Endocrine Journal 2020, **67** (11), 1071-1075

ORIGINAL

Prevalence and diagnostic significance of noninvasive follicular thyroid neoplasm with papillary-like nuclear features among tumors previously diagnosed as follicular adenoma: a single-institutional study in Japan

Mitsuyoshi Hirokawa[1)], Miyoko Higuchi[1)], Ayana Suzuki[1)], Toshitetsu Hayashi[1)], Seiji Kuma[1)] and Akira Miyauchi[2)]

[1)] *Department of Diagnostic Pathology and Cytology, Kuma Hospital, Hyogo 650-0011, Japan*
[2)] *Department of Surgery, Kuma Hospital, Hyogo 650-0011, Japan*

Abstract. The incidence of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) in papillary thyroid carcinoma (PTC) is significantly lower in Asian countries than Western countries; however, the difference remains unexplained. This study aimed to evaluate the incidence of NIFTP in tumors diagnosed as follicular adenoma (FA) in a Japanese institution and discuss the significance of NIFTP. In this study, 44 tumors were investigated, which were histologically diagnosed as FA at the Kuma Hospital in 2008. Of the 44 tumors, 13 (29.5%) were revised as NIFTP. In the remaining 31 tumors, the FA diagnosis was reconfirmed. On aspiration cytology, most of the NIFTPs were categorized into follicular neoplasm or suspicious for a follicular neoplasm. On histological examination, 9 (29.0%) of 31 FA nodules showed a nuclear score of 1. Twelve (92.3%) of 13 NIFTP nodules showed a nuclear score of 2, and the remaining nodule had a nuclear score of 3. No metastasis of FA or NIFTP was detected. There were no evidences of distant metastasis during follow-up. This is the first study to describe that NIFTP is more frequently included in tumors diagnosed as FA rather than PTC in Japan. As clinical management of FA and NIFTP is the same, in Japan, there is no reason to distinguish between FA and NIFTP. Conclusively, the necessity of using the disease entity "NIFTP" is not found in Japan.

Key words: Thyroid, Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), Follicular adenoma, Papillary carcinoma, Follicular variant

NONINVASIVE encapsulated follicular variant (NEFV) of papillary thyroid carcinoma (PTC) was reclassified as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) [1, 2]. Because of the vast majority of cases of NIFTP having indolent outcomes, adopting a new term, indicating the nonmalignant nature of the neoplasm, could prevent overtreatment and reduce the burden of a cancer diagnosis on the patients [2]. The incidence of NIFTP ranges from 13.6% to 25% of PTC cases in Western countries [1]. However, in Asian countries, incidence of NIFTP is between 0% to 4.7% [3, 4]. This large difference in incidence has not been explained.

Submitted Apr. 7, 2020; Accepted Jun. 1, 2020 as EJ20-0198
Released online in J-STAGE as advance publication Jun. 26, 2020
Correspondence to: Mitsuyoshi Hirokawa, MD, PhD, Department of Diagnostic Pathology and Cytology, Kuma Hospital, 8-2-35 Shimoyamate-dori, Chuo-ku, Kobe, Hyogo 650-0011, Japan.
E-mail: mhirokawa@kuma-h.or.jp

The American pathologists are more likely to detect nuclear features than Japanese pathologists [5]. Thus, we hypothesized that NIFTP may be included in tumors, which have been diagnosed as follicular adenomas (FAs) by Japanese pathologists. Incidence of NIFTP in tumors diagnosed as PTC has been previously reported [1-4, 6, 7], but those in the tumors diagnosed as FA have not been investigated. Herein, we reviewed the histological preparations of 59 nodules diagnosed as FA at a single institution in Japan before the disease entity of NIFTP was proposed. This study aimed to evaluate the incidence of NIFTP in the tumors diagnosed as FA in a Japanese institution. We also aimed to discuss the significance of the term NIFTP.

Materials and Methods

The study protocol was approved by the Institutional Review Board of Kuma Hospital (Hyogo, Japan) (approval

number: 20200213-5). We reviewed 1,365 cases with 1906 resected thyroid tumors that were histologically diagnosed at the Kuma Hospital in 2008. Among them, 59 tumors (3.1%) were diagnosed as FA, including 15 oxyphilic variants. The remaining 44 tumors diagnosed as FAs, were involved in this study. The diagnosis of NIFTP was based on the criteria refined by Alves *et al.* in 2018 [8]: 1) full encapsulation or partial encapsulation with clear demarcation; 2) follicular growth pattern without true papillary structures; and 3) nuclear features of PTC, defined by a nuclear score of 2 or 3. Exclusion findings were as follows: 1) psammoma bodies; 2) more than 30% solid, trabecular, or insular growth pattern; 3) lymphovascular or capsular invasion; 4) tumor necrosis; and 5) high mitotic activity (≥3 mitoses per 10 high-power fields). The review of histological data was performed by the first and fourth authors, who are specialists in thyroid pathology. A molecular test was not performed in this study. The presence of nodal metastasis was microscopically examined for regional lymph nodes removed at the time of thyroidectomy. Distant metastasis was evaluated during follow-up at 11 years. Immunohistochemical staining of Ki-67 (MIB-1; 1:200 dilution; Dako, Glostrup, Denmark) was performed using an automated Leica Bond-Max system and Bond Refine detection kit (Leica Microsystems, Wetzlar, Germany) according to the manufacturer's recommendations. The Ki-67 labeling index (LI) was estimated by counting at least 500 tumor cells.

Fine-needle aspiration cytology (FNAC) was performed using a 22-gauge needle under ultrasound (US) guidance. The aspirated materials were prepared by press and release method [9] and then immediately fixed with Cytorop (Alfresa Pharma Co., Osaka, Japan), a cytological fixative. The samples were then stained using the Papanicolaou method. FNAC results were categorized based on both the first and second editions of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) [10, 11].

Statistical analysis was performed using a Fisher's exact test or Student's *t*-test. Results with *p* values less than 0.05 were considered statistically significant.

Results

Of the 44 nodules, 13 (29.5%) were revised to NIFTP. For the remaining 31 nodules, the diagnosis of FA was reconfirmed. The clinical and pathological findings of FAs and NIFTPs are shown in Table 1. Patients with FA included 2 males and 29 females, with a median age of 55 years (range, 21–72 years). In contrast, NIFTP was more frequently seen in males (7 males, 9 females), and the difference between FA and NIFTP was statistically significant ($p < 0.01$). The size of the tumors was measured by US. The largest dimension of NIFTP ranged from 19 to 90 mm (median: 45 mm) and was not significantly different from that of FA.

On FNAC, based on the first TBSRTC of the 11 NIFTP samples, 1 (9.1%), 6 (54.5%), and 5 (45.5%) were categorized into nondiagnostic or unsatisfactory (ND/UNS), atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS), and follicular neoplasm or suspicious for a follicular neoplasm (FN/SFN), respectively. Of the 29 FAs, 2 (6.9%), 2 (6.9%), 6 (20.7%), and 19 (65.5%) were categorized into as ND/UNS, benign, AUS/FLUS, and FN/SFN, respectively. No nodules with suspicious for malignancy or malignant were present. In the first TBSRTC, NIFTP was more likely to be categorized as AUS/FLUS than FA. Three and 5 of 6 FAs and 6 NIFTPs categorized as AUS/FLUS according to the first TBSRTC were re-categorized as FN/SFN in the second TBSRTC, respectively.

For histological diagnosis of the nodules, lobectomy was performed in 25 FAs (80.6%) and 11 NIFTPs (84.6%). In the remaining cases, total thyroidectomy was performed because of the association with PTC or a presence of multiple nodules in both lobes. Pathologically, no capsular invasion was observed in both FA and NIFTP nodules. One FA revealed true papillary structure. Nine (29.0%) of 31 FA nodules showed nuclear score 1; size and shape (5 nodules), nuclear membrane irregularities (1 nodule), and chromatic characteristics (3 nodules). Twelve (92.3%) of the 13 NIFTP nodules showed nuclear score 2, and the remaining nodule had nuclear score 3. Membrane irregularities were observed in all NIFTP nodules. Ki-67 labeling indexes of more than 5% were observed in 1 (7.7%) of 13 NIFTP nodules and 4 (12.9%) of 31 FA nodules: this was not significantly different.

Lymph node dissection was performed in 9 cases associated with PTC. In 2 of them, metastatic PTC was detected in the lymph nodes at the time of the operation. No metastasis of FA or NIFTP components was detected. There were no clinical evidences of distant metastasis of FA or NIFTP components during follow-up.

Discussion

In 2016, Nikiforov *et al.* proposed renaming NEFV-PTC as NIFTP as a type of nonmalignant tumor to prevent overtreatment [1]. The incidence of NIFTP ranged from 13.6% to 25% of PTCs in the Western countries [1]. In contrast, in the Asian countries, NIFTP are estimated to represent only 0.8% cases of PTC [3]. In our hospital, NIFTP comprised 0.5% cases of PTC [4]. The

Table 1 Clinical and pathological findings of follicular adenomas and NIFTPs

	Follicular adenoma (n = 31)	NIFTP (n = 13)
Age (years) (median)	21–72 (55)	27–56 (44)
Male:Female	2:29	7:6
	$p < 0.01$	
Size (mm) (median)	10–94 (40)	19–90 (45)
Ultrasound		
Benign	12 (38.7%)	2 (15.4%)
Benign/Follicular tumor	5 (16.1%)	0 (0%)
Follicular tumor	12 (38.7%)	9 (69.2%)
Papillary carcinoma	2 (6.5%)	2 (15.4%)
Aspiration cytology	1st/2nd	1st/2nd
Nondiagnostic or unsatisfactory	2/2	1/1
Benign	2/2	0/0
Atypia of undetermined significance	6/3	6/1
Follicular tumor	19/22	5/10
Suspicious for malignancy	0/0	0/0
Malignant	0/0	0/0
Lobectomy/Total thyroidectomy	25/6*	11/2*
Histology		
Capsular invasion	0 (0%)	0 (0%)
True papillary structure	1 (3.2%)	0 (0%)
Size and shape (2 or 3)	5 (16.1%)	7 (53.8%)
	$p < 0.05$	
Membrane irregularities (2 or 3)	1 (3.2%)	13 (100%)
	$p < 0.001$	
Chromatic characteristics (2 or 3)	3 (9.7%)	7 (53.8%)
Ki-67 labeling index <5%/5–10%/>10%	27/4/0	12/1/0
Nodal metastasis at operation	2/6 (33.3%) **	0/3 (0%)
Distant metastasis during follow-up	0/31 (0%)	0/13 (0%)

NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features
*: Cases with papillary carcinoma or multiple nodules in both lobes
**: Metastatic papillary carcinoma

incidence of NIFTP in Asian countries was considerably lower than that in Western countries. Jung and Kim reported that the incidence of NIFTP increased from 0.3% to 3.4% by adopting "loose diagnostic criteria" to define NIFTP [6]. However, there is still a major difference between Asian and Western countries.

In Japan, the histological diagnosis of thyroid tumors is based on "General Rules for the Description of Thyroid Cancer" proposed by the Japan Association of Endocrine Surgery (JAES) and the Japanese Society of Thyroid Pathology (JSTP) [12]. In the classification, neither borderline tumor, tumor of uncertain malignant potential, nor NIFTP exists. Therefore, noninvasive encapsulated follicular tumors have been diagnosed as either FA or NEFV-PTC. The latter has nuclear findings characteristic of PTC. Tumors, in which nuclear findings characteristic of PTC are not present, not adequate to be defined, or focally present, have been classified as FA. Theoretically, the tumors that have been diagnoses as FA in Japan can contain NIFTP. It is reasonable to assume that 29.5% of the tumors diagnosed as FA were NIFTP in the current study. We identified 13 NIFTP among the nodules reported as FA for one year. In the same hospital, among the 10,076 nodules diagnosed as PTC for 10

years, 54 NIFTPs (0.5%) were discovered [4]; the follicular variant of PTC (FV-PTC) accounted for 19.0% of the cases. When approximating the numbers, we found that 5 to 6 NIFTPs were classified as PTC nodules diagnosed at our hospital in 1 year. We first demonstrated that NIFTP is more frequently included in nodules diagnosed as FA rather than those diagnosed as PTC, and the overall number is also more frequent in the former. We think that the evidence is one of the factors explaining the low frequency of NIFTP in PTC nodules in Japan. However, there is still a considerable difference in incidences between the Asian and Western countries. Other factors, such as race, dietary habit, or indication for resection, may be related. Further studies will be necessary to fully elucidate these issues.

The incidence of NIFTP tends to be higher than that of FA in males. The tendency was also observed between NIFTP and FV-PTCs [4]. In the previously reported cases, however, it was more prominent in females [1, 13, 14]. In the current study, most of NIFTP nodules had been categorized into AUS/FLUS or FN/SFN in the first TBSRTC, and 5 of 6 NIFTP nodules categorized as AUS/FLUS in the first TBSRTC were re-categorized into FN/SFN in the second TBSRTC. Hence, nodules showing mild nuclear changes associated with PTC are included in FN/SFN in the second TBSRTC [11]. For this reason, both NIFTP and FA could be classified into the same category, FN/SFN. Therefore, preoperatively, we cannot distinguish between NIFTP and FA, and cannot find a significance to distinguish them.

The diagnosis of NIFTP is made by a histological examination of the surgically resected specimens. However, even by histological examination it may be difficult to clearly distinguish among FA, NIFTP, and NEFV-PTC. As our results showed, FA can have a nuclear score 1 (mild nuclear changes associated with PTC). Liu *et al.* demonstrated that there was considerable observer variation in evaluation of nuclear features of PTC and rendering a diagnosis of NIFTP among Asian pathologists [15].

Here, we should consider a necessity to distinguish between FA and NIFTP. On FNAC, most of NIFTP are interpreted as FN/SFN. Thus, the management of FA and NIFTP is the same, and a lobectomy is recommended [1]. No nodal or distant metastasis is detected in both tumors. Genetically, NIFTP shares molecular alterations (*RAS* mutations) detected in FA and does not show $BRAF^{V600E}$, *RET/PTC*, or *TERT* mutations characteristic of PTC [8]. All the above findings conclude that there is no reason to distinguish between FA and NIFTP. Therefore, in Japan, use of the disease entity "NIFTP" is not necessary.

Acknowledgments

We would like to thank Editage (www.editage.com) for English language editing.

Disclosure

The authors have no conflicts of interest to declare regarding grant support or financial relationships.

References

1. Nikiforov YE, Seethala RR, Tallini G, Baloch ZW, Basolo F, *et al.* (2016) Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: a paradigm shift to reduce overtreatment of indolent tumors. *JAMA Oncol* 2: 1023–1029.
2. Thompson LD (2016) Ninety-four cases of encapsulated follicular variant of papillary thyroid carcinoma: a name change to noninvasive follicular thyroid neoplasm with papillary-like nuclear features would help prevent overtreatment. *Mod Pathol* 29: 698–707.
3. Bychkov A, Hirokawa M, Jung CK, Liu Z, Zhu Y, *et al.* (2017) Low rate of noninvasive follicular thyroid neoplasm with papillary-like nuclear features in Asian practice. *Thyroid* 27: 983–984.
4. Hirokawa M, Higuchi M, Suzuki A, Hayashi T, Kuma S, *et al.* (2017) Noninvasive follicular thyroid neoplasm with papillary-like nuclear features: a single-institutional experience in Japan. *Endocr J* 64: 1149–1155.
5. Hirokawa M, Carney JA, Goellner JR, DeLellis RA, Heffess CS, *et al.* (2002) Observer variation of encapsulated follicular lesions of the thyroid gland. *Am J Surg Pathol* 26: 1508–1514.
6. Jung CK, Kim C (2017) Effect of lowering the diagnostic threshold for encapsulated follicular variant of papillary thyroid carcinoma on the prevalence of non-invasive follicular thyroid neoplasm with papillary-like nuclear features: a single-institution experience in Korea. *J Basic Clin Med* 6: 26–28.
7. Ruanpeng D, Cheungpasitporn W, Thongprayoon C, Hennessey JV, Shrestha RT (2019) Systematic review and meta-analysis of the impact of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) on cytological diagnosis and thyroid cancer prevalence. *Endocr Pathol* 30: 189–200.
8. Alves VAF, Kakudo K, LiVolsi V, Lloyd RV, Nikiforov YE, *et al.* (2018) Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): achieving better agreement by refining diagnostic criteria. *Clinics*

(Sao Paulo) 73: e576.
9. Hirokawa M, Suzuki A, Miyauchi A (2018) Thyroid fine-needle aspiration and smearing techniques. *Video Endocrinology* 5: ve.2018.0119.
10. Cibas ES, Ali SZ (2009) The Bethesda system for reporting thyroid cytopathology. *Thyroid* 19: 1159–1165.
11. Cibas ES, Ali SZ (2017) The 2017 Bethesda system for reporting thyroid cytopathology. *Thyroid* 27: 1341–1346.
12. Japan Association of Endocrine Surgery, The Japanese society of thyroid pathology (2019) General rules for the description of thyroid cancer (8th). Kanehara-Shuppan, Tokyo, Japan (In Japanese).
13. Lee HS, Lee JW, Park JH, Kim WS, Han HS, *et al.* (2019) Comprehensive analysis for diagnosis of preoperative non-invasive follicular thyroid neoplasm with papillary-like nuclear features. *PLoS One* 14: e0218046.
14. Yan L, Sethi S, Park JW (2019) Cytologic and clinical features of NIFTP: can we diagnose based on preoperative fine-needle aspiration. *Diagn Cytopathol* 47: 1259–1266.
15. Liu Z, Bychkov A, Jung CK, Hirokawa M, Sui S, *et al.* (2019) Interobserver and intraobserver variation in the morphological evaluation of noninvasive follicular thyroid neoplasm with papillary-like nuclear features in Asian practice. *Pathol Int* 69: 202–210.