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Impact of the modification of the diagnostic criteria in the 2017 Bethesda System for Reporting Thyroid Cytopathology: a report of a single institution in Japan

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Abstract. The Bethesda System for Reporting Thyroid Cytopathology has recently been revised in 2017 (TBSRTC 2017). This study aimed to evaluate the impact of modifying the diagnostic criteria in TBSRTC 2017 at a single institute. We retrospectively reviewed cytological specimens of 10,399 thyroid nodules submitted for thyroid fine-needle aspiration cytology. Among them, 56 atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS) nodules, 16 suspicious for malignancy (SFM) nodules, and 8 malignant nodules were re-categorized into follicular neoplasm or suspicious for a follicular neoplasm (FN/SFN). The incidence of FN/SFN was increased by 0.8%, while that of AUS/FLUS, SFM, and malignant nodule was decreased by 0.5%, 0.2%, and 0.1%, respectively. In nine (60%) of the 15 nodules that were re-classified from AUS/FLUS to FN/SFN nodules and re-aspiration was performed, it was possible to judge whether they were benign or malignant. Of the 24 patients with FN/SFN nodules originally diagnosed with SFM or malignant, 16 were followed up without surgical resection. In conclusion, TBSRTC 2017 only caused minor changes in the incidence of each diagnostic category. TBSRTC 2017 was revised to avoid false positives owing to noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) that account for >10% of papillary thyroid carcinomas; however, it is not necessary in low frequency NIFTP institutes or countries. In Japan, we propose active surveillance as an accepted option for clinically managing AUS/FLUS, FN/SFN, SFM, or malignant nodules having favorable benign clinical findings or being part of the low-risk group.

Key words: Thyroid, Bethesda System, Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), Active surveillance

IN 2007, The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC 2007) was established as a standardized reporting system with a limited number of diagnostic categories for thyroid fine-needle aspiration (FNA) specimens [1-3]. TBSRTC 2007 recognizes six diagnostic categories and estimates cancer risk within each category based on literature review and expert opinions. The diagnostic categories are as follows: nondiagnostic/unsatisfactory (ND/UNS), benign, atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasm/suspicious for a follicular neoplasm (FN/SFN), suspicious for malignancy (SFM), and malignant. TBSRTC 2007 has been endorsed by the American Thyroid Association (ATA) [4], has been widely adopted in the United States, and has been applied in many countries worldwide with minor modifications [5-7]. Subsequently, the ATA guide-

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Appendix: *ATA*, American Thyroid Association; *AUS*, atypia of undetermined significance; *FLUS*, follicular lesion of undetermined significance; *FN*, follicular neoplasm; *FNA*, fine-needle aspiration; *LBC*, liquid-based cytology; *ND*, nondiagnostic; *NIFTP*, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; *PTC*, papillary thyroid carcinoma; *SFM*, suspicious for malignancy; *SFN*, suspicious for a follicular neoplasm; *UNS*, unsatisfactory; *WDTs-UMP*, well-differentiated tumors, uncertain malignant potential

lines for the management of patients with thyroid nodules was revised [4], molecular testing for cytology specimens was introduced, and noninvasive encapsulated follicular variant of papillary thyroid carcinoma (PTC) was reclassified as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) [8]. Based on these changes, TBSRTC 2007 was revised in 2017 (TBSRTC) [9, 10]. In TBSRTC 2017, the six general diagnostic categories remained unchanged. Risks of malignancy have been updated based on data since 2010 and are calculated in following two ways: when NIFTP is not considered a malignancy and when NIFTP is still included among carcinomas. Molecular testing was incorporated as an option for usual management of AUS/FLUS and FN/SFN nodules. Additionally, the diagnostic criteria for FN/SFN and malignancy were slightly modified.

Compared with Western countries, the incidence of NIFTP is considerably lower in Japan [11, 12]. Moreover, molecular testing is not routinely performed, and the clinical management for thyroid tumors is also different than that in Western countries [13-17]. This study aimed to evaluate the impact of the modification of the diagnostic criteria in TBSRTC 2017 at a single institute, Kuma Hospital, a center for excellence in thyroid care in Japan.

Materials and Methods

We retrospectively reviewed cytological specimens of thyroid nodules obtained from patients who underwent thyroid FNA at the Kuma Hospital from January to December 2015. FNA was performed by using a 22-gauge needle under ultrasound guidance. The obtained samples were expressed on a glass slide and were smeared using a press and release method [18]. They were immediately fixed with Cytorop (Alfresa Pharma Co., Osaka, Japan). For samples considered bloody or poor samples on gross examination, the needles were rinsed gently with 6 mL of CytoRich^{TM} RED collection fluid (Becton, Dickinson and Co., Franklin Lakes, NJ, USA) for liquid-based cytology (LBC) after the conventional specimens were prepared. The LBC specimens were prepared *via* the CytoRich^{TM} hand method (Becton, Dickinson and Co.). Both FNA and LBC specimens were simultaneously stained using the Papanicolaou method. Original FNA findings were classified into the following categories based on the TBSRTC 2007 criteria: (1) ND/UNS, (2) benign, (3) AUS/FLUS, (4) FN/SFN, (5) SFM, and (6) malignant. These findings were then re-evaluated based on TBSRTC 2017 criteria. In TBSRTC 2017, follicular-patterned cases with PTC-associated mild nuclear changes are classified as FN/SFN. Malignancy is limited to cases with classical PTC features such as papillae, psammoma bodies, intranuclear cytoplasmic inclusions, and multinucleated giant cells. The diagnostic criteria of ND/UNS, benign, AUS/FLUS, and SFM are unchanged. Clinical data were obtained from the patients' medical records at Kuma Hospital. Clinical management was performed based on reports during the study period.

Results

We analyzed a total of 10,399 specimens obtained from 7,341 patients. Following the TBSRTC 2007 guidelines, 1,287, 6,910, 421, 330, 172, and 1,279 were classified as ND/UNS, benign, AUS/FLUS, FN/SFN, SFM, and malignant, respectively. On re-evaluation based on the TBSRTC 2017 guidelines, 1,287, 6,910, 365, 410, 156, and 1,271 were classified as ND/UNS, benign, AUS/FLUS, FN/SFN, SFM, and malignant, respectively (Table 1). Fifty-six AUS/FLUS nodules, 16 SFM nodules, and eight malignant nodules in the TBSRTC 2007 were re-categorized into FN/SFN. All of the nodules exhibited microfollicular pattern and mild to moderate nuclear changes associated with PTC (Fig. 1A, 1B, 1C). They did not show papillary structure, metaplastic cytoplasm, ropy colloid, multinucleated giant cells, lymphocytes, and psammoma bodies. The incidence of FN/SFN increased by 0.8%, while that of AUS/FLUS, SFM, and malignant decreased by 0.5%, 0.2%, and 0.1%, respectively.

Table 2 shows the clinical management of thyroid nodules that were re-categorized into FN/SFN from AUS/FLUS, SFM, or malignant in TBSRTC 2007. Of the 56 FN/SFN nodules originally diagnosed as AUS/FLUS, 15 (26.8%) were re-aspirated, while the remaining 41 nodules (73.2%) were not. The re-aspirated nodules were classified into benign (six nodules, 40.0%), AUS/FLUS (six nodules, 40.0%), and malignant (three nodules, 20.0%). In 60% of the re-aspiration nodules, it was possible to evaluate whether they were benign or malignant. Of the nodules that were and were not re-aspirated, 60.0% and 68.3% were surgically resected, respectively. The surgery included 23 lobectomies (62.2%) and 14 total thyroidectomies (37.8%). Pathological diagnoses of the resected nodules were benign

Table 1 Cytological diagnosis of 10,399 thyroid nodules based on the TBSRTC 2007 and 2017 guidelines

	ND/UNS	Benign	AUS/FLUS	FN/SFN	SFM	Malignant	Total
TBSRTC 2007	1,287 (12.4%)	6,910 (66.4%)	421 (4.0%)	330 (3.2%)	172 (1.7%)	1,279 (12.3%)	10,399 (100%)
TBSRTC 2017	1,287 (12.4%)	6,910 (66.4%)	365 (3.5%)	410 (3.9%)	156 (1.5%)	1,271 (12.2%)	10,399 (100%)

TBSRTC, The Bethesda System for Reporting Thyroid Cytopathology; ND/UNS, nondiagnostic or unsatisfactory; AUS/FLUS, atypia of undetermined significance or follicular lesion of undetermined significance; FN/SFN, follicular neoplasm or suspicious for a follicular neoplasm; SFM, suspicious for malignancy

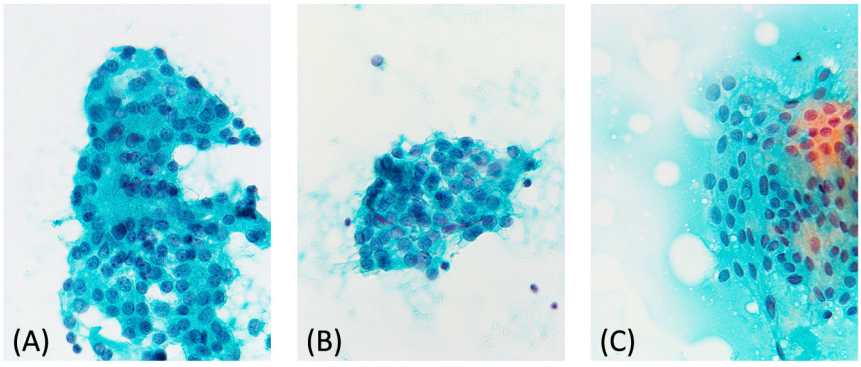

Fig. 1 Three nodules originally diagnosed as atypia of undetermined significance (A), suspicious for malignancy (B), and malignant (C) were re-categorized into follicular neoplasm or suspicious for a follicular neoplasm following the TBSRTC 2017.

Table 2 Clinical management of thyroid nodules re-categorized into FN/SFN from AUS/FLUS, SFM, or malignant following the TBSRTC 2017 guidelines

TBSRTC 2007 (*n*)	Re-aspiration, *n* (%)		Resection, *n* (%)		Histological diagnosis, *n*
AUS/FLUS (56)	15 (26.8%)	Benign, 6 (40.0%)	3 (50.0%)	Lo 1 TT 2	Adenomatous goiter, 1 Follicular carcinoma, 2
		AUS/FLUS, 6 (40.0%)	3 (50.0%)	Lo 0 TT 3	Adenomatous goiter, 1 Follicular adenoma, 1 Papillary carcinoma (NIFTP), 1
		Malignant, 3 (20.0%)	3 (100%)	Lo 0 TT 3	Papillary carcinoma (Classical), 2 Poorly differentiated carcinoma, 1
	No re-aspiration, 41 (73.2%)		28 (68.3%)	Lo 22 TT 6	Adenomatous goiter, 7 Follicular adenoma, 8 FT-UMP, 4 WDT-UMP, 5 Follicular carcinoma, 1 Papillary carcinoma (NIFTP), 3
SFM, malignant (24)	0 (0%)		8 (33.3%)	Lo 1 TT 7	Papillary carcinoma, 7 (Classical, 4; follicular, 1; solid, 1; NIFTP 1) WDT-UMP 1

TBSRTC: The Bethesda System for Reporting Thyroid Cytopathology; FN/SFN, follicular neoplasm or suspicious for a follicular neoplasm; AUS/FLUS, atypia of undetermined significance or follicular lesion of undetermined significance; SFM, suspicious for malignancy; Lo, Lobectomy; TT, total thyroidectomy; FT-UMP, follicular tumor, uncertain malignant potential; WDT-UMP, well-differentiated tumor, uncertain malignant potential; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features

lesions (n = 9); follicular adenomas (n = 9); follicular tumors, uncertain malignant potential (n = 4); well-differentiated tumors, uncertain malignant potential (WDTs-UMP) (n = 5); follicular carcinomas (n = 3), classical PTCs (n = 2), NIFTPs (n = 4), and poorly differentiated carcinoma (n = 1). Re-aspiration was not performed in all 24 FN/SFN nodules originally diagnosed as SFM or malignant, and 8 nodules (33.3%) were surgically resected. The management for the 15 of the remaining 16 nodules was follow-up without surgical resection (active surveillance). Among the resected nodules, 7 were diagnosed as PTC, including 4 classical, 1 follicular, 1 solid, and 1 NIFTP types. The remaining 1 nodule was WDT-UMP. No preoperative molecular testing was performed in all nodules.

Discussion

In TBSRTC 2017, the original six categories remain unchanged, but the diagnostic criteria and clinical management were modified, and the risks of malignancy have been updated based on data since 2010 [9]. The highlights in TBSRTC 2017 include an introduction of NIFTP as a new disease entity and an option of molecular testing for AUS/FLUS and FN/SFN nodules. The introduction of NIFTP caused various changes. The risk of malignancy was categorized in two ways: when NIFTP is not considered a malignancy and when NIFTP is still included among the "carcinomas." Regarding the diagnostic criteria, FN/SFN and malignant nodules were slightly modified. Follicular lesions that exhibit mild nuclear changes associated with PTC are included in FN/SFN. The definition and diagnostic criteria for the PTC subset of the malignant category were limited to nodules with "classical" features of PTC. Therefore, it is expected that the incidence of FN/SFN will be increased in Western countries, where the incidences of NIFTP range from 13.6% to 25% of PTC cases [8]. However, in Asian countries, NIFTP was estimated to account for only 0.8% cases of PTC [12]. In our experience, NIFTP cases comprised only 0.5% of all cases of PTC [11]. The findings indicate that the changes from TBSRTC 2007 to 2017 have minimal effect on the incidence of each category. Specifically, the changes were within 1% in each category. TBSRTC 2017 was revised to avoid false positives owing to NIFTP; however, it is not necessary in low frequency NIFTP institutes or countries.

Molecular testing was incorporated as a standard management for AUS/FLUS and FN/SFN nodules in TBSRTC 2017 [9], which reduces medical cost by avoiding unnecessary surgeries [19, 20]. However, in Japan, molecular testing has not been incorporated in the management for AUS/FLUS and FN/SFN nodules, except in a few research institutions, because it is quite costly and is not covered by medical insurances.

In our study, 56 AUS/FLUS and 24 SFM/malignant nodules were re-classified into FN/SFN category. In TBSRTC 2007, re-aspiration is not recommended as clinical management of FN/SFN nodules. Therefore, 56 AUS/FLUS nodules will lose the option of re-aspiration, which may not be beneficial for the patient. In majority of the re-aspirated AUS/FLUS nodules, it was possible to evaluate whether they were benign or malignant. Follicular lesions that demonstrate mild nuclear changes associated with PTC might as well remain in the AUS/FLUS category that has the option of re-aspiration. Otherwise, re-aspiration might be as well included in the option for clinical management of FN/SFN.

In Japan, the recommended clinical management for SFM/malignant nodules include surgical resection, lobectomy, or total thyroidectomy [21], while re-aspiration is not recommended. Meanwhile, follow-up (active surveillance) is optional in low-risk papillary microcarcinoma [22, 23]. Low risk means nodules without the following findings: nodal and/or distant metastasis, signs or symptoms of invasion to the recurrent laryngeal nerve or trachea, high-grade malignancy on cytology, and size enlargement or novel appearance of nodal metastasis during observation [23]. FN/SFN nodules usually warrant observation without surgery. However, immediate surgery is recommended when at least one of the following clinicopathological findings are observed: (1) nodules ultrasonographically suspected as being malignant; (2) nodules showing a solid content measuring larger than 40 mm in diameter; (3) serum thyroglobulin level >1,000 ng/mL; (4) nodules strongly compressing the trachea or esophagus; (5) nodules expanding into the mediastinum; (6) autonomously functioning thyroid nodules; or (7) nodules presenting cosmetic problems [24]. Of the 80 nodules re-classified from AUS/FLUS, SFM, or malignant to FN/SFN, 5 were NIFTP. According to the TBSRTC 2017, NIFTP may be categorized as FN/SFN, SFM, or malignant. Even if NIFTP is classified in any category, its clinical management is the same at our institute. Therefore, we could not find a considerable difference in revised TBSRTC guidelines for the diagnosis and management of the nodules reclassified from SFM/malignant to FN/SFN categories.

In summary, we described the impact of revised TBSRTC guidelines on the diagnosis, incidence, and management of thyroid tumors at our institute. TBSRTC 2017 did not cause major changes in the incidence of each diagnostic category of thyroid FNA. TBSRTC 2017 was revised to avoid false positives owing to NIFTP that accounts >10% of PTCs; however, it is not necessary in low frequency NIFTP institutes or countries. Given that majority of the samples with indeterminate cytology can be evaluated for malignancy or benign by re-aspiration, the option should not be excluded for such nodules. As the clinical management of thyroid nodules differs in Japan, we propose a modified clinical management specific to the Japanese practice. When AUS/FLUS, FN/SFN, SFM, or malignant nodules have favorable benign clinical findings or are part of the low-risk group, active surveillance is an accepted option of clinical management. It is cost-effective and highly accurate for triaging lethal malignancy by surgery. We believe that the proposed clinical management reduces overdiagnosis and overtreatment of borderline thyroid tumors and low-risk thyroid carcinomas.

Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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