How to Interpret Thyroid Fine-Needle Aspiration Biopsy Reports: A Guide for the Busy Radiologist in the Era of the Bethesda Classification System

OBJECTIVE. Fine-needle aspiration biopsy (FNAB) is the current primary test to risk stratify thyroid nodules. However, in up to one third of biopsies, cytology is indeterminate. The Bethesda System for Reporting Thyroid Cytopathology categorizes thyroid cytology findings into six groups, with each group assigned a putative malignancy risk. This article reviews the Bethesda System, emphasizing the key facts necessary to understand thyroid biopsy results and effectively manage patients after FNAB.

CONCLUSION. It is important to diagnose and stratify the risk of malignancy in thyroid nodules. A working knowledge of the Bethesda System permits accurate, evidence-based risk stratification of patients with thyroid nodules and thereby facilitates their management. Because it is a uniform diagnostic approach, the Bethesda System allows comparisons of different management strategies across different institutions.

Modern high-resolution ultrasound imaging can detect thyroid nodules in up to 60% of adults [1, 2]. When the ultrasound features of a thyroid nodule are not reassuring for benignity, fine-needle aspiration biopsy (FNAB) is the test of choice to determine if these nodules are benign or malignant. Reassuring ultrasound features include spongiform nodules and colloid cysts. The current guidelines do not agree about which thyroid nodules require FNAB [3]. In the past three decades, FNAB of thyroid nodules not only has reduced the number of diagnostic thyroid surgeries by 60–85% [4] but also has increased the likelihood of malignant surgical pathology from 14% to more than 50% [5, 6]. Although 85–95% of thyroid nodules are actually benign, only 60–70% of biopsied nodules are considered benign. Those considered benign require no intervention other than periodic follow-up. From 4% to 8% of nodules that undergo FNAB are diagnosed as malignant and surgery is necessary [6]. As many as 10–20% of nodules that undergo FNAB are ambiguous (indeterminate) and cannot be clearly diagnosed as benign or malignant. These indeterminate nodules may require surgery to determine if they are, in fact, benign or malignant.

The Bethesda System for Reporting Thyroid Cytopathology: Background

Indeterminate thyroid FNAB results comprise a spectrum of cytologic diagnoses that cannot clearly be diagnosed as benign or malignant even by an expert cytopathologist. One reason for this uncertainty is that some thyroid malignancies do not show cellular atypia. For example, a nodule made up primarily of small follicles (microfollicles) is considered a “follicular neoplasm”—an intentionally ambiguous term. When a microfollicular nodule is removed, a pathologist will perform multiple sections through the nodule. If the nodule is fully encapsulated without invasion, the nodule is considered a benign tumor (i.e., follicular adenoma or adenomatous nodule). However, if invasion of the tumor capsule or blood vessels is noted, then the nodule is considered malignant (i.e., follicular carcinoma). No matter how many FNAB procedures are performed, this distinction requires surgical removal and histopathologic analysis of the entire tumor because the cytopathologist cannot exclude invasion on the basis of an FNAB specimen [7, 8]. Another reason for this ambiguity is that some thyroid nodules display focal or variable degrees of cellular atypia that, if present in abundance, would permit a diagnosis of papillary thyroid carcinoma. In some...
instances, small areas of atypia may be found in a benign nodule, potentially resulting in overdiagnosis of malignancy. In other nodules, the degree of atypia may not be seen in the biopsy sample but may be more apparent in the surgical specimen (e.g., follicular variant of papillary thyroid carcinoma) [7].

The broad range of cytologic appearances and regional differences in training led to considerable reporting variation across institutions and countries. By early 2007, almost a dozen different thyroid cytology reporting systems were in use in the United States alone. The profusion of different reporting systems created a major roadblock to clinical management and research by preventing comparison of data between institutions [8, 9].

To address these issues, a multidisciplinary committee of thyroid experts—charged with developing a comprehensive and standardized system for reporting thyroid cytology—was convened in Bethesda, MD, in 2007. This meeting resulted in a standardized thyroid cytology reporting method called the “Bethesda System.” The Bethesda System identifies six diagnostic categories on thyroid nodule cytology: nondiagnostic or unsatisfactory; benign; atypia of undetermined significance; follicular neoplasm or Hürthle cell neoplasm or suspicious for a Hürthle cell neoplasm; suspicious for malignancy; and malignant.

Each category is associated with a certain risk of thyroid malignancy (Table 1), which helps the clinician develop a management strategy specific to that patient. A choice of names is provided for some of these categories (e.g., “nondiagnostic” or “unsatisfactory” for the first category and AUS or FLUS for the third category) because the committee members could not always agree on the nomenclature [8].

These categories are described in greater detail later in this article. For educational purposes, we start the discussion with the more straightforward Bethesda categories (nondiagnostic, benign, and malignant) and then discuss those that are more ambiguous (suspicious for malignancy, follicular neoplasm or suspicious for a follicular neoplasm, and AUS/FLUS).

Bethesda Category: Nondiagnostic

Definition (Table 1, Category I)

An FNAB specimen is considered nondiagnostic if it contains fewer than six follicular groups, each of which contains 10 or more cells. A thyroid nodule with a nondiagnostic FNAB result should not be considered benign because 1–4% of these masses ultimately prove to be malignant [8]. FNAB results may be nondiagnostic for a number of reasons. The first reason is that aspiration of a predominantly cystic nodule may yield predominantly acellular fluid. As a practical matter, a nodule that shrinks dramatically after fluid removal, with only a small residual volume of tissue, is often treated as a benign nodule and is followed by the clinician [10]. Conversely, a nodule with a sizeable solid component requires a repeat FNAB under ultrasound guidance to sample the solid component [10]. This repeat FNAB is particularly important because some papillary thyroid carcinomas are predominantly cystic. Investigators have estimated that up to 4% of cystic nodules may harbor papillary thyroid carcinomas [11]. The second reason FNAB results may be nondiagnostic is that the cells were poorly prepared or poorly stained: The cytopathologist considers the quality of the prepared slides to be too poor to permit evaluation. Good specimen preparation is a prerequisite for accurate pathologic interpretation.

Despite the general rule about the criteria for a diagnostic FNAB specimen, in some circumstances, an aspirate may be considered diagnostic even when it contains fewer than six follicular groups and whether each group contains 10 or fewer cells [8]. These exceptions include the following: a colloid nodule, a solid nodule with cystic atypia, a solid nodule with inflammation, painful subacute thyroiditis, and a thyroid abscess.

A colloid nodule—Abundant thick colloid in a specimen is considered satisfactory for evaluation and is categorized as benign. A solid nodule with cystologic atypia—The presence of atypia in even a few cells is sufficient to assign the nodule to a higher risk category such as “atypia of undetermined significance” or “suspicious for malignancy” depending on the nature and severity of the atypia.

A solid nodule with inflammation—Hashimoto thyroiditis (chronic lymphocytic thyroiditis), a benign autoimmune thyroid disorder, may be nodular. An FNAB specimen may yield numerous lymphocytes and may be diagnostic even when few follicular cells are present. Because malignant nodules may coexist with Hashimoto thyroiditis, it is important to be certain that FNAB targeted the nodule in question.

Painful subacute thyroiditis—Painful subacute thyroiditis (granulomatous thyroiditis) may be diagnosed by the presence of giant cells even when few follicular cells are present. A thyroid abscess—Thyroid abscesses are extraordinarily rare but can be diagnosed when a culture is positive and polymorphonuclear leukocytes are aspirated from a nodule.

Management

After a nondiagnostic FNAB result, the biopsy should be repeated if the nodule is considered suspicious on the basis of clinical or sonographic findings. Immediate on-site evaluation of sample adequacy increases the likelihood that a repeat aspiration will be diagnostic, but an on-site evaluation is often not readily available and increases the time needed for the FNAB. Although some experts recommend waiting a minimum interval of 3 months [12] before repeating FNAB to prevent false-positive interpretations due to reactive or reparative change, our data [13] suggest that waiting to repeat the FNAB is generally not necessary. A core biopsy is recommended after two nondiagnostic FNABs because it may improve the diagnostic yield [14].

Bethesda Category: Benign

Definition (Table 1, Category 2)

Approximately 60–70% of thyroid nodules that undergo FNAB are considered benign [15, 16]. A benign result can be further classified by cause as a benign follicular nodule, a colloid nodule, chronic lymphocytic (Hashimoto) thyroiditis, or granulomatous (subacute, de Quervain) thyroiditis. A benign follicular nodule is the most common benign pattern—that is, an adequately cellular specimen composed of varying proportions of colloid and benign follicular cells arranged as macrofollicles and macrofollicle fragments. These specimens typically show sheets of bland thyroid follicular cells, which represent flattened macrofollicles. If resected, virtually all benign follicular nodules would be hyperplastic nodules in a multinodular goiter or follicular adenomas (predominantly macrofollicular type). The distinction between these two benign entities cannot be made by FNAB and does not change the treatment approach. Thyroid aspirates composed of abundant thick colloid that grossly coats the glass slide and that contains rare macrofollicular fragments correlate histologically with a colloid nodule. It is important for the treating physician to understand that the risk of malignancy in “benign” nodules is not zero. Up to 3% of nodules classified as “benign” in fact prove to be malignant (i.e., the false-negative rate is up to 3%) [8].
How to Interpret FNAB Results of Thyroid Nodules

TABLE I: The Bethesda System for Reporting Thyroid Cytopathology: Risk of Malignancy and Management

<table>
<thead>
<tr>
<th>Category No.</th>
<th>Cytology Diagnostic Category</th>
<th>Malignancy Risk (%)</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nondiagnostic or unsatisfactory</td>
<td>0–3</td>
<td>Repeat FNAB</td>
</tr>
<tr>
<td>2</td>
<td>Benign</td>
<td>97–99</td>
<td>Follow-up</td>
</tr>
<tr>
<td>3</td>
<td>Malignant</td>
<td>60–75</td>
<td>Near-total thyroidectomy</td>
</tr>
<tr>
<td>4</td>
<td>Suspicious for malignancy</td>
<td>15–30</td>
<td>Near-total thyroidectomy or surgical lobectomya</td>
</tr>
<tr>
<td>5</td>
<td>Follicular neoplasm or suspicious for a follicular neoplasm</td>
<td>5–15</td>
<td>Surgerya</td>
</tr>
<tr>
<td>6</td>
<td>AUS/FLUS</td>
<td>0–3</td>
<td>Repeat FNAB or surgerya</td>
</tr>
</tbody>
</table>

Note—Modified from Ali and Cibas [8] with kind permission of Springer Science + Business Media. FNAB = fine-needle aspiration biopsy, AUS/FLUS = atypia of undetermined significance or follicular lesion of undetermined significance.

*aThe role of molecular diagnostics is being explored for the management of nodules in these categories.

Management

Given the low (but not zero) risk of thyroid malignancy in nodules diagnosed as benign, patients are followed with periodic thyroid ultrasound initially at 6- to 18-month intervals after FNAB. Some “benign” thyroid nodules are removed, particularly those that are large, cause compressive symptoms, or are a source of persistent patient anxiety [15]. A repeat FNAB should be considered if there is significant growth, defined as a greater than 50% increase in volume or a 20% increase in at least two nodule dimensions, with a minimum increase of 2 mm in a solid component [15].

Bethesda Category: Malignant

Definition (Table I, Category 3)

An FNAB cytopathology result reported as “malignant” will in fact be malignant in 97–99% of the cases. Thus, false-positive diagnoses of malignancy do occur. A malignant thyroid FNAB diagnosis accounts for 4–8% of all thyroid FNAB results [6]. Papillary thyroid carcinoma, medullary thyroid carcinoma, poorly differentiated thyroid cancer, anaplastic thyroid carcinoma, primary lymphoma, and cancer metastatic to the thyroid can be diagnosed by FNAB, whereas follicular carcinoma generally cannot. At least 95% of FNAB diagnoses made in this category will be papillary thyroid carcinoma [17]. The characteristic nuclear features of papillary thyroid carcinoma include an enlarged oval nucleus with pale chromatin, longitudinal nuclear grooves, a small eccentric nucleolus, and occasional intranuclear pseudoinclusions.

Management

When an FNAB result is malignant, surgery is required. The specific operation depends on the cytopathology and size of the nodule and is likely a total thyroidectomy with or without nodal dissection; however, surgery may be restricted to a hemithyroidectomy in some instances.

Bethesda Category: Suspicious for Malignancy

Definition (Table I, Category 4)

Thyroid nodules diagnosed as suspicious for malignancy have many of the nuclear features of malignancy, usually of papillary thyroid carcinoma; however, some of the diagnostic features of malignancy are absent or equivocal, or the evaluation of the sample is limited by low cellularity or fixation artifacts. The majority of these nodules, usually 60–75%, are malignant [8]. Although the distinction between suspicious for malignancy and AUS/FLUS is inherently subjective, nodules diagnosed as suspicious for malignancy will have more definitive or more extensive features suggestive of a malignancy.

Management

Nodules categorized as suspicious for malignancy require surgery. We generally recommend a bilateral total thyroidectomy in this situation [15]. In selected cases, the surgeon may elect to perform thyroid lobectomy with intraoperative frozen-section pathology before proceeding to total thyroidectomy in the hope of preserving a functioning thyroid remnant if the diagnosis is benign [18–22].

Bethesda Category: Follicular Neoplasm or Suspicious for a Follicular Neoplasm (Hürthle Cell Neoplasm or Suspicious for a Hürthle Cell Neoplasm)

Definition (Table I, Category 5)

The term “follicular neoplasm” is an intentionally ambiguous term, which recognizes the inability of FNAB to differentiate benign from malignant thyroid nodules when the thyroid follicles are organized into microfollicles. These small follicular groups often have crowded nuclei and scant to absent colloid. Approximately 15–30% of follicular neoplasms prove to be malignant. These nodules must be surgically removed to make this distinction. After surgery, the pathologist carefully evaluates the fibrous capsule surrounding the thyroid nodule. If either capsular or vascular invasion is present, the nodule is a follicular carcinoma. With the same architecture but no capsular or vascular invasion, the nodule is considered a benign tumor (follicular adenoma or nodular hyperplasia) [23–27]. The follicular variant of papillary thyroid carcinoma has a follicular architecture and nuclear changes of papillary thyroid carcinoma. Considerable variation occurs from institution to institution, with approximately 5–20% of cases being diagnosed as a follicular neoplasm on FNAB; follicular neoplasm has a risk of malignancy of 15–30% [8, 28, 29].

Nodules diagnosed as Hürthle cell neoplasms also prove to be malignant in 15–30% of cases [8]. Hürthle (or oxyphilic) cells have a particular cytologic appearance. Hürthle cell neoplasms are made up of a pure, often showing cellular dyscohesion, population of Hürthle cells. If the surgical pathology reveals capsular or vascular invasion, these nodules are diagnosed as follicular carcinomas, Hürthle cell (oncocytic) type. It is important to realize that Hürthle cells may also be found in benign conditions such as Hashimoto thyroiditis, follicular adenomas, or adenomatous nodules. Hürthle cell neoplasms are made up of a pure population of Hürthle cells, often showing cellular dyscohesion [8].

Management

Most follicular neoplasms require surgery. Although opinions vary, generally a hemithyroidectomy is recommended for small isolated follicular neoplasms and Hürthle cell neoplasms [30, 31]. We are more inclined to
recommend a total thyroidectomy when follicular neoplasms are larger than 4 cm, particularly in men; when bilateral nodules are present; or when the patient prefers this operation. If a hemithyroidectomy is performed and the nodule proves to be malignant, a completion thyroidectomy may be necessary to facilitate radioactive iodine therapy.

The one exception to the general rule of surgery for follicular neoplasms is the “hot” thyroid nodule (autonomous adenoma): A hot nodule may be microfollicular in appearance but is likely to be benign given that 99% of hot nodules do not harbor malignancy [15]. Radioiodine nuclear scanning should be considered for follicular neoplasms when the serum thyroid-stimulating hormone concentration is below normal or at the lower limit of normal.

**Bethesda Category: Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance**

**Definition** (Table 1, Category 6)

Approximately 10% of thyroid FNAB specimens exhibit architectural or cellular atypia and are categorized as AUS/FLUS. The terms “AUS” and “FLUS” are often used interchangeably. The risk of malignancy in nodules categorized as AUS/FLUS is estimated at 5–15% [8].

Several examples that fall into the AUS/FLUS category are illustrative:

- A biopsy of a predominantly cystic nodule may reveal cyst-lining cells with some nuclear atypia. Although the nuclear features are similar to those seen in cases of papillary thyroid carcinoma, the otherwise predominantly benign appearance does not warrant that diagnosis. This case would be considered AUS/FLUS.
- Some biopsies have specimen preparation artifacts that distort the cells, thus causing an atypical microscopic appearance. These artifacts prevent these nodules from being classified as either benign or malignant [11].

Several studies of AUS/FLUS nodules have indicated that the presence of nuclear atypia is associated with a greater risk of malignancy than AUS/FLUS nodules associated with architectural atypia only. Hence, some investigators suggest that the AUS/FLUS category might be further subdivided or that they may be differentiated into two separate categories [28, 32].

**Management**

Given the ambiguity of the AUS/FLUS category, many clinicians recommend a repeat FNAB. When FNAB is repeated, approximately 50% of cases will have results that are considered benign and will be followed clinically. In the other 50% of cases, the repeat FNAB result is equally divided between AUS/FLUS and follicular neoplasm or a higher-grade finding [8, 15, 33]. Hence, reaspiration leads to a more definitive diagnosis in 75–80% of the cases [8]. The nodules with a repeat FNAB diagnosis of AUS/FLUS, follicular neoplasm, or higher have a 25% greater risk of malignancy and require surgery [8]. Clinical and radiologic considerations are also important. Some clinicians recommend surgery for larger (3–4 cm) nodules after a single diagnosis of AUS/FLUS, and some authors advocate nodule core biopsy after an initial diagnosis of AUS/FLUS [34]. When surgery is indicated, the surgical considerations for AUS/FLUS are similar to those for follicular neoplasm.

**Conclusion**

This article has focused on the classification and interpretation of FNAB results of thyroid nodules. Advances in molecular biopsy and elastography in recent years have helped refine our ability to distinguish between benign and malignant thyroid nodules with an “indeterminate” FNAB diagnosis. The details of the molecular biologic approach and elastography are beyond the scope of this article. However, two major molecular biologic approaches are available: One strategy is to use a gene expression classifier, which analyzes hundreds of genes within a thyroid nodule. When applied to thyroid nodules diagnosed as AUS/FLUS or as follicular neoplasm, this technique classifies about half of these nodules as benign with a 5–15% false-negative rate [35]. A second approach is to analyze the presence of oncogenes in nodules with an indeterminate FNAB result [36]. When one of these oncogenes is present, the nodule is very likely malignant and a total thyroidectomy is therefore recommended. When and if to use any of these specific approaches are still uncertain.

Thyroid nodules are very common and can be detected by ultrasound in up to 60% of the general population [15]. It is important to diagnose and stratify the risk of malignancy in these nodules. A working knowledge of the Bethesda System permits accurate, evidence-based risk stratification of patients with thyroid nodules and thereby facilitates their management. Because it is a uniform diagnostic approach, the Bethesda System allows comparisons of different management strategies across different institutions.

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