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Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP): Diagnosis and Differential Diagnoses

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Abstract

Non-invasive encapsulated follicular variant of papillary thyroid carcinoma (PTC) was classified as a malignant tumor in the 3rd edition WHO classification of thyroid tumors. This is an indolent tumor and can be cured with lobectomy alone, which has been confirmed by recent studies. The non-invasive encapsulated/well circumscribed follicular cell tumors with PTC type nuclear features (PTC-N) are divided into either well differentiated tumor of uncertain malignant potential (WDT-UMP) or non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) based on whether it has questionable capsular invasions (WDT-UMP) or not (NIFTP). The WDT-UMP and NIFTP are clonal precursor tumors of invasive counterparts. PTC-N are no longer diagnostic criteria of malignancy and the invasiveness takes precedence over nuclear features in diagnosis of encapsulated follicular pattern lesions. Diagnosis of NIFTP is detailed in this study and its differential diagnoses include follicular adenoma, atypical adenoma, WDT-UMP, follicular tumor of uncertain malignant potential, minimally invasive follicular thyroid carcinoma, and invasive encapsulated follicular variant PTC. The proposal of borderline/precursor tumors in thyroid tumor classification is an attempt to reduce over-diagnosis and over-treatment of patients with these tumors. The most important role for pathologists is to advise clinical colleagues that these tumors are not malignant. Aggressive cancer treatment for those patients creates risks and offers little or no benefits to most patients.

Keywords: Thyroid, borderline, precursor tumor, dysplasia, papillary carcinoma, NIFTP, UMP

The WHO classification of endocrine organs is under revision and the editorial committee has decided to incorporate a borderline/precursor tumor category (Chapter 2A: other encapsulated follicular-patterned thyroid tumors), which encompasses uncertain malignant potential (UMP) (1) and non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) (2), into the new 4th edition thyroid tumor classification that will be published in May 2017 (3). Welch and Black divided the heterogeneous disease, cancer, into four groups: fast growing cancer (e.g. undifferentiated carcinoma), slow growing cancer (e.g. differentiated carcinoma with distant metastasis), very slow growing cancer that never causes problems because the patient will die of some other causes before the cancer is large enough to produce symptoms, and non-progressive cancer that may even disappear (4). Pathologists consider all these as malignant tumors. However, aggressive cancer treatment is not necessary for those classified as very slow or non-progressive. How to exclude these unimportant lesions is a challenge for the pathologists. A proposal of well differentiated tumor of uncertain malignant potential (WDT-UMP) and NIFTP is an attempt to identify the "very slow" cancer (requires no cancer therapy) from the "slow" cancer (needs treatment). In other organ systems, there are steps, referred to low grade dysplasia and high grade dysplasia (carcinoma in situ), between benign and malignant tumors (5). Aggressive cancer treatments are no longer accepted as an initial treatment for those dysplastic lesions (squamous intraepithelial neoplasia) of the uterine cervix (6). NIFTP is an oncogene-driven precursor tumor, which was not defined in the 3rd edition of the WHO classification (7) and belongs to a borderline/precursor tumor category (8) of either low grade dysplasia or high grade dysplasia (Figure 1). This paper focuses on how to diagnose those borderline/precursor thyroid tumors as well as on the differential diagnoses among follicular adenoma, atypical adenoma, WDT-UMP, NIFTP, minimally invasive follicular thyroid carcinoma (FTC), follicular tumor of uncertain malignant potential (FT-UMP), and invasive follicular variant papillary thyroid carcinoma (FVPTC).

Histological Diagnosis and Differential Diagnoses

In the seminal paper of NIFTP by Nikiforov *et al*, a consensus diagnostic criteria for the NIFTP was proposed (Table 1) (2). First, it should be an encapsulated/well circumscribed follicular pattern tumor (Figure 2). Second, the encapsulated/well circumscribed follicular growth pattern tumors are assessed for capsular invasion, vascular invasion and metastasis. When any one of these is present, it becomes carcinoma, either invasive encapsulated FVPTC or minimally invasive FTC. When there are questionable features of capsular invasion, it is classified into either FT-UMP (without PTC type nuclear features (PTC-N)) or WDT-UMP (with PTC-N). When it is non-invasive, the nuclear characteristics are checked. When PTC-N is present, it is NIFTP, and in cases without PTC-N, it is classified as follicular adenoma. When PTC-N is questionable (incomplete or worrisome), the nuclear assessment guide proposed

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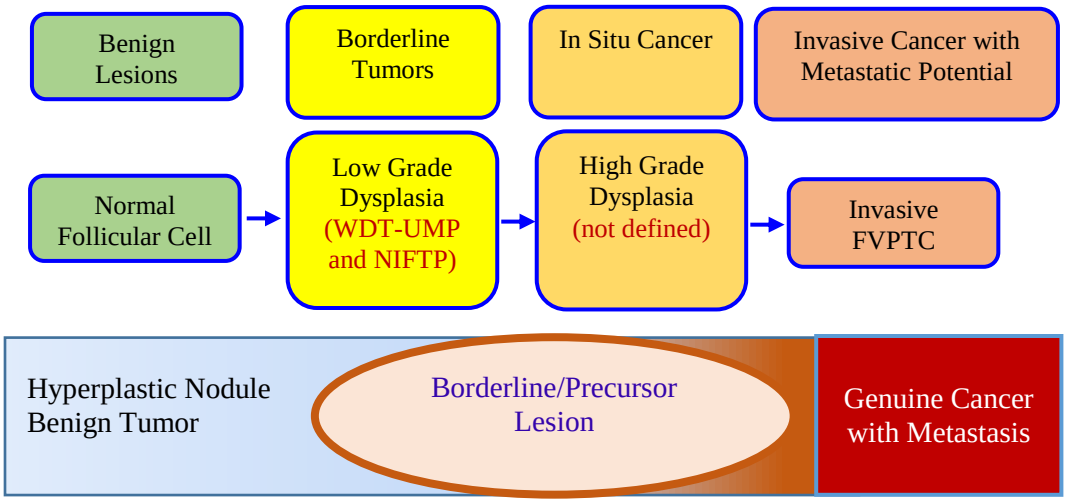


Fig. 1: WDT-UMP and NIFTP (borderline/precursor lesions) in the thyroid follicular cell tumor classification. NIFTP: Non-invasive follicular thyroid neoplasm with papillary-like nuclear features, WDT-UMP: Well differentiated tumor of uncertain malignant potential, and FVPTC: follicular variant papillary thyroid carcinoma.

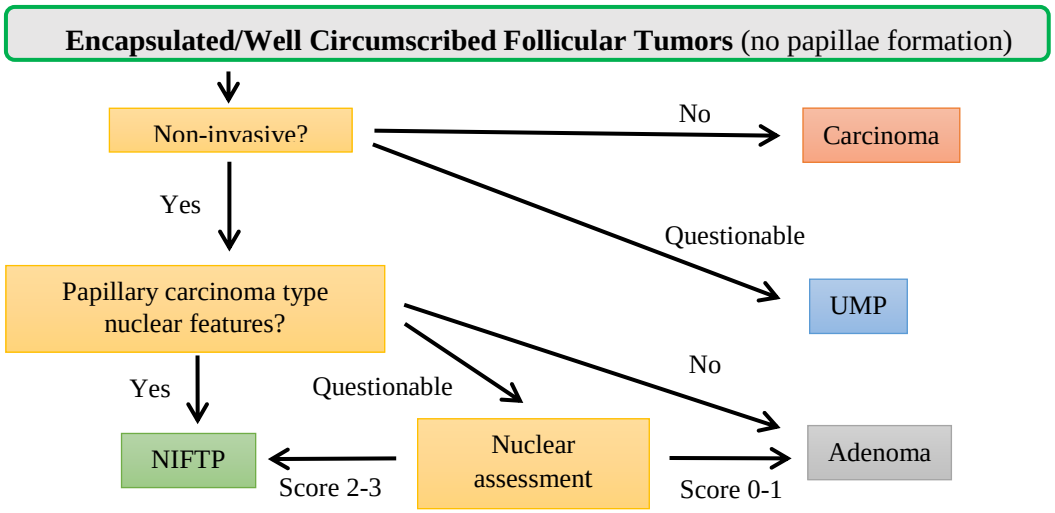


Fig. 2: Diagnostic algorithm of carcinoma, NIFTP, WDT-UMP, FT-UMP and adenoma. NIFTP: Non-invasive follicular thyroid neoplasm with papillary-like nuclear features. UMP: Uncertain malignant potential (WDT-UMP and FT-UMP). Modified from the 4th edition WHO classification of thyroid tumor presented by Tallini G. (reference 3).

by Nikiforov *et al.* helps to classify it as either NIFTP with a nuclear score 2-3 or follicular adenoma with a nuclear score 0-1 (Figure 2) (2). The diagnostic criteria of major features of PTC-N and minor features for diagnosis of NIFTP and FVPTC are shown in Table 1. Nuclear features of PTC include enlargement, crowding/overlapping, elongation, irregular contours, chromatin clearing, pseudo inclusions, and grooves. Minor features helpful for NIFTP diagnosis include dark colloid, irregularly-shaped follicle, "sprinkling" sign, follicles cleft from stroma, multinucleated giant cells within follicles, and intratumoral fibrosis. Exclusion criteria (features not seen in NIFTP) include "true" papillae >1%, psammoma bodies, tumor necrosis, high mitotic activity, and cell/morphologic characteristics of other variants of PTC (Table 1).

These features important for diagnosis of NIFTP and differential diagnoses are discussed below with four cases from our practice.

Case 1:

A 44-year-old Japanese female patient had a solid 43-mm nodule in her right lobe. It had a well demarcated regular border and solid homogeneous echo on ultrasound examination (Figure 3A). Fine needle aspiration cytology revealed a moderate number of crowded groups of follicular cells in which moderate nuclear overlapping was noted (Figure 3B). Mild nuclear enlargement and mild nuclear irregularity with powdery chromatin and rare grooves are shown in Figure 3B. Nuclear pseudo-inclusion was not

Table 1: Consensus diagnostic criteria for NIFTP proposed by Nikiforov *et al*. (modified from reference 2)

Major Features:
1. Encapsulation or clear demarcation
2. Follicular growth pattern
3. Nuclear Features of PTC
    1) Enlargement, crowding/overlapping
    2) Elongation
    3) Irregular contours
    4) Chromatin clearing
    5) Pseudo-inclusions
    6) Grooves

Minor Features:
1. Dark colloid
2. Irregularly-shaped follicles
3. "Sprinkling" sign
4. Follicles cleft from stroma
5. Multinucleated giant cells within follicles
6. Intratumoral fibrosis

Features not seen (exclusion criteria):
1. "True" papillae >1%
2. Psammoma bodies
3. Tumor necrosis
4. High mitotic activity
5. Cellular/morphologic characteristics of other variants of PTC

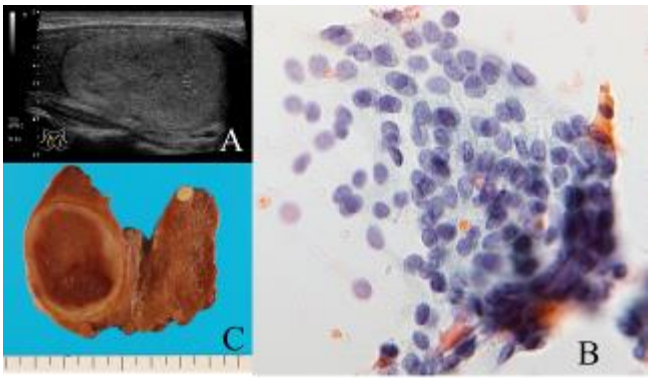
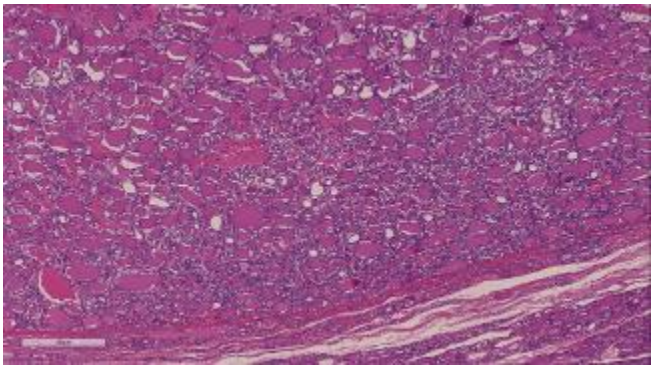


Fig. 3: Case 1 was in a 44-year-old Japanese female patient. It was a well demarcated hypoechoic nodule on ultrasound examination (A). The FNA cytology revealed nuclear irregularity with powdery chromatin and rare grooves in a crowded cluster (B). The cut surface of the right lobe demonstrates a solid 43 mm nodule (C). (B: Papanicolaou stain, x40)



⇦ Fig. 4: A well demarcated nodule composed of follicles separated by thin fibrous capsule is shown in this low magnification of case 1. It was a follicular growth pattern lesion and no papillary growth was observed. Clear spaces between neoplastic follicular cell lining and basement membrane is called a "follicle cleft from stroma". (HE stain, x4)

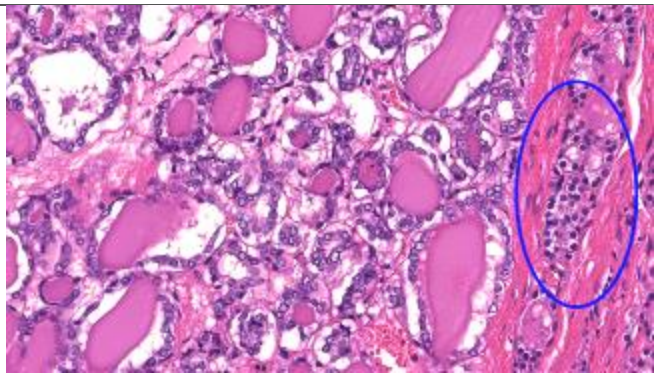


Fig. 5: Increased nuclear size, nuclear membrane irregularity and ground glass nuclei are clearly and diffusely seen in entire nodule of case 1. Please compare with those of small round densely stained nuclei of normal follicular cells in the blue circle. Clear spaces between neoplastic follicular cell lining and basement membrane is called a "follicle cleft from stroma". (HE stain, x20)

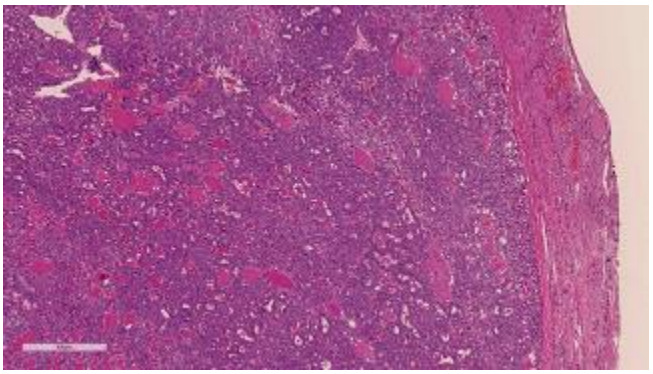


Fig. 7: Low magnification of case 2 shows an encapsulated follicular pattern lesion with no invasion. This follicle forming tumor has relatively basophilic cytoplasm. (HE stain, x 4)

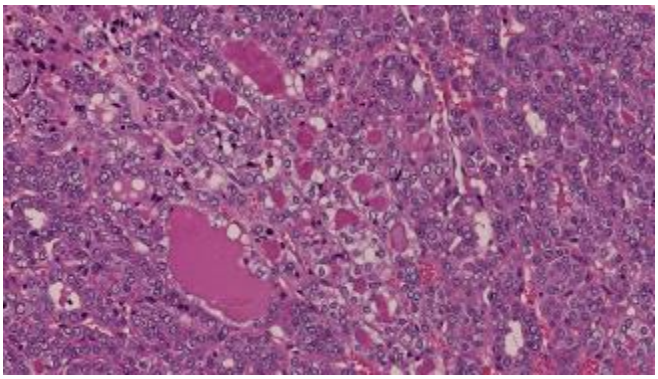


Fig. 8: Focal areas with nuclear irregularity and pale chromatin are observed in case 2. (HE stain, x20)

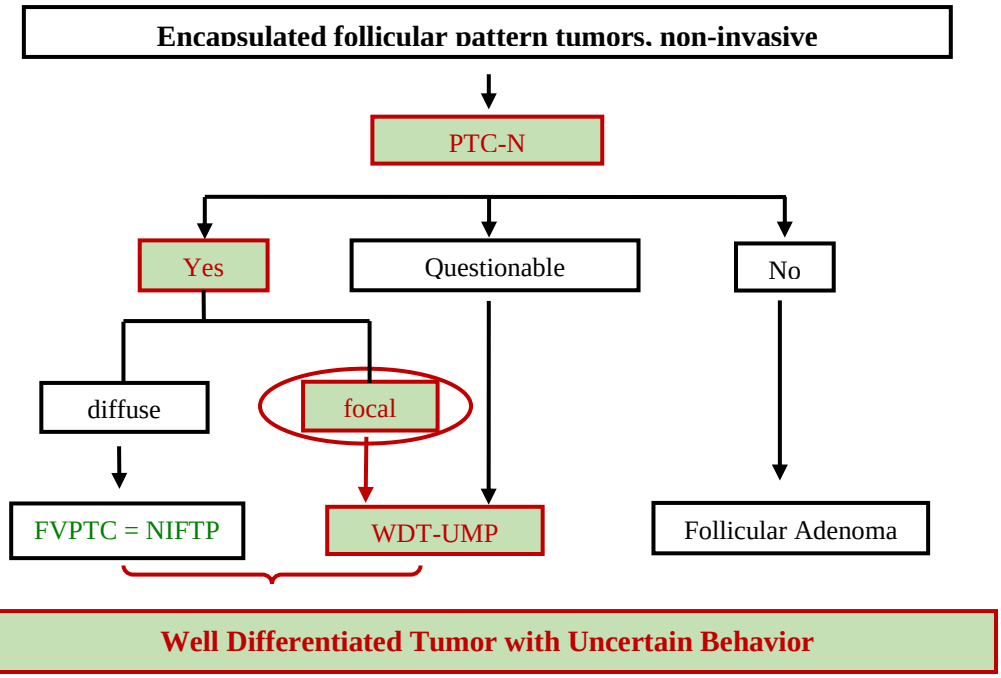


Fig. 6: Encapsulated follicular pattern tumors with PTC-type nuclear features are classified in NIFTP, but how to handle cases with focal PTC-N was not defined (modified from reference 11).

observed. The cytological interpretation in our practice was atypia of undetermined significance with the Bethesda reporting system (9) or indeterminate B (PTC cannot be ruled out) with the Japan Thyroid Association system (10). The cut surface of the right lobe from a total thyroidectomy specimen demonstrated a solid 43-mm nodule (Figure 3C).

It was an encapsulated solid nodule with a follicular growth pattern at low magnification (Figure 4). No papillary growth was observed. Increased nuclear size, nuclear membrane irregularity, and ground glass nuclei were diffusely distributed in the entire nodule (Figure 5). Please compare their nuclear size to those of benign follicular cells in the blue circle in the Figure 5. Diagnosis of NIFTP (nuclear score 3) was rendered.

A question arising is "is it NIFTP when PTC-N was found only focally in the nodule? This has not been defined yet in any reports on NIFTP. Liu *et al.* from our group classified cases with focal PTC-N into WDT-UMP and proposed a new term of well differentiated tumor with uncertain behavior (WDT-UB), to encompass all cases of diffuse PTC-N (NIFTP), focal PTC-N (not defined but proposed to combine it as WDT-UMP by Liu *et al.*), and diffuse questionable PTC-N (WDT-UMP) (Figure 6) (11).

Case 2:

A 38-year-old Japanese female patient with a solid 30-mm nodule in her right lobe.

It was an encapsulated follicular pattern lesion with no invasion. This follicle-forming tumor has relatively basophilic cytoplasm (Figure 7). Focal areas with nuclear irregularity and pale chromatin were observed (Figure 8). By our definition, it was classified as WDT-UMP. However, other groups of pathologists may classify it as NIFTP because a PTC-N of score 2 was found only focally scattered or spotted tumor areas. Distinction between WDT-UMP and NIFTP is not well established yet and the observer variation may occur. Further studies are awaited to clarify any biological significance between them, such as higher risk of progression in one and lower risk in another.

Case 3:

A 28-year-old Japanese female with a solid 19-mm nodule in her right lobe. It was an encapsulated follicular pattern tumor with no invasion.

Marked nuclear enlargement, nuclear irregularity and a few giant nuclei in the yellow circle are shown in Figure 9. Please note the nuclear inclusion indicated by the blue arrow, although it was rare in this case. Ground glass nuclei or pale chromatin pattern were rarely seen in this case. Differential diagnoses included atypical adenoma, WDT-UMP and NIFTP (12, 13).

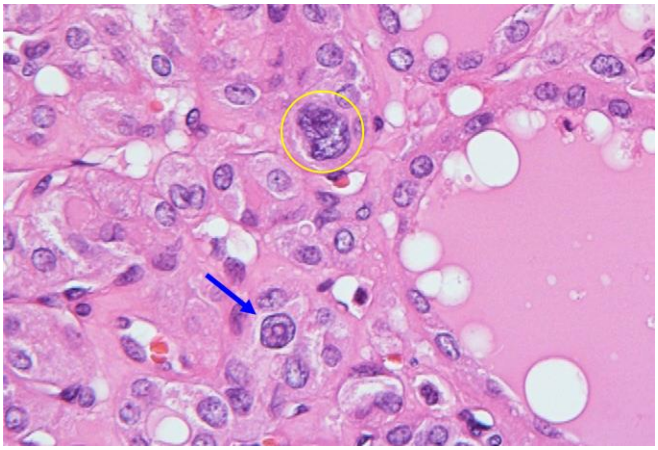


Fig. 9: A higher magnification of case 3 demonstrates marked nuclear enlargement, nuclear irregularity and a few giant nuclei in yellow circles. Note a blue arrow indicates nuclear cytoplasmic pseudo-inclusion. Ground glass nuclei or pale chromatin pattern was not discernible. (HE stain, x40)

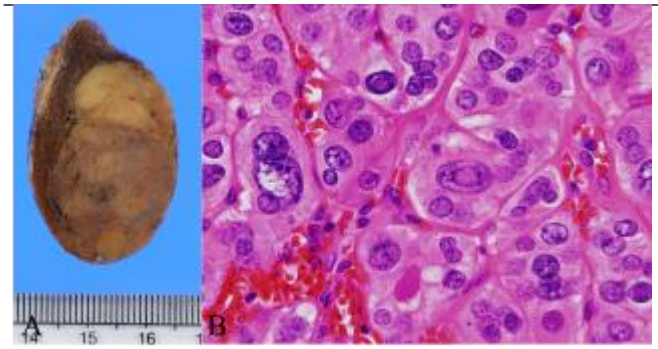


Fig. 10: A 60-year-old female patient. A: 40 mm well circumscribed nodule on the cut surface. B: Marked nuclear enlargement and multiple cytoplasmic nuclear pseudo-inclusions are easily observed. Ground glass nuclei or pale chromatin pattern was not discernible. (HE stain, x40)

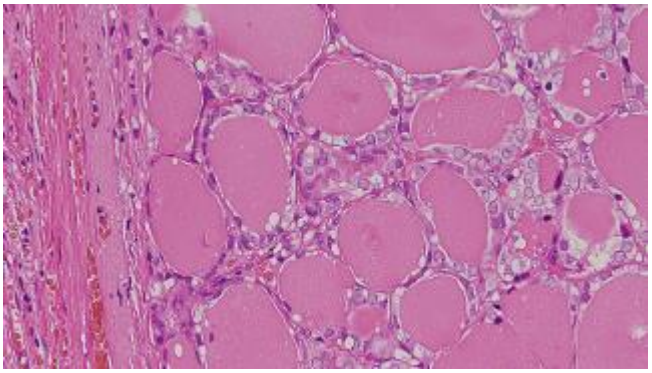


Fig. 11: "Sprinkling" of the follicles lined by cells exhibiting the characteristic PTC-N on the background of follicles with benign appearing. Please note ground glass nuclei with irregular nuclear contour. (HE stain, x40)

Case 4:

A 40-mm well-circumscribed nodule was found in a 60-year-old female patient (Figure 10A). Marked nuclear enlargement (giant nuclei) and multiple cytoplasmic nuclear pseudo-inclusions were easily observed (Figure 10B). Ground glass nuclei or pale chromatin pattern were not discernible in this case. Under the current diagnostic criteria of NIFTP as proposed by Nikiforov *et al*. (Table 1), case 3 and case 4 should be classified as NIFTP (nuclear score 2). When one regards the nuclear features of case 3 and case 4 as high grade nuclear features and does not classify them as FVPTC type nuclear features (Figure 5), encapsulated thyroid tumor of follicular cell origin with high grade features may be selected, as proposed by Rivera *et al*. (14), or atypical adenoma (12, 13). It has been reported that completely encapsulated, non-invasive, and high grade tumors with mitotic activity or necrosis, and with features compatible with poorly differentiated carcinoma according to the consensus criteria (except for lack of invasion) did not recur or metastasize for a median follow up of more than 10 years (3, 14). We would like to say, however, that strict distinction may not be important practically among follicular adenoma, atypical adenoma, WDT-UMP, FT-UMP, NIFTP, WDT-UB and encapsulate thyroid tumor of follicular cell origin with high grade features. This is because they are all artificial entities given to non-malignant thyroid lesions in definition. Mehrzrd *et al*. reported that

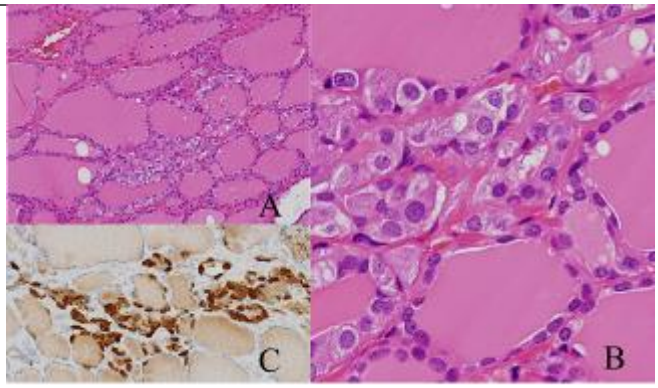


Fig. 12: A: Precursor lesion (C cell hyperplasia) of C cell carcinoma in normal looking thyroid from 10-year-old female with MEN 2a syndrome. B: Note the salt and pepper nuclear features different from the ground glass appearance of PTC type. C: The cytoplasm is positively stained for calcitonin (brown) immunohistochemically. (A: HE stain, x10, B: HE stain, x40 and C: immune-peroxidase method for calcitonin, x10)

the incidence of follicular adenomas decreased in a reverse fashion to FVPTC, resulting in a more than 10-fold increase in the ratio of FVPTC to follicular adenomas during the study period (15). The authors hypothesized that FVPTC is increasing and that this increase may reflect changes in diagnostic criteria (15). The discrepancy in the diagnosis of follicular adenoma and NIFTP does not mean misdiagnosis by pathologists. All are biologically benign after complete excision. Further studies are awaited to elucidate any biological differences among them, such as novel molecular mechanisms and risk of progression, which is important for clinical management of patients.

Minor Features of NIFTP and FVPTC

Dark colloid and irregular shaped follicles are easily observed in Figures. 5, 8 and 9. "Sprinkling" of the follicles lined by cells exhibiting the characteristic PTC-N on the background of follicles with benign appearance are shown in Figure 11. This is a hyperplastic or neoplastic growth of follicular cells within follicles between normal follicular cells and basement membrane (Figure 11). An analogous observation is referred to as "C cell hyperplasia" in normal-looking thyroid glands with MEN 2a syndrome as an early precursor lesion of hereditary C cell carcinoma (Figure 12). Follicle clefts from the stroma are shown in the Figures 4 and 5. Cleft-like spaces between the basement membrane and follicular cell lining are often seen and are characteristic features of NIFTP and invasive FVPTC. This is the morphological evidence suggesting that these follicular cells are neoplastic or dysplastic in nature. Dysplastic cells often exhibit loss of cellular cohesion and this type of detachment from the basement membrane is also seen in carcinoma in situ of the urinary bladder and uterine cervix as an artifact of detachment of dysplastic cells during tissue processing.

Multinucleated giant cells within follicles and intratumoral fibrosis may be found in NIFTP, but they are non-specific findings that are often seen in chronic thyroiditis, subacute thyroiditis, non-neoplastic hyperplastic nodules, benign follicular adenomas, and conventional PTCs.

Table 2: The reasons why the borderline tumor categories are necessary in thyroid tumor classification

1. Borderline or precursor lesions are essential steps to adapt the multistep carcinogenesis theory.
2. Some tumors in the cancer category behave as if they are benign or have very low grade malignancy.
3. The borderline category reduces observer disagreements.

Table 3: Most important (major) criteria for the diagnosis of follicular variant PTC by Lloyd *et al*. (reference 35)

1. Cytoplasmic invagination into the nucleus (25.3%)
2. Abundant nuclear grooves (100%)
3. Ground glass nuclei (97.8%)
4. Psammoma bodies (16.1%)
5. Enlarged overlapping nuclei (98.8%)
6. Irregularly shaped nuclei (100%)

Discussion

The reasons why borderline/precursor lesions are necessary for thyroid tumor classification (Table 2)

In other organ systems, there are steps, referred to as low grade dysplasia and high grade dysplasia (carcinoma in situ), as the precursor lesions of invasive carcinoma between benign and malignant tumors (Figure 1). These were not defined in the 3rd edition of WHO classification of thyroid tumors (7). It is an essential step for thyroid follicular cells in the multistep carcinogenesis theory from benign lesion to lethal carcinomas. Accumulation of genetic alterations and molecular events attributes to this progression from normal follicular cells to thyroid carcinoma with metastatic potential (Figure 1) (16-18).

Some tumors in the cancer category behave as if they are benign or as very low grade malignancy, and several groups of thyroid researchers proposed as how to handle these indolent lesions. The Williams and Chernobyl pathologists group proposed terminology for three distinct groups of thyroid tumors in 2000, which often resulted in observer disagreements (1). The three groups were WDT-UMP, FT-UMP and well differentiated carcinoma not otherwise specified (WDC-NOS). Kakudo *et al*. proposed borderline lesions in their thyroid tumor classification schema in 2009, in which WDT-UMP and FT-UMP were included in the borderline category. This classification was updated in 2011, 2012 and 2015, respectively, and the borderline category (WDT-UB) included WDT-UMP and NIFTP (topics of this special issue), and some more indolent tumors currently labeled as carcinoma. The later included intrathyroidal low-risk papillary microcarcinoma, encapsulated tumors with or without nuclear features of PTC and with or without minimal capsular invasion (encapsulated common type PTC, minimally invasive and capsular invasion only FTC, and FT-UMP) (11, 19-22). This is because all of the above carcinomas usually demonstrate indolent nature after excision. Castro *et al*., Liu *et al*., Rivera *et al*., Vivero *et al*., Howitt *et al*. and Ganly *et al*. revealed that encapsulated/well circumscribed FVPTCs were not BRAF tumors of PTC lineage but instead RAS tumors of follicular adenoma/FTC lineage (23-28).

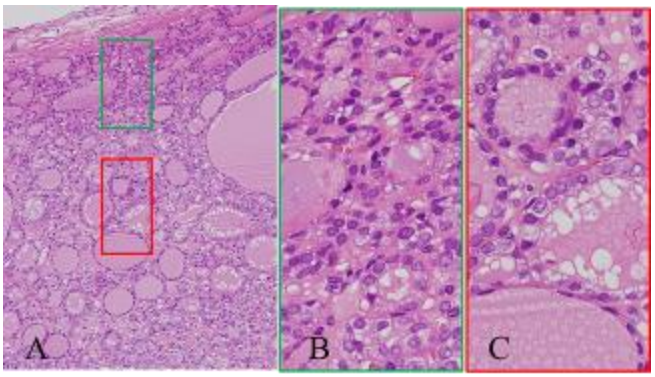


Fig. 13: Possible artifacts from fixation and tissue processing result in powdery chromatin worrisome for PTC. A: Surface of thyroid nodule is shown in the upper field and deep inside in the lower field. B: A higher magnification of surface area in the green box of A. C: A higher magnification of deeper area in the red box of A. Many nuclei are irregularly shaped, but size of nuclei is smaller in B and slightly larger in C. More nuclei in B are deeply stained and hyperchromatic, but more have a ground glass or powdery pattern in C. (HE stain, A: x4, B: x20, C: x20)

Prognosis of NIFTP and WDT-UMP

There have been many reports emphasizing the indolent nature of encapsulated/well circumscribed follicular cell carcinomas (both encapsulated PTCs and FTCs). Piana *et al*. reviewed 67 cases of fatal thyroid carcinoma in a cohort of 1009 consecutive cases of thyroid carcinoma treated at an Italian hospital with an average follow-up of 11.9 years. They found that no cancer death occurred with minimally invasive FTC (29 cases), encapsulated FVPTC with (21 cases) or without invasion (45 cases), WDT-UMP (5 cases) and FT-UMP (6 cases) (29). The Memorial Sloan-Kettering Cancer Center Group reported that none of their 57 cases of non-invasive encapsulated FVPTC developed lymph node metastasis or recurrence, whereas invasive encapsulated FVPTC could metastasize and spread like FTC. They concluded that non-invasive encapsulated FVPTC could be treated in a conservative manner sparing patients unnecessary total thyroidectomy and RAI therapy (24, 25, 28). Nikiforov *et al*. analyzed the prognosis and follow-up data of 210 patients of encapsulated FVPTC with or without invasiveness provided by 13 medical centers from five countries (2). No recurrence or metastasis was found in the 109 cases of the non-invasive encapsulated FVPTC, with an average of 14-year follow-up, while it was found in 12 patients of the 101 cases of the invasive counterpart. Two patients in the invasive group also died of the disease. These results suggest that invasiveness can stratify this type of tumor into benign or malignant categories, similar to follicular adenoma and follicular carcinoma. The gold standard of thyroid pathology, tumors with PTC-N are malignant tumors, has collapsed (7).

In old reports, many authors reported excellent prognosis in encapsulated PTC (30) and minimally invasive FTCs (31, 32). Our group also reported no recurrence/metastasis or causing specific death for 25 cases of encapsulated PTC with more than 10 years follow up in 2008 (33). Liu *et al*. from our group reported a rate of encapsulated FVPTC without invasion as low as 0.4% and WDT-UMP as 5.6% of PTCs, they confirmed no recurrence in 20 cases of WDT-UMP with more than 8 years of follow up (11).

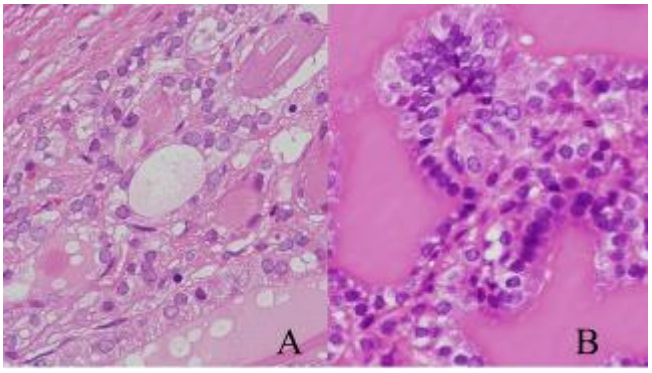


Fig. 14: Possible artifacts from fixation and tissue processing result in powdery chromatin worrisome for PTC. Both illustrations, A and B, are from the same nodule processed equally. However, the thickness of sections is different, a thin section on the left (A) and a relatively thick section on the right (B). Nuclear size and irregularity of A and B may be equal, however, there are significant differences in nuclear chromatin patterning between A and B. (HE stain, A: x40, B: x40)

Problems in Assessment of PTC-N

PTC-N has artifact problems, which should be considered when evaluating PTC-N and scoring nuclear features (34). Thyroid tissue is usually fixed in formalin solution for several days. Poor fixation may occur inside of large tissue mass, and surface of tissue may have dry artifacts where the fixative does not reach well. Figure 13 shows the surface and deep area of thyroid nodule. Many of the nuclei are irregularly shaped, but the size of nuclei is smaller in the surface area (Figure 13B) and slightly larger in the deep tumor area (Figure 13C). More nuclei in the Figure 13B are deeply stained and hyperchromatic, but more marked ground glass or powdery pattern is observed in Figure 13C.

Both illustrations of A and B in Figure 14 are from the same nodule processed equally. However, the thickness of sections is different between them, a thin section on the left (A) and a relatively thick section on the right (B). What is your interpretation for the nuclear features? You may consider a paler and ground glass nuclear chromatin pattern in the thin section than in the thick section. Possible artifacts from poor fixation, dryness, tissue processing and electric coagulation by surgical procedure result in pale chromatin pattern and worrisome nuclear feature for PTC type malignancy (34).

A conservative approach to evaluate PTC-N is recommended for cases with focal or limited nuclear changes, because some of them are not true PTC-N but tissue artifacts. Even if it is true PTC-N, they are not high-risk papillary carcinoma, as long as they are encapsulated and non-invasive (29, 30, 33). It should be any one of borderline/precursor tumors and can be cured with lobectomy alone. A benign diagnosis does not harm the patients even if NIFTP is erroneously diagnosed as follicular adenoma.

Exclusion Criteria for NIFTP

Exclusion criteria for NIFTP are listed in Table 1 (2). They are; “true” papillae more than 1%, psammoma bodies, tumor necrosis, high mitotic activity, and cellular/morphologic characteristics of other variants of PTC. However, Lloyd *et al*. reported that the important (major) criteria for the diagnosis of FVPTC included psammoma bodies found in 16.1% of their 87 cases (Table 3) (35). As presence of psammoma bodies is an exclusion criteria for NIFTP, the non-invasive encapsulated FVPTCs with psammoma bodies diagnosed by Lloyd *et al*. should not, by definition, be NIFTPs as proposed by Nikiforov *et al*. (2). Secondly, FVPTC was defined as a neoplasm with PTC-N and a predominantly follicular growth pattern (36), minor papillary growth was often accepted in FVPTC in the past (37). However, cases with papillary growth are strictly excluded from NIFTP (2). In this sense, NIFTP has a narrower definition than encapsulated non-invasive FVPTC. Further studies, however, are required to assess whether the inclusion and exclusion criteria for NIFTP should be refined.

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