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# Overview of the 2022 WHO Classification of Thyroid Neoplasms

**Zubair W. Baloch[1] · Sylvia L. Asa[2] · Justine A. Barletta[3] · Ronald A. Ghossein[4] · C. Christofer Juhlin[5,6] · Chan Kwon Jung[7] · Virginia A. LiVolsi[1] · Mauro G. Papotti[8] · Manuel Sobrinho-Simões[9] · Giovanni Tallini[10,11] · Ozgur Mete[12]**

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## Abstract

This review summarizes the changes in the 5th edition of the WHO Classification of Endocrine and Neuroendocrine Tumors that relate to the thyroid gland. The new classification has divided thyroid tumors into several new categories that allow for a clearer understanding of the cell of origin, pathologic features (cytopathology and histopathology), molecular classification, and biological behavior. Follicular cell–derived tumors constitute the majority of thyroid neoplasms. In this new classification, they are divided into benign, low-risk, and malignant neoplasms. Benign tumors include not only follicular adenoma but also variants of adenoma that are of diagnostic and clinical significance, including the ones with papillary architecture, which are often hyperfunctional and oncocytic adenomas. For the first time, there is a detailed account of the multifocal hyperplastic/neoplastic lesions that commonly occur in the clinical setting of multinodular goiter; the term thyroid follicular nodular disease (FND) achieved consensus as the best to describe this enigmatic entity. Low-risk follicular cell–derived neoplasms include non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), thyroid tumors of uncertain malignant potential, and hyalinizing trabecular tumor. Malignant follicular cell–derived neoplasms are stratified based on molecular profiles and aggressiveness. Papillary thyroid carcinomas (PTCs), with many morphological subtypes, represent the *BRAF*-like malignancies, whereas invasive encapsulated follicular variant PTC and follicular thyroid carcinoma represent the *RAS*-like malignancies. This new classification requires detailed subtyping of papillary microcarcinomas similar to their counterparts that exceed 1.0 cm and recommends not designating them as a subtype of PTC. The criteria of the tall cell subtype of PTC have been revisited. Cribriform-morular thyroid carcinoma is no longer classified as a subtype of PTC. The term "Hürthle cell" is discouraged, since it is a misnomer. Oncocytic carcinoma is discussed as a distinct entity with the clear recognition that it refers to oncocytic follicular cell–derived neoplasms (composed of > 75% oncocytic cells) that lack characteristic nuclear features of PTC (those would be oncocytic PTCs) and high-grade features (necrosis and ≥ 5 mitoses per 2 $mm^2$). High-grade follicular cell–derived malignancies now include both the traditional poorly differentiated carcinoma as well as high-grade differentiated thyroid carcinomas, since both are characterized by increased mitotic activity and tumor necrosis without anaplastic histology and clinically behave in a similar manner. Anaplastic thyroid carcinoma remains the most undifferentiated form; squamous cell carcinoma of the thyroid is now considered as a subtype of anaplastic carcinoma. Medullary thyroid carcinomas derived from thyroid C cells retain their distinct section, and there is a separate section for mixed tumors composed of both C cells and any follicular cell–derived malignancy. A grading system for medullary thyroid carcinomas is also introduced based on mitotic count, tumor necrosis, and Ki67 labeling index. A number of unusual neoplasms that occur in the thyroid have been placed into new sections based on their cytogenesis. Mucoepidermoid carcinoma and secretory carcinoma of the salivary gland type are now included in one section classified as "salivary gland–type carcinomas of the thyroid." Thymomas, thymic carcinomas and spindle epithelial tumor with thymus-like elements are classified as "thymic tumors within the thyroid." There remain several tumors whose cell lineage is unclear, and they are listed as such; these include sclerosing mucoepidermoid carcinoma with eosinophilia and cribriform-morular thyroid carcinoma. Another important addition is thyroblastoma, an unusual embryonal tumor associated with *DICER1* mutations. As in all the WHO books in the 5th edition, mesenchymal and stromal tumors, hematolymphoid neoplasms, germ cell tumors, and metastatic malignancies are discussed separately. The current classification also emphasizes the value of biomarkers that may aid diagnosis and provide prognostic information.

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**Keywords** WHO classification of thyroid tumors · Papillary thyroid carcinoma · Follicular thyroid carcinoma · High-grade thyroid carcinoma · Anaplastic thyroid carcinoma · Poorly differentiated thyroid carcinoma · Medullary thyroid carcinoma · Thyroblastoma · Cribriform-morular thyroid carcinoma · Hyalinizing trabecular tumor · Follicular nodular disease

## Introduction

The thyroid gland gives rise to the most common endocrine tumors, and therefore, it represents the largest chapter in the new 5th edition of the WHO Classification of Endocrine and Neuroendocrine Tumors. The approach taken in this edition is somewhat different from its prior iterations; there is a focus on taxonomy following the approach of Carl Linnaeus [1, 2], and cytogenesis forms the basis of framework for this new classification, with histology and molecular features defining tumor types and subtypes.

Over the last 15 years, the importance of molecular biology in thyroid pathology has both revolutionized the discipline and, at the same time, proven the inherent value of classical histopathology. It is a field in which pathologists have long recognized patterns that reflect specific molecular alterations, but the addition of molecular tools to the pathologists' armamentarium has enhanced our ability to prognosticate and predict the efficacy of targeted therapies.

This review will focus on the most important and novel changes in the new WHO thyroid tumor classification scheme (Table 1) employing a question–answer framework. We encourage the reader to use this as a framework to understand the new classification, but it is not a substitute for the actual text that provides detailed descriptions, illustrative figures, and a highly structured approach to assist in identifying the complexities of diagnosis and differential diagnosis of thyroid neoplasms.

## Question 1: What Are the New Categories of Benign Follicular Cell Thyroid Lesions and Why Are They Included in the WHO 5th Edition?

The 4th edition of the WHO classification of endocrine tumors [3] included a single benign lesion: follicular adenoma (FA). While FAs are well-recognized tumors, they occur in many different scenarios with distinct clinical, radiological, biochemical, and morphological features. In this edition, the important variants are described.

The clinical entity known as multinodular goiter has been used for pathology diagnosis but this is inappropriate, since many lesions, including thyroiditis, hyperplasias, and neoplasms, can give rise to a clinically enlarged, multinodular thyroid gland. The entity that is most commonly associated with this clinical scenario is a disorder characterized by multiple thyroid lesions composed of follicular epithelial cells that have highly variable architecture; they can be very small or very large, they range from colloid-rich macrofollicular nodules to cellular microfollicular nodules, and they can be poorly delineated or well circumscribed with absent, well-defined or incomplete capsules (Fig. 1). These lesions have not generally been classified as

**Table 1** WHO classification scheme of thyroid neoplasms, 5th edition

**Developmental abnormalities**
1. Thyroglossal duct cyst
2. Other congenital thyroid abnormalities

**Follicular cell–derived neoplasms**
1. Benign tumors
   a. Thyroid follicular nodular disease
   b. Follicular adenoma
   c. Follicular adenoma with papillary architecture
   d. Oncocytic adenoma of the thyroid
2. Low-risk neoplasms
   a. Non-invasive follicular thyroid neoplasm with papillary-like nuclear features
   b. Thyroid tumors of uncertain malignant potential
   c. Hyalinizing trabecular tumor
3. Malignant neoplasms
   a. Follicular thyroid carcinoma
   b. Invasive encapsulated follicular variant papillary carcinoma
   c. Papillary thyroid carcinoma
   d. Oncocytic carcinoma of the thyroid
   e. Follicular-derived carcinomas, high-grade
      i. Differentiated high-grade thyroid carcinoma
      ii. Poorly differentiated thyroid carcinoma
   f. Anaplastic follicular cell–derived thyroid carcinoma

**Thyroid C-cell–derived carcinoma**
1. Medullary thyroid carcinoma

**Mixed medullary and follicular cell–derived carcinomas**

**Salivary gland–type carcinomas of the thyroid**
1. Mucoepidermoid carcinoma of the thyroid
2. Secretory carcinoma of salivary gland type

**Thyroid tumors of uncertain histogenesis**
1. Sclerosing mucoepidermoid carcinoma with eosinophilia
2. Cribriform morular thyroid carcinoma

**Thymic tumors within the thyroid**
1. Thymoma family
2. Spindle epithelial tumor with thymus-like elements
3. Thymic carcinoma family

**Embryonal thyroid neoplasms**
1. Thyroblastoma

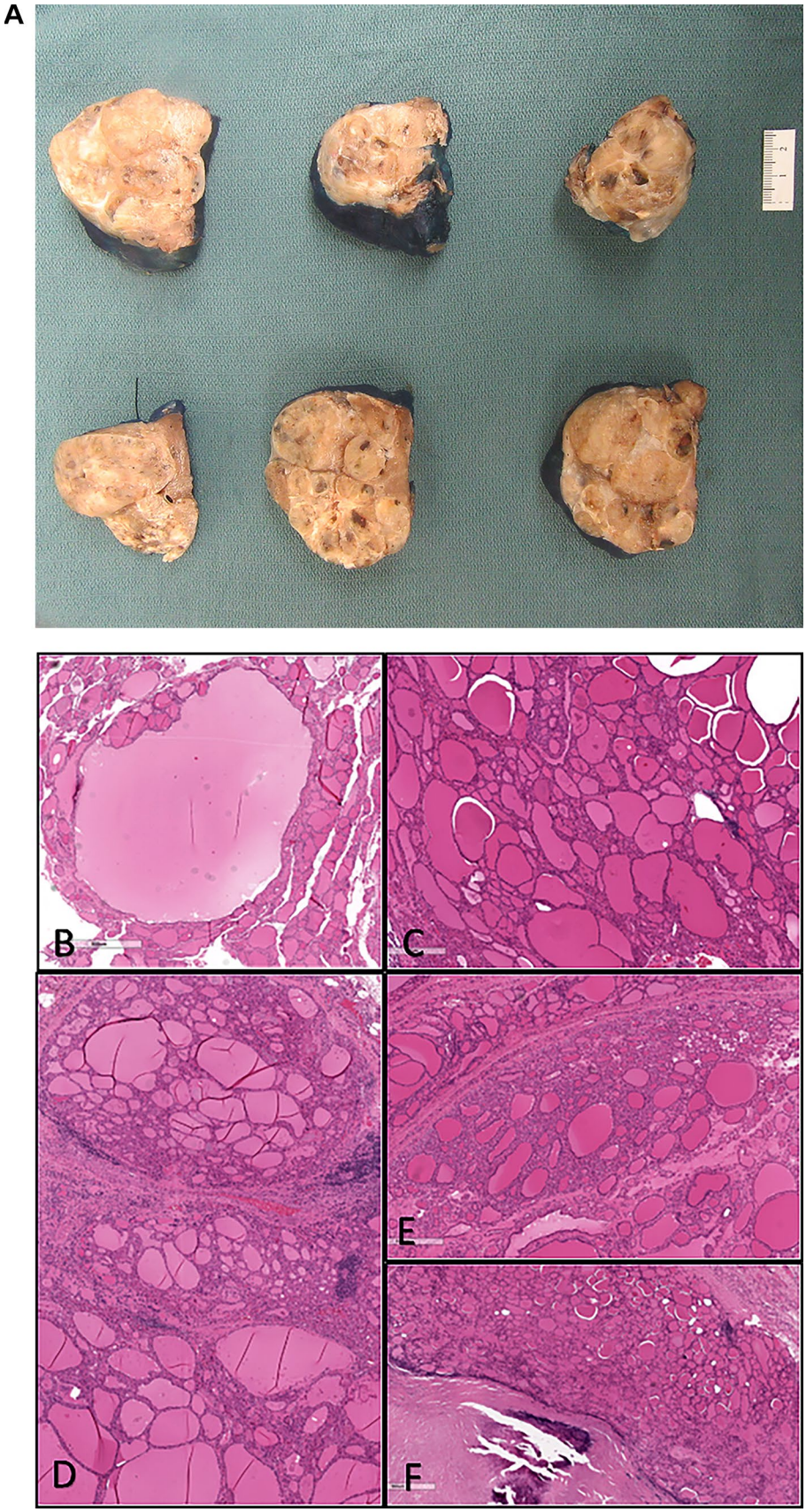


**Fig. 1** Thyroid follicular nodular disease. Grossly, the thyroid gland is enlarged with variably sized multiple nodules (**A**). By light microscopy, this disorder manifests with a spectrum of morphologies from small colloid–rich nodules with Sanderson's polsters (**B**) to large poorly defined colloid-rich macrofollicular nodules (**C**). They are usually multiple and generally show highly variable delineation and encapsulation (**D**). Some are more well-defined and microfollicular, resembling adenomas (**E**); however, while clonality studies have shown that some are monoclonal while others are polyclonal, there is no good correlation between clonality and morphology. Large lesions can have central degeneration with fibrosis and calcification (**F**)

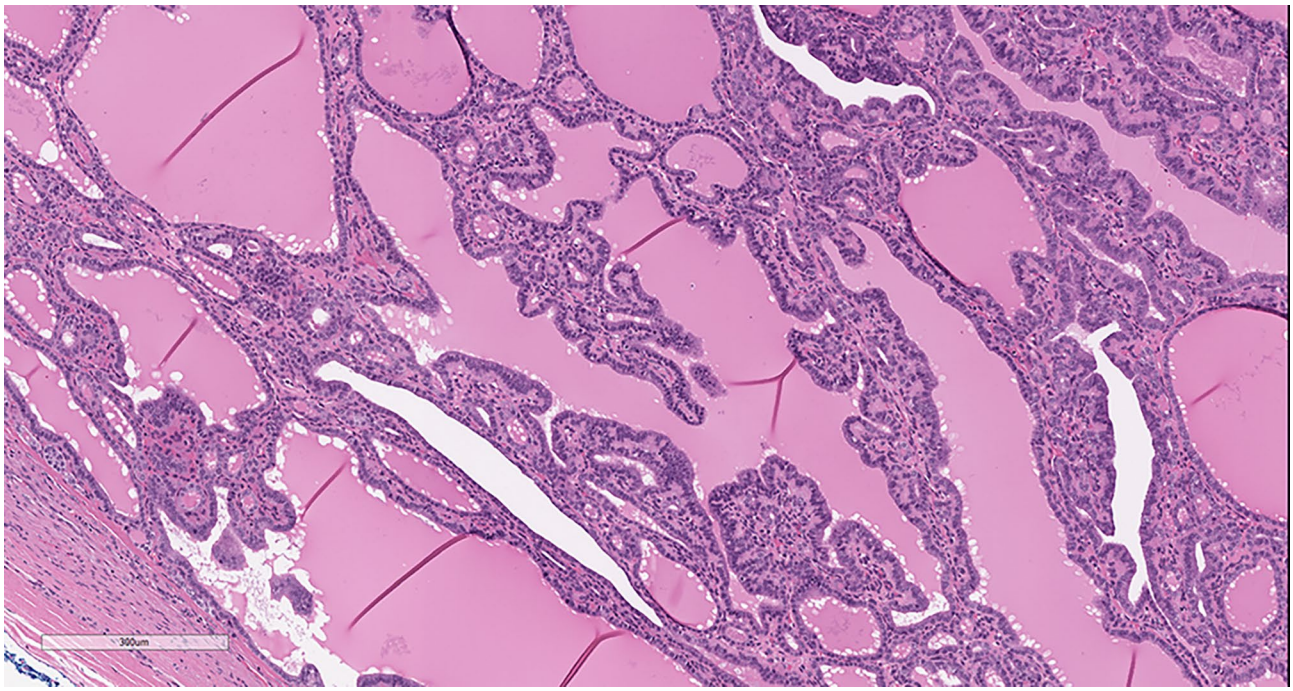


**Fig. 2** Papillary adenoma — non-invasive encapsulated neoplasm characterized by a distinct "centripetal" intrafollicular papillary architecture lacking nuclear features of PTC

neoplasms. Pathologists have used many different names for this enigmatic entity; they have been called "colloid nodules," but most common diagnostic verbiages include the term "hyperplasia" as well as "adenomatous" and "adenomatoid," reflecting the fact that the nodules in this disorder may morphologically mimic adenomas. Interestingly, multiple studies have shown that these nodules are frequently but not always clonal [4–8]; therefore, some are indeed adenomas, while others are hyperplastic. The clonality of these lesions explains why foci of malignant transformation can occur within the nodules of multinodular goiter. An alternative terminology proposed to address this enigma is "thyroid follicular nodular disease," a term that avoids defining a lesion as hyperplastic, neoplastic, or the contradictory "adenomatous hyperplasia" [9]. This term achieved consensus support from the WHO editorial board.

An unusual but clinically important tumor is follicular adenoma with papillary architecture. This is a benign non-invasive encapsulated follicular cell–derived neoplasm characterized by a distinct "centripetal" intrafollicular papillary architecture that is more organized than papillary thyroid carcinoma (PTC), lacks nuclear features of PTC, and is often associated with autonomous hyperfunction (Fig. 2). Unlike follicular adenomas that harbor *RAS* mutations, these tumors are often associated with activating *TSHR* mutations (in up to 70% of cases) or *GNAS* mutations (in a small subset) [10–12] and/or *EZH1* mutations [13, 14]. These molecular alterations result in activation of adenylyl cyclase, increased intracellular cyclic AMP, and unrestrained stimulation of function and proliferation [15]. These tumors are features of McCune-Albright syndrome due to germline mosaic *GNAS* mutations, and Carney complex, due to germline inactivating mutations in *PRKAR1A* that also cause constitutive activation of the cAMP-protein kinase A (PKA) pathway [16]. These clinical associations as well as the more common sporadic tumors that cause clinical or subclinical hyperthyroidism are important for clinic-pathological correlation, recognizing the radiological correlates of hot nodules.

The importance of oncocytic change in the thyroid cannot be overemphasized therefore oncocytic follicular adenomas now hold their own special place in the classification. The term "Hürthle cell" is discouraged; it is actually a misnomer since Hürthle described the C cells of the thyroid gland. These tumors have distinct genomic alterations in the mitochondrial genome (mtDNA) [17–20] or in the related *GRIM19* (*NDUFA13*) gene [21], and more than one-third have copy number variations [22]. It is well known that follicular adenomas can have focal oncocytic change; the definition of > 75% oncocytic cytology is used in this classification, but this remains to be proven as a valid criterion.

## Question 2: What Distinguishes the Various Low-Risk Follicular Thyroid Neoplasms?

The 2022 WHO classification of endocrine tumors has organized follicular cell–derived neoplasms into three categories: benign neoplasms, low-risk neoplasms, and malignant neoplasms. The low-risk neoplasms are borderline tumors that are morphologically and clinically intermediate between benign and malignant tumors (Table 2). These neoplasms have the potential to develop metastasis, but the incidence of metastasis is extremely low. Histologically, they are classified into three types including *non-invasive follicular thyroid neoplasm with papillary-like nuclear features* (NIFTP), *thyroid tumors of uncertain malignant potential* (UMP), and *hyalinizing trabecular tumor* (HTT). The term "tumor" was intended to reduce the risk of overtreatment for these low-risk neoplasms. These terms are the same as those in the previous edition. In the 2017 WHO classification, HTT was described in a different chapter from that of NIFTP and UMP tumors, but in the new edition, they were all combined into one category of low-risk follicular cell–derived neoplasms [3].

The diagnosis of NIFTP requires assessment of strict diagnostic criteria in a surgical resection specimen and requires meticulous microscopic examination of the entire tumor capsule/periphery to rule out invasive growth (Fig. 3A, B). The NIFTP terminology was proposed in 2016 and included as a new entity in the 2017 WHO classification [3]. Since then, there has been debate about the criterion allowing less than 1% of true papillae because some studies reported *BRAF* V600E and lymph node metastasis in a subset of NIFTPs with < 1% papillae [23–25]. To avoid misdiagnosing these malignant tumors as NIFTP, the NIFTP consensus group changed the diagnostic criterion of < 1% papillae to no well-formed papillae in 2018 [26]. However, in subsequent studies using the original criteria of < 1% true papillae, no adverse events were found in NIFTP patients [27–33]. In a study performed at Memorial Sloan Kettering Cancer Center, lymph node metastasis or tumor recurrence was not found in non-invasive encapsulated PTC even if the criterion for the percentage of papillae extended to 10% [29]. Therefore, in the absence of *BRAF* V600E mutation, the original criterion [27] allowing less than 1% true papillae remains unchanged in the 2022 WHO classification. It is important to distinguish between true papillae and pseudopapillary structures seen in NIFTP. While true papillae have a fibrovascular core lined by tumor cells with well-formed nuclear features of PTC, pseudopapillary structures are abortive (rudimentary) papillary formations without fibrovascular cores or hyperplastic-type structures called Sanderson polsters [27, 34].

The original study by the NIFTP consensus group did not include tumors ≤ 1 cm in size and oncocytic tumors fulfilling the histologic criteria of NIFTP. Therefore, these tumors were diagnosed as subtypes of PTC rather than

**Table 2** Pathological and molecular correlates of NIFTP and tumors of uncertain malignant potential, compared to other encapsulated follicular-patterned tumors

| | FA | FT-UMP | WDT-UMP | NIFTP | IEFVPTC |
|---|---|---|---|---|---|
| Category | Benign | Low-risk | Low-risk | Low-risk | Malignant |
| PTC nuclear score | 0–1 | 0–1 | 2–3 | 2–3 | 2–3 |
| Invasion | Absent | Questionable | Questionable | Absent | Present |
| High-grade morphology | Absent | Absent | Absent | Absent | Absent |
| *RAS* mutations | up to 20% | up to 20% | up to 20% | up to 60% | up to 70% |
| *BRAF* K601E, *EIF1AX*, *EZH1*, *DICER1*, *PTEN*, or *TSHR* mutations | < 10% | < 10% | < 10% | < 10% | < 10% |
| *PAX8*::*PPARG* | < 10% | < 10% | Rare | up to 30% | up to 40% |
| *THADA* fusions | < 10% | Not determined | Not determined | up to 30% | < 5% |
| *BRAF*, *RET*, *NTRK*, or *ALK* fusions | Not found | Not found | Not found | Not found | Rare |
| *BRAF* V600E | Absent | Absent | Absent | Absent | Infrequent |

Papillary thyroid carcinoma (PTC) nuclear scoring system is composed of three categories: (1) nuclear size and shape (enlarged, elongated, overlapped, and crowded), (2) nuclear membrane irregularities (irregular nuclear membranous contours, nuclear grooves, or pseudoinclusions), (3) chromatin characteristics (clearing, margination, or glassy nuclei) [27, 34]. The nuclear score is calculated as the sum of these categories, with one point scored if each category is identified. If *BRAF* V600E and high-risk mutations such as *TP53*, *PIK3CA*, or *TERT* promoter mutations are detected in benign or low-risk thyroid neoplasms, the entire tumors should be meticulously examined to exclude the malignancy

*FA* follicular adenoma; *FT-UMP* follicular tumor of uncertain malignant potential; *WDT-UMP* well-differentiated tumor of uncertain malignant potential; *NIFTP* non-invasive follicular thyroid neoplasm with papillary-like nuclear features; *IEFVPTC* invasive encapsulated follicular variant papillary carcinoma

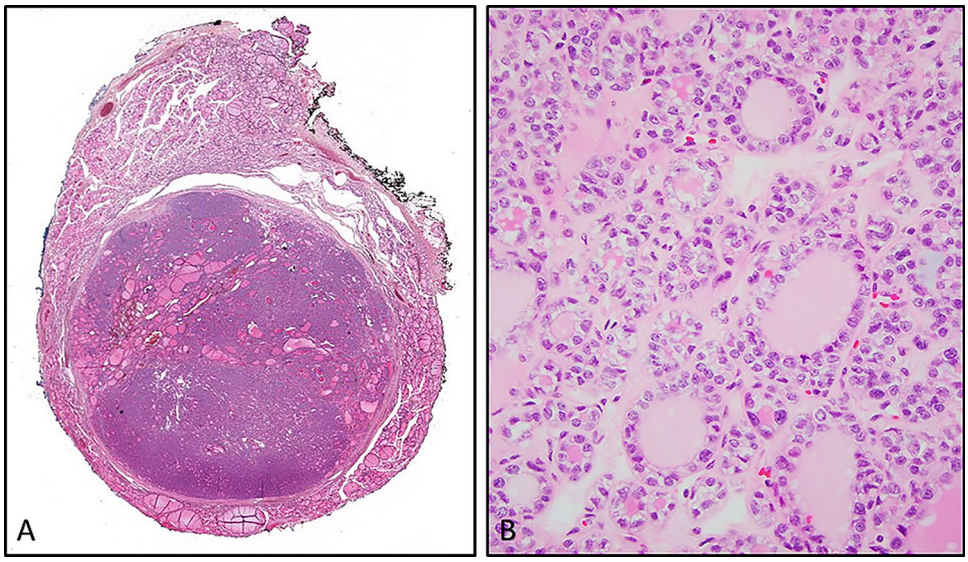


**Fig. 3** **A**, **B** Representative histologic features of non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). The NIFTP is well circumscribed with a thin fibrous capsule without invasion (**A**). The tumor is composed of small- to normal-sized follicles and has nuclear features of papillary thyroid carcinoma showing enlarged nuclei, irregular nuclear membranes, and chromatin clearing (**B**)

NIFTP. However, these tumors are considered as subtypes of NIFTP in the 2022 WHO classification because they have been shown to behave like NIFTP with negligible risk of lymph node metastasis and tumor recurrence [28, 32]. Oncocytic NIFTPs are composed of at least 75% oncocytic cells [30]. Although the term "subcentimeter NIFTP" can be applied to any tumor < 1 cm, the diagnosis is usually unattainable in tumors ≤ 2 mm because it is difficult to be sure that the tumor is non-invasive and has < 1% true papillae [32]; however, even invasive tumors of this size do not warrant aggressive management.

Tumors of UMP are defined as "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" in the 2022 WHO classification. The definition is the same as the previous edition. Thyroid tumors of UMP are divided into two subtypes according to their nuclear alterations: follicular tumor of uncertain malignant potential (FT-UMP) that lacks PTC-like nuclear features (nuclear score of 0–1) and well-differentiated tumor of uncertain malignant potential (WDT-UMP) that has more or less pronounced nuclear features of PTC (nuclear scores of 2–3). The term "atypical adenoma" is not recommended. Some of these tumors can have oncocytic features [35–37] and may display clear cells [38] or glomeruloid features and mucinous stromal changes [39]. Tumors of UMP are distinguished from follicular adenoma and NIFTP by the presence of questionable capsular or vascular invasion.

Encapsulated or well-demarcated follicular-patterned thyroid neoplasms are characterized by the high prevalence of *RAS*-like molecular alterations and the lack of *BRAF* V600E. Although molecular profiles of NIFTP are different from those of multinodular goiter, non-follicular PTC subtypes, and high-grade follicular cell–derived carcinomas, NIFTPs share molecular characteristics with tumors of UMP, follicular adenoma/carcinoma, and invasive encapsulated follicular variant PTC (Table 2). The overlap makes it difficult to distinguish NIFTP from other follicular-patterned tumors by molecular testing on pre-operative cytology specimens.

Among retrospectively reviewed PTC cases, the prevalence of NIFTP is lower in Asian countries (0.5–5%) compared to Western countries (15–20%) [33, 40–42]. The prevalence of tumors of UMP depends on whether the term is used in routine diagnostic practice. In institutions where UMP is diagnosed in daily practice, the incidence is 0.5–3% of all thyroidectomies [35, 43]. The prevalence of HTT is estimated to be less than 1% of thyroid neoplasms [44].

Thyroid lobectomy with clinical and radiologic surveillance is the treatment of choice for NIFTP and HTT. Radioiodine therapy after complete surgery should be avoided because these tumors almost always follow a benign course. UMP tumors require close follow-up since their biologic potential is not certain.

HTTs are well demarcated nodules with PTC-like nuclear changes, trabecular architecture, and a peculiar prominent intratrabecular hyaline material not seen in other thyroid neoplasms that has accumulated as the result of secretion of an active basal membrane type of protein (Fig. 4). The relationship between HTT and PTC was initially suggested by the detection of *RET::CCDC6* rearrangements [45–47]; however, these findings were not confirmed in follow-up studies [48, 49]. Recent molecular studies have demonstrated that HTT is a distinct thyroid neoplasm with a specific molecular alteration. *GLIS* gene rearrangements define HTT and have not been identified in other thyroid tumors [49, 50]. Moreover, HTTs lack *BRAF* and *RAS* mutations [47]. The two most common rearrangement types are

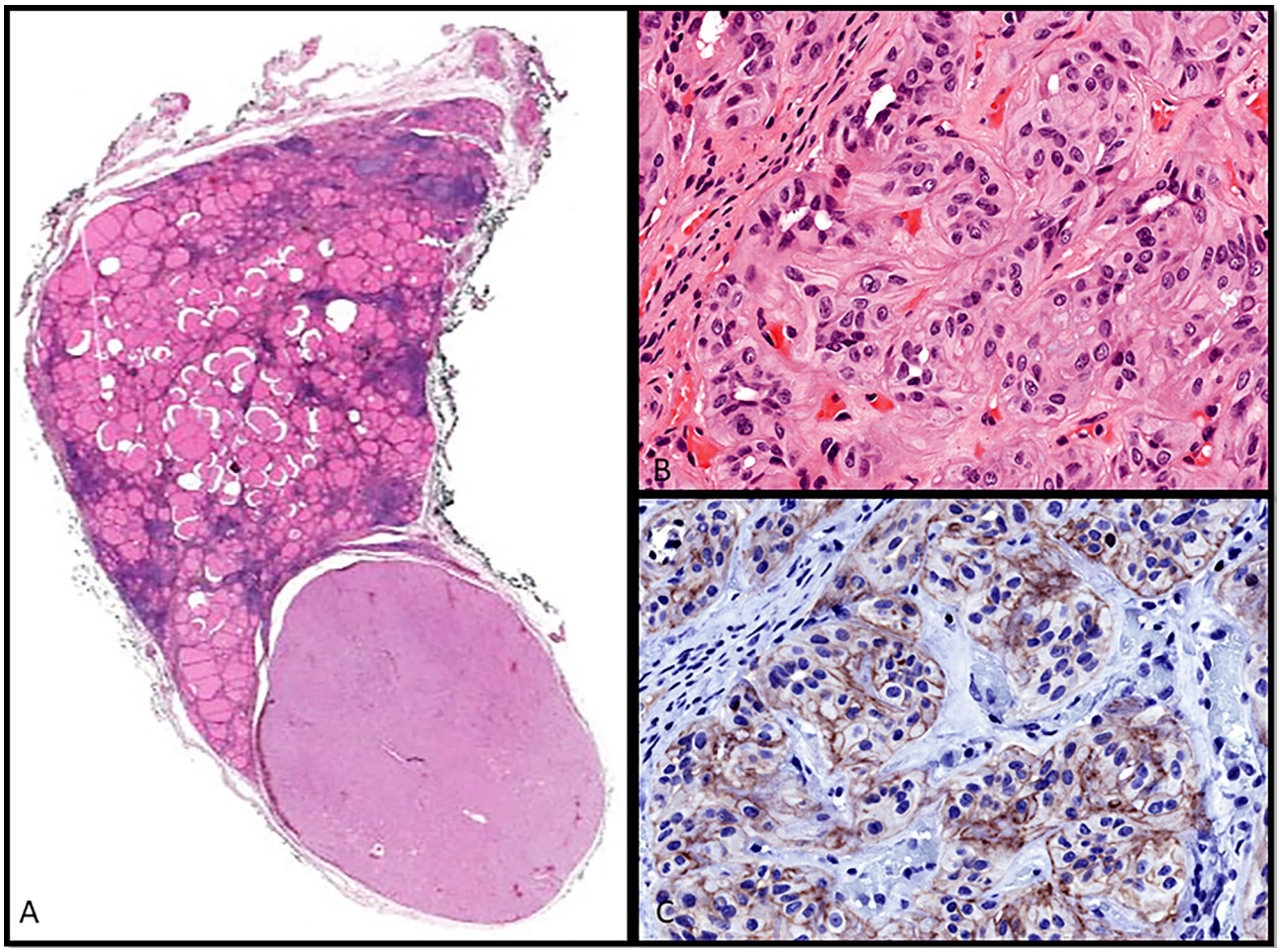


**Fig. 4** **A**–**C** Hyalinizing trabecular tumor (HTT). The HTT is solid and well delineated from surrounding thyroid tissue (**C**). Tumor cells are arranged in trabecular architecture. The cells are elongated or polygonal and oriented perpendicular to axis of trabeculae. The cytoplasm is abundant and eosinophilic with hyaline material (**D**). The MIB1 immunostain shows diagnostic membranous staining (**E**)

*PAX8*::*GLIS3* (the most frequent type) and *PAX8*::*GLIS1*, which are formed by fusions of exon 3 of *GLIS3* gene and exon 2 of *GLIS1* gene to exon 2 of *PAX8* gene, respectively [50]. These fusion gene transcripts lead to overexpression of the 3′ portions of the *GLIS* genes, which induces upregulation of extracellular matrix-related genes including collagen genes [50].

An HTT diagnosis can also be confirmed by a peculiar membrane staining of MIB1 antibody tested at room temperature, in conjunction with a positive expression of follicular markers (thyroglobulin, TTF1, and PAX8). The specific *GLIS* fusion product can be identified by molecular techniques and also by immunohistochemistry. Tumor cells with *PAX8*::*GLIS3* fusion express strong nuclear and cytoplasmic immunostaining using antibody to the C-terminus region of *GLIS3* [49, 50]. While this biomarker is largely unavailable in most diagnostic immunohistochemistry laboratories, the detection of a *GLIS* rearrangement or *GLIS* protein expression enables a pre-operative diagnosis of HTT in cytology specimens [51]. The intratrabecular eosinophilic hyaline material resembles amyloid but is negative with the Congo red stain. The hyaline material is diastase-resistant material that stains with the periodic acid-Schiff stain and is immunoreactive for collagen IV.

While thyroid lobectomy alone is curative and no metastases are found in almost all patients with HTT [44], lymph node or distant metastases have been reported in exceptionally rare cases [44, 52–54]. The malignant counterpart of HTT has tumor capsular or vascular invasion. No patients with *GLIS*-rearranged thyroid neoplasms have developed tumor recurrence or any other adverse events to date [50, 51]. However, it is unclear whether a metastatic thyroid tumor with a *GLIS* rearrangement has existed or could occur.

## Question 3: Why Is Follicular Variant of PTC Separated from the Other Subtypes of PTC? What Distinguishes It from Follicular Thyroid Carcinoma? What Are Histological Subtypes of Follicular Thyroid Carcinoma and Follicular Variant Papillary Thyroid Carcinoma?

Molecular studies have taught us that the morphologic features of differentiated thyroid carcinomas correlate with two major classes of mutations found in these tumors. *RAS*-like mutations result in tumors that have an expansile pattern of growth and subtle/less florid nuclear atypia, whereas *BRAF*-like mutations give rise to infiltrative tumors with florid nuclear atypia. The history of classification of thyroid carcinoma, which initially relied on architecture, became convoluted when classification became based more on nuclear features, the origin of "follicular variant of PTC (FVPTC)."

FVPTC has two distinct variants including the infiltrative and encapsulated forms with invasion of blood vessels or of the tumor capsule. The former subtype is an infiltrative malignancy with all the features of classical PTC except papillae. It has florid nuclear atypia, psammoma bodies, and fibrous stroma and often exhibits perineural and lymphatic invasion. In contrast, the encapsulated form resembles follicular thyroid carcinoma, growing as an expanding lesion with a well-defined border that may or may not incite a fibrous reaction to create a tumor capsule; it then invades locally into the capsule or adjacent tissue (if there is no capsule), and when there is involvement of vessels, they are frequently the blood vessels of the tumor capsule rather than lymphatics. Molecular studies have shown that infiltrative FVPTC is a *BRAF*-like tumor, a member of the PTC family, whereas encapsulated FVPTC is a *RAS*-like neoplasm; placing it closer to follicular thyroid carcinoma (FTC) than to PTC. The infiltrative FVPTC category should only be used in the absence of true papillae, and there is still a debate among experts whether infiltrative FVPTC with a *BRAF* V600E mutation may represent a classic PTC with predominant follicular growth and subtle papillae which may be identified in subsequent levels.

The distinction of encapsulated FVPTC from FTC is based entirely on nuclear morphology. The definition of FTC includes the statement that it lacks nuclear features of PTC. However, it is well known that the diagnosis of nuclear features of PTC suffers from tremendous interobserver variability [55, 56]. When subtle nuclear atypia due to convolution of nuclear membranes is included [57], virtually all FTCs have nuclear atypia, making the distinction almost academic.

Both FTC and encapsulated FVPTC have cytologic variations including oncocytic and clear cell change; however, these are not clinically relevant and therefore are not classified as subtypes in the new WHO classification. FTCs and FVPTCs that are composed of > 75% oncocytic cells with no high-grade features qualify as oncocytic carcinomas and FVPTCs [58, 59].

Both tumor types are subtyped based on the type and the form and/or degree of invasion that are essential in determining dynamic-risk stratification and clinical management. These tumors may be only minimally invasive (tumor capsular invasion only), may invade into blood vessels (angioinvasive FTC or FVPTC), or may be widely invasive and each type has a different prognosis. The 40-month disease-free survival has been reported as 97% for minimally invasive, 81% for angioinvasive, and 45% for widely invasive FTC [60], and similar clinical behaviors have been reported for encapsulated FVPTC [61].

There is still controversy about the definition of angioinvasion and whether the criteria used are more important than the number of vessels involved, but despite this, the presence of a single focus of angioinvasion (vascular invasion) in the absence of widely invasive growth is diagnostic of angioinvasive FTC or FVPTC. Minimally invasive tumors are uniformly considered to be low risk and can be treated with local resection alone. In contrast, those that are widely invasive into surrounding parenchyma or angioinvasive tumors may require completion thyroidectomy and adjuvant therapy to prevent loco-regional recurrence and/or distant metastasis, based on clinical dynamic risk assessment.

## Question 4: What Are the Diagnostic Criteria and Clinical Significance of the Subtypes of Papillary Thyroid Carcinoma?

Papillary thyroid carcinoma (PTC) is the most common malignancy of follicular cell derivation in both adult and pediatric populations [62]. PTC commonly occurs as a sporadic tumor; however, familial forms are being increasingly appreciated [63]. Until the 2017 WHO classification of thyroid tumors [3], PTC was exclusively diagnosed based on characteristic nuclear cytology regardless of growth pattern and invasive features [64, 65]. This changed with the introduction of the diagnostic term NIFTP [27]; similar to the previous edition of the WHO [3], either papillary growth or invasion was added to the definition of PTC in the 5th edition of WHO classification of thyroid tumors. Molecular studies have shown that encapsulated purely follicular-patterned lesions are *RAS*-like and more closely resemble follicular thyroid carcinomas. Thus, invasive encapsulated follicular variant lesions are not classified in the same group as PTC that is a *BRAF*-like family of malignancies [66]

The incidence of PTC has been gradually increasing worldwide; most agree that this is a consequence of current trends in screening and diagnostic practices [67–69]. Even

though a majority of diagnosed PTCs measure ≤ 1.0 cm, several authors have also reported a rise in the number of large PTCs, possibly as a result of evolving trends to diagnose PTC based on nuclear alterations [70–72].

Based on molecular data, PTC can be considered as a "less well-differentiated" form of carcinoma than follicular carcinoma or encapsulated follicular variant papillary carcinoma [9, 73]. The frequently encountered molecular events in PTC are either point mutations or gene rearrangements involving the MAPK pathway [73–77]. *BRAF* V600E is the most common molecular alteration in classic PTC and its subtypes with papillary growth pattern and infiltrative tumors with follicular architecture. These *BRAF*-like tumors show focal to diffuse papillary growth and readily identifiable characteristic nuclear features; they are most often infiltrative, but can be localized with expansile growth or pushing borders, or confined to a cyst [66, 78]. Telomerase reverse transcriptase (*TERT*) promoter mutations, as a secondary pathogenic event, are encountered in 10% of PTCs and are usually associated with an aggressive clinical course [73, 79, 80]. *RET* gene rearrangements (*CCDC6::RET* and *NCOA4::RET*) are found in classic PTC and other subtypes [81, 82]. A strong association is reported between *RET* rearrangements and radiation-induced PTC [81]. Other less common molecular variations in PTC include gene fusions in *NTRK* [83] and other genes, mutations in other genes, copy number variations, alterations in gene expression, and altered microRNA expression [73, 74, 84, 85].

In the new WHO classification of thyroid tumors, the term "variant" has been replaced by "subtype" to allow for consistency with other WHO tumor classification schemes and avoid confusion with the molecular diagnostic term "genetic variant(s)." The list of PTC subtypes with their key histologic and molecular features is depicted in Table 2.

Traditionally, PTCs measuring ≤ 1.0 cm have been called papillary microcarcinoma, papillary microtumor, occult, and incidental and occult sclerosing PTC. It is well documented in the literature that most cases of these small PTCs, when identified as incidental findings, carry an excellent prognosis, similar to other incidental neoplasms throughout the body [86, 87]. However, there does exist a group of these tumors that display aggressive pathologic features and clinical behaviors, including regional and distant metastasis and structural recurrence after surgery [88–91]. Rare cases have even been fatal to the patient, with progression to high-grade carcinoma usually present in metastatic lymph nodes [92, 93].

Therefore, it is not farfetched to conclude that all so-called incidental and occult PTCs are not created equal and in fact the terminologies used may be misleading for patients and treating clinicians. Therefore, in the 5th edition of the WHO classification of thyroid neoplasms, it is recommended that "PTC-microcarcinoma" should not be considered as a distinct subtype. This is also in alignment with clinical management guidelines which rely on multiple pathologic features rather than solely on size to develop personalized risk stratification protocols for patients diagnosed with PTC [94–96].

## Papillary Thyroid Carcinoma Subtypes (Table 3) (Figs. 5, 6, 7, 8, 9, 10, 11)

*Classic PTC* is the paradigm for all PTC subtypes; it is defined by well-formed papillae lined by tumor cells with nuclei showing a specific set of nuclear features: enlargement, peripheral margination of chromatin, clearing of nucleoplasm, irregular contours forming grooves, and resulting in cytoplasmic pseudoinclusions. Lymphatic permeation by PTC is the cause of a high rate of regional lymph node metastasis. Vascular invasion is less common [65, 97]. The encapsulated subtype is completely encased by a thick fibrous capsule which can be either intact or infiltrated partially or in its entire thickness by tumor. The encapsulated classic PTC lacking invasive features is associated with excellent clinical prognosis [65, 98–101].

Infiltrative follicular variant PTC is a *BRAF*-like lesion that has the infiltrative growth pattern of classic PTC but lacks prominent papillae; it has predominant follicular architecture but florid nuclear atypia, prominent psammoma bodies, and stromal fibrosis, and careful examination usually (but not always) identifies focal small papillary structures.

Among PTC subtypes, *tall cell* (TC), *columnar cell* (CC), and *hobnail* (HN) subtypes are of undisputable clinical significance due to their aggressive clinicopathologic features as compared to classic PTC [102–105]. The risk stratification scheme developed by the American Thyroid Association identifies these as having intermediate risk of structural recurrence [67]. The aggressive histologic subtypes of PTC can also be fully encapsulated and/or present as clinically low stage tumors lacking pathologic features such as extrathyroidal extension, lymphatic and vascular invasion, and lymph node metastasis [102, 106–109].

*BRAF* V600E mutations are most common in TC-PTC (approximately 90% of cases) as compared to other subtypes; *TERT* promoter mutations have also been reported in some cases. The other molecular events seen in TC-PTC include loss of heterozygosity for chromosome 1 and *TP53* mutations [110]. The CC-PTC is also associated with *BRAF* V600E mutation; less common are *BRAF* fusions, *RAS* mutations, *TERT* promoter mutations, and loss of *CDKN2A* and *TP53* mutations [111]. Most HN-PTC cases harbor *BRAF* V600E mutations, typically associated with mutations in *TP53*, *TERT* promoter, and *PIK3CA* [112–114].

Other subtypes of PTC are highlighted in the WHO 5th edition of thyroid neoplasms. The *diffuse sclerosing* (DS)-PTC is characterized by diffuse unilateral or bilateral

**Table 3** Key histopathologic criteria and molecular profiles of subtypes of papillary thyroid carcinoma (Figs. 4–10)

| PTC subtype | Proportion of subtype features | Key histopathologic features | Key molecular profile |
|---|---|---|---|
| Infiltrative follicular | ≥90% neoplastic follicles | • Infiltrative growth<br>• Sclerosis<br>• Multicentric tumor foci | • *BRAF* V600E and K601E, *NRAS**, *CTNNB1**mutations<br>• *RET* translocation, *NTRK* and *ALK* fusions |
| Tall cell | ≥30% tall cells | • Tightly packed follicles and papillae — AKA "tram track appearance."<br>• Tumor cell height at least 3×the width [279]**<br>• Eosinophilic cytoplasm with distinct cytoplasmic border<br>• Easily identifiable nuclear features of PTC | • *BRAF* V600E, *TERT* promoter and *TP53* mutations |
| Columnar cell | NA | • Papillary growth admixed with follicles<br>• Columnar cells with pale to eosinophilic cytoplasm and prominent pseudostratification<br>• Subnuclear vacuoles | • *BRAF* V600E, *RAS**, *TERT* promoter*, and *TP53**<br>• *BRAF* fusions, activating *BRAF* deletions, loss of *CDKN2A* and copy number alterations (recurrent gain of chromosome 1q) |
| Hobnail | ≥30% hobnail cells | • Complex papillary or micropapillary growth pattern, rare presence of follicular architecture<br>• Tumor cells with enlarged nuclei, bulging from the apical surface | • *BRAF* V600E, *TP53*, *TERT* promoter, *PIK3CA* mutations<br>• Rarely, *RET* rearrangements, moleular *CTNNB1*, *EGFR*, *ATK1*, *ATM*, *ARID2*, and *NOTCH1* |
| Solid | >50% solid trabecular growth | • Solid, trabecular or nested growth pattern with intervening thin and delicate fibrovascular bands, rarely foci of dense sclerosis<br>• Lack of tumor necrosis (including single cell necrosis) and high mitotic rate | • *CCD6::RET* and *NCOA4::RET* rearrangements (later in radiation indiuced tumors), and *BRAF* V600E*<br>• *ETV6::NTRK3* fusions |
| Diffuse sclerosing | 100% diffuse unilateral or bilateral involvement, without dominant tumor mass | • Dense sclerosis, extensive lympahtic permeation, numerous psammoma bodies and ssociated chronic lymphocytic thyroiditis<br>• Tumor cells arranged in solid nests and papillary formations with squamous metaplasia | • *RET* rearrangements (especially *NCOA4::RET* in radiation induced cases), *BRAF* V600E mutations (20% of cases) and *ALK* rearrangements (10% of cases)<br>• High frequency of *LOH* of 3p24, 9p21, 17q21, 21q22, and 22q13 |
| Warthin-like | NA | • Circumscribed or infiltrative tumor in a background of chronic lymphocytic thyroiditis<br>• Papillae lined by oncocytic cells with papillary core containing lymphoplasmacytic infiltrate | • *BRAF* V600E mutation |
| Oncocytic*** | NA | • Well-developed papillae lined by oncocytic cells | • *BRAF* V600E mutations<br>• *GRIM-19* (germline mutations) and *RET* rearrangements* |

*Rare molecular alteration; **The new criterion for the diagnosis of tall cell subtype as compared to 4th edition; ***For oncocytic-FVPTC refer to question #3

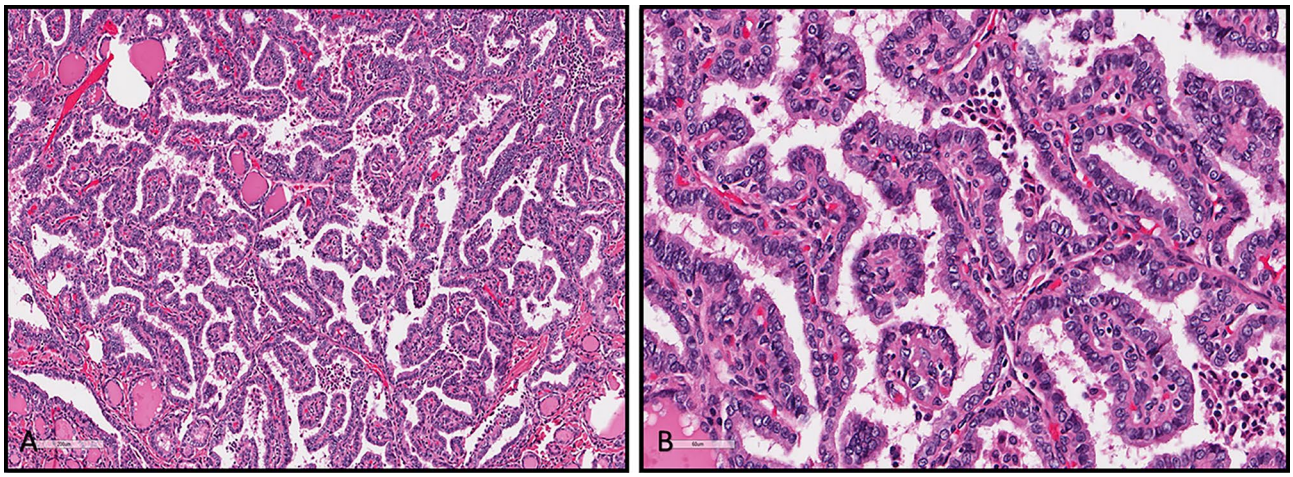


**Fig. 5** **A**, **B** Classic PTC subtype showing complex papillary growth pattern (**A**) lined by cells with nuclear features of papillary thyroid carcinoma (**B**)

involvement of the thyroid gland with extensive lymphatic infiltration, dense sclerosis, numerous psammoma bodies, and associated chronic lymphocytic thyroiditis [115, 116]. The *solid/trabecular* subtype has solid, trabecular, or nested growth pattern that can mimic poorly differentiated carcinoma but lacks necrosis and prominent mitoses. An aggressive clinical course can also be encountered in diffuse sclerosing and solid subtypes of PTC [104, 105, 117]. Other subtypes without known impact on prognosis include the following: the *oncocytic classic PTC* with well-developed papillae and tumor cells with oncocytic cytoplasm (> 75%) and PTC nuclei [58, 59, 118, 119]; the *Warthin-like PTC* essentially an oncocytic PTC with papillary growth and heavy lymphoplasmacytic infiltrate in its stroma that bears morphologic similarities to Warthin tumor of salivary glands; and the rare *clear cell* subtype [120, 121].

Other less common PTC subtypes discussed in the 5th edition of WHO classification of thyroid neoplasms include *spindle cell* PTC and PTC with *fibromatosis/fasciitis-like/desmoid-type stroma* [122–124]. The former can be difficult to distinguish from other neoplasms without the use of proper ancillary tools. The latter is an unusual tumor that has two discrete components: a *BRAF*-mutated PTC embedded within a fibromatosis that has *CTNNB1* mutation and nuclear localization of beta-catenin.

## Question 5: What Are the Subtypes and Features of "High-Grade" Thyroid Carcinoma?

The search for the criteria to identify and diagnose the group of thyroid carcinomas with a prognosis intermediate between the favorable outcome of differentiated follicular cell–derived thyroid carcinomas (papillary and follicular carcinoma) and the very poor outcome of anaplastic carcinoma has been a topic debated for decades [125]. Poorly differentiated architecture — solid, trabecular — was proposed in the mid 1980s as a criterion [126]. Insular carcinoma [127] — which combined poorly differentiated "insular" architecture with high proliferative grade (mitotic activity, tumor necrosis) — was regarded as the prototype of this tumor group [128]. The Turin consensus criteria [129] — endorsed by the 2017 [3] as well as the current WHO classification of tumors of endocrine organs — clarified the histologic criteria to diagnose a poorly differentiated thyroid carcinoma and validated its prognosis as intermediate between well and undifferentiated (anaplastic) carcinomas. As early as 2000 [130], it was proposed to grade PTC based on tumor necrosis and high mitotic rate. It has subsequently become clear that proliferative grading — defined on the basis of high mitotic activity and tumor necrosis — also identifies tumors of intermediate prognosis, regardless of histologic differentiation in terms of papillae, follicles, or solid/trabecular/insular growth patterns [125, 131–133]. Thus, the new WHO classification recognizes two groups of high-grade non-anaplastic follicular cell–derived carcinomas that have intermediate prognostic risk (Table 4):

A. Poorly differentiated thyroid carcinoma (PDTC): These are invasive, high-grade follicular cell–derived carcinomas that are histologically poorly differentiated because of their solid, trabecular, and insular growth patterns (or combinations of these) [129].
B. Differentiated high-grade thyroid carcinoma (DHGTC): These are invasive high-grade follicular cell–derived carcinomas that are still differentiated since they retain the distinctive architectural and/or cytologic properties

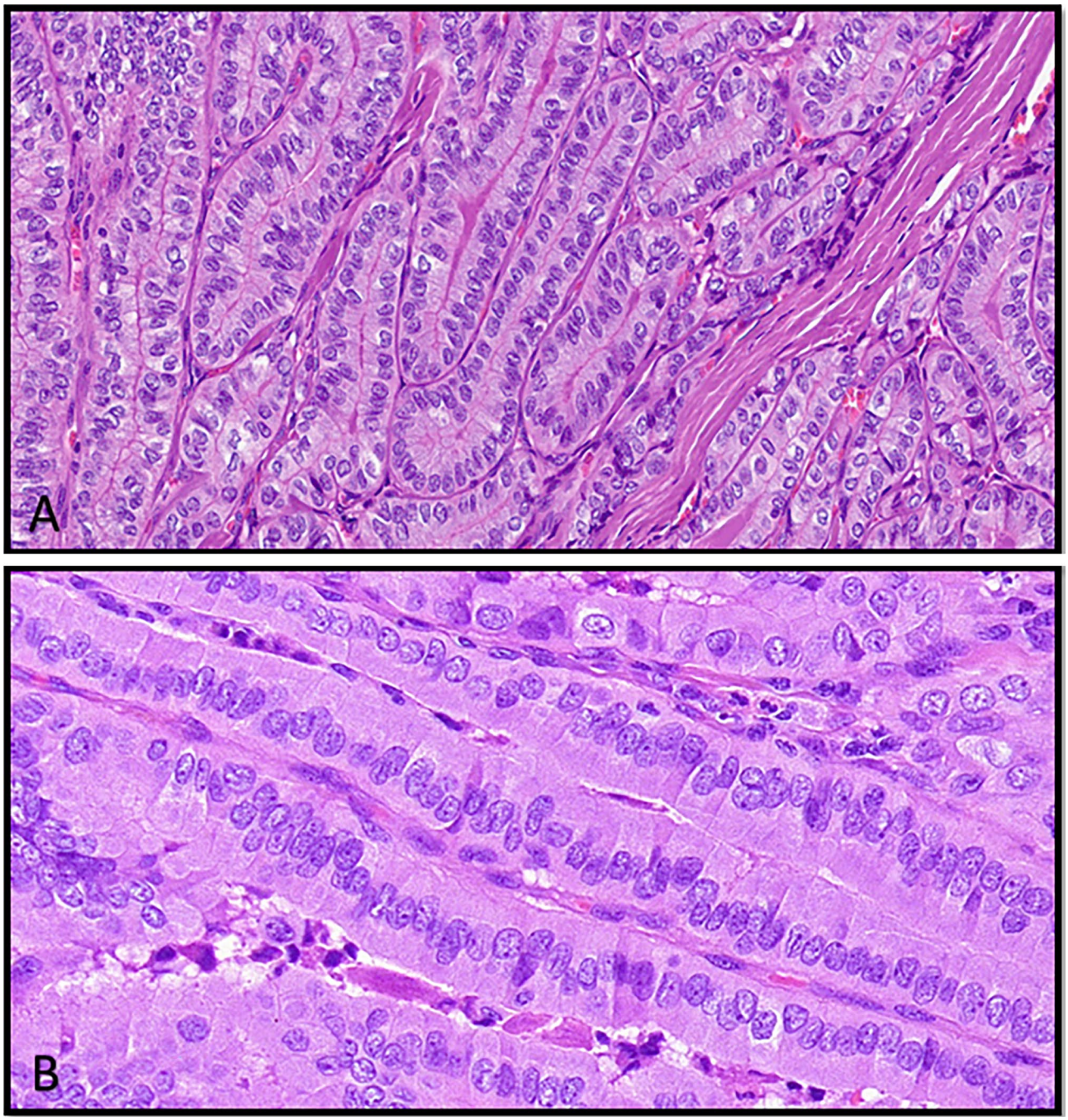


**Fig. 6** **A**, **B** Tall cell PTC subtype showing tightly packed follicles and papillae (**A**), tumor cell height at least 3 × the width, eosinophilic cytoplasm, and easily identifiable nuclear features of PTC (**B**)

of well-differentiated histotypes of carcinoma of follicular cell derivation, such as nuclear features and/or architecture of papillary carcinoma and follicular growth pattern of follicular carcinoma [132, 133].

This approach is justified by the recognition that approximately 50% of high-grade non-anaplastic thyroid carcinomas will not take up radioactive iodine [134], and new treatment modalities, in particular systemic therapies focusing on the particular molecular signature of the tumors, may be needed to treat these patients [135]

From clinical and epidemiologic viewpoints, high-grade non-anaplastic carcinomas of follicular cells, both PDTC and DHGTC, share certain characteristics. They are rare, ranging from less than 1 to 6.7% of all thyroid carcinomas. Higher frequencies are seen in Europe, and

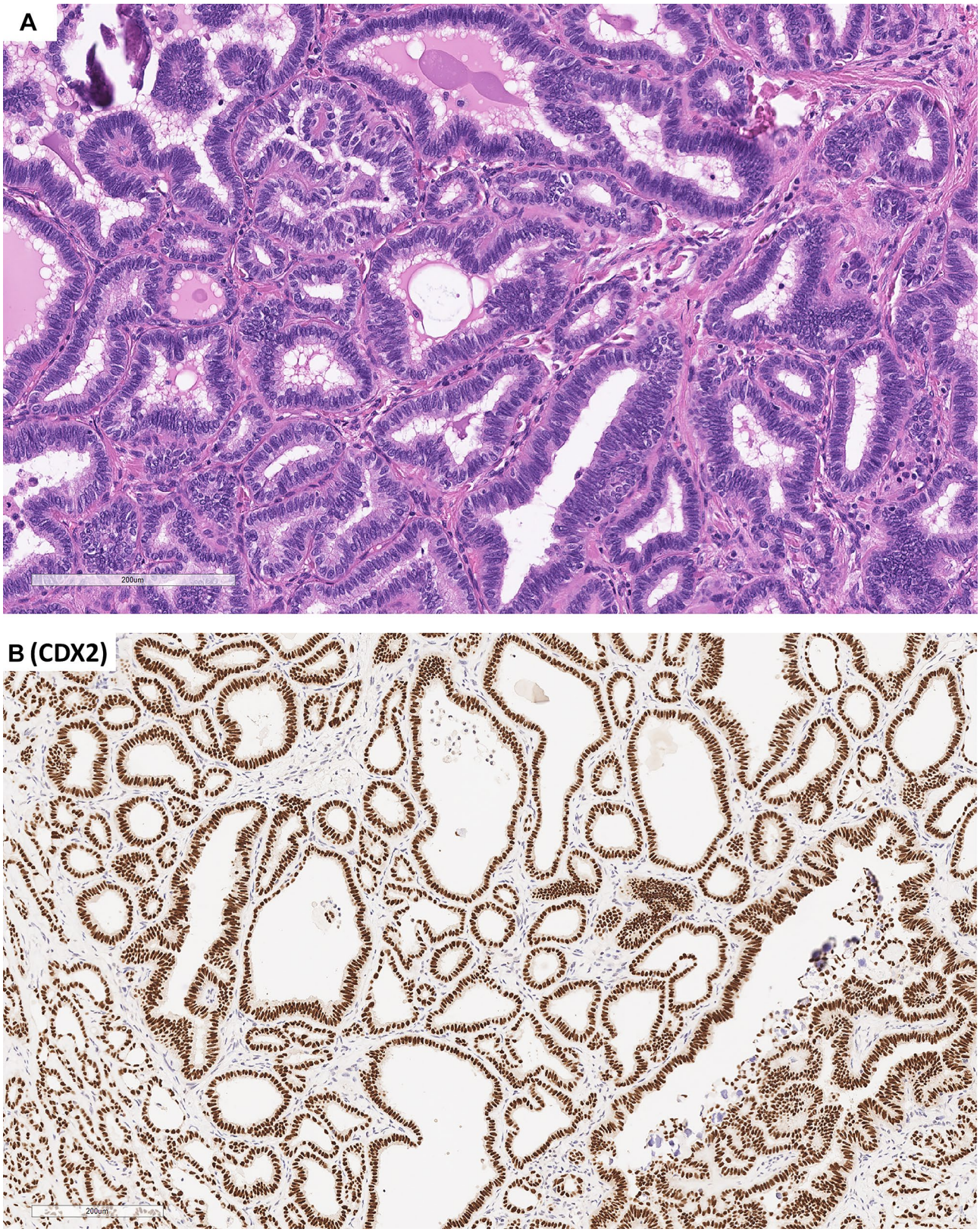


**Fig. 7** **A**, **B** Columnar cell PTC subtype consisting of columnar cells with pale to eosinophilic cytoplasm and prominent pseudostratification (**A**). CDX2 expression is noted in around 50% of these tumors (**B**)

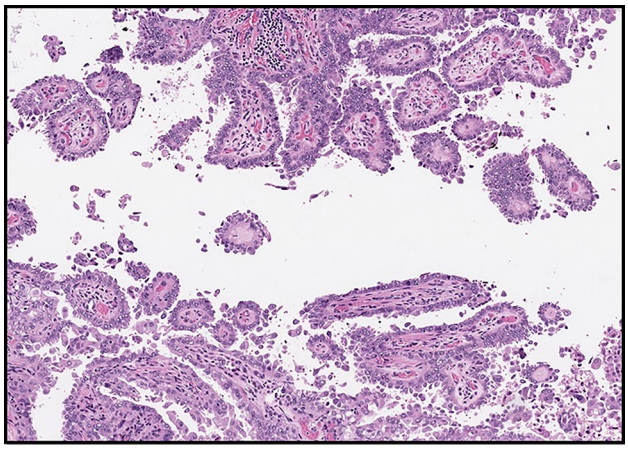

**Fig. 8** Hobnail PTC subtype showing papillary growth and tumor cells with oncocytic cytoplasm and enlarged nuclei, bulging from the apical surface

South America, while lower prevalence rates are reported in North America and Japan. This suggests the possibility of either ethnic or dietary (iodide) factors in the development of these tumors. Clinically, they occur in adults usually over age 50 and develop as rapidly growing masses and with a slight female preponderance [136]. Surgically, the tumors are often large (4 cm or more) and extend beyond the thyroid, with gross vascular invasion, infiltration of perithyroidal soft tissues and skeletal muscle, and perineural attachment or invasion. About 30 to 50% are associated with easily identifiable lymph node metastases [127, 131, 136, 137].

Pathologically, these tumors are grossly widely invasive, but may rarely appear partially encapsulated. Foci of hemorrhage and tumor necrosis may be seen macroscopically [127, 131, 136, 137].

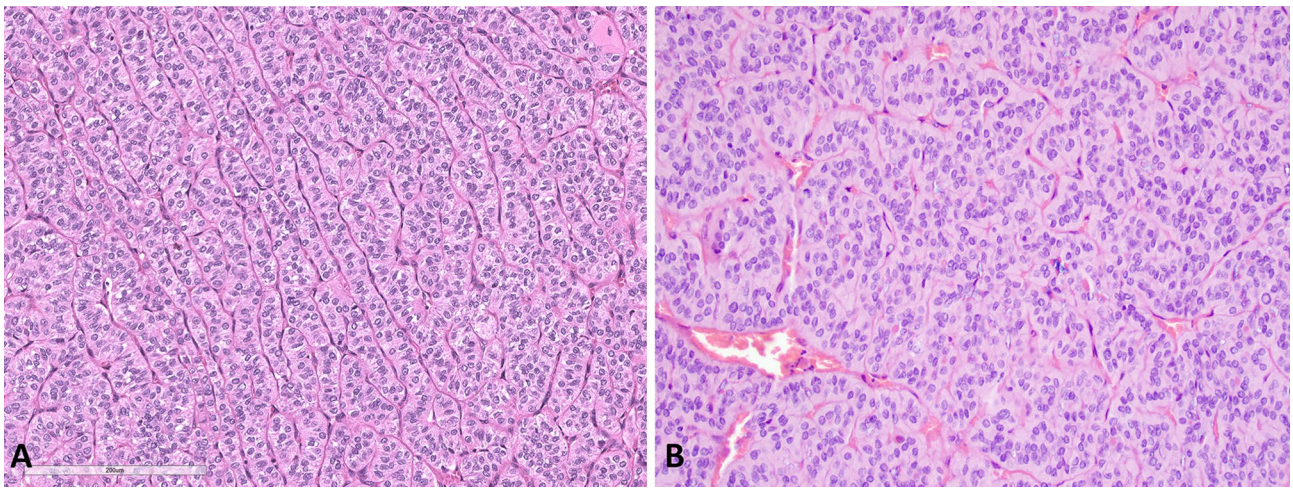


**Fig. 9** **A**, **B** Solid PTC subtype showing solid and trabecular growth pattern (**A**) with variable nuclear features of papillary thyroid carcinoma. There is no tumor necrosis. The mitotic activity is less than 3 per 2 $mm^2$

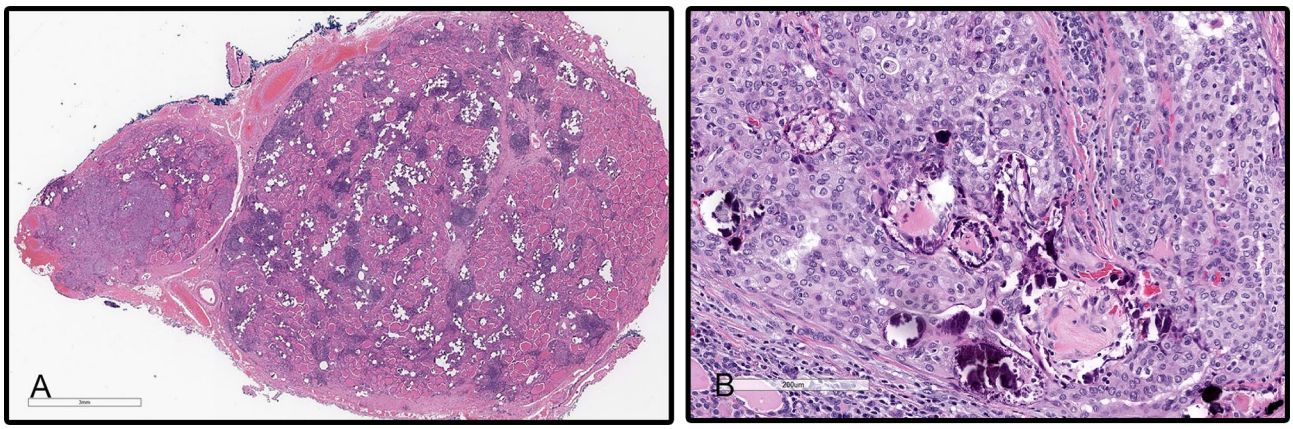


**Fig. 10** **A**, **B** Diffuse sclerosing PTC subtype. An infiltrative tumor (**A**) with numerous psammoma bodies and associated chronic lymphocytic thyroiditis.Tumor cells arranged in solid nests and papillary formations with squamous metaplasia (**B**)

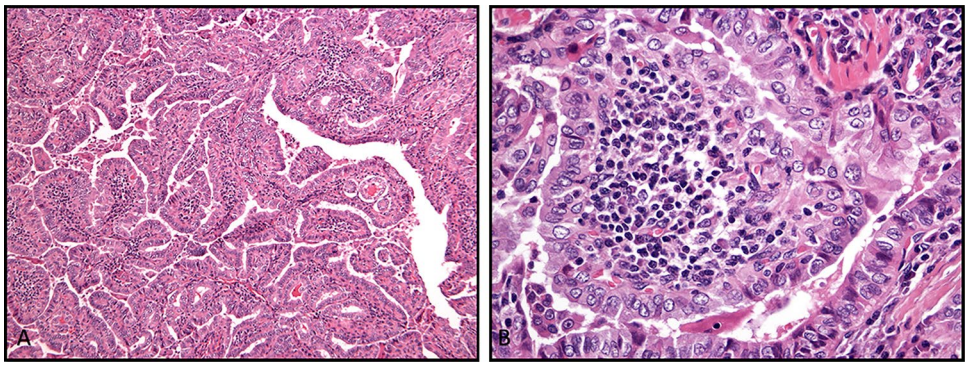


**Fig. 11** **A**, **B** Warthin-like PTC subtype showing papillary growth (**A**) with core of papillae containing lymphoplasmacytic infiltrate (**B**)

The differences between PDTC and DHGTC are found at histologic examination (Table 5) (Figs. 12–13). PDTC has solid trabecular or insular growth. In some instances, tumor cells have small dark nuclei with a convoluted "raisin-like" appearance, reminiscent of papillary carcinoma nuclei [127, 129]. Rarely, large pleomorphic nuclei may be identified. The hallmark of PDTC is the presence of tumor necrosis which may occur as small areas or large swaths of necrotic material with ghost outlines of tumor cells and nuclear dust. If tumor necrosis is absent, mitotic count should reach at least 3 mitoses per 10 high-power fields/ ~ 2 $mm^2$ for the carcinoma to qualify as poorly differentiated. Mitotically active oncocytic carcinomas often have necrosis: since they typically have solid or trabecular growth, they usually fulfill the criteria for PDTC [138, 139]. Rare PDTCs are composed of clear cells [140].

On the other hand, DHGTC shows a growth pattern similar to well differentiated tumors and this is papillary in the vast majority of cases. Nuclear features characteristic of papillary carcinoma may be present throughout, although some areas of the tumor may show nuclear enlargement and pleomorphism. The characteristic histologic feature to confirm the diagnosis is necrosis and/or excess mitotic activity (5 mitoses per 10 high-power fields/ ~ 2 $mm^2$, 400×) [131]. Vascular, lymphatic, perineural and extrathyroidal invasions are commonly found [132, 133].

The use of high-power fields is no longer supported by the new WHO classification schemes, since these vary depending on the microscope and ocular used; the WHO encourages the use of $mm^2$ that is a standard measure irrespective of the microscope used and applicable to digital whole slide images [141]. However, since the majority of studies in this

**Table 4** Prognostically relevant classification of follicular cell derived carcinomas of the thyroid

| Histotype | Differentiation (growth pattern) | Grade (mitotic activity, tumor necrosis) | Prognosis |
|---|---|---|---|
| **PTC** | Good (papillae, follicles) | Low | Excellent |
| **FTC** | | | |
| **OCA** | | | |
| **DHGTC** (papillary, follicular, oncocytic) | | High | Intermediate |
| **PDTC** | Poor (solid/trabecular/insular growth) | | |
| **ACA** | Absent (undifferentiated growth) | | Dismal |

*PTC - papillary thyroid carcinoma; FTC - follicular thyroid carcinoma; OCA - oncocytic carcinoma, DHGTC - differentiated high grade thyroid carcinoma; PDTC - poorly differentiated thyroid carcinoma; ACA - anaplastic carcinoma.*

*Tumors with mixed histologic features should be typed according to the component with highest grade and least differentiation*

**Table 5** Diagnostic criteria for high-grade follicular cell–derived thyroid carcinomas

| | PDTC (Turin criteria) | DHGTC |
|---|---|---|
| Growth pattern | Required: solid/trabecular/insular | Papillary, follicular, solid* |
| Nuclear Cytology | Required: no features of PTC | Any |
| Other features: tumor necrosis, mitosis and convoluted nuclei | Minimum requirement: one of the following three features:<br>Mitotic count ≥ 3/2 $mm^2$<br>Tumor necrosis<br>Convoluted nuclei | Minimum requirement: one of the following two features:<br>Mitotic count ≥ 5/2 $mm^2$<br>Tumor necrosis |
| Anaplastic features | Absent | Absent |

*PDTC,* poorly differentiated thyroid carcinoma; *DHGTC,* differentiated high-grade thyroid carcinoma

*Tumors with solid growth and PTC nuclear features are classified as high-grade differentiated thyroid carcinoma

field have used high-power field measures, these are retained in the description until more accurate data can be obtained.

Immunohistochemical staining in both PDTC and DHGTC indicates that they are positive for TTF1, PAX8, cytokeratins (usually cytokeratin 7), and thyroglobulin [3]. Thyroglobulin tends to be weak and focal with dot-like reactivity. The Ki67 proliferation index is high, usually in the range of 10 to 30% [142]. Ancillary immunostaining is indicated to exclude other tumor types, such as medullary carcinoma, parathyroid carcinoma, and metastases to the thyroid gland and may be used to confirm vascular invasion. Of particular concern are aggressive medullary thyroid carcinomas with mitotic activity and tumor necrosis [143–145]; these often feature solid and trabecular growth: immunostaining for calcitonin, chromogranin, and monoclonal CEA may be necessary to distinguish them from follicular cell–derived poorly differentiated tumors.

From a molecular biology standpoint, PDTC and DHGTC harbor driver mutations in *BRAF* (*BRAF* V600E), *RAS*, or — much less frequently — gene fusions (usually *RET* or *NTRK3*). In addition, they also carry aggressive secondary mutations, most frequently of the *TERT* promoter and in some cases of *PIK3CA* and *TP53* [73, 135, 146]. Poorly differentiated thyroid carcinomas are enriched in *RAS* mutations, a consequence of their strict definition that requires the absence of papillary carcinoma nuclear features [133, 146]. In contrast, the vast majority of DHGTC are *BRAF* V600E-driven since most display the cytoarchitectural features of papillary carcinoma [132, 133, 146]. This likely explains the higher propensity for cervical lymph node metastases in DHGTC [133].

In large studies, PDTCs (based on the Turin proposal) have a 10-year overall survival of 46% [147] and a 60% disease-specific survival at 10 years [133]. High-grade non-anaplastic follicular cell–derived carcinomas that do not fit the Turin proposal (i.e., DHGTC) have an approximately similar disease-specific survival (56% at 10 years) [133], although disease-free survival may be worse for high-grade papillary thyroid carcinoma compared with PDTC [132]. The prognosis of poorly differentiated oncocytic thyroid carcinoma is apparently similar to that of its non-oncocytic poorly differentiated counterpart [59, 138, 139].

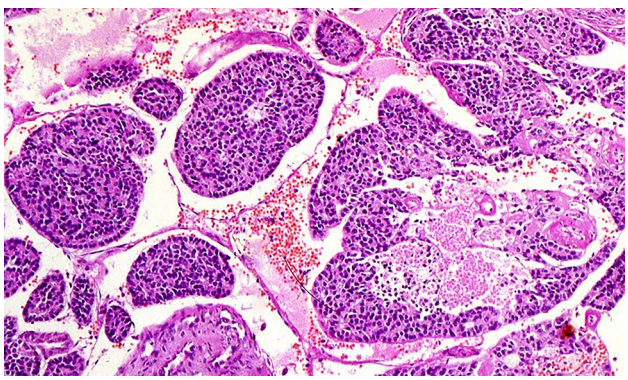

**Fig. 12** Poorly differentiated thyroid carcinoma showing solid nests, absence of nuclear features of papillary carcinoma, and tumor necrosis

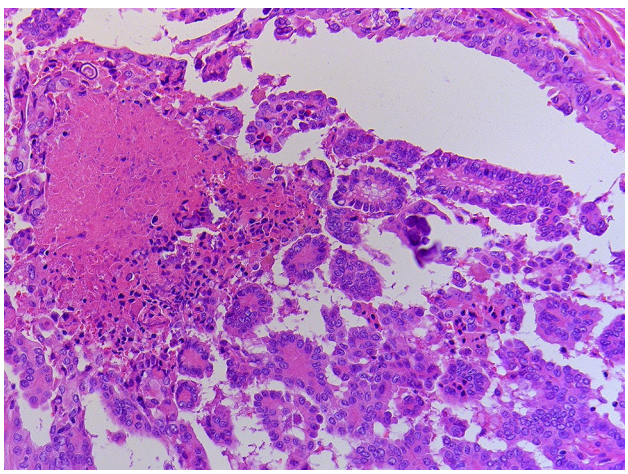

**Fig. 13** High-grade papillary thyroid carcinoma. This photomicrograph illustrates tumor necrosis in a *BRAF*-like high-grade papillary thyroid carcinoma

Rare forms of high-grade non-anaplastic follicular cell–derived carcinomas are encapsulated and confined within the thyroid [148]. Although some of these tumors are angioinvasive, once the tumor is resected, patients have median disease-specific survival of 8 to 10 years [148]. Poorly differentiated carcinoma is a rare finding in teenagers. A series of six cases culled from three institutions showed that these tumors harbor somatic mutations in *DICER1*; two of the six patients also carried germline mutations and thus had DICER1 syndrome. A 30% mortality rate due to tumor was noted [149].

## Question 6: What Is New in the Understanding of Anaplastic Thyroid Carcinoma and Why Is "Squamous Cell Carcinoma" Included in This Section?

In the previous WHO classification [3], squamous cell carcinoma of the thyroid (i.e., carcinoma composed almost entirely of squamous cells without a differentiated carcinoma component) was considered a separate entity from anaplastic thyroid carcinoma. Several lines of evidence point towards this tumor being a morphologic pattern of anaplastic thyroid carcinoma. In a recent multi-institutional study, pure squamous cell carcinoma with (Fig. 14) or without a differentiated thyroid carcinoma component displayed *BRAF* V600E mutations in 87% of cases and had an outcome similar to anaplastic thyroid carcinoma in general [150]. In addition, these squamous cell carcinomas express PAX8 and TTF1 in 91% and 38% of cases, respectively, confirming their follicular cell origin [150]. They harbor a differentiated thyroid carcinoma in three quarter of cases (almost all being papillary carcinoma). Furthermore, pure squamous cell carcinoma without any differentiated thyroid carcinoma component (i.e., fulfilling the 2017 WHO definition of squamous cell carcinoma) carries *BRAF* V600E mutations in 60% of cases and has the same prognosis as anaplastic carcinoma in general [151]. For the above reasons, squamous cell carcinoma of the thyroid is now classified as a morphologic pattern of anaplastic thyroid carcinoma. Another important addition to the anaplastic carcinoma section is the emphasis on rapid and prompt testing of all anaplastic carcinomas for the presence of *BRAF* V600E mutation.

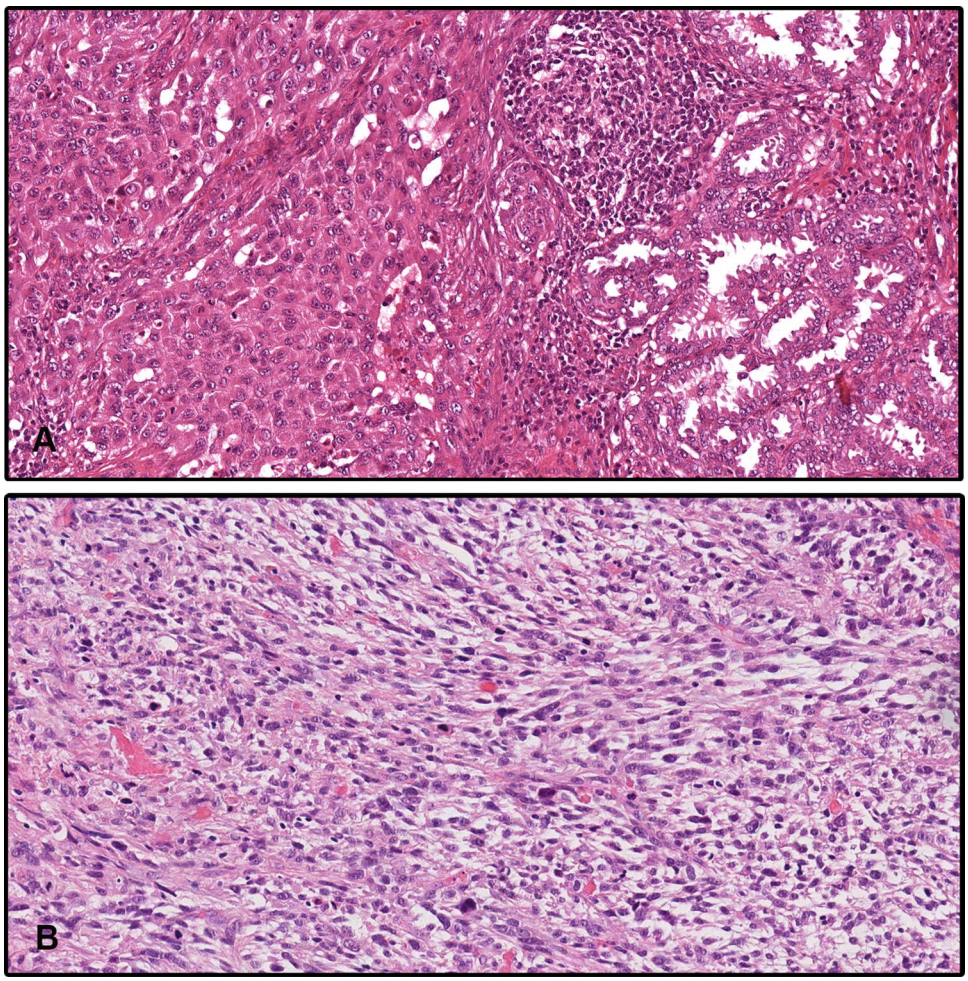


**Fig. 14** Anaplastic thyroid carcinoma with prominent squamous differentiation. The tumor is arising in association with a papillary thyroid carcinoma, hobnail subtype (**A**). Anaplastic thyroid carcinoma showing spindle cell morphology (**B**)

This testing is mandatory since the combination of BRAF and MEK inhibitors was found to be active against *BRAF* V600E–mutated anaplastic carcinoma [152]. This testing can be performed using immunostaining against the mutated protein or through genotyping.

## Question 7: What Are the Clinicopathological Correlates of Oncocytic Thyroid Carcinomas?

Oncocytic follicular cell–derived thyroid carcinomas as a group can include many different entities: oncocytic PTC, oncocytic encapsulated follicular subtype of PTC, oncocytic poorly differentiated carcinoma, and oncocytic medullary thyroid carcinoma [58, 153]. However, the term "oncocytic carcinoma of the thyroid" is used in the new WHO to refer to invasive malignant follicular cell neoplasms composed of at least 75% oncocytic cells in which the nuclear features of PTC and high-grade features are absent. This term replaces Hürthle cell carcinoma, a misnomer given that Hürthle actually described parafollicular C cells. Oncocytic cells have abundant granular eosinophilic cytoplasm secondary to a marked accumulation of dysfunctional mitochondria. Oncocytic carcinoma of the thyroid (OCA) represents the malignant counterpart of oncocytic adenoma [153]. Although there are no major substantive changes to the description of these tumors in the 2022 WHO, it is helpful to review the distinct clinicopathologic correlates of OCA.

OCA, which accounts for approaching 5% of differentiated thyroid carcinomas in the USA [154], can occur anywhere in the thyroid and usually presents as a slowly enlarging painless solitary thyroid nodule. Thyroid ultrasound cannot distinguish between oncocytic adenoma and OCA, though larger tumors have a higher rate of malignancy [155]. There are no known risk factors for developing OCA. The mean age at diagnosis is approaching 60 years, which is roughly 10 years later than the mean age of diagnosis for patient with follicular thyroid carcinoma [154, 156, 157]. OCA, although more common in women (with a 1.6 to 1 female-to-male ratio), has a lower female-to-male ratio than is seen with follicular thyroid carcinoma [157]. Histologically, OCAs are encapsulated tumors with capsular and/or vascular invasion and at least 75% oncocytic cells (Fig. 15). OCAs are subclassified into minimally invasive (those with capsular invasion only), encapsulated angioinvasive, and widely invasive (those with gross invasion through the gland) tumors due to differences in clinical outcome. When evaluating OCA, it is important not only to document extent of invasion, but also to evaluate for progression to oncocytic poorly differentiated thyroid carcinoma; thus, all tumors should be assessed for increased mitotic activity (3 or more mitoses per 10 high-power fields/ ~ 2 $mm^2$) and tumor necrosis. OCA can metastasize to lymph nodes [158]; however, some authors have shown that most of the so-called lymph nodes metastasis of OCA represent tumor plugs in veins in the neck and not lymph nodes involved by tumor [158]. The important clue is the almost perfect roundness of these tumor plugs compared to oval or somewhat irregular outline for nodal metastases [158]. OCA (like follicular thyroid carcinoma) usually spreads to distant sites via blood vessels. Distant metastasis at presentation are seen in 15–27% of patients with OCA and in up to 40% of tumors with extensive vascular invasion [159].

Prognostic parameters for OCA include patient age, tumor size, vascular invasion, extrathyroidal extension, and the presence of distant metastases [154, 160]. Distant metastases at diagnosis are the most important prognostic factor for OCA [154, 160]. For OCA, the 5-year overall survival has been reported to be 85%, but only 24% among patients with distant metastases at diagnosis compared to 91% for patients with M0 disease at diagnosis [160]. Although it is not clear that OCA is more aggressive than follicular thyroid carcinoma after adjusting for variables such as patient age, gender, and tumor stage [156, 157], due to decreased efficacy of radioactive iodine with OCA compared to follicular thyroid carcinoma, treating OCA is currently more difficult once there is disease recurrence.

Benign and malignant oncocytic thyroid tumors have both been shown to harbor homoplasmic or highly heteroplasmic (> 70%) mitochondrial DNA mutations in complex I subunit genes of the electron transport chain [18, 161, 162]. Additionally, OCAs demonstrate widespread chromosome losses that result in near-genome-wide haploidization with or without subsequent genome endoreduplication [161]. Chromosomal changes have been found to be associated with extent of invasion: most OCAs with capsular invasion only or focal vascular invasion have been shown to be diploid, whereas tumors with extensive vascular invasion and widely invasive tumors are usually polysomic and nearly always demonstrate chromosome 7 amplification [161]. Additionally, the near-haploid state has been shown to be maintained in metastases, implying selection during tumor evolution [162]. OCAs have also been shown to have recurrent DNA mutations, including *RAS* mutations (though at a lower rate than is seen with follicular thyroid carcinoma), *EIF1AX*, *TERT*, *TP53*, *NF1*, and *CDKN1A*, among others [161–163].

## Question 8: What Are the Molecular Biomarkers of Tumor Progression or Adverse Biology in Follicular Cell–Derived Thyroid Carcinomas?

While ancillary molecular testing is not required for the diagnostic workup of follicular cell–derived thyroid carcinoma, next-generation sequencing techniques are gaining

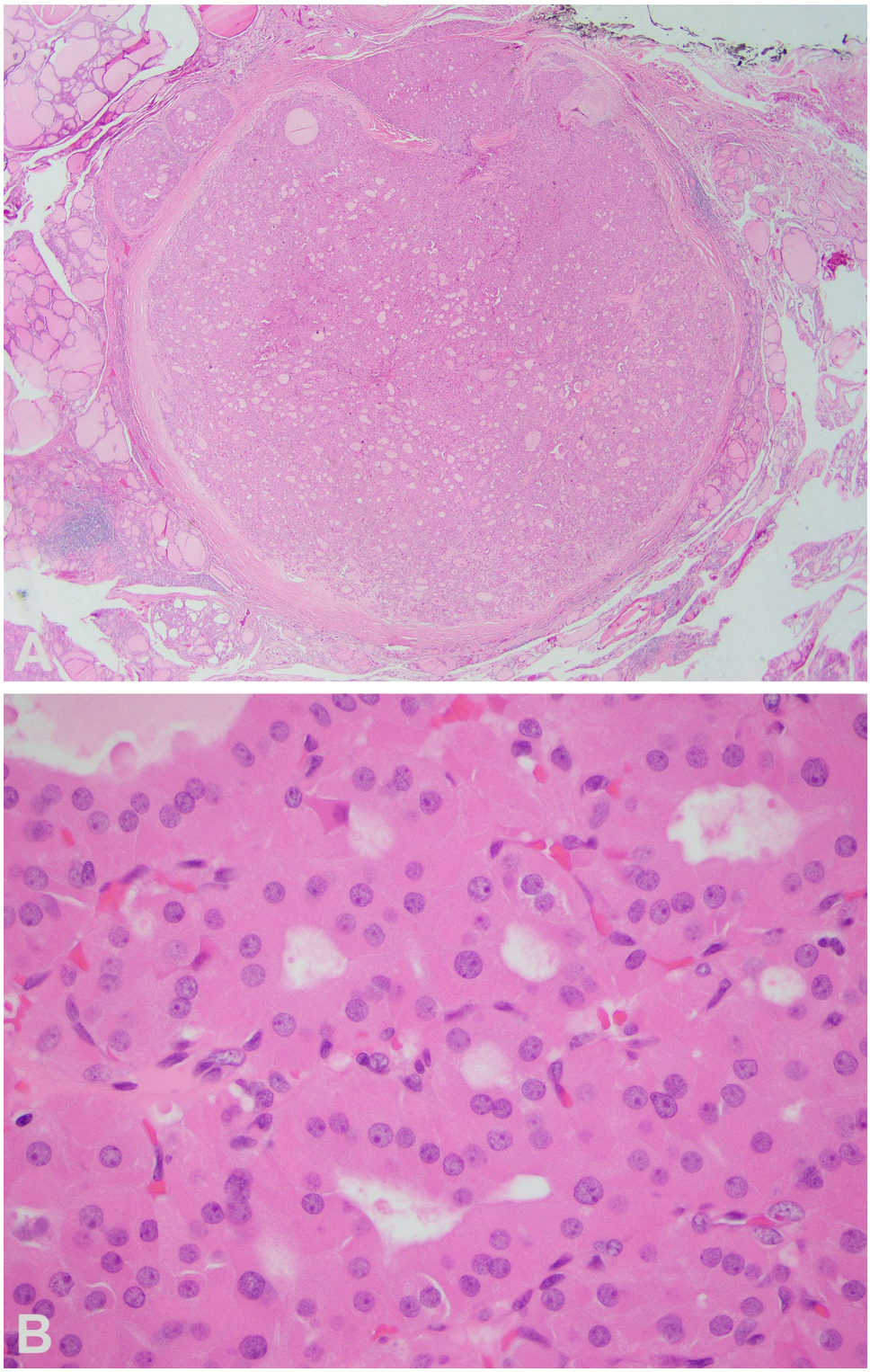


**Fig. 15** Oncocytic carcinoma of the thyroid. **A** Invasive growth through the capsule is evident at low power. **B** At high power, the cells have abundant granular cytoplasm and prominent nucleoli

ground as reliable analyses complementing gold-standard cytological and histological examinations. For example, molecular panels for pre- and post-operative analyses are routinely used by some academic centers, in which pre-operative testing of fine-needle aspiration biopsies (FNABs) may guide the patient to the right surgical procedure, while post-operative testing is focused on risk stratification and the identification of potentially actionable genetic events in case of therapy-resistant disease progression [164–166]. Indeed, follicular cell–derived thyroid carcinomas often

harbor mutations or fusions in clinically targetable genes, thus motivating why clinicians should be acquainted and up-to-date with these mechanisms.

PTCs are in general driven by very few somatic mutations or mutually exclusive fusions involving genes regulating the mitogen-activated protein kinase (MAPK) signaling cascade (Fig. 16). PTCs exhibit among the lowest mutational burden of all human cancers and are highly stable from a pan-genomic perspective with few gross alterations observed, further emphasizing the overall placid genetic background of these lesions. The recurrent p. V600E missense mutation of the *BRAF* proto-oncogene is the most common genetic alteration in PTCs and is particularly enriched in specific, high-risk PTC subtypes (such as the classical, tall cell, and hobnail variants) [167, 168]. The mutation causes activation of the MAPK signaling pathway, which in turn will stimulate extracellular signal–regulated kinases (ERK) transcriptional programs, leading to increased proliferation, angiogenesis, and invasiveness, as well as down-regulating transcription of genes responsible for thyroid differentiation (Fig. 16). While the p. V600E *BRAF* mutation may be associated to a poorer patient outcome in some series, the results are conflicting — and the mutation is also prevalent in papillary thyroid microcarcinomas, which are known to have an excellent long-term prognosis.

Additional factors besides *BRAF* mutations are thought to influence the aggressive clinical phenotype observed in subsets of PTC patients with this genetic alteration. Indeed, *telomerase reverse transcriptase* (*TERT*) promoter mutations have been found to predict worse clinical outcome in PTC patients with synchronous *BRAF* mutations, suggesting a synergic effect [169, 170]. Occurring in approximately

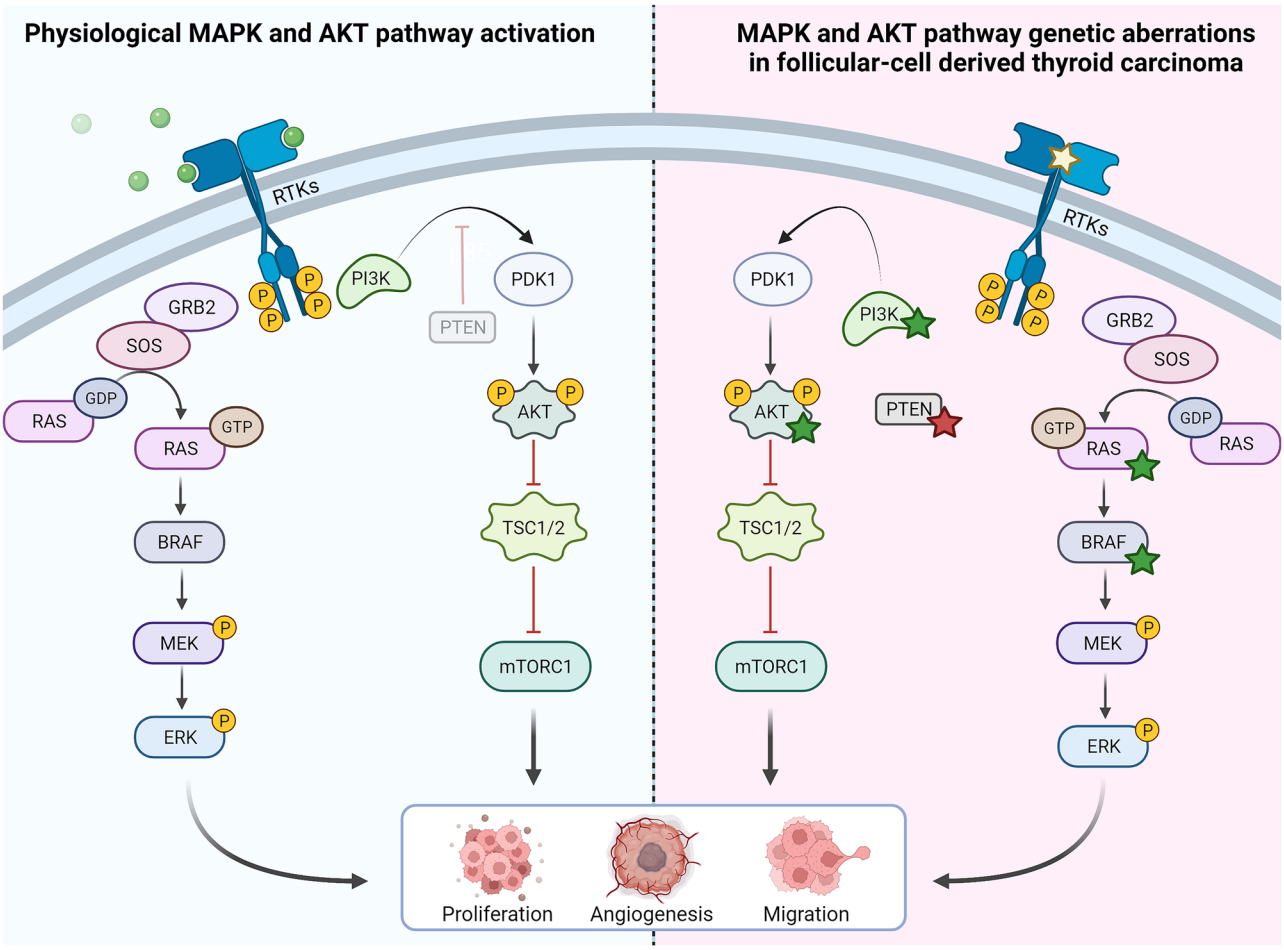


**Fig. 16** MAPK and AKT pathways in thyroid cancer. Schematic overview of the mitogen-activated protein kinase (MAPK) and AKT pathways in the physiological (left) and neoplastic state (right). Upon activation of various report tyrosine kinases (*RTKs*; including *RET* and *TRK1/3*) via extracellular ligands, the RTKs dimerize and activate the MAPK pathway via activation of RAS proteins and also stimulate the PI3K-AKT cascade via PIK3. Both pathways stimulate proliferation, angiogenesis, and migration of cells. In thyroid cancer (right), various fusion genes or mutations simulate physiological activation of the RTKs, thereby leading to constitutively active MAPK and PI3K-AKT signaling, even in the absence of extracellular ligands. *RET* and *NTRK1/3* fusions (yellow stars), activating *PIK3CA*, *AKT*, *RAS*, and *BRAF* mutations (green star) as well as deleterious *PTEN* mutations (red star), are highlighted. Created with BioRender.com

10–15% of unselected PTC cases, the recurrent *TERT* promoter mutations (C228T and C250T) are thought to enhance the *TERT* gene output, which in turn could lead to immortalization through the activation of telomerase (Fig. 17). Telomerase has the ability to maintain the length of telomeres by addition of telomeric repetitive sequences, avoiding critical shortening of the chromosomal ends after a specific number of cell divisions and thereby ensuring limitless replicative potential (Fig. 16). *TERT* promoter mutations are predominantly found in older patients (> 55 years) with large tumors that often exhibit extensive local infiltration [171, 172]. Although we lack data suggesting that the finding of a *TERT* promoter mutation in a PTC should alter the clinical management of the individual patient, the occurrence of a *TERT* promoter mutation should possibly alert the clinical team, as these mutations are highly associated with radioiodine refractory disease, distant metastases, and thyroid cancer dedifferentiation (Figs. 17–18) [135, 172–175]. Moreover, apart from promoter mutations, gain of the *TERT* gene locus at chromosome 5p15.33, aberrant *TERT* promoter methylation patterns, and *TERT* mRNA overexpression are features coupled to adverse prognosis in well-differentiated follicular cell–derived thyroid carcinomas, of which some may be of clinical utility [176–178]. Indeed, the THY1 signature platform includes chromosome 5p status as one of the parameters tested [177]. Moreover, while PTC patients < 55 years rarely exhibit *TERT* promoter mutations, the presence of detectable *TERT* promoter mRNA is associated to worse outcomes and may thus be a promising marker for future studies [178].

In terms of genomic rearrangements, PTCs may harbor fusions involving a wide variety of cancer-related genes, of

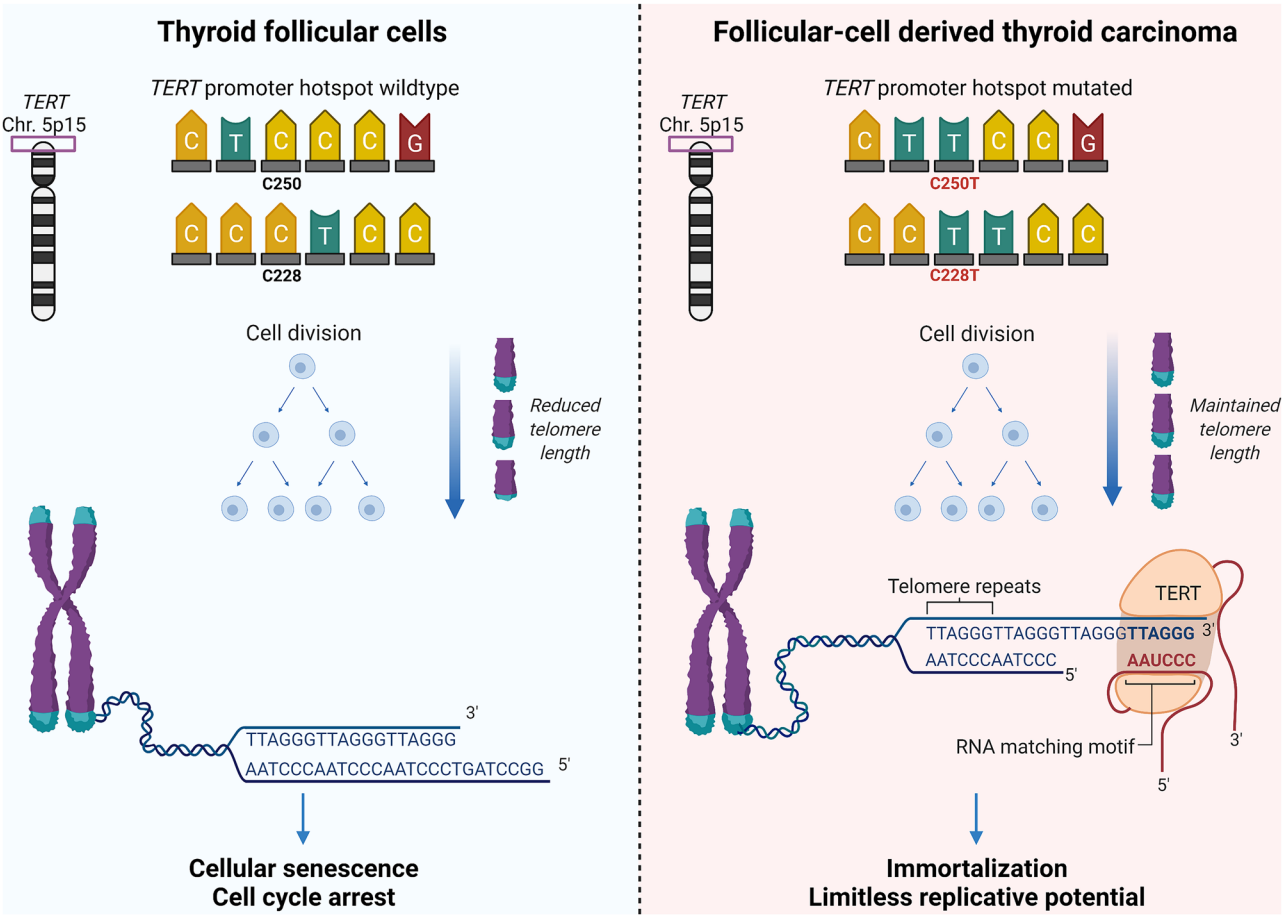


**Fig. 17** TERT functions in thyroid cancer. Left: The *telomerase reverse transcriptase* (*TERT*) gene located on chromosome 5p15 encodes the catalytic subunit of the human telomerase complex, which is imperative for immortalization of stem cells and cancer cells alike. In the normal follicular cell, the protective, repetitive sequences at the end of chromosomes (telomeres) are shortened at the 3′ end with each replicative cycle. Upon reaching a critical limit, the cell is forced into cell cycle arrest. Right: Two hotspot mutations in the promoter sequence (denoted C228T and C250T) have been established as an event signifying poor prognosis in thyroid cancer. The mutations lead to an augmented recruitment of various transcription factors and thereby increased *TERT* gene expression. TERT/telomerase will extend the telomeric repeats at the chromosomal ends, preventing telomeric shortening, and thereby contributing to immortalization. Created with BioRender.com

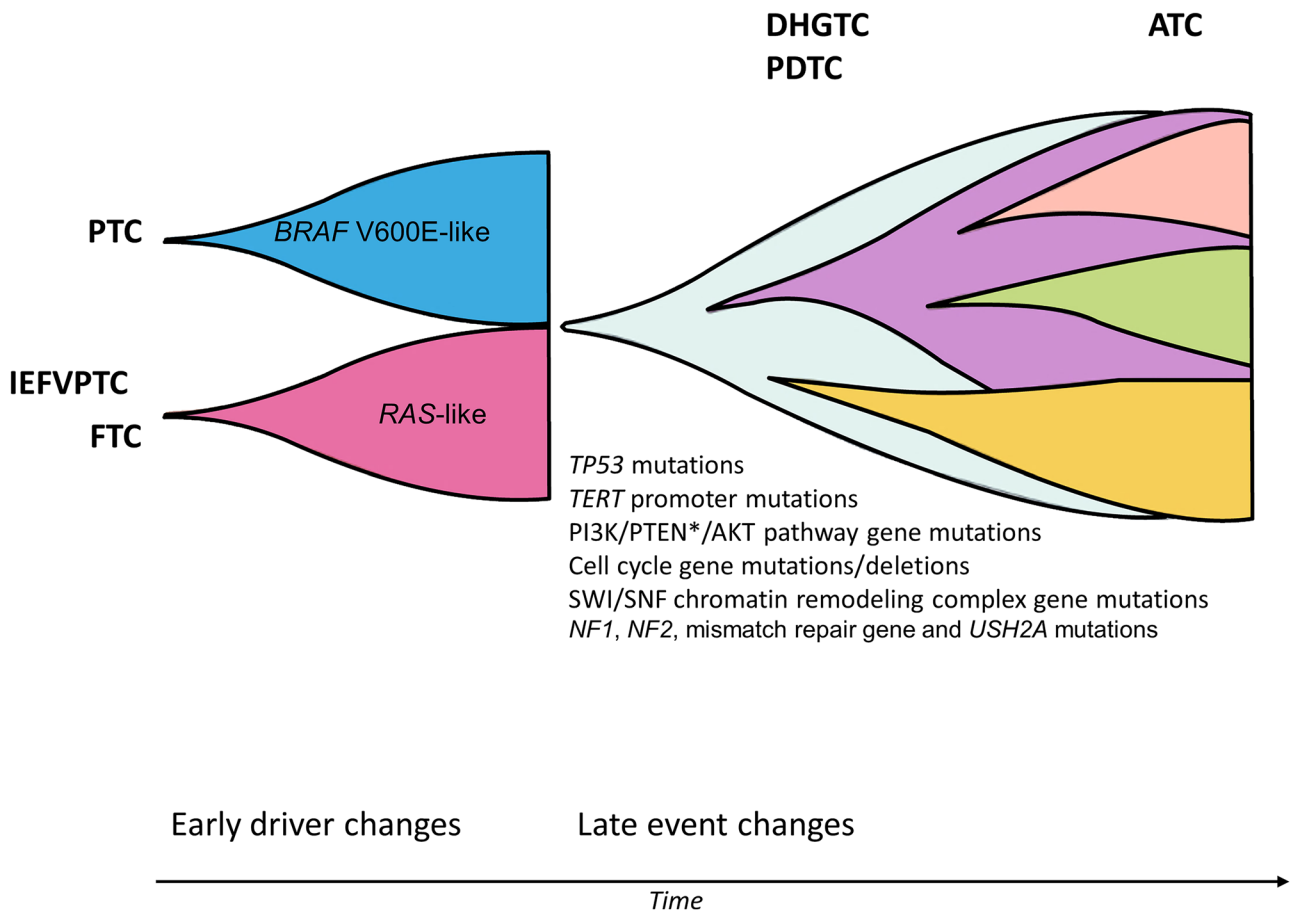


**Fig. 18** Schematic overview of the multistep process of thyroid cancer development and progression. Via modern genetic analyses, thyroid cancer can be divided into *BRAF* V600E–like and *RAS*-like tumors based on mutational and transcriptomic profiles. *BRAF* V600E–like alterations typically include gene fusions in *ALK*, *BRAF*, *RET*, *NTRK1/3*, and *MET*, while *RAS*-like alterations include *BRAF* K601E, *DICER1*, *EZH1*, *EIF1AX*, and *PTEN* mutations and gene fusions in *PPARG* and *THADA*. While many PTC subtypes adhere to the *BRAF*-like cluster, IEFVPTC and FTC in general cluster together as both entities harbor *RAS*-like aberrations. Not shown here is the third cluster composed of non-*BRAF*-/non-*RAS*-like tumors. *Note that while *PTEN* mutations are considered an early event in thyroid carcinoma with *RAS*-like alterations, additional *PTEN* pathway alterations are recurrently noted in more advanced thyroid carcinomas (DHGTC, PDTC, and ATC). PTC, papillary thyroid carcinoma; IEFVPTC, invasive encapsulated follicular variant papillary carcinoma; FTC, follicular thyroid carcinoma; DHGTC, differentiated high-grade thyroid carcinoma; PDTC, poorly differentiated thyroid carcinoma; ATC, anaplastic thyroid carcinoma

which *RET*, *NTRK1-3*, *BRAF*, and *ALK* are all clinically important to recognize due to the therapeutic value of these alterations, as they may be targeted by specific drugs. *RET* fusion partners in thyroid cancer encompass 27 different genes, of which 24 are reported in PTCs [179]. Of these, *CCDC6* is the most common partner gene, followed by *NCOA4* [179]. *RET* fusions are the most common genetic aberrancy in PTC developing after radiation exposure and are the main culprit events in pediatric PTCs overall [180]. Irrespectively of fusion partner, the RET kinase is activated due to the switch of the *RET* promoter with that of the fusion partner; activated RET receptors stimulate the MAPK and PI3K-AKT signaling pathways and thus promote tumorigenesis (Fig. 16). While not as common as *RET* fusions, *NTRK* fusions (*NTRK1* and *NTRK3*, encoding the receptor tyrosine kinases *Trk-A* and *Trk-C*, respectively, fusing with 5′ sequences of various activating genes) are detected in 3–5% of PTCs commonly seen in pediatric and adolescent patients with *BRAF* wild-type PTCs. These tumors display a predominant follicular growth pattern, often displaying a non-infiltrative tumor border, clear cell change, and less pronounced nuclear atypia as compared to *BRAF*-mutated cases [181–185]. The fusion products lead to a constitutively active receptor complex, in turn activating the MAPK and PI3K-AKT pathways.

Apart from the abovementioned genetic alterations, *PLEKHS1* gene aberrations have been established in PTCs, including promoter mutations, aberrant promoter methylation, and gene overexpression leading to AKT pathway activation and poorer patient outcomes [173, 186]. In a

recent study, *PLEKHS1* promoter mutations were present in 13% of PTCs presenting with distant metastases and associated to radioiodine (RAI) refractory disease [173], and the authors suggested that the presence of a mutation in either the *TERT* promoter, the *PLEKHS1* promoter, or the *TP53* gene (in association with either *BRAF* or *RAS* mutations) will predict worse clinical outcome in well-differentiated thyroid carcinoma [173] (Fig. 19). The authors also suggested that losses of 9q and 11q were associated with cancer-specific mortality. Another group investigated the genomic landscape of fatal differentiated and poorly differentiated thyroid carcinomas (PDTCs) and found that an overrepresentation of chromosome 1q gain, as well as mutations in the mRNA processors *MED12* and *RBM10*, encodes proteins involved in the regulation of RNA polymerase II–driven transcription and mRNA splicing functions, respectively [187]. Mutations in these genes were foremost observed in PDTCs and subsets of PTCs. Additional epigenetic aberrations include global DNA hypomethylation, which is coupled to an increased risk of distant metastases in differentiated thyroid cancer [188, 189] (Fig. 19).

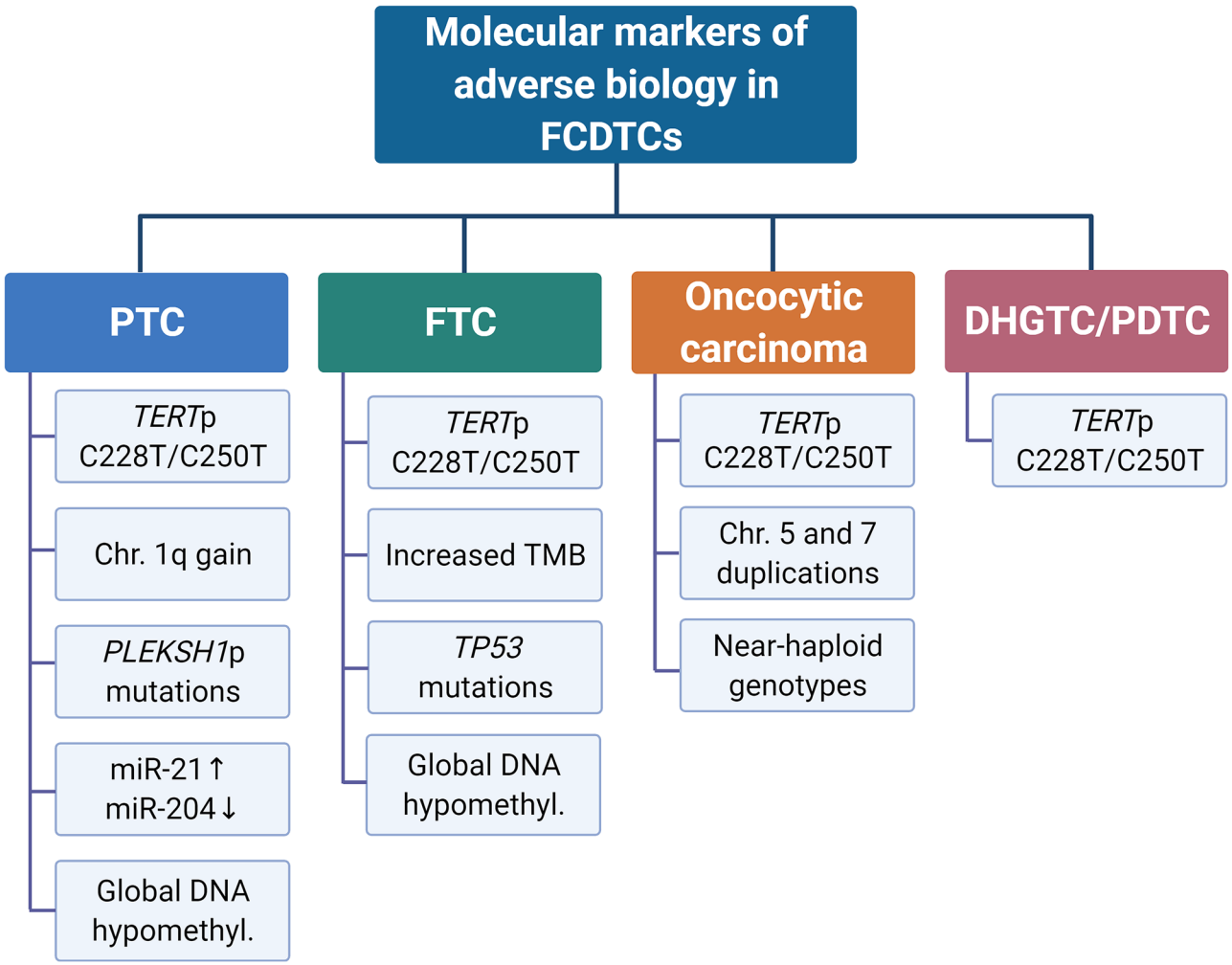


**Fig. 19** Adverse markers in follicular cell–derived thyroid carcinoma (FCDTC). In papillary thyroid carcinoma (PTC), the synergistic effect of *BRAF* V600E and *TERT* promoter mutations indicates an increased risk of distant metastases and worse overall survival. Moreover, gain of chromosome 1q as well as mutations in the *PLEKHS1* promoter (*PLEKSH1*p) may be observed in PTCs with poorer outcomes. In follicular thyroid carcinoma (FTC), *TERT* promoter mutations are associated to distant metastases and poor patient outcomes. Moreover, *TP53* gene mutations and high tumor mutational burden (TMB) have been demonstrated in subsets of cases and may predict worse prognosis. In both PTCs and FTCs, global DNA hypomethylation may signify poorer patient outcomes. Oncocytic thyroid carcinomas are usually associated to mitochondrial DNA mutations and various copy number alterations, of which intensified gross chromosomal alterations (including whole-chromosomal duplications of chromosomes 5 and 7 and near-haploid genotypes) are coupled to worse outcomes. Finally, in differentiated high-grade thyroid carcinoma (DHGTC) and poorly differentiated thyroid carcinoma (PDTC), *TERT* promoter mutations may signify an increased risk of distant metastases. Due to their overall dismal prognosis, anaplastic thyroid carcinoma (ATC) is excluded from this algorithm. Created with BioRender.com

On the microRNA (miRNA) level, several gene products have been associated to worse outcome in PTCs, including overexpression of miR-146a/b, miR-221, and miR-222 [190].

*Follicular thyroid carcinoma* (FTC) and *encapsulated follicular variant papillary thyroid carcinoma* (EFVPTC) harbor somatic mutations of *RAS* gene family members *NRAS*, *HRAS*, and *KRAS* that are recurrently found in follicular patterned tumors (Fig. 16). Of these, *NRAS* mutations are the most prevalent, most often represented by recurrent codon 61 mutations, and less often of codon 12/13 alterations. The mutations cause activation of the MAPK pathway, but not to the same extent as mutant *BRAF* — as *ERK* may dampen the effect of mutant *RAS* through a negative feedback loop inhibiting various RAF proteins which is not possible when *BRAF* itself is mutated [191]. Therefore, the MAPK signaling output is lower, which could be a plausible explanation to the improved prognosis in *RAS* mutated tumors compared to *BRAF*-mutated cases [191].

While *RET* and *TRK* fusions do not seem to play a role in the development of follicular patterned lesions, *PAX8::PPARG* rearrangements are frequently reported (10–40% of cases) [192]. This genetic aberrancy is also reported in subsets of follicular thyroid adenomas, thereby preventing it from having diagnostic properties on the preoperative level. The juxtapositioning causes a constitutively active transcription factor (*PAX8*) to overexpress the *PPARG* gene, which encodes a nuclear receptor with the ability to interact with cancer-related pathways [192]. *PAX8::PPARG* fusions and *RAS* mutations are mutually exclusive, and the rearrangement is predominantly observed in younger patients with smaller primary tumors [193, 194]. Moreover, FTCs often display alterations in genes related to the *AKT* signaling pathway, such as deleterious *PTEN* mutations, activating *PIK3CA* mutations, and *PIK3CA* copy number gain [195, 196] (Fig. 14). As *PTEN* negatively regulates *PI3K* mediated activation of the oncogenic PI3K-AKT pathway, these alterations lead to augmented *AKT* signaling and tumorigenesis (Fig. 16).

Apart from MAPK and PI3K-AKT signaling pathway alterations, a subset of FTCs may harbor mutations in miRNA processor genes *DICER1* and *DGCR8* [82, 197–199]. The mutations are believed to perturb the maturation of miRNAs, causing dysregulation of various target genes. Interestingly, a genotype–phenotype correlation may be at play for follicular-patterned differentiated thyroid carcinoma, as these cases are overrepresented in terms of *DICER1* mutations [82, 200–202]. As in PTCs, subset of FTCs (15–20%) and IEFVPTC harbors *TERT* promoter mutations, and FTCs with this alteration exhibit a specific transcriptome and miRNA landscape compared to wild type cases [198, 203]. *TERT* promoter mutations are particularly amassed in cases with distant metastases and poorer patient outcomes [37, 174, 204–206] (Fig. 17). Moreover, tumor mutational burden has also been implicated as a prognostic tool in FTC, and this factor was more confident in predicting patient outcome than conventional histological subtyping [199] (Fig. 19).

*Oncocytic carcinomas of the thyroid* are enriched for deleterious mitochondrial DNA (mtDNA) mutations, more specifically genes encoding for complex I electron transport chain proteins [18, 162, 207]. These mutations cause a reduction of ATP generation and lead to an increase in reactive oxygen species, possibly driving tumor formation [17, 162]. Another distinctive feature of oncocytic tumors is the occurrence of genome haploidization leading to uniparental disomy, which usually does not involve chromosomes 5 and 7 (155) (156) [208]. The variable involvement of different chromosomes in individual tumors by this process results in the gross chromosomal alterations frequently reported in oncocytic tumors. These include loss of chromosomes 2, 8, and 22 and gains of chromosomes 7, 12, and 17 [198, 209]. Interestingly, oncocytic thyroid carcinomas with widespread chromosomal aberrations in general may be associated with poorer patient outcomes [161, 210] (Fig. 18).

*Differentiated high-grade follicular cell–derived thyroid carcinoma* (DHGTC) and *poorly differentiated thyroid carcinoma* (PDTC) usually develop through a genetic multistep fashion from a pre-existing well-differentiated thyroid carcinoma and are therefore in large parts driven by established mutations in MAPK or PI3K-AKT signaling pathways associated with the preceding PTC or FTC [132, 211, 212] (Fig. 17). Therefore, DHGTCs and PDTCs exhibit *BRAF*- or *RAS*-like signatures depending on the early driver gene event [73, 146]. As the majority of DHGTCs develop from PTCs, the *BRAF* V600E mutation and PTC-related gene fusions are the most common "early-type" driver gene events in these lesions, while PDTCs are enriched for *RAS* mutations, indicating a relationship to FTCs or EFVPTC [132, 146] (Fig. 19). Of course, DHGTCs and PDTCs acquire numerous additional genetic changes along their path of progression, including *TP53* and *TERT* promoter mutations — of which the latter are associated with higher risk of distant metastases [146, 213] (Fig. 18). In adolescent patients with PDTC, *DICER1* mutations seem common and may reflect a coupling between high-grade features and an underlying disturbance of miRNA regulation [149].

*Anaplastic follicular cell–derived thyroid carcinoma* (ATC) has been clarified by next-generation sequencing and clonality analyses that have increased our understanding of ATCs tremendously. Nowadays, it is acknowledged that the majority of ATCs develop through dedifferentiation from a preceding well-differentiated DHGTC or PDTC, and the driver events are therefore inherited from the more differentiated tumor type [135]. Thus, ATC developing from PTCs or DHGTCs often carry *TERT* promoter mutations

with synchronous *BRAF* mutations, while ATCs arising from FTCs or EFVPTCs usually carry combinations of *RAS* and *TERT* promoter mutations [214]. Moreover, *TP53* gene mutations are commonly reported, as are deletions of *CDKN2A/B* (encoding cell cycle regulators p16 and p14, respectively) [214]. Subsets of ATC with mismatch repair (MMR) gene mutations display a hypermutator phenotype compared to non-MMR gene mutated cases, but the clinical relevance of this observation is not known [150, 215, 216].

*The use of molecular immunohistochemistry* offers tools to enhance diagnosis. Even though pathology laboratories usually do not offer comprehensive genetic analyses in routine clinical practice, it should be stressed that immunohistochemistry can act as a screening tool for specific genetic events in PTCs, not least the mutation-specific BRAF antibody (clone VE1) to screen for V600E alterations, the pan-RAS Q61R (clone SP174) antibody that detects the most common *HRAS/NRAS/KRAS* Q61R mutations as well as pan-TRK staining for *NTRK1/3* fusions and the 5A4 and D5F3 antibodies optimized for the detection of *ALK* fusions (Fig. 20). Notably, the VE1, SP174, and 5A4 antibodies have shown excellent concordance with molecular screening results [217–219]. However, the performance of pan-TRK immunohistochemistry suffers from a lower sensitivity and variable specificity [220]. In a recent study, pan-TRK staining was only positive in 3/7 PTC cases with an *ETV6::NTRK3* fusion, of which two cases only stained focally, while 2/2 *NTRK1* rearranged PTCs were both diffusely positive [183]. Thus, the staining pattern may vary in terms of which *NTRK* gene is rearranged, and staining heterogeneity may also confuse the interpretation.

PTEN immunohistochemistry may be helpful in cases in which Cowden syndrome may be suspected, as global absence of PTEN immunoreactivity in all benign and malignant follicular-patterned neoplasms is indicative of this syndrome [221, 222]. Moreover, loss of 5-hydroxymethylcytosine (5-hMC) seems to correlate with the presence of a *TERT* promoter mutation in thyroid cancer and may therefore be a promising immunohistochemical triaging marker — especially as TERT protein immunohistochemistry itself seems unreliable in this context [223, 224].

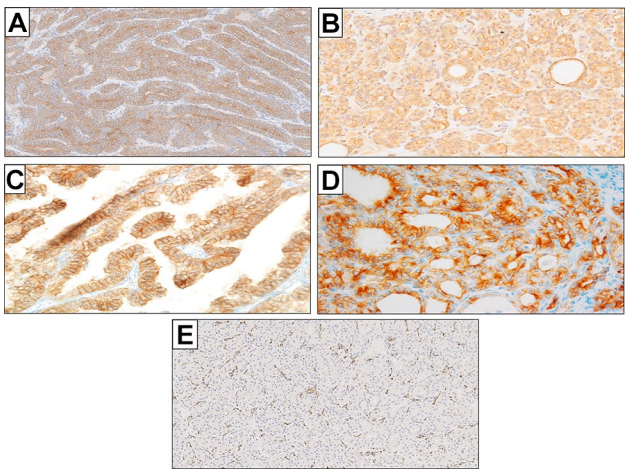


**Fig. 20** Molecular immunohistochemistry in follicular cell–derived thyroid carcinoma (FCDTC). Immunohistochemistry may aid in identification of molecular aberrancies with prognostic and/or therapeutic importance. **A** Mutation-specific BRAF antibody (clone VE1) detecting a *BRAF* V600E mutation in a tall cell variant PTC. **B** The pan-RAS Q61R (clone SP174) antibody, indicating an underlying *HRAS/NRAS/KRAS* Q61R mutation. **C** Positive pan-TRK staining indicating an *NTRK1/3* fusion. **D** The ALK 5A4 antibody optimized for the detection of therapeutically relevant *ALK* fusions. **E** PTEN global loss in a follicular patterned PTC is illustrated. This specimen had several PTEN-immunodeficient follicular patterned nodules. Subsequently, the patient was found to harbor germline pathogenic *PTEN* variant, consistent with PTEN-hamartoma tumor syndrome

## Question 9: What Is New in the Field of Medullary Thyroid Carcinoma?

The most important update for medullary thyroid carcinoma in this WHO edition is the introduction of a grading scheme. Since the definitive histologic description of medullary thyroid carcinoma in 1959 [225], there has been no widely recognized histopathological grading system for this entity. In 2020, two groups independently developed grading schemes for medullary thyroid carcinoma based on proliferative activity (mitotic count and Ki67 proliferative index) and tumor necrosis [143, 144]. The study of Al-Zumailli et al. is based on a two-tiered system with high-grade tumors defined by the presence of tumor necrosis and/or ≥ 5 mitoses per 10 high-power fields, 400 × (equivalent to approximately 2 $mm^2$ in most microscopes) [143]. Fuchs et al. designed a three-tiered grading scheme based on mitotic count, Ki67 proliferative rate, and tumor necrosis with different cutoffs [144]. Both systems were shown to be independent predictors of outcome [143, 144]. The prognostic significance of these grading systems was also validated in an independent cohort [226]. Subsequently in 2021, an international study of 327 medullary thyroid carcinoma patients developed a two-tiered grading system named "The international medullary thyroid carcinoma grading scheme." In this system, high-grade tumors are defined as having at least one of the three following features: tumor necrosis, mitotic count ≥ 5 per 2 $mm^2$, and/or a Ki67 proliferation index ≥ 5% [226] (Fig. 21). Twenty-five percent of medullary thyroid carcinoma patients had high-grade tumors using this scheme. This two-tiered grading system was independent from AJCC 8th edition stage grouping, age, sex, tumor size, margin status, post-operative calcitonin and CEA serum levels in predicting locoregional recurrence, distant metastasis-free, disease-specific, and overall survival [226]. Although this grading scheme is independent from germline *RET* mutation

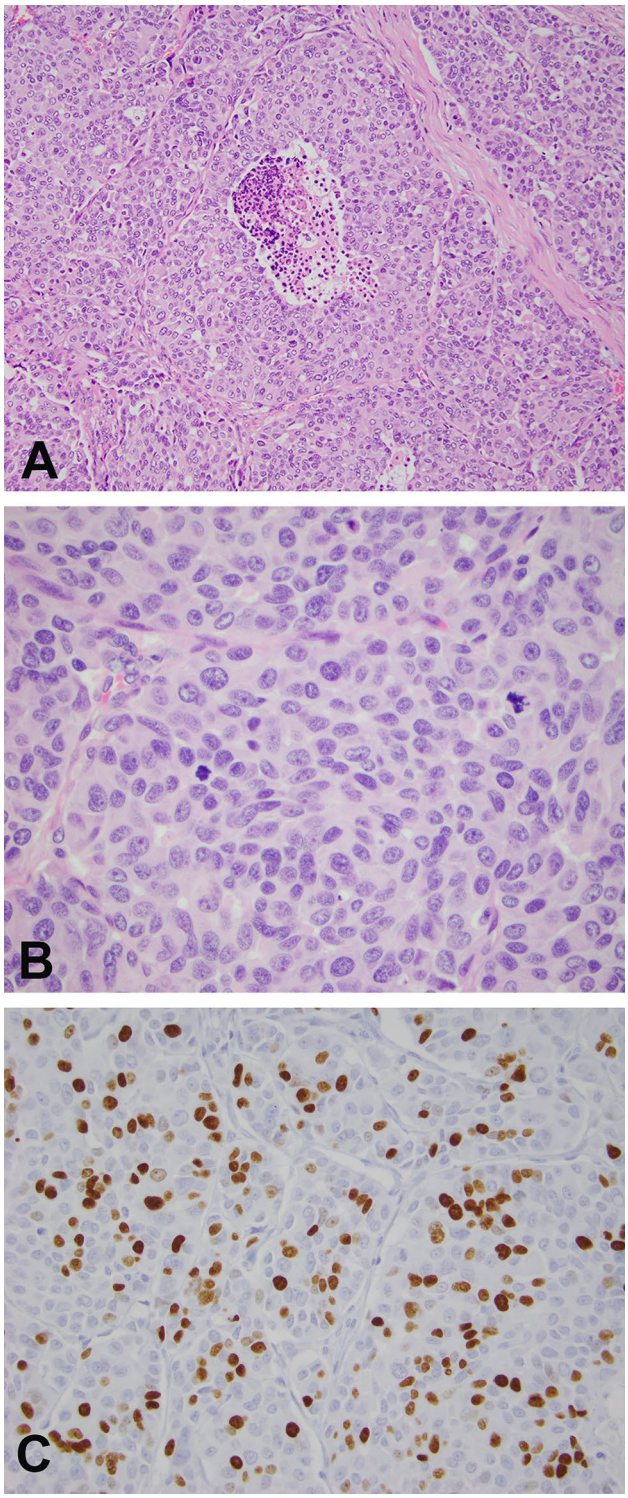


**Fig. 21** Example of a high-grade medullary thyroid carcinoma. Tumor necrosis is present (**A**). The mitotic count was 16 per 10 high-power fields (~2 $mm^2$), with readily apparent mitoses present as seen in this field (**B**), and the Ki67 proliferative index was 35% (**C**)

status in predicting outcome, its prognostic value vis-à-vis the mutations found in sporadic medullary carcinoma is still not known. In a study of 44 sporadic medullary carcinomas graded on the basis of the original 2020 publications (based on mitotic count, tumor necrosis and Ki67 proliferative rate) [143, 144], there was no correlation between grade and *RET* or *RAS* mutation status [226]. However, larger studies are needed to investigate whether there is a correlation between genotype and grade in sporadic medullary thyroid carcinomas. Because tumor necrosis can be focal, it is essential to generously sample these tumors and grading of biopsies is thus not recommended. In addition to reporting histologic grade and tumor necrosis, the precise mitotic count and Ki67 index should be recorded (both should be based on the area of tumor with highest proliferative activity). In fact, mitotic count and Ki67 proliferative rate are continuous variables; as each variable increases, outcome worsens [145]. Because of its robust independent value, this novel histologic grade may benefit high-grade patients leading to closer follow-up, low thresholds for cross-sectional imaging, and careful monitoring for distant metastasis [145]. Additionally, this histologic grade can be used as a data point in clinical trials of adjuvant therapy since it is likely that adjuvant therapy will have greatest benefit in high-grade medullary carcinomas [145].

## Question 10: The Categories of "Salivary Gland–Type Neoplasms" and "Thymic Tumors Within the Thyroid" Represent a New Approach — What Information Prompted These Changes?

The 5th edition of the WHO classification of endocrine tumors has introduced minor changes and a new approach in the chapters on "salivary gland–type neoplasms" and "thymic tumors within the thyroid." Awareness of these very rare primary tumors is relevant for appropriate diagnostic and therapeutic decisions. The group of salivary gland tumors includes mucoepidermoid carcinoma with its subtype "mucinous carcinoma," and the secretory carcinoma (corresponding to former mammary analogue secretory carcinoma). These are very rare entities with 48 and 12 reported cases, respectively [227, 228]. Sclerosing mucoepidermoid carcinoma with eosinophilia shares some features with the above tumors, but has currently been classified within the group of uncertain histogenesis tumors. Intra- or perithyroidal thymic tumors are grouped under the umbrella of thymic tumors and thymoma and spindle epithelial tumor with thymus-like elements and thymic carcinoma.

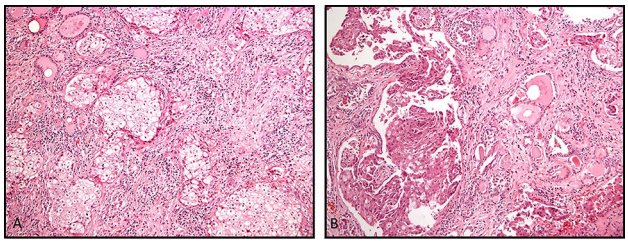

**Fig. 22** Mucoepidermoid carcinoma of thyroid, an infiltrative tumor (**A**) showing mucinous, intermediate, and squamoid tumor cells, having a solid or cystic growth pattern

*Mucoepidermoid Carcinoma.*

*Mucoepidermoid carcinoma* (MEC) has been defined as a malignant neoplasm of salivary gland type, characterized by mucinous, intermediate, and squamoid tumor cells, having a solid or cystic growth pattern (Fig. 22). Generally, epidermoid cells are cytologically bland and predominate over mucocytes in the dense fibrotic stroma of the tumor, although the proportion of each component can vary significantly. In fact, the very rare mucinous carcinoma of the thyroid has been incorporated in this entity, at the one extreme dominated by glandular differentiation, signet ring features [13], and accumulation of extracellular mucin among neoplastic cells [13].

The histogenesis of MEC is controversial; a link to ectopic salivary gland tissue or solid cell nests has been suggested. Nevertheless, up to half cases are associated with a conventional PTC or, more rarely, a follicular or oncocytic carcinoma and to lymphocytic thyroiditis. Thus, squamous metaplasia is the currently favored precursor event [229]. Immunohistochemistry may help confirm this diagnosis with cytokeratin and p63 expression, in the absence of neuroendocrine markers and calcitonin. Conversely, follicular lineage markers are expressed in a fraction of cases only, including thyroglobulin, TTF1, and PAX8. The separation of this rare tumor type from conventional thyroid tumors seems therefore justified, also based on its indolent behavior and favorable outcome after surgery [229–231], with extremely rare aggressive cases reported, usually in association with anaplastic carcinoma transformation [232–236]

*Secretory Carcinoma.*

Although only 12 cases are on record in the English literature [227–229], secretory carcinoma (SC) of the thyroid gland (also known as mammary analog of secretory carcinoma) has been incorporated in the new WHO classification of thyroid tumors as part of the salivary gland–type neoplasms. It is both morphologically and genetically similar to its mammary and salivary gland counterparts and does not share the histological and immunophenotypical features of differentiated follicular cell–derived carcinomas (Fig. 23). Rather, it contains specific molecular alterations involving the *ETV6* gene. Analogous to SC of other sites,

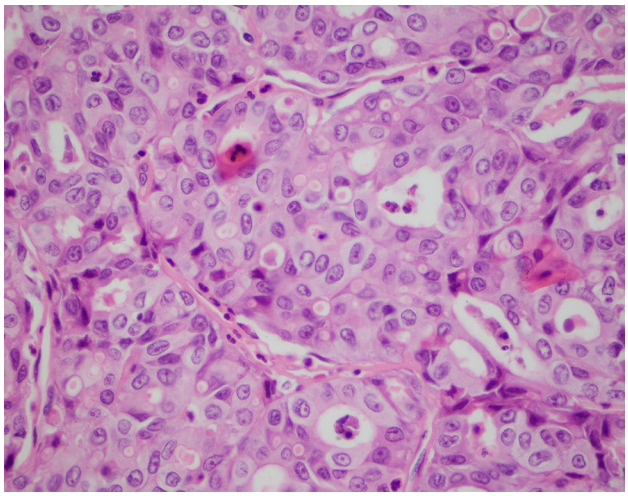

**Fig. 23** Secretory carcinoma of thyroid showing a solid and microcystic growth of eosinophilic cells with vacuolated, "bubbly" cytoplasm. Nuclear atypia is bland and occasional nuclear clearing and contour irregularities are seen

the diagnostic hallmarks include a solid, papillary, tubular, or microcystic growth of eosinophilic cells with vacuolated, "bubbly" cytoplasm; rare cases may show high-grade features [237]. Nuclear atypia is bland, and occasional nuclear clearing and contour irregularities can be detected. Immunohistochemically, SC is diffusely reactive for GATA3, mammaglobin, and S100 [83] in the absence of thyroglobulin, TTF1, and PAX8 expression [238]. Cases associated with PTCs have been reported [239].

*ETV6* translocations are the hallmark of SC, with fusion products with *NTRK3*. As a consequence, these carcinomas may respond to targeted therapy with TRK inhibitors [83, 227]. In a salivary gland SC series, a novel fusion of *ETV6* with *RET* was detected [240], but this alteration has not been reported in the thyroid, yet. Apart from these novel treatments, primary thyroid SC follows a more aggressive course than that of other locations, with locoregional recurrences and distant spread in up to 30% of cases [227–229, 241].

*Intrathyroid Thymic Tumors.*

Compared to the WHO 2017 classification [3], no major changes occurred in the new WHO scheme: three types of thymic tumors in the thyroid region are described, with benign and malignant tumors sharing a thymic epithelial differentiation included under the term "thymoma family" and "thymic carcinoma family." They are postulated to develop from either ectopic thymus (but the term "ectopic" has been discouraged) or from branchial pouch remnants differentiating along the thymic line. Hassall bodies may in fact be seen at the periphery of these tumors [13].

Thymomas develop within or attached to the thyroid, generally in the left lower lobe portion, from embryological remnants. Histologically, they resemble their mediastinal

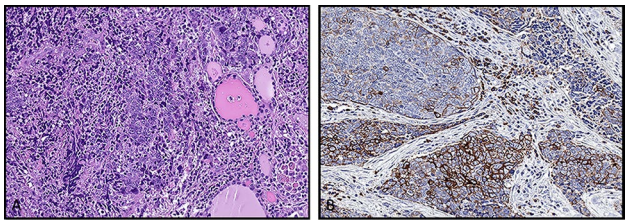

**Fig. 24** Intrathyroidal thymic carcinoma — an infiltrative tumor with solid growth pattern composing of polygonal medium size lesional cells in a lymphocytic background (**A**). The majority of tumor cells express CD5 with variable intensities (**B**)

counterparts, all subtypes being represented, with solid or lobular growth of cuboidal, spindled, or squamoid cells in a loose stroma infiltrated by immature, TdT-positive, T lymphocytes [242–246]. Rare cases are invasive, but most are well circumscribed or encapsulated tumors, occasionally entrapping thyroid follicles, and after surgery follow an uneventful course [242, 247].

*Intrathyroidal spindle epithelial tumor with thymus-like elements* (SETTLE) is a rare malignant tumor generally arising in the pediatric age or in young male adults with less than 50 cases reported in the literature [248–250]. Histologically, a lobulated growth of two epithelial cell types with spindle or cuboidal shape (the latter arranged in tubules, papillae or glands) is observed [251–254]. Tumor cells have low-grade atypia and a low proliferative activity, which helps to distinguish this tumor from sarcomas, medullary carcinoma, and sarcomatoid anaplastic carcinoma. No recurrent molecular alterations have so far been identified [255]. SETTLE has a relatively good prognosis with over 80% 5-year survival rate, although cases with locoregional and distant metastases (mostly to the lung) are on record [256, 257].

*Intrathyroid thymic carcinoma* (ITC) is a malignant tumor with thymic epithelial differentiation that affects the adult population with a slight female preponderance and a high occurrence in Asians. It develops in intra- or perithyroidal regions, generally in the lower poles as a firm, solid mass of variable size [13, 258]. The old terminologies CASTLE and lymphoepithelioma-like carcinoma are no longer recommended in the new WHO classification. Histologically, ITC shares the orthotopic thymic carcinoma features, with a lobulated growth of squamous (keratinizing or basaloid) epithelial cells in a desmoplastic stroma infiltrated by lymphocytes and plasma cells [253, 259–261] (Fig. 24). Tumor cells have poorly defined cell borders, mild nuclear atypia, distinct nucleoli, and a low proliferative activity. The ITC immunophenotype includes expression of cytokeratins, CD5, p63, CD117, CEA, p53, and bcl-2, in the absence of thyroid follicular markers (thyroglobulin, TTF1) and of EBV-related markers (EBER) [258]. Recurrent *TERT* promoter mutations have been reported in ITC, but not in mediastinal thymic carcinomas [262]. ITC is a relatively indolent neoplasm associated with a median disease-free survival of 144 months (and median overall survival not reached), as reported in a pooled analysis of 132 cases [263].

**Molecular Profile and Ancillary Tests:** Regarding salivary gland–type carcinomas, the demonstration of *MAML2* rearrangements in MEC and of *ETV6::NTRK3* fusions in secretory carcinoma may be helpful to confirm the diagnosis of these cases [238, 240, 264]. Nevertheless, no molecular profiling is essential to reach a correct diagnosis. At this moment, no molecular tests are required for the diagnostic classification of thymomas, SETTLE, and intrathyroid thymic carcinomas.

## Question 11: Why Were Sclerosing Mucoepidermoid Carcinoma with Eosinophilia and Cribriform-Morular Thyroid Carcinoma Reclassified as Tumors of Uncertain Histogenesis? What Are the Clinicopathological Characteristics of These Tumors?

The tumor previously known as the "cribriform-morular variant of papillary thyroid carcinoma" can be associated with familial adenomatous polyposis (FAP) or may occur as a sporadic form. It was originally classified as a subtype of papillary carcinoma because of the presence of papillae and in some instances diagnostic nuclear features (Fig. 25). Several studies have shown that this tumor has a molecular profile distinct from follicular cell–derived thyroid carcinoma. In contrast to the latter that harbor mutations in the MAPK pathway (e.g., *BRAF*, *RAS*), these tumors do not display *BRAF* V600E mutations [265] and only rarely have *RAS* or *PIK3CA* mutations [266, 267]. Almost all cribriform-morular tumors have genetic alterations in the Wnt/beta-catenin pathway [265] with *APC* mutations being the most common and found in both the familial and sporadic setting [266, 267]. Mutations in other genes involved in the Wnt/Beta-catenin pathway such as *CTNNB1* have also been detected [266, 267]. By immunohistochemistry, these tumors show diffuse cytoplasmic and nuclear beta-catenin expression. In addition, a recent study from two institutions questioned the follicular cell derivation of this neoplasm since it often lacks PAX8 and thyroglobulin expression while retaining TTF1 protein only in the cribriform elements [268]. The cribriform areas also express estrogen and progesterone receptors. The morulae are positive for CD5, CK5, CDX2, and CK5, but lack TTF1 expression [268] (Fig. 25).

For the above reasons, the tumor nomenclature was changed to "cribriform-morular thyroid carcinoma" in the new WHO classification scheme and the tumor is now classified under the umbrella of thyroid tumors of uncertain histogenesis.

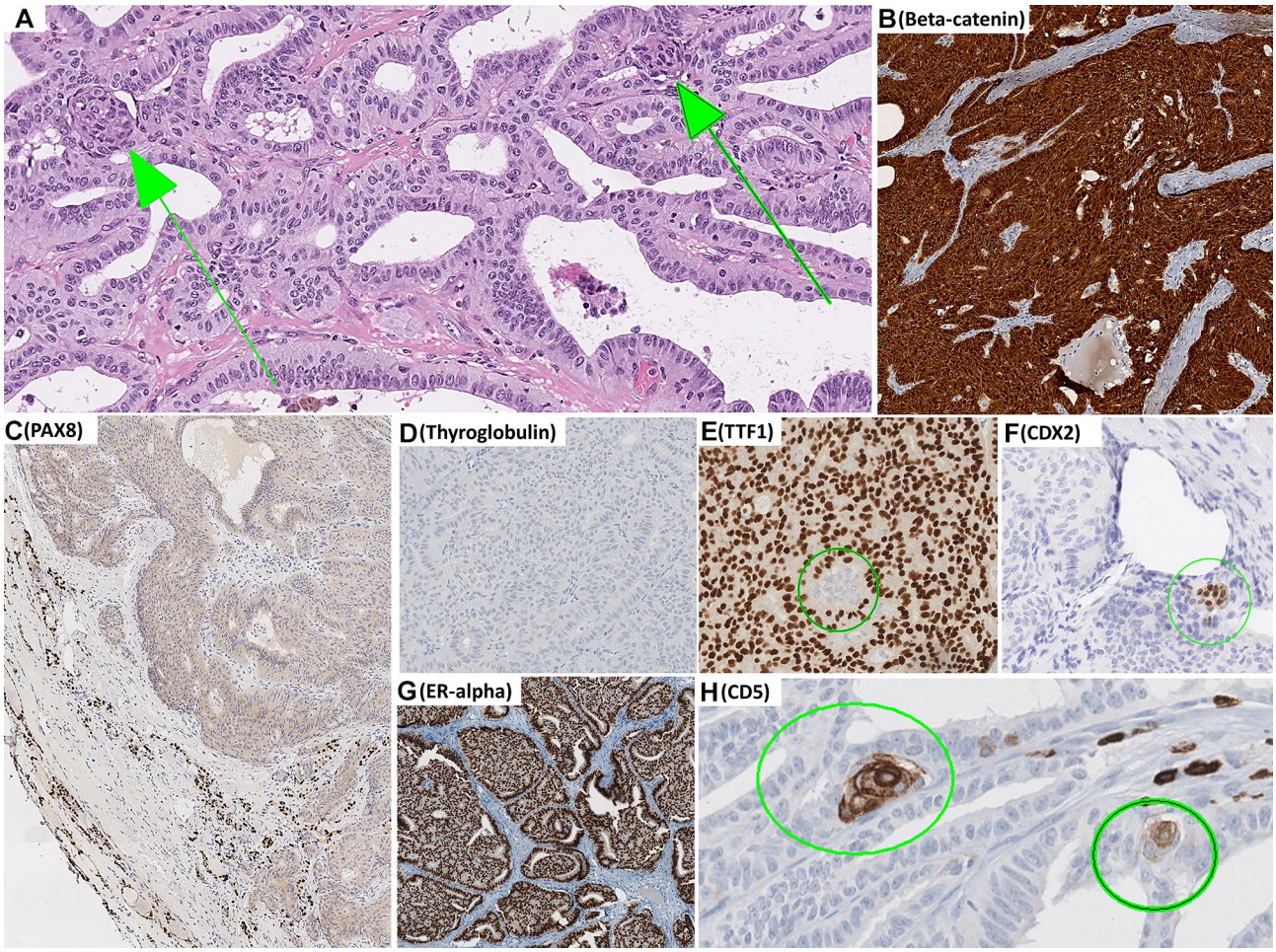


**Fig. 25** Cribriform-morular thyroid carcinoma. Tumor displays complex cribriform architecture with focal morulae (**A**; arrows indicate morulae). The hallmark of this tumor is the diffuse nuclear and cytoplasmic beta-catenin expression (**B**). Unlike follicular cell–derived thyroid carcinomas with differentiated architecture, these tumors are often negative for PAX8 (**C**) and typically negative for thyroglobulin (**D**). The cribriform component is diffusely positive for TTF1, whereas the morulae are negative for TTF1 (**E**; morular structure highlighted) and positive for CDX2 (**F**; morular structure highlighted). These tumors tend to show estrogen receptor expression (**G**). The morulae are also positive for CD5 (**H**; morular structure highlighted). Scattered intratumoral lymphoid cells also express CD5 (**H**)

*Sclerosing mucoepidermoid carcinoma with eosinophilia* (SMECE) is a rare thyroid tumor with less than 60 reported cases, characterized by a morphology partially overlapping with that of MEC, in association with a marked infiltration of lymphocytes and eosinophils in the fibrotic stroma [13, 228] (Fig. 26). A background of thyroiditis is usually observed. Association with papillary carcinoma is reported in 20% of cases. The immunoprofile resembles that of MEC with no expression of follicular markers, except for TTF1 in half of the cases [228, 245, 269–272] A few genotyped cases of SMECE lack the typical genetic alteration of mucoepidermoid carcinoma of salivary gland (i.e., *MAML2* translocation) [270, 273]. Associations with anaplastic thyroid carcinoma [274] and with NUT carcinoma [275] have been reported.

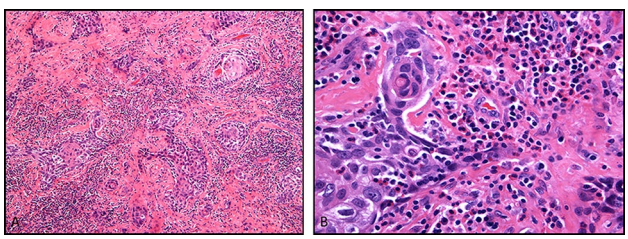

**Fig. 26** Sclerosing mucoepidermoid carcinoma with eosinophilia of thyroid tumor cells with squamous differentiation arranged in cords, tubules, and nests with marked infiltration of lymphocytes and eosinophils in the fibrotic stroma

The histogenesis of this low-grade malignant tumor is debated and the new WHO classification included this entity among tumors of uncertain histogenesis. An origin from ultimobranchial cells is favored, but the genomic profile has not identified gene alterations associated with either

MEC or PTC [245, 270, 275], with rare exceptions [274, 276]. Mutations typical of follicular cell–derived thyroid carcinomas such as *BRAF* V600E have also not been found [245]. While some have hypothesized a follicular cell origin through the mechanism of squamous metaplasia of the follicular epithelium [277], this view is not supported by the lack of PAX8 and thyroglobulin positivity [228]. Because of the presence of p63 in the tumor, some authors have favored an origin from solid cell nests [278] while other investigators acknowledge that the origin of this rare carcinoma is unknown [228].

In view of the above, a definite classification of this rare primary thyroid tumor is not yet possible. Thus, in the 5th edition of the WHO blue book, SMECE is classified under thyroid tumors of uncertain histogenesis.

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**Availability of Data and Material** Not applicable.

## Declarations

**Ethics Approval** Not applicable

**Consent for Publication** All authors consent to publication.

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## Authors and Affiliations

**Zubair W. Baloch[1] · Sylvia L. Asa[2] · Justine A. Barletta[3] · Ronald A. Ghossein[4] · C. Christofer Juhlin[5,6] · Chan Kwon Jung[7] · Virginia A. LiVolsi[1] · Mauro G. Papotti[8] · Manuel Sobrinho-Simões[9] · Giovanni Tallini[10,11] · Ozgur Mete[12]**

✉ Zubair W. Baloch
baloch@pennmedicine.upenn.edu

1 Department of Pathology & Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

2 Department of Pathology, University Hospitals Cleveland Medical Center, Case Western Reserve University, Cleveland, OH, USA

3 Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

4 Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

5 Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden

6 Department of Pathology and Cancer Diagnostics, Karolinska University Hospital, Stockholm, Sweden

7 Department of Hospital Pathology, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

8 Department of Oncology, University of Turin, Torino, Italy

9 Department of Pathology, Institute of Molecular Pathology and Immunology, IPATIMUP, University of Porto, Porto, Portugal

10 Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy

11 IRCCS Azienda Ospedaliero-Universitaria Di Bologna, Bologna, Italy

12 Department of Pathology, University Health Network, University of Toronto, Toronto, ON, Canada