Guidelines for Thyroid Nodule Evaluation

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Complex guidelines have been published for the management of thyroid nodules directed largely at endocrinologists and surgeons. These authors present guidelines for primary care practitioners working within the federal health care system.

With high-profile cases, such as the death of Chief Justice William Rehnquist in 2005 and recent reports demonstrating increases in thyroid cancer, thyroid nodules are gaining significance in the minds of many physicians.[1,2] Palpable thyroid nodules are estimated to occur in 5% of women and 1% of men in parts of the world with adequate iodine intake, although the overall incidence may be as high as 7%.[3-5] Further, high-resolution ultrasound and autopsy studies demonstrate nodules in as many as 67% of individuals.[6,7] These nodules are often proven to be benign with little effect on overall patient care or survival. Nonetheless, with the increasing incidence in thyroid cancer, thyroid nodules require full evaluation.

The evaluation of thyroid nodules has an obvious role in the due diligence of physicians in multiple specialties, but especially in primary care. Although thyroid nodules are often proven to be benign with little effect on overall patient care or survival, 5% to 10% of them are found to be cancerous, a rate that appears to be on the rise.[8,9]

The Surveillance Epidemiology and End Results Cancer Statistics Review released results demonstrating annual thyroid cancer incidence is increasing from 4.85 per 100,000 people in 1975 to 11.99 per 100,000 people in 2007. Of note, the same data does not show any significant difference in mortality between 2007 and the average for the prior 32-year period, with a death rate of 0.5 per 100,000 people. Prevalence in 2007 was reported as 434,256 patients, and approximately 30% of those cases were diagnosed within the last 5 years, which is greater than any other 5-year period.[1] Current theories on the increased incidence of thyroid cancer heavily favor improved detection techniques although no research has fully explained the recent escalation.[2]

Complex guidelines for the management of thyroid nodules and thyroid cancer have been directed largely at endocrinologists and endocrine surgeons, beginning in 1996 with the separately published American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE) guidelines.[10,11] In addition to updates to these guidelines,[3,12] other agencies, including the National Comprehensive Cancer Network and British Thyroid Association, have published guidelines as well.[13,14] However, none of these guidelines have been targeted toward the primary care practitioner.

We set out to evaluate these guidelines with emphasis put on the most recent ATA guidelines from 2009[15] and AACE/Associazione Medici Endocrinologi/European Thyroid Association (AACE/AME/ETA) guidelines from 2010[16] to establish clinical recommendations for the evaluation of thyroid nodules by primary care practitioners working within the VA, DoD, and the PHS. Where guidelines conflicted, the available facilities and unique patient population served by the targeted audience were used to determine the recommendation. Grades of recommendations are based on the U.S. Preventive Services Task Force model (Table).[17] Levels of evidence were assessed according to the Oxford Centre for Evidence-based Medicine guidelines.[18]

METHODS

A MEDLINE search was performed using the following search terms: thyroid nodule (with the modifiers diagnosis, ultrasonography, palpation, therapy, and surgery) and multinodular goiter. Relevant articles were chosen from all English language results dating until October 2010. Special attention was geared toward published clinical practice guidelines. Randomized controlled trials and meta-analyses were given greater consideration, compared with clinical case series or expert opinion.

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RESULTS

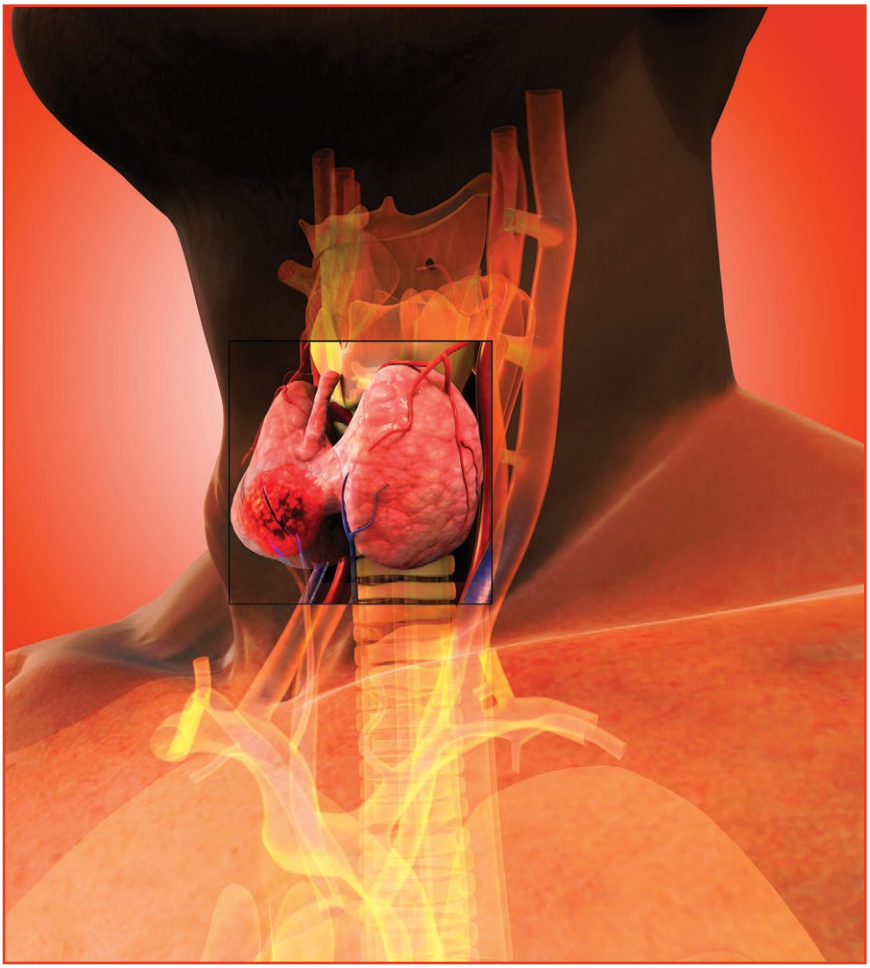
The definition of a thyroid nodule is a "discrete lesion within the thyroid gland that is palpably and/or ultrasonographically distinct from the surrounding thyroid parenchyma."[3] The diagnosis of a thyroid nodule most often begins with either a nodule palpated during routine physical examination or as an incidental finding of an imaging study performed for another purpose.

History and physical examination

Patients who have thyroid nodules require a thorough history and physical examination (Grade A recommendation). Special attention should be directed at a history of thyroid or head and neck cancer; head or neck irradiation; full body irradiation from military or other work-related exposures; symptoms of hypothyroidism or hyperthyroidism; symptoms of dysphagia, odynophagia, dysarthria; weight loss or gain; fever or night sweats; and a thorough family history of cancer—including, but not limited to, medullary thyroid cancer, papillary thyroid cancer, multiple endocrine neoplasia, familial adenomatous polyposis syndromes, Gardner syndrome, or Cowden syndrome. Physical examination should take into account the location, size, and mobility of the lesion, as well as general characteristics of the entire thyroid gland. Any lymphadenopathy present should be identified and described, as should any changes in vocal quality or ability noted with respect to previous examinations.

Laboratory tests

After the initial evaluation, serum thyroid stimulating hormone (TSH) should be measured (Grade A recommendation). The reasons this study is recommended are 2-fold. First, abnormally low serum TSH points the diagnosis toward an overtly hyperfunctioning thyroid disorder, such as Graves disease, or a hyperfunctioning adenoma, both of which are rarely malignant. Second, high-normal TSH has been shown to be an independent predictor of thyroid malignancy.[19,20]



Although proven useful in monitoring some patients with treated thyroid cancer, serum thyroglobulin measurements are found to be elevated in numerous diseases and have not shown any benefit in the evaluation of thyroid nodules (Grade D recommendation).[21]

The role of serum calcitonin levels in the routine evaluation of thyroid nodules continues to be debated. Several studies have shown that routine serum calcitonin screening can detect medullary thyroid cancer at an earlier stage and may improve survival.[22-24] However, some of these data rely on pentagastrin-stimulated testing, which is no longer available in the United States. Although a recent cost analysis suggests that routine calcitonin screening in thyroid nodules would be cost-effective in the United States, C-cell hyperplasia and micromedullary carcinomas were included in the prevalence calculations, potentially overestimating the prevalence of clinically significant medullary thyroid carcinoma.[25] These confounding factors along with the variability in assay performance between laboratory tests

Table: Grades of recommendations

Grade	Definition	Suggestions for practice
A	We recommend this with high certainty that the net benefit is substantial.	Offer or provide this service as recommended.
B	We recommend this with high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service as recommended.
C	We recommend against routinely following this course as there may be considerations that support providing the service in an individual patient. There is at least moderate certainty that the net benefit is small.	Offer or provide this service only if other considerations support the offering or providing the service in an individual patient.
D	We recommend against this service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I Statement	We conclude that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

make the effectiveness of routine calcitonin screening unclear at this time (Grade I recommendation).

Radiologic imaging

As ultrasonography (US) has become more prevalent, precise, and affordable; its role in the evaluation of thyroid nodules has evolved such that now it is invaluable. US should be used to evaluate all known or suspected thyroid nodules, as it allows for rapid, precise, and noninvasive evaluation of their size, location, and characteristics (Grade A recommendation). Additionally, US may show additional nodules or associated lymphadenopathy not identified in a physical exam. Certain characteristics seen on US connote greater likelihood of malignancy, including irregular shape, ill-defined border, solid echo structure, hypoechogenicity, lack of halo, calcifications, and intranodular vasculature.[26,27] Further, direct studies have demonstrated alterations in treatment management in as many as 63% of patients studied based on US evaluation alone.[28]

Previously the ^{123}I, ^{131}I, or ^{99}Tc pertechnetate radionuclide scans were routinely used as they provided evidence of hyperfunctioning vs hypofunctioning nodules. Use of the thyroid uptake scan (TUS) has fallen out of favor, as the information gleaned only changes in management of patients with hyper-functioning or "hot" nodules. The mandate for a true tissue diagnosis remains in the case of cold nodules.[29]

Further, TUS may delay treatment and diagnosis compared with biopsy, which can often be performed in the office. However, in patients with TSH levels below normal, TUS is advised (Grade B recommendation). Thyroid nodules that are hyperfunctioning on TUS are rarely malignant and do not require biopsy. However, these patients should be referred to a thyroid specialist for treatment.

Pathologic tissue diagnosis

The gold standard for diagnosis of a thyroid nodule is fine needle aspiration biopsy (FNAB). This technique allows for the acquisition of cells from the nodule in a minimally invasive manner. FNAB results are categorized into 6 classes: Class 1 – Nondiagnostic or insufficient specimen, Class 2 – Benign or negative for malignancy, Class 3 – Atypia, Class 4 – Follicular neoplasm, Class 5 – Suspicious, and Class 6 – Malignant.[30]

Combined with the US findings, the FNAB results will determine the treatment and follow-up for patients with thyroid nodules. Determining which thyroid nodules require FNAB is subject to some dispute, but is generally based on several factors, including history, size, and US characteristics.

Patients with a history of neck irradiation, prior thyroid cancer, or a family history of a genetic condition associated with thyroid cancer in a

first-degree relative are at increased risk for thyroid cancer.[31-33] Accordingly, a thyroid nodule of any size associated with these features should undergo FNAB (Grade B recommendation).

Previously, size was thought to play a significant role in the determination of malignancy with nodules less than 1 cm considered less likely to be malignant. However, recent studies have demonstrated that there is not necessarily a correlation between size and malignancy,[34,35] indicating that subcentimeter nodules may have the same malignant potential as larger ones.

However, with the current available evidence, recommendations cannot be made with certainty that all nodules less than 1 cm need immediate evaluation. Conversely, some nodules greater than 1 cm—such as those that are purely cystic—harbor a low risk for malignancy. However, given the challenges and inconsistencies with serially monitoring nodules in a patient population that may often relocate and seek care at multiple locations, FNAB is recommended for all thyroid nodules greater than 1 cm (Grade B recommendation).

More important than size in determining the malignant potential of a thyroid nodule are US characteristics. As stated above, US characteristics—including irregular shape, ill-defined border, solid echo structure, hypoechogenicity, lack of halo, calcifications, and intranodular vasculature—are associated with a higher risk of malignancy.[26,27] Although no signal characteristic is diagnostic, the presence of 2 or more of these US features significantly increases the risk of malignancy[27,36,37] and warrants biopsy (Grade B recommendation).

Many patients with solitary nodules on palpation will be found on US to have multiple nodules. In a patient with multiple nodules the likelihood of malignancy is similar to that of a solitary nodule.[28,38] The dominant nodules should be evaluated as individual nodules, according to the previously described criteria, with suspicious nodules being preferentially aspirated (Grade B recommendation).

FNAB can be performed by palpation or under US guidance. US-guided FNAB (USgFNAB) has demonstrated decreased error in tissue specimen collection over palpation-guided FNAB. Studies have demonstrated differences in sensitivities between palpation-guided FNAB vs USgFNAB of as much as 29% and differences in accuracy between the 2 sampling types of 3% to 20% favoring USgFNAB.[39-44] The extrapolated reasons for these significant differences include decreasing nondiagnostic samples, ensuring FNAB sampling is within the nodule, and the ability to evaluate multiple cysts or areas of different tissue within each nodule.

Nondiagnostic FNAB samples (Class 1) can be due to an inadequate sample number of cells, bloody smears, or improper slide preparation. Regardless of cause, a second aspiration should be conducted under US guidance (Grade A recommendation). Repeated aspirations are a common occurrence and do not necessarily speak to the skill of the laboratory or the technician performing the biopsy. Nodules that are nondiagnostic on multiple, repeated attempts should be referred for surgical evaluation (Grade A recommendation). Strong consideration for surgical excision should be made especially in cases of nodules with suspicious characteristics, as the rate of malignancy in nondiagnostic nodules can be as high as 7%.[45-47] Close follow-up is mandatory if surgical excision is not performed.

Repeated aspirations are a common occurrence and do not necessarily speak to the skill of the laboratory or the technician performing the biopsy.

Treatment and follow-up of patients with benign thyroid nodules

In the case of a benign tissue diagnosis on FNAB (Class 2), routine follow-up should be scheduled. All nodules require some follow-up, as even those found to be benign by FNAB have a 5% rate of false-negativity.[48,49] These patients should be re-evaluated in 6 to 18 months with repeat US (Grade A recommendation).[15,50] The decision as to when a patient should undergo repeat FNAB is under debate, and no current data suggest any specific size or percent change. The most recent guidelines suggest a 20% increase in size in 2 dimensions or 50% increase in volume,[15,16] as this has been shown to be the smallest change in nodule size on US that can be reliably reproduced.[51] Those lesions that have demonstrated growth should be re-aspirated by USgFNAB (Grade B recommendation). Additionally, any nodules with suspicious US characteristics that were

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previously not suspicious should undergo FNAB (Grade B recommendation). After initial follow-up within 6 to 18 months, if a nodule is stable, continuing follow-up can be less frequent (Grade C recommendation).

Questions over the administration of levothyroxine or other thyroid hormone analogues have led numerous studies to assess the validity of medical treatment of benign thyroid nodules. To date, current evidence does not support the use of thyroid hormone suppression for thyroid nodules in patients from areas where iodine intake is high or normal—as is the case for the United States (Grade D recommendation).[52-54] Although thyroid hormone suppression may result in a decrease in nodule size, this result is persistent only as long as thyroid hormone suppression is continued. Further, sustained thyroid hormone suppression in these patients is associated with adverse effects, such as decreased bone density in postmenopausal women and increased rates of atrial fibrillation.[55,56]

Treatment and follow-up of thyroid nodules with non-benign cytology

Patients whose FNAB results are suspicious (Class 5) or diagnostic for malignancy (Class 6) should be immediately referred to an experienced thyroid surgeon (Grade A recommendation). Except in rare cases where the risk of surgery outweighs the risk of the thyroid malignancy, these nodules should be surgically removed.

While most of these nodules are papillary thyroid carcinoma, others may be medullary thyroid carcinoma, poorly differentiated carcinoma, anaplastic thyroid carcinoma, metastatic carcinoma, and lymphoma. Specific details regarding the surgical treatment of these malignancies, including hemi- vs near-total vs total thyroidectomy, central or lateral neck dissection, and the use of postoperative ^{131}I treatment is a subject of much debate, particularly in the case of papillary thyroid carcinoma, and is well beyond the scope of this paper.

Thyroid nodules with indeterminate cytology present a diagnostic challenge. These results may be reported as "follicular neoplasm" or "Hurthle cell neoplasm" (Class 4), and have a 20% to 30% risk of malignancy.[30] Alternatively, these results may be reported as "follicular lesion" or "atypia of undetermined significance" (Class 3), which carries a 5% to 15% risk of malignancy.[30] It is reasonable to perform a repeat FNAB on nodules with Class 3 results as a more specific diagnosis will be obtained in 80% of cases.[57]

The use of molecular markers in thyroid cancer is an area of intense research. Multiple protein and genetic markers have been shown in prospective trials to improve diagnostic accuracy for indeterminate thyroid nodules.[58-60] However, this practice remains expensive and has not yet become standardized or common. Therefore, if available, molecular markers can be used but are not recommended in the routine workup of thyroid nodules with indeterminate cytology (Grade C recommendation).

^{18}FDG-PET scanning has been used with increasing frequency over the past decade in the diagnosis and treatment of a variety of malignancies. While its sensitivity for malignancy appears high, its low specificity, high cost, and variable results across studies have prevented the widespread use of ^{18}FDG-PET scanning in the evaluation of indeterminate thyroid nodules (Grade I recommendation).[61,62]

Because of the difficulty in determining which of these lesions is malignant prior to surgical removal, further evaluation by a physician specializing in the diagnosis and treatment of thyroid cancer is required for all thyroid nodules with indeterminate (Class 3 or Class 4) cytology (Grade A recommendation). Most of these lesions will ultimately be removed by thyroid lobectomy for definitive diagnosis. However, the ultimate decision to pursue surgery is one that is made between the patient and the surgeon, taking into account clinical risk factors, the patient's desire and motivation for surgery, and the patient's general health and comorbidities.

FUTURE CONSIDERATIONS

Medicine continually evolves and the evaluation and treatment of thyroid nodules will change in the future. As such, we would be remiss in our duties to not speak to the directions of the diagnostic endeavors for thyroid nodules. As previously stated, the use of molecular markers in thyroid cancer is an area of active research. It is likely that one day these markers will be used in the routine evaluation of thyroid nodules, particularly those with indeterminate cytology.

Advances in imaging will also likely assist in the evaluation of thyroid nodules. One such example is the use of magnetic resonance imaging in the diagnosis of thyroid carcinoma. Specifically, diffusion-weighted imaging shows promise for improved accuracy, sensitivity, and specificity in diagnosis of thyroid carcinoma but needs greater study.[63] Another example is the benefit to using ^{123}I TUS to guide FNAB in multinodular goiter over USgFNAB by decreasing the negative samples that are taken from "hot" nodules, as shown in recent studies.[64]

CONCLUSION

Thyroid nodules are a common finding on routine exam, neck imaging,

and autopsy. Whereas once they presented a significant diagnostic dilemma that was best left to a specialist or subspecialist, through diligent study and review, primary care practitioners can feel confident in following guidelines backed by strong evidence in the initial evaluation and management of these often benign lesions, and withhold the need for consult until a known surgical or oncological issue has fully presented.

Tests, such as the modern highly sensitive serum TSH measurements, and techniques, such as USgFNAB, move the practice of thyroid nodule evaluation firmly back into the hands of primary care practitioners, decreasing the workload and expense to an already taxed system. Following the guidelines should result in rapid, practical, and accurate diagnosis of benign thyroid nodules and malignant thyroid disease early with optimal results for our veterans.

Author disclosures

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