Thyroid biopsy

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Literature review current through: Apr 2018. | **This topic last updated:** Apr 26, 2018.

INTRODUCTION — Thyroid nodules come to clinical attention when noted by the patient; as an incidental finding during routine physical examination; or, more commonly, during a radiologic procedure, such as carotid ultrasonography, neck or chest computed tomography (CT), cervical spine magnetic resonance imaging (MRI), or positron emission tomography (PET) scanning. Their clinical importance is primarily related to the need to exclude thyroid cancer, which is present in 4 to 6.5 percent of all thyroid nodules in nonsurgical series. Thyroid biopsy is an important component of the evaluation of a thyroid nodule (algorithm 1). It is the most accurate method for evaluating thyroid nodules and selecting patients for thyroid surgery.

This topic will review the techniques, utility, limitations, and complications of percutaneous thyroid biopsies. An atlas of cytopathologic findings and overview of the diagnosis and treatment of thyroid nodules are discussed separately. (See "Atlas of thyroid cytopathology" and "Diagnostic approach to and treatment of thyroid nodules" and "Evaluation and management of thyroid nodules with indeterminate cytology".)

TECHNIQUES

Fine-needle aspiration (FNA) biopsy — FNA is a simple and safe outpatient procedure in which tissue samples are obtained for cytologic examination and, sometimes, molecular testing. FNA is performed with or without lidocaine or xylocaine anesthesia [1], by repetitively moving a 23- to 27-gauge (most commonly 25- or 27-gauge) needle through the nodule. The needle is attached to a 10 mL syringe that may be contained in a holder designed to facilitate the application of constant or intermittent suction. The aspirated material is smeared directly on slides, fixed, and stained or collected in a liquid preservative from which thin-layer preparations are made. (See 'Preparation of slide' below.)

With experience, adequate samples can be obtained in 90 to 97 percent of aspirations of solid nodules [2-6]. It is more difficult to obtain adequate specimens from nodules with extensive cystic degeneration. (See "Cystic thyroid nodules", section on 'Fine-needle aspiration'.)

Fine-needle capillary (FNC) sampling — FNC (also called fine-needle nonaspiration biopsy) is a variation of FNA in which the sample is obtained by repetitively moving within the nodule a 25- to 27-gauge needle that is not attached to a syringe [7,8]. After the needle is removed from the nodule, a syringe containing air is used to express the sample on a slide, which is smeared, stained, and submitted for cytologic interpretation. An FNA done with the syringe attached to the needle but with no negative aspiration pressure provides similar results.

Other techniques

- Cutting (core)-needle biopsy – The use of cutting-needle biopsies to obtain a core of tissue for histopathologic analysis is an alternative to FNA [9-11]. It is almost never the initial procedure of choice,

because of a higher risk of bleeding and increased patient discomfort. The major utility of core-needle biopsy is after one or more nondiagnostic FNAs. (See 'Choice of technique' below.)

Unlike FNA, which samples many areas of a nodule, a cutting needle provides only a single core. However, a repeat biopsy with histopathology may provide better information about thyroid architecture in lesions read as follicular lesion of undetermined significance (FLUS) or suspicious for follicular neoplasm [12], and this procedure may be useful for suspected lymphoma.

- Large-needle aspiration biopsy – Large-needle aspiration biopsy is similar to FNA but uses larger needles ranging from 21- to 15-gauge. The specimen is expressed into a tube, and a cell block is prepared for histopathology. The technique has been associated with a lower rate of inadequate specimens [13]. However, there have been concerns about pain and bleeding because of the larger needle used [14]. This procedure is not commonly used but is another option when repetitive FNA is nondiagnostic.

Choice of technique

- **Initial biopsy** – Initial biopsy can be guided by palpation only or by ultrasound. More than 80 percent of clinical endocrinologists in the United States use ultrasound guidance for routine thyroid FNA [15]. (See 'Ultrasound guidance' below.)

  The two most common methods used to obtain tissue from thyroid nodules are FNA, using a syringe, and FNC sampling, which is done without aspiration. In practice, endocrinologists frequently use a combination of the FNA and FNC techniques (and refer to the combined procedure as simply FNA). The American Thyroid Association (ATA) recommends FNA as the procedure of choice for evaluating thyroid nodules [16].

  The author of this topic typically does four passes with a 25- or 27-gauge needle, some with and some without suction. In a very small minority of patients, if the sample is scant, the author uses a 21-gauge needle during FNA. A 1- or 1.5-inch needle is typically used.

  FNA and FNC have been reported to result in comparable diagnostic cytologic adequacy [17]. However, in a subsequent report of 104 thyroid aspirates, the specimens obtained by FNA were significantly more likely to be nondiagnostic than those obtained by FNC (16 versus 6 percent) [18]. In a report comparing FNA and FNC at a variety of body sites, the percentage of nondiagnostic samples was the same with both techniques, but the cytologic smears obtained with FNC were of higher quality [7]. The negative aspiration pressure used for FNA may result in more tissue damage and bleeding than FNC. This is a potential problem since blood and fibrin can obscure cells and therefore limit the ability to interpret the specimen.

- **Repeat biopsy** – For patients with nondiagnostic FNA biopsies:

  - We repeat the FNA (FNA, FNC) in approximately four to six weeks, using ultrasound guidance if not used for the first FNA.
  - If ultrasound-guided FNA is nondiagnostic, a repeat ultrasound-guided FNA will yield a diagnostic cytology specimen in 75 percent of solid nodules and 50 percent of cystic nodules [19].
  - In patients with two nondiagnostic FNAs, we routinely obtain ultrasound-guided core-needle biopsy. In one study of patients who had one nondiagnostic FNA, a core-needle biopsy provided diagnostic results in 74 percent of patients, while a repeat FNA provided a result in only 52 percent of patients [20]. After two nondiagnostic FNAs, the core needle provided a result in 86 versus 29 percent for FNA [20].

PROCEDURE

Overview — Fine-needle aspiration (FNA, FNC) is a simple outpatient office procedure that requires no advanced preparation; many patients undergo FNA at their initial visit with an endocrinologist. It is usually performed on a standard examination table in the supine position with a pillow placed under the patient's shoulders to allow for increased neck extension. We usually administer a local anesthetic. For children and adults unable to cooperate with the procedure, conscious sedation may be used.

Ultrasound guidance is used for the majority of thyroid FNAs (see 'Ultrasound guidance' below). When ultrasound is not available and the nodule is palpable, FNA can be performed by fixing the nodule between the fingers of one hand and inserting the needle with the other.

Patients taking anticoagulants or antiplatelet drugs — It is important to avoid a bloody specimen because of the potential dangers of hemorrhage and because blood may obscure the cytology and may result in a nondiagnostic aspirate. Medications that can be safely discontinued (eg, aspirin, nonsteroidal antiinflammatory drugs, clopidogrel) should ideally be discontinued five to seven days before the FNA procedure. However, anticoagulants or antiplatelet drugs should not be discontinued if it places the patient at high risk of a complication, and we generally do not reschedule the procedure if the patient did not discontinue these drugs.

Nodules that are anterior and not low lying in the neck can readily be compressed against the trachea to achieve hemostasis and can usually be safely aspirated despite anticoagulation (including warfarin), using a 27-gauge needle and a minimum number of passes, with compression for 5 to 10 minutes following the procedure. Some clinicians feel that the procedure is safer when the international normalized ratio (INR) is <2. In addition, some clinicians repeat the sonogram 15 to 30 minutes after the procedure to assure hemostasis and absence of hematoma.

There are limited data on the safety of thyroid FNA in patients on systemic anticoagulation. The risk of stopping systemic anticoagulation before an FNA procedure must be weighed against the risk of complications related to clotting and thrombosis. There have been reports that not discontinuing direct oral anticoagulants (eg, dabigatran) before FNA is safe [21].

Ultrasound guidance

Indications — When available, we suggest ultrasound-guided FNA for the majority of nodules. Ultrasound-guided FNA is essential for those nodules that are:

- Nonpalpable or difficult to palpate
- Predominantly cystic
- Nondiagnostic after palpation-guided FNA
- Small and located in close proximity to blood vessels

In addition, we use ultrasound to guide FNA in an area of a goiter that is different from the rest of the goiter (ie, firmer, painful, tender, growing, or has suspicious ultrasonographic characteristics), for assessment of recurrent thyroid cancer, and for cytological evaluation of suspicious lymph nodes.

Puncturing the nodule — Real-time ultrasonography is used to observe the insertion of a needle freehand or using a special needle guide attached to the transducer. The freehand technique offers greater flexibility. With the freehand method, the needle is inserted into the skin at a distance from the transducer, aiming at the palpated nodule.

The needle trajectory can either be parallel to or at an angle to the ultrasound beam. The parallel approach is technically challenging, but it has the advantage that the image of the needle shaft may be viewed as it traverses the neck into the nodule. The needle path is observed on the screen, while the operator maneuvers the needle to puncture the nodule. Many experienced operators prefer the simplicity, speed, and lack of

complications that result when the needle is inserted oblique or perpendicular to the ultrasound beam. In this case, the needle tip is seen when it crosses the plane of the ultrasound as a very bright spot. With either method, the position of the needle tip within the nodule must be verified at the instant of sampling.

Transducers fitted with a needle guide are preferred by some clinicians, but they are cumbersome and require considerable practice and hand-eye coordination, unless a dedicated sonographer is assisting with the procedure.

Doppler ultrasound can be used to identify and avoid puncturing blood vessels that are encountered in the process of biopsy, thereby improving the specimen and cytological interpretation [22]. This feature is a distinct advantage over palpation-guided biopsy.

Lymphadenopathy — Cytological, immunocytological, and biochemical diagnosis of lymphadenopathy is facilitated by ultrasound-guided aspiration biopsy, in particular when the nodes are not palpable or are close to the jugular vein or carotid artery. Combined cytological and biochemical analysis of enlarged cervical lymph nodes can differentiate accurately between thyroid cancer metastases and inflammatory lymphadenopathy [23]. The presence of high levels of thyroglobulin in needle washings of aspirates of lymph nodes is presumptive evidence of metastatic thyroid cancer despite negative cytology, and serum antithyroglobulin antibodies do not adversely affect tissue thyroglobulin measurements [24]. (See "Differentiated thyroid cancer: Role of serum thyroglobulin".)

Tissue sampling — The sample of tissue may be obtained with or without aspiration, as described above (see 'Choice of technique' above). In addition to cytology, tissue sampling can provide cells for biochemical analysis like calcitonin in medullary cancer, parathyroid hormone in suspected parathyroid adenomas or cysts, and chromosomal and genetic information [25,26]. Molecular analysis is particularly useful in the correct diagnosis of aspirates that show follicular neoplasm or follicular lesion/atypia of undetermined significance. (See "Evaluation and management of thyroid nodules with indeterminate cytology", section on 'Molecular markers'.)

Preparation of slide — The cellular material is quickly but gently expelled directly onto a microscope slide with an air-filled syringe and suitably spread, fixed, and stained or collected in a liquid preservative from which thin-layer preparations are made. Diff-Quik and Ultrafast Papanicolaou stains are the most commonly used preparations [27]. Air-dried Diff-Quik stained smears are frequently used for on-site evaluation of the aspirated material. Background colloid is easily identified with the Diff-Quik stain. Papanicolaou stain is applied after fixing the smears in alcohol. This stain is better for identifying cellular details such as nuclear features. Most cytopathology labs use a combination of staining techniques.

Complications — FNA is a simple and safe procedure that has reduced the percentage of patients undergoing unnecessary thyroidectomy. Local pain and hematomas are the most common complications, while serious adverse events are rare. This was illustrated in a systematic review of 13 studies including 18,156 individuals undergoing thyroid biopsy [28,29]. The following findings were noted:

- Local pain and/or discomfort were minor, transient, and well tolerated, but several studies reported subsets of patients (2 to 8 percent) with moderate pain lasting up to several days. Pain was more common when deep-seated, nonpalpable nodules were biopsied, but the procedure rarely had to be discontinued because of patient discomfort. Local lidocaine or xylocaine anesthesia can help minimize pain.

- There was inconsistency in the reported frequency of hemorrhage/hematomas during or after thyroid biopsy with a range of 0.3 to 26 percent. Small- to moderate-sized hematomas were managed with cold compresses and almost always resolved spontaneously within several days. Massive hematoma with airway obstruction was seen in only a few cases.

  Other complications are rare and include acute transient thyroid swelling, infection, tracheal puncture, needle track seeding (ie, tumor implantation), and recurrent laryngeal nerve injury with vocal cord

paralysis. In another series, recurrent laryngeal nerve injury occurred in 4 out of 10,974 biopsies (0.036 percent), which resolved in all cases within six months [30].

Complications following core-needle biopsy were reported to be 0.81 percent among 6687 ultrasound-guided biopsies in one series [31]. Four patients had serious complications including massive hemorrhage, voice change, and pseudoaneurysm.

SENSITIVITY AND SPECIFICITY — The overall accuracy of fine-needle aspiration (FNA) exceeds 95 percent. The false-negative rate of a benign interpretation is 0 to 3 percent [6,32]. In one series, patients with a cytologic benign diagnosis had a 90 percent probability of benign disease [33]. When confirmed with repeat FNA, the probability increased to 98 percent.

The positive predictive value of a malignant interpretation is 97 to 99 percent [32]. As an example, in a report of 2587 sequential patients evaluated by thyroid ultrasound, 3589 nodules were aspirated under ultrasound guidance [6]. The cytologic diagnoses positive for malignancy and no malignant cells were 97 and 99.7 percent predictive, respectively. In a similar report of 4703 FNA samples, the sensitivity and specificity of thyroid FNA for the diagnosis of malignancy were 94 and 98.5 percent, respectively [34]. However, these sensitivity and specificity data are not applicable to follicular neoplasms. (See "Atlas of thyroid cytopathology", section on 'Follicular neoplasm or suspicious for follicular neoplasm' and "Evaluation and management of thyroid nodules with indeterminate cytology", section on 'Follicular neoplasm'.)

DIAGNOSTIC CATEGORIES — There are six major categories of results that are obtained based upon fine-needle aspiration (FNA) cytology (table 1), each of which indicates a different subsequent evaluation and management [5,35]. The cytopathologic changes and subsequent evaluation and management are reviewed in more detail elsewhere. (See "Atlas of thyroid cytopathology" and "Diagnostic approach to and treatment of thyroid nodules" and "Evaluation and management of thyroid nodules with indeterminate cytology".)

SOCIETY GUIDELINE LINKS — Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Thyroid nodules and cancer".)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Thyroid nodules (The Basics)")
- Beyond the Basics topics (see "Patient education: Thyroid nodules (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- The clinical importance of thyroid nodules is primarily related to the need to exclude thyroid cancer, which is present in 4 to 6.5 percent of thyroid nodules. Thyroid biopsy is an important component of the evaluation of a thyroid nodule (algorithm 1). It is the most accurate method for evaluating thyroid nodules and selecting patients for thyroid surgery. (See 'Introduction' above.)
- The two most common methods used to obtain tissue from thyroid nodules are fine-needle aspiration (FNA), using a syringe, and fine-needle capillary (FNC) sampling, which is done without aspiration. In

practice, endocrinologists frequently use a combination of the FNA and FNC techniques (and may refer to the combined procedure as simply FNA). (See 'Techniques' above and 'Choice of technique' above.)

- FNA (FNA, FNC) is a simple outpatient office procedure that requires no advanced preparation; many patients undergo FNA at their initial visit with an endocrinologist. It is usually performed on a standard examination table in the supine position with a pillow placed under the patient's shoulders to allow for increased neck extension. We usually administer a local anesthetic. (See 'Overview' above.)

- Ultrasound guidance is used for the majority of thyroid FNAs. When ultrasound is not available and the nodule is palpable, FNA can be performed by fixing the nodule between the fingers of one hand and inserting the needle with the other. (See 'Ultrasound guidance' above.)

- Medications that can be safely discontinued (eg, aspirin, nonsteroidal antiinflammatory drugs, clopidogrel) should ideally be discontinued five to seven days before the FNA procedure. However, these drugs should not be discontinued if it places the patient at high risk of a complication, and we generally do not reschedule the procedure if the patient did not discontinue these drugs.

  Anticoagulant agents such as warfarin are also preferably discontinued four to five days before FNA, if the cardiologist or neurologist feel that holding anticoagulation is safe. However, nodules that can readily be compressed against the trachea to achieve hemostasis can be safely aspirated despite anticoagulation, using a 27-gauge needle and a minimum number of passes, with compression for 5 to 10 minutes following the procedure. (See 'Patients taking anticoagulants or antiplatelet drugs' above.)

- Local pain and hematomas are the most common complications, while serious adverse events are rare. (See 'Complications' above.)

- There are six major diagnostic categories of results that are obtained based upon FNA cytology (table 1), each of which indicates a different subsequent evaluation. (See "Diagnostic approach to and treatment of thyroid nodules", section on 'Management' and "Evaluation and management of thyroid nodules with indeterminate cytology", section on 'Our approach'.)

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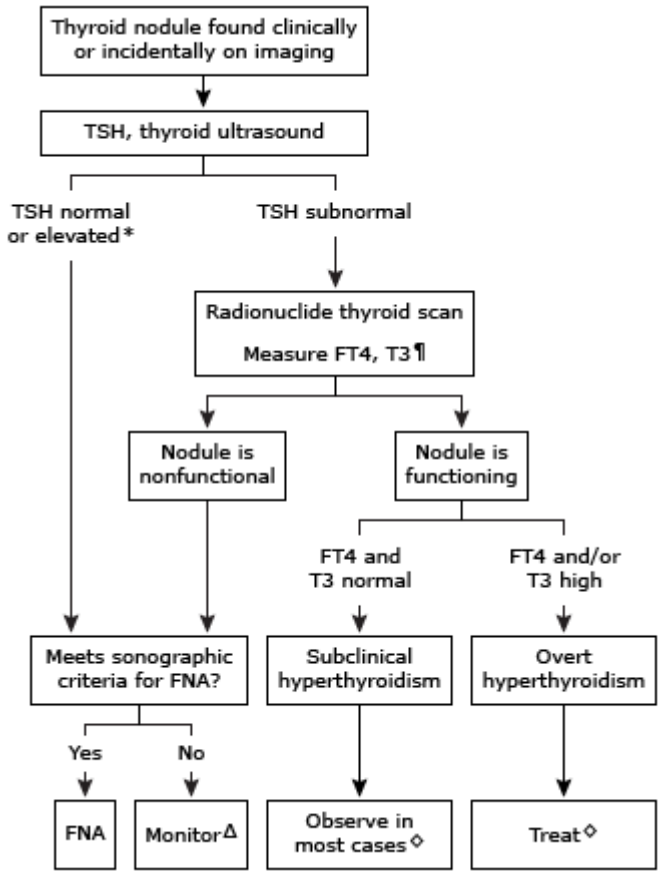
Topic 7889 Version 14.0

GRAPHICS

Initial evaluation of a patient with a thyroid nodule



This algorithm is intended to be used in conjunction with additional UpToDate content on thyroid nodules.

TSH: thyroid-stimulating hormone; FT4: free thyroxine; T3: triiodothyronine; FNA: fine-needle aspiration.
* Patients with TSH above the normal range require an evaluation for hypothyroidism. Refer to UpToDate content on hypothyroidism.
¶ Patients with TSH below the normal range require an evaluation for hyperthyroidism. Refer to UpToDate content on hyperthyroidism.
Δ Thyroid nodules that do not meet sonographic criteria for FNA should be monitored with periodic ultrasonography. The frequency of evaluation (ranging from 6 to 24 months) depends upon the sonographic features of the nodules.
◇ Selected cases of subclinical hyperthyroidism warrant treatment. Refer to UpToDate content on subclinical hyperthyroidism and toxic adenoma.

Graphic 90862 Version 4.0

Bethesda system diagnostic categories for reporting thyroid cytopathology

Bethesda class	Diagnostic category	Cancer risk
I	Nondiagnostic (unsatisfactory)	5 to 10%
II	Benign	0 to 3%
III	Atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS)	10 to 30%
IV	Follicular neoplasm (or suspicious for follicular neoplasm)	25 to 40%
V	Suspicious for malignancy	50 to 75%
VI	Malignant	97 to 99%

Data from: Cibas ES, Ali SZ. The 2017 Bethesda system for reporting thyroid cytopathology. Thyroid 2017; 27: 1341.

Graphic 106281 Version 3.0

Contributor Disclosures

Douglas S Ross, MD Consultant/Advisory Board: Medullary Thyroid Cancer Registry Consortium [Thyroid cancer]; Shire [Hypoparathyroidism (Parathyroid hormone for injection)]; Spectrix Therapeutics, LLC [Hypothyroidism (Thyroid hormone)]. Other Financial Interests: Abbott India (honorarium) [Hyperthyroidism (carbimazole, levothyroxine)]; Quest Diagnostics (honorarium) [Hyperthyroidism]. **David S Cooper, MD** Nothing to disclose **Jean E Mulder, MD** Nothing to disclose

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