The new 4th edition World Health Organization classification for thyroid tumors, Asian perspectives

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The new World Health Organization (WHO) classification of endocrine organs was published in 2017 and several amendments were made to the classification of thyroid tumors. The introduction of borderline category, including uncertain malignant potential (UMP) and noninvasive encapsulated follicular neoplasm with papillary-like nuclear features (NIFTP), significantly impacted pathology practice. The risk stratification of both papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) was emphasized as one of the most important elements in pathology reports to overcome the current problems of over diagnosis and over treatment of low-risk thyroid carcinomas. Follicular-patterned neoplasms (RAS-like tumors) were further classified into 6 prognostic groups [follicular adenoma, UMP and NIFTP, minimally invasive FTC, encapsulated angioinvasive FTC, widely invasive FTC and poorly differentiated carcinoma (PDC)]. In the PTC lineage (BRAF-like tumors), identification of aggressive variants and other prognostic factors were emphasized as they can only be judged by pathologists. PDC was defined with Turin consensus criteria more precisely, and PTC with solid/trabecular growth without high grade features was downgraded to solid/trabecular variant of PTC. Lastly, this review proposes a pathology reporting system from the perspective of Asian pathologists, which covers risk stratification recommended by the American Thyroid Association and new WHO classification of thyroid tumors. This review further introduces publications on Asian patient series treated by standard Asian thyroid practice. The authors consider these studies to provide a guide to current Asian thyroid practice, which cannot be supplemented by data elucidated from Western practice.

Key words: borderline tumor, follicular cell, pathology report, prognostic factors, risk stratification, thyroid carcinoma

The World Health Organization (WHO) classification of tumors serves as an international standard of histopathological diagnosis and the essential basis of clinical practice for neoplastic diseases for all organ systems. The 4th edition WHO Classification of Tumors of Endocrine Organs was published in 2017, in which the new thyroid tumor classification was included. Several important modifications to follicular cell tumors were made to the new WHO classification of thyroid tumors, as listed in Table 1. In this review, thyroid follicular cell tumors (follicular-patterned neoplasms, papillary thyroid neoplasms and de-differentiated carcinomas) were reviewed and important changes were highlighted. Thus, non-follicular cell tumors were excluded from this review. As a new borderline tumor entity, noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) was detailed separately in an editorial published in this journal, Pathology International, and was also excluded from this review.

This review further introduces publications on Asian patient series treated by standard Asian thyroid practice. The author
Table 1  Major revisions to thyroid follicular cell tumors in the new 2017 WHO Classification of Tumors of Endocrine Organs

1. Introduction of borderline tumors [UMP (uncertain malignant potential), NIFTP (noninvasive follicular thyroid neoplasm with papillary-like nuclear features) and HTT (hyalinizing trabecular tumor)] in the thyroid tumor classification.
2. Histological variants of papillary carcinoma (PTC) were emphasized which may have more aggressive biological behavior or may related to hereditary tumor syndrome.
3. Follicular carcinoma (FTC) was divided into three prognostic categories, minimally invasive (capsular invasion only), encapsulated angioinvasive and widely invasive.
4. Poorly differentiated carcinoma (PDC) was defined with Turin consensus criteria more precisely for its histopathological diagnosis, and PTC with solid growth without increased mitosis and/or tumor necrosis were removed from PDC and was placed in PTC as an aggressive variant (solid variant of PTC).
5. A new chapter of Hürthle cell (oncocytic) tumors was established acknowledging the peculiar biological and clinical features.
6. Prognostic value of genetic markers such as BRAF\textsuperscript{V600E} and TERT promoter mutation in thyroid carcinoma of follicular cell derivation were emphasized and detailed.
7. Entire tissue sampling and analysis of the interface between the tumor and its surrounding thyroid parenchyma was emphasized in the WHO classification.

considers these studies to provide a guide to current Asian thyroid practice, which cannot be supplemented by data elucidated from Western practice. This is because there are significant and irreconcilable differences between Asian and Western practices for management of thyroid nodules and thyroid cancer. These differences include the following: (i) Asian patient populations live in mostly iodine sufficient countries and the histological type of the majority of thyroid carcinoma is papillary thyroid carcinoma (PTC); (ii) the prevalence of the BRAF\textsuperscript{V600E} point mutation in Asian PTC cohorts is higher than that reported from Western countries;\textsuperscript{3,4} (iii) it is well-known that significant numbers of patients with low-risk papillary microcarcinoma (PMC) are treated conservatively (active surveillance) in Asia instead of by immediate surgery;\textsuperscript{5–9} (iv) resection of indeterminate thyroid nodules is quickly selected in Western practice and diagnostic surgery is more common to prevent missing malignancy due to medicolegal reasons in Western practice;\textsuperscript{10–16} and (v) approaches for low-risk thyroid carcinoma (lobectomy instead of total thyroidectomy) are more conservative in Asia.\textsuperscript{17–23} Therefore, many important publications from Asia were not well acknowledged in the WHO classification or in most Western clinical guidelines, as those data obtained from Asian practice are not reproducible in current Western practice.\textsuperscript{21–23} A review of Asian reports is important for readers practicing in Asia, and the author believes that it is not only essential to Asian practice but also to the future of Western practice because clinical management in some Western practices resembles current Asian practice, termed a multidisciplinary approach,\textsuperscript{12,13,20–26} as well as help to bridge the gaps between practices.\textsuperscript{21–23} Furthermore, this review provides a pathology reporting check list that adapts the new WHO classification of thyroid tumors and risk stratification of differentiated thyroid carcinomas recommended by the American Thyroid Association (ATA).\textsuperscript{1,12,13} One of our special missions was making a bridge between histopathological classification and clinically-relevant risk stratification of thyroid tumors.

WHAT IS NEW IN THE THYROID TUMOR CLASSIFICATION BY THE 4TH EDITION WHO CLASSIFICATION, TUMORS OF ENDOCRINE ORGANS?

There have been only a few review articles in English covering the new WHO classification of thyroid tumors.\textsuperscript{27–31} The topics these review articles were: (i) the introduction of borderline tumors (UMP and NIFTP) in thyroid tumor classification;\textsuperscript{32,33} (ii) PTC comprising 15 variants, and a new (hobnail) histologic variant being included;\textsuperscript{34} (iii) follicular thyroid carcinoma (FTC) being subdivided into three prognostic groups: minimally invasive (capsule invasion only), encapsulated angioinvasive and widely invasive; (iv) Hürthle/oncocytic cell tumors being separated from follicular adenoma/carcinoma (FA/FTC) in an independent chapter as it has a different genetic profile from those of the other types of thyroid cancer;\textsuperscript{35} (v) the diagnostic criteria of poorly differentiated carcinoma (PDC) being more precisely defined and adopting the Turin consensus criteria;\textsuperscript{36} (vi) emphasizing the prognostic value of genetic markers, such as BRAF\textsuperscript{V600E} and telomerase reverse transcriptase (TERT) promoter mutation, in thyroid carcinoma of follicular cell origin; and (vi) emphasizing examination of the entire capsule to identify or exclude invasiveness in encapsulated thyroid tumors\textsuperscript{37–41} (Table 1).

FOLLICULAR ADENOMA AND BORDERLINE TUMORS

After the introduction of borderline tumors, the definition of FA was altered and “without nuclear features of PTC (PTC-N)” was added.\textsuperscript{1} FA is a benign, encapsulated and noninvasive neoplasm demonstrating evidence of thyroid follicular cell differentiation without PTC-N. The differential diagnoses include benign hyperplastic nodule, encapsulated noninvasive PTC and minimally invasive FTC. Differential diagnosis between hyperplastic nodule and FA is not always possible without molecular studies (polyclonal proliferation vs. monoclonal
neoplasm), but it is not important clinically because both lesions are benign. Differential diagnosis between FA and malignant encapsulated carcinomas (FTC and PTC) is difficult and has caused significant observer variability in the past. The borderline tumor category was proposed to solve this diagnostic difficulty for pathologists. According to the current ATA clinical guidelines, NIFTP is a surgical disease. It requires surgical removal and histological evaluation, because it is a precursor in definition and should be removed under the Western logic. However, in Asian perspectives, accurate distinction between FA and borderline tumors (UMP and NIFTP) is not important clinically, and under-diagnosis of borderline tumors as FA does not harm to the patients because both can be treated by simple excision and cured. Most importantly, pathologists must consider a benign diagnosis first when an encapsulated thyroid nodule is limited to within the thyroid gland (intrathyroidal). Under-diagnosis of intrathyroidal encapsulated carcinomas as borderline tumors or benign tumors does not seriously harm the patients. Even if they are found to be malignant tumors and adverse events develop, they can be managed curatively as long as they are encapsulated and intrathyroidal tumors (exO, N0 and M0). In our Asian and Australasian experience, the vast majority of borderline tumors are diagnosed in the benign category (FA), and clinically significant cancers are rarely missed using this conservative approach. However, some intrathyroidal tumors are true malignant tumors and have a non-negligible risk for structural disease recurrence, such as non-encapsulated 2-4 cm PTC (5% of recurrence) and BRAF mutated <4 cm PTC (10% of recurrence), but they can be detected preoperatively by applying a multidisciplinary clinical approach by experienced clinicians and pathologists.

Take home message

We propose here a new tumor entity, low-risk intrathyroidal neoplasia, which encompasses thyroid follicular cell tumors currently classified in different categories, benign (FA), borderline (UMP and NIFTP) and low-risk thyroid follicular cell carcinoma (PMC, minimally invasive FTC and encapsulated PTC), which have a very low risk of disease recurrence after a complete excision (curative with lobectomy alone). The authors consider this terminology (low-risk intrathyroidal neoplasia instead of cancer) helpful for clinical colleagues to more easily understand that limited surgery (lobectomy) is sufficient to cure these low-risk intrathyroidal neoplasms, and aggressive cancer treatment (total thyroidectomy followed by radioactive iodine treatment) is not necessary. We also believe it can alleviate the psychological burden of a cancer diagnosis in patients.

PAPILLARY THYROID CARCINOMA

The definition of PTC in the 2004 WHO classification (the 3rd edition) was “a malignant epithelial tumor demonstrating evidence of follicular cell differentiation and characterized by distinct nuclear features” and it was changed to “PTC is a malignant epithelial tumor demonstrating evidence of follicular cell differentiation and a set of distinct nuclear features. PTC is usually invasive. Papillae, invasion or cytological features of papillary thyroid carcinoma are required” in the 2017 WHO classification (the 4th edition). These modifications were based on noninvasive encapsulated follicular variant PTC being reclassified into the borderline tumor (non-malignant) category (NIFTP) and encapsulated follicular variant PTC with incomplete capsular/lympho-vascular invasion being reclassified into the borderline tumor category [well differentiated thyroid tumor of uncertain malignant potential (WDTP-UMP)]. However, these tumors [invasive (PTC), incomplete invasive (WDTP-UMP) and noninvasive (NIFTP)] were still classified in malignant tumors as intrathyroidal encapsulated follicular variant PTC in the 2015 ATA guidelines. This was caused by several previous publications by eminent thyroid experts who emphasized that ground-glass nuclei were diagnostic for PTC-type malignancy even in noninvasive encapsulated follicular-patterned (non-papillary) thyroid nodules. Encapsulated thyroid tumors with worrisome PTC-N would have been previously referred to as PTC even in noninvasive encapsulated follicular-patterned (non-papillary) thyroid nodules in cases without invasion and/or metastasis. Significant numbers of patients with such tumors were treated aggressively, particularly in North American practice, because the 2009 ATA guidelines recommended that all PTC larger than 1 cm be treated by total thyroidectomy. However, many pathologists raised a concern regarding classifying noninvasive encapsulated follicular pattern nodules with worrisome PTC-N as cancer. After publication of the 2017 WHO classification, the identification of definite invasion, as well as the demonstration of well-developed PTC-N and true papillae have become essential components in the diagnosis of PTC. Even for encapsulated thyroid nodules with unequivocal papillae, identification of invasion, fully developed PTC-N or Braf mutation are required for a diagnosis of encapsulated conventional PTC to exclude FA with papillary hyperplasia. These stricter diagnostic criteria for encapsulated PTCs were intended to reduce overdiagnosis of indolent thyroid tumors and proper identification of aggressive variants of PTC which develop high rates of disease recurrence (Table 2).
VARIANTS OF PTC AND THEIR PREVALENCE

In addition to conventional (classic, common or usual) type PTC, 14 variants (Table 2) were listed in the new WHO classification of thyroid tumors.1 The prevalence of these variants varies among patient populations, but PMC, encapsulated, follicular and tall cell variants are relatively more common than other variants. PMC comprised more than half of the surgically treated PTC in some patient series.1,5,56,61 Follicular variant PTC is a prevalent histological variant in Western experience, and was reported to comprise 37.9% of all PTC in five Italian and American hospitals reported by Nikiforov et al.33 and 17.9% in a large international collaborative study (1126/6282 cases from 14 countries) by Shi.62 However, it was much rarer, 4.0% (2.2–9.8%), in a recent large multi-institutional Asian series.63 In the 2017 WHO classification, the prevalence of encapsulated variant PTC accounted for approximately 10% of all PTC and the solid variant constitutes 1–3% of adult PTC1 (Table 2). In a review by Fagin and Wells, 84% of all thyroid carcinomas were PTC, 33% were PMC, 32% were classic PTC, all follicular variants accounted for 27% (6% infiltrative, 4% encapsulated invasive and 17% encapsulated without invasion = NIFTP) and the tall cell variant accounted for 7% of PTC in the USA64 (Table 2).

PAPILLARY MICROCARCINOMA

The definition of PMC is a PTC less than or equal to 10 mm in diameter, regardless of the presence of high-risk features such as \( \text{BRAF}^{V600E} \) mutation, vocal cord paralysis, clinical lymph node metastasis and distant metastasis.1,5,11,56,65–70 Lo et al. suggested that a distinction should be made between clinically overt and occult PMC, despite a relatively good prognosis for PMC.87 Sugitani et al. classified PMC into three prognostic groups: symptomatic PMC with clinically apparent lymph node metastasis and/or vocal cord paralysis was malignant, and had a 30% recurrence rate and a 74.1% rate of cause-specific survival at 10 years, whereas asymptomatic PMC without these features had corresponding rates of 3% and 100%, respectively.8 More recently, a classification of PMCs into incidental and non-incidental obtained more adoption by clinicians and pathologists.71,72 Comprehensive risk stratification of PMC considers a constellation of clinical, pathological, and molecular parameters.70,73 Observation without surgical treatment is practiced for patients with low-risk PMC in several leading medical centers in Japan, Korea and the USA.4–8,68,74,75 Less than 15% of low-risk PMC grow to more than 3 mm or develop lymph node metastasis during follow-up, and most importantly, no thyroid cancer death was reported among more than 1000 patients for more than 10 years of follow-up.4–8,68,74–76 Expert thyroid pathologists proposed calling it papillary microtumor instead of carcinoma,77 and a proposal to classify PMC in the borderline tumor category was reported by Kakudo et al.48 However, papillary microtumor has not become a popular diagnosis among pathologists and clinicians because a significant amount of PMC cases (15–35%) have lymph node metastasis at surgery and rare cases (<0.4%) develop distant metastasis.65–68,71–80

ENCAPSULATED VARIANT PTC

Encapsulated variant is conventional PTC completely surrounded by a fibrous capsule that may be intact or only focally infiltrated by the carcinoma.1 Although regional lymph node metastases may be present, patients with encapsulated PTC have an excellent prognosis with a survival rate of 100% or almost 100%81–85 (Table 2). The differential diagnosis includes FA with papillary hyperplasia, WDT-UMP with minor papillary growth and FTC with incomplete PTC-N (well-differentiated carcinoma, not otherwise specified).

Table 2 Papillary thyroid carcinoma and variants

| Variants | Genetic Alterations | Clinical Behavior | Prevalence (reference) |
|----------|---------------------|------------------|------------------------|
| 1. Papillary microcarcinoma (<1 cm) | \( \text{BRAF}^{V600E} \) | excellent | 33% (64) |
| 2. Encapsulated | not specified | excellent | 1.3% (85), 1.4% (84), 10% (1) |
| 3. Follicular | \( \text{RAS} \) mutation | excellent | 6.9% (153), 5–10% (63), 17.9% (62), 27% (64) |
| 4. Diffuse sclerosing | \( \text{RET/PTC} \) | less favorable | 0.3% (153), 0.4% (103), 0.74% (102), 1.8% (104) |
| 5. Tall cell | \( \text{BRAF}^{V600E} \) | high-risk | 3.8% (62), 3.9% (153), 7% (64), 16.1% (116) |
| 6. Columnar cell | not specified | high-risk | 0.2 (115), 0.4% (153), 1.9% (85), 2.5% (116) |
| 7. Cribriform-morular | \( \text{APC} \) | excellent | 0.1% (153) |
| 8. Hobnail (micropapillary/discohesive) | \( \text{BRAF}^{V600E} \) | high-risk | 0.3% (132, 116), 1.7% (144), 2.7% (133) |
| 9. Fibromatosis/ Fasciitis-like stroma | not specified | no information | 0.06% (153) |
| 10. Solid/Trabecular | \( \text{RET/PTC3} \) (child) | high-risk | 1–3% (1), 1.8% (149), 2.1% (181), |
| 11. Oncocytic | not specified | less favorable | 1.9% (153) |
| 12. Spindle cell | not specified | no information | no information |
| 13. Clear cell | not specified | no information | no information |
| 14. Warthin-like | not specified | no information | no information |
FOLLICULAR VARIANT PTC

Follicular variant PTC is a group of tumors with an exclusively (100%) or almost exclusively follicular pattern of growth, which was subclassified into encapsulated and non-encapsulated (infiltrative) variants. The encapsulated follicular variant PTC was further divided into invasive and noninvasive.

The noninvasive encapsulate follicular variant of PTC was downgraded from carcinoma to NIFTP, and cases with incomplete invasion were downgraded from carcinoma to WDT-UMP in the 4th edition WHO classification, whereas those with definite invasion remain in the malignant category (invasive encapsulated follicular variant PTC) (Fig. 1a).

Follicular variant PTC comprises mostly low grade tumors and RAS-like tumors (Table 2). It can be classified into either borderline (WDT-UMP or NIFTP) or malignant (invasive encapsulated PTC or infiltrative PTC) according to the absence of, incomplete or definite capsular/lympho-vascular invasion.

Take home message

When any exclusion criteria for NIFTP, such as true papillae, psammoma bodies and/or BRAFV600E mutation, are present in noninvasive encapsulated follicular pattern thyroid tumors with PTC-N, they should be excluded from the borderline category and be placed in the malignant category (noninvasive encapsulated follicular variant PTC).

DIFFUSE SCLEROSING VARIANT PTC

Diffuse sclerosing variant PTC is an uncommon variant that is more frequently observed in young females. It is characterized by diffuse involvement of a single lobe or entire thyroid gland. Histologically, squamous metaplasia, stromal fibrosis, lymphocytic infiltration and psammoma bodies are common in the tumor. Marked lymphatic invasion by tumor cells is characterized by a micropapillary/dis cohesive growth pattern simulating the hobnail variant of PTC (Fig. 1b). Recent meta-analysis still considers diffuse sclerosing variant as a high-risk PTC because of a high incidence of extrathyroid invasion at surgery, advanced tumor stage at presentation and bilaterality, however there is an obvious trend in the modern institutional series that diffuse sclerosing variant PTC has no adverse effect on survival.

Figure 1  (a) Invasive non-encapsulated (infiltrative) follicular variant of papillary thyroid carcinoma. Follicular growth lined by cells with large irregular nuclei and pale chromatin are shown among background of normal thyroid follicles. (HE stain, ×20), (b) Diffuse sclerosing variant papillary thyroid carcinoma invading thyroid parenchyma through lymphatic channels. Micropapillary growth, hobnail cytological features and small psammomatous calcifications are seen in floating cell nests in the space. (HE stain, ×10).
According to the definition by the 4th edition WHO classification, tall cell variant PTC is a PTC composed of cancer cells that are 2- to 3-times taller than wide (Fig. 2a). A high incidence of extrathyroid extension at surgery, advanced tumor stage at presentation, older patient age, \textit{BRAF} mutation and \textit{TERT} promoter mutation are noted in tall cell variant PTC. In an international collaborative study, Shi et al. examined 6282 PTC cases, and tall cell variant PTC (3.8%, \( n = 239 \)) had a recurrence rate of 27.3% and mortality rate of 6.7%, whereas conventional PTC (74.8%, \( n = 4702 \)) had a recurrence rate of 16.1% and mortality rate of 2.5% (Table 2).

As the majority of PTC is histological variants in differing proportions, the most recent WHO classification defined that tall cells must account for more than 30% of all tumor cells for a diagnosis of the tall cell variant (revised from the previous definition of more than 50% by the 2004 WHO classification) (Table 3). However, Ito et al. evaluated 70 Japanese cases of tall cell variant PTC (more than 30% tall cells), and found that PTC with more than 50% tall cells significantly and independently affects the disease-free survival, whereas PTC with 30–49% tall cells did not. They concluded that the definition of more than 50% tall cells by the previous WHO classification is appropriate and that the prognostic impact of PTC with tall cell features (30–49%) is limited. In an Italian consensus, 10% was recommended as the cut-off for tall cell features. Therefore, the diagnostic criteria for tall cell variant PTC and other variants of PTC need further verification studies. In particular, what proportion of a certain feature is required for diagnosis, as estimation of % tumor area under a microscope has significant observer variation (Tables 2 and 3). Please refer to the section “How to handle multiple prognostic factors and which more greatly impact patient outcomes” below.

### COLUMNAR CELL VARIANT PTC

Columnar cell variant PTC has tall cell morphology but lacks frequent nuclear pseudoinclusions, eosinophilic cytoplasm, and distinct cell borders, which are common in tall cell variant PTCs (Fig. 2a). Columnar cell variant PTC exhibits prominent nuclear pseudostratification (Fig. 2b) and a poor prognosis. It is a rare subtype of PTC accounting for only 0.15–0.2% of all PTC (Table 2). As typical PTC-type nuclear features are not seen in columnar cell variant PTC, it was excluded from the PTC lineage and classified in other tumors in the Japanese classification of thyroid tumors proposed by the Guidelines for Clinical Practice for the Management of Thyroid Nodules in Japan 2015. The columnar cell variant PTC is difficult to differentiate from metastatic adenocarcinoma, particularly from the endometrium and colon. Carcinoembryonic antigen and TTF1 immunohistochemistry are helpful in distinguishing columnar cell variant PTC from...
metastatic adenocarcinoma of the colon because columnar cell variant PTC is negative for carcinoembryonic antigen and variably positive for TTF1. However, immunocytochemistry for estrogen receptor and CDX2 (intestinal-type differentiation marker) are not useful because they have been found to be positive in some columnar cell variant PTC.\(^{118-121}\) The prognosis of columnar cell variant PTC was revised in the current WHO classification.\(^1\) Encapsulated columnar cell variant PTC has indolent biological behavior, but cases with extrathyroid extension demonstrate aggressive clinical behavior and have a less favorable prognosis\(^ {118,122}\) (Table 2).

CRIBRIFORM-MORULAR VARIANT PTC

Cribiform-morular variant PTC can occur as a manifestation of a familial adenomatous polyposis coli or sporadic form.\(^ {123-127}\) More than half of the cases of this variant occur in patients with familial adenomatous polyposis syndrome and APC gene alteration. Eleven patients (16% female and 0% male) among 129 Japanese familial adenomatous polyposis patients developed cribiform-morular variant PTC.\(^ {127}\) This variant usually develops multiple nodules in the thyroid gland that are encapsulated. Histologically, it is characterized by round squamoid structures called morules and colloid production is present in the follicle lumen (Fig. 3a).\(^ {123,124,128,129}\) Cribiform-morular variant of PTC had a lower frequency of lymph node metastases at presentation (12%) and distant metastases (3%) as well as lower recurrence rates (8.5%) and patients' mortality rates (2%) (Table 2).\(^ {129}\)

HOBNAIL VARIANT PTC (MICROPAPILLARY/DISCOHESIVE-TYPE PTC)

Hobnail variant PTC is a newly added histological variant of PTC and was first introduced in the 4th edition WHO classification of thyroid tumors.\(^1\) Histologically, the hobnail feature consists of complex papillary structures with a fibrovascular core and micropapillary structures lacking a true fibrovascular core. These papillary structures are covered with follicular cells containing eosinophilic voluminous cytoplasm and large apically located nuclei (hobnail, teardrop or comet-like) resulted from the loss of cellular polarity and cellular cohesion (Fig. 3b). As minor hobnail features are often observed in the invasive front of conventional PTC,\(^ {130,131}\) cystic PTC, diffuse sclerosing variant PTC (Fig. 1b) and even PMC, hobnail variant PTC was defined with a cut-off of greater than 30%, which made this variant rare, and its prevalence ranged from 0.3% (South Korea) to 2.7% (Southern Italy)\(^ {132,133}\) (Table 2). The hobnail variant is a moderately differentiated PTC with aggressive behavior and poor prognosis (Table 2), which may be related to the epithelial-mesenchymal transition.\(^ {34,130,131,134-137}\) As the hobnail features (>10%) were often associated with PDC (22%) and anaplastic thyroid carcinoma (ATC) (3.8%), Amatche\(^ {1}\) et al. suggested them to be a manifestation of high-grade transformation.\(^ {138}\) Consequently, some authors suggest that minor hobnail micropapillary features (10–30%) should also be correctly identified and stated in pathology report due to potential aggressive behavior.\(^ {81,130,131,139,140}\)

Hobnail cytological features were first described in PTC by Tang et al. in 2003 as the loss of cellular cohesion/
cellular polarity.\textsuperscript{140} Hobnail features were associated with a high Ki67 labeling index and loss of retinoid receptor expression in PTC.\textsuperscript{140} Later, it was termed micropapillary/discohesive-type PTC by Bai et al., and hobnail features (>10%) were characterized by a high risk of disease recurrence.\textsuperscript{81,130,131,141,142} These tumor cells are typically positive for TTF-1 and variably positive for thyroglobulin. The Ki67 proliferation index was reported to be as high as 10%.\textsuperscript{34} \textbf{BRAF}\textsuperscript{V600E} mutation was common (72.2%), followed by \textbf{TP53} mutation (55.6%) and \textbf{TERT} mutation (44.4%) in an Italian patient cohort.\textsuperscript{137,143} Teng et al. reported 17 cases of hobnail variant PTC in a Chinese cohort, and the prevalence of \textbf{BRAF}\textsuperscript{V600E} mutation was 16/17 (94%) cases, that of \textbf{TP53} mutation was 3/17 (17.6%) and \textbf{TERT} mutation was noted in only 1/17 (5.9%).\textsuperscript{144}

\textbf{SOLID/TRABECULAR VARIANT PTC}

Solid/trabecular variant PTC was defined differently from the other PTC variants because a solid/trabecular growth pattern is common in conventional and other variants. The solid/trabecular variant is indicated when all (100%) or nearly all of a carcinoma not belonging to any of the other variants has a solid, trabecular or insular growth pattern with clear PTC-N (Fig. 4a).\textsuperscript{3} A solid/follicular pattern in PTC was often noted in pediatric patients following the Chernobyl nuclear power plant accident.\textsuperscript{145–149} It was referred to as non-aggressive solid/follicular variant PTC in children, whereas solid/trabecular variant PTC in adults has been reported to have a slightly higher risk of disease recurrence\textsuperscript{81} and a slightly increased cause-specific mortality (10% at 10 years).\textsuperscript{150} However, these studies require further validation because the diagnostic criteria for PDC were modified in the 2017 WHO classification and a significant amount of PDC was downgraded to solid/trabecular variant PTC\textsuperscript{1,36} (please refer to the PDC section below). The differential diagnosis includes FA with solid growth (absence of both conventional malignant features and PTC-N), NIFTP (absence of conventional malignant features and less than 30% solid/trabecular/insular growth), WDT-UMP (no definite invasion), conventional PTC with solid/trabecular/insular growth (presence of papillae), FTC with solid/trabecular/insular growth (presence of follicular growth pattern and absence of PTC-N) and PDC (absence of PTC-N and presence of high-grade histology, such as increased mitoses, and tumor necrosis).

\textbf{ONCOCYTIC VARIANT PTC AND WARTHIN-LIKE VARIANT}

Warthin-like variant PTC shares histological features with Warthin tumor of salivary gland origin, and the prognosis is similar with that of conventional PTC.\textsuperscript{1,34} Oncocytic variant PTC was reported to have a higher tumor recurrence rate (28% vs 11%) and cause-specific mortality (17% vs 4%) than conventional PTC,\textsuperscript{151} and this was confirmed in a Korean patient cohort (recurrence rates, 30.8% vs 11.7%) by Hong et al.\textsuperscript{152} The Warthin-like variant was included in oncocytic variant PTC in the previous WHO classification, and was regarded
as a distinctive sub-variant in the current 2017 WHO classification because of the different prognosis and histological features.1,56

OTHER PTC VARIANTS (PTC WITH FIBROMATOSIS/FASCIITIS-LIKE STROMA, SPINDLE CELL AND CLEAR CELL VARIANTS)

The PTC variants with fibromatosis/fasciitis-like stroma, spindle cell and clear cells are rare, and the prevalence of such variants was 0.06% (1/1521) for fibromatosis/fasciitis-like stroma, 0% for spindle cell and 0.06% (1/1521) for clear cell variant PTC in a Japanese patient cohort reported by Ito et al.153 (Table 2). They are low-risk PTC similar with conventional PTC, and no definite prognostic information is available.1 Therefore, the details were omitted in this review.

FOLLICULAR THYROID CARCINOMA

Follicular neoplasm is a spectrum of thyroid tumors whose major driving mutations are in RAS family of genes (RAS-like tumors),89–97 which covers benign tumor (FA), borderline tumor (FT-UMP, NiFTP and WDT-UMP), low-risk (minimally invasive FTC), intermediate-risk (encapsulated angioinvasive FTC and widely invasive FTC) and high-risk carcinoma (PDC). The distinction between benign (FA) and malignant (FTC and PDC) is based on conventional malignancy criteria (presence of capsular/lympho-vascular invasion) (Fig. 5a, b). FTC was traditionally divided into two prognostic subgroups according to the invasion pattern, minimally invasive or widely invasive.56 However, Ito et al. demonstrated this prognostic difference between minimally and widely invasive FTC diminished when cases with PDC or distant metastasis were excluded.154 O’Neil et al. combined the invasive pattern and angioinvasion, and classified FTC into three groups: (i) minimally invasive (capsule invasion only) FTC, (ii) encapsulated angioinvasive FTC and (iii) widely invasive FTC. Disease-free survival rates at 40 months of the above three groups were 97%, 81% and 46%, respectively.155 This 3-tiered risk classification was incorporated into the 2017 WHO classification1 (Table 1). In the 2015 AFIP atlas, FTC was classified into four prognostic groups: (i) minimally invasive FTC with capsular invasion; (ii) minimally invasive FTC with limited (<4 vessels) vascular invasion; (iii) minimally invasive FTC with extensive (≥4 vessels) vascular invasion; and (iv) widely invasive FTC.156 These two classifications highlighted the importance of vascular invasion in risk stratification of thyroid carcinomas.157–165 As FT-UMP and WDT-UMP were introduced in the thyroid tumor classification,1,32,33 evaluation of capsular and vascular invasion has become much stricter, and only definite invasion (Fig. 5a, b) is accepted for the diagnosis of FTC.57 Pathologists must select borderline (FT-UMP and WDT-UMP) diagnosis when only questionable invasion is found, to minimize the over-diagnosis of FTC.1,45,46,165,166 Please refer to Figures 2.16 and 2.17 in the 4th edition WHO Blue Book.

Figure 4 (a) Solid/trabecular variant papillary thyroid carcinoma. Note the papillary thyroid carcinoma-type nuclear features (pale chromatin, multiple grooves and irregular nuclear membrane). (HE staining, ×40), (b) Hurthle/oncocytic/oxyphilic cells in Hurthle cell adenoma. Hurthle cells are large cells that have eosinophilic granular cytoplasm. They have large centrally located nuclei and prominent nucleoli. (HE staining, ×40).
for examples of incomplete invasion which are not qualified for malignant diagnosis.1

HÜRTHLE/ONCOCYTIC/OXYPHILIC CELL TUMORS

The WHO classification handled Hürthle cell tumors as a separate tumor entity acknowledging the peculiar biological and clinical features of this unique group of tumors,167 and unique genetic profiles different from non-Hürthle cell FTC.35 Hürthle cells are large cells, and have abundant eosinophilic granular cytoplasm and large centrally located nuclei with prominent nucleoli (Fig. 4b). Some earlier studies suggested that all Hürthle cell neoplasms have the propensity of recurrence/metastasis and should be regarded as carcinoma,168,169 but some did not accept this hypothesis.170 The new WHO classification put an end to this fruitless argument by claiming that “Hürthle cell adenoma is benign and it will not recur”.1 A malignant diagnosis of Hürthle cell carcinoma is based on the presence of capsular and vascular invasion, similar to non-Hürthle cell FTC.167

The prognosis of patients with Hürthle cell carcinoma was believed to be poorer than that of patients with non-Hürthle cell PTC or FTC.171 However, Hürthle cell FTC was found not to have a poorer prognosis than that of non-Hürthle cell FTC in an Asian patient series.172,173 PTC cases with Hürthle cell change were reported to have higher rates of tumor recurrence (28% vs 11%) and cause-specific mortality (17% vs 4%),151 and this was confirmed in a Korean patient cohort (recurrence rate, 30.8% vs 11.7%).152 In the same vein, it was for a long time believed that Hürthle cell carcinomas do not sufficiently concentrate radioactive iodine, which is not supported by the recent findings.174

POORLY DIFFERENTIATED CARCINOMA

Poorly differentiated carcinoma is a carcinoma that both morphologically and behaviorally occupies an intermediate position between differentiated (PTC and FTC) and ATC. The diagnostic criteria for PDC are listed in the Turin proposal.36 In brief, the histological criteria for PDC are: (i) a diagnosis of carcinoma of follicular cell origin by conventional criteria (presence of invasion and/or metastasis); (ii) the presence of solid/trabecular/insular growth over more than 50% of the tumor area; (iii) the absence of PTC-N; and (iv) at least one of the following three features: convoluted nuclei (de-differentiated nuclear feature of PTC), mitotic activity (Fig. 6a) more than 3 per 10 high-power fields or tumor necrosis. Intermediate survival (60–70% at 5 years) has been reported when the solid/trabecular/insular pattern is observed in most (>50%) of the tumor area.36,175–178 However, the presence of a minor solid/trabecular/insular component also demonstrated poor survival and increased disease recurrence even when accounting for as little as 10% of the tumor area.179–181

Take home message

Sakamoto et al. proposed PDC in 1983 and defined it as solid/trabecular carcinoma (>10%) regardless of high-grade histology.182 Sakamoto-type PDC is a moderately differentiated
PTC or FTC with a 10-year disease recurrence of approximately 45–75%, but an increased cause-specific mortality was not confirmed. It is important to note that high-risk thyroid carcinoma is not restricted to cases with solid/trabecular/insular growth pattern. Hiltzik et al. reported cases with high-grade histology (necrosis and increased mitoses) as PDC, and PDC by Hiltzik’s definition included high-grade PTC and FTC, with a cause-specific survival of 50–60% at 5 years. Hiltzik-type PDC encompasses both solid/trabecular/insular carcinoma with tumor necrosis or increased mitosis (Turin PDC) and non-solid-type carcinoma (PTC and FTC) with high-grade features, which is likely equivalent to the high-risk follicular cell carcinoma proposed by Kakudo as defined by the Ki67 proliferation index (follicular cell carcinoma with Ki67 labeling index of more than 10% but less than 30%).

ANAPLASTIC (UNDIFFERENTIATED) CARCINOMA

Anaplastic thyroid carcinoma (ATC) is a highly aggressive thyroid malignancy composed of undifferentiated follicular cells (Fig. 6b). This rare type of thyroid carcinoma (1–2% of all thyroid malignancies) usually develops in elderly patients, presenting as a rapidly growing, firm and infiltrative neck mass. The prognosis of ATC is grave with a median survival period of less than 6 months and mortality rate of more than 90%. Three histological types (sarcomatoid, giant cell and epithelial) are seen in any combination and proportion in ATC. Nuclear pleomorphism, tumor necrosis, increased mitoses and infiltrative growth are characteristic features (Fig. 6b) in ATC, and its diagnosis is usually straightforward. However, a significant misclassification was reported in a study from the Anaplastic Thyroid Carcinoma Research Consortium of Japan. Hirokawa et al. reviewed 88 patients with ATC who survived less than 1 year and 68 patients with ATC who survived more than 1 year, and found that 6 (6.8%) short-term and 27 (39.7%) long-term survival cases were reclassified after central review. Of note, over-diagnosis (21.2%) occurs often for ATC by general pathologists. The differential diagnoses for ATC include PDC, PTC with squamous cell differentiation or faciitis-like stroma, primary and secondary squamous cell carcinoma, intra-thyroid thymic carcinoma, atypical adenoma, sarcoma and malignant lymphoma. Nuclear pleomorphism, tumor necrosis and increased mitoses are key for a conclusive diagnosis of ATC (Fig. 6b), and Ki67 immunohistochemistry is useful to confirm ATC and other high-risk thyroid carcinomas.

Up to half of ATC samples may contain a well-differentiated component, usually antecedent or coexisting PTC and FTC, or occasionally a minor ATC component is found on postoperative pathological examination of patients with differentiated thyroid carcinoma. Recent Korean studies addressed a significance of coincident ATC and PTC/FTC. It was reported that pure ATC (100% undifferentiated component) and ATC arising from PTC/FTC (>10% undifferentiated component, usually > 50%) have a similar behavior and unfavorable prognosis. On the other hand, PTC/FTC with

Figure 6  (a) Poorly differentiated carcinoma with solid growth. There are two mitotic figures in this field, which indicate a high proliferation potential. Note the lack of papillary thyroid carcinoma-type nuclear features, which distinguish PDC from solid variant papillary thyroid carcinoma (please refer to Fig. 4a).

(HE staining, ×40). (b) Spindle cell-type anaplastic carcinoma. Note the abnormal mitosis, high-grade nuclear atypia and lack of epithelial differentiation. (HE staining, ×20).
ATC foci (<10% of undifferentiated cells in the background of differentiated cancer) showed significantly better outcome, with a 5-year survival (81%) exceeding those of ATC (14%) and even of PDC (66%).196 Interestingly, the number of cases of pure ATC decreased over the time, while cases of ATC with coincident PTC/FTC became much more frequent (up to half of all ATC).195,196

GENETIC PROFILES AND MOLECULAR DIAGNOSIS OF THYROID TUMORS

Thyroid carcinoma is a genetically simple neoplasm with a low number of mutations. Driver gene aberrations in well-differentiated thyroid cancer are mutually exclusive, with a median one mutation per tumor, while undifferentiated cancers accumulate additional genetic alterations, so-called late events.197 Driver mutations and gene fusions are identified in over 90% of thyroid cancers, making it one of the best molecular characterized malignancies in humans.90 Collectively, the most common initiating alterations are BRAF and RAS point mutations and RET/PTC and PAX8/PPARγ chromosomal rearrangements, while TP53 mutation is a classic late event. Most somatic mutations are not thyroid specific and are commonly found in various solid cancers. MAPK and PI3K-AKT are two main signaling pathways involved in the thyroid carcinogenesis. MAPK pathway, primarily involved in development of PTC, is traditionally activated via point mutations in BRAF or RAS genes and RET/PTC rearrangements. PI3K-AKT pathway, associated with development of FTC, is activated through point mutations in RAS, PIK3CA, AKT1 and PTEN. Concurrent activation of both pathways becomes more frequent as the tumor grade increases.

Mutation profiling of key oncogenic events in thyroid tumors is shown in Fig. 7. To date, there is no reliable molecular test to differentiate adenomatous nodule, FA, NIFTP and FTC with a sensitivity and specificity approaching 100%. RAS mutations occur, on average, in 30% of FA, 30–50% of NIFTP, 30–45% of follicular variant PTC, 30–50% of FTC, 20–50% of PDC and 10–50% of ATC.1,90 Thyroid tumors with RAS mutations alone have an excellent prognosis. Tumor aggressiveness and poor clinical outcomes are higher for thyroid cancers harboring RAS mutations and additional oncogenic mutations, such as TERT promoter mutations.
and TP53, than for those with RAS mutations alone.\textsuperscript{198} PAX8/PPARG rearrangements occur in approximately 8% of FA, 10% of NIFTP, 1% of follicular variant PTC and 20–30% of FTC. EIF1AX mutation can be found in hyperplastic nodules, FA, NIFTP, FTC, PTC, PDC, ATC and Hürthle cell carcinomas.\textsuperscript{90,199–202} Cyto genetic changes occur in 50% of FA and 65% of FTC.\textsuperscript{1} PTEN and PIK3CA mutations also occur in 5% of FA and up to 10% of FTC.\textsuperscript{1} Hyperfunctioning FA has mutations in TSHR, GNAS and EZH1 genes.\textsuperscript{203} EZH1 mutations also occur in Hürthle cell adenoma and minimally invasive FTC.\textsuperscript{204} RAS mutations are frequent in NIFTP, as well as PAX8/PPARG and THADA//IGF2BP3 fusions.\textsuperscript{1,200} BRAF K601E and small insertions or deletions surrounding codon 600 of BRAF can occur,\textsuperscript{1,200} but NIFTP should not have BRAF V600E, TERT or TP53 mutations, or RET/PTC fusions, which have a risk of malignancy of nearly 100%. The Cancer Genome Atlas project clarified the mutational landscape in PTC.\textsuperscript{90} The overall genetic events in PTC consist of 75% point mutations, 15% gene fusions and 7% copy-number variations. The common genetic alterations in PTC are summarized in Fig. 8. BRAF V600E typically occurs in conventional and tall cell variant PTC. However, this mutation is rarely found in the diffuse sclerosing variant and is absent in cribriform morular variant PTC. RAS and EIF1AX mutations are more frequently found in the follicular variant than other variants. Chromosomal rearrangements involving ALK, FGFR2, LTK, MET, NTRK1, NTRK3, PPARG, RET or THADA genes occur in 15% of PTC. Progression of differentiated thyroid cancer to higher grade cancer is associated with the accumulation of mutations in other oncogenic genes, such as TP53, PIK3CA, AKT1 and TERT promoter (Fig. 7).\textsuperscript{202} The TCGA classified PTC into two major molecular groups based on their gene expression profiles: BRAF-like PTC and RAS-like PTC. BRAF-like tumors demonstrate a papillary growth pattern (conventional and tall cell variants), and have BRAF V600E mutations and rearrangement of BRAF, RET and MET genes. RAS-like tumors exhibit a follicular growth pattern and tumor capsule in more than 80% of cases, and have mutations in RAS, EIF1AX and PTEN genes, and rearrangement of PPARG, FGFR2 and THADA genes. TERT promoter mutations at low frequency, and gene fusions of ALK, NTRK1 and NTRK3 occur in both molecular groups. Somatic genomic alterations in Hürthle cell carcinomas are different from those in PTC and FTC. Hürthle cell carcinomas have MADCAM1, EIF1AX, NRAS, DAXX, PT53 and NF1 mutations, but no BRAF mutations and a lower frequency of NRAS mutation than FTC.\textsuperscript{201,205} Somatic recurrent mitochondrial mutations occur in 71% of Hürthle cell carcinomas. Unique chromosomal landscapes in Hürthle cell carcinomas involve whole-chromosome duplication of chromosomes 5 and 7, and widespread loss of chromosomes resulting in near-haploid chromosomal content.\textsuperscript{201} Once again the author would like to emphasize is that there are significant differences in genetic profiles of thyroid cancers between Asian and Western patient populations, and the prevalence of BRAF\textsuperscript{V600E} point mutation in Asian PTC cohorts is high compared to those reported from Western countries.\textsuperscript{2,3,144,206,207}
FUTURE DIRECTIONS IN CLASSIFICATION OF THYROID TUMORS.

The 4th edition WHO classification of tumors of endocrine organs covers (i) the pituitary gland, (ii) thyroid gland, (iii) parathyroid glands, (iv) adrenal cortex, (v) adrenal medulla and extra-adrenal paranglia, (vi) neuroendocrine pancreas and (vii) inherited tumor syndromes. A new concept in the WHO classification of tumors of endocrine organs is that all endocrine tumors have some metastatic potential. Therefore, previous categories of benign and malignant tumors are eliminated in some endocrine tumor classifications, such as in the neuroendocrine pancreas (PanNET G1, PanNET G2, PanNET G3 and PanNEC) and adrenal medulla (risk stratification with the Grading System for Adrenal Pheochromocytoma and Paraganglioma proposed by Kimura et al.). The author believes that this risk classification in endocrine tumors will eventually replace the traditional distinction between adenoma (benign) and carcinoma (malignant) in thyroid tumor classification (Fig. 9). It is predicted that this may occur in thyroid pathology in the near future, as the 2015 ATA clinical guidelines already recommend to risk stratify differentiated thyroid carcinomas for structural disease recurrence into 21 steps from a risk of recurrence of 1–2% for unifocal PMC to that of 30–55% for FTC with extensive vascular invasion (Table 4).

RISK STRATIFICATION OF FOLLICULAR CELL THYROID CARCINOMAS PROPOSED BY THE 2015 ATA GUIDELINES

The AJCC/TNM staging is useful for predicting disease-specific survival, a relatively rare event in thyroid cancer. Therefore, structural disease recurrence is considered as a key endpoint, which can be predicted immediately after surgery based on results of pathological examination and further used to tailor postoperative management of patients. Ten years ago, Bai et al. classified PTC into low risk and high risk groups for disease recurrence based on features of so-called aggressive histology (tall/columnar cell, micropapillary/discohesive and solid variant PTC) in 2008, and some other Japanese studies risk-stratified follicular cell thyroid carcinomas into three groups (low-risk, moderate-risk and high-risk) using clinical features, the Ki67 proliferation index and thyroglobulin doubling time. In 2009, the previous ATA clinical guidelines recommended risk stratification of differentiated thyroid carcinomas into low-risk, intermediate-risk and high-risk for structural disease recurrence using a combination of histopathological parameters and clinical features, and was updated in 2016 (Table 4) to guide management and determine the need for radioactive iodine ablation therapy, so-called risk adapted management. The histopathological parameters used for risk stratification were the presence of (i) aggressive histology (diffuse sclerosing, tall cell, columnar cell, hobnail and solid variant PTC), (ii) minor (microscopic) and gross extrathyroidal extension, (iii) more than four or fewer than four foci of vascular invasion, (iv) extranodal invasion, (v) fewer than five involved lymph nodes (less than 0.2 cm metastasis), (vi) more than five involved lymph nodes (0.2–3 cm), and (vii) intrathyroidal (ex0, N0, M0) differentiated thyroid carcinomas (Table 4). This risk stratification by the ATA will become the standard of care for appropriate management to avoid over-treatment. The same strategy (risk stratification of differentiated follicular cell carcinomas) was endorsed by the six Italian societies as a consensus in 2018 and incorporated into the pathology report template recommended by the College of American Pathologists.

HOW TO HANDLE MULTIPLE PROGNOSTIC FACTORS AND DETERMINE WHICH MORE GREATLY IMPACT PATIENT OUTCOMES

It is difficult to determine the risk attributable to one factor versus that attributable to other clinico-pathological features. This is a critical clinical problem, and one such example is the emphasis on a benign outcome for encapsulated tumors with high-grade histology when invasion is absent. Regarding the cut-off for % tumor area in aggressive histology, an Italian consensus proposed a lower cut-off (10%) for tall cell and columnar cell variant PTC instead of greater than 30% proposed by the 2017 WHO classification or greater than 50% in the previous 2004 WHO classification. Several Japanese studies reported that a small (<10%) proportion of aggressive (tall cell, solid or hobnail/micro-papillary) features or high-grade histology led to higher recurrence rates and/or increased mortality. This was confirmed in a Western patient cohort on tall cell variant PTC by Dettmer et al., but not in the other Western series by Ghossein et al.. The main reasons for the significant discrepancy among studies are the lack of unanimous diagnostic criteria and variations in individual interpretations. Therefore, pathologists must provide these prognostic parameters more objectively such as aggressive histology and their proportions. Alternatively, the less differentiated histology of PTC can be combined into one category (high-risk PTC), as recommended by Bai et al., because we believe there may be one continuous spectrum of morphological changes during the progression from low-risk PTC to high-risk PTC (Fig. 10).
Introduction of NIFTP into the thyroid tumor classification by the 4th edition WHO classification and risk stratification of differentiated thyroid carcinoma by the 2015 American Thyroid Association (ATA) guidelines impacted thyroid tumor diagnosis. The upper panel is based on the 3rd edition WHO classification and there were only two choices for diagnosis, benign or malignant, of thyroid tumors. Approximately 20% of thyroid tumor diagnoses had discrepancies (benign vs malignant) with this schema. The lower panel is based on the risk stratification by the ATA recommendation and borderline tumor category by the 4th edition WHO classification. All thyroid tumors have some potential to develop metastasis, and the distinction between benign and malignant is eliminated. Risk stratification of thyroid tumors from very low risk of recurrence to high risk of recurrence is shown as a continuous spectrum, from benign tumor to high-risk cancer.

Table 4 Clinical and histopathological prognostic parameters for structural disease recurrence in differentiated thyroid carcinomas (DTC) and recurrence rates estimated by the 2015 ATA Clinical Guidelines (modified from reference #12)

| ATA high-risk | Risk of structural recurrence |
|---------------|-----------------------------|
| (Patients who have gross extrathyroidal extension, incomplete tumor resection, distant metastases, or inappropriate postoperative serum thyroglobulin values.) | |
| 1. Follicular thyroid cancer (FTC) with extensive vascular invasion (>4 foci of vascular invasion) | (30–55%) |
| 2. pT4a gross extrathyroidal extension | (30–40%) |
| 3. pN1 with extranodal extension >3 lymph nodes involved | (40%) |
| 4. PTC >1 cm, TERT mutated + BRAF mutated | (>40%) |
| 5. pN1, any lymph node >3 cm | (30%) |
| 6. Papillary thyroid cancer (PTC), extrathyroidal, BRAF mutated | (10–40%) |
| 7. PTC, vascular invasion | (15–30%) |

| ATA intermediate-risk | |
| (Patients who demonstrate either microscopic extrathyroidal extension, cervical lymph node metastases, RAI-avid disease in the neck outside the thyroid bed, vascular invasion, or aggressive tumor histology.) | |
| 1. Clinical N1 | (20%) |
| 2. pN1, >5 lymph nodes involved | (20%) |
| 3. Intrathyroidal PTC, <4 cm, BRAF mutated | (10%) |
| 4. pT3 minor extrathyroidal extension | (3–8%) |
| 5. pN1, all lymph nodes <0.2 cm | (5%) |
| 6. pN1, <5 lymph nodes involved | (5%) |

| ATA low-risk | |
| (Patients with intrathyroidal DTC with no evidence of extrathyroidal extension, vascular invasion, or metastases) | |
| 1. Intrathyroidal PTC, 2–4 cm | (5%) |
| 2. Multifocal papillary thyroid microcarcinoma (PMC) | (4–5%) |
| 3. pN1 without extrathyroidal extension, <3 lymph nodes involved | (2%) |
| 4. Minimally invasive FTC | (2–3%) |
| 5. Intrathyroidal, 4 cm, BRAF wild-type | (1–2%) |
| 6. Intrathyroidal unifocal PMC, BRAF mutated | (1–2%) |
| 7. Intrathyroidal, encapsulated, follicular variant PTC | (1–2%) |
| 8. Unifocal PMC | (1–2%) |
Take home message

It should be noted that the risk stratification recommended by the ATA was published in 2016, a year before the borderline category was incorporated into the 2017 WHO classification. Thus, borderline tumors were still listed as cancer in the ATA risk stratification, and they had a very low risk of recurrence of less than 2% (Table 4). Tumors included minimally invasive FTC (the majority have been reclassified in FA or FT-UMP when they have no definite invasion), intrathyroidal <4 cm BRAF wild-type (noninvasive encapsulated papillary RAS mutant tumor) and intrathyroidal encapsulated follicular variant PTC (the majority have been downgraded to WDT-UMP or NIFTP when they have no definite invasion) in addition to PMC (Table 4). To summarize, all thyroid follicular cell tumors can be risk stratified using histopathological parameters as they belong to a continuous spectrum of follicular cell tumors, from benign FA, borderline tumors, low-risk, moderate-risk and high-risk thyroid carcinomas (Fig. 9).

CHECKLIST FOR PATHOLOGY REPORTS

In the modern era, pathology reports require many prognostically histological parameters necessary for patient management. Reports include the presence and extent of (i) capsular invasion, (ii) vascular invasion, (iii) extrathyroidal extension, (iv) cut margin status (completeness of surgery), and (v) the number and size of lymph nodes with metastatic carcinoma. Regarding the histological diagnosis of primary carcinoma, (vi) the presence of aggressive histology and (vii) its proportions are required in standard pathology reports for follicular cell thyroid carcinomas (Table 5). The College of American Pathologists annually updates their detailed protocol and template for the examination of specimens from patients with thyroid carcinoma. A more concise and practical protocol recommended by the Asian Working Group is summarized in Table 5.

GROSS EXAMINATION AND SAMPLING OF THYROID TUMORS

This review also emphasizes the gross examination and sampling method for thyroid tumors. In publications on NIFTP, examination of the entire tumor capsule to exclude invasion before arriving at the diagnosis of NIFTP was recommended. Complete sampling was suggested because most pathologists believe that examining more tissue blocks will increase the chance of detecting invasion. Lang et al. from Germany found that the number of tissue blocks examined positively correlated with the identification of invasion. This positive-identification rate increased to 50% when eight blocks were examined, and it became close to 100% when more than 10 blocks were examined. This is Western logic to mitigate concerns over not missing malignancies. However, it is not possible to identify all cancer with distant metastasis by this method of complete sampling as proposed by Yamashina. Glomski et al. retrospectively reviewed their practice and compared two groups of FTC: Group 1 (n = 145) whose tumor capsules

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Table 5  Proposed reporting form for thyroid tumors recommended by the Asian Working Group

**Gross examination**

Macrosopic appearance of the nodule

| Size of tumor: cm (maximum diameter) encapsulated or well circumscribed (solid, cystic) or infiltrative |
| Site of the nodule |
| Upper pole, middle, lower pole, right lobe, left lobe, isthmus, |

**Microscopic examination**

| Number of blocks sampled, thyroid ( ), lymph nodes ( ) and others ( ) |

**Histological diagnosis ( )**

1. Non-neoplastic Lesions (Hyperplastic Nodule)
2. Benign Neoplasms (Follicular Adenoma)
3. Borderline Neoplasms (Hyalinizing Trabecular Tumor, FT-UMP, WDT-UMP and NIFTP)
4. Invasive Encapsulated Well Differentiated Carcinomas (WDC)
   - PTC type (BRAF-like)
   - FTC type (RAS-like)
   - Oncocytic (Hurthle cell)
5. Infiltrative (non-encapsulated) WDC,
   - PTC type (BRAF-like)
   - FTC type (RAS-like)
   - Oncocytic (Hurthle cell)
6. WDC with Aggressive Histology
7. WDC with Minor De-differentiated Component
8. De-differentiated Carcinomas
   - Poorly Differentiated Carcinoma
   - Anaplastic (Undifferentiated) Carcinoma

**Histological variations of PTC and de-differentiated histology (Proportions in parenthesis)**

- Hobnail (micropapillary/dyscohesive) ( %)
- Tall cell ( %)
- Solid/trabecular ( %)
- Columnar cell ( %)
- Diffuse sclerosing ( %) and
- De-differentiated histology (PDC or ATC) ( %)

**Conventional (classic or common) PTC ( %) total 100%**

You may combine total aggressive histology ( %) and total de-differentiated ( %)

**Tumor capsule invasion**

- No invasion, incomplete (questionable) invasion, definite invasion

**Lympho-vascular invasion**

- Vascular invasion: v0 (no invasion), v1 (less than 4 foci), v2 (4 or more than 4 foci) lymphatic invasion: (none, focal, diffuse)

**Extrathyroid invasion (extension)**

- Minimal (microscopic) extrathyroid invasion: ex0 (no invasion), ex1 (microscopic invasion only in extrathyroid fatty tissue or strap muscle)

**Gross extrathyroid extension:** ex2: subcutaneous soft tissues, larynx, trachea, esophagus, recurrent laryngeal nerve, prevertebral fascia, neck muscles, large vessels (jugular vein, carotid artery)

**Immunohistochemical findings, if performed**

| BRAFV600E, CK19, TTF1, TG, calcitonin, CD5, |
| Ki 67 labeling index ( %) |

**Lymph node status ( )**

Number of metastatic lymph nodes/total number of lymph nodes dissected, Central compartment ( / )

Lateral (R or L) compartment ( / )

1. Size of the largest node ( cm), micro-(<2 mm) or macro-metastasis
2. Absence or presence of extranodal invasion
3. Organs directly invaded by the lymph node metastasis ( )
4. Ectopic tissue (Thyroid, Parathyroid, Thymus, Salivary Gland, Cyst, Muscle, )

**Background thyroid disease, if present**

- Hashimoto thyroiditis, lymphocytic thyroiditis, Graves' disease, cyst, ectopic tissue ( ) and Others ( )

**Remarks:**

- Medullary (C cell) carcinomas, malignant lymphomas, other rare malignant tumors of different histogenesis and secondary carcinomas should be classified separately.

- You may specify lymph node numbers and number of positive nodes.

Right: I ( / ), II & III ( / ), IV ( / ), Va ( / ), Vb ( / ), VI ( / )

Left: I ( / ), II & III ( / ), IV ( / ), Va ( / ), Vb ( / ), VI ( / )
were sampled in entirety (number of blocks was 1–44) and Group 2 (n = 73) whose examination was incomplete (number of blocks was 3–20).223 They found that all 56 cases of minimally invasive FTC in Group 2 were still diagnosed as carcinoma and not benign with missed areas of capsular invasion. Furthermore, incomplete capsule submission in the 56 cases in Group 2 did not significantly increase the probability of eventual metastatic progression [0.8% (1/123) in Group 1 vs 1.8% (1/56) in Group 2].223 This study confirmed that examination of the entire capsule cannot prevent missing a true malignancy, since one benign case developed unexpected distant metastasis even though invasion was ruled out by the entire capsule examination.223

A consensus for adequate sampling has not been established in the WHO Blue Book or in the template by the College of American Pathologists.1,211 Theoretically, primary thyroid tumors and/or microscopic invasions less than 2 mm may be over-looked within the thickness of tissue slices (usually 3 mm). Furthermore, distant metastases can occur in rare cases even without detectable primary carcinoma in the thyroid gland,48,224 and as demonstrated by a case without invasion after complete sampling.223 Furthermore, Lang et al. from Hong Kong reported that the total number of tissue blocks per centimeter of tumor was significantly correlated with the risk of distant metastasis. The 10-year distant metastasis-free survival was significantly better for FTC examined with >4 blocks/cm of tumor than that examined with <3 blocks/cm of tumor (100% vs 84.7%).225 Pathologists should be aware of this observation and the rationale behind it. Ironically, the survival rate of FTC with complete sampling was longer than that examined by incomplete sampling. Although entire capsule sampling has a higher sensitivity for detecting invasion, the majority of invasion was biologically insignificant (incomplete) and the patients did not have decreased survival. In other words, only easily identified definite invasion (Fig. 5a, b) found in less than 10 blocks is clinically significant, whereas worrisome capsular/lympho-vascular invasion identified with more than 20 blocks may have limited clinical significance. Xu et al. evaluated the number of slides per case, the sections of tumor capsule sampled per tumor and the sections of tumor capsule per centimeter of tumor in 73 FTC cases. They found that tumor sampling was not associated with the vascular invasion status or clinical outcome.226 These studies revealed that the belief that examining more blocks reduces the chance of missing lethal carcinoma was uncertain and groundless.

In the 5th edition of “Surgical Pathology” by Ackerman and Rosai, it was stated that “at least five or six sections should be taken”.227 Furthermore, Warren reported that if vascular invasion was not found in three blocks, examination of more blocks would add little information.228 The author of this review considers it impractical to take more than 20 blocks from all thyroid nodules to rule out invasion. The author recommends taking an average of 5–10 blocks from a 3 cm nodule at initial gross examination, and additional blocks may be taken later provided there are suspicious histological features for invasion (incomplete invasion) in the first 5–10 blocks. By this two-step procedure, we can significantly reduce costs and labor in pathologic practice. Please refer to the more practical sampling method recommended by the Japanese Society of Thyroid Surgeons.18,28 This method is also good for detailed examination of tumor histology because the entire capsule examination recommended in Western practice usually focuses on the tumor capsule and sacrifices a significant part of the tumor parenchyma.211,222,223

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