The Bethesda System for Reporting Thyroid Cytopathology

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Abstract

To address terminology and other issues related to thyroid fine-needle aspiration (FNA), the National Cancer Institute (NCI) hosted the NCI Thyroid FNA State of the Science Conference. The conclusions regarding terminology and morphologic criteria from the NCI meeting led to the Bethesda Thyroid Atlas Project and form the framework for The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). For clarity of communication, TBSRTC recommends that each report begin with 1 of 6 general diagnostic categories. The project participants hope that the adoption of this flexible framework will facilitate communication among cytopathologists, endocrinologists, surgeons, radiologists, and other health care providers; facilitate cytologic-histologic correlation for thyroid diseases; facilitate research into the epidemiology, molecular biology, pathology, and diagnosis of thyroid diseases; and allow easy and reliable sharing of data from different laboratories for national and international collaborative studies.

Fine-needle aspiration (FNA) has an essential role in the evaluation of euthyroid patients with a thyroid nodule. It reduces the rate of unnecessary thyroid surgery for patients with benign nodules and appropriately triages patients with thyroid cancer to appropriate surgery. Before the routine use of thyroid FNA, the percentage of surgically resected thyroid nodules that were malignant was 14%.[1] With current thyroid FNA practice, the percentage of resected nodules that are malignant surpasses 50%.[2]

It is critical that cytopathologists communicate thyroid FNA interpretations to referring physicians in terms that are succinct, unambiguous, and clinically helpful. Historically, terminology for thyroid FNA has varied significantly from one laboratory to another, creating confusion in some cases and hindering the sharing of clinically meaningful data among multiple institutions.

To address terminology and other issues related to thyroid FNA, the National Cancer Institute (NCI) hosted the "NCI Thyroid Fine Needle Aspiration State of the Science Conference." The meeting was organized by Andrea Abati, MD, and took place on October 22 and 23, 2007, in Bethesda, MD. Edmund S. Cibas, MD, and Susan J. Mandel, MD, MPH, served as moderators. Zubair W. Baloch, MD, PhD, served as chair of the Terminology and Morphologic Criteria committee. Preparations for the conference began 18 months earlier with the designation of a steering committee, coordination with cosponsoring organizations, and the establishment of a dedicated, permanent Web site.

Literature reviews were limited to English language publications dating back to 1995, using PubMed as the search engine, with key words determined by the committee members. The first draft of the committees' summary documents

was posted on the Web site and open for online discussion from May 1 to June 30, 2007. There were several subsequent drafts and online discussion periods (August 15 to September 30, 2007, and November 30 to December 15, 2007). The documents underwent revision after each comment period before reposting on the Web. The 2-day "live" conference in October 2007, attended by 154 registrants including pathologists, endocrinologists, surgeons, and radiologists, gave the committees an in-depth opportunity to present their conclusions and debate controversial areas.

The Bethesda System for Reporting Thyroid Cytopathology

The NCI conference participants acknowledged the importance of developing a uniform terminology for reporting thyroid FNA results. An inspiration for the thyroid proposal was the Bethesda System for reporting cervical cytology interpretations, first developed at an NCI workshop in 1988 and widely adopted in the United States for reporting Papanicolaou test results. It is expected that the many benefits, clinical and investigational, of the Bethesda cervical terminology will also apply to the Bethesda thyroid terminology. A uniform reporting system for thyroid FNA will facilitate effective communication among cytopathologists, endocrinologists, surgeons, radiologists, and other health care providers; facilitate cytologic-histologic correlation for thyroid diseases; facilitate research into the epidemiology, molecular biology, pathology, and diagnosis of thyroid diseases, particularly neoplasia; and allow easy and reliable sharing of data from different laboratories for national and international collaborative studies.

An online atlas of illustrations of the Bethesda diagnostic categories is currently being assembled on the Papanicolaou Society Website under the direction of Syed Ali, MD, chair of the Online Atlas Committee. A print atlas, with more than 40 contributing authors **Appendix 1**, is in press.[3]

It was apparent from the discussions at the conference and the Web postings that the primary purpose of terminology is clarity of communication. The interpretation should provide clinically relevant information that will assist referring physicians in the management of patients. The terms for reporting results should have an implied (or explicit) risk of malignancy on which recommendations for patient management (eg, annual follow-up, repeated FNA, surgical lobectomy, near total thyroidectomy) can be based.

The discussions and conclusions regarding terminology and morphologic criteria from the NCI meeting, summarized in the publications by Baloch et al,[4,5] form the framework for the terminology presented here and in atlas form.[3] It is intended as a flexible framework that can be modified to suit the needs of the particular laboratory and the patients it serves.

Format of the Report

For clarity of communication, the Bethesda System for Reporting Thyroid Cytopathology recommends that each report begin with a general diagnostic category. The 6 general diagnostic categories are shown in bold type in **Table 1**. Some categories have 2 alternative names; a consensus was not reached at the NCI conference on a single name for these categories. Each of the categories has an implied cancer risk (ranging from 0% to 3% for the benign category to virtually 100% for the malignant category) that links it to a rational clinical management guideline **Table 2**.

For some of the general categories, some degree of subcategorization can be informative and is often appropriate; recommended terminology is shown in Table 1. Additional descriptive comments (beyond such subcategorization) are optional and left to the discretion of the cytopathologist.

Notes and recommendations are not required but can be useful in certain circumstances. Some laboratories, for example, may want to state the risk of malignancy associated with the general category, based on their own data or that found in the literature (Table 2).

Nondiagnostic or Unsatisfactory

Every thyroid FNA must be evaluated for adequacy. Inadequate samples are reported as "nondiagnostic" (ND) or "unsatisfactory" (UNS). This category applies to specimens that are unsatisfactory owing to obscuring blood, overly thick smears, air drying of alcohol-fixed smears, or an inadequate number of follicular cells. For a thyroid FNA specimen to be satisfactory for evaluation (and benign), at least 6 groups of benign follicular cells are required, each group composed of at least 10 cells.[6,7] The minimum size requirement for the groups allows one to determine (by the evenness of the nuclear spacing) whether they represent fragments of macrofollicles.

There are several exceptions to the numeric requirement of benign follicular cells. Any specimen that contains abundant colloid is considered adequate (and benign), even if 6 groups of follicular cells are not identified: A sparsely cellular specimen with abundant colloid is, by implication, a predominantly macrofollicular nodule and, therefore, almost certainly benign. Whenever a specific diagnosis (eg, lymphocytic thyroiditis) can be rendered and whenever there is any atypia, the specimen is, by definition, adequate for evaluation. ND/UNS results occur in 2% to 20% of cases but ideally should be limited to no more than 10% of thyroid FNAs, excluding samples composed exclusively of macrophages.[8-10]

Specimens that consist only of cyst contents (macrophages) are problematic. Many laboratories have traditionally considered a macrophages-only sample unsatisfactory and included them in the ND/UNS category, with the understanding that, because the

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Table 1
The Bethesda System for Reporting Thyroid Cytopathology: Recommended Diagnostic Categories*

- **I. Nondiagnostic or Unsatisfactory**
  - Cyst fluid only
  - Virtually acellular specimen
  - Other (obscuring blood, clotting artifact, etc)
- **II. Benign**
  - Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc)
  - Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context
  - Consistent with granulomatous (subacute) thyroiditis
  - Other
- **III. Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance**
- **IV. Follicular Neoplasm or Suspicious for a Follicular Neoplasm**
  - Specify if Hürthle cell (oncocytic) type
- **V. Suspicious for Malignancy**
  - Suspicious for papillary carcinoma
  - Suspicious for medullary carcinoma
  - Suspicious for metastatic carcinoma
  - Suspicious for lymphoma
  - Other
- **VI. Malignant**
  - Papillary thyroid carcinoma
  - Poorly differentiated carcinoma
  - Medullary thyroid carcinoma
  - Undifferentiated (anaplastic) carcinoma
  - Squamous cell carcinoma
  - Carcinoma with mixed features (specify)
  - Metastatic carcinoma
  - Non-Hodgkin lymphoma
  - Other

* Adapted with permission from Ali and Cibas.[3]

Table 2
The Bethesda System for Reporting Thyroid Cytopathology: Implied Risk of Malignancy and Recommended Clinical Management

Diagnostic Category	Risk of Malignancy (%)	Usual Management†
Nondiagnostic or Unsatisfactory	1-4	Repeat FNA with ultrasound guidance
Benign	0-3	Clinical follow-up
Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance	~5-15‡	Repeat FNA
Follicular Neoplasm or Suspicious for a Follicular Neoplasm	15-30	Surgical lobectomy
Suspicious for Malignancy	60-75	Near-total thyroidectomy or surgical lobectomy§
Malignant	97-99	Near-total thyroidectomy§

FNA, fine-needle aspiration.
* Adapted with permission from Ali and Cibas.[3]
† Actual management may depend on other factors (eg, clinical, sonographic) besides the FNA interpretation.
‡ Estimate extrapolated from histopathologic data from patients with "repeated atypicals."
§ In the case of "Suspicious for metastatic tumor" or a "Malignant" interpretation indicating metastatic tumor rather than a primary thyroid malignancy, surgery may not be indicated.

parenchyma of the nodule has not been sampled, one cannot exclude a cystic papillary carcinoma. In such laboratories, "macrophages only" often constituted the great majority of ND/UNS cases, with rates that ranged from 15% to 30%.[2,9,11,12] Other laboratories considered the risk of a false-negative result negligible and reported macrophages only as benign.[10,11] At the 2007 NCI Conference, it was decided that cyst-fluid-only (CFO) cases should be considered a clearly identified subset of ND/UNS. The significance and clinical value of a CFO result depend in large part on sonographic correlation. If the nodule is almost entirely cystic, with no worrisome sonographic features, an endocrinologist might proceed as if the CFO were a benign result. On the other hand, it might be clinically equivalent to an ND result if the sonographic features are worrisome and the endocrinologist is not convinced that the sample is representative. In a study that segregated CFO cases and analyzed them separately, the risk of malignancy for a CFO sample was 4%.[9] The risk of malignancy for ND/UNS (not including CFO) is 1% to 4%.[8-10]

A repeated aspiration with ultrasound guidance is recommended for ND/UNS and clinically or sonographically worrisome CFO cases and is diagnostic in 50% to 88% of

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cases,[2,6,9,11,13,14] but some nodules remain persistently ND/UNS. Excision is considered for persistently ND/UNS nodules because about 10% prove to be malignant.[13]

Unless specified as ND/UNS, the FNA specimen is considered adequate for evaluation. An explicit statement of adequacy is optional.

Benign

The benefit of thyroid FNA derives in large part from the ability to make a reliably benign interpretation that avoids unnecessary surgery. A "benign" result is obtained in 60% to 70% of thyroid FNAs. Descriptive comments that follow are used to subclassify the benign interpretation. The term *benign follicular nodule* applies to the most common benign pattern: an adequately cellular specimen composed of varying proportions of colloid and benign follicular cells arranged as macrofollicles and macrofollicle fragments. If resected, virtually all benign follicular nodules turn out to be nodules of a multinodular goiter or follicular adenomas. This distinction cannot be made by FNA and is of no consequence to the patient. The false-negative rate of a benign interpretation is low (0%-3%),[2,12] but patients are nevertheless followed up with repeated assessment by palpation or ultrasound at 6- to 18-month intervals.[15] If the nodule shows significant growth or "suspicious" sonographic changes, a repeated FNA is considered.

Other benign subcategories include "consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context" and "consistent with granulomatous (subacute) thyroiditis." This is a partial list and does not include a variety of other benign conditions like infections and amyloid goiter that are occasionally sampled by FNA. Additional benign findings (eg, black thyroid, reactive changes, radiation changes, cyst lining cells) can be mentioned as descriptive diagnoses at the discretion of the cytopathologist.

Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance

Some thyroid FNAs are not easily classified into the benign, suspicious, or malignant categories. Such cases represent a minority of thyroid FNAs and in the Bethesda System are reported as "atypia of undetermined significance" (AUS) or "follicular lesion of undetermined significance." The necessity for this category was debated at the NCI conference, after which a vote (limited to the clinicians in attendance) was taken, and the majority voted in favor of this category.

The heterogeneity of this category precludes outlining all scenarios for which an AUS interpretation is appropriate. The most common scenarios can be described as follows:

A. There is a prominent population of microfollicles in an aspirate that does not otherwise fulfill the criteria for "follicular neoplasm/suspicious for follicular neoplasm." This situation may arise when a predominance of microfollicles is seen in a sparsely cellular aspirate with scant colloid. Alternatively, a more prominent than usual population of microfollicles may occur (and may be disproportionately apparent on a minority of smears) in a moderately or markedly cellular sample, but the overall proportion of microfollicles is not sufficient for a diagnosis of follicular neoplasm/suspicious for follicular neoplasm.
B. There is a predominance of Hürthle cells in a sparsely cellular aspirate with scant colloid.
C. The interpretation of follicular cell atypia is hindered by sample preparation artifact, eg,
   1. Air-drying artifact with slight nuclear and cytoplasmic enlargement, pale and slightly smudgy chromatin, and/or mildly irregular nuclear contours
   2. Clotting artifact with crowding
D. A moderately or markedly cellular sample is composed of a virtually exclusive population of Hürthle cells, yet the clinical setting suggests a benign Hürthle cell nodule, eg,
   1. Lymphocytic (Hashimoto) thyroiditis
   2. Multinodular goiter
E. There are focal features suggestive of papillary carcinoma, including nuclear grooves, enlarged nuclei with pale chromatin, and alterations in nuclear contour and shape in an otherwise predominantly benign-appearing sample (especially in patients with Hashimoto thyroiditis or with abundant colloid and other benign-appearing follicular cells).
F. There are cyst-lining cells that may appear atypical owing to the presence of nuclear grooves, prominent nucleoli, elongated nuclei and cytoplasm, and/or intranuclear cytoplasmic inclusions in an otherwise predominantly benign-appearing sample.[16]
G. A minor population of follicular cells show nuclear enlargement, often accompanied by prominent nucleoli, eg,
   1. Specimens from patients with a history of radioactive iodine, carbimazole, or other pharmaceutical agents
   2. Repair due to involutional changes such as cystic degeneration and/or hemorrhage
H. There is an atypical lymphoid infiltrate (in which a repeated aspirate for flow cytometry is desirable), but the degree of atypia is insufficient for the general category "suspicious for malignancy."
I. Not otherwise categorized

It is important to note that only nodules with atypia *of undetermined significance* should be placed in the AUS category. Recognizably benign cellular changes (eg, typical cyst lining cells, focal Hürthle cell change, changes ascribed to radioiodine therapy, black thyroid) should not be interpreted

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as AUS. A moderately or even highly cellular specimen by itself (without significant nuclear or architectural atypia) does not qualify a nodule for an AUS interpretation.

An AUS result is obtained in 3% to 6% of thyroid FNAs.[2,10] Higher rates likely represent overuse of this category when other interpretations are more appropriate. The recommended management is clinical correlation and a repeated FNA at an appropriate interval.[2,15] In most cases, a repeated FNA results in a more definitive interpretation; only about 20% of nodules are repeatedly AUS.[2] In some cases, however, the physician may choose not to repeat the FNA but observe the nodule clinically or, alternatively, to refer the patient for surgery because of concerning clinical and/or sonographic features.

The risk of malignancy for an AUS nodule is difficult to ascertain because only a minority of cases in this category have surgical follow-up. Those that are resected represent a selected population of patients with repeated AUS results or patients with worrisome clinical or sonographic findings. In this selected population, 20% to 25% of patients with AUS prove to have cancer after surgery, but this is undoubtedly an overestimate of the risk for all AUS interpretations.[2,10] The risk of malignancy is certainly lower and probably closer to 5% to 15%. An effort should be made to use this category as a last resort and limit its use to approximately 7% or fewer of all thyroid FNAs.

Follicular Neoplasm or Suspicious for a Follicular Neoplasm

The purpose of this diagnostic category is to identify a nodule that might be a follicular carcinoma (FC) and triage it for surgical lobectomy. FNA is diagnostic of many thyroid conditions (eg, papillary carcinoma, lymphocytic thyroiditis), but, with regard to follicular carcinoma, it is better considered a screening test. FCs have cytomorphologic features that distinguish them from benign follicular nodules. Although these cytomorphologic features do not permit distinction from a follicular adenoma (FA), they are reportable as "follicular neoplasm" (FN) or "suspicious for a follicular neoplasm" (SFN), leading to a definitive diagnostic procedure, usually lobectomy.[12,15,17] The term *suspicious for a follicular neoplasm* is preferred by some laboratories over *follicular neoplasm* for this category because a significant proportion of cases (up to 35%) prove not to be neoplasms but rather hyperplastic proliferations of follicular cells, most commonly those of multinodular goiter.[10,18-21] About 15% to 30% of cases called FN/SFN prove to be malignant.[2,10,19,22] The majority of FN/SFN cases turn out to be FAs or adenomatoid nodules of multinodular goiter, both of which are more common than FC. Of those that prove to be malignant, many are FCs, but a significant proportion are follicular variants of papillary carcinoma.[2,8,11,19]

Cytologic preparations typically have high cellularity, and colloid is scant or absent. The hallmark of this diagnostic category is a disturbed cytoarchitecture: follicular cells are arranged predominantly in microfollicular or trabecular arrangements. Cases that demonstrate the nuclear features of papillary carcinoma are excluded from this category. Cellular crowding and overlapping are conspicuous, and the follicular cells are usually larger than normal. Nuclear atypia or pleomorphism and mitoses are uncommon. A minor population of macrofollicles (intact spheres and fragments) can be present. Conspicuous cellularity alone does not qualify the nodule for a suspicious interpretation.[23] If the sample is cellular but mostly macrofollicular (intact spheres and flat fragments of evenly spaced follicular cells), a benign interpretation is appropriate. Benign follicular nodules often have a small population of microfollicles and crowded groups. If these constitute the minority of the follicular cells, they have little significance and the FNA can be interpreted as benign. A suspicious interpretation is rendered only when the majority of the follicular cells are arranged in abnormal architectural groupings (microfollicles, crowded trabeculae).

The general category FN/SFN is a self-sufficient interpretation; narrative comments that follow are optional.

In the World Health Organization classification, Hürthle cell adenoma and Hürthle cell carcinoma are considered oncocytic variants of FA and FC, respectively.[24] Studies suggest, however, that follicular and Hürthle cell tumors have different underlying genetics.[4,25] For this reason, and because they have such distinctive morphologic features, it is helpful to specify that a sample raises the possibility of a Hürthle cell rather than a follicular neoplasm. This interpretation applies to cellular samples that are composed exclusively (or almost exclusively) of Hürthle cells. Oncocytic cells with nuclear features of papillary carcinoma are excluded from this interpretation. A significant proportion of these cases (16%-25%) prove not to be neoplasms but rather hyperplastic proliferations of Hürthle cells in nodular goiter or lymphocytic thyroiditis.[26,27] About 15% to 45% of nodules are malignant, and the remainder of the neoplasms prove to be Hürthle cell adenomas.[22,26,27]

Suspicious for Malignancy

Many thyroid cancers, most especially papillary thyroid carcinoma (PTC), can be diagnosed with certainty by FNA. But the nuclear and architectural changes of some PTCs are subtle and focal. This is particularly true of the follicular variant of PTC, which can be difficult to distinguish from a

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benign follicular nodule.[28] Other PTCs may be incompletely sampled and yield only a small number of abnormal cells.[29] If only 1 or 2 characteristic features of PTC are present, if they are only focal and not widespread throughout the follicular cell population, or if the sample is sparsely cellular, a malignant diagnosis cannot be made with certainty. Such cases occur with some regularity, and they are best classified as "suspicious for malignancy," qualified as "suspicious for papillary carcinoma." Nodules called suspicious for papillary carcinoma are resected by lobectomy or thyroidectomy. Most (60%-75%) prove to be papillary carcinomas, and the rest are usually FAs.[2,10,12,30]

The same general principle applies to other thyroid malignancies like medullary carcinoma and lymphoma, but these are encountered less frequently than PTC. Ancillary testing (eg, immunohistochemical analysis, flow cytometry) in borderline cases is usually more helpful with medullary carcinoma and lymphoma than with PTC.

Appendix 1
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Malignant

The general category *malignant* is used whenever the cytomorphologic features are conclusive for malignancy. Descriptive comments that follow are used to subclassify the malignancy and summarize the results of special studies, if any. Approximately 3% to 7% of thyroid FNAs have conclusive features of malignancy, and most are papillary carcinomas.[10-13] Malignant nodules are usually removed by thyroidectomy, with some exceptions (eg, metastatic tumors, non-Hodgkin lymphomas, and undifferentiated carcinomas). The positive predictive value of a malignant FNA interpretation is 97% to 99%.

Summary

This document summarizes several years of work, begun as a Web-based discussion, followed by a live conference, and culminating in the production of a print and online atlas. It is the hope of all contributors to this project that this terminology proposal will be a valuable first step toward uniformity and consensus in the reporting of thyroid FNA interpretations. As with the Bethesda System for cervical cytology, it is expected that subsequent workshops will lead to further refinements to this framework.

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