Biological Behavior of Thyroid Cancer in Indeterminate Category

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Abstract

Fine needle aspiration biopsy (FNAB) is one of the most important diagnostic modalities in the initial workup of patients with thyroid nodules. The goal of thyroid FNAB is to distinguish nodules that require surgery from those that can be followed-up, thereby decreasing the number of diagnostic thyroidectomy. The FNAB diagnosis is often grouped into one of the following categories: malignant, suspicious, indeterminate, benign, or inadequate. Histologically, the indeterminate category includes benign, borderline and malignant lesions. Some new techniques have been reported to be useful in distinguishing malignant lesions from others in cytological indeterminate category, thereby decreasing the proportion of this category. However, little is known on the biological behavior of indeterminate and malignant lesions in this category. We have previously reviewed the cytological features of well differentiated tumors of uncertain malignant potential and proposed that the biological behavior of this group’s tumors is almost similar to that of benign lesions. This article briefly reviews the studies on the biological behavior of indeterminate category of thyroid FNAB in literature.

Keywords: Biological behavior, thyroid carcinoma, precursor lesion, borderline lesion

Introduction

The incidence of thyroid cancer has increased over the past four decades in many countries, including the United States and Asia countries, and this increase is primarily due to the rise in the incidence of papillary thyroid cancer (PTC) (1, 2). Fine needle aspiration biopsy (FNAB) is one of the most important diagnostic modalities in the initial workup of patients with thyroid nodules (3-5). It reduces the rate of unnecessary thyroid surgery for patients with benign nodules and appropriately triages patients with thyroid cancer to appropriate surgery. Before the routine use of thyroid FNAB, the percentage of surgically resected thyroid malignancy in all thyroid nodules was 14% (6), whereas this number surpasses 50% with current thyroid FNAB practice (7). Most FNAB diagnoses could be grouped into one of the following categories: malignant, suspicious, indeterminate, benign, and inadequate. However, cytological indeterminate thyroid nodules continue to present a diagnostic dilemma for clinicians despite its widespread use and clinical utility, because this category includes histologically benign, borderline and malignant lesions. The risk of malignancy in indeterminate category has been reported ranging from 14-42% (8-10). FNAB shows an inherent diagnostic gap for the cytologically indeterminate/follicular proliferation category because of the difficulty in determining vascular or capsular invasion, while the latter is critical to distinguish follicular thyroid adenoma (FTA) from follicular thyroid carcinoma (FTC). Furthermore, there is a substantial inter- and intraobserver variability in the cytological as well as in the histopathologic evaluation of thyroid nodules. Importantly, little is known on the biological behavior of thyroid carcinomas in the indeterminate category. The objective of this review is to evaluate the biological behavior of thyroid nodules that are initially classified into the indeterminate category.

Biological behavior of follicular cell-originated thyroid malignancy

According to their cellular origins, thyroid malignancies are divided into several types including PTC, FTC, poorly differentiated carcinoma (PDC), and undifferentiated thyroid carcinoma (UTC); and the follicular cell differentiated tumor is reported to be the most common type (4). Among those lesions, PTC accounts for 65-80% in the United States. The overall survival rate of patients with PTC is excellent and the overall incidence of tumor death from most large series studies is about 5% (11). However, there are several histologically well-characterized malignant variants that exhibit more aggressive behavior and include tall cell variant, columnar cell variant, solid variant, diffuse sclerotic variant, and several newly reported high-risk variants such as PTC with hobnail features or with loss of cellular polarity/cohesiveness (4, 11-13). PDC and UTC are known as aggressive malignancies with poor prognosis, however, the prognosis is different when FTC is taking into account; the latter can be further differentiated into two main variants: well differentiated carcinoma with capsular invasion only or with less vascular invasion; and more aggressive carcinoma with more than four vascular invasions or with diffuse infiltration (4, 11).

Nomination of well differentiated tumor of uncertain malignant potential and well differentiated tumor of uncertain behavior

PTC-type nuclear features (PTC-Ns) are characterized by nuclear enlargement, nuclear overlapping, nuclear clearing, nuclear grooves, and cytoplasmic pseudoinclusions. PTC-Ns are the diagnostic criteria for malignancy in thyroid tumors, regardless of
Encapsulated Follicular Thyroid Tumor

PTC-N

Obvious

Equivocal

Negative

Diffuse

Focal

En-FVPTC

WDT-UMP (WDT-UB)

FTA with atypia

WDT-UMP (WDT-UB)

FTA

Fig. 1. Nomenclature for encapsulated thyroid follicular tumors (modified Williams’s proposal). PTC-N, papillary thyroid carcinoma type nuclear changes; En-FVPTC, encapsulated follicular variant papillary thyroid carcinoma; WDT-UMP, well-differentiated tumor of uncertain malignant potential; FTA, follicular thyroid adenoma; and WDT-UB, well-differentiated tumor with uncertain behavior.

The encapsulation, invasiveness or papillary growth pattern (4). However, there are some variants that PTC-Ns are not evident, including columnar cell variant, Warthin-like variant, and cribriform-morular variant PTC (14, 15). PTC-Ns are also found in some benign lesions, such as hyalinizing trabecular adenoma and Hashimoto’s thyroiditis (16, 17). Significant disagreement exists in the diagnosis among those lesions when PTC-Ns are equivocal or incomplete (18-24). Therefore, Chan pointed out that strict criteria should be applied to the diagnosis of encapsulated conventional type PTC (En-CPTC) (18). In 2000, Williams proposed the terms of well-differentiated tumors of uncertain malignant potential (WDT-UMP) for morphologically non-invasive or questionable invasive encapsulated follicular tumors with questionable PTC-Ns: “well-differentiated carcinoma, not otherwise specified” for encapsulated tumors of well-differentiated follicular cells showing obvious capsular and/or blood vessel invasion but having questionable PTC-Ns; “WDT-UMP” for encapsulated tumors composed of well-differentiated follicular cells with questionable PTC-Ns, no blood vessel invasion, and absent or questionable capsular invasion; and “folicular tumor of uncertain malignant potential (FT-UMP)” for encapsulated tumors composed of well-differentiated follicular cells with questionable capsular invasion, and no blood vessel invasion nor PTC-Ns (25). One concern is the tumor capsular involvement that extends to the edge of the capsule and that cannot be explained by an irregular tumor/capsule interaction or by tumor trapped by fibrosis on the inner aspect of the capsule (25). WDT-UMP and FT-UMP in their definition have been suggested to be borderline lesions.

However, there were only several studies on the biological behavior of WDT-UMP (21, 26, 27). We studied the pathological features of 30 cases with WDT-UMP classified according to the modified Williams’ criteria, and developed our description for the nuclear changes of WDT-UMP as 2-4 times nuclear enlargement, 1-3% nuclear grooves, and rare or absent nuclear pseudoinclusions (Figure 1) (25, 28). Thus, our concept for WDT-UMP included both Williams’ WDT-UMP and encapsulated follicular-patterned tumors (En-FPT) with focal PTC-Ns. We therefore proposed a new terminology of ‘well differentiated tumor with uncertain behavior (WDT-UB)’ to distinguish ours from that of Williams. However, observer variations occur when assessing these lesions and up to 40% of these types of tumors often meet diagnostic discrepancy even among pathologists (18, 20, 24, 29).

Immunostaining of HBME-1, GAL-3 and CK19 showed different reactivity for the 30 cases of WDT-UMP. Univariate analysis revealed statistical differences in the expression of the three markers between WDT-UMP and the three groups of PTCs (En-CPTC; invasive follicular variant PTC (IFV-PTC), and invasive conventional type PTC (C-PTC), but no difference between WDT-UMP and FTA. BRAFV600E mutation is absent in WDT-UMP, however RET/PTC1 rearrangement may occur in some cases. Our studies have shown that WDT-UB behave as benign tumors, even they have PTC-Ns, either focal or equivocal. Although the case number was small, but no cases had invasion or cervical lymph node metastasis at surgery and no recurrence was demonstrated for 20 cases followed-up for 80 months. This result is different from that of En-FVPTC in literatures (30, 31). Based on our modified criteria, WDT-UMP have a favorable outcome and distinct morphological, immunohistochemical and molecular features from En-CPTC. Therefore, we have renamed the WDT-UMP and the non-invasive En-FPT with focal PTC-Ns as WDT-UB; the two diseases share PTC-Ns to a certain extent.

**Biological behavior of encapsulated follicular variant of papillary thyroid lesions**

The conventional PTC has been reported to present good clinical behavior in about 95% of cases (4, 11). It is well known that the diagnosis of encapsulated follicular-patterned thyroid lesions (En-FPLs) relies on the PTC-Ns and invasiveness, including capsular/vascular invasion for En-FPLs and mesenchymal invasion for non-encapsulated lesions. The evaluation of PTC-Ns is subjective and benign-malignant discrepancy always occurs even among specialists. Follicular growth pattern can be seen in the majority of PTC and up to 20%
to 30% of papillary growth is accepted for FVPTC in some reports (32). Rivera et al. studied the morphological subtypes of encapsulated PTC and have concluded that En-CPTC resembles C- PTC in its propensity to metastasize to lymph nodes as well as in its vascular/capsular invasive pattern, while En-FVPTC behaves more like FTC/FTA (33). However, we doubt whether the En- FVPTC is the FTC/FTA due to the subjective evaluation of PTC- Ns. Kakudo et al. proposed that En-FVPTC is a misnomer to a certain extent and strict criteria should be applied when evaluating the PTC-Ns for En-FPLs (34).

There are several different conclusions regarding the biological behavior of En-FVPTC. Baloch et al. pointed out that distant metastasis could be found in a few cases of En-FVPTC and En-FVPTC must be treated as a genuine cancer (30). However, Piana et al. found no cancer death occurred in 102 cases of En- FPLs that had been diagnosed as carcinoma because of complete capsular invasion and/or PTC-Ns with an average follow-up period of 11.9 years (35). These results support that En-FPLs with PTC- Ns and En-FPLs with capsular invasion only are truly 'non- threatening' (35). Liu et al. proposed that follicular variant PTC is a heterogeneous disease that is composed of two distinct subvariants: an IFV-PTC resembling C-PTC in its invasive growth and lymph node metastatic pattern; and En-FVPTC subvariant resembling FTA; the latter subvariant has no lymph node metastasis and recurrence during a median follow-up period of 11.1 years after lobectomy alone (36).

These studies indicate that the biological behavior of En- FVPTC is similar to that of benign lesions and it is curable even with lobectomy alone, which is same to the conclusion by our studies on WDT-UMP (28, 30, 34). Therefore, we proposed that En-FVPTC should be included into our defined group of WDT- UB; the biological behavior of which is almost always benign and the prognosis is good even with tumor resection alone.

**Indeterminate category in fine needle aspiration and the biological behavior**

To develop a uniform terminology for reporting thyroid FNA samples, the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) has been proposed by the National Cancer Institute, NIH in 2009 (37). Indeterminate category is known as atypia of undetermined significance (AUS) or follicular lesion of undetermined significance to describe the group of lesions with inadequate cytological features of malignancy (37). It is widely accepted that the cytological diagnosis of thyroid lesions often results in overdiagnosis or underdiagnosis because of overlapping features between benign and malignant lesions. Diagnosis of indeterminate is common in up to 20% of all samples (38-41). However, there are no global criteria for the cytology of WDT-UMP although it belongs to the cytological indeterminate category as it shares PTC-Ns with other lesions to a certain extent, including oval nucleus with ground glass feature and/or unusual nuclear grooves. To study the cytological features of WDT-UMP, a retrospective analysis was done for the FNAB samples of six WDT-UMPs that were confirmed in our previous study (28, 42).

No nuclear pseudoinclusions were found in the FNAB samples of adenomatous goiter (AG), FTA and WDT-UMP. Nuclear pseudoinclusions were increasingly observed in the PTC with indeterminate cytology (0.8%) and the PTC with malignant cytology (1.2%). No nuclear groove was observed in AG and FTA. However, the incidence of nuclear grooves increased gradually from WDT-UMP (4.5%), PTC with indeterminate cytology (6.2%), to PTC with malignant cytology (6.5%). The nuclear area of WDT-UMP was that between benign AG/FTA and PTC with malignant cytology. The maximum/minimum axis of WDT-UMP (0.934) lied between that of AG/FTA and that of PTC. The degree of the nuclear circularity of WDT-UMP was less than that of PTC. Questionable nuclear inclusions (artifact vacuole) may be seen in WDT-UMP, but absolute or definite nuclear inclusions with sharp borderline were not found in our six cases. These observations indicate that WDT-UMP may be often classified into the AUS, follicular neoplasm or suspicious for malignancy, which is a group of En-FPLs with equivocal PTC-Ns. This proposal has been confirmed recently by Strickland et al. and they found a significant number of non-invasive En-FVPTC (that is WDT-UMP by Williams’ proposal or WDT-UB in our study) in the indeterminate category lesions: 45% of AUS, 18% of follicular neoplasm, and 48% of suspicious for malignancy (43).

Because ~60% of PTCs or FTCs harbor somatic mutations of various genes, molecular testing for nodules in the indeterminate/follicular proliferation FNAB category has come into focus (44-49). Nikiforov et al. have shown that mutation analysis of a panel of genes (BRAF, RAS, PAX8/PPARG and RET/PTC rearrangements) helps increase the sensitivity (from 44% to 80%) and accuracy (from 93.3% to 97.4%) in detection of malignancy when compared with cytology alone for the indeterminate cytology of FNAB samples (47). Ohori et al. have demonstrated that the probability of harboring cancer in the indeterminate cytology category is 100% in the presence of one of the somatic mutations, but only 7.6% when absence of the somatic mutations (50).

As demonstrated above, the biological behavior of WDT-UB is almost always benign. Therefore, mutation analysis of a panel of genes (BRAF, RAS, PAX8/PPARG and RET/PTC rearrangements) should be applied first to rule out malignancy from the cytological indeterminate category, and follow-up instead of surgery is recommended for those without somatic gene mutations.

**Conflicts of Interest:** None

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