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Editorial note:

With the release of the 5th edition of the WHO Classification of Tumours of Endocrine and Neuroendocrine Tumours and 3rd edition of the Bethesda System for Reporting Thyroid Cytopathology, major changes have been made in thyroid pathology and cytopathology. This topical update provides a review on selected new entities and changes in terminology in thyroid pathology, and updates to the Bethesda reporting system. We welcome any feedback or suggestions. Please direct them to Dr. Angela Chan (e-mail: angelazchan@cuhk.edu.hk) of Education Committee, the Hong Kong College of Pathologists. Opinions expressed are those of the authors or named individuals, and are not necessarily those of the Hong Kong College of Pathologists.

Updates from the Thyroid WHO Classification and Bethesda System

Dr. Angela Zaneta CHAN
Department of Anatomical & Cellular Pathology, Prince of Wales Hospital, The Chinese University of Hong Kong

Introduction

All volumes of the WHO 5th edition have undergone major changes in terminology and volume structure, with an emphasis placed on taxonomy and cytogenesis. The thyroid gland represents the largest chapter in the latest 5th edition of the WHO classification of Endocrine and Neuroendocrine Tumours (2022). Thyroid tumours have been placed into several new categories to allow better understanding of the cell of origin, pathologic or molecular features, and biological behaviour. Newly recognized tumour types, subtypes and a grading system are included.

A third edition of the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) was released in 2023 and contains only minor updates, mainly to the AUS category and updated implied risk of malignancy (ROMs).

Follicular cell-derived neoplasms

Benign neoplasms

In the 4th edition, follicular adenoma was the only single entity included under the “benign” category. The new classification now includes thyroid follicular nodular disease, follicular adenoma, follicular adenoma with papillary architecture, and oncocytic adenomas.

Thyroid follicular nodular disease (TFND)

This newly included entity corresponds to the multifocal hyperplastic/neoplastic lesions that commonly occur in the clinical setting of "multinodular goitre". Some studies have shown these nodules to be clonal, while some are hyperplastic [1-3]. The term TFND achieved consensus as the best to describe this enigmatic entity, and avoids defining this lesion as hyperplastic or neoplastic, in contrast to prior names such as "colloid nodules", "hyperplasia", "adenomatoid nodule", or the contradictory "adenomatous hyperplasia".

Follicular adenoma with papillary architecture

This was previously classified as hyperfunctioning adenoma within the category follicular adenoma, and is now a separate entity. These tumours are usually well-delineated and may have a distinct capsule. Histologic features include cystic change, intrafollicular complex papillary infoldings and formation of subfollicles within follicles. The lining cells lack nuclear features of papillary thyroid carcinoma (PTC). They are generally negative for HBME-1, Galectin-3 and BRAF p.V600E immunostains. There are often associated with TSHR (up to 70%) [4-6], GNAS and/or EZH1 mutations [7,8], unlike follicular adenomas which harbour RAS mutations.

Oncocytic adenoma of the thyroid

This is now a distinct entity in the latest classification and requires encapsulation, follicular-patterned tumours with >75% oncocytic cytology and lack of capsular or vascular invasion for diagnosis. The term "Hurthle cell" is discouraged as it is a misnomer. These tumours have distinct genomic alterations in the mitochondrial genome (mtDNA) [9,10].

Low-risk neoplasms

This new category was introduced in the latest classification. These are borderline tumours that are morphologically and clinically intermediate between benign and malignant tumours with an extremely low rate of metastasis. Three tumours fall into this category, namely non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), thyroid tumours of uncertain malignant potential (UMP) and hyalinizing trabecular tumour (HTT).

Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)

The original criterion [11] of allowing less than 1% of true papillae from the 2017 WHO classification remains unchanged in the absence of BRAF V600E mutation [12], although there was debate about the percentage (0% vs 1%) of true papillae allowed. Previously, tumours ≤ 1 cm and oncocytic tumours that fulfilled the histologic criteria of NIFTP were diagnosed as subtypes of PTC. They are now considered subtypes of NIFTP, as they behave similarly to NIFTP and show negligible risk of tumour recurrence and lymph node metastasis. A diagnosis of oncocytic NIFTP requires at least 75% oncocytic cells [13].

Thyroid tumours of uncertain malignant potential (UMP)

The definition of tumors of UMP remains unchanged, which is "well-differentiated thyroid tumors with follicular architecture that are encapsulated or unencapsulated but well-circumscribed, in which invasion remains questionable after thorough sampling and exhaustive examination".

There are 2 subtypes: (1) Follicular tumour of uncertain malignant potential (FT-UMP), which lacks PTC-like nuclear features (nuclear score of 0-1), and (2) Well-differentiated tumour of

uncertain malignant potential (WDT-UMP), which has more pronounced nuclear features of PTC (nuclear scores of 2-3). If invasion has been thoroughly excluded, the term NIFTP should be used. The term "atypical adenoma" is not recommended.

Malignant neoplasms

Follicular thyroid carcinoma (FTC)

Diagnosis requires presence of capsular and/or vascular invasion. Apart from the lack of nuclear features of PTC, emphasis is placed on the lack of high-grade features and necrosis. When an FTC has areas of solid or trabecular growth, it is important to examine the mitotic count and presence of necrosis to exclude a diagnosis of poorly differentiated thyroid carcinoma (see section on PDTC). When an FTC with entirely follicular architecture has a mitotic count ≥ 5 per 2 mm^2, the tumor should be diagnosed as differentiated high-grade thyroid carcinoma (see section on DHGTC).

Invasive encapsulated follicular variant of papillary thyroid carcinoma (IEFVPTC)

This is distinguished from NIFTP solely by the presence of capsular and/or vascular invasion. Distinction from FTC is solely based on presence of nuclear features of PTC in IEFVPTC. Like FTC, it is subclassified into 3 groups: (i) minimally invasive (capsular invasion only), (ii) encapsulated angioinvasive (venous invasion +/- capsular penetration) and (iii) widely invasive. Encapsulated angioinvasive tumours are further divided into those with limited (<4 foci) or extensive (4 or more foci) vascular invasion. IEFVPTC has an identical genomic profile (RAS-like) and clinical behaviour to FTC [14,15].

Papillary thyroid carcinoma and subtypes

In the latest edition, molecular signature takes precedence over PTC nuclear features for diagnosis, and therefore only BRAF-like tumours are included in this category. IEFVPTC has been removed from this category and is now a distinct entity due to presence of RAS-like mutations [16].

The term "variant" has been replaced by "subtype" to remain consistent with other WHO tumour classification schemes, and to avoid confusion with the molecular diagnostic term "genetic variant(s)".

There are 13 histologic subtypes in total: classic, encapsulated classic, infiltrative follicular, diffuse sclerosing, solid/trabecular, tall cell, columnar cell, hobnail, clear cell, spindle cell, Warthin-like, oncocytic, and PTC with fibromatosis/fasciitis-like/desmoid-type stroma. Aggressive histologic subtypes include tall cell, columnar cell and hobnail PTCs.

Key points or changes of selected subtypes are highlighted as below:

- Infiltrative follicular: This is now the only PTC subtype with a follicular pattern. The "macrofollicular" variant is no longer considered a subtype.
- Tall cell: This is defined as cells whose height is at least three times their width (unlike two to three times in the previous edition), as well as having abundant eosinophilic cytoplasm and a prominent cell membrane. Tall cells should represent at least 30% or more of the PTC cells for diagnosis.
- Solid/trabecular: >50% solid, trabecular or nested growth pattern is required for diagnosis, unlike the "all or nearly all" cutoff in the previous edition.
- Diffuse-sclerosing: This subtype is no longer considered aggressive.

Previous subtypes/ variants that are no longer considered a subtype are:

- Macrofollicular: No longer considered a subtype.
- Cribriform-morular: No longer considered a subtype, and is listed under tumours of uncertain histogenesis.
- Papillary microcarcinoma: No longer considered a subtype, but should instead be subtyped by the histological pattern (such as classic papillary microcarcinoma, tall cell papillary microcarcinoma, etc.) as they can also display aggressive pathologic features and clinical behaviours [17-19].

High-grade follicular cell-derived non-anaplastic thyroid carcinoma

In the new classification, there are 2 groups of high-grade follicular cell-derived non-anaplastic thyroid carcinomas that have intermediate prognosis between well-differentiated carcinomas of follicular cells (papillary, follicular and oncocytic thyroid carcinoma) and anaplastic carcinoma. About 50% of these tumours will not take up radioactive iodine [20] and systemic therapy may be needed.

A. Poorly differentiated thyroid carcinoma (PDTC)

The diagnosis is based on Turin consensus criteria [21]: (i) presence of a solid/trabecular/insular pattern of growth in a tumour diagnosed as malignant based on invasive properties; (ii) absence of conventional nuclear features of papillary carcinoma; (iii) presence of at least one of the following: convoluted nuclei, mitotic count ≥ 3 per 2 mm^2, and tumour necrosis.

B. Differentiated high-grade thyroid carcinoma (DHGTC)

This new category includes follicular cell-derived carcinomas that are not poorly differentiated histologically but have high-grade features and the lack of anaplastic foci. By definition, the mitotic count must be ≥ 5 per 2 mm^2 ("hot spot" mitotic counting). Tumour necrosis is defined by karyorrhectic nuclear debris or ghost contours of dead tumour cells [22]. Tumour necrosis must be distinguished from infarct-type necrosis resulting from fine needle aspiration or regressive changes, as in the case of oncocytic tumours. Vascular, lymphatic, perineural and extrathyroidal invasions are commonly found. DHGTC should be subclassified according to their dominant histocytes, the majority of which are aggressive subtypes of PTC such as tall cell, hobnail or columnar cell [23, 24].

Anaplastic Thyroid Carcinoma (ATC)

ATC is composed of undifferentiated cells which may have focal features of thyroid follicular differentiation and/or a previous differentiated thyroid carcinoma. Primary squamous cell carcinoma (SCC) was considered a separate entity from ATC in previous WHO classifications; it is now recognized as a morphological pattern of ATC. Pure SCC without a differentiated thyroid carcinoma component carries BRAF V600E mutations in 60% of cases and has a similar outcome to ATC [25]. The majority express PAX8, confirming their follicular cell origin [26]. BRAF V600E detection by immunostaining and/or genotyping should be performed as the combination of BRAF and MEK inhibitors was found to be active against BRAF V600E-mutated anaplastic carcinoma [27].

Medullary thyroid carcinoma (MTC)

A two-tiered grading scheme for MTC has been introduced in this WHO edition. High-grade MTCs are defined as tumours with at least one of the following three features: mitotic count ≥5 per 2 mm^2, Ki67 proliferation index ≥5%, and/or tumour necrosis [28]. Grading of biopsies is not recommended as tumour necrosis can be focal. Mitotic count and Ki67 index should be based on the area of tumour with highest proliferative activity.

Thyroid tumours of uncertain histogenesis

This new category is introduced and includes sclerosing mucoepidermoid carcinoma with eosinophilia (SMECE) and cribriform-morular thyroid carcinoma (CMTC).

SMECE is a rare tumour (< 60 reported cases) and was previously considered as a subtype of salivary gland-type carcinomas of the thyroid gland. The morphology partially overlaps with MEC, along with a marked infiltration of lymphocytes and eosinophils in a background of marked stromal sclerosis [7,29]. Its origin still remains under debate, is but is favoured to be ultimobranchial body remnants [30]. It lacks the characteristic MAML2 rearrangement of mucoepidermoid carcinoma [31]. Reported genetic alterations include MET hyperploidy and point mutations in APC, NTRK3 and NF1 [32].

CMTC was previously classified as a variant/subtype of PTC, and is now a distinct entity. Almost all tumours have genetic alterations in the Wnt/beta-catenin pathway [33] which is distinct from BRAF V600E mutations in PTC [34]. Up to 53% are associated with familial adenomatous polyposis (FAP) [35]. They show nuclear expression of beta-catenin, estrogen receptor and progesterone receptor, and are often negative for markers of thyroid follicular cell differentiation (thyroglobulin and PAX8). The cribriform component is positive for TTF-1 [36].

Biomarkers

The current classification also emphasizes the value of biomarkers that may aid diagnosis and provide prognostic information.

Surrogate immunostains that can act as screening tools include: mutation-specific BRAF antibody (clone VE1) to screen for V600E mutations, pan-RAS Q61R (clone SP174) to detect HRAS/NRAS/KRAS Q61R mutations, pan-TRK for NTRK1/3 fusions, and 5A4 and D5F3 antibodies for ALK fusions.

2023 Bethesda System for Reporting Thyroid Cytopathology

A 3rd edition of the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) was released in July 2023 and contains only minor updates [37].

The new system assigns only a single distinct name for each of its six diagnostic categories: (I) nondiagnostic; (II) benign; (III) atypia of undetermined significance; (IV) follicular neoplasm; (V) suspicious for malignancy; and (VI) malignant. The use of the corresponding category number after the category name is optional.

Alternate names for 3 of the diagnostic categories: (I) “unsatisfactory”, (III) “follicular lesion of undetermined significance”, and (IV) “suspicious for a follicular neoplasm” have been discontinued to avoid confusion.

An implied risk of malignancy (ROM) for each of the six categories has been updated (Table 1) based on extensively published data since the 2nd edition of the TBSRTC in 2017 (Table 2); clinical management algorithms for each category have

also been revised. A revised ROM for each category when excluding NIFTP is also included (Table 3). Paediatric ROMs and management algorithms are newly added for the same six reporting categories (Table 4).

AUS category is now subcategorized into 2 groups: “nuclear” and “other”, with different implied ROM and molecular profile. AUS-nuclear atypia carries a significantly higher implied ROM (59%) than AUS associated with other patterns, especially architectural or oncocytic atypia (6.5%) [38]. AUS-other includes cases with architectural atypia, oncocytic atypia, and lymphocytic atypia. Cases with both mild nuclear and architectural alterations are grouped with aspirates exhibiting only nuclear atypia, since the ROM is similar regardless of presence or absence of coexisting architectural atypia.

Table 1. The Bethesda System for Reporting Thyroid Cytopathology (2023): implied risk of malignancy (ROM) with expected ranges based on follow-up of surgically resected nodules with recommended clinical management

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

Table 2. The Bethesda System for Reporting Thyroid Cytopathology (2017): implied risk of malignancy and recommended clinical management

Diagnostic category	ROM (%)	Usual management
Nondiagnostic or Unsatisfactory	5-10	Repeat FNA with ultrasound guidance
Benign	0-3	Clinical and sonographic follow-up
Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance	~10-30	Repeat FNA, molecular testing, or lobectomy
Follicular Neoplasm or Suspicious for a Follicular Neoplasm	25-40	Molecular testing, lobectomy
Suspicious for Malignancy	50-75	Near-total thyroidectomy or lobectomy
Malignant	97-99	Near-total thyroidectomy or lobectomy

Table 3. Reported decreases in the risk of malignancy (ROM) of TBSRTC (2023) diagnostic categories if excluding nodules diagnosed on surgical pathology to be "Noninvasive Follicular Thyroid Neoplasm with Papillary Like Nuclear Features (NIFTP)"

Diagnostic category	% Decrease in ROM if excluding NIFTP Mean% (range)	Estimated final ROM if excluding NIFTP
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

Table 4. The Bethesda System for Reporting Thyroid Cytopathology (2023) in Pediatric Patients with implied risk of malignancy (ROM) and possible management recommendations

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

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