

Reclassification as non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): A retrospective review in a single institution and outcome study

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Ethics Committee Approval

The study was approved by Ethics Committee of Kayseri Training and Research Hospital, Turkey (Protocol No:652/2022).

All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest

No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Since non-invasive follicular thyroid neoplasm (NIFTP) was first defined in 2016, past overtreatment status, impact for the risk of malignancy, and incidence of NIFTP have been the subject of study. Retrospective cohort studies have been published and present widely varying results in different geographic regions. This study aimed to reclassify follicular variants of papillary thyroid carcinoma (FVPTC) cases diagnosed in a single center using the defined stringent NIFTP criteria and to determine incidence, clinicopathological features, and survival of NIFTP cases.

Methods: This retrospective cohort study was conducted in a single center and consisted of patients with diagnosed follicular variant papillary thyroid carcinoma in thyroidectomy/thyroid lobectomy specimens between 2014 and 2021. Reports of FVPTC cases between 2014 and 2018 were evaluated by two experienced pathologists to identify candidates for NIFTP. Archived glass slides of the potential NIFTP cases were retrieved and reviewed independently by two pathologists.

Results: Between 2014 and 2021, 84 patients who underwent surgery were diagnosed with FVPTC. Reports of 49 patients diagnosed before 2018 were re-evaluated by two pathologists, and 20 cases were identified as candidates for NIFTP. After blind evaluation of pathology slides, five cases (10%) were diagnosed as NIFTP according to the criteria established before 2016, and two cases between 2016 and August 2018 were still diagnosed as NIFTP. Fourteen patients were diagnosed with NIFTP between 2014 and 2021. The median follow-up of the NIFTP patients was 4.3 years, and no recurrence and/or metastasis was reported.

Conclusion: NIFTP represents 7.6% of the papillary thyroid carcinoma (PTC) cases in our cohort, which is higher than the incidence rate in our country. The follow-up results of our cases were uneventful considering the indolent nature of NIFTP, but we had high thyroidectomy rates. Due to the concomitant PTC, multifocality, and uncertainties in the follow-up routine, we think it would be appropriate for these patients to remain in active follow-up.

Keywords: Noninvasive follicular thyroid neoplasm with papillary-like nuclear features, Thyroid cancer, Follicular thyroid neoplasm, Incidence, Outcome

Introduction

Despite the increase in the incidence of papillary thyroid cancer (PTC) over the last 30 years, mortality rates from PTC have remained stable [1]. Increased ultrasonographic scans and fine-needle aspiration biopsy (FNAB) rates result in overdiagnosis and unnecessary treatment. One of the reasons for this situation is the presence of low-grade/non-aggressive tumors within the PTC subgroup. FVPTC indicates a predominately follicular growth pattern with nuclear features of classic PTC [2, 3]. FVPTC is the least aggressive subtype of PTC and has shown the highest increase rate in recent years [4, 5]. FVPTC is classified as infiltrative/ non-encapsulated and encapsulated FVPTC (E-FVPTC) [6]. The infiltrative FVPTC may be associated with recurrence or metastasis and shows a molecular profile similar to classic PTC and E-FVPTC that exhibits indolent behavior and is often associated with a molecular profile seen in follicular neoplasms [7, 8]. The Endocrine Pathology Society Working Group examined E-FVPTC in 2016, and the terminology of non-invasive follicular thyroid neoplasm (NIFTP) with papillary-like nuclear features was defined along with new diagnostic criteria [9]. The diagnosis of NIFTP is based on the absence of invasion along with other histological criteria, including nuclear and architectural features. The indolent nature of NIFTP, based on this definition, allows for less radical treatment, and this terminology change is expected to reduce overtreatment and the psychological burden associated with a thyroid cancer diagnosis [9]. Patients treated for such tumors are expected to have an excellent prognosis. Rosario et al. [10] reported no NIFTP-related deaths, but a case series with one pulmonary metastasis and lymph node metastases has been reported. It has also been reported that the cases should be followed up as low-risk PTC or that current PTC follow-up routines are unnecessary [11–13]. Canberk et al. [14] reported that concomitant tumors in the contralateral lobe were not negligible (18%), and most were malignant.

The goal of this study was to retrospectively review and reclassify FVPTC cases diagnosed in a single center using the defined stringent NIFTP criteria. It also aims to determine the incidence of NIFTP and examine the clinicopathological features and survival of the cases that were diagnosed with NIFTP.

Materials and methods

The Institutional Review Board approved the study at Kayseri Training and Research Hospital (Protocol No: 652/2022). A retrospective review was performed of diagnosed papillary carcinoma in thyroidectomy/thyroid lobectomy specimens in Kayseri City Training and Research Hospital Pathology Clinic between 2014 and 2021. During this period, a search of the hospital medical record system was done using several keywords: (1) “thyroid”, (2) “follicular variant”, (3) “encapsulated”, and (4) “papillary thyroid carcinoma” for the index lesion.

Follicular thyroid cancers were excluded, and FVPTC or NIFTP pathology reports were retrieved to identify possible cases of NIFTP. After that step, reports of those cases diagnosed with FVPTC between 2014 and 2018 were evaluated by two experienced endocrine-specific pathology specialists to identify

candidates for NIFTP. Archived glass slides of the potential NIFTP cases were retrieved and reviewed independently by two pathologists. The modified current criteria revised in 2018 by Nikiforov et al. [15] for NIFTP were used (Table 1). Since no BRAFV600E mutation information about the patients was available, they were not included in the evaluation. Locoregional recurrence or metastasis during the follow-up period was defined as an adverse event.

Table 1: Consensus diagnostic criteria for Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), adapted from Nikiforov et al. [15]

Revised diagnostic criteria for NIFTP	Exclusion criteria
Encapsulation or clear demarcation	Any true papillae
Follicular growth pattern with:	Psammoma bodies
No well-formed papillae	Infiltrative border
No psammoma bodies	Tumor necrosis
<30% solid/trabecular/insular growth pattern	High mitotic activity
Nuclear score 2–3	Cell/morphologic characteristics of other variants of papillary thyroid cancer
No vascular or capsular invasion	
No tumor necrosis or high mitotic activity	

Statistical analysis

To summarize data obtained in the study, descriptive statistics were given as mean (standard deviation [SD]) and minimum–maximum (min–max) depending on the distribution of the continuous variables. Categorical variables were summarized as numbers and percentages. The Shapiro–Wilk test controlled the normality test of the numerical variables. Chi-squared and Fisher’s exact tests were used to calculate the categorical demographic characteristics of the patients. Analyses were performed with IBM SPSS Package Program version 24.0 (IBM Corporation, Armonk, NY, USA).

Results

Between 2014 and 2021, 84 out of 184 cases of papillary carcinoma with FVPTC were diagnosed. Pathology slides from 20 patients with possible NIFTP in 49 patients with FVPTC diagnosed in 2018 and before were reviewed by two experienced pathologists. Five cases were diagnosed as NIFTP according to the new criteria before 2016. Two cases between 2016 and 2018 were still diagnosed as NIFTP when re-evaluated according to the revised criteria in August 2018. The patient selection diagram and exclusion criteria of patients not accepted as NIFTP are shown in Figure 1. The clinical features of all cases are summarized in Table 2. Total thyroidectomy was performed on all patients (one with lobectomy had previously undergone contralateral lobe surgery). NIFTP represents 16.7% of FVPTC and 7.6% of PTC in our cohort of all PTCs from 2014 to 2021.

Table 2: Clinical features of cases reclassified as NIFTP

	Age	Sex	FNAC Bethesda classification	Surgery	Tumor size (mm)	Duration of follow-up (years)	RAI	Contralateral lesion
1	64	F	2	Total thyroidectomy	22	6	No	Nodular colloidal goiter
2	61	F	1	Total thyroidectomy	23	5	Yes	Papillary microcarcinoma**
3	50	F	0	Total thyroidectomy	13	6	Yes	No
4*	49	F	#	Lobectomy	10	7	No	No
5	59	M	#	Total thyroidectomy	12	8	No	No
6	44	F	2	Total thyroidectomy	15	4	Yes	Nodular colloidal goiter
7	44	M	4	Total thyroidectomy	45	4	Yes	Follicular adenoma

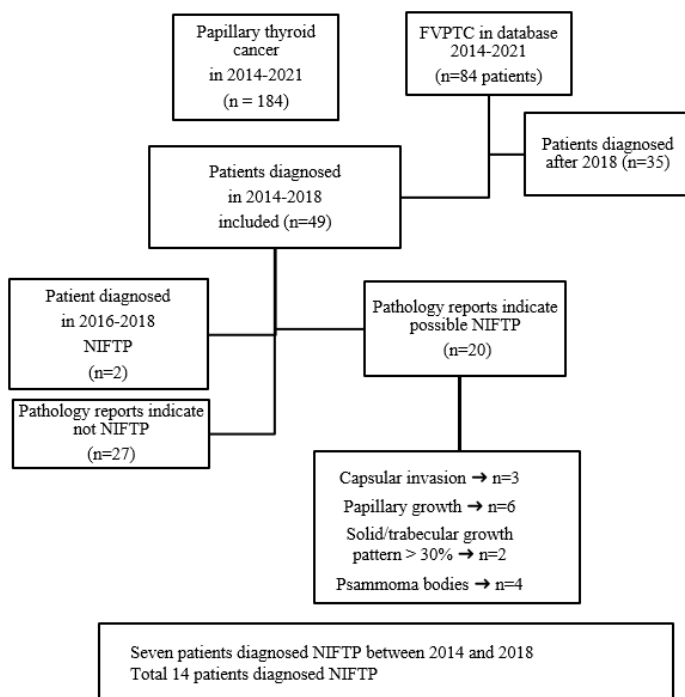
FNAC: Fine Needle Aspiration Cytology, RAI: Radioactive iodine treatment, F: Female, M: Male, * Patient with previous lobectomy, ** The other lobe tumor size 3 mm, #: Unknown

Clinicopathologic findings of NIFTP

A total of 14 patients were diagnosed with NIFTP between 2014 and 2021. The mean age of patients was 51 (8.0) years, and 78.6% of the patients were women. The mean size of the lesions was 18.2 (10.0) mm, the minimum tumor diameter was 8 mm, and the maximum was 45 mm. Six nodules were located in the right lobe and 8 in the left lobe.

Total thyroidectomy was performed in 11 (88,6%) patients, and lobectomy was performed in three patients (one had previously undergone a lobectomy on the contralateral side). The other two patients did not undergo a completion thyroidectomy to the contralateral lobe. Fine needle aspiration biopsy (FNAB) results had been obtained for 10 patients, and out of these results, three were undetermined significance, one had a follicular neoplasm, two were positive for PTC, and four had negative results.

Figure 1: Patient selection diagram. FVPTC, follicular variant of papillary thyroid carcinoma; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features



Outcome of NIFTP

The median follow-up of the NIFTP patients was 4.3 (1.86 [range 2–8]) years. Among them, seven (50%) had at least three years of follow-up (diagnosed before 2018), and no recurrence or metastasis was reported. Incidental concomitant micropapillary carcinoma focus on the contralateral lobe was observed in two patients and follicular adenoma was observed in one patient. It was observed that four patients who underwent total thyroidectomy were given radioactive iodine treatment (RAI) treatment. One of these patients had a concomitant papillary microcarcinoma focus, and the other had follicular adenoma.

Discussion

In the first study by Nikiforov et al. [9], 109 patients with a non-invasive encapsulated follicular variant of PTC (67 patients treated with only lobectomy without RAI ablation treatment) were alive with no evidence of disease at their follow-up periods (median of 13 years). Otherwise, an adverse event

was seen in 12% of invasive E-FVPTC cases, including distant metastasis and disease-related mortality. Based on these results, the first time the term “non-invasive follicular thyroid neoplasm with papillary-like nuclear features” (NIFTP) was used, and this change also was adopted by the World Health Organization in 2017 [16]. This change in diagnostic terminology aimed to reduce overtreatment and eliminate the psychosocial issues associated with a cancer diagnosis.

Another contribution of this new modification is that less total thyroidectomy is required due to the indolent nature of NIFTP, and lobectomy is sufficient for these lesions. Our results demonstrate the aggressive treatment of patients with FVPTC who were reclassified as having NIFTP. In this study with its high rate of total thyroidectomy, all patients were treated with initial total thyroidectomy except two patients (one had contralateral lobe surgery). All tumor diameters were more than 1 cm. In the most extensive studies of NIFTP patients, approximately 25%–50% underwent thyroid lobectomy as the initial procedure [13, 17]. Given that a significant number of patients with NIFTP undergo total thyroidectomy for various reasons, the impact of this reclassification on the extent of surgery is less than expected. Compared to the results of a different study involving 500 thyroidectomy patients in our clinic, our total thyroidectomy rates (96.2%) were already high [18]. This result is probably associated with an increased incidence of goiter and thyroid nodules since we are living in an endemic goiter region. The 2015 American Thyroid Association guidelines recommend that lobectomy is sufficient for the low-risk patient with a well-differentiated thyroid malignancy defined as tumors > 1 cm and < 4 cm without extrathyroidal spread or evidence of lymph node metastasis [11, 19]. However, some studies report that 43% of patients with lobectomy will require a completion thyroidectomy [20].

Multifocality and contralateral lesions are other issues of discussion for NIFTP. Canberk et al. [14] reported detection of contralateral tumoral lesions in 13 (18%) of 74 total thyroidectomy cases for NIFTP, 11 of them were malignant, and the other two were NIFTP. Also, NIFTP and FVPTC cases had statistically similar incidences of contralateral tumors. Canini et al. [21] reported that 14.7% of 68 NIFTP patients were multifocal and approximately 10% were bilateral, and Turan et al. [22] also detected 17.9% multifocal NIFTP foci in 84 patients. No difference in survival between solitary and multifocal NIFTP was found [21, 22]. In our present study, no multifocal NIFTP focus was detected, but concomitant PTC was present, and no statistically significant difference in multifocality between FVPTC and NIFTP was noted (35.7% and 14.3%, respectively).

In addition, 57.1% of NIFTP patients in our study received RAI for residual thyroid tissue for quantitative thyroglobulin evaluation and clinical follow-up. RAI treatment rates in other published reports are 44%–47% [13, 23]. Using pathological evaluation with strict application of the NIFTP criteria, the patients in our study results had excellent outcomes. Contrary to our results, in the literature, Parente et al. [13] published five patients with nodal metastases and one distant metastasis (lung) over a mean follow-up of 5.7 years. Kim et al. [24] had nine patients with positive central neck lymph nodes

(over half of these patients had concomitant classic PTCs) among 74 NIFTPs. Cho et al. [25] also followed two patients with central lymph node metastases, but no distant metastases, over a median follow-up of 37 months. An overall lymph node metastasis rate of 1.8% (range: 0%–12%) and distant metastasis rate of 0.08% (range: 0%–1%) were demonstrated in a systematic review [22]. Consistent with the literature considering the 14.3% contralateral tumor rates detected in our study and also the significant heterogeneity in the overall lymph node metastasis rate in the literature, it is recommended that these patients should remain in the follow-up routine.

The incidence of NIFTP varies considerably in retrospective studies (despite the stringent criteria defined for diagnosis) and ranges from less than 1% to 28% of all thyroid neoplasms [26]. Won et al. [27] reclassified 71% of EFVPTC as NIFTP, and the overall percentage was 27% of all PTC. Kiernan et al. [23], in a review based on a consensus diagnosis involving three pathologists, reclassified 46% of 60 FVPTC as NIFTP, and Agrawal et al. [28] reclassified 40% of non-invasive EFVPTC as NIFTP by a single pathologist. Chung et al. [29] identified only 15 (13%) NIFTP among 110 FVPTCs as determined by two expert pathology specialists, a finding that was similar to our results. When evaluated according to the geographical distribution, NIFTP incidence was very similar in North America and Europe (9.3% and 9.6%, respectively) with a significantly lower overall rate in Asia (2.1%) [30]. In reclassification studies in our country, the incidence of NIFTP was found to be 2.4%–3.9% in PTCs [14, 22]. In the present study, the incidence of NIFTP was 7.6% in all PTCs, which was higher than the incidence rates in our country. However, our FVPTC rates were also high (45.7%) among all PTCs. Turan et al. [22] reclassified 84 (17.5%) of 481 patients with FVPTC as NIFTP, a finding similar to our results. In a study recently published in our country, the most common subtype was FVPTC with 247 (53.7%) among 460 PTC cases [31]. In another study, it was the third most common subtype (23.6%) after micropapillary and classical PTC [32].

Another controversial issue is the ethical situation since these cases had been diagnosed with cancer beforehand after which the patients were treated and followed accordingly. Some authors have recommended that pathology departments implement retrospective database reviews of tumors diagnosed as FVPTC for patients currently under surveillance. If the nodules are suitable for NIFTP diagnosis, the clinicians and patients should be alerted about the new diagnosis [33].

Limitations

This study has several limitations, most notably the small number of patients and its retrospective nature. Results may not reflect the entire NIFTP population. Moreover, we did not have the molecular profile of the tumors, and FNAB results were missing in some patients. Only a limited number of patients had a follow-up period of more than three years, and we think future studies should support the long-term follow-up results of these patients.

Conclusions

Due to our high thyroidectomy rates, our results do not contribute to the question of the adequacy of lobectomy in the treatment of NIFTP. According to the literature, although

lobectomy seems sufficient in the treatment, unanswered issues remain regarding multifocality, concomitant PTC, and bilaterality for NIFTP. Also, no definitive recommendations for a follow-up routine have been put forth. In our results, no recurrence or metastasis in follow-up was found. Still, keeping these patients under active follow-up seems appropriate due to the question marks about NIFTP and no definitive recommendations/guidelines for a follow-up routine.

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