RadioGraphics

US-guided Fine-Needle Aspiration of Thyroid Nodules: Indications, Techniques, Results[1]

CME FEATURE

See accompanying test at http://www.rsna.org/education/rg_cme.html

LEARNING OBJECTIVES FOR TEST 2

After reading this article and taking the test, the reader will be able to:

- Recognize the indications for US-guided fine-needle aspiration biopsy of thyroid nodules.
- Describe the US-guided biopsy procedure and the factors that may limit material adequacy and lead to false-negative results.
- Correlate the results of cytologic analysis with the imaging findings.

TEACHING POINTS

See last page

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Fine-needle aspiration (FNA) biopsy of thyroid nodules is minimally invasive and safe and is usually performed on an outpatient basis. However, the optimal application of FNA requires not only technical skill but also an awareness of the limitations of the procedure, the indications for its use, the factors that affect the adequacy of the biopsy specimen, and the postprocedural management strategy. Ultrasonographic (US) features that are considered indications for FNA include single and multiple thyroid nodules. The results of FNA biopsy are operator dependent. In addition, the results may be affected by the lesion characteristics, the accuracy of lesion and needle localization, the method of guidance, the number of aspirated samples, the needle gauge, the aspiration technique, and the presence or absence of on-site facilities for immediate cytologic examination. With regard to postprocedural management, nodules that are diagnosed as benign on the basis of an adequate FNA specimen should be monitored with follow-up US. Circumstances that necessitate repeat FNA include sample inadequacy, nodule enlargement, cyst recurrence, or clinical or imaging findings that arouse suspicion about the presence of a malignancy even when cytologic findings in the biopsy specimen indicate benignity. Supplemental material available at *radiographics.rsnajnls.org/cgi/content/full/28/7/1869/DC1*.

Abbreviation: FNA = fine-needle aspiration

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See the commentary by Wong-You-Cheong following this article.

Introduction

Fine-needle aspiration (FNA) biopsy of thyroid nodules is a minimally invasive and safe procedure that is usually performed on an outpatient basis (1). Either palpation or ultrasonography (US) may be used for guidance of FNA, but US has several advantages over palpation (2,3). Real-time US permits visualization of the needle within the lesion, thereby facilitating accurate biopsy of small nonpalpable nodules (3). Even in palpable thyroid nodules, US guidance is superior to palpation for obtaining adequate material for an accurate cytologic evaluation (3). However, the achievement of optimal results of thyroid FNA, with increased efficacy and decreased inadequacy rates, requires not only a skillful aspiration technique and attention to the factors that affect material adequacy but also awareness of the indications for and limitations of FNA biopsy and a strategy for postprocedural management. The purpose of this article is to describe the indications and techniques for US-guided FNA biopsy of thyroid nodules; factors affecting material adequacy; interpretation of cytologic results; and appropriate follow-up strategies.

Indications

Nodular Lesion

Traditionally, the main indication for FNA biopsy of the thyroid has been the presence of a solitary nodule. The Society of Radiologists in Ultrasound suggested that FNA should be considered for a nodule 1.0 cm or more at the largest diameter if microcalcifications are present and for a nodule 1.5 cm or larger if the nodule is solid or if there are coarse calcifications within the nodule (4). The American Association of Clinical Endocrinologists recommended FNA even for nodules smaller than 10 mm whenever clinical information or US features arouse suspicion about the presence of a malignancy (5). Recent literature indicates that patients with multiple thyroid nodules have the same risk of malignancy as patients with solitary thyroid nodules (6,7). Frates et al reported that in cases of multiple thyroid nodules the risk of an individual nodule being cancerous is decreased but that the prevalence of thyroid cancer does not differ between patients with a solitary nodule and patients with multiple nodules (8). Therefore, in the presence of multiple nodules, FNA is indicated. However, before the procedure is performed, a meticulous search should be conducted with US for suspicious features. The US features that are suggestive of malignancy include microcalcifications, marked hypoechogenicity, an irregular or microlobulated margin, a longitudinal dimension larger than the cross-sectional dimension, intrinsic vascularity, direct tumor invasion of adjacent soft tissue, and metastasis to one or more lymph nodes (9–11) (Fig 1).

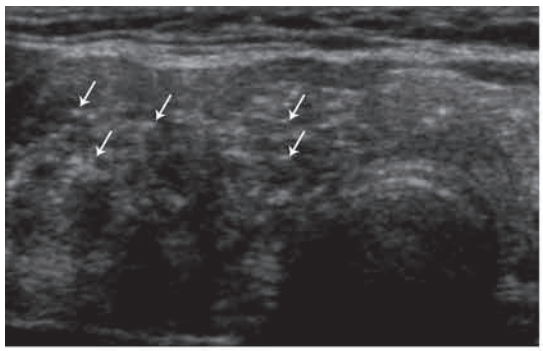
US characteristics are more useful than nodule size for identifying nodules that are likely to be malignant (6,12) (Fig 2). If only the dominant or largest nodule in a case of multiple nodules is aspirated, a thyroid cancer may be missed. Diagnostic US therefore should be performed to characterize all thyroid nodules.

Teaching Point

Diffuse Lesion

Among patients with autoimmune diseases such as Hashimoto thyroiditis, the rate of thyroid malignancy is similar to that among patients with a nonsymptomatic thyroid gland. In cases in which Hashimoto thyroiditis manifests as a nodular lesion mimicking a thyroid neoplasm, FNA must be performed to rule out lymphoma and papillary carcinoma, either of which may coexist with Hashimoto thyroiditis (13,14) (Fig 3). FNA

Figures 1, 2. Nonpalpable thyroid lesions with US characteristics of malignancy. **(1)** Transverse **(a–c, e–g)** and longitudinal **(d, h)** US images show an incidentally detected thyroid lesion with the following malignant characteristics: microcalcifications (arrows in **a**); marked hypoechogenicity **(b)**; irregular or microlobulated margins (arrowheads in **c** and **d**); height that exceeds width **(e)**; intrinsic vascularity (arrows in **f**); direct invasion of adjacent soft tissue (arrowheads in **g**); and metastasis to a lymph node (arrows in **h**) with cystic change (∗ in **h**). **(2)** Longitudinal **(a)** and transverse **(b)** US images obtained in a 47-year-old woman with a palpable thyroid mass show a 2.5-cm well-circumscribed isoechoic mass (∗ in **a**) in the left thyroid lobe, a finding suggestive of a benign nodule. At the superior aspect of the nodule, an 0.8-cm nonpalpable hypoechoic mass, with a height exceeding its width (arrow in **b**), is visible. The diagnoses at FNA biopsy were papillary carcinoma in the nonpalpable mass and adenomatous hyperplasia in the palpable mass. The surgical stage of the carcinoma was T3N1b because of extrathyroidal extension and metastasis to a level 2 lymph node.



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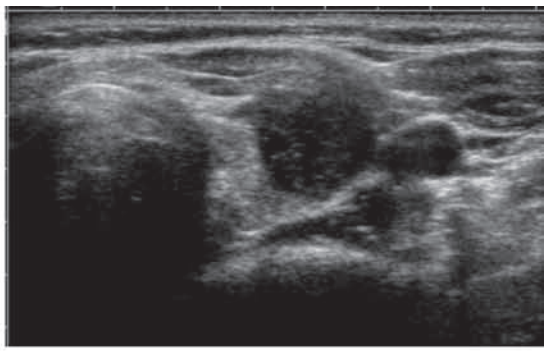

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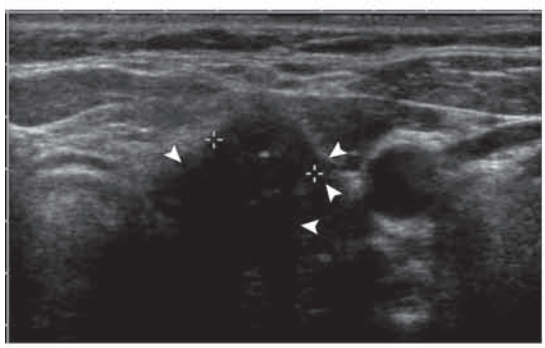

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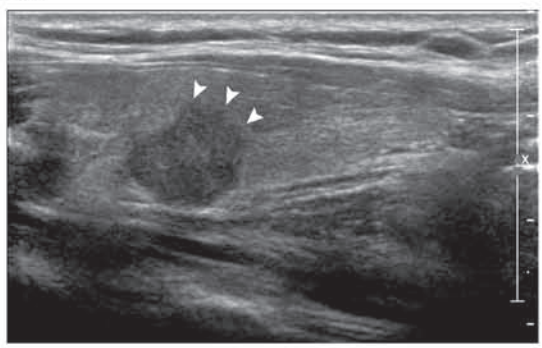

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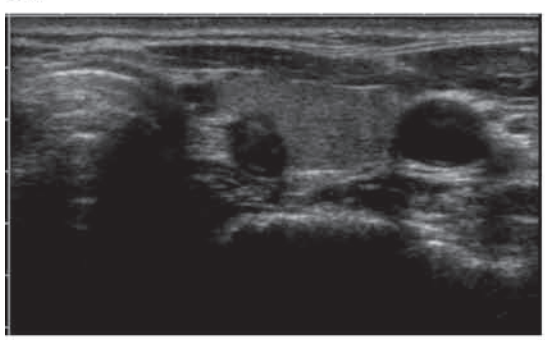

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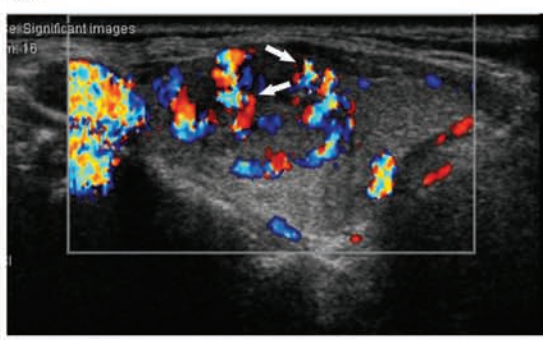

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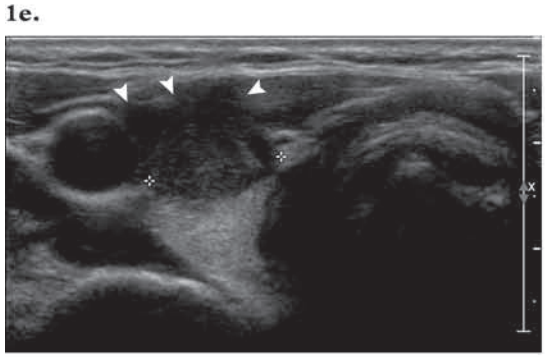

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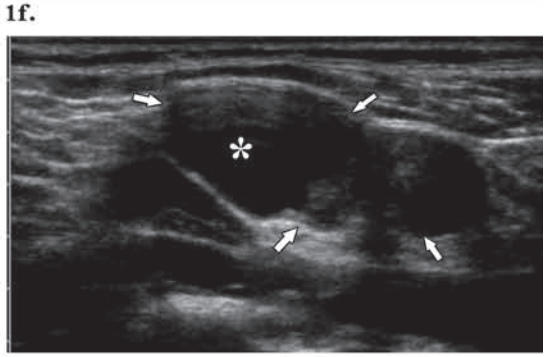

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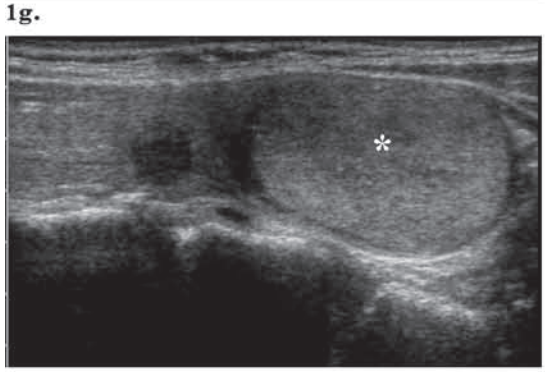

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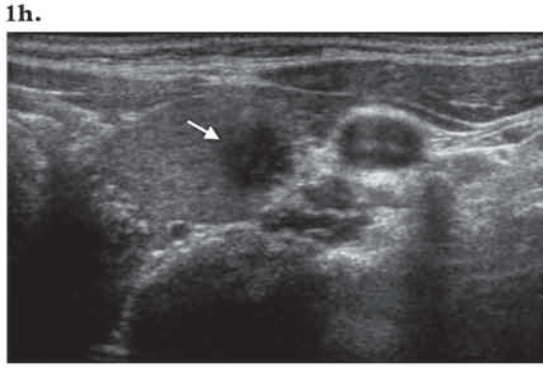

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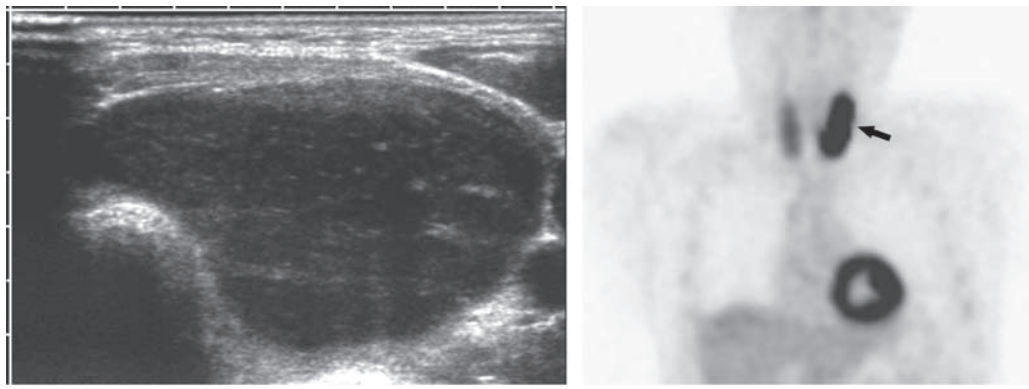

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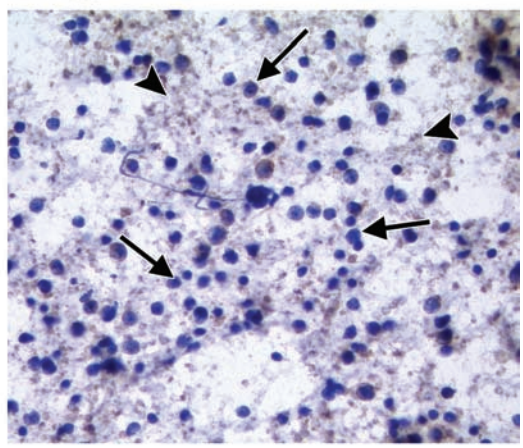


c.

Figure 3. Rapidly growing mass in the left thyroid lobe of a 57-year-old man with chronic Hashimoto thyroiditis. **(a)** Transverse US image shows a diffusely enlarged and heterogeneously hypoechoic thyroid gland. **(b)** Coronal PET scan shows increased uptake of fluorine 18 fluorodeoxyglucose in the left thyroid lobe (arrow). **(c)** Photomicrograph (original magnification, ×200; toluidine blue stain) from immunohistochemical analysis of an FNA biopsy specimen with staining for CD20 antigen shows B-cell lymphocytes (arrows) against a background of cellular debris (arrowheads), findings characteristic of diffuse large B-cell lymphoma.

is also required in cases of diffuse rapid enlargement of the thyroid gland, especially in patients older than 50 years, to rule out anaplastic carcinoma, metastasis (Fig 4), and lymphoma (15).

High Risk of Thyroid Cancer

The threshold for biopsy of a thyroid nodule in a patient with one or more risk factors for thyroid cancer is lower than that for biopsy in a patient without such risk factors. Risk factors for thyroid cancer include a family history of thyroid cancer, a history of head and neck irradiation, male sex, age of less than 30 years or more than 60 years, and a previous diagnosis of type 2 multiple endocrine neoplasia (10).

Review of FNA Results

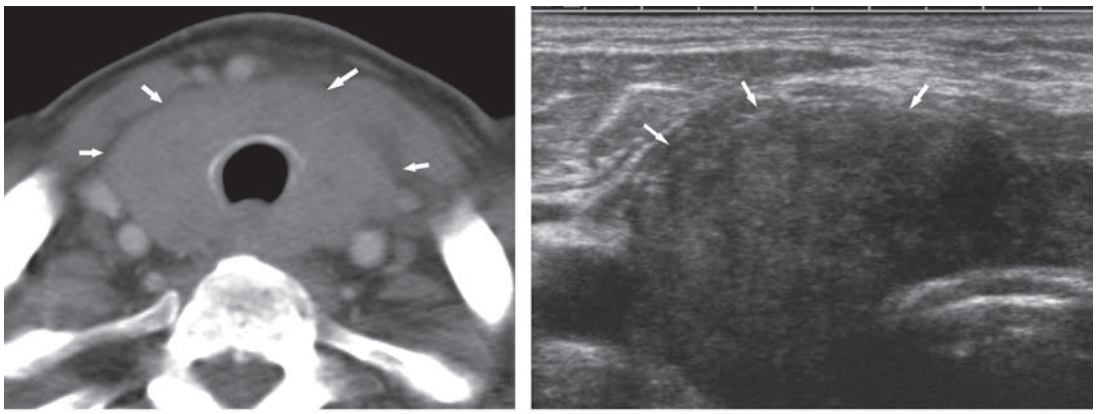
Teaching Point

FNA is the most accurate and cost-effective method for diagnostic evaluation of thyroid nodules. A review of recently published data regarding thyroid cancer detection at US-guided FNA indicates a sensitivity of 76%–98%, specificity of 71%–100%, false-negative rate of 0%–5%, false-positive rate of 0–5.7%, and overall accuracy of 69%–97% with the use of this method (16–26). In another report, which was based on a review of 12 studies, the median sensitivity and specificity were 88% and 90.5% (27). The false-negative rate with palpation-guided FNA (1%–3%) was higher than that with US-guided FNA (0.6%) (28). The literature reveals great variability in specimen cellularity, which ranges from a low of 66.4% to a high of 96.6% (28–30). Although the rate of specimen inadequacy with US-guided FNA is lower than that with palpation-guided FNA (31), US-guided FNA yields an inadequate specimen in 10%–20% of procedures—perhaps because of the absence of uniformly adopted or standardized criteria for adequacy of thyroid FNA specimens and specimen procurement techniques (32).

US-guided FNA Technique

Preprocedural Planning

Informed consent is obtained after the biopsy purpose and procedure are discussed with the patient. It should be emphasized that a high percentage of thyroid nodules are benign and that



a. b.

Figure 4. Diffuse enlargement of the thyroid gland in an 85-year-old man with a history of colon cancer. **(a)** Axial CT scan shows a diffusely enlarged thyroid gland (arrows). **(b)** US image shows a diffusely enlarged and heterogeneously isoechoic thyroid gland (arrows). Histopathologic analysis of a specimen obtained with FNA biopsy showed poorly differentiated adenocarcinoma with features identical to those seen in an earlier colon cancer specimen.

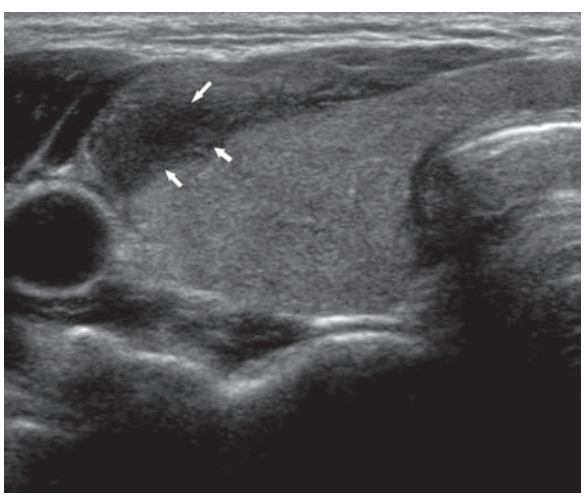


Figure 5. Transverse US image shows a localized subcapsular hematoma (arrows) that developed in the thyroid gland after FNA.

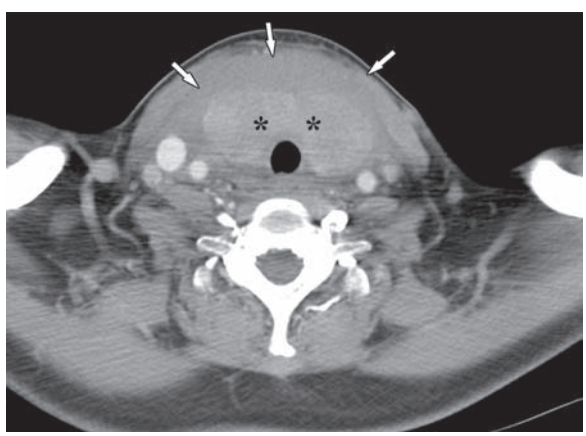
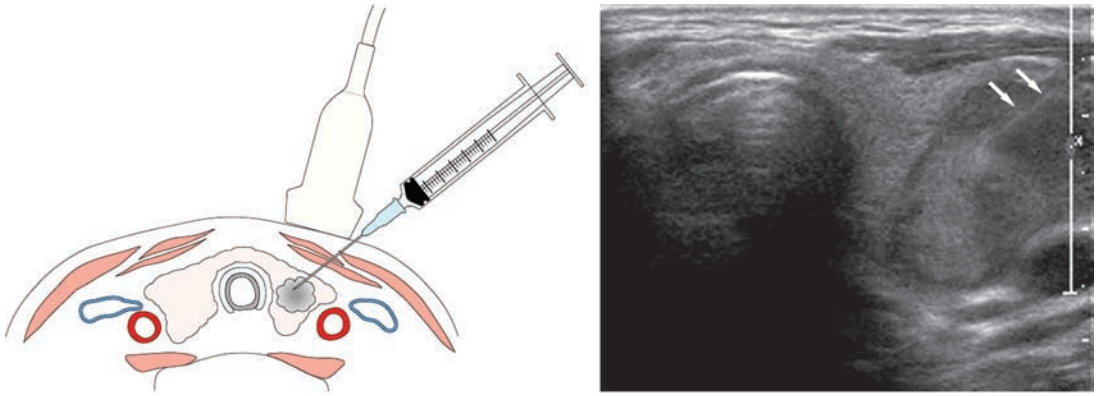


Figure 6. Axial CT scan shows extensive hemorrhages in thyroidal (*) and perithyroidal (arrows) locations after FNA in a thyroid lesion in a patient who was undergoing long-term aspirin therapy.

an adequate tissue sample with US-guided FNA may eliminate the expense and potential morbidity of surgical excision with general anesthesia. Limited intrathyroidal bleeding (Fig 5) and mild local pain radiating to the ear may occur. The most significant possible complication of the procedure is the development of a neck hematoma, but this complication is exceptionally rare (Fig 6). A screening test for coagulation is not routinely needed, but the patient should be carefully questioned about recent or current anticoagulant therapy with medicines such as aspirin and warfarin. It is generally accepted that to avoid excessive bleeding from an elective surgical procedure, anticoagulation therapy should be discontinued 4–7 days before surgery; however, the preoperative discontinuation of aspirin therapy is controversial (33). Most studies of this subject were performed in small populations, and there have been few studies about FNA in patients undergoing regular aspirin or anticoagulant therapy (34).

Patient Positioning and Preparation

For US-guided FNA, the patient is placed in a supine position with the neck slightly extended. After the lesion is localized, the overlying skin is cleansed with a 10% povidone-iodine solution and the area is draped. A high-resolution (7.5–15-MHz) linear-array transducer, with a sterile cover



a. b.

Figure 7. Parallel positioning of the fine-gauge needle for thyroid nodule biopsy. This positioning helps maximize the number of needle-generated reflected echoes perpendicular to the sound wave and is preferred by many operators. **(a)** Diagram shows insertion of the needle in a plane parallel to that of scanning. **(b)** US image, obtained with the transducer and needle positioned as in **a**, depicts the entire length of the needle (arrows) within the nodule.

placed over its head, is used for US. US gel is not necessary because the povidone-iodine solution used for skin sterilization also serves as a primary coupling agent (35).

Local Anesthesia

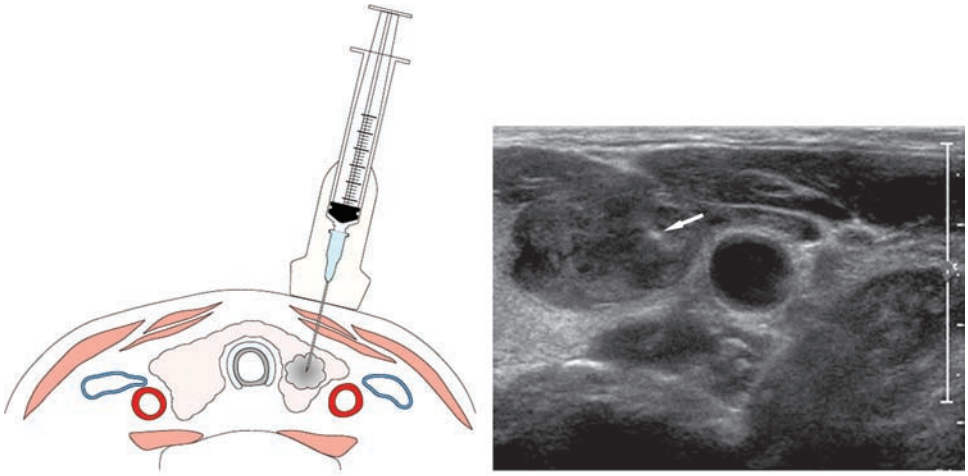
A local anesthetic may be used during the procedure. Approximately 1–2 mL of 1% lidocaine hydrochloride solution may be injected into the skin and superficial subcutaneous tissue at the predetermined site. The advantage of applying local anesthesia is that it allows repeated aspiration attempts without causing the patient any discomfort. Anesthetization directly over the thyroid capsule is useful for reducing discomfort caused by the procedure and does not significantly lengthen its duration (35). However, in cases in which fewer than two or three aspirations are planned, anesthesia may not be necessary. Oertel advocated the use of ice as a substitute for local anesthesia because it not only numbs the area but also causes vasoconstriction, which leads to less hemodilution of the aspirate (36).

Obtaining the Specimen

A 22- to 27-gauge needle is used with an attached 2–20-mL syringe. A syringe holder may or may not be used, according to the preference of the operator. The transducer is placed directly over the lesion. Before aspiration, scanning is performed in the transverse plane for lesion localization, followed by color Doppler mapping to depict any large blood vessels in and around the nodule so that vascular injury can be avoided during the procedure. The patient is instructed not to swallow or speak during the insertion of the needle. A freehand biopsy technique is used, and the syringe attached to the needle is placed just above the transducer. The needle may be introduced parallel (Fig 7; see also Movie 1 at *radiographics.rsnajnls.org/cgi/content/full/28/7/1869/DC1*) or perpendicular (Fig 8; see also Movie 2 at *radiographics.rsnajnls.org/cgi/content/full/28/7/1869/DC1*) to the transducer, and the needle tip should be carefully monitored during the procedure. When the needle reaches the target, the biopsy is performed. Biopsy specimens may be obtained with two widely used acquisition methods (Fig 9). During the procedure, all needle movements should be continuously visualized in real time. It is recommended that aspiration be performed at least twice. The collected material is placed on glass slides, smeared, and fixed in 95% ethyl alcohol. The syringe is rinsed with normal saline solution to obtain any remaining material for use in cell blocking.

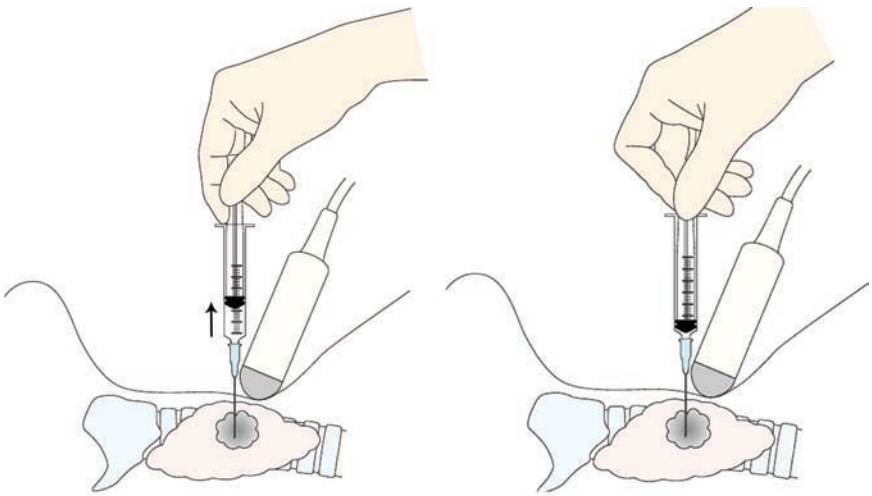
Specimen Staining

When the Papanicolaou staining method is used, the smears should be quickly placed in 95% ethyl alcohol. When Diff-Quik or Giemsa stain is used, the smear should simply be allowed to air dry. Papanicolaou staining is most commonly used for cytologic analysis of thyroid specimens, and it provides the clearest depiction of nuclear chromatin, ground-glass nuclei, and nuclear groove characteristics in papillary carcinoma (36). Diff-Quik or Giemsa stain helps visualize the characteristics of cytoplasm and colloid (36). A recently described



a. b.

Figure 8. Perpendicular positioning of the fine-gauge needle for thyroid nodule biopsy. **(a)** Diagram shows insertion of the needle in a plane perpendicular to that of scanning. A shorter needle may be used with this option, and it is less likely that the carotid artery or jugular vein may be punctured. **(b)** US image, obtained as the needle crossed from the skin entry site through the tissues of the neck and into the nodule, shows only the needle tip (arrow) where it intersected with the scanning plane.



a. b.

Figure 9. Aspiration **(a)** and nonaspiration **(b)** techniques for needle biopsy of thyroid nodules. In aspiration, the needle tip is advanced into various positions in the nodule and moved to and fro while suction is performed (arrow in **a**). Suction is halted before the needle is removed from the lesion. This procedure is repeated at least five times before the needle is finally withdrawn. In nonaspiration (capillary action), the needle is advanced into the nodule and vigorously moved to and fro while being rotated on its axis until a small amount of cellular material collects inside the needle hub. No suction is performed. This technique is useful in very hypervascular nodules, in which there is a high probability of obtaining a blood-stained specimen that is inadequate for accurate cytologic analysis.

automated processing method for preparing cytologic specimens (ThinPrep; Cytyc, Boxborough, Mass) may yield greater cellularity and better nuclear detail than conventional smear techniques, but its proper use requires specific experience (37).

Postprocedural Care

After the procedure, plaster is applied, and the patient should be instructed to manually compress

the skin entry site for a minimum of 30 minutes. The patient should be instructed to contact hospital staff or visit the emergency room if neck swelling occurs on the way home or at home.

Material Adequacy and False-Negative Results

Careful attention to the details of specimen procurement should help significantly increase the likelihood of material adequacy and decrease the frequency of false-negative findings (28–30). Both may be affected by the level of operator experience, accuracy of localization of the lesion and the needle, method of guidance (palpation or US), number of aspirations, needle gauge, sampling technique, capability for immediate on-site cytologic analysis, and many other factors.

Operator Experience

To develop and maintain the necessary level of staff expertise in an institution, the number of staff members who perform aspiration biopsies and the interpreting cytopathologists should be kept small (38). Each staff member who performs aspiration biopsies must complete at least 1–5 such procedures per month (39). It is not surprising that the institutions that most strongly promote thyroid FNA have accumulated a vast amount of technical experience that virtually guarantees optimal performance of the procedure (38,40,41). Staff members whose attempts at FNA repeatedly result in unsatisfactory specimens (>15%) should be identified and given remedial training (32).

Lesion Localization

The use of a correctly focused high-frequency (10–12-MHz) transducer may help improve the resolution and contrast of US images depicting the lesion. In addition, the selected focal zone should be just below the lesion. Adjustments in the dynamic scanning range or in the postprocessing gray-scale may help improve contrast so that the lesion appears more discrete.

No single US feature is 100% predictive, but several features are associated with a high likelihood of thyroid malignancy (9,11). Especially when there are multiple nodules in the thyroid gland, a thorough examination for suspicious US features may be helpful in targeting a nodule for aspiration, because US characteristics are more reliable indicators of potential malignancy than is nodule size (42).

Needle Localization and Lesion Targeting

Poor needle visualization is a common difficulty at US-guided FNA because of the fine caliber of the needle. If the needle is parallel to the transducer, it will be visible in its entirety. However, if the needle is inserted at a steep angle, as it must be to reach deep lesions, or if it is inserted perpendicular to the probe (short-axis technique), localization of its tip is more difficult. The tip of the needle is visible only as a bright echogenic focus on the monitor as the tip bisects the scanning plane (Fig 8b). If the needle tip is not visible, the position of the needle and transducer should be adjusted until the tip points toward the center of the lesion (Fig 10).

Palpation or US for Guidance

In a retrospective study in which the use of US was compared with that of manual palpation for guidance of FNA, researchers found that the accuracy of US-guided FNA was significantly higher than that of palpation-guided FNA (68% vs 48%), particularly for tumors smaller than 2 cm and those that were cystic or in deep locations (43) (Fig 11). US-guided FNA was more likely to result in a correct diagnosis, enabling avoidance of unnecessary thyroid surgery, than was palpation-guided FNA (2,3).

Teaching Point

Number of Aspirations

Between one and five aspirations are generally performed in each nodule (30,35,41,44). Most nodules with a diameter of 1–2 cm can be sampled adequately with three aspirations (36). Musgrave et al reported that the more regions apart from the center that were aspirated, the lower the inadequate sample rate (45); the rate was 16% with sampling of the center only, and 5.3%, 4.0%, and 2.6% with sampling of two, three, and four distinct regions apart from the center.

Needle Gauge

Usually, 20–27-gauge needles are used for thyroid FNA (10,12,23,30,35,41,44,46–50). The correlation between the gauge of the needle used and the cellularity of the FNA specimen has been debated. It was reported that the thinner the needle used for FNA, the higher the rate of sufficiency of cytologic material ($P < .01$); in particular, the sufficiency rate was 56.6% with the use of a 20-gauge needle and 82.5% with the

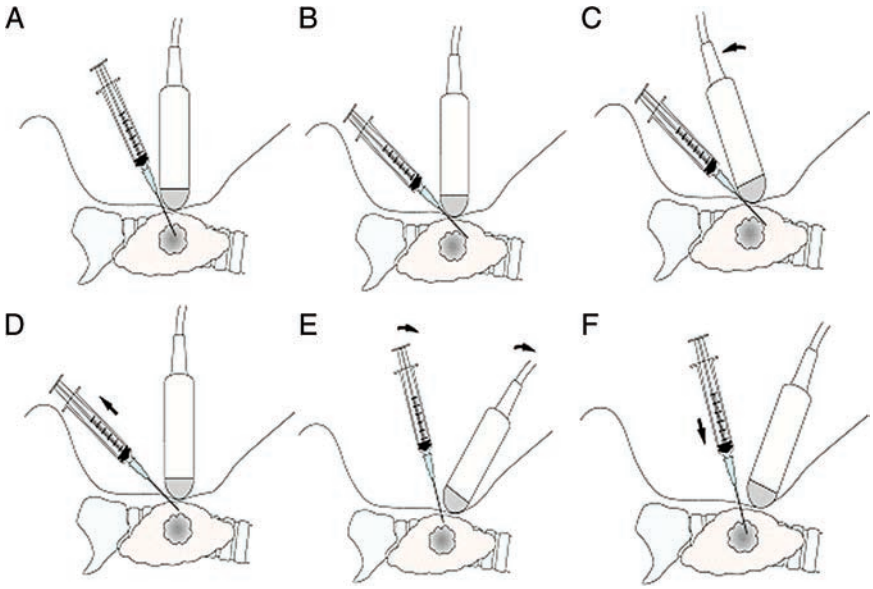


Figure 10. Diagrams show the proper technique for correcting needle alignment when the needle has been advanced to the expected location of the lesion but is not visible on US images. In *A*, the needle is correctly aligned in relation to the direction of the US beam and will be fully visible on US images. If the needle is not visible, it should be held motionless *(B)* while the transducer is rocked gently *(C)*. If the tip is not localized, the needle should be withdrawn slightly *(D)* and the orientation of the transducer axis adjusted *(E)* until visibility is achieved. The needle then should be realigned *(E)* so that the tip is centered directly above the lesion center before it is advanced in short increments ("walked") to the lesion *(F)*.

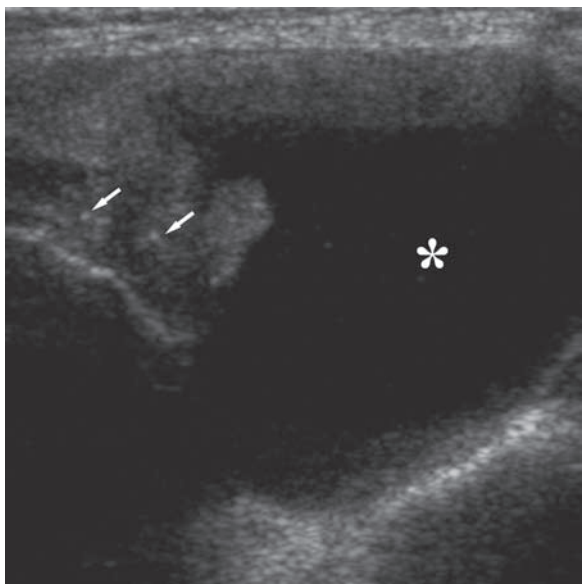
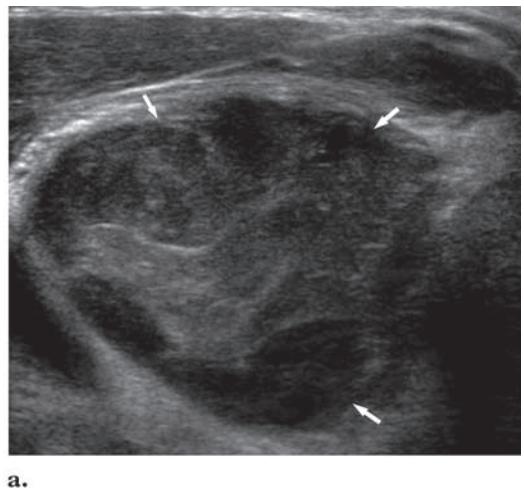


Figure 11. Papillary carcinoma in a 72-year-old woman with a palpable thyroid nodule. Approximately 3 mL of hemorrhagic fluid was aspirated from the nodule at palpation-guided FNA biopsy, but the cytologic results were nondiagnostic. Transverse US image of the left lobe of the thyroid shows a large mass with mixed echogenicity, consisting of a predominant cystic portion (*) and a mural nodule containing microcalcifications (arrows). Results of US-guided FNA biopsy of the mural nodule showed papillary carcinoma.

use of a 24-gauge needle (30). Bloodstained material, which makes microscopic evaluation more difficult, is more frequently seen in cases in which aspiration was performed with thicker needles (30). However, in two other prospective studies, no significant difference in diagnostic yield was found between cellular specimens obtained with a 23-gauge needle and those obtained with a 27-gauge needle (50) or between specimens obtained with a 21-gauge needle and those obtained with a 25-gauge needle (51). Some authors have suggested the use of a 25-gauge or thinner needle for biopsy of markedly hypervascular nodules of the thyroid (10,35,41). Some have suggested the use of a 23–25-gauge needle (30,36), and others have suggested the use of a 25-gauge or finer needle (15,35).

Comparison of Aspiration and Capillary Action

Various comparative studies of FNA with and without aspiration have shown no statistically significant difference between the two sampling



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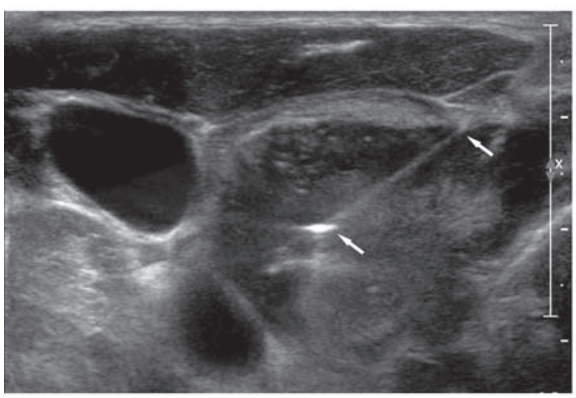

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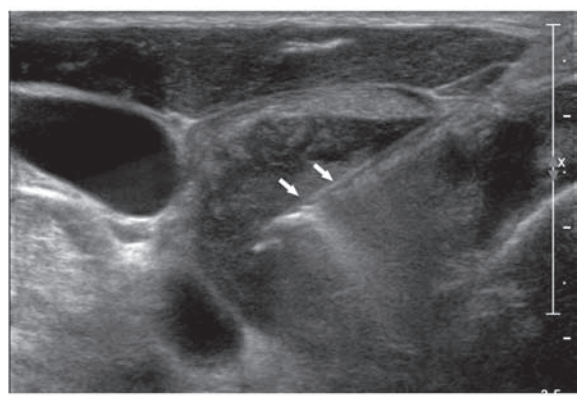


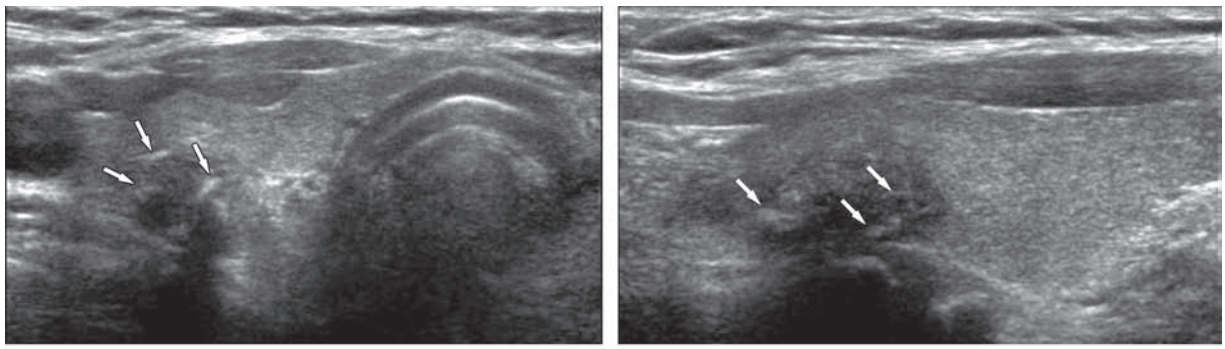
c.

Figure 12. Anaplastic carcinoma in an 80-year-old man with a palpable mass in the right thyroid lobe. **(a)** Transverse US image of the right thyroid lobe shows a large heterogeneous mass (arrows). Atypical cells were found at FNA biopsy, and a core-needle biopsy was then performed. **(b, c)** US images obtained before **(b)** and after **(c)** deployment of the 18-gauge semiautomated core-needle biopsy device show the notch (arrows in **b**) and the cutting needle after firing (arrows in **c**). The diagnosis was based on cytologic analysis of a core biopsy specimen.

techniques with regard to diagnostic accuracy (52). However, in a study by Degirmenci et al, a significantly higher rate of sufficiency of cytologic material was noted with the nonaspiration technique (76.9%) than with aspiration (49.4%) (30). The choice between nonaspiration and aspiration is a matter of operator preference. Nonaspiration fine-needle thyroid biopsy is less traumatic and even more rarely associated with complications than is FNA; however, comparative studies are lacking (27). Titton et al and Oertel have suggested that the thyroid biopsy should begin with nonaspiration (capillary action) and, if the specimens collected with that technique are inadequate, should continue with aspiration (10,36).

Comparison with Core-Needle Biopsy

In a separate prospective study in which FNA was compared with core-needle biopsy performed with a spring-activated, short-throw, 18–20-gauge needle, the diagnostic yield with core-needle biopsy of thyroid nodules exceeded that with FNA techniques by approximately 10% (53) (Fig 12). Predictably, there was also a higher complication rate with the use of the core needle (54–56). Although FNA is an established test for the evaluation of thyroid nodules with high sensitivity and accessibility, as we mentioned above, in some cases it does not yield sufficient diagnostic material even with repeated attempts; and scant aspirates or those with borderline adequacy may be a source of diagnostic error (57). However, core-needle biopsy provides a large histologic core of tissue, which may have a greater effect on surgical decision making than the cytologic diagnosis has. For these reasons, a core-needle biopsy is considered for patients in whom FNA produces only specimens of grossly scant-appearing cellularity after several passes or in patients who return for a repeat biopsy after a nondiagnostic initial FNA biopsy (10). Some authors have reported the use of core-needle biopsy as an adjunct to FNA biopsy in patients with thyroid nodules (58,59); others have reported that the



a. b.

Figure 13. Papillary carcinoma in a 51-year-old woman with a history of breast cancer surgery. Transverse **(a)** and longitudinal **(b)** US images show an irregular thyroid mass with coarse calcifications (arrows). Cytologic analysis of biopsy specimens collected in three separate procedures separated by substantial time intervals produced nondiagnostic results; the bloody smears showed either one follicular cell cluster or none. At subsequent surgery, papillary carcinoma with extensive calcifications and a lymph node metastasis (N1b) were found.

combination of FNA and core-needle biopsy seems to have the highest adequacy rate and sensitivity (60–62).

Immediate On-Site Cytologic Examination

It was previously reported that immediate on-site examination by a cytopathologist of material collected at FNA helps avoid repeat biopsy (44). However, O'Malley et al did not find a statistically significant difference in specimen adequacy between FNA biopsies of thyroid nodules with immediate cytologic analysis and those with delayed analysis, and they stated that immediate cytologic analysis prolonged the biopsy procedure considerably (49). The average procedural time was 12.5 minutes for the group with biopsy with an intraprocedural cytologic evaluation. If preprocedural planning is adequate and the procedural technique is optimal, a diagnostic specimen usually is obtained even without sample analysis by a cytopathologist during the procedure.

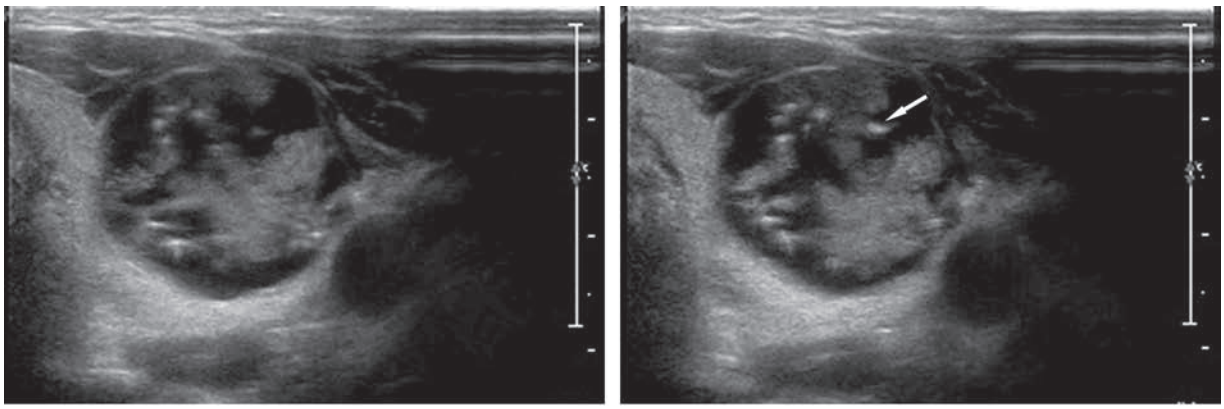
Lesion Characteristics

Size.—A large nodule is easier to sample than a smaller one, and the diagnostic yield from FNA of large nodules may be higher (10,31,43,63). However, the diagnosis of small thyroid carcinomas is critically important because thyroid carcinomas with a maximal diameter of less than 1 cm may manifest with early lymph node metastasis or extranodal invasion (9). Moreover, it has been reported that US-guided FNA has high sensitivity and accuracy for the diagnosis of malignancy both in infracentric thyroid nodules and in supracentric nodules and that there is no statistical difference in the specimen adequacy rate between nodules of different sizes (30,64). Degirmenci et al reported that the highest specimen adequacy rate was observed among nodules smaller than 1 cm (76.4%) and the lowest rate was observed among nodules larger than 3 cm (56.9%) (30). They inferred that the lower rate in larger nodules probably resulted from increased vascularity and the larger size of blood vessels, with resultant bloodstaining of the material acquired at fine-needle biopsy. Another probable cause of the inadequacy of specimens from larger nodules in the study by Degirmenci et al is that large nodules more often are cystic and contain necrotic areas. We may safely assume that the specimen insufficiency rate overall is influenced more by lesion characteristics than by mistaken targeting.

Pathologic Features.—Benign thyroid nodules have a higher chance of being inadequate for cytologic diagnosis than malignant thyroid nodules do (65). The malignancy rate among specimens from repeat biopsy or surgery of thyroid nodules for which FNA biopsy findings were nondiagnostic is reported to be about 7.1% (66).

Composition.—Specimen adequacy is not dependent on the vascularity and echogenicity of the sampled thyroid nodule (30) but on components such as cystic change, calcification, and fibrosis (27). Some investigators have suggested that inadequate cytologic results from a cystic portion of a sampled nodule should be distinguished from general specimen inadequacy (15). At FNA biopsy, areas of fibrosis, calcification (Fig 13), and cystic

Teaching Point



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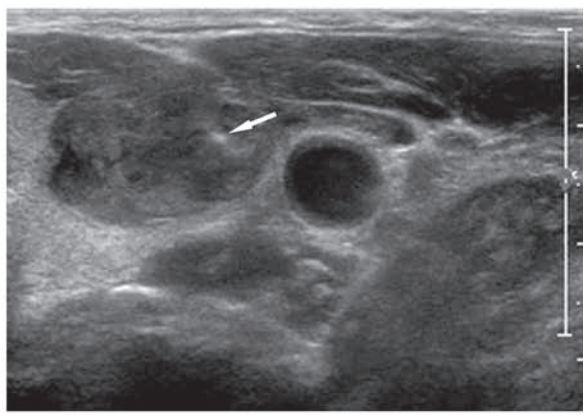


c.

Figure 14. Optimal needle biopsy technique in a largely cystic papillary carcinoma in a 54-year-old man with a palpable mass in the left thyroid lobe. **(a)** US image shows a mass with mixed echogenicity. **(b)** US image obtained at FNA shows an echogenic dot (arrow) that represents the needle tip during initial sampling of fluid within the cystic mass. **(c)** US image obtained in the same procedure as **b**, during sampling of the solid part of the mass, shows a decreased amount of fluid and increased solid appearance. The arrow indicates the needle tip.

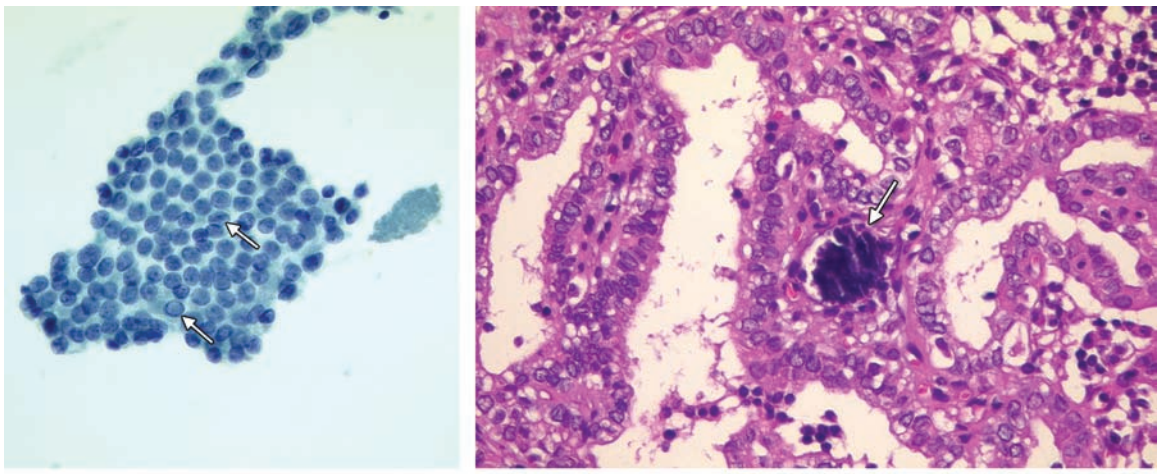
degeneration should be avoided. If the targeted lesion has a cystic portion, aspiration should be performed with a larger needle to evacuate as much fluid as possible; after that, if there is a residual solid area, then a 25- to 27-gauge needle may be used for FNA of the solid portion (Fig 14; see also Movie 3 at *radiographics.rsnajnls.org/cgi/content/full/28/7/1869/DC1*). If a nodule with mixed components is targeted, the needle should be inserted into the solid portion (15,27).

Cytologic Findings and Follow-up Strategies

To select an appropriate follow-up strategy, the radiologist must understand the cytologic findings reported by the pathologist. Moreover, for accurate comparison of imaging findings from one study to another or one medical institution to another and for effective correlation of imaging findings with cytologic results, the terminology used must be uniform.

The FNA biopsy specimens submitted for cytologic analysis may be found diagnostic (adequate for diagnosis) or nondiagnostic (inadequate for diagnosis), depending on the criteria used to define diagnostic adequacy. These criteria vary among reporters; however, the following cytologic findings have been used to define specimen adequacy: *(a)* a minimum of five or six groups of well-preserved cells, with each group containing approximately 10–15 cells (67); *(b)* six clusters of benign cells on at least two slides prepared from separate FNA biopsy samples (1); *(c)* 10 clusters of follicular cells, with each cluster containing at least 20 cells (68).

The criteria used to define specimen adequacy determine, in large part, both the nondiagnostic rate and the false-negative rate. Adherence to rigid criteria leads to higher nondiagnostic rates and lower false-negative rates; and high nondiagnostic rates exacerbate patient anxieties and lead to the performance of unnecessary repeat aspiration and unnecessary surgical excision, thereby reducing the overall efficiency and cost-effectiveness of the FNA biopsy procedure (69). There is also controversy regarding the acceptability of



a. b.

Figure 15. Classic pattern of papillary carcinoma. Photomicrographs (**a**: original magnification, ×400; Papanicolaou stain prepared with a semiautomated processing method; **b**: original magnification, ×200; hematoxylin-eosin stain) show papillary structures consisting of many neoplastic follicular epithelial cells with intranuclear cytoplasmic pseudoinclusions (arrows in **a**) and psammoma bodies (arrow in **b**).

aspirates that consist primarily of watery colloid and contain few thyroid epithelial cells (1,15). However, many investigators agree that repeat FNA should be considered if the nodule from which a nondiagnostic specimen was initially collected is solid (38,42).

Nondiagnostic Findings

A nondiagnostic finding (eg, "unsatisfactory," "inadequate," or "cellular insufficiency") is generally the result of a cytologic smear that contains too few cells to allow a diagnosis. Nondiagnostic findings may result from poor fixation, preparation, or staining or from excessive blood, necrotic material, or debris obscuring cellular details (32).

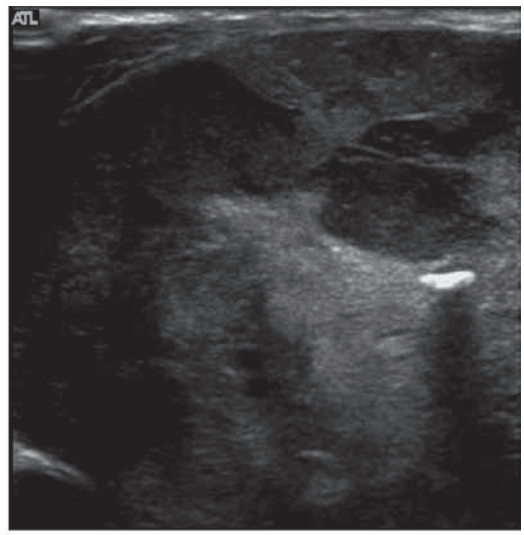
Diagnostic Findings

Cytologic findings in FNA specimens that are judged to be diagnostically adequate are further characterized as malignant, indeterminate (follicular or Hürthle cell neoplasm or possible papillary carcinoma), or benign (42).

Malignant Findings.—The most frequently occurring malignant neoplasm in the thyroid gland is papillary carcinoma. The classic papillary carcinoma manifests many neoplastic follicular epithelial cells. The neoplastic follicular cells have a moderate to abundant amount of dense cytoplasm, well-demarcated cellular borders, and enlarged nuclei that vary in size and shape. Intranuclear cytoplasmic pseudoinclusions (Fig 15a), psammoma bodies (Fig 15b), multinuclear histiocytes, and bubble gum–like colloid are observed (36).

If cytologic findings are indicative of malignancy, surgery is recommended (42). False-positive findings are rare (1%–3%), and most represent adenomas. Thyroid adenomas, especially those with solid areas, frequently include atypical cells that occasionally manifest pronounced nuclear pleomorphism. The presence of a hyalinizing trabecular adenoma of the thyroid (a rare histologic subtype of adenoma), a dyshormonogenetic multinodular goiter, or Hashimoto thyroiditis also may lead to false-positive diagnoses (27).

Indeterminate Findings.—Indeterminate findings (eg, "suspicious," "follicular lesion," and "follicular neoplasm") include follicular and Hürthle cell neoplasms and findings suggestive of papillary carcinoma. Follicular neoplasms are found in 15%–30% of FNA specimens, and it is difficult for cytopathologists to determine whether such a neoplasm is benign or malignant



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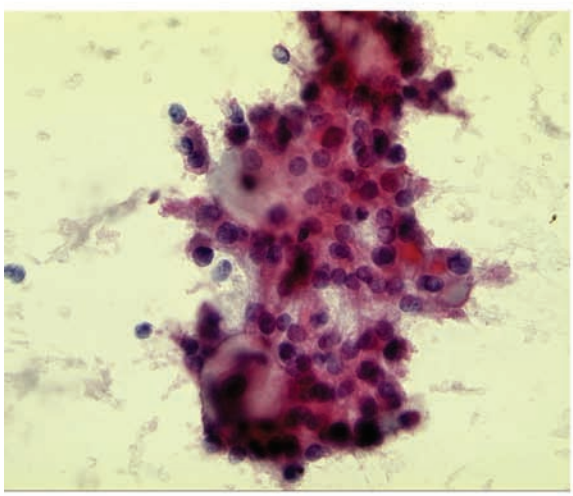

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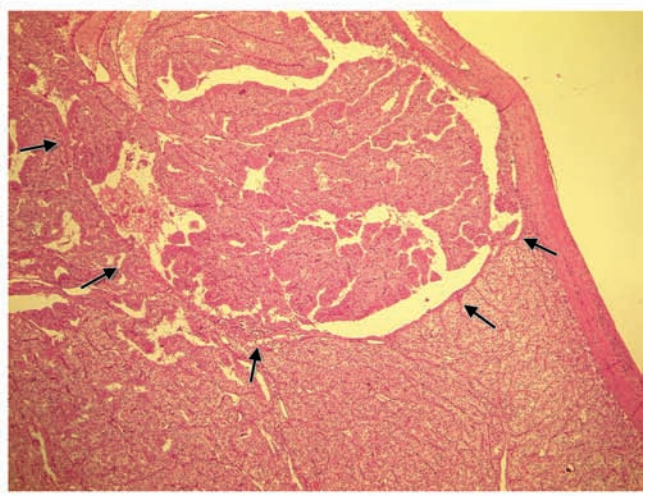


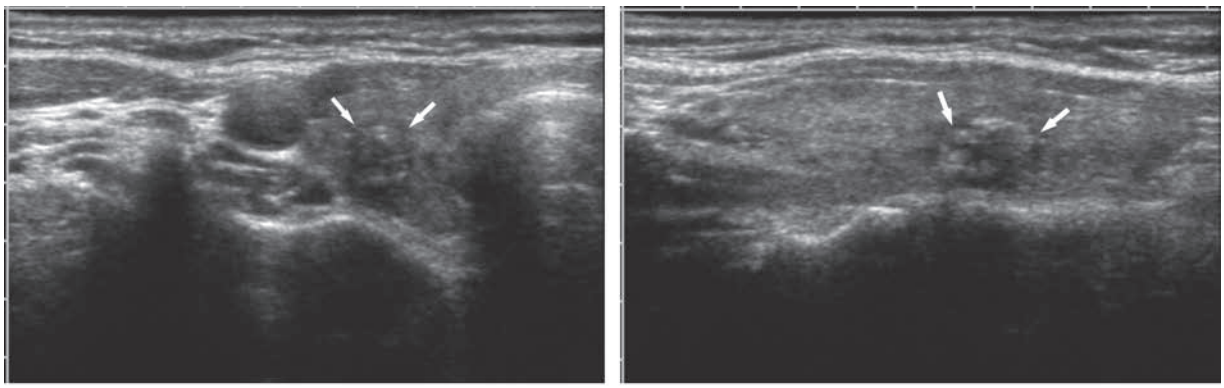
c.

Figure 16. Papillary carcinoma in a 55-year-old man with a rapidly growing mass in the right thyroid lobe. **(a)** US image shows a large, heterogeneously isoechoic thyroid mass with coarse calcifications. **(b)** Photomicrograph (original magnification, ×400; Papanicolaou stain) of a tissue specimen from FNA biopsy shows a few clusters of benign-looking follicular cells, a finding suggestive of a follicular neoplasm. **(c)** Photomicrograph (original magnification, ×200; hematoxylin-eosin stain) of a tissue specimen from subsequent surgery shows follicular papillary carcinoma (arrows) in a portion of the solid mass.

(Fig 16). Thyroid scintigraphy with radioiodine might be helpful for this purpose (42). If a concordant autonomously functioning nodule is not seen, a lobectomy or total thyroidectomy should be considered.

A cytologic diagnosis of "suspicious for papillary carcinoma" is made when specimens manifest one or more abnormalities that are associated with papillary carcinoma, such as nuclear membrane irregularity, nucleolar abnormality, and an abnormal nucleus-to-cytoplasm ratio, but do not satisfy all the criteria for a diagnosis of papillary carcinoma (32). Lobectomy or total thyroidectomy is the traditionally recommended treatment for such lesions, regardless of imaging findings at US or radioiodine scintigraphy (42). However, Kwak et al recently reported a much lower probability of malignancy in thyroid nodules described at cytologic analysis as "suspicious for malignancy" when US findings are suggestive of benignity rather than malignancy (25.5% vs 96.4%). Furthermore, the study results suggested that US and FNA biopsy are complementary and that US characteristics may be useful when seeking informed consent for thyroid surgery (70).

Benign Findings.—Most thyroid nodules are benign nonneoplastic lesions that are diagnosed at FNA biopsy either as adenomatoid nodules



a. b.

Figure 17. Papillary carcinoma in the thyroid gland of a 53-year-old woman. Transverse **(a)** and longitudinal **(b)** US images show a 1-cm-diameter, microlobulated, heterogeneously hypoechoic thyroid mass (arrows) with a height that exceeds its lateral dimension and with internal microcalcifications. Cytologic analysis of a specimen from FNA showed clusters of follicular epithelial cells, a finding suggestive of adenomatous hyperplasia. Because of the discordance between the imaging appearance and these cytologic findings, surgery was performed. A 1.1-cm papillary carcinoma was found.

(with a variable amount of colloid or an increased number of follicular epithelial cells) or as lymphocytic thyroiditis (36). If an FNA biopsy specimen is found benign at cytologic analysis, no further diagnostic imaging or treatment is required (42). Thyroid nodules diagnosed as benign on the basis of adequate FNA biopsy specimens and concordant imaging findings may be managed conservatively if they do not grow, but they require follow-up because of a low, but not negligible, false-negative rate of up to 5% with FNA (71,72). A repeat FNA biopsy should be considered if there is discordance between imaging and cytologic findings or if clinical suspicion is aroused by any finding.

Follow-up of Benign Nodules

Some authors have recommended repeat aspiration for routine follow-up of all benign nodules, to verify the initial diagnosis and, possibly, reduce the false-negative rate (73–75). However, a recent report about the results of repeat aspiration revealed a lower false-negative rate among thyroid nodules initially diagnosed as benign on the basis of both cytologic and imaging characteristics (2.1%) than among nodules with initial US findings of malignancy (13.6%) (76). Therefore, routine repeat FNA after a nodule is diagnosed as benign may yield a very low improvement in cancer detection and may be counterproductive (lead to an increased number of false-positive results, increased patient anxiety, and decreased cost-effectiveness). However, a repeat FNA biopsy should be considered if there is discordance between the findings at imaging and those at cytologic analysis (Fig 17), a growing mass, a recurrent cyst, or an inad- equate FNA sample. At least 3 months should be allowed to elapse after the initial FNA biopsy. The 3-month time lag before repeat FNA is recommended to avoid problems in cytologic interpretation that may be posed by reparative cellular atypia (eg, marked nuclear chromatin clearing, grooves, or inclusions that may be mistaken for evidence of papillary carcinoma) (77,78).

Teaching Point

For follow-up of nodules with an initial benign cytologic diagnosis and without clinical or radiologic findings suggestive of malignancy, imaging surveillance is recommended rather than repeat US-guided FNA biopsy. If nodule size is stable, the interval before the next follow-up clinical examination or US evaluation may be longer (42).

Conclusions

US-guided FNA is useful for the diagnosis of palpable or nonpalpable thyroid nodules. The routine use of this biopsy procedure has caused profound changes in the management of thyroid nodules. FNA biopsy allows prompt identification

and treatment of thyroid malignancies and avoidance of unnecessary surgery in patients with benign lesions, thereby improving the overall quality of life for patients with thyroid nodules. Furthermore, FNA helps guide treatment and helps reduce the cost of care.

The adequacy of cytologic specimens depends on several factors, including the nodule characteristics and the FNA technique used. As the person performing FNA gains experience and as lesion targeting and localization with US become more accurate, the rate of sample inadequacy should decrease.

To optimize the usefulness of FNA, every center should strive to attain and maintain a high level of expertise in all aspects of aspiration and interpretation and, toward that end, should establish clinical guidelines tailored to its patient population and FNA biopsy results.

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US-guided Fine-Needle Aspiration of Thyroid Nodules: Indications, Techniques, Results

Min Jung Kim, MD, et al

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Page 1870
US characteristics are more useful than nodule size for identifying nodules that are likely to be malignant.

Page 1872
FNA is the most accurate and cost-effective method for diagnostic evaluation of thyroid nodules. A review of recently published data regarding thyroid cancer detection at US-guided FNA indicates a sensitivity of 76%–98%, specificity of 71%–100%, false-negative rate of 0%–5%, false-positive rate of 0–5.7%, and overall accuracy of 69%–97% with the use of this method. In another report, which was based on a review of 12 studies, the median sensitivity and specificity were 88% and 90.5%.

Page 1876
US-guided FNA was more likely to result in a correct diagnosis, enabling avoidance of unnecessary thyroid surgery, than was palpation-guided FNA.

Page 1879
Specimen adequacy is not dependent on the vascularity and echogenicity of the sampled thyroid nodule but on components such as cystic change, calcification, and fibrosis.

Page 1883
A repeat FNA biopsy should be considered if there is discordance between the findings at imaging and those at cytologic analysis, a growing mass, a recurrent cyst, or an inadequate FNA sample.

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