Thyroid Aspiration Cytology
Current Status

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Abstract

In the adult population, thyroid nodules are common and are increasingly detected by ultrasound examination or other scanning techniques. Depending on their size and ultrasonographic features, these nodules may require further investigation, including tissue diagnosis. Fine-needle aspiration (FNA) has become the predominant method to obtain tissue for microscopic analysis. In October 2007, the National Cancer Institute sponsored a conference to review the state of the science for the use of FNA in the management of thyroid nodules. This conference reviewed indications for thyroid FNA and pre-FNA requirements, training and credentialing, techniques for thyroid FNA, diagnostic terminology and morphologic criteria, utilization of ancillary studies, and post-FNA testing and treatment options. The results of those discussions have been published in both print and electronic versions. The aim of the current article was to discuss indications for FNA, diagnostic terminology, and post-FNA options, issues that are important to physicians who are managing patients with thyroid nodules. CA Cancer J Clin 2009;59:99-110. ©2009 American Cancer Society, Inc.

Introduction

Fine-needle aspiration (FNA) is frequently used to diagnose thyroid nodules discovered by either palpation or imaging studies. Despite a long history of clinical application of FNA in the diagnosis of thyroid nodules and attempts by several professional organizations to clarify appropriate utilization, terminology, diagnostic criteria, post-FNA follow-up, and therapeutic options, no universally accepted guidelines or recommendations exist. Clinical practice guidelines or recommendations have been developed by many, including the Papanicolaou Society, the American Thyroid Association, the American Association of Clinical Endocrinologists, and the Italian Association for Medical Endocrinology (Associazione Medici Endocrinologi).

In October 2007, the National Cancer Institute (NCI) sponsored a conference to review the state of the science for the use of FNA in the management of thyroid nodules. The conference was preceded by a Web-based discussion among endocrinologists, surgeons, radiologists, and cytopathologists. Discussion topics were divided into six categories, each addressed by a separate committee as follows: (1) indications for thyroid FNA and pre-FNA requirements, (2) training and credentialing, (3) techniques for thyroid FNA, (4) diagnostic terminology and morphologic criteria, (5) utilization of ancillary studies in thyroid FNA, and (6) post-FNA testing and treatment options. Each discussion topic was assigned to a committee composed of endocrinologists, thyroid surgeons, radiologists, and cytopathologists. After

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the October 2007 Bethesda meeting, a summary document was published, both electronically and in print.\textsuperscript{1-5} This review was based largely on the NCI conference and summarized the state of the art for indications to perform a thyroid FNA, pre-FNA requirements, diagnostic terminology, and post-FNA testing and treatment options. Summaries of committee findings for training and credentialing\textsuperscript{6} and utilization of ancillary techniques in thyroid FNA\textsuperscript{7} can be found elsewhere.

**Indications for Performing an FNA of a Thyroid Nodule**

Indications for performing an FNA of a thyroid nodule depend on the diagnostic modality used to discover the nodule. Nodules initially detected by palpation are usually 1.0 cm or greater in dimension; they are considered clinically significant and require further evaluation.\textsuperscript{8-12} In order to determine whether FNA is indicated, evaluation of a palpable thyroid nodule requires a complete clinical history and physical examination directed to the thyroid gland and cervical lymph-node chains, as well as a serum thyrotropin (TSH) measurement to guide the strategy for diagnostic imaging.\textsuperscript{12-15} Patients with normal or elevated TSH should next undergo an ultrasound examination, whereas those with a suppressed TSH level (\textless 0.1 mIU/L) should have a radionuclide thyroid scan performed.\textsuperscript{6,8,10-14,16} In general, functioning thyroid nodules in the absence of significant clinical findings do not require investigation by FNA. Nodules that demonstrate either isofunction or hypofunction on a radionuclide scan should be further assessed by ultrasound.\textsuperscript{6-10}

Thyroid nodules initially detected by imaging studies may require investigation by FNA, depending on their size and the type of imaging method used at the time of their initial discovery. For example, thyroid nodules incidentally detected by fluorine F 18-2-fluoro-2-deoxy-D-glucose positron emission tomography (\textsuperscript{18}F-FDG-PET) have a relatively high risk of malignancy,\textsuperscript{17-20} and when uptake is localized focally within the thyroid, FNA should be performed to rule out malignancy. If uptake is diffusely increased throughout the thyroid on \textsuperscript{18}F-FDG-PET, FNA is not needed unless a thyroid ultrasound identifies a discrete nodule. Circumscribed hot nodules incidentally detected by technetium Tc 99m-sestamibi scans should undergo FNA once confirmed by thyroid ultrasound to be discrete nodules.\textsuperscript{21-24} Such nodules appear to have a high risk of malignancy (22\% to 66\%).\textsuperscript{21-25} Few data exist on the prevalence of malignancy among thyroid nodules detected by computed tomography (CT) or magnetic resonance imaging (MRI). At least 16\% of patients evaluated by CT or MRI for potential metastatic disease to cervical lymph nodes from nonthyroid head and neck primary tumors have thyroid nodules.\textsuperscript{26} Based on limited data indicating that prevalence of thyroid cancer in these patients may be as high as 10\%, they should undergo dedicated thyroid sonographic evaluation, and FNA should be considered for any nodule demonstrating sonographically suspicious features.\textsuperscript{26,27}

Thyroid nodules incidentally detected by ultrasound performed for carotid or parathyroid disease have a risk of malignancy of approximately 10\%,\textsuperscript{24-37} Such nodules should undergo dedicated thyroid sonographic evaluation. Lesions with a maximum diameter \textgreater 1.0 cm to 1.5 cm should undergo FNA, unless they are simple cysts or septated cysts with no solid elements. In some instances, FNA may be replaced by periodic follow-up (at 6-month to 18-month intervals) for nodules \textless 1.0 cm when the nodule has no sonographic features of malignancy. A nodule \textless 1.0 cm but with sonographically suspicious features should also be considered for FNA. Sonographically suspicious features include (1) microcalcifications; (2) hypoechogenic, solid nodules; (3) nodules with irregular or lobulated margins; (4) intranodular vascularity; (5) a taller-than-wide shape; and (6) signs of spread beyond the capsule of the nodule. There is a lack of consensus on the smallest size nodule that could or should be biopsied; the American Association of Clinical Endocrinologists and the Associazione Medici Endocrinologi\textsuperscript{38} suggest selection based on ultrasound appearance rather than on nodule size, whereas the American Thyroid Association\textsuperscript{8} recommendation is to perform an FNA on nodules \textlesseq\textless 1.0 cm to 1.5 cm found to appear suspicious on ultrasound.

Before proceeding with FNA of a thyroid nodule, one must decide whether it should be performed by direct palpation or with ultrasound guidance, realizing that in many cases either approach is acceptable. Because recent guidelines recommend that all pa-
Patients with palpable nodules undergo ultrasound examination, and an increasing number of biopsies are now being performed with ultrasound guidance. Published data indicate that ultrasound evaluation and ultrasound guidance reduce the rate of nondiagnostic specimens and false-negative aspirates.

When initial palpation-guided biopsy proves to be either benign or nondiagnostic, reaspiration by ultrasound-guided FNA may result in reclassification of some of these nodules and the detection of additional carcinomas. Specific ultrasound findings, such as irregular margins, microcalcifications, and intranodular vascularity, can identify nodules at increased risk for malignancy and aid in the interpretation of FNA results. Despite the potential advantages of ultrasound-guided FNA, palpation-guided FNA has been performed on many patients with a high level of success. In addition, palpation-guided FNA is less costly and more convenient compared with ultrasound-guided FNA, and palpation-guided FNA is preferred in areas of the world where health care resources are limited.

Palpation-guided FNA can be performed when a thyroid nodule is easily palpable (≥1.0 cm in diameter) and predominantly solid. Sonographic evaluation is often helpful, because physical examination may be imprecise in determining nodule size and location, confirming its origin within the thyroid rather than in adjacent tissues. Thyroid glands that are enlarged because of diffuse or asymmetrical goiter without a discrete nodule on physical examination are suboptimal targets for palpation-guided FNA. Ultrasound guidance is preferred and appears to be more sensitive than palpation-guided FNA for poorly palpable nodules, those that are predominantly cystic (>25%), small nodules (<1 cm), and when a prior FNA was nondiagnostic.

Pre-FNA Requirements

Informed consent (verbal or written) is required before thyroid FNA is performed. Legislation regulating the conditions under which consent must be obtained varies greatly by state. Physicians performing thyroid FNA need to use informed consent policies and forms based on state regulations. Thyroid FNA informed consent materials, including written documents, if used, should describe the procedure and potential risks and complications. The possibility of more frequently occurring complications (slight pain and minor hematoma) should be noted. Information should be presented in a manner that is easily understood by the patient; questions and concerns should be answered. The possibility of nondiagnostic results, and the need for rebiopsy, should be stated. Presentation of estimates of accuracy, false-negative, and false-positive percentages is not mandatory, and these estimates should be presented only when the practitioner believes such data will facilitate patient comprehension.

Federal regulations require that specific identifying information be provided to laboratories with all specimens submitted for laboratory evaluation in the United States. These data include the name and address of the person requesting the test, the patient's name or unique identifier, the patient's sex, the patient's age or date of birth, the name of the test to be performed, the specimen source, the date of specimen collection, and any additional relevant information. Discussants at the NCI meeting agreed that additional relevant information for a thyroid FNA specimen should include the nodule's location and size; any family history of thyroid cancer; and any personal history of hypothyroidism, autoimmune

FIGURE 1. Post-FNA Management for Diagnostic Categories.
thyroiditis, a positive test for antithyroid antibodies, Graves disease, and treatment with I 131 or external radiation therapy (with neck irradiation being particularly relevant).

Specifying the nodule’s location (right or left lobe; isthmus; upper pole; midpole; lower pole; etc) on the requisition form permits correlation with results of ultrasonography and subsequent histopathologic examination (if or when obtained). Documenting the location of the aspirated nodule is also important because many patients have multiple synchronous or metachronous nodules (some, but not all, of which may be biopsied). This information can be helpful to the cytopathologist evaluating the aspirate. For example, large nodules may be associated with the higher risk of malignancy,57 some cytologic features of Hashimoto thyroiditis overlap those seen in papillary carcinoma,58,59 and I 131 therapy or external-beam radiation may result in nuclear alterations that simulate those seen in malignancy.60,62 In occasional patients with Graves disease, aspirates of thyroid nodules may contain benign pleomorphic cells, which may be misinterpreted as malignant.63 Requisition forms should especially note any family history of papillary or medullary carcinoma and any personal history or neoplasms associated with familial thyroid cancer syndromes. Including information such as results of prior FNAs, history of treatment of the patient with levothyroxine, TSH level, and results of ultrasound and nuclear-medicine imaging studies is often helpful but not required.

Techniques for Thyroid FNA

Aspiration Devices, Needles, and Methods
Commonly available 25-gauge to 27-gauge needles are small enough to minimize bleeding and pain yet still large enough to obtain adequate samples of the lesion in most cases, and are therefore preferred, especially for initial biopsies. Larger needle sizes (22-gauge or 23-gauge) are generally reserved for drainage of viscous colloid cyst contents. Although some clinicians use a needle and syringe without any other device, or even a needle alone (the Zajdela technique), some may prefer to use pistol- or pencil-type syringe holders such as the Cameco Syringe Gun (Precision Dynamics Corporation, Burbank, Calif), the Tao aspirator (Tao & Tao Technology, Camano Island, Wash), and the Inrad Aspiration Biopsy Syringe Gun (Inrad, Grand Rapids, Mich).

Surface tension is strong enough to draw the sample into smaller diameter needles (analogous to blood collection in a capillary tube) and often makes devices for additional suction unnecessary. When additional suction is required (for drainage of thick cyst contents), the Zajdela technique64 can be adapted by interposing a section of intravenous tubing between the needle held by the physician and the syringe held by an assistant who applies suction with the syringe.

Regardless of whether the needle is guided by palpation or ultrasound, basic technique of thyroid FNA remains essentially the same and has been described in detail elsewhere.65 When observed with ultrasound imaging, if the nodule is complex, the wall, solid elements, and suspicious calcified areas should be sampled, and cystic areas should be avoided. Moving the needle back and forth within the nodule with about 5 to 10 oscillations per second greatly increases cell yield by cutting small fragments of tissue from the needle’s path. A dwell time of 2-5 seconds within the nodule (with continuous oscillations) generally provides good cell yield without excessive blood contamination and efficiently produces one to two slides per biopsy pass.

Most patients do not experience significant pain from the FNA procedure. However, the procedure can cause some discomfort and anxiety, both of which may be minimized by use of local anesthesia. For this reason, some experienced FNA physicians use local anesthesia for all thyroid FNAs, some do not use local anesthesia, and others individualize the decision based on factors such as nodule location and patient preference.66 For deep, nonpalpable thyroid nodules that may require more time and probing to reach the nodule, and for all core biopsies, local anesthesia is recommended.

The local anesthetic of choice is 1% lidocaine or Lidocaine 2% Epinephrine 1:100,000. Approximately 0.5 ml of anesthetic should be injected by using a long 25-gauge to 27-gauge needle. Anesthetic is slowly introduced into the subcutaneous fat (not the dermis), allowing the anesthetic to back-infiltrate the dermal nerves rather than creating a painful intradermal wheal. Local anesthetic may cause difficulty in subsequent sample evaluation if the anesthetic solution is aspirated...
and becomes mixed with the specimen, so careful attention to the volume and precise location of anesthetic is important.

**Preparation of FNA Material for Routine Examination**

The FNA specimen may be directly smeared on glass slides for air-dried or alcohol-fixed (by spraying or immersion) preparations stained by the Romanowsky or Papanicolaou techniques, respectively. Although some cytopathologists use one technique or the other exclusively, many feel that they provide complementary information and prefer a combination. It is important to identify which slides are air dried and which are fixed so that the laboratory can stain them appropriately. Poor smearing technique and issues involving specimen transportation to the laboratory have resulted in the use of liquid-based processing at some institutions or practices. Liquid-based cytology processing can be used either alone or as a supplement to direct smears. For liquid-based cytology, the aspiration needle can be flushed with a small amount (approximately 0.5 ml) of solution such as balanced saline, or Hanks solution (if same day transport to the laboratory is expected); or with a fixative, such as CytoLyle (Cytyc, Marlborough, Mass), Preservcyte (Cytyc, Marlborough, Mass), or CytoRich Red (Thermo Fisher Scientific, Waltham, Mass), which is necessary for optimal cell preservation if delayed processing is expected or may occur. Cell-rich liquid specimens can also be used for cell-block preparation when needed. Residual cyst fluid may be submitted to the laboratory in a fresh or fixed state for further processing by either liquid-based cytology or cell block. Direct smears, however, are essential for immediate assessment.

Immediate cytologic assessment is helpful, as it determines specimen adequacy and may improve triage of specimens to methods that optimize its diagnostic value.²⁶,⁶⁷-⁷³

**Optimal Number of Passes**

Although studies show that the more passes performed the higher the adequacy rate,⁶⁸,⁷³,⁷⁴ between two and five passes appear to be a reasonable number to optimize the likelihood of obtaining adequate sampling of a solid or cystic nodule. A reasonable protocol to follow when rapid interpretation is available is to take two biopsies or passes (one each from different areas of the lesion) with a representative slide from each stained for adequacy. Additional sampling of a nodule is unnecessary when a cyst is completely drained and no residual mass is identified, if a specific malignancy is identified (and no ancillary tests are deemed necessary for confirmation), or when the aspirate appears adequate. Additional biopsies are recommended when there is a residual mass after a cyst has been drained, if cellularity from the initial two passes is inadequate, or to enrich a sample for cell-block preparations or ancillary studies.

When rapid interpretation is not available, a reasonable protocol would be two to five biopsies from different sites with representative tissue from each pass smeared on one to two slides and/or the tissue rinsed in a collection tube for either liquid-based cytology or cell-block preparation.

**Adequate Sampling of Solid and Cystic Lesions**

An FNA sample must be sufficient for an interpretation with a low likelihood of a false-negative diagnosis. Depending on the clinical and ultrasonographic findings, persistently inadequate FNA results from a nodule necessitate surgery.¹⁰,⁵⁰

Adequacy defines the quality and quantity of a sample, a definition that varies not only with respect to the site sampled but also with respect to the type of lesion sampled. Hence, adequacy criteria are organ-specific. Some authors believe cellularity criteria for adequacy also vary depending on whether the aspirated lesion is solid or cystic and whether the aspirate was performed under palpation or ultrasound guidance. All thyroid FNAs must be technically adequate, with well-preserved and well-prepared thyroid follicular epithelial cells for interpretation. Aspirates that contain only cyst fluid, histiocytes, and erythrocytes are inadequate. Some authorities have recommended a minimum for cell counts (6 clusters of at least 10 follicular epithelial cells on 2 or more slides) to assure specimen adequacy.¹⁰,⁷⁴-⁷⁶

**Diagnostic Terminology and Morphologic Criteria for Cytologic Diagnosis of Thyroid Lesions**

Several classification schemes have been suggested by professional societies and by authors on the basis of their personal or institutional experience.²⁶,³⁰,³⁴,³⁸,⁷⁵-⁸²
recent survey of pathologists’ and clinicians’ perceptions of diagnostic terminology and cytopathology reports for thyroid FNAs demonstrated significant discordance between pathologists and clinicians.83

A majority of studies favor a tiered classification system for thyroid FNA reporting. Systems range from three to six or more diagnostic categories. The system currently and most commonly used contains six categories as follows: benign, lesion (atypia) of undetermined significance, follicular neoplasm, suspicious, malignant, or nondiagnostic.77,79,81-83 This scheme is summarized in Table 1 and discussed below.

I. Benign
A. Category has low risk of malignancy (<1%)
B. Category includes, but is not limited to, the following entities:
   1. Nodular goiter
   2. Chronic lymphocytic thyroiditis (Hashimoto thyroiditis)
   3. Hyperplastic/adenomatoid nodule
   4. Colloid nodule

II. Atypia (Lesion) of Undetermined Significance
A. Risk of malignancy is between 5% and 10%
B. Heterogeneous category includes cases in which the cytologic findings are not convincingly benign, yet the degree of cellular or architectural atypia is insufficient for an interpretation of follicular neoplasm, Hurthle cell neoplasm, or suspicious for malignancy.

C. Some members of Committee IV suggested that this category be optional and laboratories choosing to use it should minimize its use to represent <7% of all thyroid FNA interpretations.

III. Follicular Neoplasm (Suspicious for Follicular Neoplasm)
A. Low to intermediate risk of malignancy (20% to 30%).
B. Category applies to nonpapillary follicular-patterned lesions/neoplasms and Hurthle cell lesions/neoplasms.
C. The majority of studies have shown that up to 20% of thyroid lesions classified as follicular neoplasm are found to be malignant on surgical excision. The risk of malignancy in Hurthle cell lesions may be greater than 20% when the nodule is equal to or larger than 3.5 cm.
D. Other terms that have been used for this category include:
   1. Microfollicular proliferation/lesion,
   2. Suggestive of neoplasm,
   3. Follicular lesion,
   4. Suspicious for follicular neoplasm. This latter term is acceptable, and some laboratories prefer it for its clarity and for risk-management reasons.

IV. Suspicious for Malignancy
This term is used as
1. Suspicious for papillary carcinoma (a majority of cases in this group [50% to 75%] are found to be a follicular variant of papillary carcinoma).
2. Suspicious for medullary carcinoma (applies to cases cytologically suspicious for medullary carcinoma but in which there is insufficient specimen to perform confirmatory immunocytochemical staining for calcitonin. The cytology report may include a recommendation to assay serum calcitonin levels for confirmation of the cytologic impression).
3. Suspicious for other primary or secondary malignancies.
4. Suspicious for neoplasm because of total necrosis of lesional cells (anaplastic carcinoma).

| SUGGESTED CATEGORY          | ALTERNATE CATEGORY* | RISK OF MALIGNANCY† |
|-----------------------------|---------------------|----------------------|
| Benign                      | —                   | <1%                  |
| Atypia of undetermined      | Indeterminate follicular lesions | 5-10%              |
| Atypia of undetermined      | R/O neoplasm        | 5-10%                |
| Atypia of undetermined      | Atypical follicular lesion | 5-10%              |
| Atypia of undetermined      | Cellular follicular lesion | 5-10%              |
| Neoplasm                    | Suspicious for neoplasm | 20-30%             |
| Suspicious for malignancy   | —                   | 50-75%               |
| Malignant                   | —                   | 100%                 |
| Nondiagnostic               | Unsatisfactory      | —                    |

*These terms can be used instead of the suggested category terms (based on website response and National Cancer Institute meeting attendees).
†Data collected from literature.1,9,10,34,48,75,77,80-82

TABLE 1. National Cancer Institute Thyroid Fine-Needle Aspiration (FNA) Guidelines Committee IV: The Suggested Thyroid FNA Classification Scheme
V. Malignant

Specimen is diagnostic of papillary carcinoma, medullary carcinoma, anaplastic carcinoma, or metastatic carcinoma. When using the diagnostic category of malignant, the type of malignancy should be stated whenever possible. A diagnosis of malignant is associated with a false-positive rate of less than 1%.

VI. Nondiagnostic

Specimen is processed and examined but is nondiagnostic due to
1. Limited cellularity,
2. No follicular cells present,
3. Poor fixation, excessive blood, and/or poor cell preservation.

The cytomorphologic criteria for diagnosis of lesions of the thyroid along with differential diagnostic features have been previously well described.58,84-113

Post-FNA Options for Testing and Treatment of Thyroid Nodules

Follow-Up of Nondiagnostic FNA Results

There is no universally accepted approach to follow-up of nondiagnostic thyroid FNAs. The strategy given here is based on the American Thyroid Association’s proposal, review of the literature, and discussions at the NCI’s Conference on FNA of the Thyroid.1,8 Nondiagnostic aspirates obtained from cystic and solid nodules are treated differently in follow-up strategies. Follow-up of aspirates of cysts that contain blood and histiocytes but no epithelial component require correlation with ultrasound findings.39 Many cystic colloid nodules contain only central colloid surrounded by a thin rim of benign follicular epithelium, which explains the frequent absence of follicular epithelium in these aspirates. Cysts with these FNA findings are at very low risk for harboring a malignancy, and many authors have recommended that they are best managed by nonsurgical follow-up. Other authors51,78 noting the low, but real, incidence of cystic papillary carcinoma in these cysts recommend surgical resection after two nondiagnostic aspirations. Although the optimal timing of repeat needle aspirations has not been established, 6 months to 18 months appears reasonable. When ultrasound demonstrates suspicious areas, the NCI conference report recommends that patients with cystic lesions and a nondiagnostic aspirate should undergo repeat FNA.1,114,115 The repeat FNA should be done under ultrasound guidance with intraprocedural review of direct smears by a cytologist whenever possible.39,72 When repeat FNA still yields nondiagnostic material, close clinical and ultrasonographic follow-up is appropriate.39

Solid nodules with nondiagnostic FNA results should be aspirated under ultrasound guidance, and, when possible, intraprocedural review should be performed by a cytologist. If these repeat specimens are still nondiagnostic, surgery should be considered because malignancy is eventually diagnosed in about 9% of such cases. If the patient is likely to return for follow-up and the nodule is 1 cm or less in size, then close clinical follow-up with ultrasound examination is a reasonable alternative to surgery.39 When growth of the nodule is detected during ultrasound surveillance, then excision or, preferably, repeat FNA is recommended. In general, for both solid and cystic nondiagnostic aspirates, a waiting period of at least 3 months should elapse between the initial nondiagnostic aspirate and respiration. This waiting period allows resolution of tissue changes secondary to FNA. A shorter waiting period may be appropriate when clinical or ultrasonographic findings suggest a high suspicion of carcinoma.

Follow-Up of Benign FNA Results

Strategies for management of patients with benign FNA results vary among practitioners and institutions. Because the false-negative rate for cytologically benign thyroid nodules is as high as 5%, careful clinical follow-up of these nodules is required.40,116-118 Patients with multiple thyroid nodules have the same risk of malignancy as those with a single nodule, and the same follow-up plan is used for both groups. Nodules with suspicious ultrasound115,116 features deserve more frequent clinical and ultrasonographic follow-up after a benign FNA diagnosis. The false-negative rate may be higher when FNAs are directed by palpation rather than by ultrasound.40-42,115,116 Thus, palpation-directed FNAs may require closer clinical follow-up.

Thyroxine (T4)-suppression therapy to manage a cytologically benign nodule is no longer recommended.
Randomized trials have suggested that thyroid-hormone suppression may result in a decrease in nodule size in some patient populations with borderline low iodine intake but not in most patients ingesting sufficient iodine.116-122 Most nodules do not respond to T4-suppression therapy, and because of potential side effects of long-term TSH suppression, this practice has been abandoned in most countries.121-123 Neither recent American Thyroid Association (ATA), American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi (AACE/AME) Task Force on Thyroid Nodules guidelines, nor the NCI conference report, endorse T4-suppression therapy for a cytologically benign nodule.8,38

Nodules with benign FNA results can be followed by physical examination with ultrasound examination.39 These nodules may be reaspirated or surgically removed when significant growth occurs or worrisome changes (such as irregular margins and central hypervascularization) are noted in their ultrasonographic appearance. Ultrasonography is the best technique for detection of changes in nodule size.81,122 Although there is no universal agreement as to what constitutes a clinically significant increase, both the ATA and the NCI conference report suggest that a 20% increase in nodule diameter with a minimal increase in two or more dimensions of at least 2 mm is a reasonable definition.33 Both also recommend clinical follow-up of cytologically benign and easily palpable nodules occur at 6-18-month intervals. Obviously, when nodules are not easily palpable, follow-up with ultrasound at 6-18-month intervals is warranted.33

The total duration of the follow-up period should be at least 3 to 5 years. The repeat FNA may be performed under ultrasound guidance. When possible, immediate assessment of adequacy by a pathologist at reaspiration is appropriate. Ethanol ablation may be considered in selected patients who have predominately cystic cytologically benign nodules.

Follow-Up of FNA Specimens Diagnosed as Atypia of Undetermined Significance

The diagnostic category of atypia of undetermined significance has been defined in various ways, leading to some variability in the prevalence of malignancy in lesions in this cytologic category. Approximately 5% to 10% of nodules in the atypia of undetermined significance category are subsequently shown to be malignant, whereas the remaining 90% to 95% are adenomas or dominant nodules within a multinodular goiter.3,81 Given that this atypia category is associated with low specificity and low positive predictive value, the appropriate follow-up is controversial. Some authorities recommend repeat FNAs, repeat ultrasound scans, or radionuclide uptake studies. Reports have even suggested that use of liquid-based cytology and immunocytochemistry may improve diagnostic accuracy.38,124-128 Radiological correlation may aid in determining which cases designated atypia of undetermined significance would benefit from reaspiration or surgical intervention. Observation of ultrasonographic features such as hypoechogenicity, irregular nodule borders, calcifications, increasing size, and abnormalities of vasculature all favor a malignant nodule.33,66

The NCI report concluded that outside, expert, cytopathology consultation may be considered for some patients who have an initial diagnosis of atypia of undetermined significance. For nodules that have been cytologically designated as atypia of undetermined significance, a sodium iodide I 123 scan may be considered, especially when the TSH level is in the low or low-normal range. When the scan shows a hot nodule, clinical follow-up with repeat FNA in 3 months or 6 months is appropriate. When the scan shows a cold nodule, the patient should be referred for surgery. In patients who are suboptimal operative candidates, close clinical follow-up with repeat ultrasound to detect increasing nodule size, abnormalities of vascularization, or presence of calcifications can be performed to improve diagnostic accuracy.

Follow-Up of an FNA With the Diagnosis of Neoplasm (Follicular)

This category, also known as “Suspicious for Neoplasm” or “Neoplasm,” generally refers to follicular neoplasms, the majority of which are adenomas. This category is associated with a 20% to 30% incidence of malignancy.3,81,93,96,97

Patients with this FNA diagnosis should be referred for operative exploration. Usually, a lobectomy is performed followed by histologic examination for capsular and vascular invasion. The usefulness of frozen section in evaluation for capsular
or vascular invasion is controversial.\textsuperscript{93} The majority of participants at the NCI meeting voiced the opinion that frozen-section evaluation did not play a significant role in distinguishing follicular adenoma from follicular carcinoma. Although some surgeons request an intraoperative, frozen-section evaluation to determine the extent of thyroidectomy, this evaluation is not usually recommended. When a frozen section is not ordered, surgeons should include lobectomy plus isthmectomy in the initial surgery. An unequivocal diagnosis of follicular carcinoma is justified when subsequent histologic examination discloses capsular and/or vascular invasion. In addition, about half of the nodules in this cytologic category found to be malignant are the follicular variant of papillary thyroid cancer.\textsuperscript{80} Complete thyroidectomy is usually performed after a diagnosis of papillary or follicular carcinoma, but lobectomy alone may suffice for small, minimally invasive tumors, and treatment depends on the clinical status of the patient.

**Follow-Up of FNAs With a Diagnosis of Suspicious for Malignancy**

Approximately 50% to 75% of cytologically suspicious lesions are subsequently diagnosed as papillary carcinomas.\textsuperscript{3,93} Patients with an FNA diagnosis of suspicious for malignancy should be referred for surgical consultation. Subsequent operative intervention depends on histological review. Immunocytochemistry for calcitonin may aid in establishing a diagnosis of medullary carcinoma in cytologically suspicious cases.\textsuperscript{128,129}

**Follow-Up of Malignant FNA Results**

This FNA category refers to papillary carcinoma, medullary carcinoma, anaplastic thyroid carcinoma, lymphoma, and metastatic malignancy. Any malignancy should be classified as precisely as possible in the FNA report. When a metastasis to the thyroid from a distant primary tumor is suspected, the cytologic report should state the suspected type of primary carcinoma, and the patient should have appropriate studies performed to identify the primary site. The NCI Committee concluded that cytologic diagnosis of malignancy in a thyroid nodule should result in surgery unless clinically contraindicated, as in metastatic cancer from another primary.

Although a detailed discussion of thyroid cancer management is beyond the scope of this review, we have included some basic information that is not intended to substitute for consideration of evidence-based guidelines. Surgical intervention for primary thyroid carcinomas may initially be simple lobectomy or intraoperative frozen-section examination to determine whether a total thyroidectomy should be performed. When a frozen section is equivocal, the operative procedure is ended with lobectomy with decisions regarding further therapy based upon permanent sections. Depending on the surgeon’s discretion, total thyroidectomy may be performed for a cytological diagnosis of papillary carcinoma. There is some controversy as to whether the initial surgical treatment of papillary carcinoma should be total thyroidectomy or unilateral lobectomy. This decision is influenced by the evaluation of the patient’s clinical status, the size, the histological sub-type, the extent of the papillary carcinoma, and whether other therapies such as radioiodine should be considered. For patients with a papillary cancer measuring larger than 1 cm, there is good evidence that bilateral surgery is the procedure of choice. Total thyroidectomy accompanied by the performance of a simultaneous, prophylactic, central-compartment, lymph node dissection is controversial. For patients who have bulky disease or recurrent laryngeal nerve dysfunction, preoperative cross-sectional imaging should be considered as well as ultrasound imaging for lateral neck nodal disease. All patients with suspected papillary thyroid carcinoma or medullary thyroid carcinoma should have a preoperative ultrasound to evaluate the entire thyroid gland and to identify central and lateral neck nodes.

**Conclusion**

Fine-needle aspiration is an important technique that is used along with ultrasound for the triage of patients with thyroid nodules into operative and nonoperative candidates. The recent National Cancer Institute State of the Science meeting on thyroid aspiration cytology summarized current practice for selection of patients who should undergo FNA. In addition, the meeting covered optimal diagnostic categories and criteria along with options for post-FNA follow-up and therapy. The suggested diagnostic terminology uses six categories as follows: (1) nondiagnostic, (2) benign, (3) follicular lesion/atypia of undetermined significance, (4) follicular neoplasm, (5) suspicious for malignancy, and (6) malignant. Each category has specific morphologic features and suggested follow-up strategies.\textsuperscript{97}
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