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RESEARCH ARTICLE

Preoperative Predictors of Coexistent Papillary Thyroid Carcinoma in Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features

Papiller Benzeri Nükleer Özellikler Gösteren Noninvaziv Foliküler Tiroid Neoplazilerinde Eşlik Eden Papiller Tiroid Karsinomu için Preoperatif Öngördürücü Faktörler

Muhammet Kocabas[1], Yusuf Ozturk[2]

[1]Necmettin Erbakan University, Faculty of Medicine, Department of Endocrinology and Metabolism, Konya, Türkiye
[2]Sakarya University, Faculty of Medicine, Department of Endocrinology and Metabolism, Sakarya, Türkiye

ABSTRACT

Objective: To evaluate the clinical, ultrasonographic, and cytological characteristics of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) and to identify preoperative factors associated with coexistent papillary thyroid carcinoma (PTC).

Materials and Methods: This retrospective study included a total of 115 patients histopathologically diagnosed with NIFTP after thyroidectomy. Demographic, ultrasonographic, cytological, and pathological data were analyzed. Nodules were classified according to the European Thyroid Imaging and Reporting Data System (EU-TIRADS) and the Bethesda cytology categories. The patients were divided into two groups: "NIFTP without coexistent PTC" and "NIFTP with coexistent PTC". Comparative and logistic regression analyses were performed to identify predictors of concomitant PTC.

Results: The mean age was 46.78±13.98 years, and 74.8% were female. The mean size of NIFTP nodules was 23.15±16.70 mm. According to the EU-TIRADS classification, 44.3% of nodules were category 3, 14.8% category 4, and 37.4% category 5. Cytology results were most frequently Bethesda I (27.0%), II (32.2%), and III (24.3%). Coexistent PTC was identified in 33 patients (28.7%). In the results of univariate analysis, smaller nodule size (OR 0.956, 95% CI 0.924-0.990, p = 0.010) was significantly associated with coexistent PTC, while EU-TIRADS category 5 (OR 2.288, 95% CI 1.002-5.228, p = 0.050) showed borderline significance. In multivariate analysis, only smaller nodule size remained an independent predictor (OR 0.951, 95% CI 0.909-0.995, p = 0.030).

Conclusion: Smaller nodule size was found to independently predict coexistent PTC in NIFTP, whereas suspicious sonographic features such as solid composition, presence of a halo, or high EU-TIRADS scores were not independent predictors. Careful evaluation of smaller nodules may improve preoperative risk stratification and guide surgical decision-making.

Keywords: Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), papillary thyroid carcinoma (PTC), thyroid nodule, nodule size, predictive factors

ÖZET

Amaç: Papiller benzeri nükleer özellikler gösteren noninvaziv foliküler tiroid neoplazisi (NIFTP) olgularının klinik, ultrasonografik ve sitolojik özelliklerini değerlendirmek ve papiller tiroid karsinomunun (PTK) eşlik etmesi ile ilişkili preoperatif faktörleri belirlemek.

Gereç ve Yöntemler: Bu retrospektif çalışmaya tiroidektomi sonrası histopatolojik olarak NIFTP tanısı konulan 115 hasta dâhil edildi. Demografik, ultrasonografik, sitolojik ve patolojik veriler analiz edildi. Nodüller, Avrupa Tiroid Görüntüleme Raporlama ve Veri Sistemi (EU-TIRADS) ve Bethesda sitoloji sınıflamasına göre değerlendirildi. Hastalar "PTK eşlik eden NIFTP" ve "PTK eşlik etmeyen NIFTP" olarak iki gruba ayrıldı. Eşzamanlı PTK'yi öngördüren faktörleri belirlemek için karşılaştırmalı ve lojistik regresyon analizleri yapıldı.

Bulgular: Hastaların ortalama yaşı 46.78±13.98 yıl olup %74.8'i kadındı. NIFTP nodüllerinin ortalama boyutu 23.15±16.70 mm idi. EU-TIRADS sınıflamasına göre nodüllerin %44.3'ü kategori 3, %14.8'i kategori 4 ve %37.4'ü kategori 5 olarak değerlendirildi. Sitoloji sonuçları en sık Bethesda I (%27.0), II (%32.2) ve III (%24.3) olarak raporlandı. Otuz üç hastada (%28,7) eşzamanlı PTK saptandı. Tek değişkenli analizde küçük nodül boyutu (OR 0.956, %95 GA 0.924–0.990, p=0.010) eşlik eden PTK ile anlamlı şekilde ilişkili bulunurken, EU-TIRADS kategori 5 (OR 2.288, 95% GA 1.002-5.228, p=0.050) sınırda anlamlılık gösterdi. Çok değişkenli analizde ise yalnızca küçük nodül boyutu bağımsız bir öngördürücü olarak kaldı (OR 0.951, 95% GA 0.909-0.995, p=0.030).

Sonuç: NIFTP olgularında, daha küçük nodül boyutu eşlik eden PTK'nin bağımsız bir öngördürücüsü olarak saptanırken; solid kompozisyon, halo varlığı veya yüksek EU-TIRADS skorları gibi şüpheli sonografik özellikler ise bağımsız öngördürücüler olarak bulunmadı. Küçük nodüllerin dikkatli değerlendirilmesi, preoperatif risk sınıflandırmasının geliştirilmesine ve cerrahi karar sürecinin yönlendirilmesine katkı sağlayabilir.

Anahtar Kelimeler: Papiller benzeri nükleer özellikler gösteren noninvaziv foliküler tiroid neoplazisi (NIFTP), papiller tiroid karsinomu (PTK), tiroid nodülü, nodül boyutu, öngördürücü faktörler

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Corresponding Author: Muhammet Kocabas, Necmettin Erbakan University, Faculty of Medicine, Department of Endocrinology and Metabolism, Konya, Türkiye
e-mail: mhmmt03@gmail.com

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INTRODUCTION

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), recognized in 2016 as a reclassified form of noninvasive encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC), represents a distinct diagnostic category within thyroid pathology (1). The 2016 reclassification was prompted by evidence that these tumors exhibit a remarkably indolent course, with an exceedingly rare likelihood of recurrence or metastasis, thereby differentiating them from classical papillary thyroid carcinoma (PTC) (1, 2).

The recognition of NIFTP as a separate entity has considerably affected diagnostic terminology, operative strategies, and clinical follow-up practices. Considering that these lesions lack invasive features and high-risk molecular alterations (e.g., BRAF V600E mutation), they are now regarded as borderline neoplasms—biologically indolent, yet not entirely within the spectrum of benign thyroid disease (1, 3, 4). Therefore, precise recognition of NIFTP is crucial to avoid unnecessary aggressive treatment and to mitigate the emotional and clinical burden that often accompanies a "cancer" diagnosis (1, 5).

Despite these advances, distinguishing NIFTP from other follicular-patterned thyroid neoplasms before surgery remains challenging. Cytological evaluation through fine-needle aspiration biopsy (FNAB) frequently results in indeterminate classifications (Bethesda III or IV), primarily because of overlapping features with follicular adenoma and encapsulated PTC (6, 7). Similarly, since NIFTP nodules rarely display microcalcifications, irregular margins, or other high-risk echogenic features characteristic of malignant disease, sonographic assessment typically yields indeterminate impressions (8, 9).

Although NIFTP generally follows an indolent clinical course, several reports documented its coexistence with PTC, either within the same lobe or contralaterally, in roughly 15–46% of patients (10 - 13). Although the clinical relevance of this coexistence is not yet fully understood, it may influence surgical decision-making, particularly the choice between lobectomy and total thyroidectomy, as well as long-term follow-up protocols (14). Therefore, a comprehensive understanding of the clinical, cytological, and imaging determinants of concomitant PTC is critical to refine management strategies and to avoid unwarranted therapeutic procedures.

To clarify these issues, the present study aimed to evaluate the clinical, ultrasonographic, and cytological profiles of patients with NIFTP and to determine factors associated with the coexistence of PTC. We also investigated whether specific preoperative ultrasonographic parameters, including nodule size, composition, echogenicity, margin regularity, shape, calcification pattern, presence of a halo, and European Thyroid Imaging and Reporting Data System (EU-TIRADS) score, could serve as predictors of coexisting PTC. By elucidating these associations, this study aims to refine preoperative risk stratification and facilitate more individualized surgical decision making when NIFTP is considered in the differential diagnosis.

MATERIALS AND METHODS

Study Design and Population

This retrospective observational study included patients who underwent thyroidectomy at a tertiary referral center between January 2019 and April 2025. Among all patients who had thyroidectomy during this period, those diagnosed histopathologically with NIFTP were identified and included in the sample.

Patients with incomplete ultrasonographic, cytological, or histopathological data were excluded. Ultimately, a total of 115 patients with confirmed NIFTP were enrolled in the analysis.

Data Collection

Clinical, radiological, cytological, and histopathological data collected from institutional electronic medical records were retrospectively reviewed. Demographic variables such as age and sex, and ultrasonographic features including nodule size (maximum diameter in millimeters), composition (solid, mixed cystic, spongiform, or completely cystic), echogenicity (hypoechoic, isoechoic, or hyperechoic), margin regularity, shape (taller-than-wide or wider-than-tall), calcification pattern (microcalcification, macrocalcification, or peripheral), presence of a halo, and EU-TIRADS category were recorded.

The results of FNAB, categorized according to the Bethesda System, the type of surgery performed (total thyroidectomy or hemithyroidectomy), histopathological findings such as NIFTP focality (unifocal or multifocal), coexistence of PTC (in the same or contralateral lobe), and follow-up data including recurrence status were also collected.

The patients were divided into two groups according to the presence of coexistent PTC: those with NIFTP without coexistent PTC (Group 1) and those with NIFTP and coexistent PTC (Group 2). Comparisons among these groups were performed in terms of demographic, ultrasonographic, and cytological characteristics.

Ultrasonographic Evaluation

All thyroid ultrasonography examinations were performed using high-resolution ultrasound devices by an experienced endocrinologist. Each nodule's ultrasonographic features were recorded according to the EU-TIRADS criteria. When multiple nodules were present, the index nodule was defined as the one corresponding to the histopathological NIFTP lesion.

FNAB

FNAB was performed under ultrasound guidance with a 25-gauge needle. Cytological findings were categorized using the Bethesda system (I–VI). For the patients with multiple nodules, the FNAB result corresponding to the nodule that was later identified as NIFTP on pathology was used for the subsequent analysis.

Histopathological Evaluation

All surgical specimens were reviewed by experienced pathologists. NIFTP diagnosis was made based on the diagnostic framework outlined by the World Health Organization (WHO) (15) and the Endocrine Pathology Society (16). These criteria require that the lesion is encapsulated or clearly demarcated from the surrounding thyroid parenchyma, exhibits a predominantly follicular growth pattern, and

displays the characteristic nuclear features of PTC. In addition, the absence of capsular or vascular invasion, tumor necrosis, or increased mitotic activity is mandatory for the diagnosis.

All cases showing invasive features or true papillary structures were excluded. The presence, location, and histological subtype of any coexisting PTC were also recorded.

Follow-Up

Postoperative follow-up information was collected from patient charts in the outpatient setting. The patients were followed at regular intervals with clinical examination, thyroid function tests, and neck ultrasonography. Recurrence was defined as the reappearance of disease confirmed by imaging or histology during follow-up.

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics software (version 25.0; IBM Corp., Armonk, NY, USA). The normality of continuous variables was evaluated with the Kolmogorov-Smirnov and Shapiro-Wilk tests. The data following a normal distribution were summarized as mean ± standard deviation, whereas non-normally distributed data were presented as median with interquartile range (Q1–Q3). Categorical variables were described using frequencies and percentages. Between-group comparisons were performed using the independent-samples t-test or Mann–Whitney U test for continuous variables, and the chi-square or Fisher's exact test for categorical variables, as appropriate. Multivariate logistic regression analysis was conducted to identify independent predictors of coexistent PTC. EU-TIRADS 5 was included in the model as a composite variable representing high-risk ultrasonographic features (i.e., microcalcification, taller-than-wide shape, irregular margins, and hypoechogenicity). These component variables were not entered individually to prevent multicollinearity.

The results were presented as odds ratios (ORs) with their corresponding 95% confidence intervals (CIs). Statistical significance was defined as a p-value below 0.05.

Ethical Considerations

Necmettin Erbakan University (NEU) Medical School Ethics Committee approved the study (Approval No: 2025/2077) on October 24, 2025. The study was conducted in accordance with the Declaration of Helsinki. Due to the retrospective nature of the study, the requirement for informed consent was waived.

RESULTS

This study included a total of 115 individuals diagnosed with NIFTP. The participants had a mean age of 46.78 ± 13.98 years, and females accounted for 74.8% of the sample. Total thyroidectomy was performed in 76.5% of patients, and hemithyroidectomy in 23.5%. Most NIFTPs were unifocal (94.8%), with 5.2% being multifocal. The median follow-up period amounted to 51 months (interquartile range, 38-64 months). Only one case (0.9%) experienced recurrence during follow-up, which had initially presented as isolated NIFTP (Table 1).

The mean nodule size was 23.15 ± 16.70 mm. Most nodules exhibited a solid composition (66.1%), followed by a mixed cystic pattern (30.4%). Isoechoic echogenicity was slightly more common (47.8%) than hypoechoic appearance (41.7%). Irregular margins were observed in 21.7% of nodules, while a taller-than-wide shape was noted in 19.1%. Microcalcifications were present in 18.3%, macrocalcifications in 25.2%, and a peripheral halo was observed in 26.1% of nodules. According to the EU-TIRADS classification, 44.3% of nodules were category 3, 14.8% category 4, and 37.4% category 5 (see Table 1).

Based on FNAB results, the distribution across Bethesda categories was determined as follows: Bethesda I (27.0%), Bethesda II (32.2%), Bethesda III (24.3%), Bethesda IV (1.7%), and Bethesda V (8.7%); no cases were reported as Bethesda VI. Coexistent PTC was identified in 33 of 115 patients (28.7%). Specifically, PTC was located on the same side as the NIFTP lesion in 11 patients (9.6%) and on the contralateral side in 22 patients (19.1%). Detailed clinical, ultrasonographic, and cytological characteristics are summarized in Table 1.

Furthermore, the sample was divided into two groups: Group 1 (NIFTP only, n = 82) and Group 2 (NIFTP with concomitant PTC, n = 33). In the comparison between Group 1 and Group 2, the mean nodule size was significantly larger in Group 1 than in Group 2 (28.35 ± 16.40 mm vs. 19.60 ± 13.50 mm, p = 0.008). The presence of microcalcifications was higher in cases with concomitant PTC (30.3% vs. 13.4%), although this difference did not reach statistical significance (p = 0.064). The frequency of EU-TIRADS 5 was significantly higher in cases with concomitant PTC (51.5% vs. 31.7%, p = 0.047). No statistically significant intergroup differences were observed in terms of irregular margins, taller-than-wide shape, hypoechogenicity, or the presence of a halo (p = 0.871, 0.095, 0.254, and 0.175, respectively). FNAB cytology distributions did not differ significantly between groups (p = 0.755) (see Table 2).

In the univariate analysis, smaller nodule size (OR: 0.956, 95% CI: 0.924-0.990, p = 0.010) was significantly associated with coexistent PTC, whereas EU-TIRADS category 5 was only marginally associated (OR: 2.288, 95% CI: 1.002-5.228, p = 0.050). The results of the multivariate analysis revealed that the nodule size remained the only independent predictor of coexistent PTC (OR: 0.951, 95% CI: 0.909-0.995, p = 0.030), while EU-TIRADS category 5 was not significantly associated with coexistent PTC (p = 0.697) (see Table 3).

DISCUSSION

In a sample of 115 patients diagnosed with NIFTP, we characterized ultrasonographic, cytological, and histopathological features to explore potential predictors of coexisting PTC. The results of our analysis revealed that smaller nodule size independently predicted the presence of concomitant PTC, whereas higher EU-TIRADS categories were more common in such cases, but lost significance in multivariate modeling. Consistent with previous reports, most patients were middle-aged women, and NIFTP exhibited an indolent course, with only a single recurrence observed over prolonged follow-up.

The mean age (~47 years) and female predominance (≈75%) in our sample aligned with previous studies reporting

Table 1. Clinical, ultrasonographic, and cytological characteristics of patients with non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).

Variables	n=115
Age (years)	46.78±13.98
Gender	
Female, n (%)	86 (74.8)
Male, n (%)	29 (25.2)
Ultrasonographic features	
Nodule Size (mm)	23.15±16.70
Composition	
Solid, n (%)	76 (66.1)
Mixed cystic, n (%)	35 (30.4)
Spongiform, n (%)	2 (1.7)
Completely cystic, n (%)	2 (1.7)
Echogenicity	
Hypoechoic, n (%)	48 (41.7)
Isoechoic, n (%)	55 (47.8)
Hyperechoic, n (%)	12 (10.4)
Margins	
Irregular, n (%)	25 (21.7)
Regular, n (%)	90 (78.3)
Shape	
width < height, n (%)	22 (19.1)
width > height, n (%)	93 (80.9)
Echogenic foci	
Microcalcifications, n (%)	21 (18.3)
Macrocalcifications, n (%)	29 (25.2)
Peripheral calcifications, n (%)	0 (0.0)
None or comet-tail, n (%)	65 (56.5)
Halo	
Yes	30 (26.1)
No	85 (73.9)
EU-TIRADS	
2 (Benign)	4 (3.5)
3 (Low-risk)	51 (44.3)
4 (Intermediate-risk)	17 (14.8)
5 (High-risk)	43 (37.4)
Cytological results of FNAB	
No FNAB	7 (6.1)
Bethesda 1 (Non-diagnostic)	31 (27.0)
Bethesda 2 (Benign)	37 (32.2)
Bethesda 3 (AUS)	28 (24.3)
Bethesda 4 (Follicular neoplasm)	2 (1.7)
Bethesda 5 (Suspicious for malignancy)	10 (8.7)
Bethesda 6 (Malignant)	0 (0.0)
Type of surgery	
Total thyroidectomy	88 (76.5)
Hemithyroidectomy	27 (23.5)
Number of NIFTP foci	
Unifocal	109 (94.8)
Multifocal	6 (5.2)
Follow-up period, months	51.00 (38.00-64.00)
Recurrence	
Yes	1 (0.9)
No	114 (99.1)
Accompanied by PTC	
No	82 (71.3)
On the same side	11 (9.6)
On the opposite side	22 (19.1)

Descriptive statistics are presented using mean ± standard deviation for normally distributed continuous variables, median (25th percentile - 75th percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables.
Abbreviations: EU-TIRADS, European Thyroid Imaging Reporting and Data System; FNAB, Fine-needle aspiration biopsy; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features; PTC, papillary thyroid carcinoma;

Table 2. Comparison of preoperative ultrasonographic and cytological characteristics among patients with NIFTP alone and those with concomitant PTC

	Group 1 n=82	Group 2 n=33	p value
Age (years)	47.68±14.29	44.54±13.10	0.278
Sex			
Male, n (%)	19 (23.2)	10 (30.3)	0.576
Female, n (%)	63 (76.8)	23 (69.7)	
Ultrasonographic features			
Nodule size (mm)	28.35±16.40	19.60±13.50	0.008*
Solid	51 (62.2)	25 (75.8)	0.241
Hypoechoic	31 (37.8)	17 (51.5)	0.254
Irregular margins	17 (20.7)	8 (24.2)	0.871
width < height	12 (14.6)	10 (30.3)	0.095
Microcalcifications	11 (13.4)	10 (30.3)	0.064
Halo presence	18 (22.0)	12 (36.4)	0.175
EU-TIRADS category 5	26 (31.7)	17 (51.5)	0.047*
Cytological results			
No FNAB	4 (4.9)	3 (9.1)	0.755
Bethesda 1	25 (30.5)	6 (18.2)	
Bethesda 2	26 (31.7)	11 (33.3)	
Bethesda 3	19 (23.2)	9 (27.3)	
Bethesda 4	1 (1.2)	1 (3.0)	
Bethesda 5	7 (8.5)	3 (9.1)	
Bethesda 6	0 (0.0)	0 (0.0)	

Descriptive statistics were presented using mean ± standard deviation for normally distributed continuous variables and frequency (percentage) for categorical variables.
Group 1: NIFTP only
Group 2: NIFTP with concomitant PTC
Abbreviations: EU-TIRADS, European Thyroid Imaging Reporting and Data System; FNAB, Fine-needle aspiration biopsy; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features; PTC, papillary thyroid carcinoma
*Statistically significant, p<0.05

Table 3. Univariate and multivariate logistic regression analyses of factors associated with the coexistence of PTC in patients with NIFTP.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age	1.442 (0.585-3.554)	0.427	0.978 (0.947-1.010)	0.172
Sex, male	0.984 (0.955-1.013)	0.276	1.677 (0.616-4.565)	0.312
Nodule size	0.956 (0.924-0.990)	0.010*	0.951 (0.909-0.995)	0.030*
Solid	1.900 (0.763-4.732)	0.168	0.711 (0.225-2.247)	0.561
Halo presence	2.032 (0.842-4.904)	0.115	2.276 (0.881-5.886)	0.090
EU-TIRADS category 5	2.288 (1.002-5.228)	0.050	1.217 (0.453-3.272)	0.697

Abbreviations: CI, confidence interval; EU-TIRADS, European Thyroid Imaging Reporting and Data System; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features; OR, odds ratio; PTC, papillary thyroid carcinoma.
*Statistically significant, p<0.05

that NIFTP occurs most frequently in middle-aged women (17, 18). NIFTP is currently regarded as a follicular-derived thyroid neoplasm with indolent biological behavior, reclassified from the noninvasive EFVPTC following recognition of its excellent prognosis and absence of invasive potential (1, 11, 19).

In our sample, most nodules exhibited a solid composition and were predominantly isoechoic (47.8%) or hypoechoic (41.7%). Microcalcifications were relatively infrequent, observed in approximately 18% of cases. These ultrasonographic characteristics are broadly consistent with previous reports, which described NIFTP as typically presenting with regular margins, an oval or round shape, and a lack of overtly malignant features (20 - 22). Previous studies reported that microcalcifications are relatively uncommon in NIFTP as compared to classical PTC (23, 24). Similarly, Yang and Fried observed that NIFTP lesions frequently resemble minimally invasive encapsulated tumors, appearing as well-circumscribed nodules with smooth margins and either isoechoic or mildly hypoechoic echogenicity-features that contrast with the more suspicious ultrasound patterns of infiltrative PTC (20).

In the present study, 37.4% of NIFTP nodules were classified as EU-TIRADS 5, a proportion higher than those reported in

most previous series. By contrast, the distribution of EU-TIRADS 3 (44.3%) and EU-TIRADS 4 (14.8%) categories in the sample was largely comparable to prior studies, where most NIFTPs were assigned to low-to-intermediate EU-TIRADS risk levels. The relatively greater proportion of EU-TIRADS 5 nodules observed in our series may reflect overlapping ultrasonographic features between NIFTP and classical PTC rather than methodological or selection-related factors. Overall, these findings support previous evidence that NIFTP predominantly presents with low-to-intermediate risk sonographic patterns, although a subset may display higher EU-TIRADS scores despite their indolent histopathologic nature (23, 25, 26).

Cytologically, the sample demonstrated a predominance of Bethesda I and II categories, accompanied by a notably high proportion of Bethesda III cases. The latter finding is well aligned with previous studies showing that NIFTP is frequently associated with indeterminate cytology, most often within the Bethesda III category (7). Considering that cytology alone cannot reliably distinguish NIFTP from benign follicular lesions, definitive diagnosis depends on comprehensive histopathologic assessment (1 - 3, 6). In their systematic review and meta-analysis, Bongiovanni et al. reported that cytological diagnoses associated with NIFTP span a wide spectrum, from non-diagnostic to malignant, with most cases falling into indeterminate categories. The authors further emphasized that additional cytological and/or molecular features need to be identified to enable more accurate presurgical recognition of NIFTP (7). While the proportion of indeterminate (Bethesda III) cases in our cohort was comparable to that reported by Bongiovanni et al., we observed a relatively higher frequency of non-diagnostic (Bethesda I) and benign (Bethesda II) cytology results. This difference may reflect variations in cytologic interpretation, sample adequacy, or institutional practices, as well as subtle nuclear features that make NIFTP challenging to identify on cytology alone.

The coexistence of NIFTP with other thyroid tumors is well documented in the literature, with reported rates ranging from 14.7% to 46.3% (10, 12, 13, 19, 27). In the largest retrospective series available to date, Vignali et al. analyzed a total of 451 NIFTP cases and found that 43.7% were associated with concomitant thyroid lesions, either benign or malignant, most commonly PTC. The authors also reported that NIFTPs coexisting with malignant tumors were significantly smaller ($p < 0.001$) (11). Similarly, Seo et al. reported that 26.7% of NIFTPs coexisted with other malignant thyroid tumors, including conventional, infiltrative, and follicular variants of PTC. Importantly, the coexistence was more frequent among subcentimeter NIFTPs (43.0%) as compared to those ≥1.0 cm (17.8%), suggesting a potential association between smaller tumor size and multifocality (10). In line with earlier reports, our results demonstrated a coexistence rate of 28.7%, with smaller nodule size identified as an independent predictor of concurrent PTC. This observation may indicate that smaller NIFTPs are more likely to arise in a multifocal thyroid environment or that, due to biological or sampling factors, their reduced size increases the likelihood of detecting coexistent microcarcinomas. Consistently with this observation, our study demonstrated that smaller nodules had higher odds of harboring concurrent PTC. similarly, previous studies proposed that small PTC foci can be more easily missed during preoperative assessment and that multifocal micro-PTCs may preferentially occur alongside otherwise benign-appearing nodules, although direct comparative evidence remains limited (28, 29).

In our analysis, higher EU-TIRADS scores were more frequent among the cases with coexistent PTC; however, after adjustment for nodule size, this feature lost independent significance after, possibly reflecting collinearity and indicating that nodule size is the dominant predictive factor. Our findings highlight the importance of detailed ultrasonographic evaluation, particularly in smaller nodules diagnosed as NIFTP candidates, to screen for possible coexistent malignancy. Since NIFTP itself carries an extremely favorable prognosis and very low recurrence, the detection of synchronous PTC is clinically meaningful and may influence the extent of surgery and postoperative surveillance. While conservative management (lobectomy) is frequently preferred when imaging and cytology suggest low-risk features, surgeons and clinicians must remain cautious of potential occult PTC in the contralateral lobe, especially in populations where multifocal microscopic disease is more common.

Limitations

This study has several limitations. It is retrospective in design, which introduces inherent biases. Furthermore, interobserver variability in ultrasonographic interpretations and cytopathologic classification cannot be fully excluded. In addition, the subgroup of patients with coexisting PTC was relatively small, which may limit power in the multivariate model. Finally, our findings are based on a single-center cohort; external validation in multi-center or prospective settings would strengthen generalizability.

CONCLUSION

In summary, among patients with NIFTP, smaller nodule size emerged as an independent predictor of coexisting PTC. However, suspicious ultrasound features such as solid composition, presence of a halo, and higher EU-TIRADS scores were not independently predictive in multivariate modeling. These findings suggest that closer attention to smaller thyroid nodules and careful imaging reassessment may be warranted when NIFTP is considered in the differential diagnosis or when planning surgery for indeterminate or low-risk follicular-patterned lesions. Further validation of these predictors through well-designed, multicenter prospective studies is warranted to enhance preoperative risk assessment and to optimize clinical decision making.

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Address correspondence to: *Muhammet Kocabaş, Necmettin Erbakan University, Medical Faculty, Department of Endocrinology and Metabolism, Konya, Türkiye*
e-mail: *mhmmt03@gmail.com*

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