Overview of Diagnostic Terminology and Reporting

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With its inception, The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) established a uniform, tiered reporting system for thyroid fine needle aspiration (FNA) specimens. Using TBSRTC, the cytopathologist can communicate thyroid FNA interpretations to the referring physician in terms that are succinct, unambiguous, and clinically useful [1, 2].

Since the widespread acceptance of TBSRTC into clinical practice, further refinement of the diagnostic categories, recommended management strategies (e.g., molecular testing, repeat FNA vs. surgery), and their implied risks of malignancy continued to occur [3–5]. The goal of preoperative FNA and cytologic analysis is to inform conservative management of thyroid nodules unlikely to cause harm, while conversely leading to surgical management aimed at effectively treating thyroid cancer. Data increasingly support comparable efficacy in applying less invasive management strategies to certain thyroid cancers [6]. In fact, among nodules shown

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S. Z. Ali, P. A. VanderLaan (eds.), *The Bethesda System for Reporting Thyroid Cytopathology*, https://doi.org/10.1007/978-3-031-28046-7_1

to be malignant, TBSRTC classification may predict the aggressiveness of the tumor. With this in mind, clinicians are increasingly favoring surgical lobectomy, limiting routine use of radioactive iodine for ablative purposes, and even considering nonoperative monitoring approaches for small thyroid malignancies [3, 7, 8]. The new TBSRTC third edition notes these options for each category, though acknowledges that cytology alone should not dictate the full management of thyroid nodule care. Integrated multivariable assessment of each impacted patient should occur, allowing the most informed and individualized treatment decisions [6, 8, 9].

New to this third edition are the following:

1. Unification of diagnostic categories under a single name. The diagnostic category of "Nondiagnostic/Unsatisfactory" is now termed as "Nondiagnostic" only, the category "Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance (AUS/FLUS)" termed as "Atypia of Undetermined Significance (AUS)" only, and the category "Follicular Neoplasm/Suspicious For a Follicular Neoplasm (FN/SFN)" termed as "Follicular Neoplasm (FN)" only.
2. Data informing use of TBSRTC in the pediatric population is now included. The risk of malignancy (ROM) is higher in children compared to adults, and while TBSRTC should still be used for interpreting pediatric thyroid nodule cytology, adjusted risk of malignancy estimates should be applied [10–18].
3. Refined risk of malignancy estimates, incorporating more extensive published data since the second edition of TBSRTC.
4. More formalized subcategorization of AUS based on ROM: AUS with nuclear atypia vs. AUS-other.
5. Whenever possible, the terminology used in TBSRTC has been harmonized with the latest 2022 WHO classification of Thyroid Neoplasms.
6. A broadening of Chap. 10 to incorporate all high-grade follicular-derived carcinomas, including poorly differentiated thyroid carcinoma (PDTC) as well as differentiated high-grade thyroid carcinoma (DHGTC).
7. Brand new chapters covering clinical perspectives and imaging studies (Chap. 13) and the use of molecular and other ancillary tests (Chap. 14).
8. New and updated images to better illustrate diagnostic criteria and cytologic features.

Format of the Report

For clarity of communication, each thyroid FNA report should begin with a general diagnostic category. TBSRTC diagnostic categories are shown in Table 1.1.

Each category has an implied cancer risk, which ranges from 1% to 2% overall for the "Benign" category to virtually 100% for the "Malignant" category. As a function of these risk associations, each category is linked to evidence-based clinical management guidelines, as shown in Table 1.2 and discussed in more detail in the chapters that follow.

Table 1.1 The Bethesda System for Reporting Thyroid Cytopathology; diagnostic categories

I. Nondiagnostic
Cyst fluid only
Virtually acellular specimen
Other (obscuring blood, clotting artifact, drying artifact, etc.)
II. Benign
Consistent with follicular nodular disease (includes adenomatoid nodule, colloid nodule, etc.)
Consistent with chronic lymphocytic (Hashimoto) thyroiditis in the proper clinical context
Consistent with granulomatous (subacute) thyroiditis
Other
III. Atypia of Undetermined Significance
Specify if AUS-nuclear atypia or AUS-other
IV. Follicular Neoplasm
Specify if oncocytic (Hürthle cell) type
V. Suspicious for Malignancy
Suspicious for papillary thyroid carcinoma
Suspicious for medullary thyroid carcinoma
Suspicious for metastatic carcinoma
Suspicious for lymphoma
Other
VI. Malignant
Papillary thyroid carcinoma
High-grade follicular cell-derived non-anaplastic thyroid carcinoma
Medullary thyroid carcinoma
Undifferentiated (anaplastic) carcinoma
Squamous cell carcinoma
Carcinoma with mixed features (specify)
Metastatic malignancy
Non-Hodgkin lymphoma
Other

It is important to note that the traditional method of estimating the ROM, which is based on histologic follow-up (i.e., dividing the number of patients with cancer by the total number of patients with surgical follow-up), overestimates the risk of malignancy, particularly for the Nondiagnostic, Benign, and AUS categories, where there is selection bias given the relatively small proportion of nodules that undergo excision. On the other hand, when calculated using the total number of FNA specimens (with and without surgical follow-up) as the denominator, assuming that unresected nodules are benign, the ROM is most certainly underestimated. The actual ROM is expected to be in the midrange of the values obtained using these calculations, which take into account only cytologic-defined risk, though optimal risk determination should be individualized and incorporate as many predictive variables as possible. The best current risk estimates based on surgically resected nodules are depicted in Table 1.2, with footnotes clarifying ROM estimates provided when appropriate.

Table 1.2 The Bethesda System for Reporting Thyroid Cytopathology: implied risk of malignancy (ROM) with expected ranges based on follow-up of surgically resected nodules with recommended clinical management [19–47]

Diagnostic category	ROM[a] Mean% (range)	Usual management[b]
Nondiagnostic	13 (5–20)[c]	Repeat FNA[d] with ultrasound guidance
Benign	4 (2–7)[e]	Clinical and sonographic follow-up
Atypia of Undetermined Significance[f]	22 (13–30)	Repeat FNA[d], molecular testing, diagnostic lobectomy, or surveillance
Follicular Neoplasm[g]	30 (23–34)	Molecular testing[h], diagnostic lobectomy
Suspicious for Malignancy	74 (67–83)	Molecular testing[h], lobectomy or near-total thyroidectomy[i]
Malignant	97 (97–100)	Lobectomy or near-total thyroidectomy[i]

[a] These ROM estimates are skewed by selection bias, as many thyroid nodules (especially those diagnosed as Benign or AUS) may not undergo surgical excision

[b] Actual management may depend on other factors (e.g., clinical, sonographic) besides the FNA interpretation

[c] The risk of malignancy varies with the type/structure of the nodule, i.e., solid vs. complex vs. ≥50% cystic. Nondiagnostic aspirates from solid nodules are associated with a higher risk of malignancy as compared to those showing ≥50% cystic change and low-risk ultrasonographic features. See Chap. 2 for discussion

[d] Studies have shown diagnostic resolution with repeat FNA [48–50]

[e] This ROM estimate is based on follow-up of surgically resected nodules, which is skewed by selection bias since the vast majority of thyroid nodules classified as benign do not undergo surgical excision. Based on long-term follow-up studies, the best overall ROM estimate for a benign FNA is approximately 1–2% [51–55]

[f] This category can be further subclassified into specimens with nuclear vs. non-nuclear atypia; the ROM appears to be higher for cases with nuclear atypia. See Chap. 4 for discussion [56, 57]

[g] Includes cases of follicular neoplasm with oncocytic features (Hürthle cell neoplasm) [58, 59]

[h] Molecular analysis can be performed to assess the type of surgical procedure (lobectomy vs. total thyroidectomy)

[i] 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

As noted above, TBSRTC can be applied for reporting pediatric thyroid FNA specimens. The implied risk of malignancy for each diagnostic category based on published studies to date is depicted in Table 1.3.

The reclassification of some encapsulated follicular patterned thyroid neoplasms as noninvasive follicular thyroid neoplasm with papillary like nuclear features (NIFTP) has implications for the implied ROM, as NIFTP tends to behave in a more indolent fashion. Based on published literature to date, the overall reduction in ROM for each category is accounted for in Table 1.4 [19, 66, 76–78].

For some of the general diagnostic categories, subcategorization can be informative and is often appropriate; recommended terminology is shown in Table 1.1. Additional descriptive comments (beyond such subcategorization) are optional and left to the discretion of the cytopathologist. Notes and recommendations can be useful, especially with relation to the NIFTP terminology (see Chaps. 4, 5, 7, and 8). Some laboratories, for example, may wish to state the risk of malignancy associated

Table 1.3 The Bethesda System for Reporting Thyroid Cytopathology in Pediatric Patients with implied risk of malignancy (ROM) and possible management recommendations [10, 12–18, 60–65]

Diagnostic category	ROM Mean% (range)	Possible management recommendations
Nondiagnostic	14 (0–33)	Repeat FNA with ultrasound guidance
Benign[a]	6 (0–27)	Clinical and sonographic follow-up
Atypia of Undetermined Significance	28 (11–54)	Repeat FNA or surgical resection
Follicular Neoplasm[b]	50 (28–100)	Surgical resection
Suspicious for Malignancy	81 (40–100)	Surgical resection
Malignant	98 (86–100)	Surgical resection

[a] ROM is skewed by selection bias since a majority of thyroid nodules classified as benign do not undergo surgical excision

[b] Includes cases of follicular neoplasm with oncocytic features (Hürthle cell neoplasm)

Table 1.4 Reported decreases in the risk of malignancy (ROM) of TBSRTC diagnostic categories if excluding nodules diagnosed on surgical pathology to be "Noninvasive Follicular Thyroid Neoplasm with Papillary Like Nuclear Features (NIFTP)" [19, 66–75]

Diagnostic category	% Decrease in ROM if excluding NIFTP[a] Mean% (range)	Estimated final ROM if excluding NIFTP[b] Mean%
Nondiagnostic	1.3 (0–2)	12
Benign	2.4 (0–4)	2
Atypia of Undetermined Significance	6.4 (6–20)	16
Follicular Neoplasm	7.1 (0.2–30)	23
Suspicious for Malignancy	9.1 (0–40)	65
Malignant	2.6 (0–13)	94

[a] Based on weighted average (mean) reduction in malignancy with expected ranges calculated from refs. [19, 66–75]

[b] Based on estimated average (mean) ROM values from Table 1.2 minus values presented in this table

with the general category, based on their own cytologic–histologic correlation or that found in the literature (Table 1.2). Sample reports, which we hope will be a useful guide, are provided in the remaining chapters.

Acknowledgment The authors would like to acknowledge the work in earlier editions of this chapter of Drs. Hossein Gharib and Stephen Raab.

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