Chapter 6d. Fine-Needle Aspiration Biopsy of the Thyroid Gland

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Revised 19 November 2012

Abbreviations

FNA, fine-needle aspiration

FNNA, fine-needle nonaspiration

HBME-1, human bone marrow endothelial cell-1

PEI, percutaneous ethanol injection

T , thyroxine

US-FNA, fine-needle aspiration with ultrasonographic guidance

6d.1. INTRODUCTION

Fine-needle aspiration (FNA) biopsy of the thyroid gland is an accurate diagnostic test used routinely in the initial evaluation of nodular thyroid disease (1-6). Epidemiologic studies suggest that nodular thyroid disease is a common clinical problem, with a prevalence of 4% to 7% in the adult population in North America and an annual incidence of 0.1%, which translates into approximately 300,000 new nodules in the United States (1). A survey of clinical members of the American Thyroid Association revealed that most endocrinologists (96%) perform FNA biopsy for diagnosis of thyroid nodules (7). In addition, FNA with ultrasonographic guidance (US-FNA) is used routinely in follow-up surveillance of patients with thyroid cancer. Therefore, we estimate that more than 300,000 thyroid FNA biopsies will be performed this year in the United States alone. Worldwide, the number of thyroid aspirations is most likely in the millions. Thus, the importance of FNA biopsy in thyroid practice cannot be overemphasized.

This chapter describes biopsy techniques, cytologic diagnosis, complications, FNA results, diagnostic pitfalls, and other information that may be useful to clinicians who manage patients with nodular thyroid disease

6d.2. DEFINITIONS

Diagnosis of thyroid nodules by needle biopsy was first described by Martin and Ellis (8) in 1930, who used an 18-gauge needle aspiration technique. Subsequently, cutting needle biopsy with Silverman or Tru-Cut needles was used for tissue examination. None of these techniques gained wide acceptance because of fear of malignant implants in the needle track, false-negative results, and serious complications. However, Scandinavian investigators introduced small-needle aspiration biopsy of the thyroid in the 1960s, and this technique came into widespread use in North America in the 1980s (9).

For FNA biopsy, most use "fine" or "thin" (22- to 27-gauge) needles; most commonly used is a 25-gauge needle. As the name indicates, the biopsy technique uses aspiration to obtain cells or fluid from a mass. In contrast to percutaneous large-needle biopsy, which obtains tissue specimens and requires histologic fixation, aspiration biopsy offers

cytologic examination of the specimen. Another technique, fine-needle nonaspiration (FNNA) biopsy, avoids aspiration but still permits cytologic review of thyroid masses.

Although the FNA technique appears simple, considerable time and experience are required to acquire and maintain skillful biopsy technique. Debate continues about who is best qualified to perform FNA biopsy, but it is clear that the best results are obtained if the person performing the biopsy has mastered the technique. In the opinion of the author, endocrinologists are best qualified to perform FNA biopsy because they are most experienced in thyroid palpation, they acquire and maintain expertise in performing biopsies, and they provide definitive and continued care to patients with nodular thyroid disease.

6d.3. EQUIPMENT

The basic equipment needed to perform FNA biopsy is simple and relatively inexpensive (2,6,10). The following items are essential (Fig. 1):

Figure 1. FNA biopsy equipment is simple and inexpensive. It includes an alcohol wipe, 4X4-inch gauze pads, 10-mL plastic syringes, 25-gauge 1 1/2-inch stiff, noncutting, bevel-edged needles, glass slides, alcohol bottles, and a pistol-grip mechanical syringe holder.

1. A syringe holder or syringe pistol—most commonly used is the Cameco syringe pistol (Belpro Medical, Anjou, Quebec) shown in Figure 1. The pencil-grip syringe holder is another syringe-holding device (developed by Tao and Tao Technology, Incorporated, Camano Island, WA).

2. Disposable 10-mL plastic syringes

3. Disposable 25- or 27-gauge needles, 1 1/2 inches long

4. Glass slides, with 1 end frosted on 1 side, 1.0 mm thin (Gold Seal, Erie Scientific Company, Portsmouth, NH)

5. Alcohol prep sponges

6. Alcohol bottles for immediate wet fixation of smears

7. Gloves—current regulations of the Occupational Safety and Health Administration require that the person performing a biopsy wear protective gloves

8. Containers for cystic fluid collection and transportation to the cytology laboratory

9. Laboratory slips with the patient's name, clinic number, biopsy sites, and other relevant information to be transferred to the cytology laboratory

10. Lidocaine—1% lidocaine should be available for those who prefer biopsy with local anesthesia

6d.4. THE PATIENT

The thyroid gland should be palpated carefully and the nodule(s) to be biopsied identified. The procedure should be explained carefully to the patient, and all the patient's questions should be answered completely. We inform our patients that local anesthetic is not used, that the biopsy will take several minutes, that 2 to 4 aspirations are made, and that we expect no serious complications, but there will be slight pain with minor hematoma or swelling at the biopsy site(s).

The biopsy can be performed with the patient on a hospital bed or in the office on an examining table. In either place, a nurse or clinical assistant should always be available to assist with the procedure. The patient may be seated or supine; we prefer the supine position. The patient is placed supine with the neck hyperextended to expose the thyroid; for support, a pillow is placed under the shoulders (Fig. 2 A). The patient is asked not to swallow, talk, or move during the procedure. It is best to talk to the patient and keep him or her informed of the progress of the biopsy. After the biopsy has been completed, firm pressure is maintained on the biopsy site(s). The patient is then asked to sit for a few minutes. Occasionally, patients have dizziness or pain. It is best to observe patients for a few minutes, and if no problems are noted, they are allowed to leave. We prefer that a nurse or clinical assistant be present for help during the procedure.
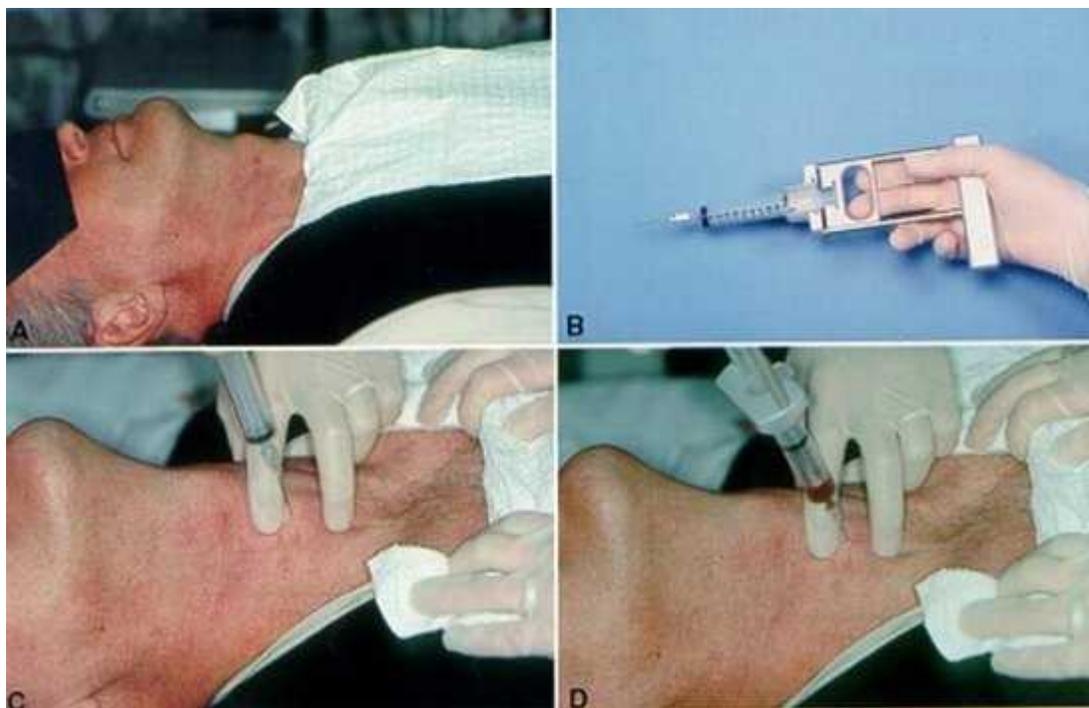
Figure 2. A, Position of patient during FNA. Supine position and a pillow under the patient's shoulder allow hyperextension of the neck and maximal exposure. B, Syringe is placed in syringe holder. C, Nodule is identified and stabilized with operator's "nonaspirating" hand. The operator stands on the side of the patient opposite that of the thyroid nodule. Current Occupational Safety and Health Administration regulations require the use of gloves because of concern about blood-borne diseases. D, With a quick motion, the needle passes through the skin and enters the nodule. Immediate mild suction follows. As soon as aspirate appears, suction is released and the needle is withdrawn.

6d.5. THE TECHNIQUES

6d.5.1. FNA Biopsy

Numerous reports, reviews, and even textbooks provide detailed descriptions of various FNA biopsy techniques (10-16). Although most reports agree on the principles of the technique, variations have been described to improve results. It is important to position the patient correctly, to identify and locate the mass, to provide adequate light during the biopsy, and to have a clinical assistant available for help. The physician performing the biopsy should be positioned at the patient's side, preferably contralateral to the lesion. The nodule(s) to be aspirated is identified, and the overlying skin is cleansed with alcohol. The use of povidone-iodine (Betadine) or sterile technique is not necessary. A 10-mL plastic syringe is attached to a Cameco syringe holder and held in the right hand by a right-handed operator (Fig. 2 B). Two fingers of the free (left) hand firmly grasp the nodule while the other hand holds a pistol-grip syringe holder (Fig. 2 C). The needle is then rapidly inserted through the skin and into the nodule. Once the needle tip is in the nodule, gentle suction is applied while the needle is moved in and out within the nodule vertically (Fig. 2 D). This maneuver allows the dislodging of cellular material and easy suction into the needle. During this period of 5 to 10 seconds, suction is maintained, and as soon as fluid or aspirate appears in the hub of the needle, the suction is released and the needle is withdrawn. The appearance of fluid suggests that the nodule is cystic; suction is maintained and all the fluid aspirated. It is important to release the syringe plunger and remove the vacuum before withdrawing the needle; this allows the aspirate to remain in the needle and not be sucked into the syringe. Next, the needle is detached from the syringe (Fig. 3 A), and 5 mL of air is drawn into the syringe (Fig. 3 B). The needle is reattached to the syringe, and with the bevel facing down, 1 drop of aspirated material is forced onto each of several glass slides

(Fig. 3 C). It is important that all slides be labeled and placed in order on a nearby table before the aspiration. Smears are prepared by using a second glass slide in a manner similar to that of making blood smears (Fig. 3 D). The slides for wet-fixation should be placed immediately in 95% alcohol for staining with the Papanicolaou stain. For Giemsa staining, air-dried smears are necessary, and prepared slides are left unfixed and transported to the laboratory
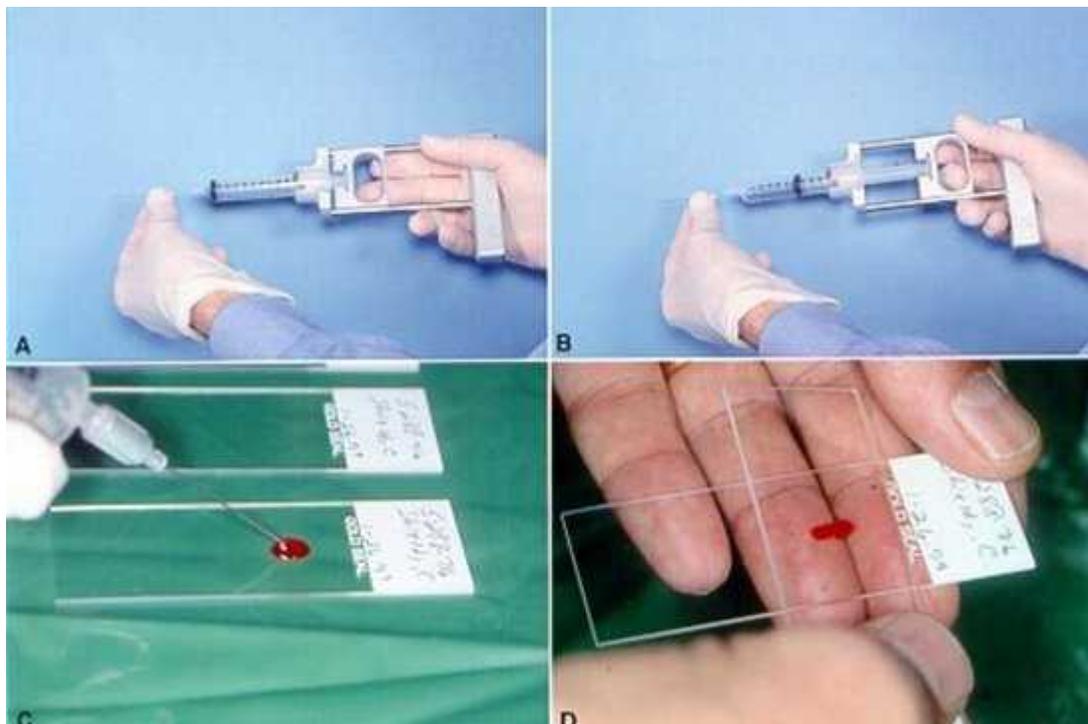

Figure 3. A, The needle is removed quickly from the syringe. B, Five milliliters of air is aspirated into the syringe, and the needle is placed back on the syringe. C, With the needle bevel facing down, 1 drop of aspirated material is expelled onto each of several glass slides. Slides are labeled and placed on the table before aspiration, ready for use. D, With a second slide, smears are prepared in a manner similar to that for blood smears. Slides are then immediately wet-fixed by placing them in an alcohol bottle.

Usually, 2 to 4 aspirations are made (11,13,14), although some authors suggest at least 6 punctures should be made (17). Frequently, 8 to 10 slides are made for each nodule. Preferably, the aspirates should be obtained from the peripheral areas and different parts of the nodule, in a sequential manner, to ensure representative sampling (11,13). For larger nodules, the deep center of the mass should be avoided because it is more likely to contain degeneration and fluid, decreasing the chance of a diagnostic specimen. For cystic lesions, the fluid should be completely aspirated and FNA attempted on residual tissue. Aspirated fluid should be placed in a plastic cup and saved for cytologic evaluation. We use a new needle and syringe for each biopsy

6d5.2. FNNA Biopsy

The FNNA technique has been described by several authors (6,13,18). This technique is thought to minimize trauma to thyroid tissue and to reduce blood contamination. For this technique, patient preparation is similar to that for FNA. However, no syringe or suction is necessary. The hub of a 25-gauge needle is held in a pencil-grip fashion, and the needle is gently inserted into the nodule and then moved in and out for 5 to 10 seconds (Fig. 4). Aspirate flows into the needle through capillary action, and as soon as aspirate appears in the hub, the needle is withdrawn and at-

tached to a syringe with air inside. Next, the plunger is used to expel the material onto glass slides. The procedure is repeated several times, and the slides are prepared as described above for FNA.

Figure 4. FNNA biopsy showing the needle, position, and direction for biopsy. After the needle is placed into the target tissue, it is moved with short in-and-out movements until aspirate appears in the hub. The needle is then withdrawn.

6d.5.3. After Biopsy

After the biopsy has been completed, firm pressure is applied to biopsy site(s) with a 4×4-inch gauze pad. Once bleeding has stopped, an adhesive bandage is placed on the puncture site(s), and the patient is observed for a few minutes and, if there are no problems, allowed to leave (Fig. 5).

Figure 5. Immediately after FNA and FNNA, firm pressure is applied to the biopsy sites. When the procedure is finished, an adhesive bandage is applied, and the patient is allowed to sit for a few minutes before dismissal.

6d.6. COMPLICATIONS

Thyroid FNA biopsy is very safe. No serious complications such as tumor seeding, nerve damage, tissue trauma, or vascular injury have been reported (10-16). Needle puncture causes slight pain and some skin discoloration at the aspiration site(s). However, even a minor hematoma is uncommon. Patient use of anticoagulants or salicylates does not preclude FNA biopsy. Needle track implantation of thyroid carcinoma is extremely rare; it has been poorly documented and is not considered a real problem by most experts (19). Postaspiration hemorrhage within a cystic lesion can occur, and the author has seen 1 patient who, within several hours after FNA biopsy, developed severe pain from bleeding into the nodule that warranted surgical excision. The specimen contained fresh blood consistent with hemorrhage caused by biopsy. However, this is the only example we have had among more than 25,000 biopsies performed at our institution during the past 3 decades.

6d.7. CYTOLOGIC DIAGNOSIS

Aspirates from normal glands often have scant thyroid follicular cells and colloid. Wet-fixed smears are usually prepared with a modified Papanicolaou stain, which shows nuclear detail. Air-dried smears are often prepared with a Romanovsky stain. May-Grünwald-Giemsa is a modified Romanovsky staining procedure that is sometimes used in thyroid cytologic preparations. The cytologic diagnosis includes 4 categories: benign (negative), suspicious (indeterminate), malignant (positive), or unsatisfactory (nondiagnostic).

6d.7.1. Benign Cytology

Aspirates obtained from multinodular goiters, benign microfollicular adenoma, or normal hyroid are referred to as "colloid nodules" and show loosely cohesive sheaths of follicular epithelium, colloid, blood, and rare macrophages. Colloid nodules are the most common cytology and contain an abundance of colloid with sparse follicular cells. There is considerable variation in the number of cells as well as the type and amount of colloid present (Fig. 6).
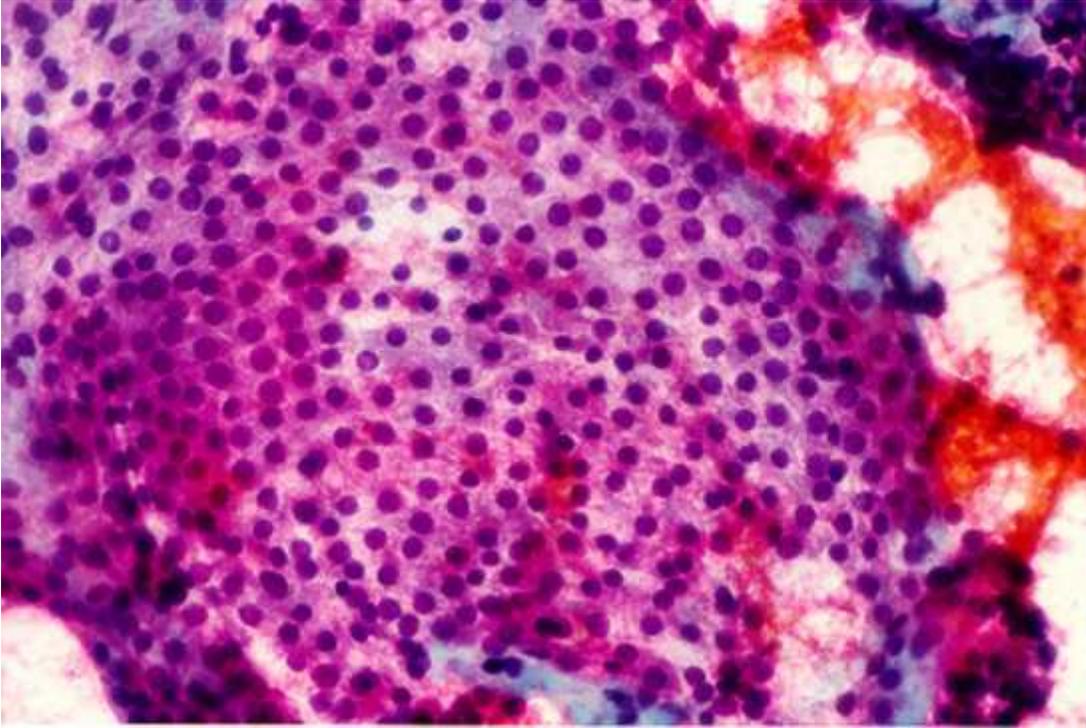
Figure 6. Colloid nodule. Sheath of normal thyroid epithelium shows uniform nuclei and pale cytoplasm. (Papanicolaou; ×100.)

Another benign diagnosis is Hashimoto's thyroiditis. It has a fairly characteristic pattern on FNA smears, showing hypercellularity with lymphocytes, Hürthle cells, and minimal or no colloid (Fig.
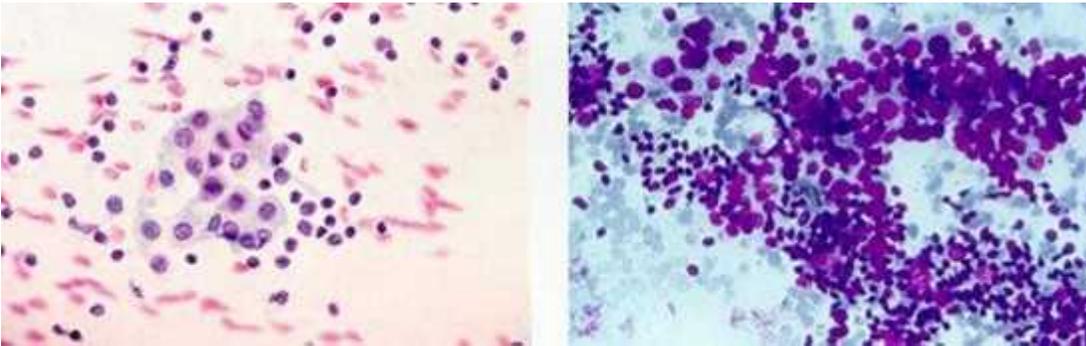

Figure 7. Hashimoto's thyroiditis. A, Group of Hürthle cells, with large cytoplasm and prominent nuclei, surrounded by a teratogeneous population of lymphocytes. (Papanicolaou; ×60.) B, Hypercellular aspirate with lymphocytes and Hürthle cells. (May-Grünwald-Giemsa; ×250.)

Subacute (granulomatous) thyroiditis is a rare condition with a benign aspirate. Typically, the smear shows multinucleated giant cells, epithelioid histiocytes, and scattered inflammatory cells (Fig. 8).
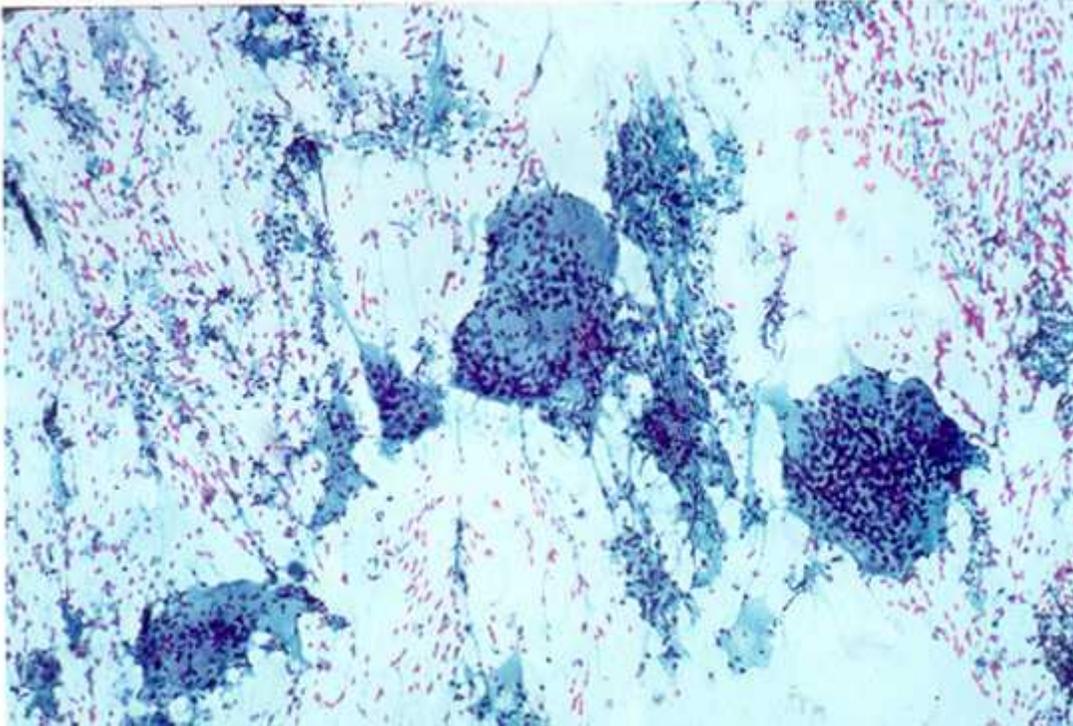
Figure 8. Subacute thyroiditis. Large multinucleated giant cells in a mixed inflammatory background. Absence of colloid is noticeable. (Papanicolaou; ×64.)

6d.7.2. Malignant Cytology

Papillary carcinoma, the most common thyroid malignancy, is readily diagnosed by FNA. Typically, cytology shows a papillary configuration, large irregular nuclei, and nuclear grooves. Psammoma bodies may or may not be present, but if present, they are highly suggestive of papillary thyroid carcinoma (Fig. 9).
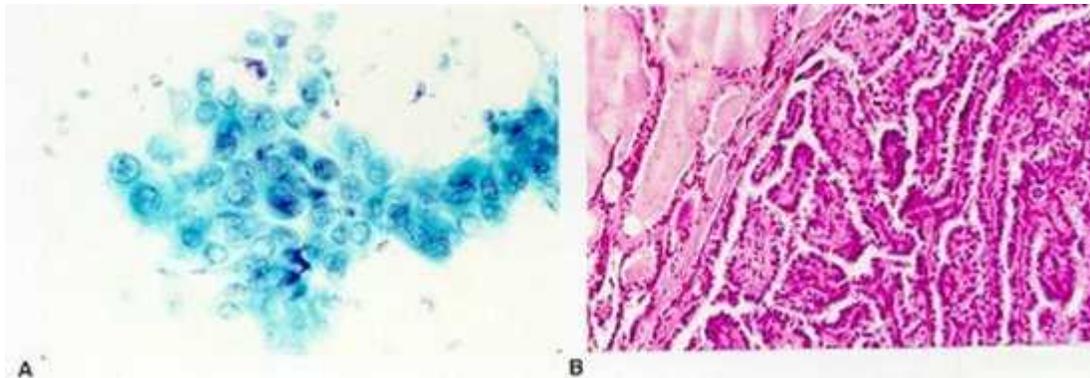

Figure 9. Papillary thyroid carcinoma. A, Follicular cells with large irregular nuclei, nuclear grooving, and pale chromatin. (Papanicolaou; ×400.) B, Histologic preparation showing typical papillary configurations. (Hematoxylin-eosin; ×50.)

Medullary thyroid carcinoma accounts for 5% to 10% of thyroid cancers and may present as a thyroid nodule or neck mass. Typically, aspirates from a medullary thyroid carcinoma are hypercellular, composed of large, poorly cohesive

cells, and are predominantly spindle-shaped. Amyloid is often, but not invariably, present, and there is no colloid (Fig. 10).
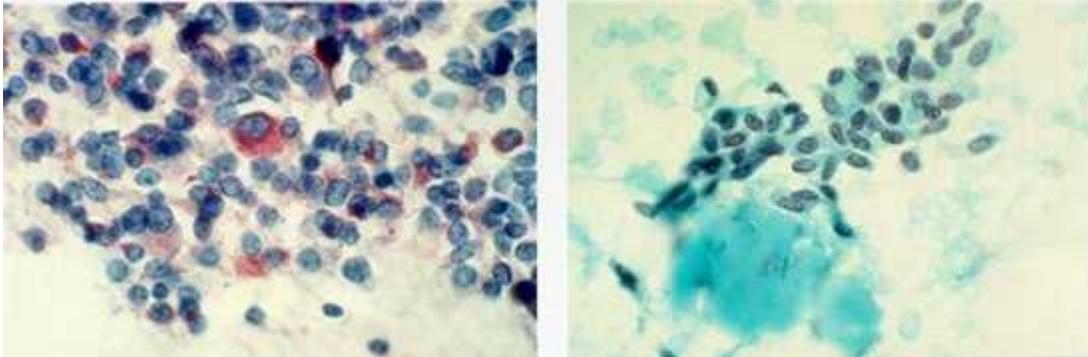

Figure 10. Medullary thyroid carcinoma. A, Cellular specimen staining positively for calcitonin with immunoperoxidase. (×100.) B, Loosely cohesive fragments of spindle-shaped cells. Amyloid is present as amorphous blue material intimately associated with neoplastic cells. (Papanicolaou; ×400.)

High-grade carcinoma can be diagnosed cytologically, but distinguishing between primary and metastatic cancer is not easy

6d.8. FNA RESULTS

The accumulated experience of the past 3 decades has confirmed the reliability and usefulness of FNA as a diagnostic test (1,2,6,10-15,17,20-25). The role of FNA biopsy in the evaluation of thyroid nodules is now firmly established, and FNA has become the initial test because it is both safe and cost-effective. In most clinics, FNA has become a standard test, performed most often by an endocrinologist

6d.8.1. Diagnostic Cytology

An adequate specimen of good technical quality is considered diagnostic or satisfactory and may be "benign," "suspicious," or "malignant." A benign cytologic diagnosis is reported for 50% to 90% of the specimens (average, 70%) (11,15,23,26,27). From 10% to 30% of FNA cytologic specimens may be suspicious for malignancy or indeterminate (average, 20%) (26,27). A malignant or positive cytologic diagnosis varies from 1% to 10% (average, 5%). For example, Caruso and Mazzaferri (26) reported the following results from 9 series that included more than 9,000 patients: benign, 74%; malignant, 4%; inadequate, 11%; and suspicious, 11%. We reviewed more than 18,000 specimens from 7 large series and obtained similar cytologic results: benign, 69%; malignant, 4%; suspicious, 10%; and nondiagnostic, 17% (27).

6d.8.2. False-Negative Rates

False-negative results mean missed malignancy. False-negative rates generally vary from 1.5% to 11.5% (average, <5%) (17,20,26,28). The false-negative rate is defined as the percentage of patients with "benign" cytology in whom malignant lesions are later confirmed on thyroidectomy. The frequency of false-negative cytologic diagnosis depends on the number of patients who subsequently have surgery and histologic review. In most retrospective series, less than 10% of patients with a benign cytologic diagnosis subsequently have thyroid surgery, suggesting that false-negative rates should be interpreted with some skepticism (26,27). Despite this note of caution, most authorities

agree that the true false-negative rate is less than 5% if all patients have thyroid surgery. False-negative rates are lower in centers experienced with the procedure and with cytologic interpretation by expert cytopathologists.

6d.8.3. False-Positive Rates

False-positive rates vary from 0% to 8% (average, 3%) (20,26,27). A false-positive diagnosis indicates that a patient with a "malignant" FNA result was found on histologic examination to have benign lesions.

6d.8.4. Causes of False Diagnoses

Interpretive or sampling errors account for false diagnoses (13,14,27,28). Hashimoto's thyroiditis probably is the most common cause of false-positive cytology. Misclassification of follicular and Hürthle cell adenomas as papillary carcinomas accounts for other errors. FNA biopsy of thyroid lymphomas may produce lymphocytes that can be interpreted as Hashimoto's thyroiditis, accounting for a false-negative diagnosis. Inadequate or improper sampling accounts for some false-negative errors. For example, nodules smaller than 1 cm may be too small for accurate needle placement, and nodules larger than 4 cm are too large to allow proper sampling from all areas, thereby increasing the likelihood of misdiagnosis. Finally, the cytopathologist should establish and observe criteria to exclude a diagnosis of malignancy (2,6,10,25).

6d.8.5. The Problem of Cellular Tumors

Hypercellular specimens from follicular or Hürthle cell lesions may have features suggestive of, but not diagnostic for, malignancy (1,4,10,14,23). Thus, the cytopathologist labels these "suspicious for malignancy" because cytologic features neither confirm nor rule out malignancy. Histologic examination is necessary for definitive diagnosis (Fig. 11). Hypercellularity may be seen with nonneoplastic lesions, and Hürthle cell changes may be seen in patients with lymphocytic thyroiditis. The diagnosis of follicular neoplasm is indicative of an underlying malignancy in 14% of cases and Hürthle cell neoplasm in 15% (21,27). Many pathologists maintain that benign and malignant follicular or Hürthle cell tumors cannot be distinguished on the basis of aspirated cells only and the lesion must be removed for histopathologic examination (2,13,14,29). However, Kini (30) believes that follicular adenomas and follicular carcinomas usually can be differentiated on the basis of nuclear size but Hürthle cell lesions are difficult to diagnose cytologically.

Figure 11. A-Ultrasonographically guided fine-needle aspiration (FNA). A, Patient position, examiner position, and a 7- to 13-Mhz linear array transducer.

Figure 11. B, Scanning technique.

Figure 11. C, Needle placement in interventional ultrasonographically guided FNA.
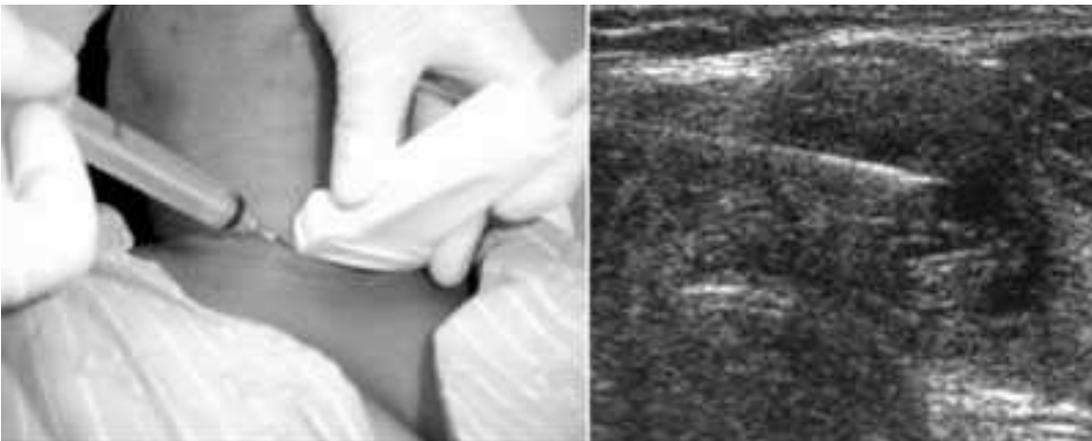

Figure 11.D, Needle placement in interventional ultrasonographic procedure showing placement on patient (left) and in ultrasonographic scan (right).

- **Advance needle in and out of lesion**
- **Without suction**
- **Oscillate and fan needle tip through lesion**
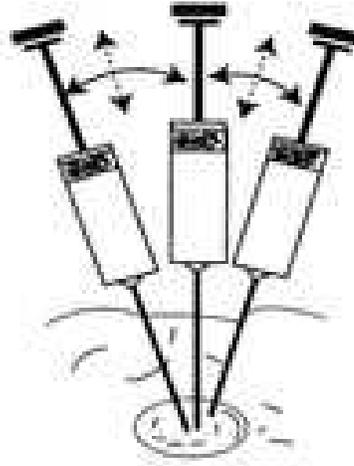- **Release suction and remove needle**

Figure 11. E, Four steps in ultrasonographically guided FNA.

Several authors have discussed the problem of follicular neoplasm. In a study of 149 patients with the cytologic diagnosis of follicular neoplasm, Tuttle et al (31) reported that risk of malignancy was higher for males, solitary nodules, and nodules larger than 4 cm. In a study of 219 patients with follicular neoplasm, Schlinkert et al (32) showed that nodules are more likely malignant in younger patients, in males, if the nodule is solitary, and if it is larger than 4 cm. More recently, Baloch et al (33) studied 184 cases of follicular neoplasm and reported that risk factors for malignancy included male sex, older age (>40 years), and larger nodules (>3 cm). Overall, they found that 70% of these lesions are benign.

Recent studies suggest that immunohistochemical and genetic markers may be helpful in separating benign from malignant follicular lesions (1,4,34,35). Molecular Marker tests are new tools for further assessing nodules with indeterminate, suspicious or atypical fine needle aspiration results. Combination of cytology and molecular marker results can improve diagnosis and treatment of thyroid neoplasms in these select cases. Molecular alterations that are involved in the pathogenesis of thyroid cancer can be detected by these tests. Nodules with indeterminate cytology that lack these alterations are less likely to be malignant (6% to 28% risk). [34] More than 70% of papillary thyroid carcinomas harbor a point mutation in BRAF or RAS or RET/PTC rearrangement, and greater than 70% of follicular thyroid carcinomas harbor either RAS mutations or PAX 8/PPAR gamma rearrangements.

Another test using a gene expression classifier (GEC) showing good results was recently published. [35] This prospective multi-center study confirmed previous findings demonstrating the ability of the GEC to help rule out malignancy in nodules with indeterminate FNA. When the GEC is benign, the negative predictive value (NPV) is described as greater than 94% (risk of malignancy less than 6%) for nodules with a cytopathology result of Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance (AUS/FLUS) or Suspicious for Follicular/Hurthle Cell Neoplasm diagnosis 85% (risk of malignancy 15%). [35] When the GEC result is Suspicious, the Positive Predictive Value (PPV) is described as approximately 40% (risk of malignancy 40%) for nodules with a cytopathology AUS/FLUS or Suspicious for follicular or Hurthle cell neoplasm diagnosis and 75% (risk of malignancy 75%) for nodules with a cytopathology Suspicious for Malignancy diagnosis. [35]

6d.8.6. Nondiagnostic Cytologic Results

Inadequate specimens are labeled "nondiagnostic" or "unsatisfactory" and account for 2% to 20% of specimens (average, 15%) (2,6,26,27). Several factors influence nondiagnostic rates for FNA results, including the skill of the operator, vascularity of the nodule, criteria used to judge adequacy of the specimen, and the cystic component of the

nodule (36-39). Overall, a satisfactory smear contains at least 6 clusters of well-preserved cells, with each group consisting of at least 10 to 15 cells. Reaspiration yields satisfactory specimens in at least 50% of cases that are considered nondiagnostic on initial FNA (17,29). Although it has been suggested that more aspirations increase the diagnostic rates, the optimal number of aspirations is a matter of debate. In general, most reports indicate that 2 to 4 aspirates per nodule are adequate (13,14,29).

Chow et al (40) found a 7% malignancy rate in 153 patients with initial nondiagnostic smears. Among 27 patients treated surgically, 37% had cancer. Reaspiration with US guidance was diagnostic in 66% and 56% without US; overall, 62% of reaspirations were diagnostic.

6d.8.7. Diagnostic Accuracy

Analysis of the data reveals that the sensitivity of FNA ranges from 65% to 98% (mean, 83%), and specificity ranges from 72% to 100% (mean, 92%) (11,20,26). The predictive value of a positive or suspicious cytologic result is approximately 50%. The overall accuracy for cytologic diagnosis approaches 95% (Table 1).

Table 1. Summary Data From Literature Survey on Thyroid FNA*

Feature	Mean	Range	Definition
Sensitivity, %	83	65-98	Likelihood that patient who has disease has positive test results
Specificity, %	92	72-100	Likelihood that patient without disease has negative test results
Positive predictive value, %	75	50-96	Fraction of patients who have positive test who have disease
False-negative rate, %	5	1-11	FNA negative; histology positive for cancer
False-positive rate, %	5	0-7	FNA positive; histology negative for cancer
FNA, fine-needle aspiration.*From AACE/AME Task Force on Thyroid Nodules (2). Used with permission.			

6d.8.8. FNA Guidelines

Guidelines have been published to help improve the adequacy and accuracy of cytology specimens (2). FNA biopsy should be performed by individuals who have had training in both thyroid examination and thyroid biopsy. Thyroid FNA in the hands of experienced operators achieves high diagnostic accuracy. Aspirates should be obtained from different portions of the nodule, preferably peripheral areas, in an organized and sequential manner. It is essential to ensure that an adequate number of follicular cells is present. A cytopathologist, preferably one with experience in thyroid cytology, should review and interpret the slides. If reaspiration yields insufficient material, US-FNA biopsy is the next test. In the event that the final result is still insufficient, surgical excision is warranted for most nodules.

Several reports have offered suggestions to minimize false-negative rates (1,2,6,17). In a review of thyroid FNA, Belfiore and La Rosa (10) suggested the following steps to reduce false-negative results:

1. Acquire and maintain adequate biopsy expertise

2. Avoid making a diagnosis with a suboptimal sample

3. Be cautious with cystic degeneration, Hürthle cells, or lymphocytes

4. Repeat FNA at least once during follow-up

5. Repeat FNA or recommend surgery when nodule is suspicious by clinical or US examination

To minimize false-negative results, we follow the steps summarized in Table 2.

Table 2. Steps to Improve Accuracy of Fine-Needle Aspiration and Lead to Better Nodule Management*

Step	Explanation
Endocrinologist performs biopsy	Offers better thyroid examination; accumulates experience with FNA
Experienced cytopathologist reviews slides	Improves cytologic interpretation
Careful with small (<1 cm) or large (>4 cm) nodules	Increased chance of misdiagnosis; US-FNA improves accuracy
2-4 aspirates from different nodule sites	Improves cytologic sampling
Rebiopsy if cytology is nondiagnostic	One-half will be diagnostic on reaspiration
Nondiagnostic cytology is not negative	Risk of cancer is low but not ruled out
Aspirates with no follicular cells are nondiagnostic	These should not be considered "negative for malignancy"
Excise nodules yielding "suspicious" cytology	20% chance of malignancy
Excise clinically suspicious, cytologically benign nodules	Clinical impression overrides FNA diagnosis
FNA, fine-needle aspiration; US-FNA, ultrasound-guided FNA.*Modified from Gharib (6). By permission of Mayo Foundation for Medical Education and Research.	

6d.9. US-FNA BIOPSY

Published thyroid guidelines and reviews state that thyroid US should not be used as a screening test in the general population (1,2). However, US is recommended for all patients with a single palpable nodule or a multinodular goiter or in a patient suspected of having a nodule (1) (Table 3). Current US machines are safe, easy to use, relatively inexpensive, with high resolution, and widely available. It is important to note that US results are quite operator-dependent.

Table 3. Indications for Thyroid Ultrasound Examination*

Palpable solitary nodule
Palpable multinodular goiter
Suspicion of nodule in patient with difficult neck palpation
Prior history of neck radiation
Family history of medullary thyroid carcinoma, multiple endocrine neoplasia type 2, or papillary thyroid carcinoma
Unexplained cervical adenopathy
Preoperative thyroidectomy for cancer; long-term postoperative surveillance
*Data from AACE/AME Task Force on Thyroid Nodules (2).

An ever-increasing number of practicing endocrinologists are getting training to use US in routine practice. US is now used to supplement physical examination when neck palpation is difficult, a thyroid mass is present, a nodule needs careful measurement, or an impalpable thyroid lesion is suspected. As a result of this widespread use, many small (<1.5 cm) thyroid "incidentalomas" are noted, creating what has been referred to as a "thyroid epidemic" (1,41,42). Such a finding has been an unintended consequence of thyroid US use and has created a management dilemma for the clinician.

Sonographic characteristics of thyroid nodules include the following:

1. echogenicity: hypo- or hyperechoic

2. calcifications: micro- or eggshell

3. margins: well-defined or irregular

4. vascularity: high or low

5. shape: tall or wide

The overall predictive value of US for malignancy is summarized in Table 4. Although no single US feature is diagnostic for malignancy, the specificity is highest for microcalcifications and lowest for echogenicity. The presence of at least 2 suspicious US criteria reliably identifies 85% to 93% of thyroid malignancies (1).

Table 4. Value of US Features Predicting Thyroid Malignancy*

US feature	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %
Microcalcifications	26.1-59.1	85.8-95.0	24.3-70.7	41.8-94.2
Hypoechogenicity	26.5-87.1	43.4-94.3	11.4-68.4	73.5-93.8
Irregular margins or no halo	17.4-77.5	38.9-85.0	9.3-60.0	38.9-97.8
Solid	69.0-75.0	52.5-55.9	15.6-27.0	88.0-92.1
Intranodule vascularity	54.3-74.2	78.6-80.8	24.0-41.9	85.7-97.4
More tall than wide	32.7	92.5	66.7	74.8

US, ultrasonography.*From Frates et al (43). Used with permission.

Recent reports and reviews confirm that when FNA is used with US guidance, sensitivity, positive predictive value, and negative predictive value increase significantly (1,44-47). US can be used to assist FNA or guide FNA, the latter being more accurate. US-FNA permits precise needle placement in a nodule, thereby increasing both the rate of satisfactory aspirates and the diagnostic accuracy (1,2,44,47). Although US-FNA is useful for small (<1.5-1.0 cm) thyroid nodules, many endocrinologists currently use US-FNA even for easily palpable lesions.

It is now established that neither nodule size nor number can preclude or predict malignancy (1,43). Patients with multiple nodules have the same risk of thyroid cancer as those with a solitary nodule. Moreover, approximately 50% of patients with a single nodule on palpation have additional thyroid nodules on thyroid US examination (41). US-FNA helps select the nodule or nodules that need biopsy. Recent American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi guidelines (2) suggest selection of nodules for FNA on the basis of US features, whereas the Society of Radiologists in Ultrasound recommends FNA for nodules larger than 1.0 to 1.5 cm in diameter (43). This issue remains controversial.

Percutaneous ethanol injection (PEI) during ultrasonographic guidance was first used for recurrent or persistent hyperparathyroidism, especially in surgically high-risk patients. More recently, alcohol therapy has been applied to thyroid nodules (1,2,48-52). Lippi and colleagues (50) reported results of a large, multicenter Italian study that included 429 patients: 56% had toxic nodules and 44% had hyperfunctioning but nontoxic nodules. Under ultrasonographic guidance, ethanol was injected into the nodules and 12 months after treatment, 74% of the patients were biochemically euthyroid. Papini and coworkers (49) reviewed the role of PEI in the treatment of benign thyroid nodules. They found indications for treatment of patients with toxic hot nodules, nontoxic hot nodules, toxic multinodular goiters, and thyroid cysts. In patients with solitary nodules, the nodules with a volume less than 10 mL were more likely to respond to treatment with complete remission than were nodules with a large volume.

PERCUTANEOUS ETHANOL INJECTION

Percutaneous ethanol injection (PEI) during US guidance was first used for recurrent or persistent hyperparathyroidism, especially in surgically high-risk patients. More recently, alcohol therapy has been applied to thyroid nodules (1,2,48-52). Lippi and colleagues (50) reported results of a large multicenter Italian study that included 429 patients: 56% had toxic nodules and 44% had hyperfunctioning but nontoxic nodules. Under US guidance, ethanol was injected into the nodules and 12 months after treatment, 74% of the patients were biochemically euthyroid. Papini and coworkers (49) reviewed the role of PEI in the treatment of benign thyroid nodules. They found indications for treatment of patients with toxic hot nodules, nontoxic hot nodules, toxic multinodular goiters, and thyroid cysts. In patients with solitary nodules, nodules with a volume less than 10 mL were more likely to respond to treatment with complete

remission than were nodules with a large volume. PEI is performed on outpatients. The procedure is short, never exceeding 10 minutes, and requires no local or general anesthesia. US-guided PEI is safe and effective in centers with experience. Valcavi and Frasoldati (53) used PEI to treat benign thyroid cysts. Complications included transient dysphonia and pain; no permanent injuries were recorded. Two-thirds of the patients required only 1 injection to reduce nodule size. Of note, there is often an acute, marked increase in the serum level of thyroglobulin but only a slight increase in the serum level of thyroid hormones. There is no evidence that injected ethanol enters the circulation, because serum levels of ethanol do not increase after PEI.

Zingrillo and colleagues (54) treated large (>10 mL) cold benign thyroid nodules in 41 patients with PEI. Follow-up ranged from 12 to 36 months. Symptoms were markedly reduced. The authors concluded that PEI is a safe and effective treatment of symptomatic, large, cold, benign nodules and should be considered an alternative treatment for high-risk surgical patients or when patients refuse surgical treatment.

In a prospective randomized trial, Bennedbaek and colleagues (55) compared the effect of a single PEI treatment with suppressive doses of thyroxine (T 4) in euthyroid patients with a single solid colloid thyroid nodule. The thyroid nodules were small (estimated volume, <10 mL). After 12 months, the median nodule reduction in the PEI group was greater than in the T 4group, indicating that a single PEI treatment is more effective than thyroxine therapy.

6d.10. FNA PITFALLS

The experience as well as the expertise of the cytopathologist is critical in avoiding pitfalls. Determining the adequacy of an aspirate, cellular atypia, application and interpretation of immunostains, and differentiation of lymphocytic thyroiditis from lymphoma are but a few of these problems. Larger nodules are more likely to yield false-negative results. To improve sampling, aspirates should be obtained from multiple sites of the nodule rather than repeatedly from a single spot. The absence of malignant cells in an otherwise acellular specimen does not exclude malignancy. It is good practice to select nodules for biopsy in a multinodular gland by US evaluation. In patients with multiple nodules, FNA is best performed with US, selecting nodules for FNA when US features are suspicious (1,2), remembering that usually no more than 2 nodules need FNA.

6d.11. REBIOPSY

Opinions on indications for reaspiration are divided, some favoring (10,56), others not favoring (2,6,57) routine rebiopsy. Lucas et al (57) reported no advantage in routine rebiopsy, whereas Chehade et al (56) found that repeated biopsy may decrease the rate of false-negative FNA from an average of 5.2% to less than 1.3%. Recent thyroid nodule guidelines from the American Association of Clinical Endocrinologists and the Associazione Medici Endocrinologi (2) did not suggest routine rebiopsy of FNA-benign nodules.

Indications for rebiopsy are listed in Table 5 and include an enlarging FNA-benign nodule or a nodule that does not shrink on

Table 5. When to Repeat FNA

FNA, fine-needle aspiration.
Enlarging FNA-benign nodule
Recurrent cysts
Initial FNA nondiagnostic
Large (≥4 cm) nodule
Follow-up of FNA-benign nodule (?)

T4-suppressive therapy. Additional indications are recurrent cysts or an initial FNA that is not diagnostic. In the opinion of this author, in clinics or centers with FNA experience, routine rebiopsy is not necessary. However, for those who begin FNA biopsy in their practice, rebiopsy in 12 to 18 months may provide reassurance to the physician as well as the patient that cancer was not missed and false-negative rates remain low.

6d.12. REFERENCES

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