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Follicular Neoplasms in the 4th Edition WHO Classification of Endocrine Organs

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Abstract

The 4th edition World Health Organization (WHO) classification of tumors of endocrine organs was published in 2017. Several revisions were made for thyroid tumor classification. The introduction of borderline tumors, follicular tumor of uncertain malignant potential (FT-UMP), well differentiated tumor of uncertain malignant potential (WDT-UMP) and noninvasive encapsulated follicular neoplasm with papillary-like nuclear features (NIFTP), in the thyroid tumor classification has significantly impacted diagnosis and clinical practice for thyroid nodules. Follicular neoplasm is a group of thyroid neoplasms characterized by follicular growth pattern, which is the main topic of this review. They are generally RAS mutated tumors and have a common molecular mechanism of tumorigenesis. They have overlapping morphological features, and are often found on histology of surgically-treated cytological indeterminate nodules. This group was further classified into 6 prognostic groups (follicular adenoma, FT-UMP, minimally invasive capsular invasion only follicular thyroid carcinoma (FTC), encapsulated angioinvasive FTC, widely invasive FTC, and FTCs with distant metastasis). Risk stratification of thyroid carcinomas has become an essential component of pathology reports.

Key Words: Thyroid carcinoma, follicular neoplasm, borderline tumor, thyroid gland, risk classification, pathology, FNA cytology

Introduction

The consensus and editorial meeting of the 4th edition WHO classification of tumors of endocrine organs was held in April, 2016, and the final version was published in July of 2017 (1). I will summarize follicular thyroid neoplasms (RAS-like tumors) in this review. The cytological term, follicular neoplasm (FN), encompasses follicular adenoma (FA), follicular variant of papillary carcinoma (FVPTC), follicular carcinoma (FTC) and borderline tumors (follicular tumor of uncertain malignant potential (FT-UMP), well differentiated tumor of uncertain malignant potential (WDT-UMP) and noninvasive encapsulated follicular neoplasm with papillary-like nuclear features (NIFT)). These neoplasms are generally RAS-mutated tumors and have a common molecular mechanism of tumorigenesis (3-5). They have overlapping morphological features and are often found on histology of surgically-treated cytological FN nodules (6-10).

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Follicular adenoma

FA is a benign non-invasive encapsulated neoplasm exhibiting thyroid follicular cell differentiation without nuclear features of papillary thyroid carcinoma (PTC-N) (Figure 1).

The statement, without nuclear features of papillary thyroid carcinoma, was incorporated into the definition of FA in the 4th edition WHO classification of thyroid tumors. This was because a borderline tumor category was introduced, and borderline tumors and FA were distinguished by the presence (NIFTP) or absence (FA) of PTC-N (1). An example of FA is shown in Figure 1. This thyroid nodule has a thin fibrous capsule, and is composed of normo-follicular and micro-follicular structures (Figure 1A). Please note the small round nuclei with densely stained chromatin and lack of PTC-N (Figure 1B). How are FA and hyperplastic nodules (HNs) distinguished? When a single nodule with a fibrous capsule is observed, the diagnosis of FA is straightforward. However, many pathologists do not diagnose FA in a multinodular gland, preferring to designate all lesions as HN. FA is a neoplasm, and therefore, has a clonal origin. Without molecular tests, it may not always be possible to distinguish FA from HN. However, this distinction may be not important practically because both are benign nodules and observer variation is significant. Benign follicular nodule is a non-committal term suggested by Rosai for when histological distinction between HN and FA is not possible (11).

Distinction between FA and FTC

The only histological feature that reliably distinguishes FTC from FA is the presence of vascular or capsular invasion, highlighting the importance of adequate sampling of the tumor capsule interface to search for invasion.

Figures 2 and 3 are illustrations showing 5 examples of capsular invasion (Figure 2) and 6 examples of incomplete capsular invasion (not sufficient for malignancy) (Figure 3). Figure 4 is an example of minimally-invasive angioinvasive encapsulated FTC. Grossly, invasive foci are rarely noted (Figure 4A), but under microscopy, vascular invasions can be observed, as in Figure 4B. In widely invasive-type FTCs, invasion is usually identified grossly (Figure 5) as well as by ultrasound examination. (The gross appearance of widely invasive FTC is available in Figure 2.50,

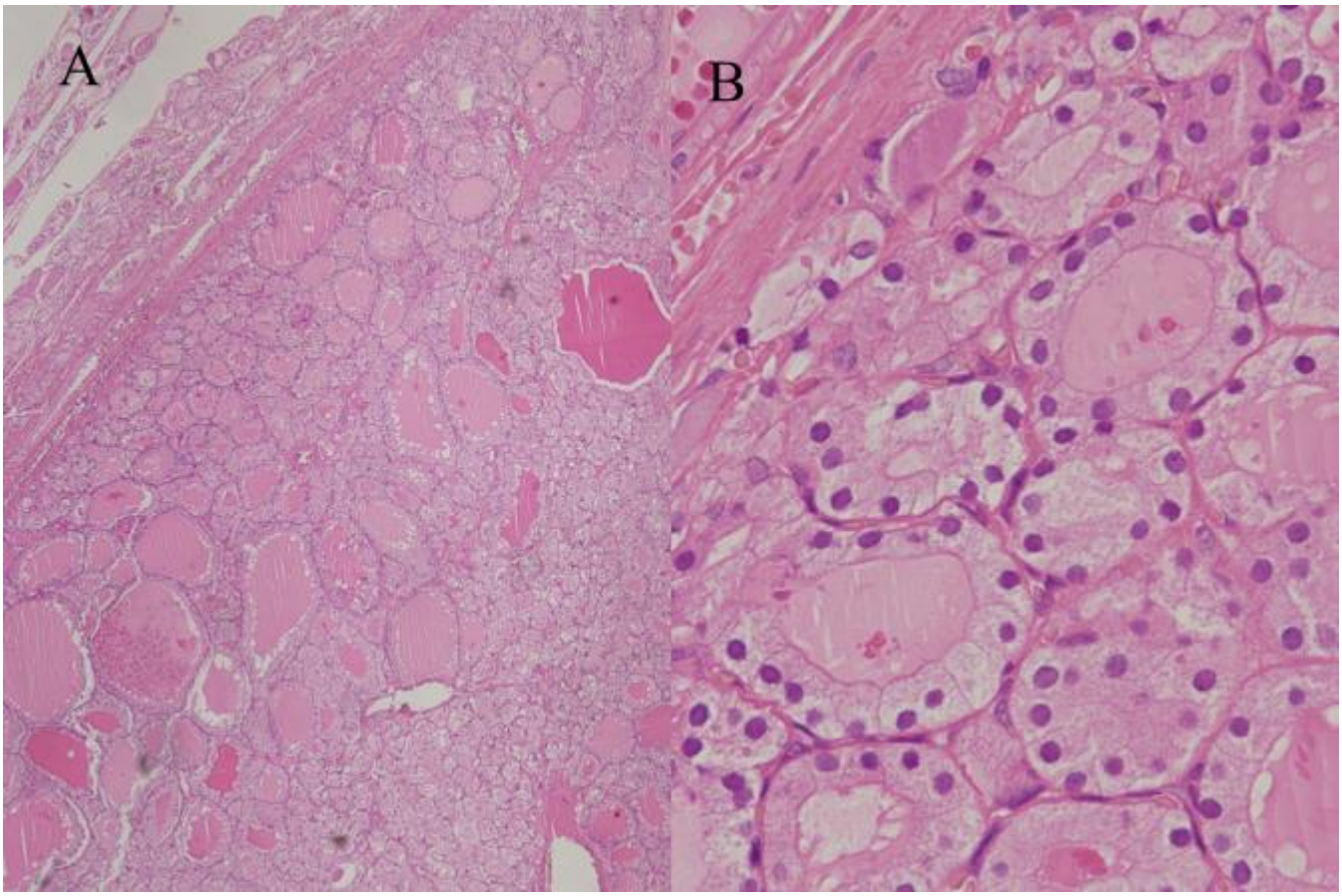

Fig. 1. Follicular adenoma. Follicular pattern tumor with thin fibrous capsule in left field (A: HE stain, x4) and a higher magnification in the right field (B: HE stain, x40). Note there is no papillary thyroid carcinoma type nuclear features and the tumor cells have round nuclei with densely stained chromatin.

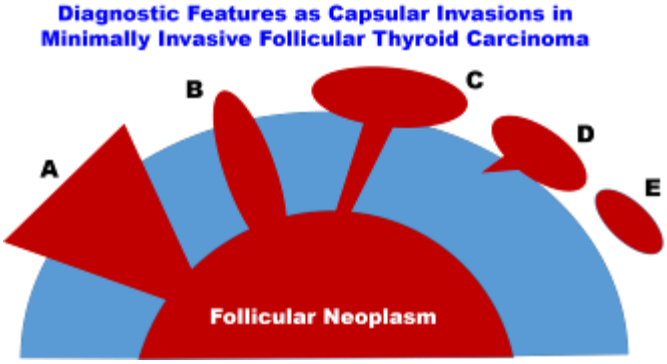

Fig. 2. Diagnostic features as capsular invasions in minimally invasive follicular thyroid carcinoma. Red area indicating follicular pattern tumor (follicular neoplasm) invading into thick fibrous capsule (blue area) and beyond the capsule. Direct continuity is found in A, B and C, while it is not identified in D and E. All of them are regarded as true invasion acceptable as an evidence of malignancy.

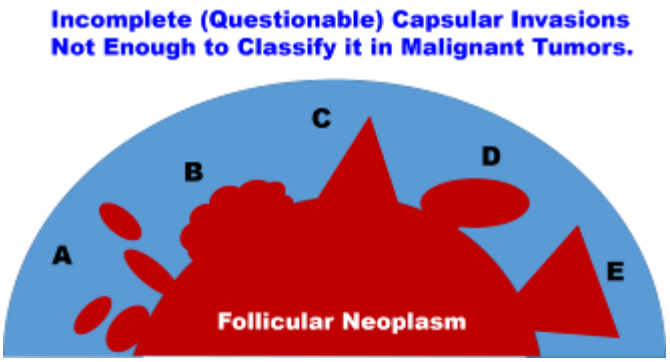

Fig. 3. Incomplete (questionable) capsular invasions in uncertain malignant potential. They are not enough to classify in malignant tumors (minimally invasive follicular thyroid carcinoma or invasive encapsulated follicular variant papillary thyroid carcinoma). Red area indicating follicular pattern tumor (follicular neoplasm) invading into thick fibrous capsule (blue area) but remaining within capsule. All of them (type A - E) are not accepted as diagnostic features of malignancy or as an evidence to apply aggressive cancer therapy to the patients.

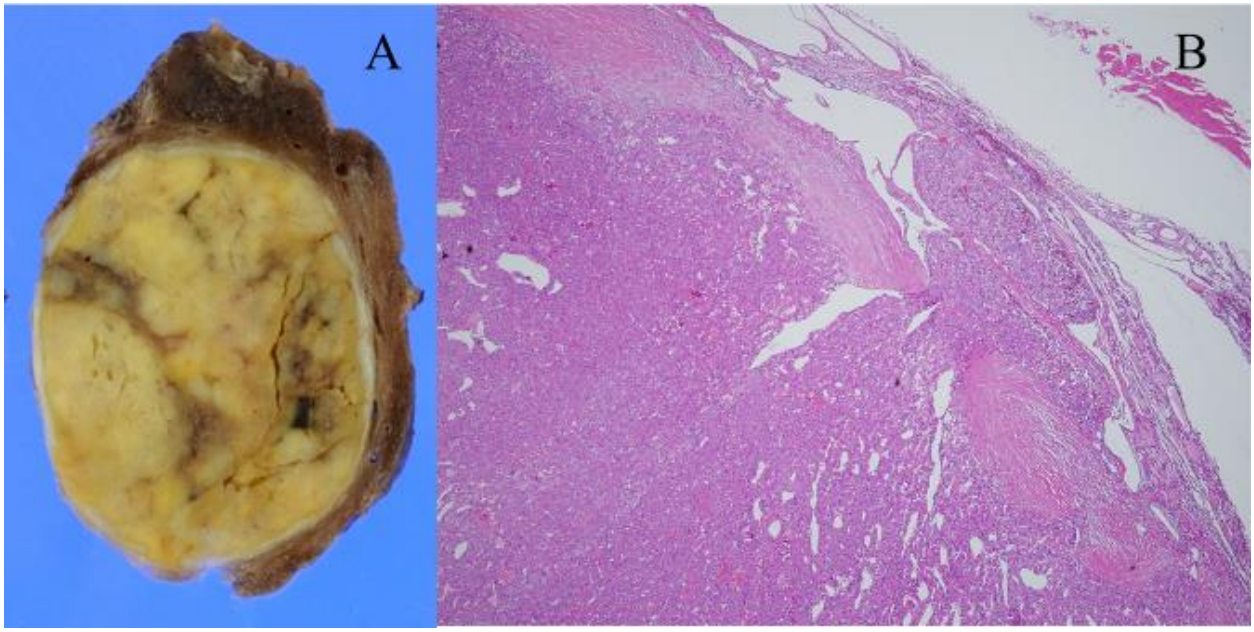

Fig. 4. Minimally invasive encapsulated angioinvasive follicular thyroid carcinoma. A solid nodule in the thyroid gland is completely encapsulated and invasion by tumor is not grossly identifiable confidently (A). Microscopic examination demonstrated a vascular invasion (B: HE stain, x4).

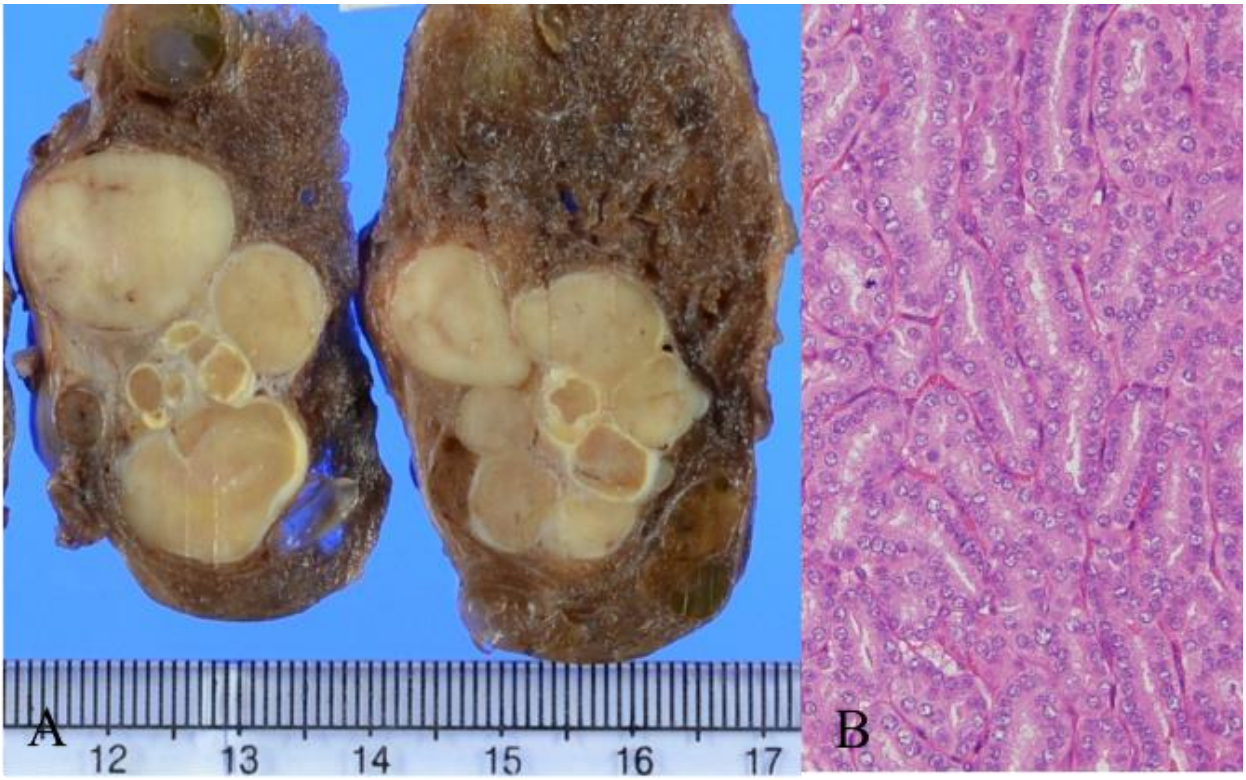

Fig. 5. Widely invasive follicular thyroid carcinoma. Multiple invasions by tumor nests into thyroid parenchyma are grossly identified on cut surface (A). Follicle (tubular) growth pattern is seen in the tumor without papillary thyroid carcinoma type nuclear features (B: HE stain, x20).

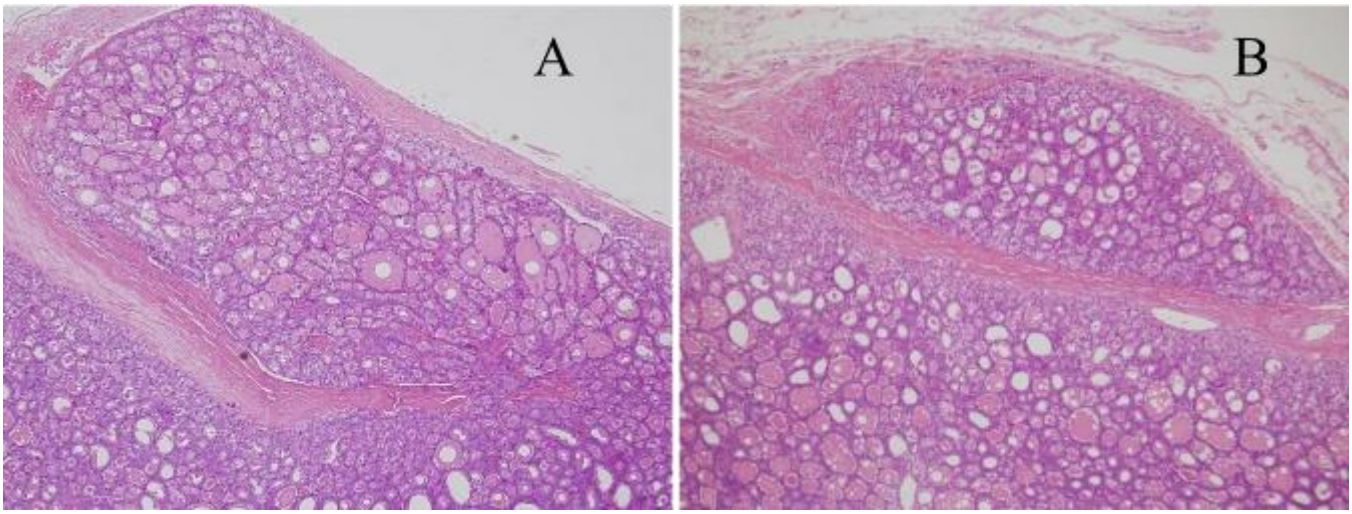

Fig. 6. Diagnostic (true) capsular invasion for minimally invasive follicular thyroid carcinoma. 6A showing an example of type C capsular invasion illustrated in the Fig. 2, and 6B showing an example of type E capsular invasion illustrated in the Fig. 2. (HE stain, x4)

microscopic capsular invasion in Figure 2.54 and vascular invasion in Figure 2.53 of the WHO textbook.) Examples of true invasion diagnostic for malignancy (FTC) are shown in Figure 6, Figure 6A presents an example of type C capsular invasion, as illustrated in Figure 2, and Figure 6B shows an example of type E capsular invasion, as illustrated in Figure 2.

In 2000, Williams proposed the term "uncertain malignant potential (UMP)" to solve the diagnostic difficulties for capsular invasion and PTC-N (12). This was further divided into FT-UMP and WDT-UMP. WDT-UMP is an encapsulated tumor composed of well-differentiated follicular cells with questionable PTC-N, no blood vessel invasion and capsular invasion that is either questionable or absent. FT-UMP is an encapsulated tumor composed of well-differentiated follicular cells with questionable capsular invasion, no blood vessel invasion and no PTC-type nuclear changes.

An example of type C incomplete capsular invasion is shown in Figure 7 from my practice. Although incomplete features are difficult to illustrate, the 4th edition WHO classification of tumors of endocrine organs presented questionable (incomplete definitive malignant diagnosis) invasions in Figure 2.16 (questionable capsular invasion in WDT-UMP). A hook-like protrusion of type D or E in the Figure 3, tumor cells that penetrated deep into but not completely throughout the capsule was illustrated (1). What is your interpretation for such a lesion? Mine is capsular invasion from minimally-invasive FTC. However, according to the WHO, this is insufficient for malignancy. I believe that many previous FTCs may be reclassified as benign FT-UMPs according to this stricter criteria of capsular invasion.

A recent study by Cipriani *et al*. from the USA reviewed 66 cases of FTC, and found that change in diagnosis occurred in 47 (71%) cases (13). Twenty-four cases were changed to PTC and 18 cases were changed to benign FA. No recurrence or cancer death was found among 18 cases in which diagnoses were changed to FAs. I consider these FTCs reclassified as FAs to be FT-UMPs as observer variation was significant. After review and reclassification of 66 cases of FTCs, significant changes occurred in prognoses of Cipriani's series. The median thyroid cancer-specific survival (CSS) for the FTC group (n = 18) was 19 years. The median thyroid CSS for the poorly differentiated carcinoma (PDC) group (n = 5) was eight years. There were no thyroid cancer-specific deaths in the FA or PTC groups reclassified from FTC (13).

Classification of FTC

In the 3rd edition WHO classification, FTCs were divided based on their degree of invasiveness into two major categories (14). Minimally invasive FTCs have limited capsular and or vascular invasion (Figure 4), whereas widely invasive FTCs have widespread infiltration into adjacent thyroid tissue and/or blood vessels (Figure 5). In minimally invasive FTCs, invasiveness is not visible grossly and can be identified only under microscope (Figure 4B).

Ito *et al*. reported a significant difference between the two types of FTCs. The 10-year CSS was higher (97.2%) for minimally invasive FTCs and slightly poorer (84.2%) for widely invasive FTCs (15). However, the CSS rates of widely and minimally invasive FTCs had no prognostic difference when cases of PDC and/or distant metastasis (DM) were excluded (15). Therefore, the invasiveness, minimally or widely, was not an independent prognostic factor. When invasiveness was combined with angioinvasion, FTCs were risk stratified into 3 groups: group 1: capsular invasion-only minimally invasive FTCs, group 2: angioinvasive minimally invasive FTCs, and group 3: angioinvasive widely invasive FTCs. O'Neill *et al*. examined FTCs in 3 groups. Disease-free survivals were 97% for Group 1, 81% for Group 2 and 46% for Group 3 (16). Based on O'Neil's study, the new WHO classification divided minimally invasive FTCs into 2 subgroups, capsular invasion-only minimally invasive FTC and encapsulated angioinvasive FTC (Figure 8). Furthermore, Xu *et al*. reported that the degree of angioinvasion correlated with prognosis in well-differentiated thyroid carcinomas (17). They demonstrated that the majority of low grade follicular cell-derived thyroid carcinomas followed an indolent clinical course and were associated with very low mortality. However, extensive vascular invasion is correlated with decreased recurrence-free survival for encapsulated low grade follicular cell derived carcinoma. They reported that in patients without distant metastasis at presentation, 5 of 19 (26%) patients with extensive vascular invasion developed recurrence (17). Vascular invasion and extensive vascular invasion

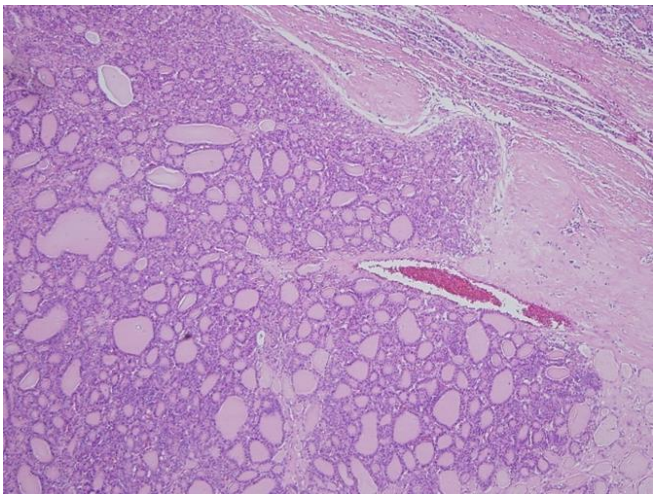

Fig. 7. Questionable capsular invasion, an example of type C in Fig. 3, incomplete capsular invasion (HE stain, x4).

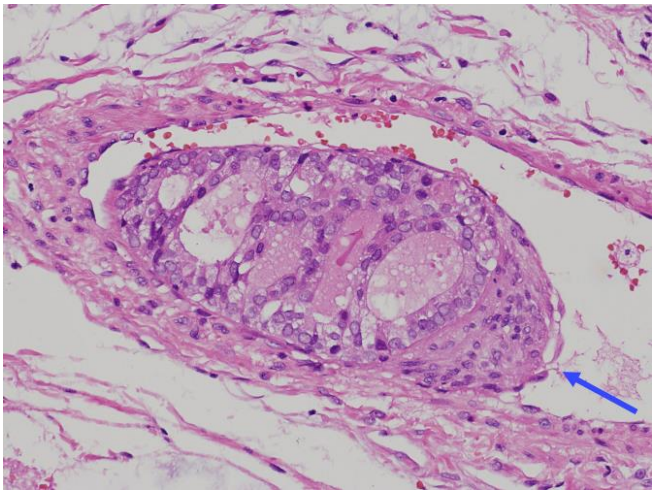

Fig. 9. Vascular invasion by tumor cell nest in widely invasive follicular thyroid carcinoma. A tumor cell mass covered with endothelial lining attached to venous wall is shown. A blue arrow indicating organized thrombus involving tumor mass (HE stain, x10).

were emphasized in the 2015 ATA clinical guidelines (18). The pathological parameters emphasized by the 2015 ATA guidelines include 1) aggressive histology, 2) capsular invasion, 3) the presence and extent of vascular invasion, 4) extrathyroidal extension, 5) the number of lymph nodes with metastatic disease, and 6) the size of metastatic foci. It is increasingly important for pathologists to report these parameters and for clinicians to understand their potential impact on patient management.

How to identify and confirm true vascular invasion in encapsulated thyroid nodules

Many textbooks, including the WHO classification of tumor of endocrine organs (1), emphasize that tumor cells of true vascular invasion should be adherent to vessel walls, and be either covered with endothelium or in the context of thrombus (Figure 9). Further evidence of true vascular invasion is thrombus attached to tumor nests, either fresh fibrin thrombus or organized thrombus (Figure 9). Mete and Asa reported that distant metastases were found more in PTCs, FTCs and PDCs with angioinvasion (19).

How can you be sure that all cases with incomplete invasion are really benign?

In the WHO classification of tumor of endocrine organs, questionable vascular invasion was illustrated in Figure 2.17 as irregular outgrowth of neoplastic cells within vascular spaces of the tumor capsule and tumor cells closely intermixed with vascular spaces of the tumor capsule (1).

Figure 10 is from a consultation case for a 61-year-old female (Figure 10). The patient had a thyroid nodule in the left lobe and was treated with lobectomy at a local hospital approximately 14 years ago. At that time, her nodule was diagnosed as FA. She was found to have a metastatic thyroid carcinoma at her sacral vertebrae. She was referred to our hospital for further treatment. Completion thyroidectomy revealed only benign cysts in her right lobe. The previous benign diagnosis (FA) was revised to follicular carcinoma based on the presence of distant metastasis, although only questionable invasion was noted on review of available histological samples of the primary thyroid tumor (Figure 10).

There have been cases of atypical thyroid nodules that later developed distant metastasis or had distant metastasis at presentation despite the lack of invasion (20-22). This is usually attributed to inadequate sampling (1, 23). Lang *et al*. from Germany reported that number of tissue blocks positively correlated with identification of invasion (23). It increased to 50% when 8 sections were examined, and it became close to 100% when more than 10 sections were examined (23). Based on this observation, many pathologists believe that examining more sections increases the detection rate of invasion (1, 24, 25).

2004 WHO Classification	2015 AFIP Classification		2017 WHO Classification
minimally invasive	minimally invasive	with capsular invasion	minimally invasive
		with limited vascular invasion (< 4 vessels)	encapsulated angioinvasive
		with extensive vascular invasion (>4 vessels)	
widely invasive	widely invasive		widely invasive

Fig. 8. Three prognostic classification of follicular thyroid carcinoma. 2004 WHO (Ref. 14), 2015 AFIP (Ref. 2) and 2017 WHO (Ref. 1).

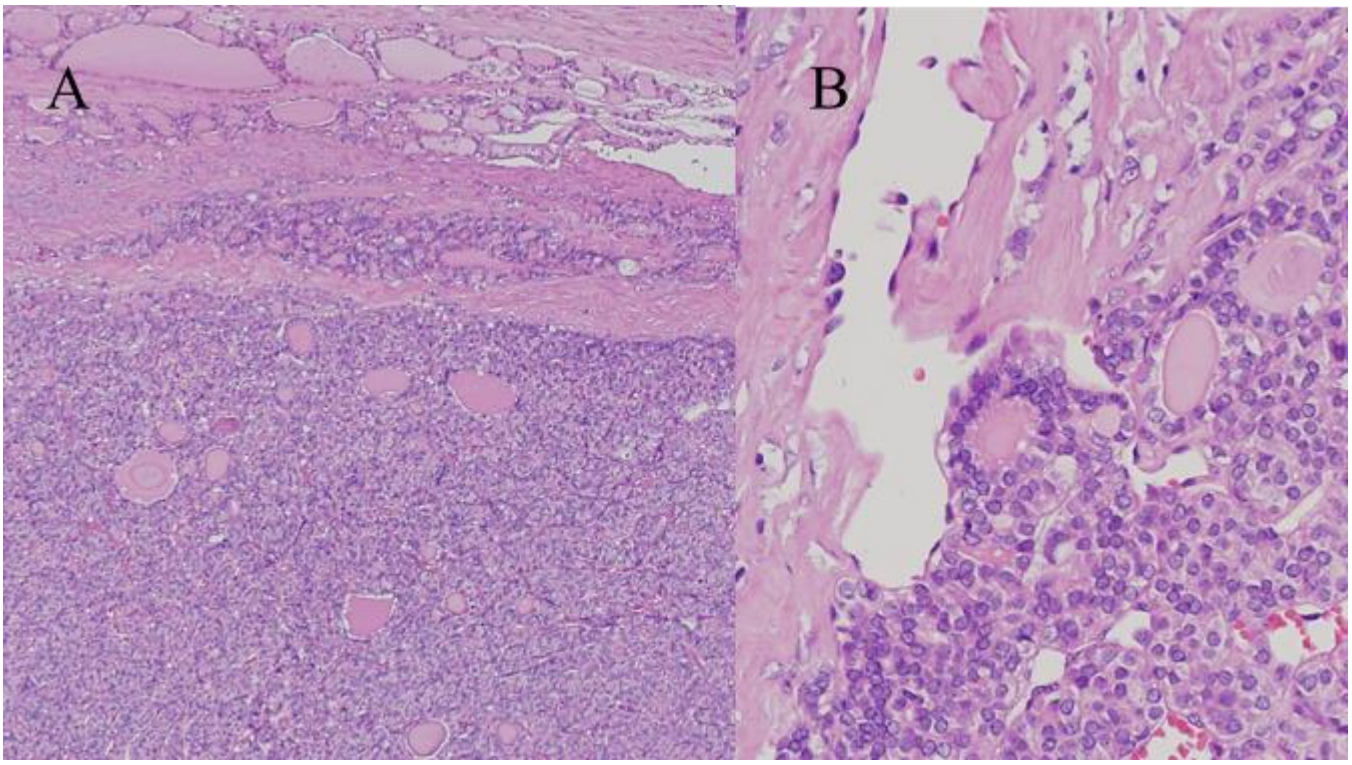

Fig. 10. A consultation case, 61 years old female who developed distant metastasis. She was found to have a metastatic thyroid carcinoma at her sacral vertebrae. Review of histological slides of the primary thyroid nodule treated at local hospital 14 years ago revealed only questionable capsular invasion (A: HE stain, x4) and questionable vascular invasion (B: HE stain, x10) not diagnostic for definitive malignancy (FTC).

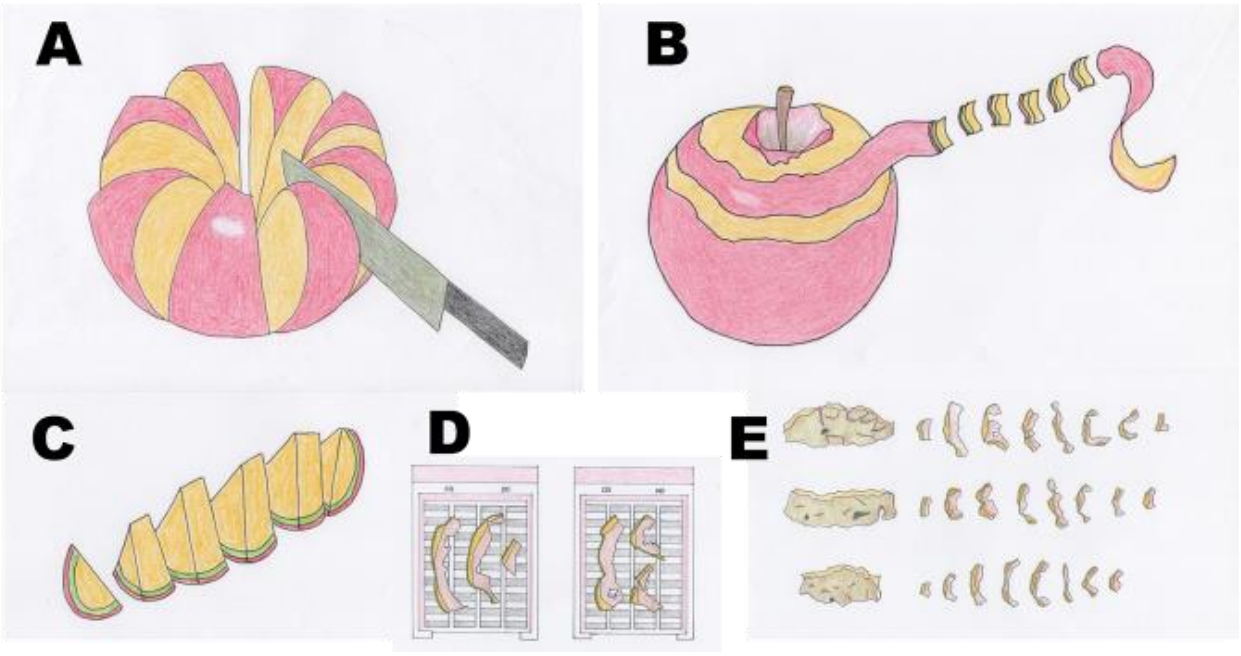

Fig. 11. How to examine entire tumor capsule. Yamashina *et al*. introduced how to examine thyroid nodule (Ref. 24). The nodule was cut into multiple slices as shown in A. A piece of slice was further cut perpendicular to capsule as shown in C. Alternatively the entire capsule may be removed like peeing the skin off apple (B) and capsule parts were cut into multiple pieces perpendicularly (E). Only for capsular parts was careful attention and the parenchymal part of the tumors was trimmed off to minimize the number of paraffin blocks (D).

Yamashina reported how to examine the entire capsule, which is often recommended in Western practice. The entire capsule was removed and cut into multiple pieces perpendicularly (Figure 11). Only capsular parts were paid attention, and the parenchymal part of the tumors was trimmed off to minimize the number of paraffin blocks. With this method, a 3-cm nodule can be examined with approximately 20 blocks (24). The definition of adequate capsular sampling of thyroid nodules is controversial, and varies by practice and institution (25). A survey on sampling techniques among 58 pathologists in 5 Asian countries by Bychkov *et al*. disclosed that 22% do not examine the entire capsule of thyroid nodules (10). The author of this review believes that there are several reasons for why the entire capsule is not sampled according to the methods introduced by Yamashina. One reason is cost. The preparation of histological sections is covered by national health insurance up to 8600 Japanese yen (approximately 80.4 US dollars)/organ, and the doctor's fee for histological diagnosis is 4500 Japanese yen (approximately 42.0 US dollars)/organ in Japan as of 2018. The total cost for one HE section (including tissue container, fixative, tissue embedding, sectioning and staining reagents, glass slide, labor cost and depreciation cost) is approximately 1000 Japanese yen (approximately 10 US dollars). Therefore, a maximum of 8 sections per case is allowed within the budget of pathology laboratories in Japan. When 100 encapsulated nodule cases are received, an average of 20 sections from 100 nodules requires 2000000 yen (approx. 20000 US dollars), whereas an average of 8 sections from 100 nodules requires 800000 yen (approx. 8000 US dollars). This results in a savings of 1200000 Japanese yen/100 thyroid nodules. As such, do more sections increase the chances of identifying invasion? Figure 12 is from my recent consultation case. I was surprised that only 2 blocks were sampled from this 3.6-cm nodule (Figure 12). Although the number of samples was inadequate, multiple invasions were not missed in these 2 HE sections (Figure 12). Figure 13 is an encapsulated angio-invasive FTC from my practice. As you can see here, vascular invasion in fibrous capsules is present everywhere (Figure 13). The first and second sections easily demonstrated invasion in the majority of cases because invasion was observed throughout. More than 5 sections are not necessary for such cases. In 1956, Warren stated that if vascular invasion was not found in three blocks, examination of more blocks would add little information (26). Lang *et al*. from Hong Kong reported that the total number of tissue blocks per centimeter of tumor significantly correlated with the risk of distant metastasis (27). If more than 4 blocks/1 cm of tumor is needed to identify invasion, it is clinically insignificant and not important for the patient. It is likely either FT-UMP or WDT-UMP, and not lethal cancer. However, Xu et al. from the USA concluded differently (17). They 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 among 73 cases. Their study included 13 cases with recurrence and 60 cases without recurrence. For each case, they examined a median of 13 slides (range, 1-47; mean ± SEM, 14 ± 1), 6 tissue sections of tumor capsule (range, 1-21; mean ± SEM, 7 ± 1), and 2.4 sections of tumor capsule per centimeter of tumor (range, 0.6-7.0; mean ± SEM, 2.7 ± 0.2). They concluded that the tumor sampling did not differ across different time periods (i.e., before or after 2000) and was not associated with vascular invasion status or clinical outcome ($P > .05$) (17).

How to examine encapsulated thyroid nodules recommended by the Japanese Society of Thyroid Surgery (JSTS) published in the General Rules for the Description of Thyroid Cancer in 2015

The method for examining encapsulated thyroid nodules recommended by the Japanese Society of Thyroid Surgery (JSTS) was published in the General Rules for the Description of Thyroid Cancer in 2015 (28). Figure 14 is an example of how to examine thyroid nodules according to the JSTS. Multiple sagittal cuts of a thyroid nodule are shown. Peripheral slices are cut perpendicular to the tumor capsule to avoid tangential cuts (Figure 14). Gross examination is an essential step to reduce sampling, but it can be omitted when all slices are submitted for histological examination. In my practice, usually 8 to 10 blocks are sampled from a 3-cm thyroid nodule (2.7-3.3 blocks/1 cm of tumor) when it is a solid tumor or any lesion with suspected invasion. In grossly benign nodules, less than 5 blocks are usually sampled (1.7 blocks/1 cm tumor). Only when questionable invasions were identified, more sections to be added. Please remember that the 5th edition of "Surgical Pathology" by Ackerman and Rosai, published by Mosby in 1974, stated that "at least five or six sections should be taken" (29).

Distant metastasis

The pathological parameters for high-risk structural disease recurrence in the 2015 ATA guidelines with other high-risk prognostic factors included distant metastasis, gross extrathyroid extension, incomplete tumor resection and lymph nodes >3 cm (18). According to Kaplan-Meier cause specific survival (CSS) curves for patients with FTCs who underwent curative or non-curative surgery, FTC patients with distant metastasis have a poorer prognosis than curatively treated patients (15).

Risk stratification of FN

Therefore, FTCs can be risk stratified into 4 prognostic groups: capsular invasion-only minimally invasive FTCs, FTCs with angio-invasion, widely invasive FTCs and FTCs with distant metastasis (Figures 8 and 15). Capsular invasion-only FTCs are indolent tumors after simple excision, similar with follicular adenomas, except that they have capsular invasion (30, 31). Thus, they are not benign tumors by definition, but have a very low risk of recurrence, metastasis and cancer death. They were divided into FT-UMP and capsular invasion-only minimally invasive FTCs by the 4th edition WHO classification, and many of them are downgraded to borderline tumor (FT-UMP) when capsular invasion is not complete or definite (1, 13). This was intended to reduce overdiagnosis and overtreatment of capsular invasion-alone minimally invasive FTCs that were treated in the past with total thyroidectomy and radioactive iodine treatment.

Conclusions

1. The introduction of borderline tumors into the thyroid tumor classification significantly impacted pathology and clinical practice.
2. Follicular neoplasms were classified into 6 prognostic groups (FAs, FT-UMPs, capsular invasion only minimally invasive FTCs, encapsulated angioinvasive FTCs, widely invasive FTCs and FTCs with distant metastasis).
3. Risk stratification of thyroid carcinomas has become an essential component of pathology reports.

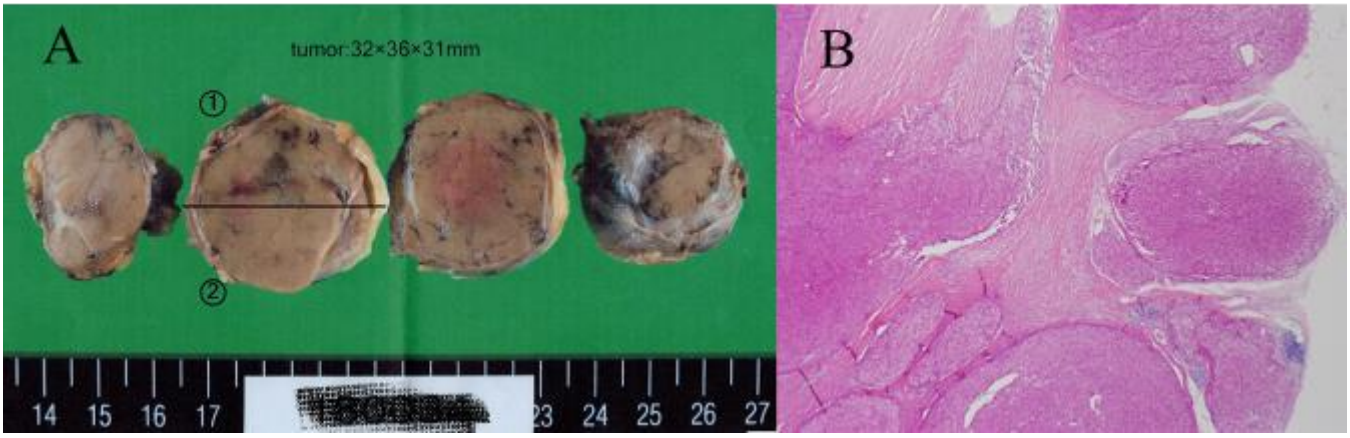

Fig. 12. Only one or two sections were enough to identify invasion in many cases. From a 3.6 cm nodule, only two sections were processed (A) but the two sections successfully demonstrated multiple capsular invasions (B: HE stain, x4).

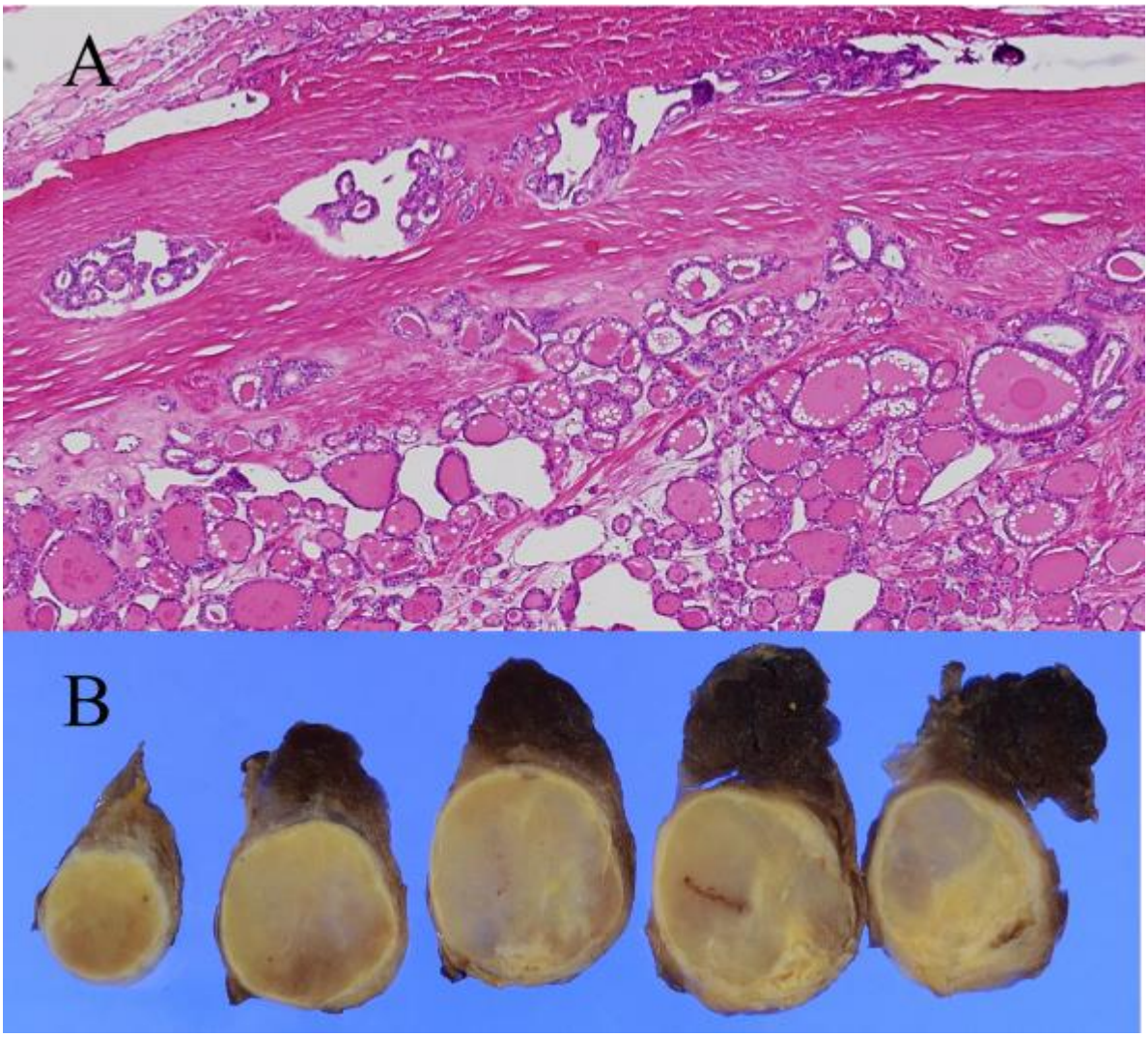

Fig. 13. Extensive vascular invasion. In minority of well differentiated thyroid carcinomas (both papillary carcinoma and follicular carcinoma), an extensive vascular invasion (more than 4) was an indicator for poor prognosis. It can be detected easily with only one or two sections (A: HE stain, x10), while it was not visible grossly (B).

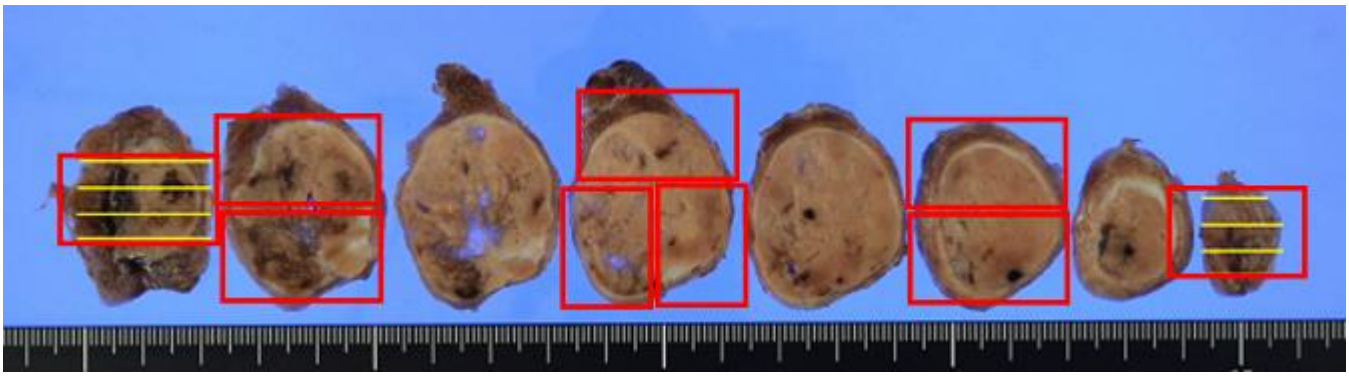

Fig. 14. How to examine encapsulated thyroid nodules recommended by the Japanese Society of Thyroid Surgery. Multiple sagittal cuts of a thyroid nodule are shown. Peripheral slices are cut perpendicular to the tumor capsule. Red boxes indicate sampling areas. Including peripheral slices, usually 8 to 10 blocks per case are sampled from a 3 cm solid nodule in my practice.

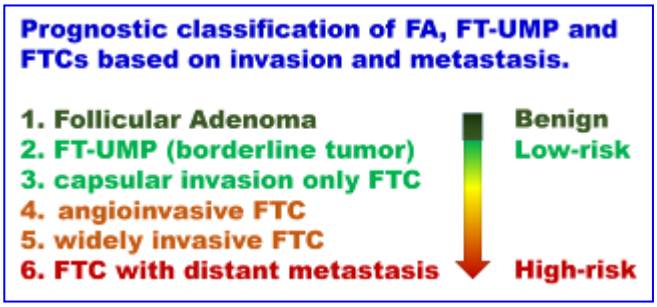

Fig. 15. Prognostic classification of follicular adenoma (FA), follicular tumor of uncertain malignant potential (FT-UMP) and follicular thyroid carcinoma (FTC) based on invasion and metastasis. Follicular neoplasms can be risk stratified into 6 prognostic groups: FA, FT-UMP, capsular invasion-only FTCs, angio-invasive FTCs, widely invasive FTCs and FTCs with distant metastasis.

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