REVIEW

The 2022 WHO classification of thyroid tumors: novel concepts in nomenclature and grading

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Abstract

The fifth edition of the Classification of Endocrine and Neuroendocrine Tumors has been released by the World Health Organization. This timely publication integrates several changes to the nomenclature of non-neoplastic and neoplastic thyroid diseases, as well as novel concepts that are essential for patient management. The heterogeneous group of non-neoplastic and benign neoplastic lesions are now collectively termed as ‘thyroid follicular nodular disease’ to better reflect the clonal and non-clonal proliferations that clinically present as multinodular goiter. Thyroid neoplasms originating from follicular cells are distinctly divided into benign, low-risk and malignant neoplasms. The new classification scheme stresses that papillary thyroid carcinoma (PTC) should be subtyped based on histomorphologic features irrespective of tumor size to avoid treating all sub-centimeter/small lesions as low-risk disease. Formerly known as the cribriform-morular variant of PTC is redefined as cribriform-morular thyroid carcinoma since this tumor is now considered a distinct malignant thyroid neoplasm of uncertain histogenesis. The ‘differentiated high-grade thyroid carcinoma’ is a new diagnostic category including PTCs, follicular thyroid carcinomas and oncocytic carcinomas with high-grade features associated with poorer prognosis similar to the traditionally defined poorly differentiated thyroid carcinoma as per Turin criteria. In addition, squamous cell carcinoma of the thyroid is now considered a morphologic pattern/subtype of anaplastic thyroid carcinoma. In this review, we will highlight the key changes in the newly devised fifth edition of the WHO classification scheme of thyroid tumors with reflections on its applicability in patient management and future directions in this field.

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Introduction

The fifth edition of the World Health Organization (WHO) Classification of Endocrine and Neuroendocrine Tumors is a timely publication that easily lends itself to the years of experience in the field of diagnostic and molecular thyroid pathology. It contains appropriate changes to nomenclature, grading and prognostication of thyroid proliferations based on pathologic features and molecular profile. Therefore, it is important that endocrinologists and practicing physicians who manage thyroid nodules acquaint themselves with this new
classification scheme (Baloch et al. 2022) (Fig. 1). Several tumor entities have been renamed to stay congruent with underlying tumor biology and/or histogenesis as well as molecular profiles. The role of diagnostic and predictive biomarkers is coupled with morphological parameters and tumor proliferation to enable dynamic clinical risk stratification and prognosis.

In this brief review, important changes and updates are highlighted in order to orientate the reader further.

**Benign follicular cell-derived thyroid tumors**

Clinically, the term ‘goiter’ relates to an enlarged thyroid gland, a finding that is associated with various neoplastic and non-neoplastic disorders. Goiter often presents as a nodular and rarely as a diffuse process. Most agree that the terms ‘colloid nodules,’ ‘multinodular goiter,’ ‘adenomatous goiter’ and ‘multinodular hyperplasia’ often used by pathologists are not reflective of the underlying pathology besides the mere confirmation of clinical findings. Molecular analyses of individual nodules in such cases have revealed that a good proportion of goitrous nodules is monoclonal and represents neoplastic proliferations making it impossible to distinguish between non-neoplastic and benign neoplastic follicular neoplasms i.e. adenomas on the basis of morphology alone (Mete & Asa 2012). In addition, most of the adenomatous nodules encountered in patients with DICER1, PTEN and PTEN-like syndromes (Harrer et al. 1998a,b, Derwahl & Studer 2002) also represent multiple follicular adenomas (Wasserman et al. 2018, Cameselle-Teijeiro et al. 2021). Therefore, an umbrella term of ‘follicular nodular disease’ (FND) has been proposed in the latest WHO classification, to avoid the above-mentioned issues (Baloch et al. 2022).

In the 2017 WHO classification scheme of thyroid neoplasms, follicular adenoma was the only entity included in the benign follicular cell-derived tumors; however, in the fifth edition, ‘follicular adenoma with papillary architecture’ (previously termed as papillary adenomatous/hyperplastic nodule) is also included in

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**Main diagnostic groups of the 2022 WHO Classification of Thyroid Neoplasms**

<table>
<thead>
<tr>
<th>Benign Lesions</th>
<th>Low-risk Neoplasms</th>
<th>Malignant Thyroid Neoplasms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid follicular nodular disease</td>
<td>Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)</td>
<td>Follicular thyroid carcinoma (FTC)</td>
</tr>
<tr>
<td>Follicular thyroid adenoma</td>
<td>Follicular thyroid tumor of uncertain malignant potential (FT-UMP)</td>
<td>Invasive encapsulated follicular variant papillary thyroid carcinoma (IEFV-PTC)</td>
</tr>
<tr>
<td>Follicular thyroid adenoma with papillary architecture</td>
<td>Well-differentiated thyroid tumor of uncertain malignant potential (WD-UMP)</td>
<td>Oncocytic carcinoma of the thyroid (OCA)</td>
</tr>
<tr>
<td>Oncocytic adenoma</td>
<td>Hyalinizing trabecular thyroid tumor (HTT)</td>
<td>Differentiated high-grade thyroid carcinoma (DHGTC)</td>
</tr>
</tbody>
</table>

- Papillary, follicular or solid growth
- Invasive features
- Any nuclear cytology
- At least one of:
  - Mitotic count ≥5/2 mm²
  - Necrosis
- Solid, trabecular or insular growth
- Invasive features
- No PTC nuclear features
- At least one of:
  - Mitotic count ≥3/2 mm²
  - Necrosis
  - Convoluted nuclei

**Subtypes**
- Infiltrative follicular
- Tail cell
- Columnar cell
- Hobnail
- Oncocytic

**Poorly differentiated thyroid carcinoma (PDTC)**

- Anaplastic features
- Undifferentiated phenotype

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**Figure 1**

Overview of the main diagnostic groups of the 2022 WHO classification of thyroid tumors. Not included here are mixed medullary and follicular cell-derived carcinomas, salivary gland-type carcinomas of the thyroid, thyroid tumors of uncertain histogenesis, intrathyroid thymic tumors and embryonal thyroid neoplasms. MI, minimally invasive; EAI, encapsulated angioinvasive; WI, widely invasive. Created using BioRender.com.
the benign neoplasm category. Follicular adenoma with papillary architecture is a well-demarcated and non-invasive, often encapsulated tumor with intra-follicular centriptel papillary growth, and the lesional cells lack nuclear features of papillary thyroid carcinoma (PTC) (Mete & Asa 2012, Baloch et al. 2022). These tumors are often associated with autonomous hyperfunction and may therefore appear as hot or warm nodules on radionuclide thyroid scan (Mete & Asa 2012). Molecular analyses have shown that these are driven by TSHR, GNAS or EZH1 mutations and alterations that activate the protein kinase A (PKA) pathway (Parma et al. 1993, Goza et al. 2010). These tumors may also occur in the setting of McCune-Albright and Carney complex syndromes; both are PKA pathway-related conditions driven by GNAS and PRKAR1A mutations, respectively (Kamilaris et al. 2019, Nosé et al. 2022). Moreover, non-functional follicular adenomas with papillary architecture can harbor DICER1 mutations, and a subset of these have been reported in association with DICER1 syndrome (Wasserman et al. 2018, Cameselle-Teijeiro et al. 2021, Juhlin et al. 2021). Thus, the association between thyroid function and related tumor syndromes makes the distinction between these tumors clinically significant. Furthermore, a diagnosis of oncocytic follicular adenoma requires >75% of tumor cells to exhibit oncocytic features (Baloch et al. 2022). Overall, oncocytic thyroid tumors represent a distinct entity of thyroid neoplasms, supported by specific genetic aberrations including mitochondrial DNA mutations and increased copy number alterations (Gopal et al. 2018, Doerfler et al. 2021, McFadden & Sadow 2021).

Low-risk follicular cell-derived thyroid neoplasms

The naming of a group of thyroid neoplasms as ‘low risk’ was introduced in the fourth edition of the WHO classification of thyroid tumors. This was groundbreaking as it really identified a group of tumors based on their pathologic features (most with interobserver variability) and molecular profiles which was completely aligned with the clinical behavior. However, the new WHO classification has revolutionized this concept by integrating this term into the classification framework and also by expanding its spectrum to include: non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), thyroid tumors of uncertain malignant potential (consisting of follicular thyroid tumors of uncertain malignant potential (FT-UMPs) and well-differentiated tumors of uncertain malignant potential (WD-UMPs)) and hyalinizing trabecular tumors (HTTs) (Baloch et al. 2022). Collectively, when rendered in light of strict diagnostic criteria, these entities clinically behave in more or less benign fashion and do not require aggressive treatment modalities. Except for HTT, these neoplasms are mostly RAS-driven, and detection of any non-RAS-like molecular signature (e.g., BRAF p.V600E) or high-risk molecular alterations (e.g., TERT promoter mutations) prompts re-evaluation of pathologic features to exclude overt malignancy.

NIFTP is a well-demarcated or encapsulated and non-invasive neoplasm, completely follicular-patterned with PTC-related nuclear atypia lacking high-grade features (mitoses/necrosis) (Hodak et al. 2016, Thompson 2016). Most NIFTPs are RAS-driven or exhibit codon 601 BRAF mutations, and presence of BRAF p. V600E mutation is an exclusion criterion for NIFTP in the new WHO classification of thyroid neoplasms. A subset of NIFTP may harbor gene fusions (THADA gene fusions or PAX8::PPARG) (Baloch et al. 2022). In the fifth edition of WHO classification, the diagnostic term NIFTP can be applied to sub-centimeter lesions (in the absence of the BRAF p.V600E mutation, excluding lesions measuring less than 0.3 cm) and oncocytic lesions (with >75% oncocytic cells) fulfilling the strict diagnostic criteria (Baloch et al. 2022).

Thyroid tumors of uncertain malignant potential are rare lesions in which histological confirmation of capsular and/or vascular invasion is equivocal. These tumor entities require extensive microscopic assessment of the entire capsule/tumor interface, as a single focus of invasive focus would disqualify these diagnoses.

HTTs are follicular cell-derived thyroid neoplasms with PTC-related nuclear atypia, trabecular growth pattern, extracellular hyaline matrix and specific PAX8::GLIS1 and PAX8::GLIS3 fusions (Nikiforova et al. 2019). Metastases associated with HTT have only been reported in single, historic cases and never in an HTT with a verified GLIS fusion (Baloch et al. 2022). While molecular testing will confirm the diagnosis, the entity is well-known to exhibit membranous Ki67 immunoreactivity if stained using the MIB1 clone at room temperature (Leonardo et al. 2007).

Follicular thyroid carcinoma and follicular variant of papillary thyroid carcinoma

Follicular thyroid carcinomas are mostly RAS-driven, invasive tumors lacking nuclear cytology of PTC.
In the 2017 WHO classification, FTC was subdivided into three different subtypes to reflect the overall prognosis based on tumor capsule invasion and foci of vascular invasion: minimally invasive FTC, encapsulated angioinvasive FTC and widely invasive FTC. This histological stratification is retained in the 2022 WHO classification, as the extent of the invasive features correlates to patient survival (Baloch et al. 2022). The related RAS-driven entity follicular variant of PTC (FVPTC) is similar to FTC in terms of predominant growth patterns but exhibits subtler nuclear features of most PTCs that are linked to BRAF p.V600E-like molecular alterations.

FVPTCs are now subdivided into infiltrative and encapsulated subtypes. Infiltrative FVPTCs are BRAF-driven tumors with florid nuclear atypia with invasion of the surrounding thyroid parenchyma and lymphatic vessels (thus behaving as bona fide PTCs). This diagnostic category has been challenged by some experts who believe that these tumors represent infiltrative classic PTC with predominant follicular growth. Encapsulated FVPTCs are RAS-driven lesions with a similar invasive pattern as FTCs (capsular and/or proclivity to vascular invasion rather than lymphatics) (Baloch et al. 2022). Similar to FTC, FVPTCs also exhibit a correlation between the extent of invasion and patient prognosis (Xu et al. 2015). To better reflect this, the 2022 WHO classification therefore subdivides FVPTCs as either minimally invasive, encapsulated angioinvasive or widely invasive.

The term Hürthle: the end of a famous misnomer

In the former fourth edition of the WHO guidelines, oncocytic thyroid carcinoma was listed as a separate entity, apart from follicular thyroid carcinoma (FTC) due to its unique histology, molecular profile and patient prognosis. In the fifth edition, this distinction is retained, but the nomenclature ‘Hürthle’ is discouraged, as it derives from Karl Hürthle, a German histologist who actually described parafollicular C cells in the canine thyroid gland rather than oncocytic cells of the thyroid (Caturegli & Ruggere 2005). In the fifth edition of the WHO guidelines, oncocytic carcinoma of the thyroid (OCA) requires histological evidence of malignancy (capsular and/or vascular invasion) and absence of high-grade features (tumor necrosis and/or ≥5 mitoses per 2 mm²) and pathologic stratification into minimally invasive, encapsulated angioinvasive and widely invasive subtypes is recommended similar to FTC (Baloch et al. 2022). Similar to high-grade features, morphologic dedifferentiation should also be recognized given the poor prognosis associated with oncocytic poorly differentiated thyroid carcinoma (Lukovic et al. 2021).

High-grade follicular cell-derived carcinomas: morphologic validation of clinical outcomes

It is well-known that a subset of differentiated thyroid carcinomas (PTCs, FTCs) exhibiting high-grade pathologic features such as increased mitotic index and the presence of tumor necrosis are associated with aggressive clinical course similar to tumors classified as poorly differentiated thyroid carcinoma (PDTC) (Hiltzik et al. 2006, Gnemmi et al. 2014). The diagnosis of PDTC is made based on the so-called Turin criteria; (1) presence of a solid/trabecular/
insular growth pattern, (2) absence of the conventional nuclear features of papillary carcinoma and (3) presence of at least one of the following: convoluted nuclei; >3 mitoses per 2 mm$^2$ (10 high-power fields) and tumor necrosis (Volante et al. 2007). However, some experts have considered a mitotic index $\geq$ 5 mitoses per 2 mm$^2$ and/or tumor necrosis as indications of a poorly differentiated phenotype even in the absence of morphologic dedifferentiation (Hiltzik et al. 2006). In the fifth edition of the WHO classification, an intermediate entity of ‘differentiated high-grade thyroid carcinoma’ (DHGTC) is therefore introduced for PTCs and FTCs/OTCs with $\geq$ 5 mitoses per 2 mm$^2$ and/or tumor necrosis to highlight high-risk differentiated thyroid carcinomas (Baloch et al. 2022). The tumors classified as such may have retained PTC-related nuclear atypia or a follicular growth pattern and features that are not acceptable for a PDTC diagnosis (Fig. 3). From a molecular standpoint, DHGTCs and PDTCs may be BRAF- or RAS-driven lesions, which are due to whether the preceding lesion was a PTC or FTC (Baloch et al. 2022). Interestingly, DHGTCs are mostly derived from BRAF-driven PTCs, while PDTCs often exhibit aberrant RAS signaling, indicating a relationship between FTCs and FVPTCs (Wong et al. 2021). In the process of dedifferentiation, additional genetic alterations are usually seen in DHGTCs and PDTCs, including TERT promoter and TP53 gene mutations (Paulsson et al. 2020, Baloch et al. 2022). In addition, an association with mutations in the micro-RNA master regulator DICER1 is also noted in some PDTC cases in adolescents (Chernock et al. 2020).

**Anaplastic thyroid carcinoma**

In the fourth edition of the WHO classification, squamous cell carcinoma (SCC) of the thyroid gland was listed as a separate entity from anaplastic thyroid carcinoma (ACA); however, studies have shown both clinically behaved in a similar manner. The molecular profiling has solved this diagnostic conundrum; a vast majority of SCC of the thyroid harbor BRAF p.V600E mutations and exhibit TTF1 and PAX8 immunoreactivity, proving the follicular cell
origin (Lam et al. 2001, Xu et al. 2020). Moreover, SCCs of the thyroid can be seen in conjunction with welldifferentiated thyroid carcinoma, and similarly, a subset of ACAs display easily recognizable squamous differentiation – making it logical to classify SCC of the thyroid as a morphological pattern/subtype of ACA rather than a separate entity (Baloch et al. 2022). The new classification also encourages routine use of BRAF p.V600E mutation-specific VE1 immunohistochemistry in all patients with ACA given the potential benefit of BRAF and MEK inhibitor therapies (Baloch et al. 2022).

Grading of medullary thyroid carcinoma: not a WHO grading but a recommendation for clinical risk assessment

Recently, an international study has recommended two-tiered grading of medullary thyroid carcinoma. This is based on strong association between worse patient outcomes and high-grade pathologic features such as tumor necrosis and an elevated mitotic count or Ki67 proliferation index (Alzumaili et al. 2020, Fuchs et al. 2020, Asa & Mete 2022, Vissio et al. 2022, Williams et al. 2022, Xu et al. 2022). By using this approach, MTCs are defined as high-grade tumors based upon the presence of at least one of the following parameters: tumor necrosis, mitotic count ≥5 per 2 mm² and/or a Ki67 proliferation index ≥5% (Fig. 4). The majority (approximately 75%) of MTCs in this study were low-grade tumors, showing absence of necrosis, few mitotic figures and a low Ki67 index. This grading system was an independent predictor of worse outcome irrespective of TNM stage, RET mutational status and various additional clinical parameters and is therefore highlighted in fifth edition of WHO classification of thyroid neoplasms in order to identify patients with higher risks of recurrences and adverse outcome (Xu et al. 2022). Of note, this approach requires extensive sampling to avoid missing focal areas with necrosis and the Ki67 index needs to be appreciated in hotspot areas (with the highest proliferative activity) (Baloch et al. 2022). Recent evidence also highlights the importance of other clinicopathological variables (Le et al. 2022) and tumor histological features (Khandakar et al. 2022).

Salivary gland-type neoplasms and intrathyroidal thymic tumors

Intrathyroidal salivary gland-type neoplasms are exceedingly rare neoplasms and include mucoepidermoid carcinoma (MEC) and secretory carcinoma (SC) (Baloch et al. 2022). A majority of experts agree that these tumors may originate from ectopic salivary gland elements located in the thyroid pseudo-capsule or within thyroid parenchyma. Both tumors display morphologies similar to their counterparts in the salivary glands, but they also show diverse epidemiologic, molecular and prognostic
features that differ from their salivary gland counterparts (Chambers et al. 2021).

Thyroid MECs are usually composed of mucinous, intermediate and squamous cells that are arranged in solid and cystic growth, confirmed by positive p63 and CK5 immunostaining. MAML2 gene rearrangements are not as frequent as in their salivary gland counterparts (Tonon et al. 2003) since thyroid MECs have been reported to represent metaplastic follicular cell-derived thyroid carcinomas in some manifestations (Baloch et al. 2000, Chambers et al. 2021).

The hallmark pathologic features of SC are eosinophilic cells with vacuolated cytoplasm. Similar to SC of salivary gland, they are positive for GATA3, mammaglobin, GCDFP15 and S100 protein, while consistently negative for TTF1 and thyroglobulin (Baloch et al. 2022). However, variable PAX8 reactivity can occur (Asa & Mete 2018). To date, all thyroid SCs displayed ETV6::NTRK3 fusions (Skálová et al. 2010). Unlike most salivary gland SCs, thyroid SCs tend to be associated with a more aggressive clinical outcome and have been particularly reported in a later age onset. Interestingly, both MEC and SC have been reported to co-occur with follicular cell-derived thyroid carcinomas.

The intrathyroidal thymic tumors include thymoma and thymic carcinoma families and ‘intrathyroidal spindle epithelial tumor with thymus-like elements’. These are classified similar to the fourth edition of WHO classification of thyroid tumors (Baloch et al. 2022). The tumor formerly known as ‘thyroid carcinoma showing thymic-like differentiation’ is now termed as ‘intrathyroidal thymic carcinoma’ (ITC) to lessen the ambiguity regarding origin of this rare malignancy. No diagnostic molecular profile of these lesions is available at this time; ITC may display TERT promoter mutations, which are generally absent in mediastinal thymic carcinomas (Tahara et al. 2020).

### Thyroid tumors of uncertain histogenesis

The ‘cribriform-morular variant of papillary thyroid carcinoma’ has been renamed to ‘cribriform-morular thyroid carcinoma’ in the fifth edition of WHO classification of thyroid tumors (Boyraz et al. 2021, Baloch et al. 2022, Nosé et al. 2022). The hallmark of these tumors is the presence of nuclear and cytoplasmic beta-catenin expression. The reasons for this nomenclature change are the following (Boyraz et al. 2021): (1) these tumors lack expression of thyroglobulin, are often negative for PAX8 (or can be very focal/weak positive) and only express TTF1 in focal areas with cribriform patterns; (2) aberrant expression of estrogen and progesterone receptors is noted within the cribriform areas, while the morular component expresses CD5, CK5, CDX2 and CD10 proteins, not observed in follicular cell-derived lesions and (3) these lesions are driven by genetic aberrancies in the Wnt pathway, most notably APC gene mutations resulting in nuclear localization of beta-catenin. Based on these findings, the definite histogenesis of this lesion is disputable but definitely argues against a follicular cell-derived origin.

On a similar note, the exact origin of the rare entity ‘sclerosing mucoepidermoid carcinoma with eosinophilia’ is also not known. These tumors lack PAX8 and thyroglobulin expression, although focal/variable TTF1 immunoreactivity may be seen (Baloch et al. 2022). Molecular analyses show neither mutations encountered in follicular cell-derived thyroid carcinoma nor gene fusions that are usually observed in the salivary gland counterpart. Due to the p63 positivity, some believe these...
lesions derive from solid nest cells (ultimobranchial body remnant cells) or squamous metaplasia, but this needs to be proven by further analysis (Chan et al. 1991, Hunt et al. 2004, Baloch et al. 2022).

Molecular biomarkers: current and future use

In the era of personalized medicine, assessment of the genetic alterations underlying the development of each individual tumor is believed to influence how we classify based on pathologic features, prognosticate and treat. While virtually all thyroid tumors are diagnosed using histomorphologic features (sometimes accompanied by immunohistochemistry), there will be an increasing need to characterize these lesions from a molecular standpoint, especially for cases that respond poorly to conventional treatment protocols. The development of thyroid cancer is a multistep process involving both early driver changes as well as late event changes. The well-differentiated thyroid carcinomas (PTC and FTC) usually are BRAF- or RAS-driven (Nikiforov 2004, Cancer Genome Atlas Research Network 2014, Paulsson et al. 2020, Baloch et al. 2022). BRAF-driven events include BRAF p.V600E mutations as well as gene fusions involving ALK, BRAF, RET, NTRK1/3 and MET, while RAS-driven lesions exhibit mutations in N/K/HRAS mutations, BRAF (K601E), DICER1, PTEN and PAX8::PARG fusions (Baloch et al. 2022). If the tumor progresses to either DHGTC, PDTC or ACA, additional genetic events take place, including mutations in the TERT promoter, TP53, cell cycle genes, chromatin-remodeling genes and mismatch repair genes (Kunstman et al. 2015, Pozdeyev et al. 2018, Paulsson et al. 2020, Stenman et al. 2021). In the fifth edition of WHO classification of thyroid tumors, a balanced approach is taken to highlight the potential therapeutic value of detecting RET fusions or BRAF p.V600E mutations in PTC, as well as NTRK1/3 and ALK fusions in PTC or FTC. Moreover, the need for reflex testing of all ACAs for BRAF p.V600E mutations is also emphasized.

Parting thoughts

The present is an exciting time for the field of endocrine pathology (Asa et al. 2022). The traditional paradigms for diagnosis and classifying thyroid tumors based purely on morphologic features are now enriched by thorough understanding of management-centric histologic features (low- vs high-grade features), immunohistochemical and molecular characterization. These altogether have led to the diagnostic framework for the 2022 WHO classification of thyroid lesions, which by no means is to be perceived to increase the workload in the everyday practice of thyroid pathology – but rather having pathologists as part of the multidisciplinary team in era of precision medicine. We also believe that this new classification scheme serves as a fertile ground for future iterations which will incorporate more molecular data to provide a robust scheme for classifying thyroid neoplasms.

Declaration of interest

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