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Review Article

Encapsulated papillary thyroid carcinoma, follicular variant: A misnomer

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Papillary thyroid carcinoma (PTC) has long been diagnosed based on its unique nuclear features (PTC-N); however, significant observer discrepancies have been reported in the diagnosis of encapsulated follicular patterned lesions (EnFPLs), because the threshold of PTC-N is subjective. An equivocal PTC-N may often occur in non-invasive EnFPLs and benign/malignant disagreements often create serious problems for patients' treatment. This review collects recent publications focusing on the so-called encapsulated follicular variant of papillary thyroid carcinoma (EnFVPTC) and tries to emphasize problems in the histopathological diagnosis of this spectrum of tumors, which covers encapsulated common-type PTC (EncPTC), EnFVPTC, well-differentiated tumor of uncertain malignant potential (WDT-UMP), follicular adenoma (FA) with equivocal PTC-N and minimally invasive follicular carcinoma (mFTC). We propose that EnFVPTC and other EnFPLs with equivocal PTC-N should be classified into a unified category of borderline malignancy, such as well-differentiated tumor of uncertain behavior (WDT-UB), based on their homogeneous excellent outcome. It is suggested that the unified nomenclature of these lesions may be helpful to reduce significant observer disagreements in diagnosis, because complete agreement in the diagnosis of an EncPTC, EnFVPTC or FA by all pathologists may be not possible for this problematic group of tumors. In conclusion, a malignant diagnosis of EnFVPTC should not be used to cover this spectrum of tumors until uncertainty about the nature of this lesion is settled, whether it is benign, precancerous or malignant.

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The nuclear features of papillary thyroid carcinoma (PTC-N) are one of the most important cytological criteria in the diagnosis of thyroid tumor, and PTC-N is the golden standard for the diagnosis of PTC, almost equal to papillary structure and invasive growth.[1–4] The arbitrary evaluation of PTC-N enables pathologists to diagnose those non-invasive encapsulated follicular patterned lesions (EnFPLs) as an encapsulated follicular variant of papillary thyroid carcinoma (EnFVPTC).[1–6] For EnFVPTC, the diagnosis of malignancy completely relies on PTC-N; however, debates continue on this type of tumor in diagnostic criteria, immunophenotype, genetic profiles and biological behavior. As a result, many researchers have published many reports to solve these issues, the nature of this tumor and its relation to common type PTC (cPTC) etc.; however, no firm conclusion has been reached, because there are major diagnostic discrepancies and uncertainty in the detailed diagnostic criteria among those studies.[7–10] Some researchers apply EnFVPTC to encapsulated follicular patterned lesions (EnFPLs) with equivocal PTC-N, either focal or diffuse in the nodule,[11–14] while our group proposed that EnFVPTC should be applied only to those cases with unequivocal PTC-N throughout the tumor.[15,16] We proposed that cases of diffuse equivocal PTC-N or focal PTC-N should not be included in the malignant category. They were therefore classified separately as a borderline malignancy in our studies and by other groups.[15–17] We are in favor of several terminologies for borderline malignancy of these lesions, such as well-differentiated tumor of uncertain behavior (WDT-UB), which has been introduced for the endocrine pancreas in the World Health Organization (WHO) classification,[4,18] or well-differentiated tumor of uncertain malignant potential (WDT-UMP) proposed by Williams

for lesions in which PTC-N was incomplete;[19] therefore, previous publications on EnFVPTC using different series of patients based on different diagnostic thresholds of PTC-N are not comparable. Even genetic data on EnFVPTC in the literature might include heterogenous EnFPLs whose PTC-N were not enough for a malignant diagnosis by the other groups of pathologists. This review focuses on well-differentiated follicular cell tumors, particularly on EnFVPTC and its related lesions, and also tries to emphasize problems with this spectrum of tumors, which includes encapsulated common-type PTC (EncPTC), EnFVPTC, diffuse/infiltrative FVPTC, WDT-UMP, follicular adenoma (FA), FA with artificial nuclear clearing and minimally invasive follicular carcinoma (mFTC).

HISTORY AND DEFINITION OF FVPTC

Follicular growth pattern can be seen in the majority of PTC in various proportions and FVPTC was initially applied to invasive carcinoma, which showed predominantly follicular histological architecture.[5] This means that FVPTC is a follicular pattern dominant PTC, and a minor proportion of typical papillary growth is usually accepted. In some reports, up to 20% or even 30% of papillary growth was accepted for FVPTC and, in such cases, FVPTC was almost equal to PTC with a dominant follicular growth pattern.[20,21] When PTC-N became of paramount importance for the diagnosis of malignancy in non-invasive EnFPLs, equal to papillary growth and invasiveness, the definition of FVPTC was expanded to encompass all EnFPLs with PTC-N, and finally its differential diagnosis included benign FA and hyperplastic adenomatous nodules. This is evident in the literature, in which significant numbers of EnFVPTCs were retrieved from benign thyroid tumors. Widder *et al*. reported that as many as 26 (22%) cases of EnFVPTC were retrieved from 118 cases of FA.[22] Furthermore, a significant rate of benign and malignant disagreement occurs among pathologists when reviewing follicular patterned lesions (FPLs), since borderline features of PTC-N may occur frequently.[7–10]

DIAGNOSTIC CRITERIA FOR ENFVPTC (DEFINITION OF PTC-N AND ITS PROPORTION IN THE TUMOR)

The diagnosis of EnFVPTC has become one of the hottest topics in thyroid pathology mainly because of the too-liberal use of the PTC-N criteria. The characteristic nuclear features of PTC include: (i) cytoplasmic inclusions in the nucleus; (ii) nuclear grooves; (iii) ground glass (powdery chromatin, dispersed chromatin or clearing); (iv) elongated overlapping nuclei; and (v) nuclear irregularity (variation in size and shape).

In a recent survey of the diagnostic criteria for FVPTC, Lloyd *et al*. reported that the most important criteria were cytoplasmic inclusions, abundant nuclear grooves and ground glass nuclei. Using these three features, seven of the 10 reviewers made a diagnosis of FVPTC with a cumulative frequency of 100% in cases of metastasis.[9] We should point out that one of the authors (KK) of this review article was reviewer number 9 in Lloyd's analysis, and had the highest (37.9%) rate of benign diagnosis in 87 thyroid tumors.[9] This diagnostic attitude for PTC-N is not extremely radical or isolated from the international standard, and it is supported by many authorities. Some authors of previous reports, such as Austin L Vickery, suggested in 1983 that an EnFPL with equivocal PTC-N and failing to show any invasion should be considered benign because these tumors behave in an indolent fashion.[1] Juan Rosai stated that disease without capsular and vascular invasion and with imperfectly developed PTC-N should be called benign FA and he also added that, for the diagnosis of EnFVPTC to be made, PTC-N needs to be displayed predominantly throughout the neoplasm.[3] Their criteria for PTC-N, required for EnFVPTC, may be the most stringent among the literature, equivalent to our diagnostic strategy, and this strict criterion was also recommended by Chan in 2002.[23] On the other hand, some researchers have expressed their concern about missing a few cases that might develop distant metastasis and tried to include cases of only focal PTC-N, either equivocal or unequivocal, as malignant tumors,[11,12] an opinion we do not share. Renshow pointed out that this tendency to overdiagnose FVPTC is due to the litigation climate in pathology practice.[24] It is of interest to note that there was a diagnostic variation between American pathologists and Japanese pathologists in that American pathologists made more malignant diagnoses (FVPTC) than Japanese pathologists, reported by Hirokawa *et al*.[8] This strict diagnostic strategy for FVPTC might be possible only in Japan, since Japanese pathologists are fortunate not to be usually subject to litigation.

BORDERLINE CATEGORIES AND WDT-UMP

The pairs of benign FA and malignant FTC, EnFVPTC and cPTC share significant overlapping cytological features, and there is no clear cut-off criterion between them. Since there is no discrete distinguishing criterion between benign and malignant lesions, the best practical solution would be to include an indeterminate category in the lists of diagnosis as proved in current cytology diagnosis. This pivotal change and revolution in thyroid tumor classification has been proposed by many authors and these lesions should be classified into a borderline category,[3,4,15–17,19] 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.[11] As is clear from the cytology, an inde-

terminate category makes it possible to allow differences of opinion and diagnostic disagreements, and eventually decreases observer variations significantly. Such a category has been introduced to subclassify these problematic entities by Williams, who proposed WDT-UMP to encompass non-invasive EnFPLs with equivocal PTC-N[19].

Liu *et al*. in our group collected 30 (1.1%) cases of WDT-UMP from 2648 cases of thyroid specimens, in which 501 cases (18.9%) of PTC were examined in the same period.[16] The incidence of WDT-UMP was in a similar range to the 1.5% (16/1078 cases) reported by Hofman *et al*. in France in 2009 and slightly higher than the 0.5% (5/1009 cases) reported by Piana *et al*. in Italy in 2011.[17,25]

PROGNOSIS OF ENFVPTC AND WDT-UMP

There have been many publications on FVPTC and most reported its low grade malignant nature.[20,26,27] When prognostic analysis was carried out on a combined series of patients, both encapsulated and diffuse/infiltrative, the benign nature of non-invasive EnFVPTC could not be elucidated. Passler *et al*. analyzed their 247 cases of PTC, including 37 cases of FVPTC. They found 12 (32%) cases of FVPTC with lymph node metastases at surgery, recurrence in three and no cancer deaths; however, in this study, the histological prognostic distinction of encapsulated and non-encapsulated FVPTC was not surveyed.[26]

Tielens *et al*. and Pusler *et al*. pointed out that the primary lesions of FVPTC tend to be smaller than those of cPTC[20,26] and the size difference might be associated with the better prognosis of FVPTC. However, it was not confirmed in a larger series ($n = 14\,756$) using the Surveillance, Epidemiology and End Results database for 1988 to 2006, a national cancer registry created by the National Cancer Institute of USA.[27] With respect to staging at presentation, although there were fewer T1 cases of FVPTC tumors compared with cPTC (55.5% and 59.0%, respectively), no trend toward earlier- or later-stage disease for either PTC subtypes was found ($P = 0.450$), reported by Lin and Bahttacxharyya.[27] Unfortunately again, tumor parameters of encapsulation and invasiveness was not studied in this analysis and they concluded that these patients with FVPTC and cPTC carry very similar prognoses.[27]

In Liu's clinicopathological study on 78 cases of FVPTC from Memorial Sloan-Kettering Cancer Center, they divided FVPTC into three groups: (i) non-encapsulated diffuse/infiltrative group; (ii) encapsulated invasive group; and (iii) encapsulated non-invasive group. None of the 43 patients with encapsulated and non-invasive tumor developed recurrence, including 31 patients who underwent lobectomy alone.[13]

Piana *et al*. reviewed a cohort of 1009 consecutive cases of thyroid carcinoma treated at a single institute in Italy. They found 45 patients with EnFVPTC without invasive growth, 21 cases of EnFVPTC with capsular and/or vascular invasion, WDT-UMP in five and FT-UMP in six cases among 1009 cases.[25] No cancer death occurred in the patients with EnFVPTC, WDT-UMP or FT-UMP with an average follow-up period of 11.9 years, while 67 patients from the cohort died as a result of their thyroid carcinoma.[25]

It was confirmed in our series that 20 cases of WDT-UMP in our definition, including EnFPLs with diffuse equivocal PTC-N (#2 in Table 1) or focal unequivocal PTC-N (#3 in Table 1), in a follow-up study for an average of eight years, had no recurrence even if lymph node dissection and radioiodine (RI) treatment were not performed.[16] From those data, no cancer deaths in patients with EnFVPTC or WDT-UMP were confirmed in the above three different series of patients, and it would be a rare observation if they were biologically malignant tumors.

Table 1 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 (DM)

	CI	VI	PTC-N	HG	DM	WHO	Our Category
1	–	–	–	–	–	FA	Benign
2	–	–	Eq	–	–	WDT-UMP	WDT-UB
3	–	–	Focal	–	–	EnFVPTC	WDT-UB
4	–	–	UnEq	–	–	EnFVPTC	WDT-UB
5	Eq	–	–	–	–	FT-UMP	WDT-UB
6	UnEq	–	–	–	–	mFTC	WDT-UB
7	UnEq	NA	Eq	–	–	WDC-NOS	WDA
8	+	NA	UnEq	–	–	PTC	WDA
9	NA	<4	–	–	–	mFTC	WDA
10	NA	>4	–	–	–	wFTC	MDA
11	–	NA	NA	+	–	PDC	MDA
12	–	–	NA	NA	+	not defined	PDC

+: present; –: absent.

Focal, only focally or partly seen in the tumor; NA, not applicable.

<4: less than 4 foci; >4: more than 4 foci.

EnFVPTC, encapsulated follicular variant of PTC; Eq (equivocal), questionable or incomplete, and not definite for diagnosis; FA, follicular adenoma; FTC, follicular thyroid carcinoma; FT-UMP, follicular tumor of uncertain malignant potential; MDA, moderately differentiated follicular cell adenocarcinoma; mFTC, minimally invasive FTC; PDC, poorly differentiated follicular cell carcinoma; PTC, papillary thyroid carcinoma; UnEq (unequivocal), definite or fully developed; WDA, well-differentiated follicular cell adenocarcinoma; WDC-NOS, well-differentiated carcinoma, not otherwise specified; WDT-UB, well-differentiated tumor of uncertain behavior; WDT-UMP, well-differentiated tumor of uncertain malignant potential; wFTC, widely invasive FTC; WHO, World Health Organization classification of thyroid tumors in 2004.

TREATMENT FOR ENFVPTC AND WDT-UMP

Some researchers are not comfortable treating EnFVPTC patients as having a biologically malignant tumor, which

requires total thyroidectomy and neck dissection followed by RI treatment. Piana *et al.* concluded that the prognostic data in the literature and in their study support that EnFPLs with PTC-N and EnFPLs with capsular invasion only are truly 'non-threatening'.[25] Chan reviewed a number of publications on EnFVPTC, and found that distant blood-borne metastasis rarely occurred, so he concluded that it is fully justified to err on the benign side where there are uncertainties in the diagnosis.[23] He also stated that it would not be a disservice to the patients even if a genuine FVPTC was misdiagnosed as FA, because simple excision of the lesion is curative. Rivera *et al.* concluded that non-invasive EnFVPTC could be managed like mFTC by lobectomy without RI therapy.[14] Rosai *et al.* also stated that 'a conservative diagnostic attitude and even more important, a conservative therapeutic approach for EnFVPTC are warranted'.[3]

There are several different conclusions regarding the treatment of EnFVPTC. Baloch and LiVolsi pointed out that distant metastasis was found in a few cases of EnFVPTC and they emphasized that EnFVPTC must be treated as a genuine cancer.[11,12]

EnFVPTC has been found to be associated with cervical lymph node metastasis in up to 25% of cases and this is enough evidence to confirm that these lesions should be regarded as malignant;[4,5,15,28] however, as a result of recent progress in cancer treatment, particularly in the early stage, non-invasive carcinomas and low-grade tumors, most pathologists have experienced that the threshold of diagnosing whether they are benign and malignant has been manipulated artificially, because of changing trends in treatment strategy and for the patients' quality of life.[4] This trend is evident in the WHO tumor classification of various organ systems, which also aims to accommodate the multistep carcinogenesis theory in the tumor classification. We have proposed the application of borderline terminology not only for EnFVPTC, but also for a certain group of thyroid tumors, including EnFPLs and related tumors.[15,29,30] We believe that they are in the early phase of carcinogenesis (precancerous), borderline, very low grade malignancy or mimicry. Almost no patients with these tumors develop recurrence or die after simple excision, as shown in this review. The groups of thyroid tumors that should be included in the borderline category are (i) papillary microcarcinoma; (ii) EncPTC; (iii) EnFVPTC; (iv) WDT-UMP; (v) FT-UMP; and (vi) capsular invasion only FTC.[30] Needless to say, borderline lesions must have no lymph node metastasis at diagnosis and, if present, low-grade malignancy should be applied to these cases because of a positive node.[30] A distant metastasis may be present in patients with EnFPLs at presentation, and those thyroid tumors should be treated as an aggressive type, as reported by several authors,[31–41] which is incorporated in our classification as PDC (Table 1).[30] The incidence of distant metastases at the time of initial presentation in differentiated thyroid cancer was approximately 4% and the overall long-term survival in patients presenting initially with distant metastasis was approximately 50% reported by Shaha *et al.*[36] From Lee's analysis, the overall survival rates in patients presenting with distant metastasis at 5 and 10 years were 83.8% and 72.1%, respectively, and the cause-specific survival rates were 68.5% and 26.8%.[37]

To explain the benefits of avoiding unnecessary surgical treatments, unavoidable complications after thyroid surgery for PTC were reported by Ito Y *et al.*[39] From their analysis of 1207 patients with PTC, 59 patients (4.4%) showed permanent recurrent nerve paralysis, which occurred in 52 cases because of direct invasion by carcinoma. Accidental nerve injury was observed in four patients (0.3%) and permanent recurrent nerve paralysis for unknown reasons in three 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 two (0.2%), two (0.2%), five (0.5%), three (0.3%), and five (0.5%), respectively.[39] When total thyroidectomy with modified radical neck dissection is performed for patients with EnFPL with PTC-N, approximately 10% will suffer at least one of the above complications in addition to 100% permanent hypothyroidism. It is a time to change treatment strategy from a total thyroidectomy with lymph node dissection to a less aggressive surgery, such as a lobectomy, for these borderline tumors, because they are almost benign and neither tumor recurrence nor cancer death occurs after simple excision. It is of note that this is important not only for the patients' quality of life but also to save medical economy.

GENETIC STUDY ON ENFVPTC AND WDT-UMP

Recent analysis of EnFPLs with PTC-N using molecular techniques shed new light on this entity as not being a PTC type malignancy. Zhu *et al.* determined the prevalence of RET/PTC, PAX8-PPARγ, and RAS mutations in the FVPTC and compared with cPTC.[40] As supported by many other papers, they proved that FVPTC is characterized by a high prevalence of RAS mutations, a low prevalence of RET/PTC-1 rearrangement and the absence of FTC-specific PAX8-PPARγ rearrangement.[14,40–45] This observation strongly suggests that FVPTC is not a subtype of PTC, which usually does not contain RAS mutations.[4,14,40–45] Rivera *et al.* demonstrated that BRAF mutation was absent in EnFVPTC, while a high rate of RAS mutation was present, which indicated that EnFVPTC belonged to FA/FTC group rather than PTC group.[14] These results highlighted a theoretical weak point in the diagnosis of EnFVPTC that there was no molecular evi-

dence to support that EnFVPTC was one part of PTC, and the histological criterion for malignancy solely relied on PTC-N. These authors concluded that PTC-N should not be used as absolute evidence of malignancy in tumors without any other evidence of malignancy.[14]

It is of note that DNA microarray gene analysis of thyroid tumors successfully discriminated benign and malignant tumors, including borderline lesions;[46,47] however, Fontaine *et al*. showed the heterogeneity of borderline tumors and highlighted the molecular similarities between some cases and true carcinomas.[46] From these data, we conclude that EnFPLs with PTC-N contain heterogenous tumors in benign, precancerous, malignant categories and possibly unrelated lesions; thus, PTC-N is only a helpful guideline for the diagnosis of PTC but not a specific diagnostic criterion for malignancy.

IMMUNOHISTOCHEMICAL PROFILES OF ENFVPTC AND WDT-UMP

Numerous immunohistochemical analyses on thyroid tumors have been published and the results significantly improved the more accurate diagnosis of thyroid tumors; however, it was evident that no single immunohistochemical marker was sensitive enough for an absolute diagnosis of malignancy with optimal specificity.[13,14,28,48–53] As for immunohistochemical characterization of FVPTC, Nakamura N *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 most effective in distinguishing FA from FVPTC.[50]

Papotti *et al*. concluded that PTC nuclear features were not mere artifacts and that these nuclear changes suggest that WDT-UMP is pathogenetically linked to PTC from their analysis of GAL3 and HBME1 in 13 cases of WDT-UMP.[52] Scognamiglio *et al*. performed immunohistochemical studies of their 11 cases using a panel of four antibodies (HBME-1, GAL3, CK19 and CITED1), and reported that six cases were bona-fide PTC and the remaining five cases showed intermediate expression profiles between PTC and FA.[28] The authors further concluded that these lesions might be biologically borderline lesions that were not fully malignant, corresponding to the UMP category.[28]

From the above immunohistochemical studies of EnFPLs with PTC-N or WDT-UMP, most of the authors reported their intermediate immunohistochemical characteristics between FA and PTC, and concluded that these lesions could be borderline and could be precursor lesions of PTC.[52,53] These observations are another reason why FPLs with PTC-N should be combined in unified terminology under an acceptable umbrella rather than to subdivide them meticulously and to pursue non-existing accurate diagnosis (Table 1).

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