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The 2023 Bethesda System for reporting thyroid cytopathology

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Since the publication of the first edition in 2010, The Bethesda System for Reporting Thyroid Cytopathology has allowed cytopathologists to use a standardized, category-based reporting system for thyroid fine needle aspirations. The third edition builds on the success of the 2 earlier editions and offers several key updates. The most important is the assignment of a single name for each of the 6 diagnostic categories: (i) nondiagnostic; (ii) benign; (iii) atypia of undetermined significance; (iv) follicular neoplasm; (v) suspicious for malignancy; and (vi) malignant. Each of the categories has an implied risk of malignancy (ROM), which has been updated and refined based on data reported after the second edition. The third edition offers an average ROM for each category, in addition to the expected range of cancer risk. The atypia of undetermined significance subcategorization is simplified into 2 subgroups based on the implied ROM and molecular profiling. A discussion of pediatric thyroid disease has been added, and pediatric ROMs and management algorithms are discussed in the relevant sections. Nomenclature has been updated to align with the 2022 World Health Organization Classification of Thyroid Neoplasms. Two new chapters have been added: one that addresses the significant and expanded use of molecular and ancillary testing in thyroid cytopathology, and another that summarizes clinical perspectives and imaging findings in thyroid disease.

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Introduction

The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) established a simplified, 6 category-based reporting system for thyroid fine needle aspiration (FNA). The first 2 editions of TBSRTC (2010 and 2017) significantly achieved the goal of standardizing thyroid cytopathology reporting and were widely adopted.[1-4] The monographs were translated into 7 different languages, becoming one of the most widely used diagnostic and reporting tools in thyroid cytopathology. Using the terminology of TBSRTC, cytopathologists can effectively communicate thyroid FNA interpretations to the referring physician in succinct, unambiguous, and clinically useful terms. As further refinement of the diagnostic categories, recommended management strategies (eg, molecular testing, repeat FNA versus surgery), and their implied risks of malignancy continue to occur,[5,6] the time had come to consider another revision of TBSRTC.

The third edition of the atlas, the previous editions of which are widely used by cytopathologists, with both cytologic illustrations and written criteria for diagnostic categorization, will be in print as of the summer of 2023. The atlas is updated and has expanded chapters devoted to the 6 reporting categories, 2 new chapters, updated text, new illustrations, and refined definitions, morphologic criteria, and explanatory notes.[7]

As with the previous 2 editions, TBSRTC 2023 recommends that every thyroid FNA report begin with 1 of the 6 diagnostic categories. The third edition (2023) addresses one of the limitations of the prior editions that had led to some confusion, namely, having alternative names for 3 of the diagnostic categories. This has been resolved, with TBSRTC 2023 recommending a single designation for each of the 6 categories, discontinuing the previously used terms of "unsatisfactory," "follicular lesion of undetermined significance," and "suspicious for a follicular neoplasm."

TBSRTC 2023 recommends the following as the 6 reporting category names: (i) nondiagnostic; (ii) benign; (iii) atypia of undetermined significance (AUS); (iv) follicular neoplasm; (v) suspicious for malignancy (SFM); and (vi) malignant (Table 1). TBSRTC 2023 continues to recommend that the names of the categories (and not just their numerical designations) should be used for reporting results and publishing scientific investigations to avoid confusion with the Thyroid Imaging and Reporting System (TI-RADS) and other reporting systems that are primarily numeral-based. Adding a category number after the

Table 1 The 2023 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 (formerly 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-derived carcinoma
Medullary thyroid carcinoma
Undifferentiated (anaplastic) carcinoma
Squamous cell carcinoma
Carcinoma with mixed features (specify)
Metastatic malignancy
Non-Hodgkin lymphoma
Other

Abbreviation: AUS, atypia of undetermined significance.
Adapted, with permission, from Ali and VanderLaan.[7]

category name is an acceptable, optional practice (eg, benign [Bethesda II], AUS [Bethesda III]).

The widespread adoption of TBSRTC proves that it is built on a reporting framework with a probabilistic approach (ie, implicit risk of malignancy [ROM]) for each diagnostic category. TBSRTC 2023 provides each category with an implied cancer risk. Based on prospectively analyzed large series with surgical follow-up reported since the 2017 edition, the ROMs have been updated (Table 2). Keeping TBSRTC updated with clinical practice guidelines, each reporting category has an updated and revised management algorithm, as recommended by the American Thyroid Association and other professional endocrine organizations. In addition to the revision of the category designations, updated ROMs, and revision in the management plans, other significant changes in TBSRTC 2023 include the following:

1. Revised nomenclature for certain thyroid lesions in alignment with the recently published 2022 World Health Organization (WHO) Classification of Thyroid Neoplasms.[8]
2. The addition of 2 new dedicated chapters, recognizing the importance of clinical perspectives and imaging findings and the expanding landscape of molecular testing in thyroid disease.
3. An expanded discussion on the reporting and management of pediatric thyroid disease. TBSRTC can be adequately applied for reporting pediatric thyroid cytopathology. Based on published studies, the ROMs have been calculated for the 6 reporting categories for this age group and linked with the commonly practiced guidelines[9,10] (Table 3).
4. An official endorsement of TBSRTC by the European Federation of Cytology Societies, an umbrella organization of cytology professionals composed of 26 individual national organizations.

Format of the report

To effectively and clearly communicate the cytopathologic interpretation, TBSRTC 2023 continues to recommend that each report begin with 1 of the 6 general diagnostic categories. Because of their ambiguous and less clearly descriptive nature, numerical designations alone (eg, Bethesda IV) are discouraged for the purposes of FNA reporting and scientific publication, although the numerical designations can be used in conjunction with the category name, such as "follicular neoplasm (Bethesda IV)."

Each of the categories has an implied cancer risk that links it to an evidence-based clinical management guideline (Table 2). For several reporting categories, some degree of subcategorization is recommended that further clarifies the FNA diagnosis, such as "suspicious for malignancy (Bethesda V) - suspicious for papillary thyroid carcinoma." Additional descriptive notes such as clinical recommendations or explanations regarding the differential diagnoses and comments beyond such subcategorization are optional and left to the discretion of the cytopathologist.

The revised and updated range and average ROMs are depicted in Table 2. These best current risk estimates are based on surgically resected nodules with the tabular footnotes clarifying the ROM estimates where appropriate. The

Table 2 The 2023 Bethesda system for reporting thyroid cytopathology: implied ROM with expected ranges based on follow-up of surgically resected nodules with recommended clinical management.

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 ultrasound 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]

Abbreviations: FNA, fine needle aspiration; ROM, risk of malignancy.

[a]These ROM estimates are skewed by selection bias, because many thyroid nodules (especially those diagnosed as benign or atypia of undetermined significance) might not undergo surgical excision.

[b]Actual management could depend on other factors (eg, clinical, ultrasound findings), in addition to the FNA interpretation.

[c]The ROM varies with the type and structure of the nodule (ie, solid versus complex versus ≥50% cystic); nondiagnostic aspirates from solid nodules are associated with a higher ROM compared with those showing ≥50% cystic changes and low-risk ultrasound features.

[d]Studies have shown diagnostic resolution with repeat FNA.

[e]This ROM estimate is based on follow-up of surgically resected nodules, which is skewed by selection bias because most thyroid nodules classified as benign do not undergo surgical excision; using long-term follow-up studies, the best overall ROM estimate for a benign FNA is ∼1% to 2%.

[f]This category can be further subclassified into specimens with nuclear versus non-nuclear atypia, the ROM appears to be higher for cases with nuclear atypia.

[g]Includes cases of follicular neoplasm with oncocytic features (formerly Hürthle cell neoplasm).

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

[i]In the case of "suspicious for metastatic tumor" or a "malignant" interpretation indicating a metastatic tumor rather than a primary thyroid malignancy, surgery might not be indicated.

Adapted, with permission, from Ali and VanderLaan.[7]

Table 3 The 2023 Bethesda system for reporting thyroid cytopathology in pediatric patients with implied ROM and possible management recommendations.

Diagnostic category	ROM Mean % (range)	Possible management recommendations
Nondiagnostic	14 (0-33)	Repeat FNA with ultrasound guidance
Benign[a]	6 (0-27)	Clinical and ultrasound 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

Abbreviations: FNA, fine needle aspiration; ROM, risk of malignancy.
[a]ROM is skewed by selection bias because most thyroid nodules classified as benign do not undergo surgical excision.
[b]Includes cases of follicular neoplasm with oncocytic features (formerly Hürthle cell neoplasm).
Adapted, with permission, from Ali and VanderLaan.[7]

traditional method of estimating the cancer risk, which is based on histologic follow-up (ie, dividing the number of patients with cancer by the total number of patients with surgical follow-up), overestimates the ROM, particularly for the nondiagnostic, benign, and AUS categories, for which a selection bias exists, given the relatively small proportion of nodules that undergo excision.

As with the previous edition, the effect of "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) on the ROM estimates has been considered. Although NIFTP is a surgical disease and cannot be definitively diagnosed using FNA, the cytologic features of this indolent tumor tends to lead to classification on FNA as either AUS (Bethesda III), follicular neoplasm (Bethesda IV), or SFM (Bethesda V), thereby affecting the resultant ROM calculations. Based on new prospective studies since the publication of the second edition, the revised ROM for each category when excluding NIFTP is shown in Table 4, information that could help guide more conservative clinical management of some nodules.

Nondiagnostic

TBSRTC 2023 has discontinued the option of using the term "unsatisfactory" for the first category; henceforth, the sole term "nondiagnostic" is recommended. TBSRTC 2023 reiterates that every thyroid FNA should be evaluated for sample adequacy, which is defined by both the quantity and quality of the cellular (mostly follicular) and colloid components. Application of adequacy criteria ensures a low false-negative rate and more accurate interpretation of the FNA. Similar to prior editions, with some exceptions (eg, cases with abundant colloid or aspirates with abundant lymphocytic infiltrate), TBSRTC 2023 continues to recommend a minimum of 6 groups of well-preserved, well-visualized follicular cells, with each group comprising $\geq$10 cells, for an adequate sample (quantity). Despite the presumed advantages of lowering the follicular cell count for specimen adequacy (eg, fewer nondiagnostic FNA and, thus, fewer repeats),[11,12] no clear consensus has yet been reached regarding a lower threshold. Therefore, the original adequacy criteria from TBSRTC 2017 have been retained until robust published studies validating a lower cell count are available. Regarding the quality, thyroid FNA preparations that are considered satisfactory for evaluation should show cells that are well-preserved, well-stained, and easily visualized. Certain limiting factors such as abundant obscuring blood or extensive air-drying artifacts could be included in adequacy statements. "Unsatisfactory" is a term applied to the adequacy statement and is no longer considered synonymous with "nondiagnostic." An

Table 4 Reported decreases in the ROM of TBSRTC diagnostic categories if excluding nodules diagnosed by surgical pathologic examination as NIFTP.

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

Abbreviations: NIFTP, noninvasive follicular thyroid neoplasm with papillary like nuclear features; ROM, risk of malignancy; TBSRTC, The Bethesda System for Reporting Thyroid Cytopathology.
[a]Based on the weighted average (mean) reduction in malignancy, with the expected ranges.
[b]Based on the estimated average ROM values from Table 2 minus the values reported in the present Table.
Adapted, with permission, from Ali and VanderLaan.[7]

unsatisfactory specimen, by definition, contains no diagnostic information.

Aspirates that consist of cyst fluid only with or without macrophages continue to be interpreted as nondiagnostic (Bethesda I). An optional note could be added in the report that in the absence of worrisome ultrasound findings (eg, a purely cystic lesion with no solid areas or mural nodules), the clinician might consider the FNA interpretation as if it were a benign result.

The ROM for a nondiagnostic FNA is difficult to calculate because most such nodules are not surgically resected. Among surgically excised nodules initially reported as nondiagnostic, the ROM is 5% to 20% (average, 13%), which clearly overrepresents the incidence of malignancies compared with the entire cohort of nondiagnostic nodules owing to selection bias.

A repeat aspiration with ultrasound guidance is recommended for cytologically nondiagnostic nodules and will yield diagnostic results in 60%-80% of cases, particularly in the nodules with a smaller cystic component.[13] Regarding the interval for a repeat FNA after an initial nondiagnostic FNA, the data are slightly conflicting. Some studies have clearly depicted lower diagnostic yields if the repeat FNA is performed sooner than 3 months.[14] However, the previous approach of waiting for 3 months before a repeat FNA seems to be less crucial.[15,16] Additionally, the American Thyroid Association guidelines now state that there is no need to wait several months before repeating the FNA.[4]

Benign

The success and clinical value of thyroid FNA centers on its ability to reliably identify benign thyroid nodules and, thus, avoid unnecessary surgical resection for most patients with nodular thyroid disease. A benign (Bethesda II) FNA diagnosis is associated with a very low ROM when these nodules undergo surgical resection (range, 2%-7%; average, 4%). Because relatively few nodules with a benign (Bethesda II) FNA will actually undergo surgery (footnotes of Table 2 and the chapter on the benign diagnostic category), the best overall ROM estimate based on long-term follow-up studies is approximately 1% to 2%. In light of the 2022 WHO classification of thyroid tumors, the use of the term "follicular nodular disease" is preferred to refer to the spectrum of changes previously designated as colloid nodule, hyperplastic nodule, adenomatous nodule, or benign follicular nodule.[17]

Atypia of undetermined significance

TBSRTC 2023 discontinues the term "follicular lesion of undetermined significance" to avoid confusion with reporting terminology and management; henceforth, only the term "AUS" is used. AUS is one of the three "indeterminate" cytopathologic interpretations that convey a diagnosis that is not definitively benign or malignant.

The AUS category is reserved for cases with atypia that is insufficient for either of the other 2 indeterminate categories of "follicular neoplasm" and "suspicious for malignancy." Among the 3 indeterminate categories, AUS has the lowest ROM (average, 22%; range, 20%-32%), again based on surgical resection data, which likely overestimate the overall ROM for this category. Furthermore, the malignancy risk differs according to the cytomorphologic nature of the atypia leading to the AUS interpretation. Specifically, AUS with nuclear atypia has a significantly higher ROM compared with AUS associated with other patterns, particularly those characterized by architectural atypia alone or a predominance of oncocytes.[18,19] Recently reported data suggest that the AUS subclassification for pediatric patients, similar to that currently used for adults, might provide further risk stratification. One study showed that nuclear atypia was associated with an ROM of 59% compared with 6.5% for architectural or oncocytic atypia.[20] TBSRTC 2023 has introduced further simplification of the AUS subcategorization into 2 groups: "nuclear" (previously "cytologic") and "other." The latter includes cases with architectural atypia, oncocytic atypia, and lymphocytic atypia, among others. The new subclassification of AUS puts emphasis on the importance of distinguishing nuclear atypia (which conveys a relatively higher risk) from all other AUS morphologic patterns (conveying a relatively lower risk) to improve communication regarding the ROM between cytopathologists and the clinical team managing the patient. This 2-tiered subclassification is also supported partly by molecular studies performed on AUS cases clearly delineating the "nuclear" from the "other" subgroup.[21] Updates to the AUS category in TBSRTC 2023 also includes management practices, the role of molecular testing, and discussion of concerns specific to pediatric patients.

Follicular neoplasm

To ensure clear and unambiguous communication, TBSRTC 2023 recommends discontinuing the use of term "suspicious for a follicular neoplasm," given the potential confusion of this category with a different category that also incorporated "suspicious" in the title (ie, "suspicious for malignancy [Bethesda V]"). As such, only "follicular neoplasm" should be used as the sole name for this category. The diagnostic criteria proposed in the second edition are reaffirmed in this third edition. This category is intended for those aspirates that are at least moderately cellular and composed of follicular cells, most of which show significant architectural abnormality in the form of microfollicles and/or crowding, trabeculae, or single cells. Based on the relaxing of the morphologic criteria in the second edition of TBSRTC to possibly include all cases suspected to be NIFTP, the third edition provides a more detailed description of the diagnostic

clues for potential cases of this entity.[22,23] If possible, prospective cytologic recognition of potential NIFTP cases in thyroid FNAs is important to avoid overdiagnosing them as "malignant - papillary thyroid carcinoma" or "suspicious for malignancy - suspicious for papillary thyroid carcinoma," diagnostic categories that could unnecessarily result in aggressive surgical procedures, because the recommended treatment for NIFTP is conservative surgery (eg, lobectomy) in view of its indolent behavior. It is, therefore, reiterated that follicular-patterned aspirates with only mild nuclear changes (ie, mild degree of enlargement, contour irregularity, and/or chromatin clearing) are best classified as follicular neoplasm if true papillae are absent and intranuclear pseudoinclusions are either absent or very rare. Because the reporting category name is now simply "follicular neoplasm" and not "suspicious for a follicular neoplasm," cytopathologists have the option of adding the following statement to the report to acknowledge that not all aspirates diagnosed as "follicular neoplasm (Bethesda IV) will ultimate be proved to be neoplastic on evaluation of the surgical resection specimen: "Although the cytologic features are in keeping with a follicular neoplasm, approximately 30% of cases diagnosed as follicular neoplasm (Bethesda IV) on FNA turn out to be benign follicular nodular disease on surgical resection." Molecular testing results can be used to supplement the risk assessment in lieu of proceeding directly to surgery.[6] The recommended management of follicular neoplasm is surgical excision of the nodule, most often hemithyroidectomy or lobectomy.

Regarding the previous term "follicular neoplasm, Hürthle cell type," TBSRTC 2023 recommends "follicular neoplasm - oncocytic follicular neoplasm" to align with the 2022 WHO Classification of Thyroid Neoplasms. This diagnosis is associated with a significant ROM (range, 25%-50%). The criteria for this diagnosis are essentially unchanged from those described in the first 2 editions: a virtually exclusive population of oncocytes, usually scant to absent colloid, rare to absent background lymphocytes, and, often, with the presence of nuclear and cellular size variations. The differential diagnosis includes benign nodules with focal oncocytic hyperplasia and other neoplasms with oncocytic features, most importantly medullary thyroid carcinoma and subtypes of papillary thyroid carcinoma.

Suspicious for malignancy

The diagnostic category of SFM (Bethesda V) is used when the cytomorphologic features of a thyroid FNA are worrisome for papillary thyroid carcinoma, medullary thyroid carcinoma, lymphoma, or another malignant neoplasm but are quantitatively and/or qualitatively insufficient for a definitive malignant (Bethesda VI) diagnosis. SFM as a TBSRTC category is quite heterogeneous; however, most cases under SFM are classified as "suspicious for papillary thyroid carcinoma." As the usual management is surgical (either lobectomy or near total thyroidectomy), the diagnosis of SFM should be used judicially. Some, but not all, of the cases in this category raise the possibility of a follicular variant of papillary thyroid carcinoma or NIFTP. For this subset, adding an optional note clarifying that "the cytomorphologic features are suspicious for a follicular variant of papillary thyroid carcinoma or its indolent counterpart NIFTP" could be considered. In such cases, deescalating the surgical management with lobectomy rather than total thyroidectomy could be a good approach.

Malignant

TBSRTC category "malignant (Bethesda VI)" is used whenever the cytomorphologic features are conclusive for malignancy. The descriptive comments that follow are used to subclassify the malignancy and summarize the results of special studies, if any.

The diagnostic morphologic criteria of common thyroid malignancies have not changed. A few updates included in the 2023 edition are as follows:

1. The term "papillary thyroid carcinoma, variants" is now changed to "papillary thyroid carcinoma, subtypes" in accordance with the WHO tumor classification recommendation to avoid confusion with the term "genetic variant(s)," which is based on the molecular classification.
2. The previously recognized subtype of papillary thyroid carcinoma, "cribriform morular variant" is now designated as a separate tumor entity.
3. The new term "high-grade follicular-derived thyroid carcinoma" is now endorsed, which replaces the older nomenclature of "poorly differentiated thyroid carcinoma."

Conclusions

The third edition of TBSRTC builds on the success of the prior editions of this atlas and reporting system. This new edition not only provides up-to-date ROM estimates for each diagnostic category but also harmonizes the terminology with the latest WHO classification of thyroid neoplasms and covers the increasingly important molecular alterations encountered in thyroid neoplasms, ensuring that TBSRTC remains relevant and clinically useful. With updated images, sample reports with explanatory notes, and further refined diagnostic criteria, the third edition of TBSRTC will continue to help cytopathologists accurately and reproducibly classify thyroid nodule FNAs to clearly reflect the ROM that will guide clinical management.

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