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Non-invasive follicular thyroid neoplasm with papillary-like nuclear features; a single centre study

TW Wijesiri, LKB Mudduwa, TG Liyanage

Department of Pathology, Faculty of Medicine, University of Ruhuna, Galle, Sri Lanka.

Correspondence: Dr. T. W. Wijesiri
e-mail: *thiliniwwijesiri@gmail.com*
https://orcid.org/0000-0003-3585-3751
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ABSTRACT

Introduction: Papillary carcinoma of the thyroid is the commonest cancer in the thyroid with an increasing incidence over the past few decades. A subset of papillary carcinomas was re-classified into "Non-invasive Follicular Thyroid Neoplasm with papillary-like nuclear features" (NIFTP) in late 2017, due to the excellent prognosis they exhibit. Identification of NIFTP is important because surgical management and follow up is similar to follicular adenoma, thus reducing the psychological burden to patient, eliminating unnecessary exposure to radiation and economic burden to the society. This study intended to assess the prevalence and the inter-observer consistency in identifying NIFTP in the study sample.

Methods: This retrospective, descriptive, cross-sectional study included all thyroid specimens received at our department in 2017. Thyroid neoplasms with a potential for reclassification to NIFTP were reassessed according the WHO criteria by two investigators who were blinded to the previous and each other's diagnoses.

Results: Out of the 256 thyroid specimens received, 74/256 (28.90%) considered to have potential to be reclassified as NIFTP which included 34 cancers. Only 5/74 (6.75%) satisfied the criteria for NIFTP. Three NIFTPs had been reported as papillary microcarcinoma and the other two as follicular variant of papillary carcinoma. Inter-observer consistency in re-classifying the 74 tumours was 94.6%, with a 100% consistency in diagnosing NIFTP. Following re-classification, the proportion of cancers in the study sample reduced to 56/256 (21.87%) from 61/256 (23.82%). The prevalence of NIFTP in the study sample was 1.95% (5/256).

Conclusions: The prevalence of NIFTP in the study sample is comparable to the Asian population. The current study reports a high inter-observer consistency in recognizing NIFTP among potential lesions, most likely due to the strict adherence to WHO criteria.

Keywords: *Inter-observer consistency, NIFTP, thyroid cancer.*

Introduction

Papillary carcinoma of thyroid is the commonest cancer occurring in the thyroid gland with excellent survival. Its incidence has been increasing dramatically over the past few years (1).

In the past, a subgroup of papillary carcinomas was categorized into the group "Encapsulated Follicular Variant of Papillary Carcinoma" (EFVPC). A subset of this type of tumours without capsular or vascular invasion was known as Non-invasive EFVPC. During the recent past, many studies have been done on these tumours and it has been found that these are very indolent tumours with a very good prognosis (2, 3). According to the "WHO Classification of Tumours of Endocrine Organs-2017" these tumours are now separated from the group of thyroid carcinoma and included in the

group "Other encapsulated follicular-patterned thyroid tumours" and currently been known as "Non-invasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP), a term now been welcomed internationally (4).

Identification of NIFTP is very important because surgical management and follow up is different to conventional papillary carcinoma and is similar to patients with follicular adenomas (5). It will prevent the over treatment of patients hence reducing the financial burden on the health care system (6). This change in nomenclature is expected to reduce the rate of thyroid malignancies being diagnosed and it will reduce the psychological burden on patients when their neoplasm is labeled as a "cancer".

We intended to determine the prevalence, clinicopathological and cytological characteristics of NIFTP and interobserver consistency in diagnosing NIFTP in this study.

Methods

This was a cross sectional, descriptive study with retrospective data collection, which included 256 thyroid specimens. Thyroidectomy specimens of all patients who underwent thyroidectomy at the Professorial Surgical Unit of the Teaching Hospital Karapitiya, which were received at the Department Pathology in the year 2017 were included. Thyroid specimens diagnosed as one of the following were re-evaluated; follicular adenomas, follicular carcinomas, Hürthle cell adenoma, Hürthle cell carcinoma, Follicular Variant of Papillary Thyroid Carcinoma (FVPTC), well differentiated tumour of uncertain malignant potential (WTUMP), considering their potential to be reclassified.

Benign conditions like colloid goitre, thyroiditis, hyperplastic nodules and malignant lesions which do not have the morphology of NIFTP (conventional papillary carcinoma, medullary carcinoma and anaplastic carcinoma) were excluded from the study. Hyperplastic nodules were not re-evaluated because, if there were suspicious nuclear features of papillary carcinoma, the tumour would have invariably be categorized into well differentiated tumour of uncertain malignant potential (WTUMP), which is included in the study population. Duplication of specimens was avoided.

haematoxylin and eosin (H&E) slides of selected specimens were assessed for the quality for re-evaluation. New H&E slides were prepared from the relevant paraffin blocks when the original slides were faded. The cases included in the study were reclassified according to the new (2017) WHO classification of tumours of the thyroid gland (4). The first and third authors re-evaluated the slides and they were blinded to each other's diagnosis and the previous diagnosis.

Table 1: WHO diagnostic criteria for NIFTP

• Encapsulation or clear demarcation
• Follicular growth pattern with all of the following; o <1% papillae o No psammoma bodies o <30% solid, trabecular, or insular growth pattern
• Nuclear features of papillary carcinoma (i.e. nuclear score of 2-3)
• No lympho-vascular or capsular invasion
• No tumour necrosis
• No high mitotic activity (<3 per 10 hpf)

According to the WHO criteria to diagnose NIFTP of thyroid (Table 1), capsule of the lesion should be thoroughly sampled to exclude capsular and vascular invasion. In our setup, when there is a capsulated lesion, they are thoroughly examined and the capsule is well sampled to exclude capsular and vascular invasion. Therefore, it was assumed that this criterion is already considered at the time of reporting.

Clinicopathological characteristics which include age, sex, FNAC diagnosis category of the tumour, type of surgical intervention, tumour size, background thyroid pathology, any concurrent tumours, and the cytopathological features of NIFTP were analysed.

Percentage of patients with NIFTP in the selected study sample was calculated. Inter-observer variability of diagnosing NIFTP in thyroid specimens was assessed using Kappa index.

Results

Clinicopathological findings

A total of 256 thyroid specimens have been reported during the study period. Majority of the patients were females (93.8%) and most patients were aged between 41 - 60 years (41.4%). Nearly half of the thyroid specimens were colloid goiters (44.5%) and 97/256 (37.8%) contained a neoplasm.

Out of the total number of thyroid specimens received, 74/256 (28.90%) had tumours with a potential to be reclassified as NIFTP. Out of the selected sample, 34/74 were malignant tumours. Original diagnosis according to the old classification of the study sample is shown in Table 2. Out of all papillary carcinomas, half (50%) were papillary micro-carcinomas, nearly half (41.6%) had conventional type and only 3/36 were follicular variant papillary carcinomas.

Out of the total number of thyroid tumours with potential to be classified as NIFTP, only 5/74 (6.75%) satisfied the criteria for NIFTP.

All of them were females and age ranged from 25 - 60 years. Three of them had presented as solitary thyroid nodules and two were incidental findings in colloid goiters. One had the FNAC diagnosis as Thy 5, which indicate malignancy and others had Thy 2 and Thy 3 in similar proportions. Thy 2 had been assigned to two tumours that were incidental findings in colloid goiters. Three NIFTPs had been reported as papillary microcarcinoma and the other two as follicular variant of papillary carcinoma in their original reports. One of the FVPC was an encapsulated variant which was surrounded by a thick fibrous capsule without capsular or vascular invasion. Sizes of the NIFTP ranged from 5 mm to 25 mm and there were no papillae, solid component, psammoma bodies or mitoses in these tumours and the papillary nuclear features were diffuse with a score of 3/3 according to the WHO criteria. There were no concurrent tumours identified in the thyroid in any of the five cases.

Table 2: The original histopathological diagnosis of the study sample according to the original diagnosis

Thyroid pathology	Frequency	Percentage
Colloid goitre	114	44.5%
Chronic autoimmune thyroiditis	29	12.9%
Colloid goitre with autoimmune thyroiditis	2	0.8%
Follicular adenoma	24	10.5%
Follicular carcinoma minimally invasive	7	2%
Follicular carcinoma widely invasive	8	3.1%
Hürthle cell adenoma	7	3.5%
Hürthle cell carcinoma minimally invasive	6	1.6%
Hürthle cell carcinoma widely invasive	1	0.4%
Papillary carcinoma	15	3.5%
Follicular variant papillary carcinoma	3	1.2%
Papillary microcarcinoma	18	7%
Hyperplastic nodule	19	7.4%
Anaplastic carcinoma	1	0.4%
Medullary carcinoma	2	
Total	**256**	**100%**

Tumours that were reclassified are highlighted.

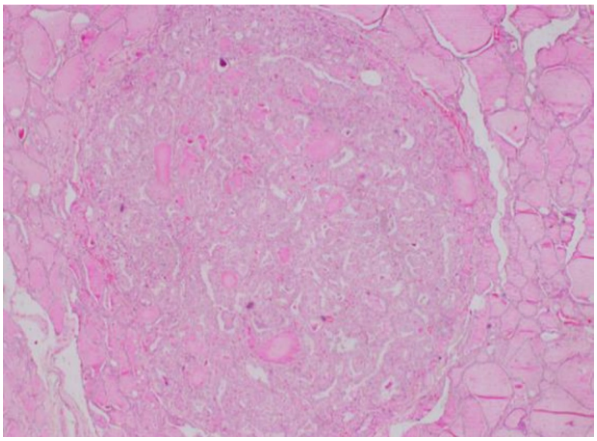

Figure 1: NIFTP (H&E x10)

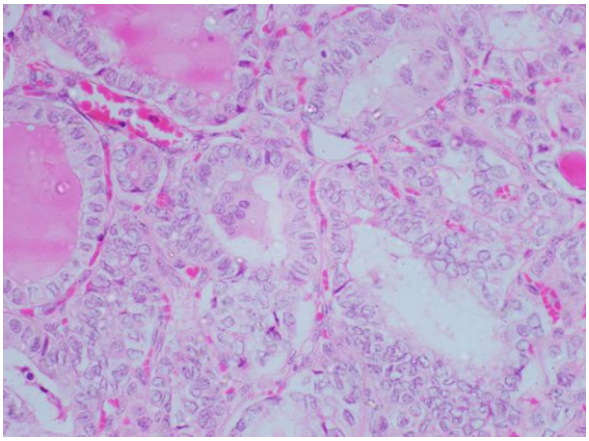

Figure 2: Tumour composed of follicles lined by cells with papillary nuclear features (H&E x 40)

Table 3: Clinicopathological characteristics of NIFTP in the study sample

Specimen	Age / Sex	Clinical presentation	FNAC diag.	Original diagnosis	Size (mm)	Capsule	Background	Revised diagnosis
1	54 / F	STN	Thy 3	FVPC	25	Yes	CAT	NIFTP
2	38 / F	MNG	Thy 2	Papillary microcar.	5	No	CG	NIFTP
3	69 / F	STN	Thy 3	FVPC	15	No	LT	NIFTP
4	25 / F	STN	Thy 5	Papillary microcar.	9	No	CG	NIFTP
5	60 / F	MNG	Thy 2	Papillary microcar.	6	No	CG	NIFTP

STN - Solitary thyroid nodule, MNG - Multinodular goitre, FVPC - Follicular variant papillary carcinoma, CAT - Chronic autoimmune thyroiditis, CG - Colloid goitre, LT - Lymphocytic thyroiditis

Inter-observer consistency in re-classifying the 74 tumours was 94.6% and the disagreement was for Hurthle cell and follicular adenomas. In our study, kappa index for diagnosing NIFTP by the two observers was 1 making the inter-observer consistency in diagnosing NIFTP 100%. Following re-classification, the proportion of cancers in the study sample reduced to 56/256 (21.87%) from 61/256 (23.82%). The prevalence of NIFTP in the study sample was 1.95% (5/256).

Discussion

Thyroid cancer is the commonest endocrine cancer and its incidence has increased in the last three decades all over the world (7, 8). The increase is almost exclusively due to increases in the incidence of papillary carcinoma of the thyroid, with no significant change in other histological subtypes (1). In USA, it is the most common cancer of thyroid gland accounting for 87.8% of all thyroid cancers (1).

In Sri Lanka, papillary thyroid carcinoma accounts for 71.99 % thyroid malignancies and it is the second leading cancer in females and leading cancer of females between 15-34 years of age (9). The worldwide increase in thyroid cancer incidence is claimed to be due to the increased diagnostic intensity and environment and lifestyle changes (10).

Papillary carcinoma of thyroid is diagnosed by its characteristic nuclear features; nuclear enlargement, overlapping, clearing, nuclear grooves and intranuclear pseudo-inclusions. Subtypes of papillary carcinoma includes, classic papillary thyroid carcinoma, papillary microcarcinoma, encapsulated variant, follicular variant, diffuse sclerosing variant, oncocytic variant, tall cell and columnar cell carcinoma and cribriform-morular variant (11). In the past, FVPTC was categorized into encapsulated and non-encapsulated/ infiltrative and diffuse/aggressive/multi-nodular types. Encapsulated Follicular variant of Papillary Carcinoma (EFVPC) was again divided in to invasive and non-invasive subtypes depending on the presence of capsular and vascular invasion (12). According to USA data, FVPTC accounts for 29.2% of all PTC variants (1).

Many research reports are available regarding non-invasive FVPTC in the literature and they describe this tumour subtype as having a benign behaviour (2, 3). In 2016, a group of experts in endocrine neoplasia led by Dr. Nikiforov had assessed the tumours previously known as "noninvasive encapsulated follicular variant of papillary thyroid carcinoma (FVPTC)." They have measured the frequency of adverse outcomes in patients with non-invasive and invasive EFVPTC. The parameters they have assessed were death from disease, distant or loco-regional metastases, and structural or biochemical recurrence. The diagnosis was based on a set of reproducible histopathological criteria. Results of this study proved that NIFTPs has a very low risk of malignancy with excellent prognosis compared to invasive EFVPC. Based on the findings of this study they have reclassified papillary thyroid carcinomas previously known as non-invasive follicular variant of papillary thyroid carcinoma to "non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)" (2). This new term was included in the "WHO Classification of Tumours of Endocrine Organs-2017" with strict diagnostic criteria.

The molecular characteristics of NIFTPs are found to be similar to follicular adenomas and carcinomas been harboring RAS gene mutations, PAX8/ PPARG translocations and THADA fusions. BRAF V600E that are characteristically seen in papillary carcinomas are not identified in these tumours if strict diagnostic criteria for NIFTP are applied (14).

The current study aimed at describing the newly defined tumour entity NIFTP in terms of prevalence, clinicopathological features and the inter-observer consistency in diagnosing NIFTP.

In Asian countries the rate of NIFTP (1.6%) is low compared to non-Asian countries (13.3%). (15). Difference in the rate is contributed by the threshold for diagnosing PTC nuclei, difference in the nature of PTCs, and different established clinical practices. In our study, the proportion of NIFTP among thyroid diseases was 1.95%, which was similar to that of Asian countries.

In our study, inter-observer consistency in diagnosing the limited number of NIFTPs included was 100% most likely due to the strict adherence to the WHO defined criteria in diagnosing NIFTP. However, the authors believe that this figure may become less in a larger sample. The inter-observer consistency of 94.6% in reclassifying the thyroid tumours with potential to be reclassified as NIFTP is also as an important finding as it indicates the applicability of the diagnostic criteria in identifying the NIFTPs among other lesions. Out of the 5 NIFTPs identified in the study sample, two were previously diagnosed as FVPC and others as papillary microcarcinomas. In previous studies, a subset of follicular adenomas were reclassified as NIFTP, but in our study none of the benign conditions were re-categorized as NIFTP. Studies have shown that cytological categories of NIFTP can come under any cytological category but are commonly included in the indeterminate categories which include atypia of undetermined significance/ follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasm/ suspicious for follicular neoplasm (FN/SFN) and suspicious for malignancy (15). In our study, two NIFTPs were reported as follicular proliferations and one as malignant (papillary carcinoma) in FNAC and the other two were incidental findings in colloid goiters.

In conclusion, the prevalence of NIFTP in the study sample was in consistence with the figures for Asia. Although the prevalence is low, identification of NIFTP is important to reduce the over diagnosis and over treatment of thyroid tumours with an indolent behaviour. The current study reports a high inter-observer consistency in recognizing NIFTP among potential lesions, most likely due to the strict adherence to WHO criteria.

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