but for routine scanning of the thyroid, 131I exposes the patient to excessive thyroidal irradiation and should not be used. 123I scanning is recommended because it avoids the problem with technetium and also the radiation burden of 131I.

A thyroid scan by any commonly used isotope does not identify the presence of a nodule but rather assesses regional uptake or function. As an initial study, it is particularly useful in evaluating asymmetric nodular goiter, hypertrophied lobes simulating nodules or masses, and substernal masses. As a secondary study, scanning is useful for patients with suppressed TSH levels. The scan may reveal an autonomous or functioning nodule. Patients with nodules found to be cytologically benign by fineneedle aspiration (FNA) biopsy would not benefit from subsequent nuclear imaging unless thyroid hormone suppression is being considered as treatment; then a nuclear scan will identify functioning nodules, for which administration of thyroid hormone could lead to thyrotoxicosis. In suspicious or nondiagnostic FNA nodules, nuclear imaging might also be diagnostically helpful. Most clinical endocrinologists have evaluated thyroid nodules for a long time with nuclear scanning, are comfortable interpreting the results, and are aware of the limitations.

Certainly, not all patients with thyroid nodules require nuclear imaging. In many centers, thyroid FNA biopsy has supplanted nuclear thyroid imaging as the initial technical procedure in evaluating nodules. AACE recommends that the physician use clinical judgment in considering the appropriateness of a thyroid nuclear scan, as it applies to each individual case.

Ultrasonography of the Thyroid Gland

Thyroid ultrasonography is exquisitely sensitive in ascertaining the size and number of thyroid nodules, but ultrasound is not a test to determine if a nodule is benign or malignant. The value of this study is highly dependent on the skill and experience of the operator. When ultrasonography is performed by the examining endocrinologist, it may reveal subtle characteristics of the nodule that can help in the decision to recommend surgical intervention and can be used in guiding FNA biopsy.

Thyroid ultrasonography is not routinely recommended in the initial evaluation of a thyroid nodule unless the endocrinologist uses this technique to guide FNA biopsy. Although ultrasound studies may be useful occasionally in conjunction with FNA biopsy and thyroid scans, another important use is in the follow-up of a nodule once the decision is made not to operate. It provides an objective and sensitive indicator of whether a nodule is increasing or decreasing in size over time. Obviously, a nodule that is decreasing in size is unlikely to require surgical treatment, whereas a nodule that is enlarging would at least warrant a repeat FNA biopsy. Lastly, ultrasonography can be most helpful in the long-term follow-up of patients with thyroid cancer by detecting small or otherwise inaccessible nodules that could represent recurrence of cancer.

Magnetic Resonance and Computed Tomographic Imaging of the Thyroid

Magnetic resonance imaging and computed tomography offer very little in the diagnosis of a thyroid nodule and are very costly. These studies have no role in the assessment of nearly all patients with thyroid nodules.

FNA Biopsy

A major advance in the diagnosis of the thyroid nodule has been achieved with the perfection and common use of FNA biopsy. FNA biopsy is now believed to be the most effective method available for distinguishing between benign and malignant thyroid nodules. AACE advocates FNA biopsy of all thyroid nodules when the possibility of malignancy is appreciable and when the patient is a candidate for surgical or nonsurgical cancer treatment. AACE also recommends FNA biopsy even when suspicion of cancer is very high because foreknowledge of the cancer cell type aids in the planning of the surgical procedure.

Several FNA biopsy series and reviews have been performed to establish the efficacy of this procedure. Members of the committee for these guidelines have reviewed these series. Mazzaferri et al. reported on 10 series with 9,119 patients: results of needle biopsy were benign in 74%, inadequate or suspicious in 22%, and malignant in 4% of those series. Gharib et al. evaluated 7 series with a total of 18,183 FNA: 69% were benign, 27% were suspicious or nondiagnostic, and only 4% were malignant. The suspicious or nondiagnostic group were approximately equally divided; of the suspicious group of nodules, 10 to 30% were ultimately malignant.

Complex analysis reveals that FNA biopsy sensitivity varies from 68 to 98% (mean, 83%) and specificity varies from 72 to 100% (mean, 92%). In many centers, the surgical yield of thyroid cancer in excised thyroid nodules has increased from about 15% to about 45%. Therefore, FNA biopsy represents a tremendous advance.

A major problem diminishing the potential benefit of FNA biopsy is the unskilled physician performing the biopsy or the inexperienced cytopathologist interpreting the specimens. Poor needle technique leads to a higher proportion of unsatisfactory biopsy specimens and probably a higher rate of surgical procedures. In the case of more than one discrete nodule in a thyroid gland, the FNA biopsy should be performed on all accessible nodules and not only on the largest. The endocrinologist is well trained and expert in performing the biopsy and is the best suited physician to use the FNA biopsy data to formulate the recommendations.

Inexperienced cytopathologists may report a very high proportion of follicular lesions or suspicious biopsy specimens, perhaps from lack of confidence in interpreting those nodules that are benign. The endocrinologist and the cytopathologist should work as a team, with bidirectional feedback on difficult cases.

Another concern is the report of "no malignant cells seen" in a specimen that is hypocellular or acellular; the result is a false conclusion of a benign FNA biopsy specimen. To guard against this error, the cytopathologist should adhere to appropriate criteria for specimen adequacy, including at least six to eight cell clusters smeared on slides or from Cytospin cell preparations or red blood cell lysing solution preparations. The number of slides necessary or recommended is variable and usually 2 to 12 slides are obtained, from several needle passes.

The cytopathologist's report should contain a reference to the cellularity of the specimen and whether it is sufficient for diagnosis. With all but the smallest nodules, different areas should be aspirated. The gauge of the needle varies from 22 to 29, depending on the vascularity or fibrous consistency of the nodule. Care should be taken to avoid excessive blood dilution, crush artifact, or air-drying of wet-fixed material. When feasible, microscopic evaluation during the procedure provides immediate information on adequacy of the aspirate and results in lower rates of unsatisfactory specimens.

FNA Biopsy of Cystic Thyroid Nodules

Cystic nodules, representing 10 to 25% of all thyroid nodules, present additional diagnostic challenges. The incidence of malignancy in cysts is probably less than that of solid nodules; nonetheless, complex cystic nodules may be malignant. Few are thin-walled cysts that collapse completely with needle evacuation. Most have a partially solid component. Initially, the cystic fluid, if not excessively viscous, should all be aspirated, and the fluid should be sent to the cytopathologist for a Cytospin preparation. The character of the cystic fluid can vary greatly in color and viscosity. No fluid characteristics exclude malignancy. FNA biopsy can also be performed on the remaining solid component of the nodule. Water-clear, colorless fluid suggests a parathyroid cyst.

The problem is that of a high yield of unsatisfactory (acellular) specimens. It may be helpful to insert the needle in the periphery of the nodule on the initial or subsequent attempt. Most endocrinologists will repeat the FNA biopsy after an unsatisfactory attempt, and in this instance, ultrasound-guided FNA biopsy to find the solid component of the thyroid nodule could be most helpful.

Cytopathologic Diagnoses

The following benign and malignant diagnoses can be made by thyroid FNA biopsy if an adequate specimen is obtained.

- Hashimoto's thyroiditis
- Colloid nodule (nodular goiter)
- Subacute (granulomatous) thyroiditis
- Papillary carcinoma
- Follicular carcinoma
- · Medullary carcinoma
- Anaplastic carcinoma
- Malignant lymphoma
- · Carcinoma metastatic to the thyroid

Intermediate or suspicious diagnoses include the following:

- Suspicious for papillary carcinoma
- Cellular follicular lesion or follicular neoplasm
- Hürthle cell neoplasm

MANAGEMENT OF THYROID NODULES

Malignant Thyroid Nodules on FNA Biopsy

The treatment for nearly all identified malignant thyroid nodules is thyroidectomy. Exceptions include some patients with anaplastic thyroid cancer or lymphoma. The incidence of false-negative thyroid FNA biopsy results is low; therefore, most patients with benign FNA biopsy findings can undergo follow-up without surgical treatment if they are monitored carefully and at periodic intervals. The evaluation should include a careful interval history and physical examination, appropriate thyroid function tests, and, if deemed necessary in the judgment of the endocrinologist, ultrasonography or repeated biopsy.

In fact, many endocrinologists will repeat the biopsy after a period (6 to 24 months) in benign FNA biopsy nodules that remain essentially unchanged and will rebiopsy at any time that the nodule enlarges or otherwise becomes suspicious. Patients with stable benign FNA biopsy nodules can undergo follow-up indefinitely.

AACE believes that the patient should enter into the management decision-making process with the endocrinologist after being informed of the relative risks of surgical intervention versus surveillance. Occasionally, a surgical procedure will be appropriate despite clearly benign FNA biopsy findings in anxious or cancer-phobic patients or for patients with progressively growing or initially very large nodules.

Suspicious and Nondiagnostic FNA Biopsy Findings

In general, thyroid nodules with suspicious FNA biopsy results should be surgically removed if shown not to be autonomous in function. From 10 to 30% of follicular lesions on FNA biopsy can prove malignant on surgical pathologic study. Very small follicular lesions (1 cm or less) or some Hürthle cell lesions in the setting of Hashimoto's thyroiditis could be managed by clinical follow-up.

For nondiagnostic FNA biopsy specimens of cystic or solid nodules, the FNA biopsy should at first be repeated, because 30 to 50% of nodules can subsequently be characterized cytopathologically. Some repeatedly nondiagnostic FNA biopsy nodules can simply be observed clinically, but others should be removed surgically—particularly the larger nodules. Again, clinical judgment and experience are critical in this decision.

The Autonomously Functioning "Hot" Thyroid Nodule

For practical purposes, autonomous thyroid nodules are never malignant. Although rare exceptions to this have been reported, FNA biopsy is seldom necessary if the nodule is known to be autonomous. All patients with toxic autonomous thyroid nodules require treatment. These toxic nodules tend to be large (>2.5 cm), and physical and laboratory features of thyrotoxicosis are present. Radioactive iodine (¹³¹I) is the treatment of choice for most patients with toxic nodules. Thyroid lobectomy is appropriate for younger patients, those with larger nodules, those whose nodules have a substantial hemorrhagic or cystic component, or any patient who prefers surgical treatment. The clinician should discuss the relative merits of these approaches and, if possible, the patient should participate in the treatment decision.

Many patients with autonomous nodules and subclinical hyperthyroidism (normal thyroxine and triiodothyronine levels and suppressed TSH) should be treated at the time of diagnosis. These patients may deny symptoms, but of special concern is the older patient who should be treated more aggressively because of the cardiac implications of subclinical hyperthyroidism. Younger, healthy patients with autonomous thyroid nodules and minimally suppressed TSH levels could be monitored clinically for a finite period without treatment because a small but significant proportion of these nodules may undergo cystic degeneration or infarct; thus, the subclinical hyperthyroidism would be resolved. Clinical judgment is important in the management of these cases. When treatment is being considered, the options are similar to those for the toxic autonomous thyroid nodule.

Functioning thyroid nodules with normal TSH need not be treated but are more difficult to diagnose. Thyroid hormone-suppressed nuclear imaging is useful in selected cases in distinguishing autonomous from nonautonomous nodules. In instances of ambiguity related to thyroid nodule function, FNA biopsy is indicated. Patients with these autonomous nodules should undergo follow-up and periodical reassessment. The time interval is variable.

The Incidentally Discovered Small Thyroid Nodule

With carotid Doppler ultrasonography—or, less commonly, parathyroid ultrasonography—a high number of incidental thyroid nodules are being identified in older patients. This result is not surprising, when the prevalence of thyroid nodules in this group is considered. Most are 1 cm or less, partially cystic, and not palpable. Often, multiple nodules have been reported.

The index of suspicion for cancer in these nodules is indeed very low, and most can be followed with no further imaging studies or biopsy. In cases of a sonographically suspicious nodule (irregularly contoured or large and nonpalpable), ultrasound-guided FNA biopsy is appropriate.

Levothyroxine Suppression Treatment

An enduring controversy is the role of levothyroxine suppression treatment for patients with benign thyroid nodules. Proponents argue that this treatment reduces the size of some nodules, but opponents refute the efficacy of such therapy. Published studies support both sides of this issue. AACE recommends individual clinical judgment about this treatment. Levothyroxine prescribed as a diagnostic trial for nodule reduction is of little value in the decision to operate and is not recommended. Such a trial is no substitute for FNA biopsy.

A closely related controversy is whether to treat euthyroid patients with levothyroxine after a thyroid lobectomy for a benign nodule. The literature on this point is controversial, and AACE believes that the endocrinologist should make this decision in conjunction with the patient, after the benefits and risks have been reviewed.

Treatment with levothyroxine is not without risks. Excessive doses have been associated with cardiac

arrhythmias and osteoporosis. Older patients are poor candidates for levothyroxine suppression, as are patients with TSH levels at the lower limit of normal. Levothyroxine treatment guidelines have been published in the AACE Clinical Practice Guidelines for the Evaluation and Treatment of Hyperthyroidism and Hypothyroidism.

Thyroid Nodules in Pregnancy and Childhood

Thyroid nodules discovered during pregnancy should be managed the same as a nodule discovered in a nonpregnant patient except that radionuclide scanning is contraindicated. FNA biopsy can be performed during pregnancy or deferred until the postpartum period if the pregnancy is advanced. If the nodule is malignant, surgical removal is relatively safe during the second trimester, or the procedure can be deferred until after the pregnancy.

Thyroid nodules are less common in children and probably more often malignant than those in adults. Two recent reports used FNA biopsy for diagnosis and management of thyroid nodules in pediatric patients; the results were colloid nodule in 55%, Hashimoto's thyroiditis in 29%, and malignancy in 15%. Papillary thyroid carcinoma was the most common malignant lesion discovered. FNA biopsy has an important role in pediatric patient management, as it does in the adult patient. Clearly, most pediatric thyroid nodules are benign and can be managed medically. Surgical intervention is imperative only when the cytologic diagnosis is suspicious or malignant.

CONCLUSION

These conceptual guidelines set forth by the AACE present a consensus of approaches to the assessment and treatment of patients with thyroid nodules. The field is highly complex, and a considerable diversity of opinion prevails. The spectrum of that diversity of opinion is represented by the Thyroid Nodule Task Force of AACE that developed these guidelines. One goal is to emphasize the importance of clinical judgment by an experienced clinician. Cost-effective management can be obtained through sound judgment by the clinician and appropriate intervention.

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