



Original contribution

“The other side of the coin”: understanding noninvasive follicular tumor with papillary-like nuclear features in unifocal and multifocal settings[☆]



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Summary The recent description of noninvasive follicular tumor with papillary-like nuclear features (NIFTP) creates several diagnostic and therapeutic challenges for both the pathologist and the attending clinician. Given the concern about overtreatment of these neoplasms, the best way to manage the patients by a surgical procedure and postsurgical follow-up is still under discussion. We aimed to identify predictors of synchronous disease (eg, bilateral cancers) that can influence the appropriate type of surgery and long-term surveillance. We reevaluated the original diagnosis and the presence of contralateral lesions in 94 cases retrieved from our archives that were seen between 2010 and 2017. In 74 cases, the diagnosis was NIFTP, and in 20 cases, the diagnosis was infiltrative follicular variant of papillary thyroid carcinoma (IFVPTC). Bilateral disease was found in 17% of the cases. In 13 (18%) of those cases, NIFTP was the primary lesion, and in 3 (15%), it was IFVPTC. The contralateral disease was predominantly invasive: 6 cases of micropapillary carcinoma, 5 of papillary thyroid carcinoma, 3 of IFVPTC, and 2 of NIFTP. Despite the higher frequency of contralateral disease in NIFTP, there was no statistically significant difference with IFVPTC. In the patients with multifocal NIFTP, 2 (15%) of the contralateral malignancies showed microscopic extra-thyroidal extension ($P < .05$). We conclude that close monitoring of the contralateral lobe is appropriate in patients with FVPTC, particularly NIFTP, if they are not submitted to total thyroidectomy.

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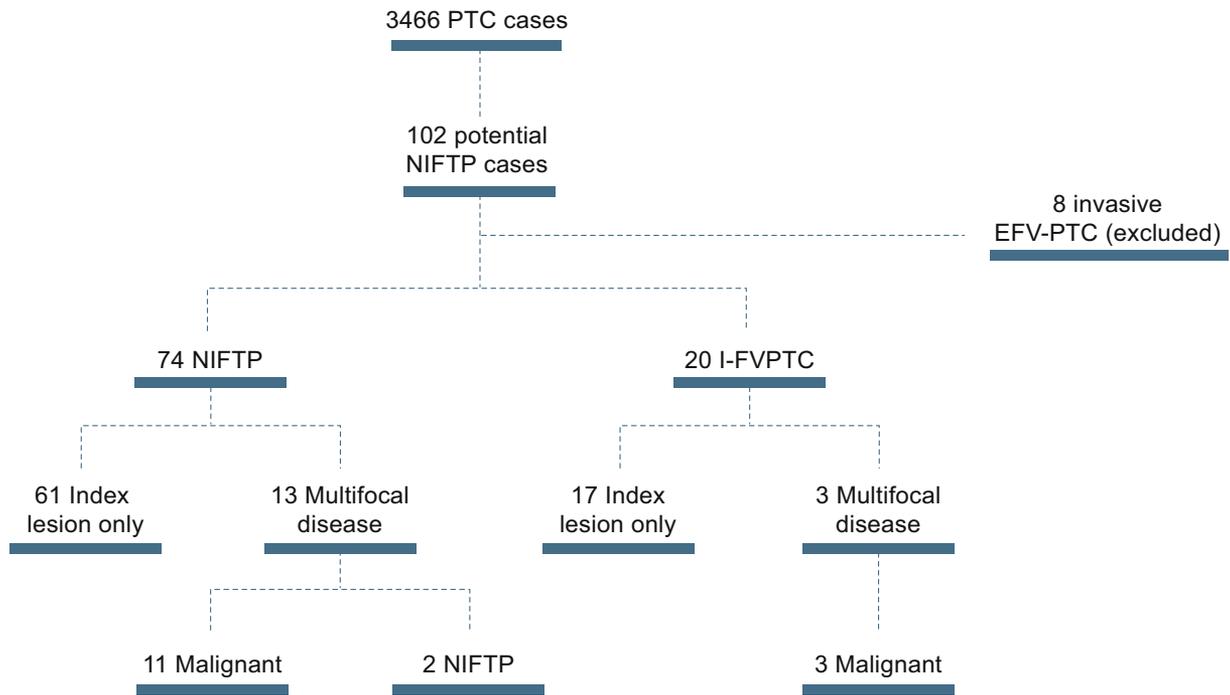


Fig. 1 Study flow diagram.

1. Introduction

Recently, an encapsulated/well-delimited and noninvasive subset of follicular variant of papillary thyroid carcinoma (PTC) has been named “noninvasive follicular tumor with

papillary-like nuclear features” (NIFTP) [1]. This new entity is considered a low-grade malignancy that creates a new challenge not only for the cytopathologist, who is asked to recognize it preoperatively, but also for clinicians, who need to design a follow-up protocol that will avoid overtreatment

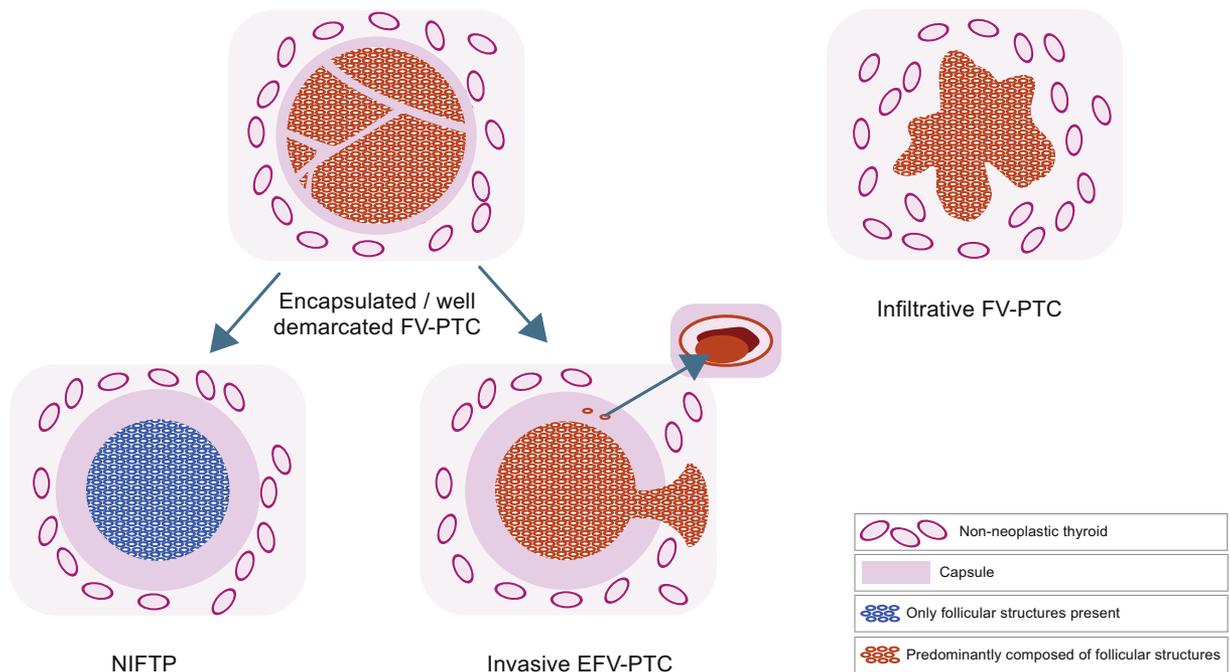


Fig. 2 The FVPTC follicular variant of PTC. *Invasive EFVPTC showing capsular or vascular invasion.

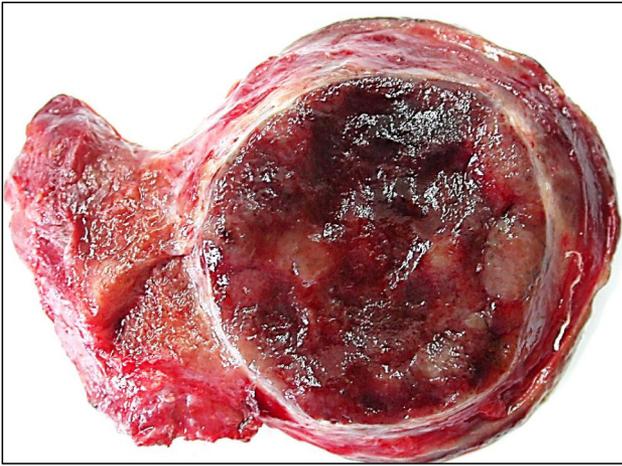


Fig. 3 Macroscopic features of NIFTP. Nodule is sharply demarcated from adjacent parenchyma by well-formed capsule.

while removing all cancers. This change in the diagnostic paradigm of one of the most controversial entities in endocrine pathology may seem “sudden,” but the less aggressive treatment (lobectomy versus total thyroidectomy) was quickly advocated by all guidelines. However, the requirement for active surveillance after lobectomy is still under discussion [2-4].

The follicular variant is a unique entity and that some authors consider a dysplastic-like process of the thyroid [5]. Regarding the multistep carcinogenesis theory of sequential progression of well-differentiated thyroid carcinoma [6], the current study aimed to identify predictors that correlate with synchronous disease, as the presence of bilateral cancers in patients with NIFTP may influence the surgical procedure and the long-term surveillance.

2. Materials and methods

A retrospective review was performed of thyroid nodules identified as the follicular variant of PTC at our institution between September 2010 and July 2017. During this period, a query was made using the following words: “thyroid,” “follicular variant,” “encapsulated,” and “papillary thyroid carcinoma” for the index lesion. Among the 3466 PTC cases that went through bilateral total thyroidectomy during the study period, 102 potential NIFTP cases were identified as the index lesion among cases with the final diagnosis of infiltrative follicular variant of PTC (FVPTC); 8 cases were excluded because they were invasive encapsulated follicular variants of

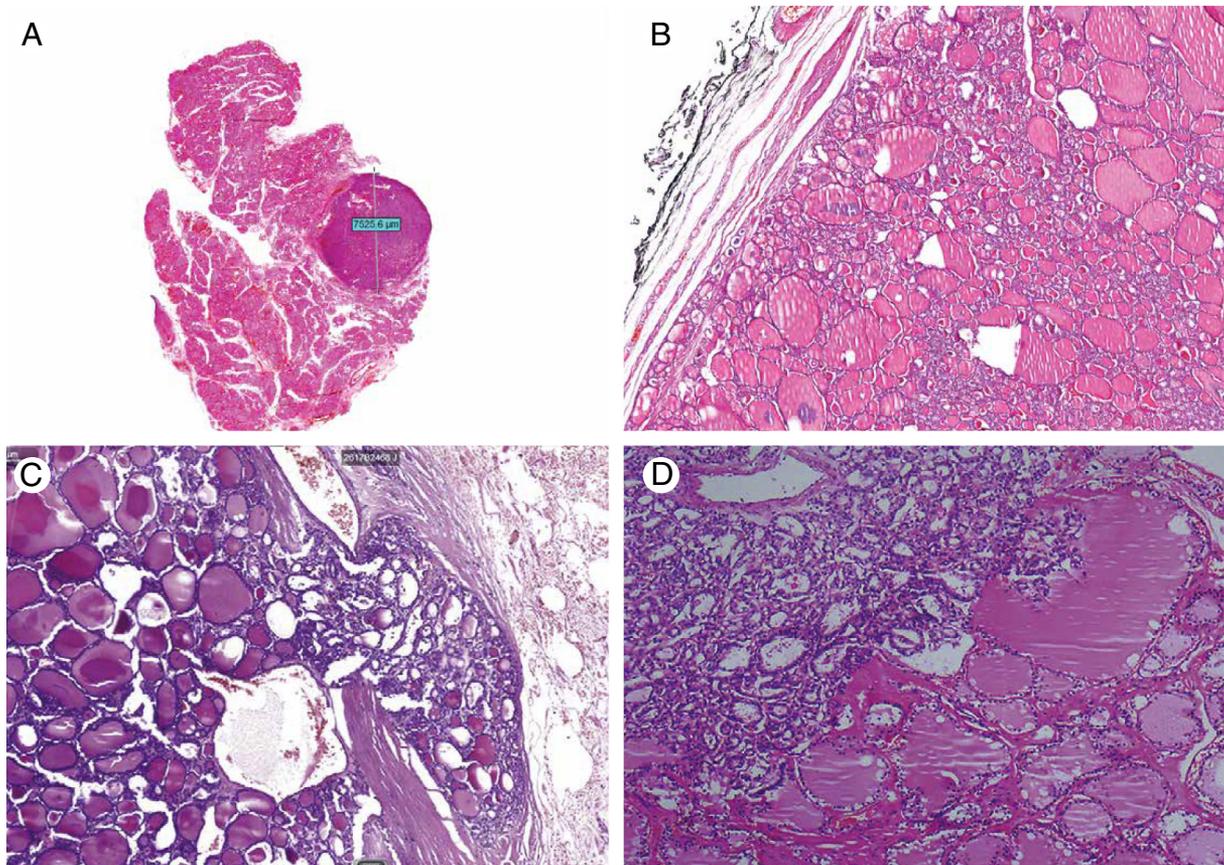


Fig. 4 Examples of tumors. A, NIFTP: 7.5 mm in size, well demarcated from adjacent nonneoplastic thyroid tissue at scanning magnification. B, NIFTP has entirely follicular pattern, and sharp demarcation is visible. C, Invasive follicular variant of PTC with capsule invasion in mushroom shape. D, FVPTC without any demarcation or capsule.

PTC (EFVPTC). The remaining 94 cases, which were included, were FVPTC (encapsulated noninvasive or infiltrative) with a minimum size of 3 mm (Figs. 1 and 2). Macroscopic and microscopic examples of the cases are depicted in Figs. 3 and 4. The size measurements were not available for 1 tumor. Because of the indolent behavior of encapsulated FVPTC, including those with focal capsular invasion, only the cases that were encapsulated noninvasive (corresponding to NIFTP) and unencapsulated infiltrative FVPTC were accepted as the target population. With this approach, the authors aimed to compare the most “indolent” tumors (namely, NIFTP) with the most “aggressive” forms (namely, infiltrative FVPTC).

The sampling of these cases followed the protocol used in our hospital. All encapsulated nodules in each lobe were examined in their entirety. The largest dimension was used to determine the number of cassettes according to the largest dimension, which is 3 cm. Because all capsulated nodules were sampled with nonneoplastic tissue around them, nodules <2 cm were placed in one cassette. The smallest diameter was used to decide the section number with 1 cm equaling 10 sections. With this approach, all nodules were sampled, including the entire parenchyma, the capsule, and some nonneoplastic tissue around the capsule. The slides were reviewed by 3 thyroid pathology specialists (S. C., F. T., Ü. İ.), who confirmed that the index lesions were either noninvasive follicular variant of thyroid papillary carcinoma or infiltrative follicular variant of thyroid papillary carcinoma (IFVPTC). Cases were reevaluated according to the strict histomorphologic criteria for NIFTP using current World Health Organization terminology [7] and the recent modification of the diagnostic criteria of NIFTP [8,9]. Tumors with any well-formed papillae or a focal solid/trabecular pattern were classified as encapsulated PTC and excluded from the study [8,9]. The IFVPTC group was selected based on the absence of capsulation, and invasion was analyzed in the areas of neoplastic follicles juxtaposed with nonneoplastic follicles at the periphery of the lesion. If the neoplastic and nonneoplastic follicles were intermingled in the periphery of the lesion, this was identified as “infiltrative growth.” Solitary lesions had only one focus (index lesion), whereas “multifocal lesions” were those with tumor in the contralateral lobe also. There were no cases with other foci in the same lobe.

The variables selected to analyze and characterize our cases are listed on Table 1, some of which were used to compare NIFTP and IFVPTC as well as solitary and multifocal lesions. Statistical analysis was carried out using Number Cruncher Statistical System 2007 (Kaysville, UT) Statistical Software Version 5.2. Descriptive statistical analysis (mean, SD, median, first quartile, third quartile, frequency, percentage, minimum, maximum) was performed. Quantitative variables were compared using the Shapiro-Wilk test and the Mann-Whitney *U* test. To compare qualitative variables, Fisher exact test was applied. Statistical significance was defined as $P \leq .05$. This study was performed in accordance with the national regulations for the handling of biological specimens, the samples being

available exclusively for research purposes in retrospective studies, as well as in compliance with the Declaration of Helsinki.

3. Results

Ninety-four patients were eligible for our study, of whom 78.7% were women. Among the 94 thyroidectomies, the index lesion was most commonly present in the right lobe, and in 41.4% of the cases, the nonneoplastic thyroid tissue showed nodular hyperplasia. The mean size of the lesions was 22.97 mm.

Seventy-four (78.7%) of the lesions that were originally identified as FVPTC were relabeled NIFTP. This means that the incidence of NIFTP in our sample corresponds to 2.1% of the PTC cases, in accordance with previous studies [10]. Despite the initial description of NIFTP (which should be a single lesion >1 cm), nodules <1 cm also were included in the current study, as in other studies [11]. An IFVPTC diagnosis was maintained for the 20 remaining tumors (21.2%).

Table 1 Characteristics of lesions

Characteristic	n (%)
Invasion	
Capsular invasion (mean)	20 (2.05)
LVI (%)	2 (2.1)
ETE (%)	4 (4.3)
LN (%)	1 (1.1)
Size (mm) ^a , mean (min-max)	
Size IL	22.97 (3-70)
Size CL	6.75 (2-14)
Lesion borders (%)	
Capsule	91 (96.8)
Well-delimited	3 (3.2)
Nonneoplastic thyroid (%)	
Lymphocytic thyroiditis	29 (30.8)
NCH	65 (69.2)
Lobe IL (%) ^b	
Right	71 (77.2)
Left	21 (22.8)
Lobe CL (%) ^c	
Right	3 (18.8)
Left	13 (81.3)
Multifocality (%)	
Solitary nodule	78 (83)
Multifocal nodules	16 (17)
Histologic type CL (%) ^c	
IFVPTC	3 (18.8)
PTC	5 (31.3)
PMC-FV	6 (43.8)
NIFTP	2 (6.3)

Abbreviations: CL, contralateral lesion; IL, index lesion; LN, lymph node metastases; NCH, nodular colloid hyperplasia; PMCFV, papillary microcarcinoma follicular variant.

^a When available.

^b Data available in 92 cases.

^c Data available in 16 cases.

Table 2 FNA cytology diagnosis of index lesion

Characteristic	n (%)
B-CLT	1 (1.1)
BFN	6 (6.4)
FLUS/AUS	5 (5.3)
SFN/FN	39 (41.5)
SFM	25 (26.6)
M	7 (7.4)
Not available	11 (11.7)

Abbreviations: B-CLT, benign chronic lymphocytic thyroiditis; BFN, benign follicular nodule; FLUS/AUS, follicular lesion of undetermined significance/atypia of undetermined significance; M, malignant; SFN/FN, suspicious for follicular neoplasm/follicular neoplasm; SFM, suspicious for malignancy.

Preoperative fine-needle aspiration (FNA) diagnoses were obtained in 83 cases, with the most common being “suspected malignancy,” corresponding to 41.5% of the cases (Table 2). Contralateral disease was found in 17% of the patients, with diameters ranging from 2 to 14 mm. Among these 16 lesions, 6 were micropapillary carcinomas (FVPTC; 38%), 5 were

Table 3 Comparison of the characteristics of IFVPTC (n = 20) and NIFTP (n = 74)

	IFVPTC, n (%)	NIFTP, n (%)	<i>P</i>
Age, median	40	41	.279 ^a
Size, median			
IL (n = 93)	29.5	20	.031 ^{a,b}
CL (n = 16)	3	6	.452 ^a
Sex			.759 ^c
Female	15 (75)	59 (79.7)	
Male	5 (25)	15 (20.3)	
Nonneoplastic thyroid			.170 ^c
Lymphocytic thyroiditis	8 (40)	21 (28.4)	
NCH	12 (60)	53 (71.6)	
Lobe IL (n = 92)			.127 ^c
Right	12 (63.2)	59 (80.8)	
Left	7 (36.8)	14 (19.2)	
Lobe CL (n = 16)			.489 ^c
Right	1 (33.3)	2 (15.4)	
Left	2 (66.7)	11 (84.6)	
LVI	2 (10)	0	.043 ^{b,c}
ETE	2 (10)	2 (2.7)	.198 ^c
LN	1 (5)	0	.213 ^c
Histologic type CL (n = 16)			.500 ^c
IFVPTC	2 (66.7)	1 (7.7)	
PTC	0	5 (38.5)	
PMCFV	1 (33.3)	5 (38.5)	
NIFTP	0	2 (15.3)	

Abbreviations: CL, contralateral lesion; IL, index lesion; LN, lymph node metastases; NCH, nodular colloid hyperplasia; PMCFV, papillary microcarcinoma follicular variant; Q, quartile.

^a Mann-Whitney *U* test.

^b *P* < .05.

^c Fisher exact test.

Table 4 Solitary (n = 61) versus multifocal (n = 13) noninvasive follicular thyroid neoplasm

	n (%)	n (%)	<i>P</i>
Age, median	43	39	.267 ^a
Size IL, median (n = 73)	20	9	.035 ^{a,b}
Sex			.999 ^c
Female	48 (78.7)	11 (84.7)	
Male	13 (21.3)	2 (15.4)	
Nonneoplastic thyroid			.517 ^c
Lymphocytic thyroiditis	15 (24.6)	6 (46.2)	
NCH	46 (75.4)	7 (53.9)	
Lobe of IL (n = 73)			.999 ^c
Right	48 (80)	11 (84.6)	
Left	12 (20)	2 (15.4)	
LVI	0	0	–
ETE	0	2 (15.4)	.029 ^{b,c}
LN	0	0	–

Abbreviations: CL, contralateral lesion; IL, index lesion; LN, lymph node metastases; NCH, nodular colloid hyperplasia; PMCFV, papillary microcarcinoma follicular variant.

^a Mann-Whitney *U* test.

^b *P* < .05.

^c Fisher exact test.

classical PTC (31%), 3 were IFVPTC (19%), and 2 were NIFTP (13%). All tumors <1 cm (6 micropapillary PTC) had predominant follicular pattern, and 5 were infiltrative.

The differentiation between NIFTP and IFVPTC, as index lesions, revealed no statistically significant differences in patient age or sex or in the most affected thyroid lobe or the most frequent type of nonneoplastic lesion (Table 3). However, the IFVPTC nodules were larger than the NIFTPs (mean, 29.5 mm versus 20 mm; *P* = .031), and lymphovascular invasion (LVI) was found in 2 cases of IFVPTC (2/20 versus 0/74; *P* = .043). Despite the higher frequency of contralateral disease in NIFTP, there was no statistically significant difference in IFVPTC (17.5% NIFTP versus 15% IFVPTC).

Fifty-three percent (7/13) of the multifocal NIFTPs tended to have a minor dimension, which was more than in the than solitary lesions (average, 9 mm versus 20 mm; *P* = .035; Table 4). In the group of multifocal NIFTPs, we found that 15% (2/13) of the contralateral malignancies showed microscopic extrathyroidal extension (ETE; *P* < .05). Most of the contralateral lesions in both groups were malignant.

In the group of patients with IFVPTC, 1 of 3 with multifocal disease presented with lymph node metastasis, yet there was no statistically significant difference here or in other features compared with unifocal IFVPTC (Table 4).

4. Discussion

Despite the clearly established clinical and histologic features of well-differentiated, poorly differentiated, and undifferentiated types of follicular cell-derived carcinomas, the “less

than well-differentiated neoplasms,” namely, NIFTP and neoplasia of undetermined malignant potential, need to be better understood biologically in light of the multistep carcinogenesis theory [6]. Since the introduction of the concept of NIFTP in 2016 [1], much new knowledge about this entity has been published [2-4,8-10], and this entity was included in the fourth edition of the World Health Organization Classification of *Tumors of Endocrine Organs* [7].

These NIFTP tumors currently are interpreted as a premalignant lesion, so it is expected that other neoplastic lesions can be present elsewhere in the remaining thyroid parenchyma [2,4-6]. The current study was designed to evaluate the presence of synchronous disease in a series of NIFTP cases submitted to total thyroidectomy. Despite the limitations of a retrospective study, our cases were reviewed histologically by 3 pathologists, and the surgical specimens were extensively sampled using a protocol that ensures the sampling of the entire nodule and the interface between the tumor and adjacent parenchyma. Our incidence of NIFTP among the cases previously diagnosed as follicular variant of PTC was 2.1%, which is in the range found in previous reports [9-11].

In our study, the percentage of patients with bilateral disease was 17%. Most of the contralateral lesions were malignant, namely, papillary microcarcinoma, FVPTC, or classic PTC. There was no statistical difference between contralateral malignant lesions and the index lesion (IFVPTC and NIFTP). Nonetheless, we found a higher number of multifocal cases in the context of NIFTP, and index lesions <1 cm were associated with contralateral lesions with microscopic ETE.

There are few studies addressing multifocal and contralateral disease in the context of NIFTP, and most of the studies describe well-differentiated thyroid cancer in the era before NIFTP was identified [3,10-21]. In a study by Ibrahim and associates [12], of 39 cases of PTC with contralateral disease, 24 were FVPTC, showing that the follicular variant frequently is accompanied by bilateral disease. In a study of FVPTC by Sullivan and colleagues [20], contralateral disease was present in 35% of the 124 patients. In their series, LVI was almost 5-fold more frequent in cases with contralateral disease. Although most of these malignancies were papillary microcarcinomas, 2 cases of aggressive variants of PTC and 1 follicular carcinoma were found as high-grade malignancies in the contralateral lobe. A study by Samuels et al [21] also addressed the high prevalence of adverse clinical and pathological findings in bilateral disease in a pediatric group of FVPTC lesions, and these authors recommend total thyroidectomy in this population.

In our study, 18% (13/74) of the cases of NIFTP were associated with contralateral tumors, 11 of them being malignant: 5 PTC, 5 microcarcinoma PTCFV, and 1 IFVPTC. The other 2 tumors were NIFTPs. There were no aggressive variants of PTC or any other high-grade malignant thyroid tumors in the contralateral lesions of our cases, in contrast to other studies of contralateral findings in FVPTC [3,12-21]. One group of authors [11] reported the association of NIFTP with other tumors, such as microcarcinomas; however, there are no systematic studies using strict criteria as in this series.

Currently, hemithyroidectomy is accepted as the most appropriate diagnostic and therapeutic management of NIFTP [3,4,8,9]. In fact, the introduction of the concept of NIFTP has as one of its goals de-escalation of treatment [1,3,4,8,9]. However, there are no preoperative or intraoperative features to unveil the presence of disease in the contralateral lobe. According to recently published guidelines, the presence of clinically significant contralateral nodules, lymph node metastasis, tumor fixation, vocal cord paralysis or voice change, irregularities in the capsule, or ETE suggest a need for total thyroidectomy [4]. In addition, the patient should be informed about the possibility of a need for a second operation and should be able to express his/her willingness to undergo a hemithyroidectomy with its risk of a second operation or to have a total thyroidectomy initially. The 2015 American Thyroid Association guidelines [22,23] suggest that lobectomy is sufficient for the low-risk patient with a well-differentiated thyroid malignancy, defined as tumors >1 and <4 cm without evidence of ETE or lymph node metastases. This statement is still controversial, with some studies showing that approximately 43% of the patients undergoing lobectomy will later require completion of the thyroidectomy [24].

After the shift in the nomenclature to NIFTP in 2016 [1], the 2015 ATA Guidelines [24] Task Force published a review article on the new nomenclature of EFVPTC saying: “It is also unclear how these patients should be monitored.” Given the low risk of recurrence, the recommendations in the 2015 ATA guidelines [22] (lobectomy sufficient—remnant ablation not recommended), these general recommendations would not be different for patients with tumors classified as NIFTP. Until more long-term follow-up data are available, occasional monitoring with serum thyroglobulin assay and neck ultrasound scanning can be considered, depending on patient context, but this is not mandatory. The length of time between follow-up evaluations in NIFTP is not yet defined by the available data.

There have not been enough prospective studies to provide guidance for the surgical management of patients with suspected noninvasive EFVPTC and NIFTP [3]. Our study showed that bilateral disease is common in FVPTC in cases where the primary lesion was either NIFTP or IFVPTC, frequently in the form of invasive disease. We also demonstrated that both nodules with microscopic extrathyroidal (ETE) invasion and multifocal lesions tend to be associated with an index lesion with small dimensions more often than is true of solitary lesions. Six of the 13 NIFTP multifocal lesions in our series were <1 cm, 5 being associated with PTC (83%) in the contralateral lobe and 1 with ETE. Interestingly, we found no adverse pathologic characteristics in solitary NIFTP or IFVPTC lesions.

In conclusion, our findings reinforce previous suggestions that bilateral and multifocal disease are part of the spectrum of NIFTP neoplasms [8-11]. Until more prospective data become available, because of risk of tumor multifocality that is illustrated by our and previous cases, careful preoperative neck ultrasound scanning and appropriate use of FNA

cytology examination are critical in the management of suspected NIFTP. The extent of surgery should be guided by the ultrasound findings in both lobes, cytology results, and clinical judgment.

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