Original Article

The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC): A report of 2,781 cases in a Chinese population

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Abstract

Objective: To evaluate the diagnostic utility of The Bethesda System for Reporting Thyroid Cytology (TBSRTC) at Peking University Cancer Hospital, the incidence of noninvasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP), and the impact of reclassification on cytopathological outcomes.

Methods: We performed a retrospective study of thyroid fine-needle aspiration (FNA) cases between April 2014 and March 2019. The FNA results were classified according to TBSRTC. Post-surgery histological findings were followed up.

Results: A total of 2,781 thyroid FNAs were performed. The incidences of the 6 diagnostic categories (DCs I−VI) were 14.8%, 17.1%, 15.8%, 2.3%, 11.6% and 38.5%, respectively. A total of 1,122 patients (40.3%) had corresponding histological results. NIFTP accounted for 0.4% of papillary thyroid carcinoma (PTC) cases, and there was no significant difference in the risk of malignancy (ROM) for each TBSRTC DC between "NIFTP=carcinoma (Ca)" and "NIFTP≠Ca". When "NIFTP=Ca", the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of TBSRTC were 98.0%, 84.0%, 99.4%, 58.3%, and 97.5%, respectively. When "NIFTP≠Ca", the sensitivity, specificity, PPV, NPV and accuracy of the TBSRTC were 98.1%, 81.5%, 99.3%, 61.1%, and 97.5%, respectively.

Conclusions: TBSRTC is effective in the preoperative diagnosis of thyroid nodules in Peking University Cancer Hospital. The impact of the reclassification of NIFTP on cytopathological outcomes is limited because of its low incidence, and the revised ROMs are not suitable for Asian patients.

Keywords: Bethesda system; thyroid; FNA; cytopathology; NIFTP

Introduction

Fine-needle aspiration (FNA) of the thyroid gland is a rapid, cost-effective, safe and widely accepted method in the preoperative evaluation of thyroid nodules. The Bethesda System for Reporting Thyroid Cytology (TBSRTC) was proposed in 2007 at the National Cancer Institute Thyroid Fine Needle Aspiration State of the Art and Science Conference held in Bethesda, Maryland and was published in January 2010 (1). The TBSRTC consists of 6 diagnostic categories (DCs), and each diagnostic category is associated with a specific risk of malignancy (ROM) and a recommendation for clinical management. Therefore, TBSRTC can not only aid clinicians in the treatment of the thyroid nodules of their patients, but also provide a uniform diagnostic terminology for pathologists to communicate relatively more effectively with clinicians and to share data between different laboratories easily.

Due to the advances in the molecular diagnosis of thyroid nodules and the introduction of the new pathologic

entity "noninvasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP)" and the others factors, TBSRTC II was published in the spring of 2018 (2). The foremost modification in the revised version involves the ROMs. Primarily, the ranges of the ROMs have been updated according to the most recent data in the literature. Moreover, each DC is associated with two different ROMs: One considers NIFTP as a carcinoma, and one considers NIFTP as a tumor with low malignant potential. Therefore, the reclassification of NIFTP is of great significance for the cytological interpretation of thyroid nodules because the ROMs for TBSRTC DCs would decrease as reported in Western practice (3-6), and the revised 2015 American Thyroid Association (ATA) guidelines cites data from TBSRTC II (7). However, some Asian studies have shown high ROMs in the indeterminate FNA categories and low incidences of NIFTP in their thyroid FNA practice (8-10). Some authors have analyzed the multifactorial reasons for the discrepancies between Asian and Western studies (8,11). Thus, the incidences of NIFTP and the impact of reclassification on cyto-pathological outcomes remain unclear, and whether the revised ROMs are suitable for Asian patients remains to be further studied (8,11).

In addition, since its introduction, TBSRTC has become one of the most quoted pathological terminology and reporting systems in the published scientific literature (12). However, to date, the majority of published studies refer to original TBSRTC, and various studies have investigated different ROMs and have reported discrepancies in malignancies in their respective institutions.

We adopted this reporting system in 2015 and no retrospective study was performed at Peking University Cancer Hospital after adopting this system. Thus, we analyzed our data of thyroid FNAs over nearly four years after using TBSRTC in correlation with post-surgery histological results to investigate the validity of this reporting system. The ROM for each DC was examined and compared with the first and second edition of TBSRTC. A further aim was to convey the ROM of each DC in Peking University Cancer Hospital to clinical colleagues to contribute to optimizing patient care.

Materials and methods

Thyroid FNA cases

We conducted a computer search by using the keyword "TBSRTC" for all thyroid FNAs performed at Peking University Cancer Hospital between April 2014 and March 2019, and the retrospective study was approved by the Ethics Committee of Beijing Cancer Hospital (No. 2018KT101). FNAs were performed by surgeons or sonographers either by palpation or ultrasound guidance. The aspirates were prepared as direct smears stained with hematoxylin-eosin and/or liquid-based cytology stained with Papanicolaou stain. Diagnostic terminology was used according to the recommended 6 categories of TBSRTC: Nondiagnostic or unsatisfactory (ND/UNS; I); Benign (B; II); Atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS; III); Suspicious for follicular neoplasm or follicular neoplasm (SFN/FN; IV); Suspicious for malignancy (SM; V); and Malignant (M; VI). We calculated the incidences of each DC of the FNAs performed by surgeons or sonographers and compared the results from the sonographer and surgeon groups.

Follow-up cases

Histologic follow-up was retrieved in Peking University Cancer Hospital. The FNA results were correlated with post-surgery histological results.

Statistical analysis

True-negative cases included FNA benign cases confirmed as benign via histopathology. The true-positive cases had FNA category DC VI findings and malignant final histology. For "NIFTP=Ca" and "NIFTP≠Ca", the ROM for each DC was evaluated, and the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of TBSRTC were assessed individually. We compared our findings with the first and second editions of TBSRTC.

Statistical analysis was performed using IBM SPSS Statistics (Version 20.0; IBM Corp., New York, USA). The variables were mainly categorical, and the test used was the Chi-square test. A P value less than 0.05 was considered significant.

Results

Patients and distribution of diagnostic categories in all cases

A total of 2,781 thyroid FNAs were performed. The average patient age was 46.7 years, with a range of 15−89

years old. There were 2,109 women (75.8%) and 672 men (24.2%) with the female to male ratio of 3.1:1.0. For all 2,781 FNAs, the incidences of DCs I−VI were 14.8%, 17.1%, 15.8%, 2.3%, 11.5% and 38.5%, respectively. When the sonographer and surgeon groups were compared in terms of nondiagnostic FNA proportion, no significant difference was found (P>0.05). The overall distribution of diagnoses of thyroid FNAs performed by sonographers and surgeons are presented in *Table 1*.

There were a total of 13 cases of repetitive thyroid FNAs performed in Peking University Cancer Hospital during the study. The 13 cases were all categorized as suspicious malignant by clinicians, while the first FNA results were not malignant or suspicious malignant (DCs I−IV). A repetitive FNA was performed on 2 (2/42, 4.8%) patients

with DC I findings and on 9 (9/90, 10.0%) patients with DC III findings (*Table 2*). A total of 66.7% (6/9) of the DC III patients resolved into definitive diagnostic categories. The percentage of FNA repetition and the repetitive and final histologic diagnosis after the first FNA in the study cohort are shown in *Table 2*.

Post-surgery histological findings and ROMs in follow-up cases

Of the study population, 1,122 (40.3%) patients had corresponding follow-up partial or total thyroidectomy in Peking University Cancer Hospital. A total of 132 (11.8%) patients had nonneoplastic lesions, 17 (1.5%) patients had benign neoplasms, 969 (86.4%) patients had malignant

Table 1 Distribution of diagnoses of thyroid FNAs

Diagnostic category	Total		Sonographers groups		Surgeons groups	
	n	%	n	%	n	%
ND/UNS (DC I)	411	14.8	261	14.3	150	15.7
B (DC II)	476	17.1	369	20.2	107	11.2
AUS/FLUS (DC III)	439	15.8	282	15.4	157	16.4
SFN/FN (DC IV)	64	2.3	35	1.9	29	3.0
SM (DC V)	319	11.5	234	12.8	85	8.9
M (DC VI)	1,072	38.5	645	35.3	427	44.7
Total	2,781	100	1,826	100	955	100

FNA, fine needle aspiration; ND/UNS, nondiagnostic or unsatisfactory; DC, diagnostic category; B, benign; AUS/FLUS, atypia of undetermined significance or follicular lesion of undetermined significance; SFN/FN, suspicious for follicular neoplasm or follicular neoplasm; SM, suspicious for malignancy; M, malignant.

Table 2 Percentage of FNA repetition and repetitive and final histologic diagnosis after the first FNA

Case	First FNA diagnosis	Repetitive FNA diagnosis	Percentage of repetition (%)	Histologic diagnosis
1	I	II	4.8 (2/42)	Nodular goiter
2	I	V		PTC
3	II	V	2.8 (1/36)	Granuloma
4	III	III	10.0 (9/90)	Nodular goiter
5	III	VI		PTC
6	III	II		PTC
7	III	V		PTC
8	III	VI		PTC
9	III	V		PTC
10	III	VI		PTC
11	III	VI		PTC
12	III	VI		MTC
13	IV	II	3.4 (1/29)	Nodular goiter

FNA, fine needle aspiration; PTC, papillary thyroid carcinoma; MTC, medullary thyroid carcinoma.

neoplasms, and 4 (0.4%) patients had NIFTP. The flowchart of case screening is presented in *Figure 1*. When "NIFTP=Ca", the ROM for each DC was 59.5% for DC I, 41.7% for DC II, 50.0% for DC III, 34.5% for DC IV, 78.5% for DC V, and 99.4% for DC VI. When "NIFTP≠Ca", the ROM for each DC was 57.1% for DC I, 38.9% for DC II, 50.0% for DC III, 31.0% for DC IV, 78.5% for DC V, and 99.3% for DC VI. The distribution

of the cytologic-histologic correlation of the nodules within the excised thyroid glands and the ROM for each category are presented in *Table 3*.

Diagnostic utility of TBSRTC

When "NIFTP=Ca", the sensitivity, specificity, PPV, NPV and accuracy of TBSRTC were 98.0%, 84.0%, 99.4%, 58.3% and 97.5%, respectively. When "NIFTP≠Ca", the
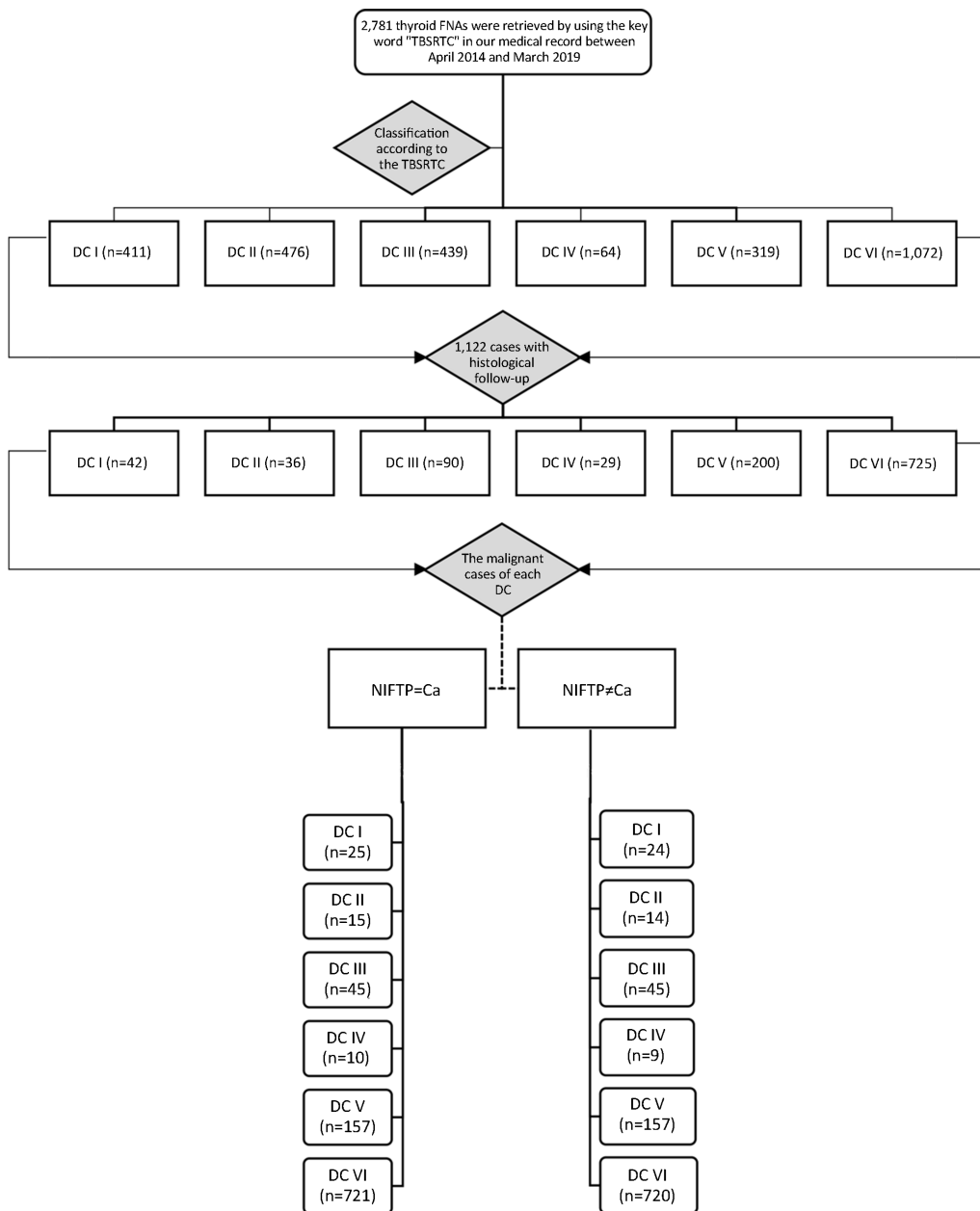

Figure 1 Flowchart of case screening. FNA, fine needle aspiration; TBSRTC, The Bethesda System for Reporting Thyroid Cytology; DC, diagnostic category; NIFTP, noninvasive follicular thyroid neoplasms with papillary-like nuclear features.

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Table 3 Distribution of cytologic-histologic correlation of nodules within excised thyroid glands and ROM

DC	FNA (n)	Excision [n (%)]	ROM (NIFTP=Ca) (%)	ROM (NIFTP≠Ca) (%)	Non-neoplastic lesion (n)	Neoplastic lesion (n)							
						Benign neoplasm	NIFTP	Malignant neoplasm					
								Total	PTC	MTC	FTC	ATC	ITTA
I	411	42 (10.2)	59.5	57.1	17	0	1	24	24	–	–	–	–
II	476	36 (7.6)	41.7	38.9	20	1	1	14	14	–	–	0	–
III	439	90 (20.5)	50.0	50.0	39	6	–	45	43	2	–	–	–
IV	64	29 (45.3)	34.5	31.0	12	7	1	9	8	–	1	–	–
V	319	200 (62.7)	78.5	78.5	41	2	–	157	149	7	1	–	–
VI	1,072	725 (67.6)	99.4	99.3	3	1	1	720	710	7	–	2	1
Total	2,781	1,122 (40.3)	86.7	86.4	132	17	4	969	948	16	2	2	1

ROM, risk of malignancy; DC, diagnostic category; FNA, fine needle aspiration; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features; Ca, carcinoma; PTC, papillary thyroid carcinoma; MTC, medullary thyroid carcinoma; FTC, follicular thyroid carcinoma; ATC, anaplastic thyroid carcinoma; ITTA, intrathyroidal thymic adenocarcinoma.

sensitivity, specificity, PPV, NPV and accuracy of the TBSRTC were 98.1%, 81.5%, 99.3%, 61.1% and 97.5%, respectively (*Table 4*).

Discussion

FNA plays an important role in the preoperative assessment of thyroid nodules (13-17). TBSRTC consists of 6 DCs, each associated with a corresponding ROM that translates directly into clinical management and this had contributed to the wide acceptance of TBSRTC internationally. TBSRTC has also facilitated the communication between cytopathologists and clinicians and has become highly accepted in the clinical community, as shown by its endorsement by the ATA as part of the revised 2015 ATA guidelines for the management of thyroid nodules in adults (7).

We reported 15.8% of AUS/FLUS and 38.5% of malignant cases with a ratio of 2.4. This figure conformed to the range of 1.0−3.0 recommended by Krane *et al*. (18), indicating the reasonable use of the AUS/FLUS category in Peking University Cancer Hospital. A ratio of AUS:M >3.0 is likely because of the overdiagnosis of AUS or underdiagnosis of M. AUS:M ratios <1.0 are mostly due to low AUS rates, and the sensitivity might decrease when the ratio is <1.0 (18). Moreover, the indeterminate cases (DC III, IV and V) occupied 29.7% of all thyroid FNAs in our study, which was close to the data (1/3) reported by a comprehensive review and meta-analysis (19), demonstrating that thyroid cytopathology has limitations and that we properly applied TBSRTC.

We had a higher proportion of DC I (14.8%) in this study than the no more than 10% of specimens proposed by TBSRTC. The reason for ND/UNS depends on the FNA operator in most cases, and a high proportion of DC I reflects poor technique in sampling, slide preparation or

Table 4 Diagnostic utility of TBSRTC

Variables	NIFTP=Ca	NIFTP≠Ca
True-positive cases (a) (n)	721	720
False-positive cases (b) (n)	4	5
False-negative cases (c) (n)	15	14
True-negative cases (d) (n)	21	22
Sensitivity [a/(a+c)] (%)	98.0	98.1
Specificity [d/(b+d)] (%)	84.0	81.5
PPV [a/(a+b)] (%)	99.4	99.3
NPV [d/(c+d)] (%)	58.3	61.1
Diagnostic accuracy [(a+d)/(a+b+c+d)] (%)	97.5	97.5

TBSRTC, The Bethesda system for reporting thyroid cytopathology; NIFTP, noninvasive follicular thyroid neoplasms with papillary-like nuclear features; Ca, cancer; PPV, positive predictive values; NPV, negative predictive values.

fixation. Previous studies have underscored the fact that the most significant diagnosis problem associated with FNA is the inadequate extraction of materials during the procedure (20). Therefore, efforts should be aimed at reducing the proportion of inadequate FNA to a minimum, or at least within acceptable limits (10%). It is imperative that noncytopathologist thyroid FNA operators (sonographers and surgeons in our hospital) receive adequate normative quality training related to FNA technology and sample preparation (21).

An adequate specimen ensures a low false-negative rate and is dependent on the technique of the aspirator. Undoubtedly, the non-diagnostic FNA proportion reflects the skill level of the FNA performer; that is, the lower the proportion of DC I, the higher the skill level of the FNA performer. We found that the non-diagnostic results of FNA by sonographers and surgeons were similar, and the results was consistent with those in the literature (22-24), demonstrating that although surgeons are not experts in the use of ultrasound guidance (USG), USG-guided FNA can also be performed by surgeons in their clinical practice.

Although investigations such as repetitive FNA or molecular testing for AUS/FLUS have been proposed by the latest guidelines of the ATA (7), only 13 cases of repetitive thyroid FNAs were performed in Peking University Cancer Hospital during the study, and there were two major reasons for the low proportion of repetitive aspirations. First, our clinicians preferred referring to clinical and ultrasound features for indeterminate patients by thyroid FNA, and they might recommend a diagnostic lobectomy for suspicious patients. Second, Chinese patients tend to choose another hospital to have a repetitive thyroid FNA or have an operation directly instead of having two FNAs in one hospital. However, 66.7% of DC III patients

had definitive results via repetitive aspirations, in accordance with the information reported in other studies to resolve the dilemma in up to 50% of cases of AUS/FLUS (III) (25), demonstrating that repetitive FNA contributes to optimizing patient care.

We compared the ROMs calculated in the current study with those reported for the first and second edition TBSRTC, and with two reviews of meta-analysis covering a large study of cases (Table 5). For "NIFTP=Ca" and "NIFTP≠Ca", we found that the ROMs in DC I, II and III were much higher than those recommended in the original and revised TBSRTC guidelines. Our observed ROMs were also slightly elevated for DC V and DC VI. The malignancy rates of DC IV were 34.5% and 31.0%, which were higher than the original edition TBSRTC (15%−30%) but were in line with the revised edition (25%−40% and 10%−40%).

There are three possible reasons for these elevated ROMs in the present study. First, the resected cases were often operated because of worrisome ultrasound features thus, the "surgical follow-up" bias resulted from a selected group. Our increased rates of malignancy in DC I and DC II may reflect other suspicious clinical features that prompted the election of surgical excision. Therefore, our low resection rates of DC I, II and III (10.2%, 7.6% and 20.5%, respectively) and the large number of patients who did not undergo surgery may cause these results to be biased. Second, our high malignancy rate for DC III suggests that the ROM might be higher than the estimated. This underscores the importance of using this terminology carefully. However, we admit that some lesions were classified under DC III because the specimens were suboptimal. A badly smeared, fixed, or stained preparation is thus classified as AUS/FLUS because of technical

Table 5 Comparison of risk of malignancy among different studies

DC	Present study			First edition TBSRTC	Second edition TBSRTC		Bongiovanni et al. (12)		Sheffield et al. (19)	
	N	NIFTP=Ca (%)	NIFTP≠Ca (%)	(%)	NIFTP=Ca (%)	NIFTP≠Ca (%)	N	%	N	95% CI (%)
I	42	59.5	57.1	1−4	5−10	5−10	530	16.8	641	11−26
II	36	41.7	38.9	0−3	0−3	0−3	1,563	3.7	2,176	4−9
III	90	50.0	50.0	5−15	10−30	6−18	957	15.9	805	19−38
IV	29	34.5	31.0	15−30	25−40	10−40	1,791	26.1	2,183	27−40
V	200	78.5	78.5	60−75	50−75	45−60	501	75.2	886	50−79
VI	725	99.4	99.3	97−99	97−99	94−96	1,020	98.6	1,353	98−100

DC, diagnostic category; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features; Ca, carcinoma.

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reasons that do not depend on the nature of the lesion itself or any associated clinical conditions (26). Third, Chinese patients tend to be more concerned about false positive results than about false negative results, which may pressure cytopathologists to underdiagnose FNA cases to avoid making false-positive diagnoses, and a strict triage of patients with indeterminate thyroid nodules for surgery is usually applied, which ultimately leads to low resection rates and high ROMs for indeterminate nodules.

According to TBSRTC II, the ROM ranges needed to take into account whether NIFTP is considered a carcinoma. In our study, when "NIFTP=Ca", the ROM for DC was 59.5% for DC I, 41.7% for DC II, 50.0% for DC III, 34.5% for DC IV, 78.5% for DC V, and 99.4% for DC VI. When "NIFTP≠Ca", the ROM for each DC was 57.1% for DC I, 38.9% for DC II, 50.0% for DC III, 31.0% for DC IV, 78.5% for DC V, and 99.3% for DC VI. Considering "NIFTP≠Ca" in the statistical analysis, the ROM for DC has changed little, and there were no significant differences in ROMs between "NIFTP=Ca" and "NIFTP≠Ca", which was different from reports in Western practice that indicated the ROMs would decrease when "NIFTP≠Ca". Thus, the impact of reclassification on cytopathological outcomes is limited, and the revised ROMs are not suitable for Asian patients. The results were easy to understand because we found only 4 cases of NIFTP according to the histological results. The four cases were cytologically classified as DC I, DC II, DC IV and DC VI, consistent with the previous reports describing that most NIFTP cases were cytologically classified as intermediate categories (27,28), and notably, DC VI was supported the view that NIFTP cases could be cytologically reported as malignant (9,29). The cytological characteristics of NIFTP are not specific and show slightly or moderately expressed nuclear features of papillary thyroid carcinoma (PTC) without specific morphological features. However, the introduction of NIFTP was essential to address a subset of low-risk thyroid neoplasms that were overtreated, and we await reliable criteria that might lead to a diagnosis of NIFTP on cytological specimens. In our study, cases of NIFTP accounted for 0.4% of PTC cases, which was consistent with the incidences of NIFTP in Asian countries and considerably lower than those in the Western countries (8), showing that the diagnostic threshold of PTC-type nuclear features is subjective and that these rigid diagnostic criteria may be adopted by our department. Another explanation might be that our practices for patients with indeterminate thyroid nodules are relatively conservative, resulting in a reduced incidence of NIFTP in Peking University Cancer Hospital. Furthermore, the reliability and accuracy of any reporting system is built on experience, including not only cytologic interpretations but also years of follow-up of regarding cytologic and histologic correlations, and the diagnosis of NIFTP is not an exception. Therefore, educational programs related to the term of NIFTP, such as local seminars, should be provided to ensure that most pathologists adopt the term NIFTP in their daily practice and enhance interobserver reproducibility for this diagnosis.

The sensitivity, PPV and diagnostic accuracy all exceeded 90.0%, indicating that thyroid FNA is an important part of preoperative diagnosis. The relatively low NPV (58.3%) showed that despite a thyroid nodule being initially diagnosed as benign by FNA, it may have potential for malignancy. Therefore, to avoid missed malignancies, nodules should be carefully reevaluated by repetitive FNA, ultrasonography, molecular analysis, or multidisciplinary discussion. Moreover, notably, the cases of DC II do not mean ''negative for malignancy'', and patients with suspicious clinical features should have a repetitive FNA, undergo close clinical follow-up or even have a diagnostic lobectomy.

Similarly, there are two main limitations of our study. First, the incidence of NIFTP was calculated upon the post-surgery histological reports. If we had reviewed the slides of all cases diagnosed as encapsulated follicular variant of papillary thyroid carcinoma (eFV-PTC), some noninvasive eFV-PTC might have been reclassified to NIFTP and the incidence of NIFTP would increase. However, unfortunately, we cannot recheck all cases of eFV-PTC because not all cases were diagnosed in our histological reports, and some pathologists diagnosed with only PTC without a subtype. Nevertheless, we believe the impact should be minimal, considering that a symposium related to NIFTP was held in the Department of Pathology. Second, the post-surgery histological results were based on the reports in Peking University Cancer Hospital, and some patients who underwent surgery in other hospitals were not included in our follow-up.

Conclusions

TBSRTC is effective in the preoperative diagnosis of thyroid nodules in Peking University Cancer Hospital with high sensitivity, PPV and accuracy for cancer diagnosis and

low specificity and NPV. Therefore, to avoid missed malignancies, nodules should be carefully reevaluated by repetitive FNA, ultrasonography, molecular analysis, or multidisciplinary discussion. The incidence of NIFTP was considerably low, and there was no significant difference in the ROM between "NIFTP=Ca" and "NIFTP≠Ca", which was different from the reports in Western practice indicating that ROMs would decrease when "NIFTP≠Ca". Thus, the impact of reclassification on cytopathological outcomes is limited, and the revised ROMs are not suitable for Asian patients.

Acknowledgements

Footnote

References

1. Ali SZ, Cibas ES. The Bethesda system for reporting thyroid cytopathology: definitions, criteria and explanatory notes. Berlin: Springer, 2010.

2. Cibas ES, Ali SZ. The 2017 Bethesda system for reporting thyroid cytopathology. Thyroid 2017;27: 1341-6.

3. Faquin WC, Wong LQ, Afrogheh AH, et al. Impact of reclassifying noninvasive follicular variant of papillary thyroid carcinoma on the risk of malignancy in the Bethesda System for Reporting Thyroid Cytopathology. Cancer Cytopathol 2016;124:181-7.

4. Ibrahim AA, Wu HH. Fine-needle aspiration cytology of noninvasive follicular variant of papillary thyroid carcinoma is cytomorphologically distinct from the invasive counterpart. Am J Clin Pathol 2016;146:373-7.

5. Howitt BE, Chang S, Eszlinger M, et al. Fine-needle aspiration diagnoses of noninvasive follicular variant of papillary thyroid carcinoma. Am J Clin Pathol 2015;144:850-7.

6. Maletta F, Massa F, Torregrossa L, et al. Cytological features of "non-invasive follicular thyroid neoplasm with papillary-like nuclear features" and their correlation with tumor histology. Hum Pathol 2016;54:134-42.

7. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid 2016;26: 1-133.

8. Bychkov A, Hirokawa M, Jung CK, et al. Low rate of noninvasive follicular thyroid neoplasm with papillary-like nuclear features in Asian practice. Thyroid 2017;27:983-4.

9. Hirokawa M, Higuchi M, Suzuki A, et al. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features: a single-institutional experience in Japan. Endocr J 2017;64:1149-55.

10. Bychkov A, Keelawat S, Agarwal S, et al. Impact of non-invasive follicular thyroid neoplasm with papillary-like nuclear features on the Bethesda system for reporting thyroid cytopathology: a multi-institutional study in five Asian countries. Pathology 2018;50:411-7.

11. Bychkov A, Jung CK, Liu Z, et al. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features in Asian practice: perspectives for surgical pathology and cytopathology. Endocr Pathol 2018;29:276-88.

12. Bongiovanni M, Spitale A, Faquin WC, et al. The Bethesda System for reporting thyroid cytopathology: a meta-analysis. Acta Cytol 2012;56:333-9.

13. Danese D, Sciacchitano S, Farsetti A, et al. Diagnostic accuracy of conventional versus sonography-guided fine-needle aspiration biopsy of thyroid nodules. Thyroid 1998;8:15-21.

14. Cibas ES. Fine-needle aspiration in the work-up of thyroid nodules. Otolaryngol Clin North Am 2010;43:257-71.

15. Tamhane S, Gharib H. Thyroid nodule update on diagnosis and management. Clin Diabetes Endocrinol 2016;2:17.

16. Melany M, Chen S. Thyroid cancer: ultrasound imaging and fine-needle aspiration biopsy. Endocrinol Metab Clin North Am 2017;46:691-711.

17. Cramer H. Fine-needle aspiration cytology of the thyroid: an appraisal. Cancer 2000;90:325-9.

18. Krane JF, Vanderlaan PA, Faquin WC, et al. The

atypia of undetermined significance/follicular lesion of undetermined significance:malignant ratio: A proposed performance measure for reporting in the Bethesda system for thyroid cytopathology. Cancer Cytopathol 2011;120:111-6.

19. Sheffield OS, Masoudi H, Walker B, et al. Preoperative diagnosis of thyroid nodules using the Bethesda System for Reporting Thyroid Cyto-pathology: a comprehensive review and meta-analysis. Expert Rev Endocrinol Metab 2014;9:97-110.

20. Baskin HJ. Ultrasound-guided fine-needle aspiration biopsy of thyroid nodules and multinodular goiters. Endocr Pract 2004;10:242-5.

21. Raab SS, Vrbin CM, Grzybicki DM, et al. Errors in thyroid gland fine-needle aspiration. Am J Clin Pathol 2006;125:873-82.

22. Bohacek L, Milas M, Mitchell J, et al. Diagnostic accuracy of surgeon-performed ultrasound-guided fine-needle aspiration of thyroid nodules. Ann Surg Oncol 2012;19:45-51.

23. Bhatki AM, Brewer B, Robinson-Smith T, et al. Adequacy of surgeon-performed ultrasound-guided thyroid fine-needle aspiration biopsy. Otolaryngology Head Neck Surg 2008;139:27-31.

24. Bozkurt H, İrkörücü O, Aziret M, et al. Comparison of 1869 thyroid ultrasound-guided fine-needle aspiration biopsies between general surgeons and interventional radiologists. Ann Med Surg 2016;10: 92-102.

25. Ratour J, Polivka M, Dahan H, et al. Diagnosis of follicular lesions of undetermined significance in fine-needle aspirations of thyroid nodules. J Thyroid Res 2013;2013:250347.

26. Bongiovanni M, Papadakis GE, Rouiller N, et al. The Bethesda system for reporting thyroid cytopathology explained for practitioners: frequently asked questions. Thyroid 2018;28:556-65.

27. Kim M, Kim JE, Kim HJ, et al. Cytologic diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features and its impact on the risk of malignancy in the Bethesda System for Reporting Thyroid Cytopathology: An Institutional Experience. J Pathol Transl Med 2018;52:171-8.

28. Brandler TC, Zhou F, Liu CZ, et al. Can noninvasive follicular thyroid neoplasm with papillary-like nuclear features be distinguished from classic papillary thyroid carcinoma and follicular adenomas by fine-needle aspiration? Cancer Cytopathol 2017;125:378-88.

29. Hahn SY, Shin JH, Lim HK, et al. Preoperative differentiation between non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) and non-NIFTP. Clin Endocrinol 2017; 86:444-50.