GUIDELINES OF THE CANADIAN SOCIETY OF CYTOPATHOLOGY

The Bethesda System for Reporting Thyroid Cytopathology

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*The CSC endorses The Bethesda System for Reporting Thyroid Cytopathology (2017). The following document is a short summary of the highlights of the Bethesda guidelines. Further details can be found in the original Atlases (Refs 1 and 2)

Introduction:

TBSRTC is an evidence-based standardized reporting system for thyroid FNA specimens. Since 2009, TBSRTC has been widely adopted in the U.S. and in many places worldwide, and has been endorsed by the American Thyroid Association. In 2017, TBSRTC was revised and updated to incorporate new data/developments in the field of thyroid pathology.

Every thyroid FNA report should begin with one of six diagnostic categories, the names of which remain unchanged since they were first introduced: (I) Nondiagnostic OR Unsatisfactory; (II) Benign; (III) Atypia of undetermined significance (AUS) OR Follicular lesion of undetermined significance (FLUS); (IV) Follicular neoplasm OR Suspicious for a follicular neoplasm; (V) Suspicious for malignancy; and (VI) Malignant. For some categories, some degree of subcategorization can be informative and is often appropriate (see below). Additional descriptive comments (beyond such sub-categorization) are optional and left to the discretion of the cytopathologist. There is a choice of two different names for some of the categories. A laboratory should choose the one it prefers and use it exclusively for that category. Synonymous terms (eg, AUS and FLUS) should not be used to denote two distinct interpretations. Each of the categories has an implied cancer risk that links it to an evidence-based clinical management guideline (Table 1). The recent reclassification of some thyroid neoplasms as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) has implications for the risk of malignancy and management, and this is accounted for in TBSRTC 2017 with regard to diagnostic criteria and optional notes (see below) which can be useful in helping guide surgical management.

Nondiagnostic (ND) or Unsatisfactory

Inadequate samples are reported as ND or Unsatisfactory (UNS). Examples include specimens with obscuring blood, poor cell preservation, and an insufficient sample of follicular cells. For a thyroid FNA specimen to be satisfactory for evaluation (and benign), ≥6 groups of benign follicular cells are required, each group composed of ≥ 10 cells. The minimum requirement for group size allows one to determine (by the evenness of the nuclear spacing) whether it represents a fragment of a macrofollicle. The exceptions to the numerical requirement of benign follicular cells remain unchanged in TBSRTC 2017. Any specimen that contains abundant colloid is adequate and benign, even if six groups of follicular cells are not identified. Whenever a specific diagnosis (eg, lymphocytic thyroiditis) can be rendered, and whenever there is any significant atypia, the specimen is, by definition, adequate for evaluation. Specimens that consist only of cyst contents (ie, macrophages, Fig.1) are a subcategory of ND/UNS which can be reported as such:

Nondiagnostic: Cyst fluid only (see Note).

Note: Specimen processed and examined but nondiagnostic because it consists almost exclusively of histiocytes. Recommend correlation with cyst size and complexity on ultrasound to assist with further management of the lesion.

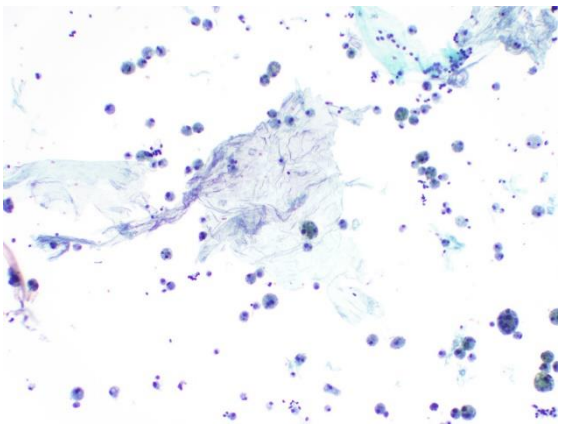

Figure 1: Nondiagnostic: cyst fluid only. Aspirate consisting mainly of histiocytes with scant colloid and no follicular cells.

Benign

TBSRTC 2017 has essentially made no changes to the usage, definition, or criteria for this category. Although not required, it is recommended to further subclassify a benign aspirate as benign follicular nodule, thyroiditis, or other less common entities. Distinction between nodular hyperplasia/goiter from macro-follicular adenoma is not possible by FNA, but this distinction is not clinically important. Therefore, they are reported as BFN. The cytologic features and diagnostic accuracy of BFN are generally similar between conventional smears and liquid based preparations. Specimens of BFN show varying proportions of colloid and bland-looking follicular cells arranged predominantly in macrofollicular or honeycomb architecture (flat sheets) (Fig. 2).

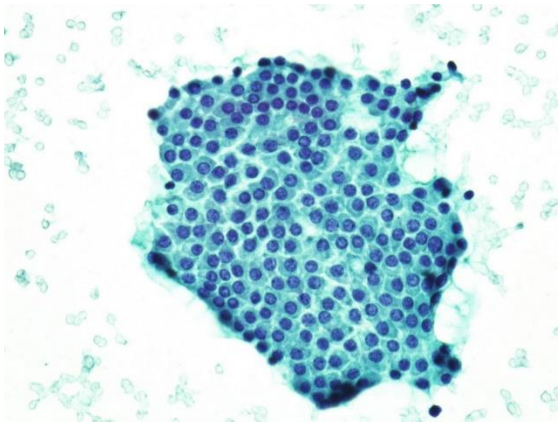

Figure 2: Benign
Benign follicular cells arranged in macrofollicles consistent with benign follicular nodule.

AUS or FLUS

AUS/FLUS should be reserved for specimens that contain cells with architectural and/or nuclear atypia that is insufficient for an interpretation of FN/SFN, SM, or malignant and where the atypia is more marked than what can be attributed confidently to benign changes. TBSRTC recommends subclassification of the atypia., as follows:

(i) Cytologic atypia: this may take one of several different forms: focal nuclear changes, extensive but mild nuclear changes, atypical cyst lining cells, or ‘‘histiocytoid’’ cells.

(ii) Architectural atypia: this is often a sparsely cellular sample but one that is comprised mostly of microfollicles.

(iii) Cytologic and architectural atypia: Cytologic atypia and architectural atypia are not mutually exclusive. This pattern is often associated with NIFTP at resection.

(iv) Hurthle cells: this is often a sparsely cellular sample comprised exclusively of Hurthle cells. Alternatively, AUS/FLUS may be used for a moderately or markedly cellular sample composed exclusively (or almost exclusively) of Hurthle cells if the clinical setting suggests a benign Hurthle cell nodule, such as in chronic lymphocytic (Hashimoto) thyroiditis or a multinodular goiter (see below).

(v) Atypia, not otherwise specified: for other less common scenarios including psammoma bodies and treatment-related atypia (Fig. 3).

Descriptive language such as ‘‘cytologic atypia’’ and ‘‘architectural atypia’’ is preferred (rather than ‘‘rule out papillary carcinoma,’’ etc.) due to its less provoking nature and potential risk of confusion with a “suspicious” category. AUS/FLUS should be considered as a category of last resort and should be used judiciously. TBSRTC 2017 recommends that an effort be made to limit its use to approximately 10% of all thyroid FNAs. Compromising factors like sparse cellularity, air-drying artifact, obscuring blood, and excessive clotting artifact do not warrant an AUS/FLUS diagnosis if there is no discernable atypia. If the artifacts are focal, clearly recognizable, and associated with benign material elsewhere, such cases should be diagnosed as Benign.

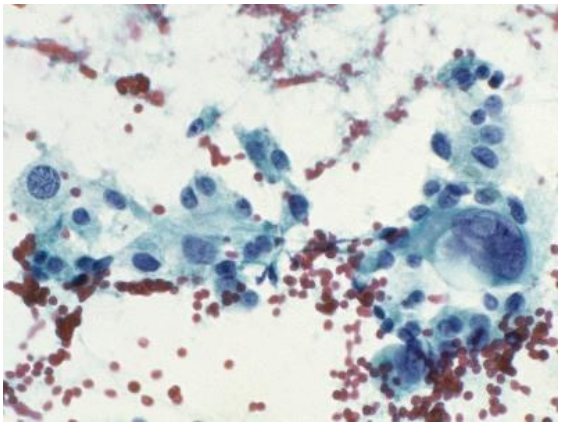

Figure 3: AUS.
Treatment-related (radioiodine) nuclear atypia.

Follicular Neoplasm (FN) or Suspicious for a Follicular Neoplasm (SFN)

FN/SFN refers to a moderately or markedly cellular aspirate comprised of follicular cells, most of which are arranged in an altered architectural pattern characterized by significant cell crowding and/or microfollicle formation and associated with scant colloid. In order to improve reproducibility, microfollicle is defined by crowded, flat groups of 15 follicular cells or less, arranged in a circle that is at least two-thirds complete (Fig.4). An important defining feature of the microfollicle is the crowding and overlapping of the follicular cells. TBSRTC 2017 includes a modification to the original definition and diagnostic criteria for this category in light of NIFTP. In TBSRTC 2009, cases that demonstrated the nuclear features of papillary thyroid carcinoma (PTC) were excluded from this category. The new definition states that ‘‘Follicular-patterned cases with mild nuclear changes (increased nuclear size, nuclear contour irregularity, and/or chromatin clearing) can be classified as FN/SFN so long as true papillae and intranuclear pseudoinclusions are absent. If the cytologic features raise the possibility of follicular variant of PTC (FVPTC) or NIFTP (ie,

a predominance of microfollicles and only mild or focal nuclear changes), the following optional note (or something similar) may be useful:
Note: Although the architectural features suggest a follicular neoplasm, some nuclear features raise the possibility of an invasive FVPTC or its recently described indolent counterpart, NIFTP; definitive distinction among these entities is not possible on cytologic material.

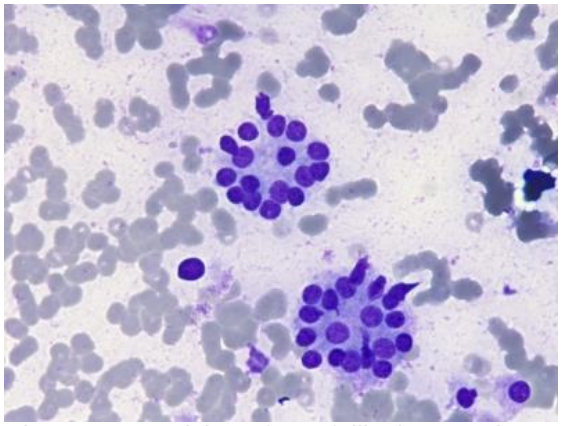

Figure 4: Suspicious for a follicular neoplasm. Aspirate composed of microfollicles.

FN/SFN, Hürthle Cell (Oncocytic) Type

In TBSRTC, FNA specimens that are suspicious for a Hürthle cell (oncocytic) neoplasm (FN/SFN-HCT) are distinguished from those suspicious for a non-Hürthle cell follicular neoplasm (FN/SFN) for two reasons: (1) there is a striking morphologic difference between these two cytologic patterns, which raises different diagnostic considerations, and (2) there are data to suggest that follicular and Hürthle cell carcinomas are genetically different. A moderately or markedly cellular aspirate from a solitary nodule that is composed virtually exclusively of Hürthle cells is generally reported as FN/SFN-HCT. Considering the rarity of Hürthle cell carcinoma in a background of lymphocytic thyroiditis, cases with obvious Hashimoto thyroiditis and Hürthle cells should typically be diagnosed as Benign. On the other hand, it is acceptable to diagnose a moderately to markedly cellular sample composed exclusively of Hürthle cells as AUS/FLUS when the clinical setting suggests a benign Hürthle cell nodule, such as in lymphocytic thyroiditis or a multinodular goiter. If interpreted as AUS/FLUS, an explanatory note that "benign Hürthle-cell hyperplasia is favored" but that an "oncocytic neoplasm cannot be ruled out" can be very helpful. The goal is to provide the clinical team with the opportunity to avoid an unnecessary lobectomy in some of these patients.

Figure 5: suspicious for a Hürthle cell (oncocytic) neoplasm. Aspirate composed entirely of Hürthle cells.

Suspicious for Malignancy (SM)

SM is for aspirates which show features that are highly suggestive of malignancy but are not unequivocal for malignancy, because of insufficient quantitative and/or qualitative features. SM category should be subcategorized into PTC (most common), medullary thyroid carcinoma (MTC), lymphoma, and others (NOS). Some cases in this category raise the possibility of FVPTC or NIFTP (Fig. 6). For this subset of cases, the following optional note (or something similar) may be useful for clinical management:
Note: The cytomorphologic features are suspicious for FVPTC or its indolent counterpart NIFTP.

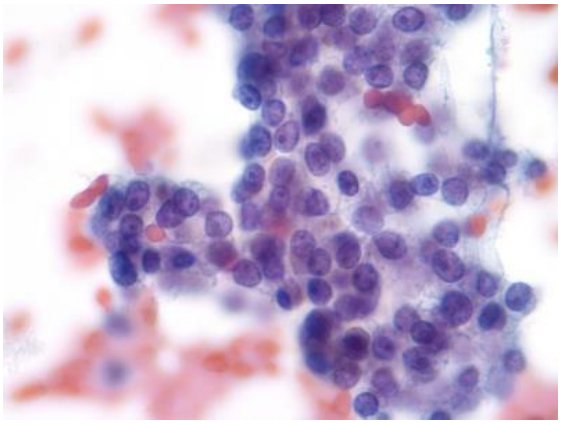

Figure 6: Suspicious for malignancy. Clusters of follicular cells with architectural and nuclear atypia suspicious for FVPTC/NIFTP.

Malignant

The Malignant category' is used whenever the cytomorphologic features are conclusive for malignancy. Descriptive comments that follow are used to subclassify the malignancy (ie, PTC, MTC, ATC, etc…) and summarize the results of ancillary studies, if any. TBSRTC 2017 has modified the definition and criteria for PTC cases; to avoid false-positives due to NIFTP, it suggests limiting use of the malignant category to cases with ''classical'' features of PTC (true papillae, psammoma bodies, and nuclear pseudoinclusions). Nevertheless, a small number of malignant cytologic interpretations may stilll be followed by a histologic NIFTP diagnosis, and thus the following optional note may be used when the diagnosis ''malignant; papillary thyroid carcinoma'' is made:

Note: A small proportion of cases (3–4%) diagnosed as malignant and compatible with papillary thyroid carcinoma may prove to be NIFTP on histopathologic examination

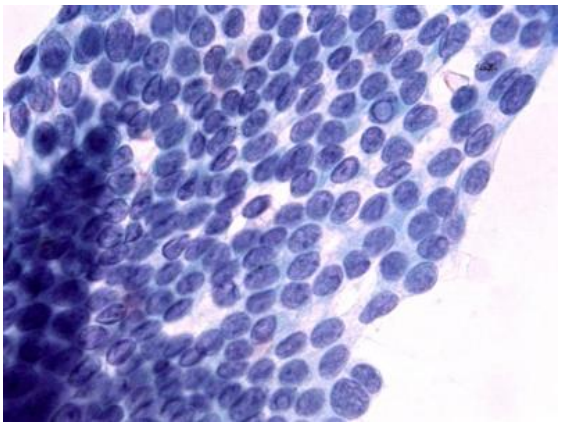

Figure 7. Malignant. Papillary thyroid carcinoma. Sheets of follicular cells with nuclear grooves and nuclear pseudoinclusions.

Table 1. The Bethesda System for Reporting Thyroid Cytopathology 2017: implied risk of malignancy and recommended clinical management

Diagnostic Category	Risk of Malignancy without NIFTP	Risk of Malignancy with NIFTP	Usual Management
Non-Diagnostic or Unsatisfactory	5-10%	No significant changes	Repeat FNA with ultrasound guidance
Benign	0-3%	No significant changes	Clinical and sonographic follow-up
Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance	10-30%	6-18%	Repeat FNA, molecular testing, or lobectomy
Follicular Neoplasm or Suspicious for a Follicular Neoplasm	25-40%	10-40%	Molecular testing, lobectomy
Suspicious for Malignancy	50-75%	45-60%	Near-total thyroidectomy or lobectomy
Malignant	97-99%	94-96%	Near-total thyroidectomy or lobectomy

References: 1. *Ali SZ, Cibas ES. The Bethesda system for reporting thyroid cytopathology: definitions, criteria and explanatory notes. New York, NY: Springer;* 2009, **2.** *Ali SZ, Cibas ES. The Bethesda system for reporting thyroid cytopathology: definitions, criteria and explanatory notes. New York, NY: Springer; 2018.*

Acknowledgments: all images were selected with permission from the online image Atlas provided by the Papanicolaou Society and the Bethesda System for Reporting Thyroid Cytopathology website. Additional images/cases can be seen at: http://www.papsociety.org/atlas.html