CLINICAL PRACTICE

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Thyroid Nodules

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This *Journal* feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A 40-year-old woman presents with a thyroid nodule, 2.0 cm by 2.0 cm on palpation. The nodule, located on the right side of the gland, was found on routine physical examination. She has no history of childhood radiation exposure or family history of thyroid abnormalities. She reports no symptoms of nervousness, weight loss, palpitation, fatigue, or neck discomfort. Ultrasonography confirms a thyroid nodule, 2.0 cm by 2.0 cm by 2.5 cm (volume, 5.23 cm^3), on the right side of the gland that does not have ultrasonographic characteristics associated with an increased risk of cancer; there is no cervical adenopathy. How should her case be managed?

THE CLINICAL PROBLEM

Palpable thyroid nodules occur in approximately 4 to 7% of the population, but only about 8 to 16% of thyroid nodules harbor thyroid cancer.[1-6] Ultrasonography of the thyroid is more sensitive than palpation and detects thyroid nodules in 19 to 67% of the population among persons without suspected thyroid disease[7]; in one study, ultrasonography revealed nodules in 67 of 100 asymptomatic persons (22 of those screened had a solitary nodule and 45 had multiple nodules).[8]

The differential diagnosis of an apparent thyroid nodule includes thyroidal and nonthyroidal conditions. Subacute thyroiditis and chronic lymphocytic thyroiditis may result in a nodular appearance; in rare cases, infiltrative disorders (e.g., hemochromatosis) or a metastatic tumor, parathyroid cyst, lipoma, or paraganglioma can mimic a thyroid nodule.[9] Risk factors for thyroid cancer[10-14] are reviewed in Table 1; the frequency of nodules increases with age.[1] The natural history of thyroid nodules is variable, but the majority of benign nodules remain relatively stable in size.[15] In a prospective, multicenter, observational study involving 992 patients who had a thyroid nodule with benign cytologic findings on fine-needle aspiration and who were followed for 5 years, 15% of patients had an increase in nodule size (mean change in the largest diameter, 4.9 mm), and 19% had a decrease.[15] Thyroid cancer was identified in five (0.3%) of the original nodules, of which only two had increased in size.

STRATEGIES AND EVIDENCE

PERTINENT HISTORY AND PHYSICAL EXAMINATION

Figure 1 provides an algorithm to address thyroid nodules. An appropriate history includes questions relating to a history of head or neck irradiation and a family history of thyroid cancer. Rapid growth of a thyroid nodule may suggest the pres-

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KEY CLINICAL POINTS

THYROID NODULES

- Thyroid nodules are common; the majority are benign.
- Thyroid ultrasonographic characteristics and especially the results of ultrasonographically guided fine-needle aspiration are helpful in determining whether a nodule is likely to be benign or malignant.
- The risk of cancer is approximately 14% for a thyroid nodule that is interpreted as atypia of undetermined significance or follicular lesion of undetermined significance and approximately 25% for a nodule that is interpreted as follicular neoplasm or possible follicular neoplasm. Such nodules should be considered for molecular analysis.
- In the absence of growth or suspicious clinical or radiologic findings, thyroid nodules with a benign finding on fine-needle aspiration can be managed by observation.
- Patients whose fine-needle aspirates are interpreted as "suspicious for malignancy" or as malignant should be referred for a thyroidectomy.

ence of a thyroid cancer, although it may also occur from hemorrhage into a benign thyroid nodule or cyst.

Recent onset of hoarseness may be due to tumor invasion of the recurrent laryngeal nerve. Dysphagia or anterior neck discomfort may suggest a malignant nodule, although these symptoms may also occur with a benign nodule. A family or personal history of thyroid cancer, breast cancer, or colon cancer may suggest Cowden's syndrome,[16] as may a history of skin, tongue, or mucosal small nodules (i.e., hamartomas) or of macrocephaly.[16] In rare cases, a thyroid nodule may reflect one of the hereditary nonmedullary thyroid cancer syndromes such as familial adenomatous polyposis, Werner's syndrome, Carney complex type 1, or Gardner's syndrome.[17,18] A history of papillary thyroid cancer in at least one first-degree family member is associated with an increased risk of a nodule being malignant.[19-21]

Physical examination should focus on the thyroid gland and the lateral and central neck and should assess for supraclavicular and submandibular adenopathy. Nodules that are firm or immobile are more likely to harbor cancer than those that are soft or mobile. Large, firm cervical nodes ipsilateral to the thyroid nodule should suggest the possibility of local metastases from thyroid cancer.

Table 1. Clinical Findings Associated with an Increased Risk That a Thyroid Nodule Is Malignant.*

History of differentiated thyroid cancer in at least one first-degree relative
History of external-beam radiation or exposure to ionizing radiation as a child or adolescent
Prior tissue or cytologic diagnosis of thyroid carcinoma
Male sex
Focal uptake of ^{18}F-fluorodeoxyglucose by the thyroid
Personal or family history of multiple endocrine neoplasia type 2 or familial medullary thyroid cancer
Serum calcitonin level >50 to 100 pg/ml
Residence near a nuclear-reactor accident

* Adapted with permission from the American Thyroid Association (ATA) guidelines.[4]

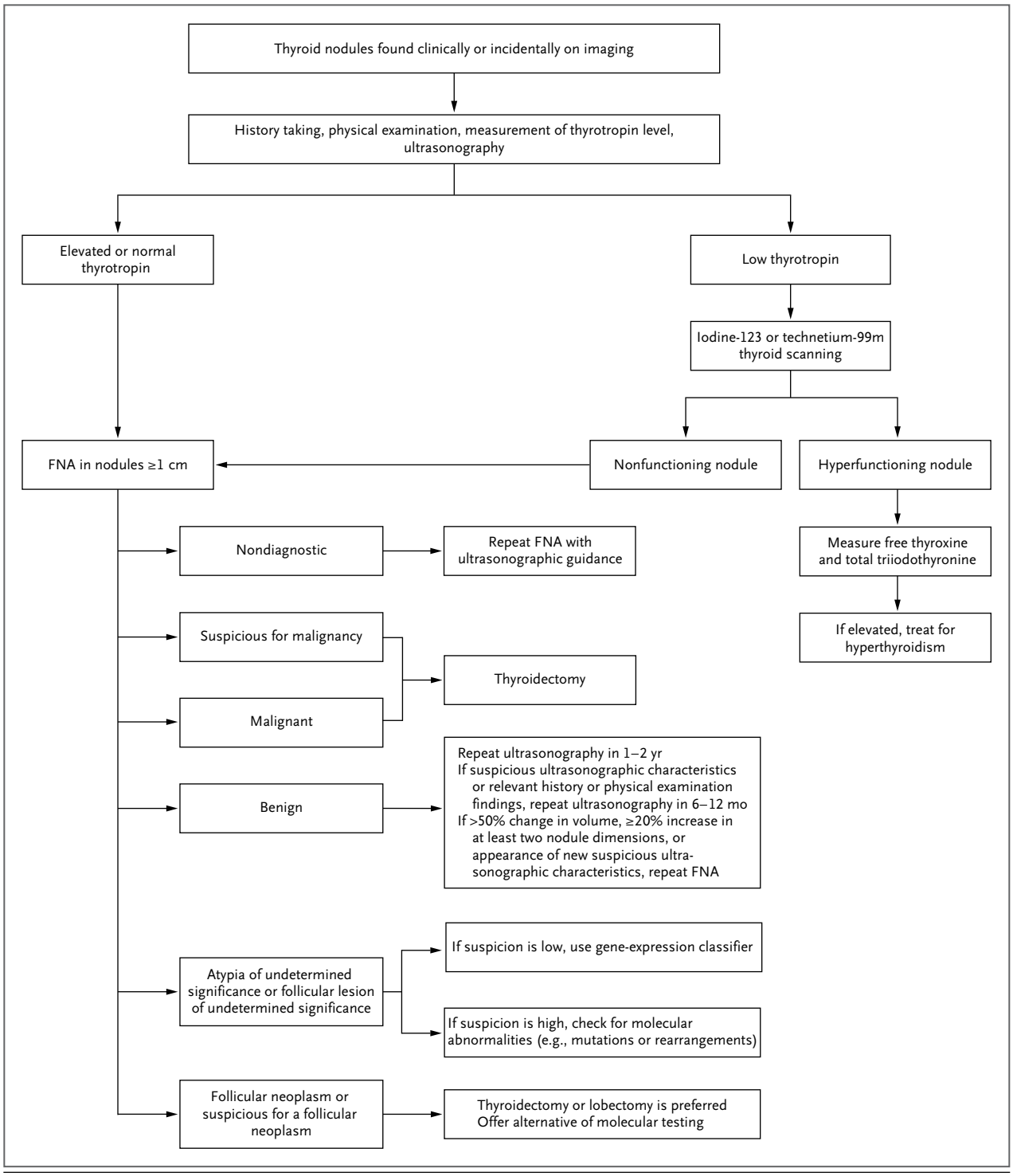
LABORATORY STUDIES

Serum thyrotropin levels should be measured routinely in a person with a thyroid nodule. A low

Figure 1 (facing page). Algorithm for Evaluation of Thyroid Nodules.

This algorithm is devised mainly for thyroid nodules 1 cm or larger in greatest dimension and is for general application; decision making depends on clinical and radiologic-imaging risk stratification. The 2015 American Thyroid Association guidelines[13] recommend fine-needle aspiration (FNA) for nodules 1 cm or larger with a high- or intermediate-suspicion pattern on sonography, nodules 1.5 cm or larger with a low-suspicion pattern on sonography, and nodules 2 cm or larger with a very-low-suspicion pattern on sonography. Cervical lymph nodes with suspicious features should be aspirated.[13] In a multinodular gland, nodules 1 cm or larger carry an independent risk of cancer, and the same recommendations apply regarding when to perform FNA.[13] If a gene-expression classifier suggests a benign lesion in a patient with a low suspicion for cancer, the patient can usually be monitored closely; if the findings of the gene-expression classifier are suspicious, the risk of cancer depends on many factors, including the pretest probability of cancer. In this case, the decision for surgery or monitoring must take into account the entire clinical context. In a patient who has a nodule that has a high suspicion of being cancerous, if specific mutations (e.g., *BRAF* or *RAS* mutations) are present, a total thyroidectomy is recommended; if no specific mutations are noted, the decision for a thyroidectomy or monitoring depends on the entire clinical context.

or undetectable level suggests a hyperfunctioning nodule. In a euthyroid patient, routine measurement of thyroid peroxidase or thyroglobulin antibodies is not indicated.[4] Serum thyroglobulin measurement is not useful in evaluating a nodule. Routine measurement of serum calcitonin has been suggested for the early detection of medullary thyroid carcinoma but is not recommended in the American Thyroid Association (ATA) guidelines.[4,13,22-24]



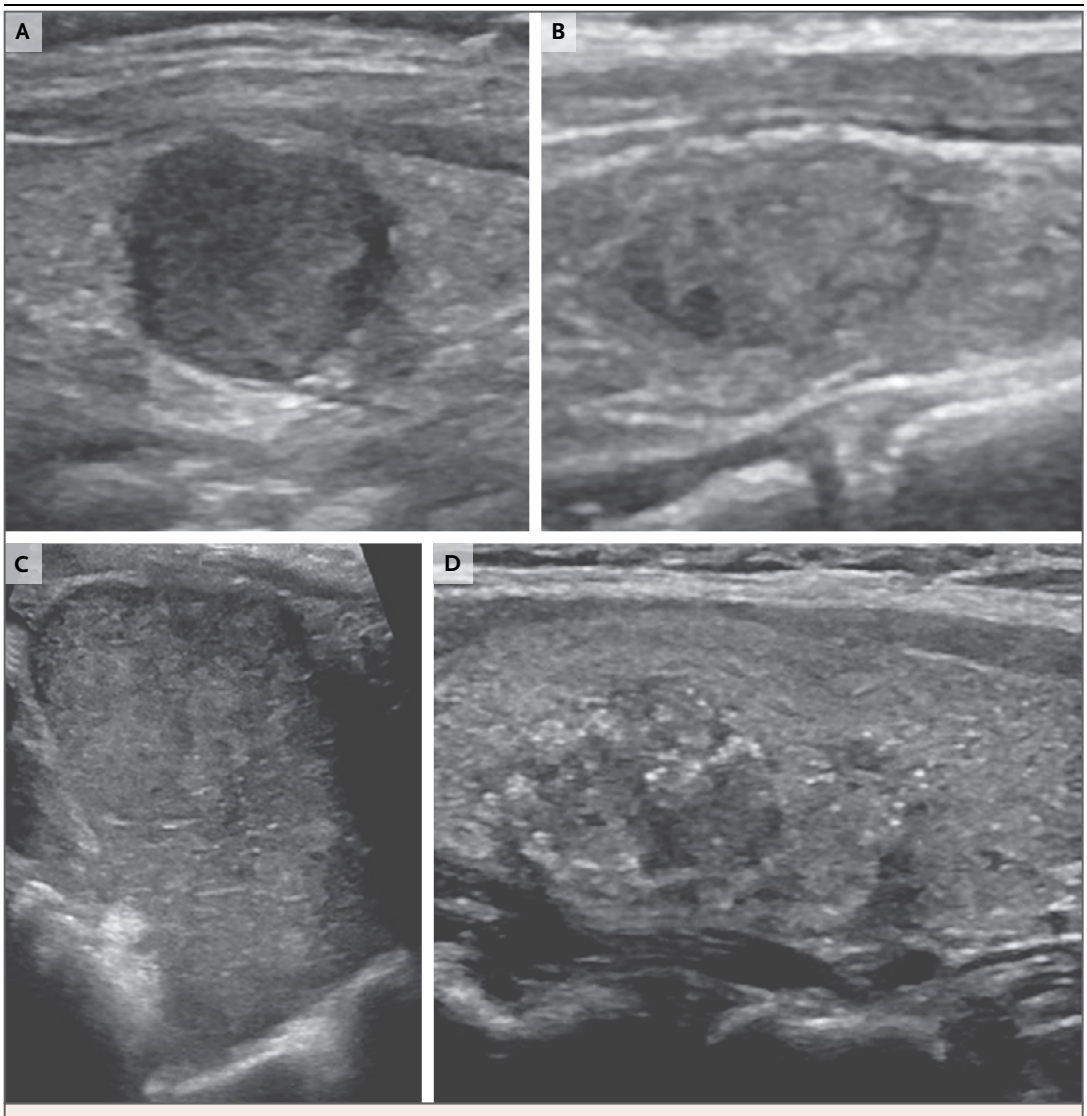


Figure 2. Ultrasonographic Images of Thyroid Nodules.

Panel A shows a papillary thyroid carcinoma with hypoechogenicity. The other panels show nodular features that raise suspicion for cancer. Panel B shows a thyroid nodule with blurred or indistinct margins. Panel C shows a nodule that is higher (2.5 cm) than it is wide (1.6 cm). Panel D shows a nodule with microcalcifications.

IMAGING STUDIES

All patients should undergo ultrasonography of the thyroid to document the number, size, and characteristics of thyroid nodules and to assess for the presence of cervical lymphadenopathy.[4] Ultrasonographic nodular features that may suggest cancer[25,26] are shown in Figure 2, and in Figure S1 and Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. Additional imaging (e.g., magnetic resonance imaging or computed tomography) is not routinely indicated except when features of aggressive thyroid cancer (e.g., extensive adenopathy or tracheal invasion) are suggested. A radioisotopic (iodine-123 or technetium-99m) scan with measurement of radioisotope uptake to confirm autonomous function is indicated only if the thyrotropin level is suppressed.

FINE-NEEDLE ASPIRATION OF THE THYROID

Fine-needle aspiration, preferably performed under ultrasonographic guidance, is the most sensitive and cost-effective method to assess the nature of thyroid nodules and the need for surgery.[27] The number of needle passes recom-

mended is two to five.[28] Immediate cytologic evaluation is helpful to ensure adequate specimens. The 2015 ATA guidelines[13] (Table S1 in the Supplementary Appendix) recommend fine-needle aspiration for nodules 1 cm or larger in the greatest dimension that have a high- or intermediate-suspicion pattern on sonography, nodules 1.5 cm or larger that have a low-suspicion pattern on sonography, and nodules 2 cm or larger that have a very-low-suspicion pattern on sonography. Cervical lymph nodes with suspicious features should be aspirated.[13] In a multinodular gland, nodules 1 cm or larger carry an independent risk of cancer, and the same recommendations apply regarding when to perform fine-needle aspiration.[13]

Fine-needle aspiration samples should be interpreted by an experienced cytologist according to the Bethesda classification system[29] (Fig. 3 and Table 2). If the cytologic findings are interpreted as nondiagnostic, fine-needle aspiration should be repeated within 1 to 2 months in an effort to obtain sufficient cells for a more definitive diagnosis. A benign cytologic interpretation indicates a low likelihood of cancer and generally does not require repeat fine-needle aspiration unless suspicious features (e.g., increasing nodular size or enlarging cervical adenopathy) are noted during monitoring.[13,31] However, false negative cytologic results occur in approximately 5 to 10% of cases overall, with higher rates reported for large nodules (11.7% for nodules ≥3 cm vs. 4.8% for those <3 cm) (see the Management section, below).[30-32] Nodules with cytologic findings that are interpreted as malignant or "suspicious for malignancy" have a 94 to 100% and 53 to 97% chance, respectively, of being malignant (usually papillary thyroid cancer)[13,30] (Table 2). Indeterminate nodules present a special problem in management.

MOLECULAR ANALYSIS OF THYROID FINE-NEEDLE ASPIRATION

Molecular analysis (in a laboratory that is accredited by the College of American Pathologists and certified according to the Clinical Laboratory Improvement Amendments) should be considered in the case of thyroid fine-needle aspiration results that are interpreted as atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS) or follicular neoplasm or suspicious for a follicular neoplasm (FN/SFN). Patients with cytologic results interpreted as "suspicious for malignancy" should, in general, be referred directly for thyroid lobectomy or total thyroidectomy. One molecular approach is to analyze the specimen by means of a gene-expression classifier to rule out cancer. In a report that assessed messenger RNA expression of 167 genes from fine-needle aspiration samples from nodules 1 cm or larger in diameter that were interpreted as indeterminate, the negative predictive value of the gene-expression classifier was 95% for AUS/FLUS and 94% for FN/SFN, and the positive predictive value was 38% for AUS/FLUS and 37% for FN/SFN.[33] These results suggest that, in general, patients with AUS/FLUS or FN/SFN whose results are negative on this molecular analysis can reasonably be monitored without immediate thyroidectomy.

An alternative molecular approach is to directly assess the fine-needle aspirate for specific genetic abnormalities associated with thyroid cancer (including *BRAF* and *RAS* mutations, *RET/PTC* translocation and *TERT* promoter mutations for papillary thyroid cancer, and *RAS* and *PIK3A* mutations and *PAX8–PPARγ* translocation for follicular thyroid cancer).[12,34] When applied to nodules interpreted as AUS/FLUS or FN/SFN, mutational analysis indicates cancer in approximately 20 to 40% of fine-needle aspiration samples, with a positive predictive value of 87 to 88% and a negative predictive value of 86 to 94%.[12,35] If the sample is positive for a *BRAF* mutation, the chance of cancer is close to 100%,[36] and if the sample is positive for a *RAS* mutation, the chance of cancer is 80 to 90%.[12] A mutational analysis may be helpful in the case of nodules classified as "suspicious for malignancy" to confirm the diagnosis and to aid in surgical planning (i.e., lobectomy vs. total thyroidectomy, with or without central lymph-node dissection), although data are lacking to determine the effect of this additional information on outcomes. Adding to the complexity of management, the interpretation of a thyroid fine-needle aspiration may be poorly reproducible between cytologists,[37] and the most effective use of molecular testing remains uncertain.

MANAGEMENT

Although the cornerstone of the management of a thyroid nodule is the cytologic findings on fine-needle aspiration, these findings should be considered in the context of the clinical and ultrasonographic findings. When a sample is

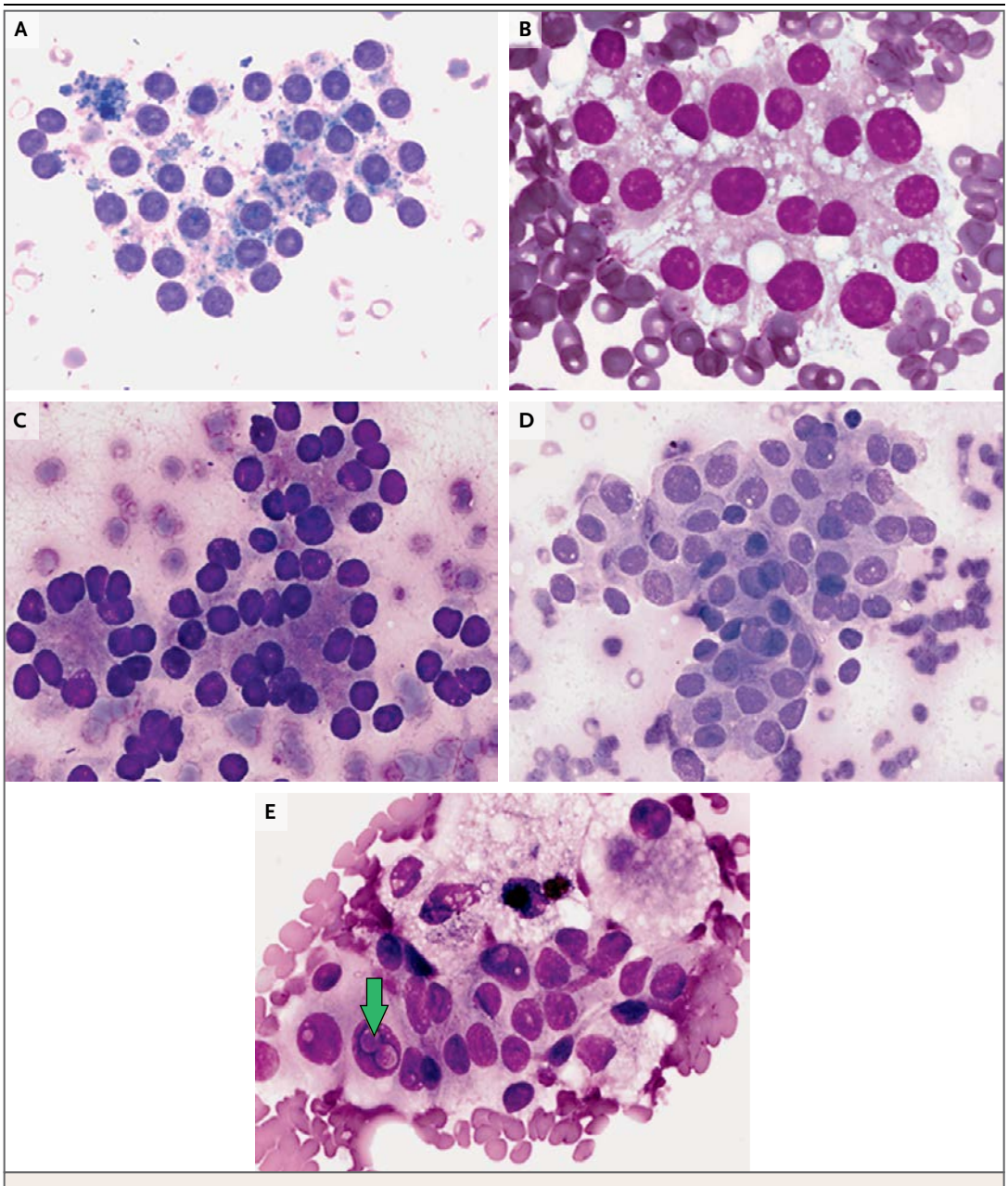


Figure 3. Thyroid Fine-Needle Aspiration Specimens.

The figure shows nodules in five different categories of the Bethesda System for Reporting Thyroid Cytopathology.[29] Panel A shows a benign nodule. The thyroid follicular cells are evenly spaced and have a small and uniform nuclear size. Panel B shows atypia of undetermined significance. In an otherwise benign aspirate, rare groups of follicular cells show nuclear enlargement. The patient underwent a thyroidectomy, and final pathological analysis showed benign nodular hyperplasia. Panel C shows a follicular neoplasm. Smears contain a cellular aspirate with only scant colloid. The follicular cells are of normal size but form microfollicles (abnormal architecture). Final pathological analysis showed follicular adenoma. Panel D shows a nodule "suspicious for malignancy" (papillary carcinoma). Aspirate shows some features of papillary carcinoma, such as hypercellularity, nuclear enlargement, hyperchromasia, and an increased nuclear-to-cytoplasmic ratio. However, no definitive nuclear pseudoinclusions were identified. Thyroidectomy was performed, and the final pathological analysis showed a follicular variant of papillary carcinoma. Panel E shows a malignant nodule (papillary carcinoma). Smears show a cellular aspirate with numerous abnormal follicular cells containing enlarged hyperchromatic nuclei. Nuclear pseudoinclusions are present (arrow).

adequate and is evaluated by an experienced cytologist who documents a benign finding on fine-needle aspiration and there are no suspicious clinical or ultrasonographic findings, we generally recommend repeat ultrasonography in 1 to 2 years (assuming that no apparent growth or concerning clinical findings are noted earlier). A recent study involving follow-up of more than 2000 cytologically benign nodules, however, suggested that a longer time interval of 2 to 4 years may be reasonable.[38] For cases with suspicious sonographic features, an indeterminate fine-needle aspirate, or relevant adverse clinical history or physical examination findings, it is reasonable to perform repeat imaging earlier, in 6 to 12 months. If there is evidence of nodule growth (>50% change in volume or ≥20% increase in at least two nodule dimensions with an increase of ≥2 mm), a repeat fine-needle aspiration is recommended.[4] It is important to measure all three nodule dimensions, to calculate the nodule volume, and to compare the results with those of the previous and initial ultrasonograms.

When evaluation has failed to achieve a definitive characterization of the nodule as either benign or malignant, management options include either continued close monitoring or a thyroidectomy. There is no role for thyroid hormone treatment for a biochemically euthyroid patient who has a benign nodule.

A total thyroidectomy is generally recommended in the following situations: the nodule has a specific oncogene abnormality with a high positive predictive value for cancer (e.g., *BRAF* mutation); the fine-needle aspirate is interpreted as malignant or "suspicious for malignancy"; there is bilateral nodular disease with an indication for surgery in at least one nodule; there is a history of radiation to the head or neck during childhood or adolescence or a family history of thyroid cancer; or the nodule is larger than 4 cm in diameter. Total thyroidectomy should also be considered in patients who do not meet any of these criteria but who have clinically significant cardiorespiratory disease or other coexisting conditions, in order to avoid the possible need for a second procedure (completion thyroidectomy). Total thyroidectomy is best performed by an experienced thyroid surgeon in a comprehensive care medical center.[39] When patients undergo total thyroidectomy, they incur small risks of permanent hypocalcemia (approximately 0.2 to 1.9%) and voice change owing to damage to the recurrent laryngeal nerve (0.4%).[39,40] Lifelong exogenous levothyroxine therapy (with periodic monitoring) is required in all patients who have undergone a total thyroidectomy as well as in many patients who have undergone thyroid lobectomy.[41]

Table 2. Diagnostic Categories of Thyroid Nodules and Risk of Cancer.*

Diagnostic Category†	Percent Risk of Cancer‡
	median (range)
Nondiagnostic or unsatisfactory	20 (9–32)
Benign	2.5 (1–10)
Atypia of undetermined significance or follicular lesion of undetermined significance	14 (6–48)
Follicular neoplasm or suspicious for a follicular neoplasm	25 (14–34)
Suspicious for malignancy	70 (53–97)
Malignant	99 (94–100)

* Adapted with permission from the 2015 ATA guidelines.[13]
† The categories are those of the Bethesda System for Reporting Thyroid Cytopathology.[29]
‡ Values are based on the meta-analysis of eight studies reported by Bongiovanni et al.[30] The risk was calculated on the basis of the number of nodules in each diagnostic category that were surgically excised, and the time between thyroid fine-needle aspiration and surgery can vary among individual cases and among studies. In our review of the published literature, the false negative rate of a nodule with a benign finding on fine-needle aspiration is about 5 to 10%.[30-32] The false negative rate of a thyroid fine-needle aspiration depends on multiple factors, including the adequacy of the sample obtained, the experience of the cytologist, and the size of the nodule.

AREAS OF UNCERTAINTY

Although the ATA guidelines recommend fine-needle aspiration only for nodules that are 1 to 2 cm or larger in the greatest dimension, further evaluation of smaller nodules may be warranted in the presence of suspicious ultrasonographic or clinical findings,[13] although it is not known whether this approach results in improved outcomes. Whether large thyroid nodules (e.g., >4 cm) should be considered for surgery even in the context of a benign finding on fine-needle aspiration is controversial. In one report,[42] the risk of cancer (mainly papillary thyroid cancer) did not increase consistently with increasing nodule size, although among malignant nodules, the proportion with follicular cancer increased with nodule size. However, a study of a series of patients with nodules 4 cm or larger who were

undergoing fine-needle aspiration and surgery suggested that larger nodules were associated with an increased risk of cancer, even in the absence of suspicious ultrasonographic features.[43]

For nodules that are cytologically indeterminate on biopsy, questions remain regarding whether to perform molecular analysis and which molecular test to use in various circumstances. The use of next-generation sequencing or whole-genome sequencing, including the use of microRNA, has been proposed as a means of better distinguishing between benign and malignant nodules,[44,45] but more data are needed to inform the role of these methods in practice.

For thyroid nodules with benign findings on fine-needle aspiration, there is uncertainty regarding the appropriate frequency of follow-up ultrasonography; whether repeat fine-needle aspiration is indicated is also controversial, though this has been suggested for nodules with clinically or sonographically suspicious features.[46-48]

Concern has been raised about the overdiagnosis and overtreatment of thyroid nodules and thyroid cancer and about the clinical significance of incidentally discovered papillary microcarcinoma, which may have a biologically indolent behavior.[49] A case series showing favorable outcomes without surgical intervention among patients with small nodules without worrisome features, but suggestive or diagnostic of papillary cancer on fine-needle aspiration, suggests that this approach may suffice in lieu of more aggressive management, although confirmatory data are needed.[49,50]

GUIDELINES

The ATA has published guidelines for the evaluation and management of thyroid nodules, and these guidelines were updated recently.[13] The guidelines suggest that molecular testing may be useful after consideration of clinical and radiologic findings and after a discussion with the patient regarding the advantages and disadvantages of such an approach.[13] The recommendations in the current article are generally concordant with the ATA guidelines and with a separate set of guidelines from the American Association of Clinical Endocrinologists–Associazione Medici Endocrinologi–European Thyroid Association.[24] The latter guidelines differ from the ATA guidelines[13] in recommendations for repeat fine-needle aspiration; largely on the basis of expert opinion, these guidelines suggest that repeat fine-needle aspiration may be performed in 6 to 18 months in selected patients who have an initial benign finding on fine-needle aspiration. These guidelines also suggest that on initial evaluation, nodules considered to be suspicious on historical or sonographic grounds should be considered for aspiration if they are less than 10 mm in diameter.[24]

CONCLUSIONS AND RECOMMENDATIONS

The discovery of a thyroid nodule, as in the woman described in the vignette, should prompt a careful history taking and physical examination, measurement of thyrotropin levels, and an ultrasonographic examination. Nodule size, clinical context, and ultrasonographic characteristics guide the decision to perform fine-needle aspiration. Fine-needle aspiration is indicated in the patient described in the vignette on the basis of the nodule size (≥2 cm in greatest dimension), even in the absence of suspicious characteristics; when suspicious ultrasonographic characteristics are present, fine-needle aspiration is recommended for nodules 1 cm or larger. The fine-needle aspirate should be interpreted by an experienced cytopathologist according to the Bethesda classification system.[29] If the aspirate shows benign cytologic features, we would generally recommend repeating thyroid ultrasonography in approximately 1 to 2 years to ensure that there has been no clinically significant growth. In the absence of growth or suspicious clinical or sonographic findings, we would generally not repeat the thyroid fine-needle aspiration.

If the cytologic findings are indeterminate, a second review by an experienced cytologist may be useful; options for management include a repeat fine-needle aspiration in 6 to 12 months or mutational analysis or molecular profiling to better estimate the risk of cancer. In selected circumstances, surgery may be indicated. Although long-term outcome trials are required to better inform the use of these ancillary tests, we would tend to use a gene-expression classifier (which has a high negative predictive value and high sensitivity) if there is low suspicion for cancer and to consider mutational analysis (which

has a high positive predictive value and high specificity) if the clinical or radiologic features raise suspicion for cancer and the likelihood of referral for thyroidectomy is higher. Alternatively, the patient could proceed to diagnostic surgery, if she is uncomfortable with the uncertainty associated with watchful waiting and depending on her personal preferences. If further testing is performed but is inconclusive, diagnostic lobectomy is often reasonable; however, nodules with more suspicious findings on cytologic analysis may justify total thyroidectomy, depending on the estimated risk of cancer, the experience and skill of the surgeon, and the patient's preference.

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