Classification of thyroid follicular cell tumors: with special reference to borderline lesions

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Abstract. We propose a new classification of thyroid follicular cell tumors which is correlated with patient's prognosis. It is unique as to two new categories: borderline malignancy between benign and malignant, and moderately differentiated adenocarcinoma (MDA) as a differentiation classification to stratify tumor aggressiveness. As to diagnostic criteria, we recommend invasiveness (capsular and vascular invasion) to separate benign and malignant and it should not be based on presence or absence of papillary thyroid carcinoma (PTC) type nuclear features (PTC-N). Thus borderline malignancy in our new classification includes some of the formerly malignant tumors and they are 1) papillary microcarcinoma, 2) encapsulated conventional PTC (EncPTC), 3) encapsulated follicular variant PTC (EnFVPTC), 4) well differentiated tumor of uncertain malignant potential (WDT-UMP), 5) follicular tumors of uncertain malignant potential (FT-UMP), and 6) capsular invasion only follicular thyroid carcinoma (FTC). Review of the literature revealed that those thyroid tumors have consistently excellent outcome. Well differentiated follicular cell adenocarcinoma (WDA) in our classification includes common type PTC and low-risk follicular carcinoma (FTC). They are invasive (diffuse infiltrative) common type PTC and minimally invasive type FTC with less than 4 foci of angioinvasion. Moderately differentiated follicular cell adenocarcinoma (MDA) includes FTC with angioinvasion (more than 4), aggressive variants of PTC, such as tall cell, columnar cell, solid, loss of cellular polarity/cohesiveness (hobnail) variants and encapsulated carcinoma with high grade histology. Poorly differentiated carcinoma (PDC) includes PDC of WHO definition, insular carcinoma, tumors with minor anaplastic transformation and tumors with distant metastasis at presentation.

Key words: Thyroid carcinoma, Borderline, Prognosis, Diagnosis, Pathology

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THERE are no ideal histopathologic criteria which can separate benign and malignant lesions perfectly. From a review of the literature, this can also be said to be true of thyroid tumor classification as well. There was a significant observer variation in evaluating PTC-N in encapsulated follicular patterned lesions (EnFPLs) even among expert pathologists [1-6]. There were few exceptional patients, whose tumors perfectly met benign histopathologic criteria, but developed unexpected metastasis years after the surgery [7-11]. Such

patients may not show any evidence of malignancy (invasiveness) even after meticulous examination of the primary tumor in the thyroid, and therefore such tumors were once called as metastasizing "adenoma" in old textbooks. Other researchers then discovered that PTC-N was specific to PTC type malignancy, and it became the golden standard in thyroid pathology [8, 9, 12]. Some perfectionists using PTC-N tried to classify those rare tumors which developed metastasis in the malignant category. As a result EnFVPTC, EnPTC and small PTC became popular diagnoses in thyroid pathology [8-11]. When one applies more lax criteria for PTC-N evaluation, as a result a large number of patients of EnFPLs with PTC-N, irrespective of invasiveness, become malignant [10-14]. In the majority of those cases the tumor does not recur, metastasize, or

Table 1 Classification of Thyroid Follicular Cell Tumors, from our previous proposal published in 2009 (20) revised in 2011.

Category	Terminology	WHO classification	10-year CSS
Benign	FA	FA	100%
Borderline	WDT-UB	NA	99-100%
Malignant			
1) low-risk	WDA	PTC and FTC	97-100%
2) moderate-risk	MDA	PTC and FTC	81-96%
3) high-risk	PDC	PDC	50-80%
4) lethal	UC	UC	-

WHO classification: corresponding terminology used in World Health Organization classification of thyroid tumors, 10-year CSS: 10 year cause specific survival rates, FA: follicular adenoma, NA: not applicable, PTC: papillary thyroid carcinoma, FTC: follicular thyroid carcinoma, PDC: poorly differentiated carcinoma, UC: undifferentiated carcinoma.

WDT-UB: well differentiated tumor of uncertain behavior. This borderline category is composed of encapsulated tumors with or without nuclear features of PTC and with or without minimal capsular invasion, which includes encapsulated common type PTC, encapsulated follicular variant of PTC, WDT-UMP, minimally invasive and capsular invasion only type FTC and FT-UMP in WHO classification and Williams classification (29). Regional lymph node metastasis may be found in some of the borderline lesions, and those cases should be classified in WDA because of lymph node metastases. Those cases with distant metastasis should be classed in PDC. Recurrence may develop in tumors that belong to borderline category but should be regarded in very few cases as exceptions.

WDA: well differentiated follicular cell adenocarcinoma, which includes common type PTC and low-risk FTC. They are minimally invasive type FTC with less than 4 foci of angioinvasion and non-capsulated invasive (diffuse infiltrative) common type PTC. Tumors with marked vascular invasion (more than 4 foci), high grade histology (increased mitoses and necrosis) and distant metastasis at presentation should be excluded from WDA category. MDA: moderately differentiated follicular cell adenocarcinoma. MDA includes FTC with angioinvasion (more than 4) and aggressive PTC variants, such as tall cell, columnar cell, solid, loss of cellular polarity/cohesiveness (hobnail) variants and encapsulated carcinoma with high grade histology (30). PDC in our classification includes PDC of WHO definition, insular carcinoma, tumors with minor anaplastic transformation and cases with distant metastasis at presentation. These diagnoses should be applied to the primary thyroid tumors and higher risk category may be found in the metastatic sites and recurrences.

result in cancer death [14-20]. This review proposed a new prognostic classification of thyroid tumors which accommodated these grey zone tumors and extremely low grade malignant tumors and placed them in the borderline malignant category, whose original version was reported by our group in 2009 [20]. Another unique point of the classification was the differentiation classification on follicular cell carcinomas (both PTC and FTC), by which patient outcome could be stratify [20]. This classification was designed to cover all forms of follicular cell tumors, thus C-cell carcinoma, malignant lymphoma and other rare tumors, such as intrathyroidal epithelial thymoma/carcinoma showing thymus-like differentiation, were excluded from this review, because they are not follicular cell-derived tumors [9].

The new classification of thyroid follicular cell tumors

The new classification explained in the Table 1 were modified from our previously proposed classification of thyroid follicular cell tumors published in 2009, in which borderline category and moderately differentiated category were unique and differentiated from established and existing classifications of thyroid tumors such as the WHO classification [9, 20]. In this review, we further converted some of the encapsulated tumors from the malignant category to the borderline category as revisions, because our prognostic analysis and recent analyses on FPLs by others proved that those groups of tumors had extremely good outcomes and no cancer death occurred [15, 18, 19, 21-

Table 2 Differential Diagnosis of Encapsulated Follicular Patterned Lesions, classified into 12 groups depending on the criteria of capsular invasion and/or infiltrative growth (CI), vascular invasion (VI), papillary carcinoma type nuclear features (PTC-N), high grade histology (HG), and distant metastasis (M).

	CI	VI	PTC-N	HG	M	Category	(WHO)
1	-	-	-	-	-	benign	(FA)
2	-	-	Eq	-	-	borderline	(EnFVPTC)
3	-	-	UnEq	-	-	borderline	(EnFVPTC)
4	-	-	Focal	-	-	borderline	(EnFVPTC)
5	+	NA	UnEq	-	-	WDA	(PTC)
6	+	-	-	-	-	borderline	(FTC, m)
7	NA	<4	-	-	-	WDA	(FTC, m)
8	NA	>4	-	-	-	MDA	(FTC, w)
9	-	NA	NA	+	-	MDA	(PDC)
10	-	-	NA	NA	+	PDC	(not defined)
11	Eq	-	-	-	-	borderline	(FT-UMP)
12	+	+	Eq	-	-	WDA	(WDC-NOS)

(WHO): Terminologies used in WHO classification of thyroid tumors (9) or Williams classification (29) are listed in parentheses: FA: Follicular Adenoma; PTC: Papillary Thyroid Carcinoma; EnFVPTC: Encapsulated Follicular Variant Papillary Thyroid Carcinoma; FTC, m: Follicular Thyroid Carcinoma, minimally invasive; FTC w: Follicular Thyroid Carcinoma, widely invasive; WDA: Well Differentiated follicular cell Adenoarcinoma proposed by Kakudo (20), WDA includes non-capsulated invasive common type PTC in addition to minimally invasive FTC and WDC-NOS with less than 4 vascular invasion; MDA: Moderately Differentiated follicular cell Adenocarcinoma proposed by Kakudo (20), which includes aggressive variants of PTC in addition to FTC with more than 4 vascular invasion and EnFPL with high grade histology; PDC: Poorly Differentiated Carcinoma; FT-UMP: Follicular tumor of uncertain malignant potential; WDC-NOS: Well Differentiated Carcinoma, Not Otherwise Specified; Eq (equivocal): questionable or incomplete, and not definite for diagnosis; UnEq (unequivocal): definite or fully developed. +: present, -: absent, Focal: only focally or partly seen in the tumor; NA: not applicable. <4: less than 4 foci, >4: more than 4 foci.

24]. Another important point for pathologists that is recommended in this classification, is that invasiveness was used as the essential diagnostic criterion to differentiate benign and malignant in all forms of follicular cell tumors, irrespective of PTC-N, while in the other classifications PTC-N and invasiveness were independently applied to the two differentiated thyroid carcinomas, PTC type and FA/FTC type. We believe that the same histopathologic criterion should be applied to all thyroid tumors, and it should be invasiveness (capsular invasion and vascular invasion) which is a standard diagnostic criterion in many other organs. Concerning FVPTC and follicular patterned lesions (FPLs), we concluded that PTC-N alone was not enough evidence to evaluate malignancy. This is because the molecular mechanism of PTC-N has yet to be fully elucidated, as well as the fact that PTC-N is sometimes unstable and enhanced possibly by poor fixation [25]. From a review of the large numbers of publications on thyroid carcinomas, it was not justified to call all non-invasive encapsulated tumors as malignant even if they shared nuclear atypia or nuclear abnormality equivalent to those seen in clinically apparent carcinomas [8, 26-28]). When invasiveness was applied to EnFPLs without PTC-N, both FTC minimally invasive and FTC widely invasive can be differentiated from benign adenoma. In our proposal, this criterion should be applied equally to all EnFPLs irrespective of PTC-N, and can be divided into two groups: 1) encapsulated non-invasive lesions (benign) and 2) invasive lesions (borderline or malignancy), which was first emphasized in our previous publication (20). Both lesions, if they have PTC-N, are EnPTC (malignant) in the existing classifications such as the WHO classification, but as pointed out by many authors the former usually behaves as if it is benign [14-24]. They were further divided into five groups (#2, #3, #4, #5 and #12) as shown in Table 2. Only groups 5 and 12, EnFPLs with capsular invasion, remained in the (low-risk) malignant category while the other groups without invasion were converted to

the borderline category in our classification.

The borderline category (well differentiated tumor of uncertain behavior: WDT-UB) in our classification included EncPTC, EnFVPTC, WDT-UMP, minimally invasive and capsular invasion only type FTC and FT-UMP of the WHO classification and Williams classification [29]. Regional lymph node metastasis may be found in some of those lesions, and those tumors should be classified in the low-risk malignant category on the basis of lymph node metastases. Our low-risk malignant category (well differentiated follicular cell adenocarcinoma: WDA), included common type PTC, low-risk FTC and well differentiated carcinoma not otherwise specified (WDC-NOS) irrespective of lymph node metastasis [20, 21]. They were minimally invasive type FTC with less than 4 foci of angioinvasion and non-capsulated invasive (diffuse infiltrative) common type PTC. Tumors with marked vascular invasion (more than 4 foci), high grade histology (increased mitoses and necrosis) and distant metastasis at presentation should be excluded from the borderline and WDA category, because their more aggressive nature was reported [10, 12, 23, 24, 30-34]. Moderately differentiated follicular cell adenocarcinoma (MDA) included FTC with angioinvasion (more than 4) and aggressive PTC variants, such as tall cell, columnar cell, solid, loss of cellular polarity/cohesiveness (hobnail) variants and encapsulated carcinoma with high grade histology [8, 9, 20, 30-35]. PDC in our classification included PDC of WHO definition, insular carcinoma, tumors with minor anaplastic transformation, and cases with distant metastasis at presentation [8, 9]. These diagnoses should be applied to the primary thyroid tumors in curatively treated patients and a higher risk category may be found in the metastatic tumors and recurrences. Ten-year cause specific survival rates (CSS) of those patients who were curatively treated are shown in the column of 10-year CSS in Table 1.

Prognosis of patients with borderline lesions

Liu *et al*. and Rivera *et al*. applied capsulation and invasion to EnFVPTCs and divided them into three groups according to their biological behavior [15, 18]. None of their 43 cases of encapsulated non-invasive group had nodal metastasis at surgery or developed recurrence with a median follow-up of 11.1 years [15, 18]. Piana *et al*. found minimally invasive FTC with capsular invasion and without vascular invasion in 23 cases, minimally invasive FTC with vascular invasion in 6 cases and WDC-NOS in 6 cases in their 1009 cases, and no cancer death was recorded in the 35 patients [19].

Liu *et al*. from our group confirmed that none of the 20 cases of WDT-UMP in our definition and having follow up data (#2 and #4 in the Table 2) developed tumor recurrence during follow-up of average 8 years [28]. In a thorough review on FTC by Sobrino-Simoes *et al*., there were prognostic data mentioned as unpublished results on borderline lesions [24]. In their retrospective study, there was not a single case of FT-UMP or a WDT-UMP potential, nor any case of encapsulated, noninvasive FVPTC which developed nodal metastasis and/or blood borne metastasis. Piana *et al*. found WDT-UMP in 5 and FT-UMP in 6 cases in their 1009 cases, and no cancer death occurred in any of the 11 patients [19].

In the study of Bai *et al*. from our group, using 25 cases of EncPTCs with or without minimal capsular invasion, these PTCs were classified as malignant because of 60% lymph node metastasis at operation, turned out to be almost benign after surgical resection, showing no recurrence and no cause-specific death after a mean follow-up of more than 141 months [21]. From those data, the prognosis of the patients with EnFPLs irrespective of PTC-N was extremely different from those observed in genuine cancer patients. Therefore encapsulated PTC (both EnFVPTC and EncPTC) without metastasis were also included in the borderline category in our revised classification (Table 1). A peculiar thyroid tumor reported by Carney *et al*., hyalinizing trabecular adenoma, was renamed as hyalinizing trabecular tumor in recent WHO classification. It is an encapsulated tumor of follicular cell origin characterized by trabecular growth, eosinophilic hyaline substance, and marked PTC-N showing levels greater than true PTC [9, 36]. A differential diagnosis between this entity and EnPTC with trabecular growth pattern was difficult to achieve within the framework of existing classifications. In our new classification this problem was solved sagaciously by placing them both in the same borderline category which was consistent with their almost always benign outcomes [36].

Papillary microcarcinoma became a new member of the borderline malignancy in our classification, when it had no extrathyroid extension, lymph node metastasis, or distant metastasis. This revision was made because Zuo *et al*. from our group [37] and others [38-45] have

reported its excellent prognosis. In our study massive extrathyroid extension was the only significant prognostic factor for unfavorable outcomes in microcarcinoma [37]. Some surgeons even recommend observation than immediate surgery to those patients with microcarcinoma, which also supports our conclusion that they are not rapidly progressive malignant diseases which require immediate extirpation [38, 40], although the others recommend that the treatment should be equal to that applied to the patients with conventional PTC [45].

Differentiation Classification of follicular cell carcinomas (WDA, MDA and PDC)

This classification was first introduced by Kakudo *et al*. in 2009 for prognostic stratification of the patients with thyroid follicular cell tumors [20]. In brief, common type PTC was divided in two groups: WDA (PTC with invasion and/or nodal metastasis) and MDA (high-risk PTC, such as tall cell, columnar cell, solid, loss of cellular polarity/cohesiveness and hobnail variants) [8, 9, 11, 20, 21, 35, 46-49]. FTC type carcinoma was also divided into two groups depending on invasiveness but it was modified in this review because of recent prognostic data [23, 24, 30-34].

The FTC at present is classified into three prognostic groups as minimally invasive FTC without angioinvasion, minimally invasive FTC with angioinvasion and widely invasive FTCs [23, 24, 31-34]. Collini *et al*., Ghossein *et al*. and D'Avanzo *et al*. reported that encapsulated FTC with four or more foci of vascular invasion have a significant higher recurrence rate even if vascular invasions are microscopic [31, 32, 34]. The tumor was called a grossly encapsulated FTC with extensive angioinvasion by those authors, and we regarded it as moderate-risk MDA category in our classification (Table 1). The capsular invasion only FTC and encapsulated PTC (both follicular variant and conventional type) were downgraded from malignant to borderline category because neither recurrence nor cancer death occurred. Therefore these modifications were also incorporated in Table 2 (#2, #3, #6, #7 and #8) as additional modifications to our previous classification explained in Table 1.

Distant metastasis may be found in a few patients with thyroid carcinomas at presentation, and such cases with distant metastasis were reported as aggressive and associated with more cause specific death[10, 15, 18, 19, 23, 31-34, 50]. Franssila reported that the mortality rates were 83% for patients with distant metastases, 28% for patients with extrathyroid tumors, and 4% for patients with intrathyroid tumors [50]. In our new classification, cases with distant metastasis at presentation were grouped in the PDC category, because of their different nature from those tumors without distant metastasis. PDC in our classification includes PDC of WHO definition, insular carcinoma [9], and tumors with minor anaplastic transformation, in addition to the cases with distant metastasis at presentation. The diagnosis should be applied to the primary thyroid tumor which may be upgrade to higher risk categories when they are found at metastatic sites and in recurrent tumors, as a progression of the tumor.

The problems in FPLs with PTC-N

PTC type nuclear feature (PTC-N) is one of the most important cytological criteria in the diagnosis of thyroid tumors. As a result PTC-N became a golden standard for diagnosis of PTC, almost equal to papillary structure and invasive growth [8, 9, 12]. This criterion makes it possible for pathologists to diagnose noninvasive lesions whether they are benign (FA) or malignant (EnPTC) with confidence [8, 9, 14, 50-52]. For the encapsulated (non-invasive) FPLs, the diagnosis of malignancy relies on PTC-N (e.g., nuclear enlargement, overlapping, clearing, grooves, and cytoplasmic pseudoinclusions). There is an ongoing debate regarding this type of tumor, as to diagnostic criteria, immunophenotype, genetic profile, true nature, and biologic behavior, and to date no firm conclusions have yet been reached and no complete agreement has yet been drawn from any of these publications, because there exist considerable disagreement and uncertainty as to detailed diagnostic criteria for their diagnosis [1-6]. Some researchers apply EnFVPTC to EnFPLs with equivocal PTC-N, either focal or diffuse in the nodule [10, 11, 15, 18], while our group proposed that EnFVPTC should be applied only to those cases with unequivocal PTC-N throughout the tumor [28]. We proposed that cases with diffuse equivocal (not enough, imprecise, inconclusive, subtle, questionable or incomplete for definite diagnosis) PTC-N or cases with focal PTC-N should not be included in the malignant PTC category [8, 26, 27]. The latter group was separately classified as borderline malignancy in our studies [18, 20] and by some other groups [53]. Finally an algorithmic diagnostic approach on EnFPLs was proposed by Chetty in 2011 including EnFPLs with questionable PTC-N [54].

We are favor of several terminologies which belong to borderline malignancy to call this type of tumors. They were well differentiated tumor of uncertain behavior (WDT-UB) which has been introduced in endocrine pancreas in WHO classification [9, 55], and WDT-UMP (well differentiated tumor of uncertain malignant potential) which was proposed by Williams in 2000 for lesions in which PTC-N was incomplete [29]. The other researchers accepted minimal nuclear feature and equivocal PTC-N as evidence of PTC type malignancy and diagnosed those EnFPLs as EnFVPTC [10, 11, 15, 18].

The borderline categories in diagnosis and proposal by Williams

As pointed out by many authorities, the problem in EnFPLs with PTC-N is clear [1-6, 27, 29, 54, 56]. The EnFPLs (benign FA and adenomatous nodule, malignant EnFVPTC and common type PTC) share significant overlapping cytological features [57], and there are no clearcut criteria to apply a minimal diagnostic threshold. The lesson from the diagnostic system currently used in cytology to solve this difficult situation is that, when there are no non-overlapping distinguishing criteria between benign and malignant lesions, the best practical solution would be to include an indeterminate category in the list of diagnosis and classification. This epoch-making development in thyroid tumor classification to apply a borderline category instead of either benign or malignant to this problematic entity, was proposed to deal with these problematic entities by many authors, [8, 9, 20, 29, 27, 54, 56], although Baloch and LiVolsi were hostile to this reform and claimed that this terminology led to confusion among clinicians and only added to the existing controversy [10]. As is clear in cytology, an indeterminate or borderline category makes it possible to allow for differences in opinions and diagnostic criteria, and eventually decreases observer variation significantly. Such a category has already been introduced to thyroid tumor diagnosis by Williams in 2000 who proposed WDT-UMP to encompass non-invasive EnFPLs with equivocal nuclear changes of PTC and FT-UMP for EnFPLs with equivocal capsular invasion [29]. The borderline terminology or indeterminate reporting system also solves other important issues: it diminishes diagnostic discrepancy between benign and malignant, and gives us good reasons to escape from litigation. Chan also recommended that, if there were serious concerns about litigation, it would be preferable to use the terminology proposed by Williams rather than to over-diagnose PTC [27].

Incidence and concordance rate of borderline lesions

As to the incidence of WDT-UMP, Liu *et al*. collected 30 cases from our 2648 cases of thyroid specimens, and which were examined in the Department of Human Pathology, Wakayama Medical University between 1990 and 2009. The incidence of WDT-UMP in our series among 2648 thyroid specimens was 1.1% and 501 cases (18.9%) of PTC examined in the same period [28]. The incidence of WDT-UMP in our series was in a similar range to the 1.5% (16/1078 cases) of Hofman *et al*. from France in 2009 and 0.5% (5/1009) reported by Piana *et al*. from Italy in 2011 [19, 53].

Hofman *et al*. further analyzed concordance rates among 4 pathologists and reported as 87% (14/16 cases) for the diagnosis of WDT-UMP and 53% (8/15 cases) for FT-UMP [53]. It was assumed that the differential diagnosis of WDT-UMP included more benign FA cases than malignant EnFVPTC ones, because clear cut PTC would not fit in the differential diagnosis of borderline lesions. It was confirmed in our retrospective survey on 2648 cases, 30 cases of WDT-UMP were retrieved from the benign category, and their original diagnoses were 10 cases of adenomatous nodule and 20 cases of FA, but none from PTC [28]. Hofman et al. pointed out that the borderline category (WDT-UMP and FT-UMP) tipped more toward benign than of malignant. When 31 cases of WDT-UMP and FT-UMP were reviewed by 4 pathologists independently, a pending malignant diagnosis was made in only 1/16 (6%) in WDT-UMP and 1/15 (7%) in FT-UMP [53]. As we soon realized an introduction of the borderline category to pathology reports may create a serious problem to clinicians, and should be used as rarely as possible. The incidence in our practice and those reported, around 1%, may be acceptable for clinicians because they were almost all benign and had a good reproducibility in diagnosis.

Prognostic analyses of EnFPLs and borderline lesions

Piana *et al*. reviewed 67 cases that died of thyroid carcinoma in a cohort of 1009 consecutive cases of thyroid carcinoma treated at a single institute in Italy with average follow-up of 11.9 years [19]. They found 29

cases with minimally invasive FTC (23 cases with capsular invasion only and 6 cases with vascular invasion), 45 patients with EnFVPTC without invasive growth and 21 cases of EnFVPTC with capsular and/or vascular invasion. No cancer death was found in the groups. They found WDT-UMP in 5 and FT-UMP in 6 cases in the 1009 cases, and no cancer death occurred among the 11 patients. They concluded that encapsulated FPLs (minimally invasive FTC, EnFVPTC, WDC-NOS, WDT-UMP and FT-UMP) are associated with an extremely favorable outcome and they do not play a significant role in the fatality of thyroid carcinoma [19].

Treatment of the borderline lesions

Some surgeons and endocrinologists are not inclined to treat patients with EnFPLs as if they have an aggressive carcinoma, which includes total thyroidectomy with neck dissection followed by RI treatment. Chan reviewed a number of publications on EnFVPTC, and found that lymph node metastasis occurred in approximately 25% of cases, but distant blood-borne metastasis almost never occurred (it occurred in only 1 patient) [27]. He concluded that it is fully justified to err on the benign side where there were uncertainties in the diagnosis [27]. He also stated that it would not be a disservice to the patients even if a genuine FVPTC were misdiagnosed as FA, because simple excision of the lesion was already curative. Rivera *et al*. concluded that non-invasive EnFVPTC could be managed like minimally invasive follicular carcinoma by lobectomy without RI therapy [18]. Sobrino-Simoes *et al*. commented on the therapy for non-angioinvasive EnFVPTC and minimally invasive FTC capsular invasion alone, and suggested that lobectomy or lobectomy plus isthmectomy should be enough [24].

Austin L. Vickery, an authority on the history of thyroid pathology, supported this view in early 1980s and suggested that an EnFPL with equivocal PTC-N that failed to show any invasion should be considered benign, because these tumors behave in an indolent fashion [26]. Rosai *et al*. also recommended in their AFIP atlas in 1992, that "thus, a conservative diagnostic attitude and even more important, a conservative therapeutic approach are warranted" [8].

There were several different conclusions for the treatment on EnFVPTC. One of them was by Scognamiglo *et al*., who observed that although these lesions may be biologically borderline lesions that are not fully malignant, these lesions all should be treated as PTC clinically [58]. Other authors, like Baloch *et al*., pointed out distant metastasis was found in a few cases of EnFVPTCs, although in most cases, capsular or vascular invasion were present, and they emphasized that all EnFVPTC must be treated as a genuine cancer [10, 11].

The EnFVPTC have been found associated with cervical lymph node metastasis in up to 25% of the cases and this fact is evidence enough that these lesions should be regarded as malignant as written in most textbooks [8, 9, 11, 15, 18, 27]. However, recent progress in cancer treatment, particularly in early stage, non-invasive or early invasive carcinomas and low grade tumors, most pathologists experienced that the threshold of benign and malignant was being manipulated artificially, because of changing trends in treatment strategy and concerns for the patients' quality of life. There were several malignant tumors in the past that have become borderline category in recent tumor classifications. Those examples are 1) atypical endometrial hyperplasia (non-invasive endometrial adenocarcinoma), 2) high grade squamous intraepithelial lesion (carcinoma in situ of the cervix), 3) serous borderline tumor of the ovary (microinvasive serous cystadenocarcinoma) and 4) well differentiated endocrine tumor of uncertain behavior of the pancreas (invasive islet cell carcinoma, intra-pancreas and less than 2cm) [9, 55, 59]. In this review, we proposed to apply borderline terminology not only to EnFVPTC, but also to a certain group of thyroid tumors including EnFPLs and related tumors, which we believe can be treated with lobectomy alone, and for which no additional treatments are necessary. Almost all of the patients eventually developed no recurrence and no cancer death after simple excision. These groups of thyroid tumors included in the borderline category in our classification are 1) papillary microcarcinoma (<1 cm) [37, 38, 40, 41, 42], 2) encapsulated cPTC [21, 22], 3) EnFVPTC [15, 18, 19], 4) WDT-UMP [29], 5) FT-UMP [29], and 6) capsular invasion only FTC [19, 24, 60]. Needless to say, the borderline lesion must have no lymph node metastasis at diagnosis and, if present, low grade malignancy (WDA in our classification) should be applied to those cases because of positive lymph node metastasis. A distant metastasis may present in patients with EnFPLs at presentation, although in most cases, capsular or vascular invasion by the primary tumor is present [10, 15, 27]. Those thyroid tumors should be treated as an aggressive type

of thyroid carcinoma as reported by several authors [8, 23, 24, 31-34, 60], which was incorporated as PDC in our classification (Table 1).

Although Pacini *et al*. recommended total thyroidectomy based on their analysis of bilaterality and multifocality in the thyroid obtained from thyroidectomy specimens from 182 cases of patients who had initially undergone lobectomy for PTC. They believe PTC should be treated with total thyroidectomy when diagnosed before surgery [61]. We believe this was more related to a risk of second malignancy (multiplicity) in the remnant thyroid rather than aggressiveness of the primary tumor. It is well known that microcarcinoma of the thyroid is a fairly common finding in autopsy patients. Lang *et al*. found thyroid microcarcinomas in 63 (6.2%) of 1020 autopsy cases with 46% multicentricity and 14% lymph nodal metastasis [33]. They concluded that these tumors have no propensity to increase to clinically apparent thyroid disease [33].

Our Practice on EnFVPTC

As a lifetime quality control of our practice, we have made a retrospective study on our benign diagnosis in a series of 2978 cases which were examined and signed-up by a single pathologist, KK, between 1990 and 2005, one of the authors of this review. Please note that our practice on EnFPLs was extremely conservative and that our diagnosis was on the benign side. This is clearly documented by the fact that the highest rate (37.9%) of benign diagnosis was made by one of us among the 10 expert pathologists in the series of 87 FVPTCs conducted by Llyod *et al*. in 2004 [5]. For this reason we were afraid significant numbers of missing malignancy might be brought to light from this retrospective study. In this study, we searched for any unexpected recurrence or metastasis during follow up. It was reported by Ito *et al*. in 2008 that there were three patients who developed distant metastasis (lung and bone) 27 to 37 months after the surgery [7]. Another two cases were found to have distant metastasis at surgery and the initial benign diagnoses were revised because of distant metastases (brain and lung). There were no cases that belonged to conventional EnFVPTC among the 5 cases, but there were one non-invasive encapsulated macrofollicular variant PTC (a subtype of FVPTC) [62], one FTC with incomplete (no endothelial lining) vascular invasion, and one FTC with vascular invasion indistinguishable from

endothelial hyperplasia, and finally they were interpreted as our misdiagnoses. The second one contained only one focus of questionable vascular lesion in which endothelial lining was not evident, one of the criteria for definite vascular invasion [9]. The third one had invasive focus into surrounding thyroid parenchyma, but it was initially interpreted as an endothelial reaction to fine needle aspiration trauma rather than true invasion, so-called WAFT (Worrisome histologic alterations following fine needle aspiration of the thyroid) [63]. No reasonable explanations could be made for the remaining two cases, cases 1 and 3 in the Ito paper, who had distant metastasis at presentation, even though their primary tumors looked quite innocuous [7]. We were afraid of any sampling error or missing primary lesions in those two cases, but no proof could be made. This retrospective study and our interpretations may not give us complete support for our conservative diagnosis on FPLs, but it made us more confident in our strict diagnostic approach for PTC-N in which malignant diagnosis was given only in those cases with diffuse and unequivocal PTC-N. Eventually under-diagnosis (missing malignancy judging by recurrence or metastasis) on PTC-N was found in only one case (0.03%) in about 3000 benign diagnoses. We are reasonably sure that our conservative diagnostic approach for FPLs helped a significant number of patients avoid unnecessary aggressive treatment, without exposing them to unexpectedly high risk of recurrence or metastases, although more distant metastasis may appear later due to the relatively short (3 to 17 years) observation period.

The benefit of avoiding unnecessary aggressive surgical treatments is seen in the unavoidable complications caused by thyroid surgery for PTC reported by Ito *et al*. in 2008 [22]. From their analysis of 1207 patients with common type PTC and 149 cases of EnPTC, 59 patients (4.4%) showed permanent recurrent nerve paralysis because of direct invasion by carcinoma in 52 cases. Accidental nerve injury was observed in 4 patients (0.3%) and permanent recurrent nerve paralysis for unknown reasons was observed in 3 patients (0.2%). Permanent hypoparathyroidism was observed in 69 (9.9%) of 700 patients who underwent total thyroidectomy. Of 1053 patients who underwent modified radical neck dissection, accessory nerve paralysis, pneumothorax, facial nerve paralysis, Horner's syndrome, and chyle leakage requiring reoperation were observed in 2 (0.2%), 2 (0.2%), 5 (0.5%), 3 (0.3%), and

5 (0.5%), respectively [22]. When one applies total thyroidectomy with modified radical neck dissection to patients who have EnFPL with PTC-N, approximately 10% of them will suffer one or more of the above complications, in addition to 100% of permanent hypothyroidism. When your pathologists are conservative or strict in evaluating PTC-N and capsular invasion, your patients will have significantly less surgical complications after less aggressive treatment accompanied by almost no recurrence and no cancer related death.

Molecular profiles of thyroid tumors, EnFVPTC and related lesions

Numerous immunohistochemical analyses on thyroid tumors have been published and the results improve diagnosis of thyroid tumors significantly. However, it was evident that no single immunohistochemical marker was sensitive enough for absolute diagnosis of malignancy with an optimal specificity [58, 64-69]. As to immunohistochemical characterization on FVPTC, Nakamura *et al*. concluded that a combination of markers consisting of a panel of HBME-1(Hector Battifora mesothelial cell 1), GAL3 (a member of the beta-galactosidase-binding protein family), and CK19 (cytokeratin 19) or a panel of HBME-1, CITED1 (aspartic acid

D-rich-terminal domain), and GAL3 were usually most effective in distinguishing FA from FVPTC [69].

Immunohistochemical studies on thyroid borderline lesions such as WDT-UMP and the immunohistochemical results were essentially similar to the studies on FVPTCs. The positive rates of those markers indicated that those lesions were intermediate between FA and PTC [15, 28, 53, 58, 64-69].

Finally it has to be mentioned that the possible role of molecular analysis in the diagnosis of well differentiated thyroid follicular cell tumors. All the molecular features such as aneuploidy, RAS mutations, and PAX8-PPARγ rearrangements, which are characteristic features of FTC, were also frequently observed in FA and were therefore almost useless for diagnostic purposes. It is worthy of note that DNA microarray gene analysis on thyroid tumors successfully discriminated benign and malignant tumors including borderline lesions [70-73]. Fontaine *et al*. showed in their analysis the heterogeneity of borderline tumors and highlighted the molecular similarities between some cases and true carcinomas [70]. Although markers such as RET/PTC, RAS or PAX8-PPARγ remained in basic research, continuous progress in molecular studies on thyroid tumors hopefully will answer those issues to become useful diagnostic and therapeutic tools in the future.

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