The Second Edition Bethesda System for Reporting Thyroid Cytopathology

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The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC)

- The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), a uniform and standardized reporting system for thyroid fine needle aspiration (FNA), was originally established in 2009 and updated in 2017. The system is widely accepted in the United States and globally.
- It is specifically designed for the reporting of thyroid follicular and C-cell–derived lesions based on clearly outlined diagnostic criteria.
- The succinct and unambiguous reports and clarity of communication allows clinicians to manage their patients based on recommended clinical management guidelines.
- The 2nd Edition of TBSRTC retained the original six diagnostic categories, which span the spectrum of benign and malignant thyroid lesions and the indeterminate diagnoses (Table 2.1). (From this point, "TBSRTC" in this atlas refers to the 2nd Edition.)
- Three categories are "indeterminate for malignancy":
  - Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance (AUS/FLUS)
  - Follicular Neoplasm or Suspicious for a Follicular Neoplasm (FN/SFN)
  - Suspicious for Malignancy (SM)
- FN/SFN includes a category of Hürthle cell (oncocytic) lesions, entitled FNHCT or SFNHCT.
- A non-thyroid entity presenting as a thyroid nodule, such as a parathyroid gland, is also reported using TBSRTC categories.
- Each TBSRTC diagnostic category is associated with an implied risk of malignancy (ROM) based on an analysis of the available literature, and each translates directly into a clinical management algorithm (Table 2.2).

Table 2.1 Recommended diagnostic categories for the second edition Bethesda system for reporting thyroid cytopathology

I.	Nondiagnostic or Unsatisfactory[a, b]
II.	Benign
III.	Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance[b]
IV.	Follicular Neoplasm or Suspicious for a Follicular Neoplasm[a] (Specify if Hürthle cell [oncocytic] type)
V.	Suspicious for Malignancy
VI.	Malignant

Modified from Ali and Cibas [1]; with permission
[a]Adequacy criteria are the same for conventional smears (CS) and LBP
[b]The two terms for these categories are synonymous. A laboratory should choose the one it prefers and use it exclusively for that category

Updates in TBSRTC

- The 2nd edition of TBSRTC was unveiled in light of many recent advances and developments in the field of thyroid disease:
  - The category of Noninvasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP) was introduced and has led to an increased use of the indeterminate categories and changes in the TBSRTC-implied ROM for various categories.
  - In 2015, the American Thyroid Association (ATA) updated the management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer and incorporated the role of molecular testing for management [10]. The ATA has endorsed TBSRTC
  - Ultrasound (US)–based risk stratification systems for thyroid nodules have been improved, including 2015 ATA guidelines [9], 2016 Korean Thyroid Association (KTA)/Korean Society of Thyroid Radiology (KSThR) guidelines [21], and the new 2017 American College of Radiology (ACR) guidelines [23].
  - The use of liquid-based preparations (LBP) for thyroid cytology has increased.

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Table 2.2 TBSRTC: updates in the implied risk of malignancy (ROM) and recommended clinical management

Diagnostic category	2009 ROM, %	2017 ROM, %	2017 ROM with NIFTP, %	Usual management,[c] 2017	Optional note, 2017
Nondiagnostic or Unsatisfactory (ND/Unsat)	1–4	5–10	No significant change	Solid nodules, repeat FNA with US; cystic nodules correlated with US. Re-aspiration, if clinically indicated	None
Benign	0–3	0–3	No significant change	Clinical & US follow-up at intervals of 6–18 mon for 3–5 y	None
Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance (AUS/FLUS)	~5–15	10–30	6–18	Repeat FNA or molecular test	None
Follicular Neoplasm or Suspicious for a Follicular Neoplasm (FN/SFN)	15–30	25–40	10–40	Molecular test or lobectomy	Histopathologic follow-up usually show follicular adenoma, follicular carcinoma, and follicular variant of papillary thyroid carcinoma (FVPTC), including its recently described indolent counterpart, NIFTP.
Suspicious for Malignancy (SM)	60–75	50–75	45–60	Total thyroidectomy or lobectomy[a,b]	Suspicious for FVPTC and NIFTP; definitive distinction not possible on cytological material
Malignant (PMC)	97–99	97–99	94–96	Surgical consultation for-total thyroidectomy[b]	About 3–4% of cases diagnosed as PTC may prove to be NIFTP on histopathological examination, reducing the PPV of the Malignant category from 99% to about 94–96%.

Modified from Ali and Cibas [1]; with permission
NIFTP noninvasive follicular thyroid neoplasm with papillary-like nuclear features, *PMC* positive for malignant cells, *PPV* positive predictive value, *US* ultrasound
[a]Some studies recommend molecular analysis to assess the type of surgical procedure
[b]Management decision may vary for metastatic and lymphoid tumors
[c]Actual management may depend on other factors (e.g., clinical, sonographic) besides the FNA interpretation

  - Information and knowledge of molecular pathology of thyroid disease has vastly increased in the past few years. Thyroid molecular testing is increasingly being used in conjunction with indeterminate cytologic diagnoses. Molecular testing enhances the sensitivity of cytologic diagnosis and leads to more informed and better patient management.
- Specific updates in the TBSRTC reflect many of these advances:
  - Proper use of diagnostic category terminology
    - Three TBSRTC categories have two names each: ND/Unsat, AUS/FLUS, and FN/SFN. These terms are synonymous and should not be used interchangeably or to denote two distinct interpretations.
    - TBSRTC recommends that only one term should be applied to each category.
  - Nondiagnostic or Unsatisfactory (ND/Unsat) category with "Cyst fluid (macrophages) only"
    - These cases should be reported as ND/Unsat with an explanatory note.
    - The 2015 ATA guidelines has updated the management recommendation for ND/Unsat samples including cystic lesions. They recommend that if a nodule shows an initial ND/Unsat cytology result, FNA should be repeated with US guidance and, if available, with rapid on-site evaluation (ROSE).
  - Recommended interval to repeat FNA for ND/Unsat cases
    - Originally, the recommendation was to wait for >3 months to repeat FNA, to allow biopsy-related reactive changes to subside.
    - TBSRTC permits shorter interval times, though the potential for reactive atypia and cellular changes remains.
  - Increasing use of LBP
    - TBSRTC acknowledges the increasing use of LBP for processing of thyroid FNA specimens, and provides more examples of LBP cases and comparison with conventional smears (CS) for various entities.
  - AUS/FLUS category, with subcategorization of AUS/FLUS
    - AUS and FLUS are synonymous terms; each laboratory should use only one term.
    - The use of *AUS* for cases with nuclear atypia, *FLUS* for cases with architectural atypia, and *AUS/FLUS*

to denote that both types of atypia are present is discouraged.
    - Subcategorization for the AUS/FLUS category is recommended to help guide management. (*See* Chap. 5)
- Risk of malignancy (ROM)
    - Implied ROM in TBSRTC is based upon a selected group of studies that included large cohorts of cases or meta-analyses (*see* Table 2.2).
    - The introduction of NIFTP has had the most significant impact on ROM.
- Inclusion of newly described entities, including mammary secretory analogue of thyroid gland, which is a primary thyroid carcinoma harboring *ETV6-NTRK3* fusion.
- Expanded differential diagnoses for various lesions (as covered in later chapters)
- Optional notes, comments, and recommendation can be given for some categories such as FN/SFN, SM, or Malignant. (*See* Table 2.2.)
    - A note would be most useful in cases with cytologic features of papillary thyroid carcinoma (PTC) but a follicular architecture, indicating that the differential diagnosis includes follicular variant of papillary thyroid carcinoma (FVPTC) or its indolent counterpart, NIFTP. The cytologic diagnosis alone or in conjunction with molecular testing will help guide clinical management.
    - An optional note is also recommended for metastatic tumors and lymphomas.
- Molecular testing (*See* Chap. 15)
    - Currently, three molecular tests are commercially available for use as an adjunct to cytology: ThyGenX®/ThyraMIR™ combination test (Interpace Diagnostics Group, Parsippany, NJ); Afirma® Genomic Sequencing Classifier (GSC), (Veracyte, South San Francisco, CA); and ThyroSeq® v3 genomic classifier (CBLPath, Rye Brook, NY, and University of Pittsburgh Medical Center, Pittsburgh, PA).
    - The tests, when used for the 15–30% of samples of indeterminate cytology, further enhance the accuracy of the preoperative cytologic diagnosis and can be recommended for management.
    - Tests are also useful in follicular-patterned lesions such as NIFTP.
- Intra-laboratory quality control monitoring
    - TBSRTC recommends regular quality assurance (QA) monitoring for laboratories, to prevent overuse of the AUS/FLUS category, which should not exceed 10%.
    - Continuous cytohistologic correlation is also essential to maintain quality.
    - Continuous correlation of cytology and molecular test results also should be instituted.

Modifications in TBSRTC

- Use "oncocytic" instead of "Hürthle cell" in FN/SFN category.
- Suggests to diagnose PTC only when the following features of classic PTC are present:
    - True papillae
    - Psammoma bodies
    - Frequent inclusions; Krane et al. [14] recommend >3 intranuclear pseudoinclusions (INPI) to establish a diagnosis of PTC.

Ultrasonographic Patterns for Risk Stratification of Thyroid Nodules for FNA

- Certain sonographic features of a thyroid nodule are associated with an increased ROM, but no single predictor has been found to have a high positive predictive value (PPV) for cancer.
- Many professional societies have published guidelines to aid in the selection of thyroid nodules for US-guided FNA (USGFNA), including the 2015 ATA guidelines [9], 2016 Korean Thyroid Association (KTA)/Korean Society of Thyroid Radiology (KSThR) guidelines [21], and the new 2017 American College of Radiology (ACR) guidelines [23].
- These guidelines recommend that only nodules with suspicious or high-risk US characteristics be aspirated.
- High-risk characteristics of a thyroid nodule on US include a solid or hypoechoic nodule or a solid and hypoechoic component of a partially cystic nodule with one or more of the following features: irregular margins, taller-than-wide morphology, microcalcifications, disrupted rim calcifications, and extra-thyroidal extension (ETE).

Suggested Reading

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