Noninvasive follicular thyroid neoplasm with papillary-like nuclear features and the risk of malignancy in thyroid cytology: Data from Singapore

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ABSTRACT

Introduction: The impact of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) on the risk of malignancy (ROM) in fine-needle aspiration cytology (FNAC) per The Bethesda System for Reporting Thyroid Cytopathology has not been well reported in Singapore.

Methods: We retrospectively identified 821 thyroid nodules with preoperative FNAC from 788 patients out of 1,279 consecutive thyroidectomies performed between January 2010 and August 2016 in a tertiary general hospital in Singapore. Possible cases of NIFTP were reviewed for reclassification and the impact of NIFTP on ROM was analysed.

Results: The incidence of NIFTP was 1.2% (10 out of 821). If NIFTP is considered benign, ROM in Bethesda I through VI were 8.6%, 3.5%, 26.3%, 20.0%, 87.7%, 97.0% versus 8.6%, 4.2%, 28.1%, 26.7%, 89.2% and 100% if NIFTP is considered malignant. Eight patients with NIFTP had follow-up of 15 to 110 months. One had possible rib metastasis as evidenced by I¹³¹ uptake but remained free of structural or biochemical disease during a follow-up period of 110 months. None had lymph node metastasis at presentation, nor locoregional or distant recurrence.

Conclusion: Classifying NIFTP as benign decreased ROM in Bethesda II through VI, but the benignity of NIFTP requires more prospective studies to ascertain. The impact of NIFTP on ROM in our institution also appears to be lower than that reported in the Western studies.

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INTRODUCTION

As only 5–10% of thyroid nodules harbour malignancy, fine-needle aspiration (FNA) is important in triaging nodules requiring surgical excision from nodules that may be observed.^{1,2} This approach allows risk stratification that can reduce the rate of benign lesion removal by diagnostic lobectomies³ and its associated postoperative morbidity.⁴ However, thyroid cytology reports should convey a reproducible risk of malignancy (ROM) in order to facilitate surgical decision making. The Bethesda System for Reporting Thyroid Cytopathology

(TBSRTC), published in 2009,⁵ is a 6-tier system with standardised nomenclature. Using TBSRTC, cytopathologists can report FNAs to the referring physician in terms that are succinct, unambiguous and clinically useful.⁵ In 2017, the second edition of TBSRTC⁶ was published, in which ROM was revised especially for the indeterminate categories and according to the benignity of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). NIFTP is a subgroup of noninvasive/encapsulated follicular variant papillary thyroid carcinoma

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CLINICAL IMPACT

What is New

- This study from Tan Tock Seng Hospital in Singapore evaluates the impact of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) on the risk of malignancy in thyroid fine-needle aspiration cytology categorised by the Bethesda system.

Clinical Implications

- Understanding the risk of malignancy in thyroid cytology and the impact of NIFTP in the Singapore context can help clinicians manage patients with thyroid nodules more appropriately.

(PTC) that can be treated as indolent, perhaps benign, tumours. It is diagnosed on histopathology using strict criteria first proposed by Nikiforov et al.⁷ NIFTPs are known to have a very low recurrence rate (near zero),⁸ therefore its diagnosis may reduce the patient's psychological burden and decrease over-treatment. However, little is known in terms of the ROM per TBSRTC in a Singapore patient population and how the introduction of NIFTP may affect the ROM. Such information should be sought in order to help clinicians in Singapore counsel their patients more precisely on the implications of their FNA results. Worldwide, the impact of NIFTP on ROM depends on the incidence of NIFTP in each population. Several studies from different countries and institutions including a recent meta-analysis showed a wide variation in the prevalence of NIFTP among lesions diagnosed as PTC.⁹⁻¹² In this study, we aim to determine the ROM in various Bethesda categories in the setting of a tertiary general hospital in Singapore and how NIFTP would affect ROM in a multiethnic Southeast Asian population.

METHODS

After approval from the Domain Specific Review Board of National Healthcare Group, Singapore (reference number 2017/01150), we retrieved electronic medical records of patients who underwent hemithyroidectomies, total thyroidectomies or completion thyroidectomies in the Department of Otorhinolaryngology or General Surgery between January 2010 and August 2016 in Tan Tock Seng Hospital, Singapore. Out of 1,279 patients, 491 were excluded as they did not have preoperative thyroid FNA or the FNA report was not available, or the site of FNA could not be determined. This left 788

patients with 821 FNAs on different thyroid nodules, in whom we could match the cytology to histology. Matching of preoperative FNA to postoperative histology was performed by the senior author (HL) and co-author (RT). The senior author verified all matching performed by the co-author and resolved all queries. Special attention was paid to papillary thyroid microcarcinomas (PTMCs). The senior author reviewed all PTMCs to determine if they were subjected to FNA. PTMC was matched to the cytology if FNA was ultrasound-guided and the site of FNA matched the site of PTMC on the histopathology of the thyroidectomy specimen. Otherwise, the PTMC was considered incidental. As FNA was performed under ultrasound guidance (USG) in 58.3% of nodules (479 out of 821), close attention was also paid to the matching of FNAs that were not performed under USG. A third author (BL) reviewed the medical records to verify the matching. In most of these nodules (326 out of 342), the clinicians stated that they performed the FNA on the palpable or dominant nodule and indicated the location of the FNA. In the other 16 patients, no nodule was clearly dominant, but the histology of the thyroid gland showed benign multinodular goitre or lymphocytic thyroiditis uniformly throughout the thyroidectomy specimen. Therefore, their cytology could be matched to these diagnoses. In addition, we collected each patient's age at thyroidectomy, sex and ethnicity. For patients with NIFTP, the size of NIFTP, postoperative treatment, results of structural and biochemical follow-up were also collected to determine the occurrence of locoregional recurrence or distant metastasis.

Cytological preparation

FNA was performed using a 23- or 25-gauge needle attached to a disposable plastic syringe. Samples obtained were expelled onto 4 to 8 glass slides and smeared. Half of these smears were placed in 95% alcohol for Papanicolaou staining and the other half left to air dry before Giemsa or Hemacolor staining. Cell block preparations were made when adequate material was available. Cytotechnologists were routinely on site to assess the adequacy of FNA samples.

Classification of cytology and histology

FNA specimens were interpreted by pathologists from our institution using TBSRTC^{5,6} and categorised into 1 of 6 categories: (I) nondiagnostic or unsatisfactory, (II) benign, (III) atypia of undetermined significance or follicular lesion of undetermined significance (AUS or FLUS), (IV) follicular neoplasm, (V) suspicious for malignancy, and (VI) malignant. For the purpose of this study, all cytology reports were reviewed again by a head

and neck pathologist (second author MMB) to confirm the Bethesda category. This pathologist also reviewed the histological reports of all thyroid nodules and standardised the diagnostic nomenclature according to the 2017 World Health Organization classification of endocrine tumours.¹³

Reclassification of NIFTP

To identify NIFTP, histological slides of all follicular or Hürthle cell adenomas, adenomatoid nodule with atypia, follicular neoplasm of uncertain malignant potential, and follicular variant papillary thyroid carcinomas (FVPTCs) were reviewed by MMB and reclassified as NIFTP if they fulfill the criteria described by Nikiforov et al.,⁷ as follows:

Inclusion criteria

The tumour is:

- Encapsulated or well demarcated
- Follicular patterned
- Demonstrates at least focal nuclear features of papillary thyroid carcinoma

Exclusion criteria

- Infiltration/tumoural capsular invasion
- Solid/trabecular or insular growth greater than 30%
- True papillary growth (with fibrovascular cores) (even 1 well-formed papillary structure)
- Psammoma bodies
- Tall cell, hobnail cell, columnar cell, or cribriform morular morphology
- Necrosis
- Mitoses greater than 3 per 10 consecutive high-power fields (HPF) (in solid/microfollicular areas)

Entire nodule and complete tumour-capsule interface of encapsulated nodules or nodules with atypia indeterminate of papillary thyroid carcinoma were routinely evaluated in our Department of Pathology prior to 2016. Therefore, they are sufficient for the definitive diagnosis of NIFTP in this study.

Follow-up

Patients diagnosed with thyroid cancer postoperatively were routinely followed up with thyroglobulin and antithyroglobulin antibodies, free T4, thyroid stimulating hormone (TSH), structural imaging of the neck, and prescribed levothyroxine for TSH suppression if the cancer was papillary or follicular carcinoma. Response to treatment was classified according to the guidelines of American Thyroid Association¹⁹ and patients with

biochemical indeterminate or incomplete response without structural neck disease would be referred for consideration of radioactive iodine.

Statistical evaluation

Statistical analysis was performed using STATA SE version 14.2 (StataCorp, College Station, US). Categorical data were tabulated as frequencies and percentages. Continuous data were summarised as mean, median and range. Shapiro-Wilk test was performed to assess normality. Fisher's exact test was performed to compare categorical variables. All *P* values were 2-sided and *P* < 0.05 was considered significant.

RESULTS

Demography and histology

Age at thyroidectomy ranged from 14 to 88 years with a median of 52 years. There was female predominance for malignant pathology/incidental PTMC (78.4%) and benign pathology/NIFTP (79.8%). The distribution of ethnicity in patients with malignant pathology/incidental PTMC was 71.2% Chinese, 10.2% Malay, 7.2% Indian and 11.4% others, while that for benign pathology/NIFTP was 80.2% Chinese, 7.5% Malay, 5.5% Indian and 6.8% others. Table 1 shows the histological diagnoses of the thyroid nodules subjected to FNA: 22.7% were malignant, 76.1% were benign and 1.2% were NIFTPs. The most common malignancy subjected to FNA was conventional-type papillary thyroid carcinoma (122/186, 65.6%) followed by follicular thyroid carcinoma (36/186, 19.4%). The most common benign lesion subjected to FNA was nodular or multinodular goitre (563/625, 90.1%) followed by follicular or Hürthle cell adenoma (34/625, 5.4%).

Histopathology of NIFTP

Upon review of the 16 FVPTCs, 3 were reclassified as NIFTP, 3 were encapsulated noninvasive FVPTCs and 10 were encapsulated invasive FVPTCs. The 3 encapsulated, noninvasive FVPTCs were not NIFTP as focal true papillae formation was present, and one showed >30% solid/trabecular pattern. There were 38 follicular adenomas, of which 5 showed atypia, raising concern of papillary thyroid carcinoma. Upon review, these were classified as NIFTP. One adenomatoid nodule with atypia and 1 follicular neoplasm with uncertain malignant potential was also reclassified as NIFTP (Fig. 1).

Clinical features of NIFTP

Table 2 shows the clinical features of the 10 NIFTP diagnosed retrospectively. Cytologically, 1 was

Table 1. Histological diagnoses of all thyroid nodules that underwent fine-needle aspiration (FNA)

Histology	Number of nodules (%) Total=821
Malignant	186 (22.7)
Papillary thyroid carcinoma (PTC)	135 (16.4)
Conventional ^a	106 (12.9)
Follicular variant PTC (FVPTC)	13 (1.6)
- Encapsulated invasive	10 (1.2)
- Encapsulated non-invasive	3 (0.4)
Microcarcinoma ^b (PTMC) biopsied by FNA	16 (1.9)
Follicular carcinoma	36 (4.4)
Minimally invasive	21 (2.6)
Encapsulated angioinvasive	8 (1.0)
Widely invasive	7 (0.9)
Oncocytic (Hürthle cell) carcinoma	7 (0.9)
Encapsulated angioinvasive	6 (0.8)
Widely invasive	1 (0.1)
Medullary carcinoma	5 (0.6)
Poorly differentiated carcinoma	1 (0.1)
Anaplastic carcinoma	1 (0.1)
Metastatic adenocarcinoma	1 (0.1)
Noninvasive follicular thyroid neoplasm with papillary-like nuclear features	10 (1.2)
Benign	625 (76.1)
Multinodular goitre/Nodular thyroid hyperplasia	515 (62.8)
Follicular/Hürthle cell adenoma	33 (4.0)
Lymphocytic or Hashimoto thyroiditis	21 (2.6)
Benign cyst	4 (0.5)
Granulomatous thyroiditis	1 (0.1)
Graves' disease	1 (0.1)
Incidental ^c papillary thyroid microcarcinoma	50 (6.1)
Actual diagnoses of the nodule biopsied by FNA	
- Multinodular goitre/Nodular thyroid hyperplasia	48 (5.8)
- Follicular/Hürthle cell adenoma	1 (0.1)
- Lymphocytic or Hashimoto thyroiditis	1 (0.1)

FNA: fine-needle aspiration; PTMC: papillary thyroid microcarcinoma

^a Larger than 1cm in the longest dimension^b Up to 1cm in the longest dimension^c Not the nodule biopsied by fine-needle aspiration

Fig. 1. (A) Papanicolaou (PAP) stain of the cytology and (B) corresponding haematoxylin and eosin stain of the histology from one of the patients diagnosed with NIFTP. Clusters of follicular cells with nuclear atypia featuring enlarged nuclei with pale chromatin and nuclear grooves can be seen with PAP stain, while histology of the nodule showed follicular patterned cells with nuclear enlargement, clearing, membrane irregularities and grooves.

diagnosed as suspicious of PTC (Bethesda V) and 1 as PTC (Bethesda VI). Two were benign (Bethesda II) with no nuclear atypia of PTC seen. Out of the remaining 6 indeterminate cases (1 Bethesda IV and 5 Bethesda III), nuclear atypia of PTC was present in 5 cases. However, the quality and quantity of nuclear atypia was variable and features such as nuclear pseudoinclusions, papillae or psammoma bodies were absent. Histologically, the original diagnoses of these NIFTP were 5 follicular adenomas with atypia, 3 follicular variant PTCs (FVPTCs), 1 adenomatoid nodule with atypia and 1 follicular neoplasm of uncertain malignant potential. The median duration of follow-up was 61 months. Two patients were lost to follow-up. In 1 of the 3 patients originally diagnosed as FVPTC, postoperative I¹³¹ whole-body-scan showed uptake in the rib without structural lesion on SPECT-CT. This was suggestive of bone metastasis. However, he remained free of structural or biochemical disease over a follow-up of 110 months after I¹³¹. The other 2 patients had either biochemically indeterminate or excellent response without structural recurrence. Therefore, no patient with NIFTP developed locoregional recurrence or distant metastasis during follow-up. Moreover, the sonographic features of 7 out of 10 NIFTP could be ascertained. All were solid to predominantly solid but the echogenicity varies from hyperechoic to markedly hypoechoic, with 3 showing heterogenous echogenicity. Six had colour Doppler sonography and all showed internal vascularity. None had features associated with high likelihood of malignancy, namely, taller-than-wider orientation, microcalcification, irregular margin, extrathyroidal extension or lymphadenopathy.

Risk of malignancy in FNA cytology and the impact of NIFTP

Table 3 describes histologically proven ROM in each Bethesda category compared to the reference ranges published by TBSRTC in 2017.⁶ Frequency of cytological categories in decreasing order are: benign (35.0%), AUS or FLUS (32.9%), non-diagnostic or unsatisfactory (18.4%), suspicious for malignancy (7.9%), malignant (4.0%), and follicular neoplasm or suspicious for follicular neoplasm (1.8%). ROM per Bethesda category increases sequentially similar to the reference ranges in TBSRTC. When NIFTP is considered benign, ROM in our study was higher than the reference ranges in Category II (3.5%), III (26.3%), V (87.7%), VI (97%), and within the reference ranges in Category I (8.6%) and IV (20.0%). When NIFTP is considered malignant, ROM increases by 0%, 0.7%, 2.2%, 7%, 1.5% and 3% in each Bethesda category, respectively, and falls mostly within the reference

range, except in category II (4.2%), V (89.2%) and VI (100%), in which our ROM was slightly higher.

DISCUSSION

We present here data from Singapore on the risk of malignancy (ROM) in each Bethesda category of thyroid cytology and how NIFTP impacts the ROM. Considering NIFTP benign, our ROM was noticeably higher than the reference range of TBSRTC in Bethesda Category III. Several reasons can explain this. First, in this surgical series, there could be selection bias as surgeons consider not only cytology but also sonographic features, size, symptoms or signs of malignancy when recommending thyroidectomy. Second, the lack of ultrasound guidance in some of the FNAs can result in geographic miss in the sampling of the malignant portion of the nodule, leading to higher rates of indeterminate cytology.

With regards to the frequency of diagnosis per Bethesda category, we found a higher proportion of category III, 32.9%, compared to 10.5% in a multi-institutional Asian study conducted by Bychkov et al.¹¹ Although TBSRTC recommends limiting frequency of category III (AUS/FLUS) to less than 10%,⁴ reproducibility in AUS/FLUS is at best fair,¹⁴ and studies with low AUS/FLUS rates can have a relatively higher number of false negatives or positives depending on which categories these lesions with borderline cytomorphology get classified.¹⁴ Our study did not have false positives for category VI, our ROM in category V was higher than the reference range of TBSRTC and the frequency of category IV was low (1.8%). These suggest a low threshold of classifying cytologically indeterminate or suspicious nodules into AUS/FLUS in our institution.

Since AUS/FLUS is common in our practice, refining ROM in AUS/FLUS is important. Gan et al.¹⁵ and Lim et al.¹⁶ subclassified AUS/FLUS into architectural or nuclear atypia. For lesions with architectural atypia, repeating FNA or clinical follow-up may be sufficient whereas surgery may be favoured in lesions with nuclear atypia given the higher ROM. Molecular testing may also refine ROM in indeterminate categories.^{17,18} However, the cost of molecular testing is preventing its routine use in all indeterminate cases. How to select a Bethesda III or IV nodule for molecular testing in a cost-effective way deserves more research.

The introduction of NIFTP in 2016 has implications on the management of thyroid nodules and influenced the ROM in each Bethesda category, especially in categories III and IV.^{19,20} However, the prevalence of NIFTP and the impact of NIFTP reclassification on the

Table 2. Clinical characteristics of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) and outcomes of follow-up

Age (year)	Sex	Size ^a , cm	Original diagnosis	Bethesda category	Duration of follow-up, month	Modalities of follow-up	Response to treatment per American Thyroid Association classification	Locoregional recurrence or distant metastasis
69	M	2.7x1.7x1.8	FVPTC	6	24	Sonography, thyroglobulin, TSH suppression, no radioactive iodine	Biochemically indeterminate	No
50	F	2.1x1.5x1.2	FVPTC	3	15	100mCi of I ¹³¹ , sonography, thyroglobulin, TSH suppression	Excellent	No
30	F	4.0x2.5x1.0	FVPTC	2	110	180 mCi of I ¹³¹ over 2 doses 8 months apart, thyroglobulin, TSH suppression	Excellent	Possible metastasis to the right 3 rd rib due to I ¹³¹ uptake but no lytic changes on SPECT-CT, I ¹³¹ uptake resolved 8 months later
38	M	4.5x3x3	FAWA	4	–	–	NA	–
33	F	6.0x5.0x3.0	FAWA	5	102	Sonography	NA	No
35	F	1.2 ^b	FAWA	3	45	Sonography	NA	No
74	M	5.5 ^b	FAWA	3	65	Sonography	NA	No
61	F	5.5x4.5x3.5	FAWA	3	57	Sonography	NA	No
58	F	1.8 ^b	AGWA	3	–	–	NA	–
38	M	3.0x2.8x1.8	FNUMP	2	98	Sonography	NA	No

AGWA: adenomatoid goitre with atypia; FAWA: follicular adenoma with atypia not definitive of papillary thyroid carcinoma; FNUMP: follicular neoplasm with uncertain malignant potential;

FVPTC: follicular variant of papillary thyroid carcinoma; NA: not applicable because the original diagnosis was benign; TSH: thyroid stimulating hormone; WBS: whole body scan

^a Based on formalin-fixed paraffin-embedded thyroidectomy specimen^b Only the longest dimension was measured

– Lost-to-follow-up

Table 3. Comparing the risk of malignancy (ROM) of thyroid cytology in our institution with the Bethesda reference range, stratified by benignity of NIFTP

Bethesda category	Number of nodules (%) Total=821	ROM if NIFTP is malignant, % (no. of cancer)	ROM if NIFTP is benign, % (no. of cancer)	ROM quoted by the 2017 TBSRTC, if NIFTP is malignant ^a (%)	ROM quoted by the 2017 TBSRTC, if NIFTP is benign ^a (%)
I. Non-diagnostic or unsatisfactory	151 (18.4)	8.6 (13)	8.6 (13)	5–10	5–10
II. Benign	287(35.0)	4.2 (12)	3.5 (10)	0–3	0–3
III. AUS or FLUS	270 (32.9)	28.1 (76)	26.3 (71)	10–30	6–18
IV. Follicular neoplasm or suspicious for follicular neoplasm	15 (1.8)	26.7 (4)	20.0 (3)	25–40	10–40
V. Suspicious for malignancy	65 (7.9)	89.2 (58)	87.7 (57)	50–75	45–60
VI. Malignant	33 (4.0)	100 (33)	97.0 (32)	97–99	94–96

AUS: atypia of undetermined significance; FLUS: follicular neoplasm of undetermined significance; NIFTP: noninvasive follicular thyroid neoplasm with papillary-like nuclear features; TBSRTC: The Bethesda System for Reporting Thyroid Cytopathology

^a Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. *Thyroid* 2017;27:1341-6.

Bethesda categories may differ in various populations. A recent meta-analysis by Rana et al.¹² found the overall incidence of NIFTP to be 6.0% among PTCs or thyroid malignancies, with a significantly lower overall incidence in Asia (2.1%) compared to North America or Europe (9.3% and 9.6%, respectively), and a multi-institutional Asian study by Bychkov et al. found NIFTP in only 2.9% of all excised nodules.¹¹ To our best knowledge, studies from Singapore have yet to address the impact of NIFTP classification on the rates of malignancy in thyroid cytology. Our incidence of NIFTP from a tertiary hospital in Singapore was 5.1% among PTCs (10 NIFTP out of 195 PTCs and NIFTP). This was slightly higher than that reported by Bychkov et al. or Rana et al., but consistent with the wide variation in the incidence of NIFTP between Asian countries from 0.4% in China²¹ to 14.4% in India.²² Reasons for the discrepancy between Asian and Western studies may be multifactorial, including variation in the incidence of FVPTCs between continents,²³ racial and ethnic predispositions to PTC,²⁴ and varying threshold of diagnosing nuclear features of PTC.

In terms of the cytology of NIFTPs, we found that 50% were Bethesda III, 20% Bethesda II, and 10% each for Bethesda IV, V and VI. Our proportion of Bethesda IV and V are relatively low compared to a meta-analysis by Ruanpeng et al.²⁰ and a multi-institutional Asian study by Bychkov et al.¹¹ In these studies, NIFTP appears to be most commonly Bethesda

III (34.2%) or IV (22.7–32.2%), followed by V (22.4%). This difference is consistent with the relatively low frequency of Bethesda IV in our institution. Moreover, the proportion of Bethesda III also appears relatively high in our study, perhaps because we also reviewed cases of follicular adenoma and adenomatous nodule with atypia in addition to encapsulated follicular variant of PTC. As most of the studies on NIFTP were conducted in the US and Europe, our data contribute to a growing body of literature from Asia on the different impact of NIFTP on thyroid cancers in our region.

Finally, even though TBSRTC permits the classification of NIFTP as benign, the benignity of NIFTP is still debated. A recent Canadian series found that up to 6% of NIFTP patients had nodal or distant metastases,²⁵ suggesting that NIFTP behaved as a low-risk thyroid cancer. One of our patients had possible iodine avid bone metastasis, although he was alive with an excellent response to therapy nearly 10 years since treatment. Nonetheless, we had few NIFTP patients and not all had long-term follow-up. Further studies worldwide are required to support the benignity of NIFTP.

Our study has several limitations. First, the estimation of ROM was based only on patients who underwent thyroidectomies. Inclusion of patients whose thyroid nodules are observed is necessary to estimate more accurately the ROM of Bethesda I to III. Second, this is a single institutional experience with a small number of NIFTP, therefore may not reflect the true impact of NIFTP on thyroid cytology in Singapore. Third, the

retrospective matching of cytology to histology could lead to errors, but this error is likely random and the verification of matching mitigated it. The chance of error should also be balanced among the different cytological categories. Nonetheless, a prospective study may be done to further validate the ROM found in this study.

CONCLUSION

Our study describes the demography of patient with thyroid nodules who underwent FNA and thyroidectomy, the histology of their nodules, and the ROM per 2017 TBSRTC from a tertiary general hospital in Singapore. While TBSRTC is one of the most validated FNA classifications today, variation in ROM exists worldwide. Compared to Western studies, we found a higher frequency and ROM in the Bethesda III category but a lower impact of NIFTP on ROM. Understanding the risk of malignancy of thyroid cytology in the Singapore context can help clinicians more appropriately manage patients with thyroid nodules.

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