Review Article on Differentiated Thyroid Carcinomas

How to handle borderline/precursor thyroid tumors in management of patients with thyroid nodules

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Abstract: Thyroid carcinomas originating from follicular cells have the prognosis of heterogeneous diseases, but pathologists classify them all as malignant disease. Epidemiologists have issued a stern warning regarding over-diagnosis and overtreatment of patients with indolent thyroid tumors that cause no harm to the patients. Review of the literature revealed that there were several proposals of borderline/precursor tumors to some indolent thyroid carcinomas. Thyroid tumor of uncertain malignant potential (UMP) was first proposed by Williams for encapsulated follicular pattern thyroid tumors to solve problems due to observer variation. Rosai *et al.* proposed to rename papillary microcarcinoma (PMC) to papillary microtumor as the overwhelming majority of them are of no clinical significance. Liu *et al.* proposed well-differentiated tumor with uncertain behavior (WDT-UB) which covered WDT of UMP (WDT-UMP) and non-invasive encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC). The EFVPTC without invasion was renamed as non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) by an international panel of pathologists. A new prognostic classification of thyroid tumors was proposed by Kakudo *et al.*, in which extremely low risk tumors were grouped in a borderline tumors category. The borderline/precursor thyroid tumors included encapsulated tumors [capsular invasion only follicular carcinoma, encapsulated papillary carcinoma without invasion, WDT-UMP and follicular tumor of UMP (FT-UMP)] and non-encapsulated tumors (PMC). The UMP and NIFTP were incorporated in the 4th edition WHO classification of thyroid tumors as a new tumor entity in chapter 2-2A: other encapsulated follicular patterned thyroid tumors. Their behavior codes were decided to be 1 (borderline or uncertain behavior), and not 0 (benign), 2 (*in situ* carcinoma) or 3 (malignant). These borderline/precursor thyroid tumors are indolent tumors biologically and should be treated more conservatively than as previously recommended for thyroid follicular cell carcinomas [total thyroidectomy (TTX) followed by radio-active iodine (RAI) treatment] by western clinical guidelines.

Keywords: Borderline tumor; non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP); microcarcinoma; precursor tumor; thyroid; uncertain malignant potential (UMP)

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Proposal of borderline/precursor thyroid tumors

In 2009, our group proposed a new classification of thyroid tumors, which was characterized by a borderline tumor category (1), and it was updated in 2011, 2012 and 2015 (*Table 1*) (2-6). Surprisingly, no borderline/precursor lesions of follicular cell tumor lineage were defined in the previous 3rd edition of the WHO classification of thyroid tumors (7), whereas in C cell tumor lineage, C cell hyperplasia (C cell carcinoma *in situ*) was defined as a precursor or early stage of C cell carcinoma (8-11). The borderline/precursor tumors in the thyroid follicular cell tumor classification proposed by Kakudo included encapsulated tumors [capsular invasion only follicular carcinoma, encapsulated papillary carcinoma without invasion, well-differentiated tumor of uncertain malignant potential (WDT-UMP) and follicular tumor of UMP (FT-UMP)] and non-encapsulated tumors [papillary microcarcinoma (PMC)] (*Table 1*) (3,6).

Table 1 The borderline tumor category in prognostic classification of follicular cell tumors using Ki-67 labeling index proposed by Kakudo (1-6)

Benign tumors (Ki-67 LI: <3%)
Follicular adenoma
Borderline (precursor) tumors (Ki-67 LI: <3%, and T1, N0, EX0 and M0)
Encapsulated tumors
Capsular invasion only follicular carcinoma
Encapsulated papillary carcinoma without invasion
Well-differentiated tumor of uncertain malignant potential
Follicular tumor of uncertain malignant potential
Non-encapsulated tumors (formerly called papillary microcarcinoma)
Papillary micro-tumor (<1 cm)
Malignant tumors (invasive carcinoma and >1 cm)
Low risk (Ki-67 LI: <5%)
Moderate risk (Ki-67 LI: 5–10%)
High risk (Ki-67 LI: 10–30%)
Undifferentiated carcinoma (Ki-67 LI: >30%)

Indolent thyroid tumors

Encapsulation and well-circumscribed or expansive growth were reported to be significant indicators of favorable prognosis of thyroid carcinomas by many authors (12-16). Piana *et al.* analyzed their 1,009 consecutive cases with thyroid carcinoma treated at a single Italian hospital with average 11.9 years follow-up (15). They found no cancer death in their 66 cases of encapsulated follicular variant PTCs (45 cases without invasion and 21 cases with invasion), 29 cases of minimally invasive follicular carcinomas (23 cases with capsular invasion only and 3 cases with vascular invasion), 6 cases of well differentiated carcinoma, not otherwise specified, 5 cases of WDT-UMP and 6 cases of FT-UMP (15). Memorial Sloan Kettering Cancer Center group reported that their non-invasive encapsulated follicular variant PTCs treated with surgery alone did not developed recurrence or metastasis (17-19) and it was confirmed by Nikiforov *et al.* with their large (n=109) patient series (20). In non-encapsulated tumors, PMC of the thyroid has been reported as a common finding, 11.5% on autopsy and 25–30% on ultrasound examination (21). It was concluded that PMC was a normal finding in adult autopsy thyroid glands in Finland by Harach *et al.* because it was found in more than 35% of autopsy patients and did not cause any symptoms or direct cause of patient's death (22).

Active surveillance to the patient with PMC

An observation trials of patients with clinical PMC was initiated by Miyauchi *et al.* in 1993 (23) and conducted by two independent groups of surgeons in Japan (24-29). Observations in these patient cohorts proved that more than 86% of PMCs were stable (no change), decreased in size or disappeared during an average 5-year follow-up (30). The remaining 14% of patients accepted surgery after a certain period of clinical follow-up. Those patients accepted surgery after lymph node metastasis or tumor enlargement were detected, or when patients changed their mind and dropped out from the observation program (24-29). It was clearly demonstrated that the vast majority of intrathyroidal (low risk) PMCs were very slow growing carcinoma (cancer that never causes problems because the patient will die of some other cause before the cancer is large enough to produce symptoms) defined by Welch and Black (31), or an IDLE (indolent lesion of epithelial origin, which are currently labelled as cancers and their precursors that are unlikely to cause harm if they are left untreated) proposed by Esserman *et al.* (32). All patients who dropped out from this program were treated with so-called rescue (delayed) surgery successfully without increased mortality and morbidity, and no persistent disease or cancer death was reported in those patients during more than 5 years of follow-up (23-29). In Kuma hospital patient series (n=1,235), 8% of patients showed tumor enlargement by 3 mm or more at 10 years of observation, and 3.8% of patients showed novel appearance of lymph node metastasis at 10 years (23).

Assignment to observation and immediate surgery groups was not random but based on the patient's choice after thorough consultation. Please note that the follow-up (observation without surgery) group of patients with PMC in these studies was not a control group with no treatment because these patients could select surgical treatment at any time freely (23). The aim of this active surveillance program of patients with PMC is to avoid unnecessary immediate surgery, which may create significant risk of overtreatment and treatment-related complications, while at the same time identify patients with a potentially higher risk for progression, such as growing thyroid nodules,

blurred tumor margins or new lymph node enlargements by ultrasound image. These authors concluded that immediate surgery for PMC is not necessary, and observation with full follow-up (so-called active surveillance) is one choice for those patients. Miyauchi concluded, although he still offers two options, immediate surgery or observation, to patients with low-risk PMC at Kuma hospital, that he now strongly recommends observation as the best choice (23). Under this clinical practice at Kuma Hospital, PMCs occupied only about 10% of surgically treated primary thyroid carcinomas (personal communication).

Treatments of PMC in western practice

While in the past US practice, 73.4% of 29512 patients with PMC were treated with total thyroidectomy (TTX) and 31.3% of patients were treated with radio-active iodine (RAI) from an analysis of the Surveillance, Epidemiology and End Results database by Wang *et al.* (33). Permanent hypothyroidism is unavoidable in all patients who receive TTX and a significant proportion of patients who are treated with lobectomy later develop hypothyroidism, as a result, and life-long thyroid hormone administration is necessary for these patients. Surgical complications (hematoma, infection, hypoparathyroidism or laryngeal nerve dysfunction) were reported in 15.1% of 1,379 patients treated with thyroidectomy (5.6% in lobectomy and 18.0% in TTX) for follicular neoplasm (FN) nodules in 26 Italian hospitals (34) and Leboulleux *et al.* concluded that permanent complications from surgery cannot be decreased to less than 1–3% even in high-volume tertiary care centers with experienced surgeons (21). Incidence of second primary malignancy in patients with thyroid cancer treated with RAI was reported to be high in salivary gland malignancies and leukemia (35). Lang *et al.* found that non-synchronous second primary malignancies accounted for 18.7% of all death in differentiated thyroid cancers, and mortality of second primary malignancies was very high (43.5%) (36). Thyroidnews <thyroidnews@news.thyroid.org>, released from the American Thyroid Association (ATA) on 18th of August, 2016, stated that (I) do not perform thyroid fine needle aspiration (FNA) on nodules less than 1 cm unless there is evidence of extrathyroidal extension or of lymph node or distant metastases; and (II) restrict surgery to lobectomy and avoid RAI to those with low risk features. The cancer diagnosis by pathologists for thyroid nodules, less than 1 cm, is not accepted or almost denied by the ATA management guidelines officially. This was a strategy by the ATA to reduce overtreatment of indolent thyroid tumors (37), although expert pathologists already proposed to rename PMC to papillary micro-tumor in 2003 (38) and Kakudo *et al.* classified it in the borderline tumor category (3,6). These proposals for borderline/precursor tumors in the thyroid tumor classification were attempts by pathologists to stop over-diagnosis of indolent tumors. In a same time, the concept of active surveillance for patients with PMC proposed by a Japanese surgeon (23) was endorsed by the ATA thyroid cancer management guidelines as an alternative to immediate surgery and is adopted by the leading thyroid clinics in Korea, USA and EU countries (21,39-41). Although Nickel *et al.* suggested that clinicians may not be ready to accept nonsurgical options or change in terminology until evidence to support these options and changes is stronger (42).

Proposal of NIFTP and the new 4th edition of the World Health Organization classification of endocrine organs

Several authors reported the controversial nature of the follicular variant of papillary thyroid carcinoma (FVPTC). It is a heterogeneous group of tumors, including non-invasive encapsulated FVPTC, invasive encapsulated FVPTC and invasive non-encapsulated (infiltrative) FVPTC, which are different biologically and have different genetic alterations (17-19,43-45). However, patients with these were treated equally as for thyroid carcinoma with TTX and RAI in western practice (46,47). This was due to the 3rd edition WHO classification of thyroid tumors. There is a follicular variant in the chapter for PTC. It states that approximately one third of the tumors are encapsulated. Although complete encapsulation, lymph node and rare hematogenous metastasis can occur, the prognosis of these tumors is similar to that of usual papillary carcinoma (7). With this incorrect description, it was estimated that more than 45,000 patients with the non-invasive encapsulated FVPTC (EFVPTC) were treated with TTX and RAI annually worldwide (20).

Revision of this statement was an urgent issue for the WHO editorial committee. In 2015, an international working group for re-examination of the EFVPTC was conducted by Professor Yuri Nikiforov at the University of Pittsburgh. After examination of 210 cases (109 cases without invasion and 101 cases with capsular and/or vascular invasion), the working group concluded that non-invasive EFVPTC was a neoplasm of very low

malignant potential. No further surgery after complete excision or RAI therapy is required for majority of these tumors based on prior studies of non-invasive EFVPTCs. This working group proposed a new terminology, "non-invasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP), for this lesion to replace the cancer terminology (20). The working group further postulated it as an oncogene driven clonal tumor and a precursor tumor to invasive EFVPTC. Following this publication, the WHO editorial committee decided to incorporate a new chapter, 2-2A: other encapsulated follicular patterned thyroid tumors, in which there were two sub-chapters, UMP and NIFTP, in the 4th edition WHO classification of tumors of endocrine organs (48). They were given a behavior code of 1 (borderline or uncertain behavior) by the WHO committee (48).

Incidence of NIFTP and diagnostic criteria of borderline/precursor tumors

It is well-known that there is significant observer variation in evaluation of PTC-type nuclear features in encapsulated follicular pattern thyroid tumors between eastern and western pathologists (49-51). This may be caused by a protective diagnostic attitude in western practice postulated by several authors (52-55) and a stricter diagnostic criterion of PTC was recommended by some authors (1-4,49,50,56,57). Therefore, the diagnostic frequency of NIFTP (non-invasive EFVPTC) was different among practices due to varying diagnostic thresholds for PTC-N. From western practice, rates of NIFTP were usually high and Strickland *et al.* and Thompson from the USA reported their incidences of NIFTP as high as 25% of malignancies, Faquin *et al.* reported 23% of PTCs from their analyses of five American and Italian academic centers (58-60), Pusztaszeri *et al.* from Switzerland reported their rate of NIFTP was 13.8% (61) and few authors reported less than 10% (15,62). From Asian practice, Bychkov *et al.* summarized 9 institutions from 6 Eastern and Southeastern Asian countries and reported very low rates, average 0.8% (range, 0–4.7%) of NIFTP (63). This observation is in the line from other Asian studies where NIFTP accounted for 0.4% in Japan (2), 0.4% in China (64) and 0.3–3.4% in Korea (65), whereas some authors reported a very high rate, 27% by Canberk *et al.* from Turkey (66).

NIFTP and UMP

To solve observer variation in diagnosis of EFVPTC, Williams proposed WDT-UMP and defined it as an encapsulated tumor composed of well-differentiated follicular cells with well or partially developed PTC-type nuclear changes, and exhibiting questionable capsular or vascular invasion (67). These NIFTP and WDT-UMP had significant overlap in original proposals as shown in *Table 2*, and the 4th edition WHO classification tried to separate them and modified the diagnostic criteria slightly as shown in *Table 3* (48). However, our group proposed to classify both WDT-UMP and NIFTP (NIFTP was an encapsulated non-invasive FVPTC in 2011) into one borderline tumor category and named it WDT with uncertain behavior (WDT-UB) in 2011 (*Table 4*) (2). This strategy may be easier and possibly minimizing observer variation in diagnosis of borderline tumors, if they have negligible differences for clinical purposes, such as in clinical management workflow. However, in this review, the author would like to recommend readers to diagnose these lesions separately because we are not sure yet that they are actually in the same disease entity of borderline/precursor tumor that can be treated similarly. We need further studies to clarify any progression risk of each borderline/precursor thyroid tumors and confirm active surveillance of these tumors does not create any increased-risk of mortality of the patient. I believe it is possible to confirm or deny those questions, simply because differences between Western and Asian practices provide a good experimental design, as the western practice serves a surgery group to borderline/precursor tumors and Asian practice serves a non-surgical control group (active surveillance until progression appear).

Are they surgical diseases?

Is NIFTP a surgical disease? Many authorities in western practice concluded that NIFTP is a surgical disease (68) because only thorough examinations of the entire tumor capsule can establish the non-invasive nature of the tumor. It was emphasized by many authors under western logic and way of thinking that the first priority was given to avoiding missing malignancy rather than minimizing invasive tests. In Asian society, a Chinese philosophy, Xiao Jing (the body, hair and skin, and all have been received from the parents, thus one does not dare damage them—this is the beginning of Xiao) has deep impacts on clinical practice, which is almost an equivalent principle to "*primum non nocere*" (first, do not harm

Table 2 Recommended nomenclatures for encapsulated well differentiated follicular-pattern thyroid tumors on the basis of the presence or absence of papillary thyroid carcinoma (PTC) type nuclear features and capsular/vascular invasion proposed by Williams ED in 2000 (67)

PTC type nuclear features	Capsular/vascular invasion		
	Present	Questionable/incomplete	Absent
Present	Follicular variant PTC		
Questionable/incomplete	Well-differentiated carcinoma, NOS	Well-differentiated tumor of uncertain malignant potential (WDT-UMP)	
Absent	Follicular carcinoma	Follicular tumor of uncertain malignant potential (FT-UMP)	Follicular adenoma

NOS, not otherwise specified.

Table 3 A new definition of follicular variant PTC, NIFTP (non-invasive follicular thyroid neoplasm with papillary-like nuclear features) and WDT-UMP in the 4th edition WHO classification (48)

PTC type nuclear features	Capsular/vascular invasion		
	Present	Questionable/incomplete	Absent
Present	Follicular variant PTC	Well-differentiated tumor of uncertain malignant potential (WDT-UMP)	Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)
Questionable/incomplete	Well-differentiated carcinoma, NOS		
Absent	Follicular carcinoma	Follicular tumor of uncertain malignant potential (FT-UMP)	Follicular adenoma

NIFTP comprises non-invasive part of follicular variant PTC and WDT-UMP.

Table 4 Well-differentiated tumor with uncertain behavior proposed by Liu *et al*. covers both NIFTP and WDT-UMP (2)

PTC type nuclear features	Capsular/vascular invasion		
	Present	Questionable/incomplete	Absent
Present	Follicular variant PTC	Well-differentiated tumour with uncertain behavior (WDT – UB) = WDT – UMP + NIFTP	
Questionable/incomplete	Well-differentiated carcinoma, NOS		
Absent	Follicular carcinoma	Follicular tumor of uncertain malignant potential	Follicular adenoma

Observer variation between NIFTP and WDT-UMP is not a problem in this schema and both are borderline/precursor tumors and biologically benign after excision.

patients) in the Hippocratic Oath of western society (69,70). Many endocrinologists and endocrine surgeons in Japan often feel guilty and are ashamed of their improper risk stratification if the nodule turns out to be a benign nodule after surgery (71). Diagnostic surgery is harmful and should be minimized to the patient, even if the surgery is restricted to a lobectomy. Significant numbers of patients later develop hypothyroidism and a few exhibit hypoparathyroidism and/or laryngeal nerve dysfunction (21,23,29,30,34,41,72,73). A surgical wound or scar on the patient's neck is 100% unavoidable, which violates Xiao Jing, and surgery is acceptable in Asia only when the disease is intolerable or life threatening (70).

Preoperative diagnosis of borderline/precursor tumors

Some authors reported preoperative diagnosis of NIFTP are possible or at least can be suggested on cytological

examination (61,74-84). Most NIFTPs display only poorly developed PTC type nuclear features including nuclear enlargement and delicate nuclear grooves, but nuclear cytoplasmic inclusions were not found in majority of cases. They were often classified in the indeterminate (AUS/FLUS, FN/SFN or suspicious for malignancy) cytological categories (61,74-84). The author of this review has proposed to rename indeterminate category to dysplastic category to accept borderline/precursor tumors (70). A thyroid nodule in FN/SFN cytological category is usually not life threatening at more than 99% probability (85,86) and many of them belong to borderline/precursor tumors (58,60,70,75,77,87). Liu *et al.* concluded that Bethesda reporting system and cytological diagnosis imparts important prognostic information about cancer type, variant, and risk of recurrence because they were few in the FN/SFN nodules (88). However, in western practice, high resection rates (60–80%) and very low risks of malignancy (ROMs) (10–30%) were reported in the FN/SFN cytological category, simply because diagnostic surgery on the patient with a FN/SFN nodule was recommended by the Bethesda reporting system and it was often accepted by the patient (45,46,89-91).

Risk stratification of patients with indeterminate nodule and active surveillance of patients with borderline/precursor tumors

This author would like to emphasize that proper risk stratification of indeterminate thyroid nodules is paramount for reducing overtreatment, and this strategy in Japan made ROMs of indeterminate nodules (both AUS/FLUS and FN/SFN) very high in general (more than 50%) and resection rates low (less than 50%) (70,90-92). As a personal view, this author has a different answer to the question, "Is NIFTP a surgical disease?" Based on our experience with FN/SFN nodules, "No, borderline/precursor thyroid tumors including NIFTP are not surgical diseases". As majority of borderline/precursor tumors including NIFTP and WDT-UMP are classified into so-called indeterminate cytological categories (58,60-62,66,75,78,81,87), thyroid ultrasound helps triage higher risk patients to surgery and patients with benign finding can be followed (93-98). Nakamura *et al.* compared two groups of FN/SFN nodules that underwent active surveillance or immediate surgery. They demonstrated that growing nodules had a higher ROM on histology than that in the immediate surgery group (93). As the majority of cases with indeterminate nodules are borderline/precursor tumors and can be followed without invasive tests as long as they have benign clinical features recommended by the JTA clinical guidelines (71,92,93,99,100), the author advises endocrinologists and endocrine surgeons in western practice to recommend surgery to patients with FN/SFN nodules provided that they have clinical high-risk features, and a careful follow-up is enough for patients with benign clinical features. It is also emphasized from western practice that proper triage of patients with FN/SFN nodule is of paramount importance to decrease unnecessary surgeries (101,102). In 2015 ATA management guidelines, this strategy was partly incorporated in recommendation 16 to apply risk stratification of patients with FN/SFN nodules (37). It states that diagnostic surgical excision is the long-established standard of care for the management of FN/SFN cytology nodules in western practice. However, after consideration of clinical and sonographic features, molecular testing may be used to supplement malignancy risk assessment data in lieu of proceeding directly with surgery (37). It means molecular tests may help triage patients with indeterminate nodules in this risk stratification, but not yet available widely in the world outside USA and their positive and negative predictive values are not high enough. The ATA guidelines further commented that it is important to note that long term outcome data on companion use of molecular marker status to guide therapeutic decision-making is currently lacking (37). It is beyond the scope of this review to go into the molecular tests and their detailed usefulness and limitations. Please refer to the other publications in this focused issue.

Treat, not-treat, or close follow-up

Please consider that Welch and Black estimated an over-diagnosis probability of 99.7% to 99.9% when an entire thyroid cancer reservoir is detected (31). The above estimate does not mean that diagnostic surgery is not justified for patients with indeterminate thyroid nodules. From shared decision-making processes, some patients with indeterminate nodules may wish to remove them and to be free from the psychological burden of having a possible cancer, even if it is rare. For this purpose, clinicians must be fully aware of the demerits of diagnostic surgery and probability of treatment-related complications, as well as the ROM of the patient (103). Furthermore, careful follow-up of patients with indeterminate nodules is one choice of treatment options in clinical guidelines of Japan and

this risk stratification of the patient using clinical tests minimizes missing malignancy and unnecessary diagnostic surgery (71,92,93,104-106). This conclusion was supported by Wienhold *et al*. who emphasized that improper risk stratification of patients increased the number of surgeries for diagnostic purposes and very low ROMs at histology, as low as less than 7%, almost equal to the background risk of malignancy, elucidated from their analysis of billing data to a health insurance company in Germany (107).

Conclusions

It is essential to establish more accurate histological criteria to identify true cancers that may recur or metastasize and result in cancer death in significant proportion of the patients if left untreated. It is also essential to exclude benign follicular adenoma and indolent borderline/precursor tumors from lethal cancers because they can be treated with simple excision. Unfortunately, borderline/precursor tumors were often treated equally and as radically as lethal malignant thyroid tumors in western clinical practices. Although in Asian practice the borderline/precursor tumors were neglected and were handled as if they were completely benign tumors. I believe we need a bridge between the practices to fill the gaps. I hope the introduction of the borderline tumor category in thyroid tumor classification will open a new era where pathologists have 3 choices for their diagnoses: benign, borderline, or malignant. Pathologists are no longer forced to decide between benign and malignant—it can be a borderline or precursor tumor. I believe this causes significant changes not only in pathology practice, but also brings significant impacts to clinical management of patients. It opens a new era for endocrinologists and endocrine surgeons to have three treatment options for patients with thyroid nodules, treat, not treat, or close follow-up (active surveillance), which would be different from the current clinical management with two choices (treat or not treat). This has already been employed in clinical management of patients with low-risk PMC and FN/SFN nodule in Japan, and active surveillance (observation without immediate surgery) has become one of the treatment options. It was incorporated to some extent in the 2015 ATA clinical guidelines. This author predicts it may be incorporated into clinical management of all thyroid borderline/precursor tumors in the future to reduce over-diagnosis and overtreatment of patients with indolent thyroid nodules.

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Footnote

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