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Predictive factors of non-invasive follicular thyroid neoplasm with papillary-like nuclear features: A single-center study

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ABSTRACT

Objective: Distinguishing preoperative criteria and postoperative histological features of non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) from those of other thyroid tumors with follicular architecture and papillary nuclear features (non-NIFTP) is crucial to prevent overtreatment. In this study, we aim to identify the predictive factors of NIFTP.

Material and Methods: We conducted a retrospective study in which we collected cases of thyroid tumors with follicular architecture and papillary nuclear features diagnosed between 2012 and 2022. Clinicopathological characteristics, therapeutic modalities, and follow-up were compared between NIFTP and non-NIFTP tumors.

Results: Forty cases of NIFTP and 44 cases of non-NIFTP were identified. NIFTP accounted for 8.83% of all PTCs and 33.6% of all thyroid tumors with follicular architecture and papillary nuclear features. NIFTP was associated with younger age (p=0.005), isoechoic nodules on ultrasound (US) (p=0.004), regular contours (p=0.028), absence of microcalcifications (p=0.005), and predominance in European Thyroid Imaging Reporting and Data System 2 and 3 scores (p<0.001). They predominantly exhibited a nuclear score of 2 (p<0.001), focal nuclear abnormalities (p=0.015), and a thin capsule (p=0.004). No case of NIFTP showed distant or lymph node metastases. Multivariate analysis identified a nuclear score of 2, focal nuclear abnormalities, and a thin tumor capsule as independently associated with NIFTP.

Conclusion: Our findings demonstrated the indolent nature of NIFTP and the utility of cervical US in raising preoperative suspicion for this entity. Because findings regarding the Bethesda classification were not available in our study, a prospective multicenter study with a larger sample size and a longer follow-up period is warranted to address this limitation.

Keywords: NIFTP, thyroid cancer, clinical, pathology, follow-up

INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common malignant endocrine tumor, with its incidence and prevalence increasing worldwide (1). In Tunisia, it represents 83.2% of differentiated malignant thyroid tumors (2). The follicular variant is the second most common subtype of papillary carcinoma, it accounts for about 20% of thyroid cancers (3). It was traditionally subdivided into a non-encapsulated form that infiltrates the thyroid parenchyma and an encapsulated form. The encapsulated form was further subdivided into two variants: An invasive encapsulated variant (showing capsular and/or vascular invasion) and a non-invasive encapsulated variant (4).

Currently, the new World Health Organization (WHO) 2022 classification considers the invasive encapsulated follicular variant of papillary thyroid carcinoma (IEFVPTC) as a distinct entity among malignant tumors and no longer includes it among PTCs (4,5). In 2016, Nikiforov et al. (6,7) proposed replacing the term "non-invasive encapsulated follicular variant of papillary carcinoma" with the new term NIFTP, meaning "non-invasive follicular thyroid neoplasm with papillary-like nuclear features", because of its indolent nature and favorable prognosis. NIFTP is defined by rigorous diagnostic criteria introduced in 2016 and revised in 2018.

The introduction of NIFTP has had a major impact on therapeutic management. Indeed, the American Thyroid Association (ATA) and French learned societies

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include these nodules among lesions for which conservative management with lobectomy alone is recommended (8,9). There is growing interest in distinguishing the preoperative ultrasound and cytological characteristics of NIFTP from those of other thyroid carcinomas with follicular architecture and papillary-like nuclear features, and in identifying postoperative histological differences. This would help reduce extensive surgery and prevent unnecessary radioactive iodine treatment. This study aimed to identify predictive factors for NIFTP.

MATERIAL and METHODS

Study Design and Population

This single-center retrospective study collected cases of thyroid tumors with follicular architecture and papillary-like nuclear features that were diagnosed in the Department of Pathology between January 2012 and December 2022 and that underwent thyroid surgery in the Department of Otolaryngology-Head and Neck Surgery.

Patients who had other concomitant types of thyroid cancer or those whose clinical records or histological slides were unavailable were excluded from this study.

In this study, two population groups were defined: Patients diagnosed with NIFTP and those with non-NIFTP tumors [namely IEFVPTC, the infiltrative follicular subtype of PTC (IFPTC), and Differentiated High-Grade Thyroid Carcinoma (DHGTC)].

A favourable opinion on the conduct of this study was issued by the Ethics Committee of the Faculty of Stax (decision no: 34/24, date: 10.07.2024) which is in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual patients included in this study for the use of their clinical data. All participants were informed about the purpose of the publication, and their privacy and confidentiality were protected in accordance with ethical standards.

Data Collection and Case Definition

-Clinical, biological and ultrasonography (US) findings: Were collected from medical files and they concerned: Age, sex, personal and family history of malignant thyroid tumors, functional signs, data from clinical examination and indirect laryngoscopy, thyroid function test [free thyroxine (FT4), thyroid-stimulating hormone (TSH)], preoperative neck US data (including the number of nodules, microcalcifications, echogenicity, regular or irregular border, the presence of suspicious lymphadenopathy and the European Thyroid Imaging Reporting and Data System [(EU-TIRADS) classification (10)] and cytological data from preoperative thyroid fine-needle aspiration. Cytological reports were reclassified according to the 2023 Bethesda system (11).

-Type of surgery: The type of thyroid surgery performed with or without lymph node dissection was specified.

-Pathological criteria:

Two pathologists reexamined all pathology reports and archival histology slides in a double-blind review. Cases were reclassified according to the latest WHO 2022 classification (4,5). The diagnosis of NIFTP was made based on diagnostic criteria proposed by Nikiforov et al. (6,7) and validated by the WHO 2022 classification (4,5).

-Pathological data concerned: Tumor size, tumor location, multifocality, histological type, nuclear score [was assessed according to Nikiforov et al. (6,7)], focal or diffuse papillary-like nuclear features, mitotic index [number of mitoses per mm^2 at high magnification (×400)], encapsulated or well-circumscribed nodule, tumor capsule thickness [a capsule is considered thick if it is more than 0.2 mm thick (12)], capsular invasion (was defined as a complete penetration of the capsule), lymphovascular invasion, solid/trabecular/insular growth pattern, psammoma bodies or microcalcifications, colloid appearance, lymphocytic thyroiditis associated and lymph node metastasis.

-Adjuvant treatment and follow-up have been specified: Administration of radioactive iodine treatment or hormonal therapy, and monitoring for tumor recurrence or distant metastasis.

Follow-up duration was calculated from the date of pathological diagnosis to the date of death from any cause or the date of the last available follow-up.

Statistical Analyses

Data were analyzed using SPSS software (version 23.0). Continuous variables were presented as mean ± standard deviation when they were normally distributed and as medians with interquartile ranges when they were not normally distributed. Categorical variables were expressed as numbers and percentages.

Correlation studies to compare characteristics of NIFTP and non-NIFTP groups were performed using Pearson's chi-square test for categorical variables (when the expected value for each cell is five or higher) or Fisher's exact test. For continuous variables, we used the Student's t-test (when normality was confirmed) or the Mann-Whitney U test.

To identify factors associated with NIFTP, a multivariate logistic regression analysis was conducted, incorporating factors identified as significant in the univariate analysis, and 95% confidence intervals (CIs) were calculated.

The threshold of statistical significance was set at 5% (p-value ≤ 0.05).

RESULTS

Case Selection

A total of 84 patients were included in the study. Figure 1 presents a flow chart of our patients.

Diagnosis After Slide Reexamination and NIFTP's Rate

After reexamination of all pathology reports and archival histology slides by two pathologists cases were reclassified as follows: 40 cases of NIFTP (of which 16 were reclassified as NIFTP from 2012 until 2018), 21 cases of IEFVPTC, 22 cases of IFPTC, and one case of DHGTC.

Thus, isolated NIFTP represented 8.83% of all PTC (453 cases of PTC were diagnosed between 2012 and 2022) and 33.6% of all thyroid tumors with follicular architecture and papillary nuclear features.

Comparison of Clinical, Biological and Cytological Characteristics Between NIFTP and Non-NIFTP Groups

The clinical, biological, and cytological variables in the NIFTP and non-NIFTP groups are outlined in Table 1. The two groups differed significantly only in age. The mean age was 40.9 years (±11.4) and 49.48 years (±15.3) in the NIFTP and non-NIFTP groups respectively (p=0.005). The difference was also significant when a threshold of 55 years was used (p=0.026). The mean age of the IFPTC group was 52.59 years, which was significantly different from that of the NIFTP group (p=0.001). The mean age of the IEFVPTC group was 47.57 years (p=0.051).

Preoperative thyroid fine-needle aspiration results were available for five patients in the NIFTP group [benign (category II) in two cases, atypia of undetermined significance (category III) in two cases, and suspicious for malignancy (category V) in one case] and for twelve patients in the non-NIFTP group [malignant (category VI) or suspicious for malignancy (category V) in only 4 cases]. No statistically significant differences in cytological findings were observed between the two groups (p=0.528) (Table 1). However, the limited availability of cytological data precludes a valid comparison using the Bethesda classification.

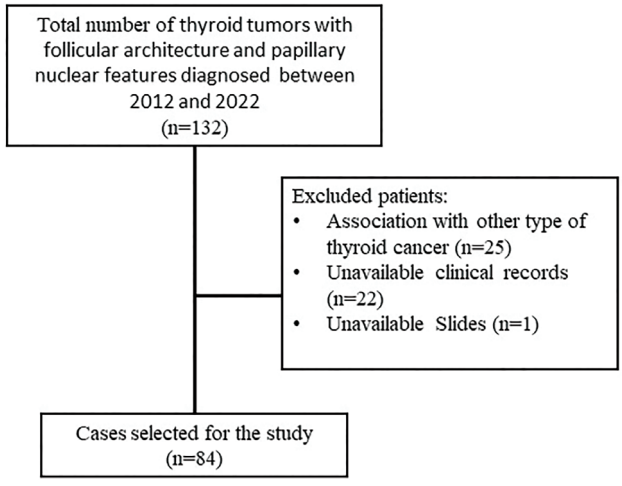

Figure 1. Flow-chart of patient's selection.

Type of Surgery

For the NIFTP group, total thyroidectomy was performed in 27 patients (67.5%) and lobectomy in 13 patients (32.5%). For the non-NIFTP group, total thyroidectomy was performed in 41 cases (93.2%) and lobectomy in 3 cases (6.8%). Seven (17.5%) of NIFTP patients and 33 (75%) of non-NIFTP patients underwent lymph node dissection.

Since the implementation of the 2015 ATA Guidelines recommending conservative management for NIFTP, rates of total thyroidectomy with lymph node dissection have decreased notably. Before 2018, 93.75% of patients with NIFTP underwent total thyroidectomy (15 out of 16 patients), while only 6.25% underwent lobo-isthmectomy (1 out of 16 patients). Lymph node dissection was carried out in 37.5% of cases. After 2018, the rate of total thyroidectomy decreased to 50% (12 out of 24 patients), and lymph node dissection was performed in only 4.2% of cases (1 out of 24 patients).

Comparison of Preoperative Neck Ultrasonographic Characteristics Between NIFTP and Non-NIFTP Groups

A preoperative neck US was performed in all patients in the NIFTP group and in 43 patients in the non-NIFTP group. Only one patient underwent a computed tomography scan to evaluate a plunging goiter. The nodule was solitary in 9 patients with NIFTP and in 11 patients with non-NIFTP.

In the US, NIFTPs were more often isoechoic (55% vs. 25.6%), whereas non-NIFTPs were predominantly very hypoechoic (27.9% vs. 5%) (p=0.004). IFPTC is significantly more often very hypoechoic than NIFTP (42.9% vs. 5%; p=0.001). IEFVPTC is more often hypoechoic than NIFTP (47.6% vs. 22.5%), but this difference is not statistically significant (p=0.63). The presence of irregular contours was significantly greater in the non-NIFTP group (p=0.028). Regular contours were observed in 92.5% of NIFTP cases and 90.5% of IEFVPTC cases. In contrast, irregular contours were observed in only 7.5% of NIFTP cases compared with 42.9% of IFPTC cases; this difference was statistically significant (p=0.002).

A significant association was found between the presence of microcalcifications and the diagnosis of non-NIFTP (p=0.005). No significant difference was observed between the two groups in the presence of suspicious lymphadenopathy on US.

Applying the EU-TIRADS classification, a significant difference between NIFTPs and non-NIFTPs was observed. 67.4% of non-NIFTPs were grouped in scores 4 and 5, and 77.5% of NIFTPs were

Table 1. Clinical, biological and cytological characteristics of NIFTP and non-NIFTP groups				
		NIFTP	**Non-NIFTP**	**p-value**
Age	Mean, years (±SD)	40.9 (±11.4)	49.48 (±15.3)	**0.005**
	≥55 years, n (%)	6 (15)	16 (36.4)	**0.026**
	<55 years, n (%)	34 (85)	28 (63.6)	
Sex	Female, n (%)	34 (85)	37 (84.1)	0.908
	Male, n (%)	6 (15)	7 (15.9)	
Family history of thyroid cancer	Present, n (%)	2 (5)	3 (6.8)	0.546
	Absent, n (%)	38 (95)	41 (93.2)	
Clinical presentation	Nodule, n (%)	36 (90)	34 (77.3)	0.130
	Incidental discovery, n (%)	3 (7.5)	10 (22.7)	
	Hyperthyroidism, n (%)	1 (2.5)	0	
Signs of compression	Present, n (%)	14 (35)	16 (36.4)	0.896
	Absent, n (%)	26 (65)	28 (63.6)	
Thyroid loge examination	Normal, n (%)	3 (7.5)	8 (18.2)	0.328
	Single nodule, n (%)	31 (77.5)	29 (65.9)	
	Multiple nodules, n (%)	6 (15)	7 (15.9)	
Indirect laryngoscopy	Vocal cord paralysis, n (%)	0	2 (5.4)	0.182
	Without abnormality, n (%)	32 (100)	35 (94.6)	
Thyroid function test	Euthyroidism, n (%)	38 (95)	41 (97.6)	0.587
	Hypothyroidism, n (%)	1 (2.5)	1 (2.4)	
	Hyperthyroidism, n (%)	1 (2.5)	0	
Bethesda category	I, II, III and IV, n (%)	4 (80)	8 (66.7)	0.528
	V and VI, n (%)	1 (20)	4 (33.3)	

SD: Standard deviation, NIFTP: Neoplasm with papillary-like nuclear features.

grouped in scores 2 and 3. No non-NIFTP nodule is classified as EU-TIRADS 2 in our series. A single NIFTP nodule was classified as EU-TIRADS 2, and six were classified as EU-TIRADS 5 (Table 2).

Comparison of Histopathological Characteristics Between NIFTP and Non-NIFTP Groups

The histopathological characteristics and differences between NIFTP and non-NIFTP groups are summarized in Table 3. The main differences between NIFTP and IEFVPTC are presented in Table 4, while the key differences between NIFTP and IFPTC are outlined in Table 5.

Nuclear score 3 was significantly more prevalent in the non-NIFTP group (59.1%), whereas NIFTP cases predominantly exhibited nuclear score 2 (87.5%) (p<0.001) (Figure 2a and 2b). Additionally, nuclear abnormalities were diffuse in 59.1% of non-NIFTP cases but focal in 67.5% of NIFTP cases (p=0.015).

Regarding encapsulation, 35 NIFTP and 22 non-NIFTP cases demonstrated encapsulation (21 cases of IEFVPTC and one case of DHGTC). A thin capsule was significantly more common in NIFTP cases (57.1%) than in non-NIFTP cases (18.2%) (p=0.004) (Figure 2c and 2d). Figure 3 illustrates capsular invasion in an IEFVPTC case.

Among the non-NIFTP tumors, ten exhibited lymphovascular invasion (22.7%) (Figure 4). Figure 5 illustrates extrathyroidal extension observed in a case of IEFVPTC.

For the NIFTP group, no lymph node metastases were found in the seven patients who underwent lymph node dissection. In the non-NIFTP group, ten tumors (22.7%) presented lymph node metastases; of these, three cases (30%) had capsular rupture. This difference was statistically significant (p=0.001).

Adjuvant Treatment and Follow-up

Levothyroxine-based hormone therapy was prescribed in 26 cases of NIFTP and 43 cases of non-NIFTP. Radioactive iodine treatment was administered to 12 patients (30%) diagnosed with NIFTP and to 29 patients (65.9%) diagnosed with non-NIFTP tumors. No patient received adjuvant treatment with radioactive iodine after 2018.

For the NIFTP and non-NIFTP groups, the median follow-up durations after surgery were 16 and 25 months, respectively.

None of the NIFTP cases showed distant metastases. Among non-NIFTP cases, metastases were detected in two cases (4.54%). In one case, metastasis occurred in the parotid gland 16 months after diagnosis, while in the second case pulmonary metastasis

developed a decade later. Among the 84 patients in our study, only one patient diagnosed with IFPTC experienced a lymph node relapse with capsular rupture and skin infiltration after a postoperative period of 6 years.

Multivariate Analysis of Parameters Associated with NIFTP

In this analysis, a nuclear score of 2, focal nuclear abnormalities, and a thin tumor capsule were independently related to NIFTP. Age under 55 years and regular border status in the US tended to be statistically significant (Table 6).

DISCUSSION

Our study identified some predictive factors for NIFTP that can guide the preoperative diagnostic approach. Indeed, in young patients with specific cervical US findings (isoechoic nodules, absence of microcalcifications, regular borders, and an EU-TIRADS score of 2 or 3), the diagnosis of NIFTP is strongly suggested. Additionally, the analytical study confirmed the strong association of nuclear grade 2, focal nuclear features, and a thin capsule with the diagnosis of NIFTP. The benign profile of NIFTP was also demonstrated in our series.

After a review of histological slides, we found a rate of 33.6% for thyroid tumors with follicular architecture and papillary nuclear features, and 8.83% for PTC. The global rate reported in the literature varies significantly. According to a meta-analysis, NIFTP accounted for approximately 6% of all PTC, with considerable heterogeneity among included studies (CI: 4.4-8.2). The frequency of NIFTP was higher in North America (9.3%) and Europe (9.6%) compared to Asia (approximately 2.1%) (13). The frequency of NIFTP was 16.9% of all thyroid tumors with follicular architecture and papillary nuclear features and 1.54% of all PTC in the study of Richard et al. (14) covering 40 years. In another meta-analysis including 1563 cases of NIFTP from 29 studies, its frequency among all thyroid tumors with follicular architecture and papillary nuclear features was 43.5% and 4.4% among PTC (15).

These figures reflect changes over time and may vary by study populations and methodologies. Many specimens couldn't be evaluated for capsular invasion because of limitations in slide assessment inherent to the study's retrospective design.

Limited information is available for comparing clinical and biological characteristics between the two groups. In the study of Singh et al. (16) 21 patients with NIFTP were also significantly younger than 153 patients with non-NIFTP (p=0.023).

In other studies, there was no significant disparity in age observed between the two groups of patients (17,18). Female predominance was observed in all studies, including the multi-institutional study by Chereau et al. (19) with 76% of women among 363 NIFTP cases; in the canadian study by Larouche et al. (17) there wasn't a significant difference between the two groups. This aligns with our findings: 85% of cases in the NIFTP group and 84.1% in the non-NIFTP group were women. (18,19). The clinical presentation and the laboratory findings of NIFTP are non-specific and similar to those of other thyroid neoplasms (20,21), which explains the absence of significant differences in terms of clinical symptoms and biological analysis between the two study groups.

The aim of comparative studies between these two tumor groups was primarily to highlight the advantages of cytology and cervical US to facilitate preoperative diagnosis of these tumors. The goal is to mitigate the risk of unnecessary surgical procedures.

Table 2. Preoperative neck ultrasonography characteristics of NIFTP and non-NIFTP groups

		NIFTP	Non-NIFTP	p-value
Echogenicity	Hypoechoic, n (%)	9 (22.5)	16 (37.2)	**0.004**
	Strong hypoechogenicity, n (%)	2 (5)	12 (27.9)	
	Isoechoic, n (%)	22 (55)	11 (25.6)	
	Hyperechoic, n (%)	7 (17.5)	4 (9.3)	
Regular border	Present, n (%)	37 (92.5)	32 (74.4)	**0.028**
	Absent, n (%)	3 (7.5)	11 (25.6)	
Microcalcification	Present, n (%)	2 (5)	12 (27.9)	**0.005**
	Absent, n (%)	38 (95)	31 (72.1)	
Suspicious lymphadenopathy	Present, n (%)	6 (15)	9 (20.5)	0.514
	Absent, n (%)	34 (85)	35 (79.5)	
EU-TIRADS	Scores 2 and 3	31 (77.5)	14 (32.6)	**<0.001**
	Scores 4 and 5	9 (22.5)	29 (67.4)	

NIFTP: Neoplasm with papillary-like nuclear features, EU-TIRADS: European Thyroid Imaging Reporting and Data System.

Cervical US is the gold standard for evaluating thyroid nodules, as it enables preoperative nodule characterization and malignancy risk stratification based on the EU-TIRADS classification. Our study revealed significant disparities in US nodule characteristics between the NIFTP and non-NIFTP groups. Similar findings were reported in the study by Hahn et al. (22), which included 34 NIFTPs and 174 non-NIFTPs. Compared with non-NIFTP cases, NIFTPs were more commonly hyperechoic or isoechoic (p=0.043), exhibited regular borders (p=0.001), and lacked calcifications (p=0.031). Similarly, the review by Yang et al. (23), reported that NIFTPs typically exhibited well-circumscribed, oval/round nodules with a hypoechoic rim, often accompanied by hypervascularity on Doppler imaging. In contrast, IEFVPTCs were characterized by hypoechogenicity with irregular or lobulated margins and frequently displayed hypervascularity on Doppler. The US characteristics of IFPTCs included at least one malignant grayscale feature, such as marked hypoechoicity, a taller-than-wide shape, microcalcifications, or blurred margins. Doppler imaging in this group commonly showed avascularity. In a study by Boursier et al. (21), 77% of nodules corresponding to NIFTP were classified as EU-TIRADS 2, 3 or 4, while 84.5% of nodules corresponding to non-NIFTP were classified as EU-TIRADS 5. The difference between the two groups was statistically significant (p<0.001). In our study, 77.5% of NIFTPs had EU-TIRADS scores 2 and 3. However, in a Canadian study, including 44 NIFTP and 159 patients in the non-NIFTP group, there was no statistically

Table 3. Histopathological and clinical characteristics of NIFTP and non-NIFTP groups

		NIFTP	Non-NIFTP	p-value
Tumor size	Mean, mm (±SD)	24.18 (±21.52)	21.90 (±28.36)	0.205
	≥4 cm, n (%)	9 (22.5)	9 (20.5)	0.329
	<4 cm, n (%)	31 (77.5)	35 (79.5)	
Tumor location	Bilateral, n (%)	5 (12.5)	8 (18.2)	0.888
	Right lobe, n (%)	19 (47.5)	21 (47.7)	
	Left lobe, n (%)	15 (37.5)	14 (31.8)	
	Isthmus, n (%)	1 (2.5)	1 (2.3)	
Multifocality	Present, n (%)	7 (17.5)	10 (22.7)	0.551
	Absent, n (%)	33 (82.5)	36 (77.3)	
Nuclear score	Score 2, n (%)	35 (87.5)	18 (40.9)	**<0.001**
	Score 3, n (%)	5 (12.5)	26 (59.1)	
Nuclear features	Diffuse, n (%)	13 (32.5)	26 (59.1)	**0.015**
	Focal, n (%)	27 (67.5)	18 (40.9)	
Mitosis	Present, n (%) Range/2 mm^2	12 (30) 0-2	11 (25) 0-6	0.608
	Absent, n (%)	28 (70)	33 (75)	
Tumor capsule thickness	Thin, n (%)	20 (57.1)	4 (18.2)	**0.004**
	Thick, n (%)	15 (42.9)	18 (81.8)	
Solid/trabecular/insular growth pattern	Present, n (%)	6 (15)	8 (18.2)	0.696
	Absent, n (%) % of the nodule	34 (85) 5-10%	36 (81.8) 5-40%	
Dense colloid	Present, n (%)	29 (72.5)	30 (68.2)	0.666
	Absent, n (%)	11 (27.5)	14 (31.8)	
Lymphocytic thyroiditis associated	Present, n (%)	8 (20)	14 (31.8)	0.219
	Absent, n (%)	32 (80)	30 (68.2)	
Lymph node metastasis	Present, n (%)	0	10 (22.7)	**0.001**
	Absent, n (%)	7 (100)	34 (77.3)	
Type of surgery	Total thyroidectomy, n (%)	27 (67.5%)	41 (93.2%)	**0.003**
	Lobo-isthmectomy	13 (32.5%)	3 (6.8%)	
Lymph node dissection		7 (17.5%)	33 (75%)	**<0.001**

SD: Standard deviation, NIFTP: Neoplasm with papillary-like nuclear features.

Table 4. Comparison of characteristics between NIFTP and IEFVPTC				
		NIFTP	**IEFVPTC**	**p-value**
Echogenicity	Hypoechoic, n (%)	9 (22.5%)	10 (47.6%)	0.063
	Strong hypoechogenicity, n (%)	2 (5%)	3 (14.3%)	
	Isoechoic, n (%)	22 (55%)	7 (33.3%)	
	Hyperechoic, n (%)	7 (17.5%)	1 (4.8%)	
EU-TIRADS	Scores 2 and 3	31 (77.5%)	7 (33.3%)	0.001
	Scores 4 and 5	9 (22.5%)	14 (66.7%)	
Microcalcifications	Present, n (%)	2 (5%)	6 (28.6%)	0.016
	Absent, n (%)	38 (95%)	15 (71.4%)	
Nuclear score	Score 2, n (%)	35 (87.5%)	13 (61.9%)	0.045
	Score 3, n (%)	5 (12.5%)	8 (38.1%)	
Nuclear features	Diffuse, n (%)	13 (32.5%)	10 (47.6%)	0.247
	Focal, n (%)	27 (67.5%)	11 (52.4%)	
Tumor capsule thickness	Thin, n (%)	25 (62.5%)	4 (19%)	0.001
	Thick, n (%)	15 (37.5%)	17 (81%)	
Lymph node metastasis	Present, n (%)	0	3 (14.3%)	0.037
	Absent, n (%)	40 (100%)	18 (85.7%)	

NIFTP: Neoplasm with papillary-like nuclear features, EU-TIRADS: European Thyroid Imaging Reporting and Data System, IEFVPTC: Invasive encapsulated follicular variant of papillary thyroid carcinoma.

Table 5. Comparison of characteristics between NIFTP and IFPTC				
		NIFTP	**IFPTC**	**p-value**
Echogenicity	Hypoechoic, n (%)	9 (22.9%)	6 (28.6%)	**0.001**
	Strong hypoechogenicity, n (%)	2 (5%)	9 (42.9%)	
	Isoechoic, n (%)	22 (55%)	4 (19%)	
	Hyperechoic, n (%)	7 (17.5%)	2 (9.5%)	
EU-TIRADS	Scores 2 and 3	31 (77.5%)	6 (28.6%)	**0.000**
	Scores 4 and 5	9 (22.5%)	15 (71.4%)	
Microcalcifications	Present, n (%)	2 (5%)	6 (28.6%)	**0.016**
	Absent, n (%)	38 (95%)	15 (71.4%)	
Nuclear score	Score 2, n (%)	35 (87.5%)	4 (18.2%)	**0.000**
	Score 3, n (%)	5 (12.5%)	18 (81.8%)	
Nuclear features	Diffuse, n (%)	13 (32.5%)	16 (72.7%)	**0.002**
	Focal, n (%)	27 (67.5%)	6 (27.3%)	
Lymph node metastasis	Present, n (%)	0	7 (31.8%)	**0.000**
	Absent, n (%)	40 (100%)	15 (68.2%)	

NIFTP: Neoplasm with papillary-like nuclear features, EU-TIRADS: European Thyroid Imaging Reporting and Data System, IFPTC: Infiltrative follicular subtype of PTC, PTC: Papillary thyroid carcinoma.

significant difference when comparing US characteristics between the two study groups (17).

Cytological findings are also informative in thyroid pathology, but they remain insufficient for a definitive diagnosis and for distinguishing NIFTP from other thyroid tumors with follicular architecture and papillary nuclear features. In a study conducted by Boursier et al. (21), a notable distinction was observed between the two groups: NIFTP cases were mainly classified according to the Bethesda classifications III (27.3%), IV (18.2%), and V (36.4%). Conversely, most of the non-NIFTP cases fell into categories V (49%) and VI (28.6%) of the Bethesda classification system (p=0.004). In the study of Jang et al. (24) both the NIFTP

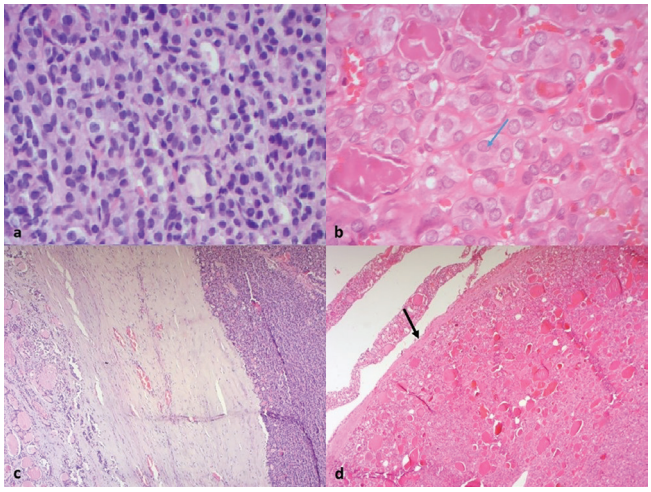

Figure 2. a: NIFTP tumor with nuclear score 2 (HE*200), b: NIFTP tumor with nuclear score 3 (HE*400, note: pseudo-inclusion in blue arrow), c: Thick capsule in a NIFTP tumor (HE*50), d: Thin capsule in a NIFTP tumor (black arrow) (HE*50).

NIFTP: Neoplasm with papillary-like nuclear features, HE: Hematoxylin and eosin.

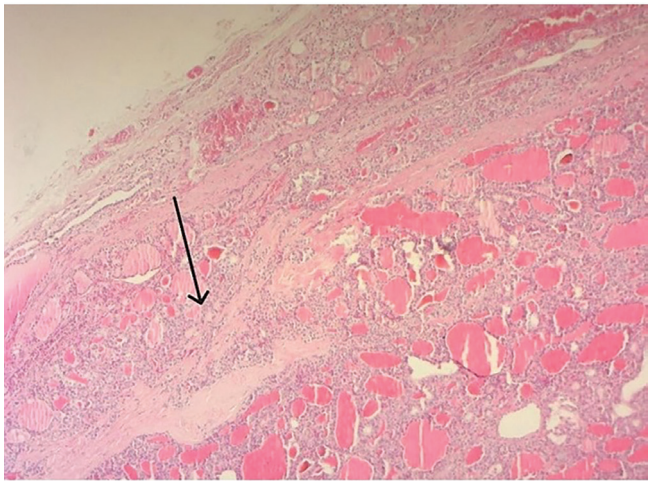

Figure 3. Capsular invasion in IEFVPTC (black arrow) (HE*50).

IEFVPTC: Invasive encapsulated follicular variant of papillary thyroid carcinoma, HE: Hematoxylin and eosin.

and IEFVPTC groups exhibited relatively benign characteristics, with a majority of patients categorized under Bethesda category III [(25.8% and 25.6%, respectively) or IV (34.8% and 30.2%, respectively)]; in contrast, the IFPTC group demonstrated more malignant features, with a higher proportion of patients falling into category V (28.6%) or VI (47.6%) ($p<0.001$) (24). Ruanpeng et al.'s (15) meta-analysis revealed that the majority of NIFTP cases reported in the literature are identified within the III (34.2%), IV (22.7%), and V (22.4%) categories. In other studies, there was no significant difference in Bethesda categories between NIFTPs and non-NIFTPs (17). As in our study, this result was observed, likely because of the low number of cytology tests performed.

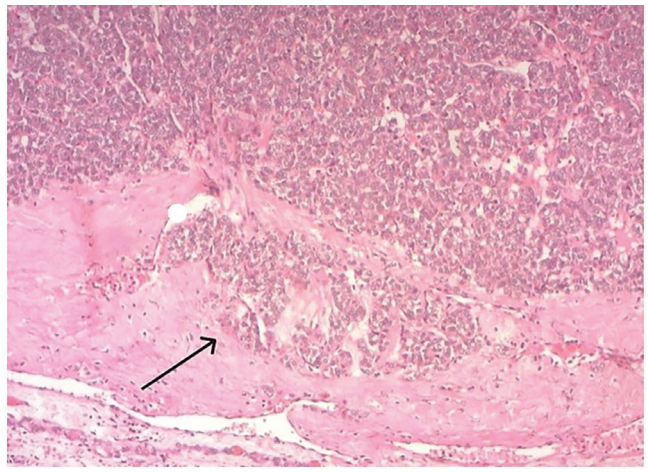

Figure 4. Angioinvasion in IEFVPTC (HE*100).

IEFVPTC: Invasive encapsulated follicular variant of papillary thyroid carcinoma, HE: Hematoxylin and eosin.

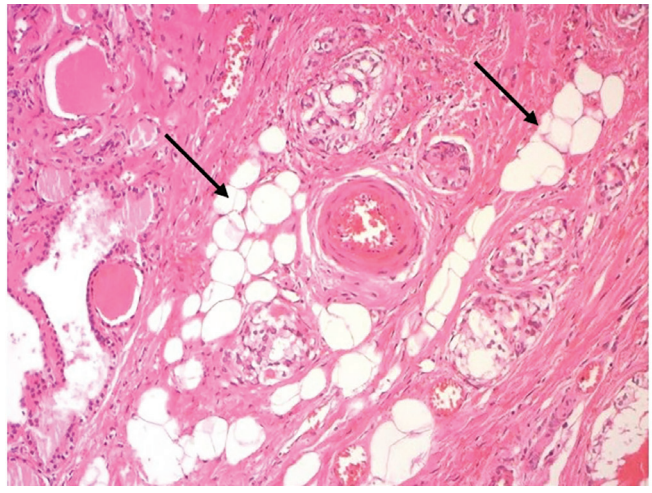

Figure 5. Extrathyroid extension in IEFVPTC (black arrows indicating adipocytes) (HE*100).

IEFVPTC: Invasive encapsulated follicular variant of papillary thyroid carcinoma, HE: Hematoxylin and eosin.

Focusing on histopathological characteristics that could predict the diagnosis of NIFTP is crucial to avoid subjectivity in the analysis of thyroid nodules. In 2022, in an Italian study conducted by Vignali et al. (25) including 451 NIFTP cases, 85.4% of these lesions exhibited a nuclear score of 2, while only 14.6% had a nuclear score of 3. Moreover, a review suggests that the papillary-like nuclear features of NIFTP are generally more subtle than those of PTC and can present as focal, diffuse, or multifocal. These nuclear features tend to be more pronounced at the periphery of the tumor, especially in the subcapsular area and in the more cellular or microfollicular zones. Intranuclear inclusions are also inconspicuous and rare in NIFTP (26).

Table 6. Multivariable logistic regression adjusted odds ratios for NIFTP			
Variable	**Odds ratio**	**95% CI**	**p-value**
Age <55 years-old	6.633	(0.826-53.273)	0.075
Echogenicity	1.061	(0.122-9.211)	0.957
Regular border	0.067	(0.004-1.184)	0.065
Microcalcification	6.030	(0.399-91.137)	0.195
EU-TIRADS score 2 or 3	0.000	(0.000-0)	0.999
Nuclear score 2	0.018	(0.002-0.175)	**<0.001**
Focal nuclear features	0.106	(0.020-0.558)	**0.008**
Thin tumor capsule	15.342	(2.134-110.286)	**0.007**
Lymph node metastasis	0.000	(0.000-0)	1.000
CI: Confidence interval, EU-TIRADS: European Thyroid Imaging Reporting and Data System, NIFTP: Neoplasm with papillary-like nuclear features.			

The revised criteria by Nikiforov et al. (6,7) emphasize that NIFTP is often characterized by moderately expressed papillary-like nuclear features (nuclear score 2). A nuclear score of 3 should raise concerns about the diagnosis of NIFTP and may suggest a variant of papillary carcinoma. It is recommended to thoroughly examine the entire tumor capsule in cases with pronounced papillary-like nuclear features (nuclear score 3) and to assess the whole tumor to rule out the presence of papillary structures (7,27). In a study conducted by French et al. (12) that included 92 lesions, 39 NIFTPs, 15 non-invasive EFVPTCs, and 38 IEFVPTCs, a statistically significant difference in capsular thickness was noted among these neoplasms. The tumor capsule was significantly thinner in NIFTPs, with a mean thickness of 0.08 mm (p=0.022), and significantly thicker in IEFVPTCs, with a mean thickness of 0.53 mm (p=0.0006). This study concluded that a capsule thickness greater than 0.2 mm should raise suspicion of encapsulated FVPTC and prompt a more meticulous evaluation of the tumor by conducting additional section levels to ensure that a small focus of invasion was not overlooked before considering a diagnosis of NIFTP (12).

In our study, none of the NIFTP cases exhibited lymph node metastases, whereas 22.7% of non-NIFTP cases demonstrated metastases—findings that align with several previous reports (28-30). This indolent behavior extended into our follow-up period, during which no NIFTP cases showed distant metastases, in contrast to two in the non-NIFTP group. While the majority of literature supports this low-risk clinical course (15,19,30), controversies regarding the non-malignant behavior of these tumors persist. Some studies have documented lymph node involvement in NIFTP patients (24,31,32), and Parente et al. (31) reported that among 102 cases, one patient developed pulmonary metastasis and five were diagnosed with nodal metastasis over an average follow-up of 5.7 years.

According to Rosario et and Mourão (33), the presence of these metastases does not necessarily confirm potential for dissemination and may be attributable to various factors. It could result from insufficient sampling of the entire tumor and capsule in some retrospective studies. Secondly, microcarcinomas that went undetected by US examination of the remaining lobe in lobectomy patients or that were missed on histological slides might contribute to these metastases. Additionally, another possibility could be the regression of the microcarcinoma after the formation of metastases (33).

After the histopathological diagnosis of NIFTP, completion thyroidectomy or radioactive iodine treatment is not necessary (34). In a study by You et al. (35), total thyroidectomy was less frequently performed for NIFTP compared to non-NIFTP cases (48.9% versus 69.1%). This trend can be attributed to the findings of fine needle aspiration, which often falls into the Bethesda categories III and IV, as well as the absence of preoperative lymph node metastases, directing the therapeutic approach towards lobectomy.

To our knowledge, this is the first study in our country to identify the clinical, US, cytological, and histopathological predictive factors for NIFTP and to compare its characteristics with those of other thyroid tumors with follicular architecture and papillary nuclear features. A double-blind re-evaluation of all histological slides from cases presenting vesicular architecture with papillary-type nuclear atypia over an 11-year period was performed by two pathologists. These cases were reclassified according to the latest WHO classification of 2022. We conducted a univariate statistical analysis supplemented by a multivariate analysis, which yielded important results that can guide clinicians and pathologists in the management of these tumors.

Study Limitations

However, our study is subject to several limitations due to its retrospective design. There may be uncertainty regarding the inclusion of all tumors presenting the characteristics of NIFTP before the introduction of this entity. Additionally, the relatively small number of patients included and the missing data further contribute to the limitations of our study. The relatively short

follow-up period, compared to other studies, is a limitation of our study and limits the evaluation of long-term survival data.

CONCLUSION

O ur study reaffirms the indolent nature of NIFTP. Furthermore, we demonstrated the usefulness of cervical US in suspecting NIFTP preoperatively and in guiding therapeutic decisions. However, our study did not yield significant results regarding the Bethesda classification; a prospective multicenter study with a larger sample size and a longer follow-up period is needed.

Ethics

Ethics Committee Approval: A favourable opinion on the conduct of this study was issued by the Ethics Committee of the Faculty of Stax (decision no: 34/24, date: 10.07.2024) which is in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent: Informed consent was obtained from all individual patients included in this study for the use of their clinical data.

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Footnotes

Author Contributions

Concept - S.M., R.K., T.S.B.; Design - S.M., R.K., T.S.B.; Data Collection or Processing - Y.L.; Analysis or Interpretation - Y.L.; Literature Search - Y.L.; Writing - S.M., M.T., M.Z., F.K., N.G., T.S.B., I.C., M.M.

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