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Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features and the Practice in Qilu Hospital of Shandong University, China

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Abstract

Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) was introduced to cover a group of non-invasive encapsulated follicular-patterned thyroid lesions with very low malignant behavior. This nomination may have a great impact on the incidence of thyroid malignancy and the practice for endocrine pathologists. To demonstrate the proportion of the thyroid follicular cell-originated malignancy and the incidence of NIFTPs in China, the surgical samples during the period of 2007 to 2016 were reviewed by three pathologists in Qilu Hospital, China. There were 5561 cases of thyroid malignancies in total and 5412 of them were papillary thyroid carcinoma (PTC). Of the PTC, 132 were proved to be follicular variant of papillary thyroid carcinoma (FVPTC) (including three subtypes: non-encapsulated infiltrative, encapsulated invasive, and encapsulated non-invasive), and only 20 (0.37% in all PTCs and 0.23% in all thyroid malignancies) were diagnosed as NIFTP. Therefore, only a very small proportion of NIFTP was observed and it is expected to have only minor or negligible impact on the incidence of thyroid malignancy in the practice at Qilu Hospital.

Keywords: Non-invasive follicular thyroid neoplasm with papillary-like nuclear feature, follicular variant of papillary thyroid carcinoma, incidence of thyroid malignancy, China

Introduction

Since the introduction of follicular variant of papillary thyroid carcinoma (FVPTC) in 1970s, it has significantly contributed the increased incidence of papillary thyroid carcinoma (PTC). According to their biological behaviors and molecular changes, FVPTCs have further been divided into three variants recently, including non-encapsulated infiltrative, encapsulated invasive, and encapsulated non-invasive (1, 2). The latter is proved by several research centers to have nearly no recurrence even after a simple excision (1-4). Esserman *et al*. proposed the term of indolent lesion of epithelial origin for those lesions labeled currently as cancer or precursor, which are unlikely to cause harm if they are left untreated (5). They estimated that 15-75% of the lesions currently treated as cancer was clinically unimportant lesions. Similarly, Kakudo *et al.* suggested the non-invasive FVPTC as a borderline thyroid malignancy (6, 7).

Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) has been proposed recently by Nikiforov *et al*. to cover the group of non-invasive encapsulated follicular-patterned thyroid lesions with very low malignant behavior, which includes the non-invasive encapsulated FVPTC (EFVPTC) (8). According to this proposal, PTC-type nuclear features (PTC-N) are no longer the only diagnostic criterion of malignancy and the invasiveness takes precedence over nuclear features in the diagnosis of PTC-type malignancies. The role of invasiveness become more important to evaluate the biological feature of thyroid tumors. Although the incidence of thyroid carcinoma has recently increased rapidly all over the world, there is no obvious increase of the fatality rate. These findings can be attributable to any one of the followings: 1) early diagnosis of the malignancy, 2) improvement of the treatment, and 3) overdiagnosis of non-invasive encapsulated FVPTC as carcinoma. However, there is no report on the incidence of FVPTC in the practice of China. Therefore, this study introduced our practice of thyroid tumors and NIFTPs at Qilu Hospital, China.

Materials and Methods

The surgical pathology files of 5561 cases with thyroid follicular cell-originated malignancies from 2007-2016 were reviewed from the database of the Department of Pathology, Qilu Hospital, Shandong University, China. An approval was obtained from Qilu Hospital ethics committees and the patients gave their written informed consent. Hematoxylin and eosin-stained slides of all tumors were reviewed by three pathologists (Z. L., Y. S., and X. Z.) with attention to PTC-N. The diagnosis of PTC, FVPTC, follicular thyroid carcinoma (FTC), poorly differentiated thyroid carcinoma, or undifferentiated carcinoma was made based on the 2004 WHO classification (9). The diagnosis of NIFTP was made based on the Nikiforov's proposal as encapsulated follicular-patterned tumor with a complete capsule or clear demarcation of the tumor from adjacent thyroid tissue, and focally or diffusely well-developed nuclear features (Score 3) (8). It was very important that FVPTC included only those of follicular thyroid cell-originated tumor with pure follicular growth pattern, and those with "minor papillae more than 1%" were excluded. Therefore, in the present study, NIFTPs were equal to the non-invasive encapsulated PTC with focally or diffusely well-developed PTC-type nuclear features in the practice of Western pathologists (Figures 1 and 2).

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Table 1. Thyroid malignancies of follicular thyroid cell-origination in Qilu Hospital of Shandong University from 2007 to 2016

Year	PTC	FTC	PDC	UTC	Sample Quantity	Incidence of PTC (%)*
2007	80	3	0	0	20537	0.39
2008	81	2	0	0	21910	0.37
2009	138	1	0	0	23236	0.59
2010	148	4	0	0	23832	0.62
2011	249	4	2	1	26856	0.93
2012	482	4	13	3	34664	1.39
2013	706	10	20	1	39037	1.81
2014	916	6	16	0	42574	2.15
2015	1090	12	20	0	47920	2.27
2016	1522	17	7	3	52610	2.90
Total	5412	62	78	8	333176	1.62

*PTC in all samples of Department of Pathology, Qilu Hospital Shandong University, China. PTC: papillary thyroid carcinoma; FTC: follicular thyroid carcinoma; PDC: poorly differentiated carcinoma, UTC: undifferentiated thyroid carcinoma

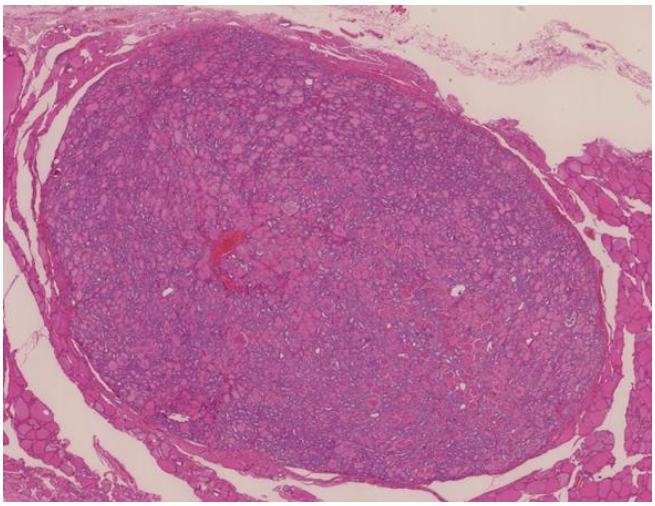

Fig. 1. A follicular-patterned thyroid lesion with clear demarcation, unequivocal PTC type nuclear changes and focal papillae (<1%).

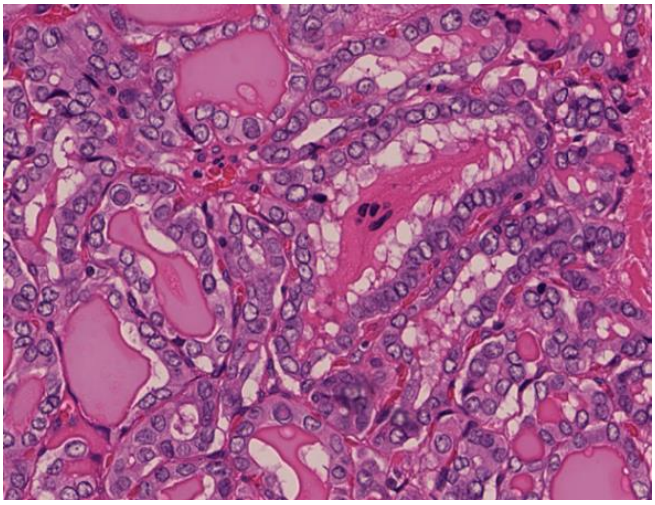

Fig. 2. The PTC-type nuclear features, including nuclear enlargement, enlongation, overlapping, nuclear grooves, pseudoinclusion, and ground glass chromatin (Score 3 according to the Nikiforov's proposal).

Results

Qilu Hospital is a major general teaching hospital established in 1890, currently providing more than 3,000 inpatient beds. The samples submitted to the Department of Pathology include both biopsy and surgical samples, and there were totally 333,176 samples in our Department from 2007 to 2016. The samples increased about 2.6 times (52610/20537) in year 2016, compared with 2007 as shown in Table 1, probably due to the expansion of the hospital in 2011. A total of 5561 cases of thyroid tumors were reviewed and of them 5412 were PTC. PTC was still the main part of thyroid malignancies within the last ten years (Figure 3). Female patients increased more over male patients (Figure 4). The proportion of PTCs in all malignancies was 7.4 times higher in 2016 than in 2007, and this increase may be due to the introduction of thyroid fine needle aspiration in year 2014.

There were 132 cases (2.43% in all PTCs and 1.53% in all thyroid diseases) that were proved to be FVPTC (including non-encapsulated infiltrative, encapsulated invasive, and encapsulated non-invasive). Among them, only 20 cases (0.37% in all PTCs and 0.23% in all thyroid diseases) were diagnosed as NIFTP (noninvasive encapsulated FVPTC).

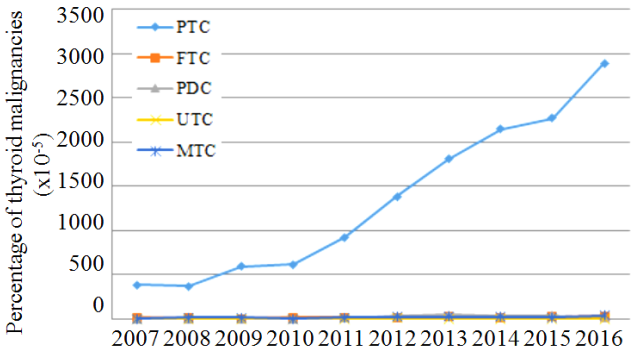

Fig. 3. Proportion of different types of thyroid tumors relative to all tumors in the Department of Pathology, Qilu Hospital from 2007 to 2016.

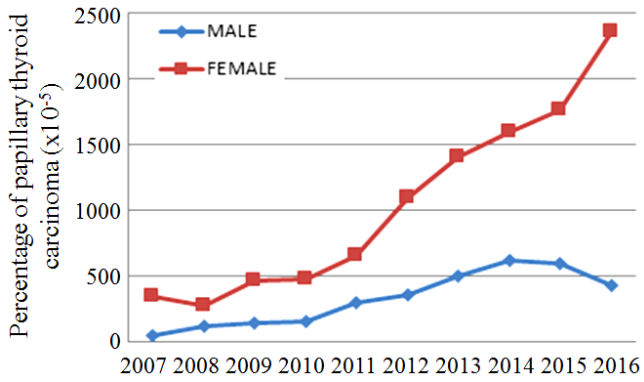

Fig. 4. The proportion of papillary thyroid carcinoma from male and female patients in all thyroid tumors in the Department of Pathology, Qilu Hospital, from 2007 to 2016.

Discussion

Above all, PTC type nuclear features and capsular/vascular invasion are morphological criteria to differentiate PTC from FTC. However, controversial debate is increasing especially on those tumors with follicular growth pattern and questionable PTC-N. It has been reported that the Asia pathologists use more strict criteria on the evaluation of PTC-N than the Western pathologists (10-13).

In 1960s, Lindsey S. identified several thyroid tumors with PTC-N and psammoma bodies from FTC (according to the criteria at that time), which showed papillae in the lymph node metastasis (14). They proposed that the clinical behavior of those tumors was nearly the same with PTC, and should be named as FVPTC. In 1977, Chen and Rosai studied 6 cases of FVPTC and pointed out that the incidence of this kind of tumor was very low, at about 1.7% (15). FVPTC was further introduced by WHO classification of endocrine tumor in year 2004, and the incidence of FVPTC increases gradually after that (9, 16). Infiltrative FVPTC is further demonstrated to share similar molecular and biological features with conventional PTC (1). Non-invasive EFVPTC and invasive EFVPTC show similar molecular and biological features with follicular thyroid adenoma and FTC, respectively, therefore, the debate on clinical behavior of non-invasive FVPTC is becoming a hot topic (3, 4).

In the year 2000, Williams proposed two types of thyroid tumors: "well differentiated tumors of uncertain malignant potential (WDT-UMP)" to cover a group of thyroid follicular patterned tumor with or without questionable invasion and questionable PTC-N, and "follicular thyroid tumor of uncertain malignant potential (FT-UMP)" to cover a group of thyroid follicular patterned tumor with questionable capsular invasion, without vascular invasion, and PTC-N. In year 2011, our group have demonstrated that non-invasive EFVPTC and Williams' WDT-UMP share same morphological, immunohistochemical and molecular characteristics and should be combined into one group as "well differentiated tumor with uncertain behavior (WDT-UB)". We reported a relatively low rate of encapsulated FVPTC without invasion as 0.4% and that of WDT-UMP as 5.6%, and emphasized that the diagnosis of 'carcinoma' should not be used to cover this spectrum of tumors until the uncertainty about the nature of this lesion is settled (4, 6). In 2016, Nikiforov *et al.* proposed the diagnostic term, NIFTP, to cover the group of encapsulated/well demarcated non-invasive follicular thyroid lesions with a certain PTC-N (8). The biological features of NIFTP are similar with follicular thyroid adenoma and harbor mutations in *RAS*, and *PPARγ* or *THADA* gene fusions and only one case showed $BRAF^{K601E}$ mutation but without $BRAF^{V600E}$ mutation.

In our practice, 132 cases (2.43% in all PTCs and 1.53% in all thyroid diseases) were proved to be FVPTC and only 20 cases (0.37% in all PTCs and 0.23% in all thyroid diseases) were diagnosed as NIFTP (non-invasive encapsulated FVPTC), which is in the line of the previous study from an independent Japanese institution (4). There was a very lower incidence of NIFTP in Asian than in Western countries (8). Therefore, only minor or negligible impact of NIFTP on the incidence of malignancy in thyroid nodules is expected in our practice at Qilu hospital. That is, only very small part of the patients is affected by the paradigm shift from 'non-invasive encapsulated FVPTC' to NIFTP.

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