



Papillary Thyroid Microcarcinomas Detected by Nuclear Medicine Imaging: Distinct Clinicopathological Features Compared with Conventional Modalities

Nükleer Tıp Görüntüleme Yöntemleriyle Saptanan Papiller Tiroid
Mikrokarsinomlarının Klinikopatolojik Özellikleri: Konvansiyonel Yöntemlerle
Karşılaştırma

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Abstract

Objectives: Papillary thyroid carcinomas detected by nuclear medicine imaging techniques may have a worse prognosis than those identified by conventional methods. However, it remains unclear whether this applies to papillary thyroid microcarcinomas (PTMCs).

Methods: Patients diagnosed with PTMC at Hacettepe University Faculty of Medicine between 2008 and 2020 were categorized into three groups: (1) incidental PTMCs (Inc-PTMC; n=249), (2) non-incidental PTMCs (NonInc-PTMC; n=134), and (3) PTMCs detected by nuclear medicine imaging methods (NM-PTMC; n=24). Tumor pathological characteristics, including multifocality, extrathyroidal extension, vascular invasion, and lymph node involvement, were analyzed. Logistic regression analysis was performed to assess the association between detection method and tumor aggressiveness while adjusting for potential confounders.

Results: Patients in NM-PTMC group were significantly older at diagnosis (54.7±11.2 years) than those in Inc-PTMC (51.1±11.3 years) and NonInc-PTMC (46.9±11.7 years, p=0.001) groups. Tumor size was larger in NM-PTMCs (4.8±2.5 mm) and NonInc-PTMCs (5.3±2.2 mm) compared to Inc-PTMCs (3.4±2.4 mm, p<0.0001). Multiple logistic regression analysis revealed that NM-PTMCs had a markedly higher risk of cervical lymph node metastasis compared with both Inc-PTMCs [odds ratio (OR): 36.04; 95% confidence interval (CI): 6.02-215.59, p=0.001] and NonInc-PTMCs (OR: 8.68; 95% CI: 1.15-65.22, p=0.036). NM-PTMC also had an increased risk of positive surgical margins compared with Inc-PTMC (OR: 5.08; 95% CI: 1.57-16.39, p=0.006), whereas only NonInc-PTMC had a higher risk of extrathyroidal extension (OR: 3.19; 95% CI: 1.48-8.84, p=0.003). The detection method was not associated with multifocality.

Conclusion: Nuclear medicine-detected PTMCs may differ in their clinicopathological profile from other PTMC subgroups and may represent an intermediate phenotype between Inc-PTMC and NonInc-PTMC.

Keywords: Papillary thyroid microcarcinoma, incidental, non-incidental, nuclear medicine, ¹⁸F-FDG PET/CT

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Öz

Amaç: Nükleer tıp görüntüleme yöntemleriyle saptanan papiller tiroid kansinomlarının, konvansiyonel yöntemlerle saptananlara kıyasla daha kötü prognoza sahip olabileceği düşünülmektedir. Ancak bu durumun papiller tiroid mikrokarsinomları (PTMK) için de geçerli olup olmadığı net değildir.

Yöntem: Hacettepe Üniversitesi Tıp Fakültesi'nde 2008-2020 yılları arasında PTMK tanısı alan hastalar üç gruba ayrıldı: (1) insidental PTMK'lar (Inc-PTMK; n=249), (2) non-insidental PTMK'lar (NonInc-PTMK; n=134) ve (3) nükleer tıp görüntüleme yöntemleriyle saptanan PTMK'lar (NM-PTMK; n=24). Multifokalite, ekstrasitroidal yayılım, vasküler invazyon ve lenf nodu tutulumu dahil olmak üzere tümörün patolojik özellikleri değerlendirildi. Saptama yöntemi ile tümör agresifliği arasındaki ilişkiyi, olası karıştırıcı faktörlere göre düzelterek değerlendirmek amacıyla lojistik regresyon analizi yapıldı.

Bulgular: NM-PTMK grubundaki hastalar tanı sırasında ($54,7 \pm 11,2$ yıl), Inc-PTMK ($51,1 \pm 11,3$ yıl) ve NonInc-PTMK ($46,9 \pm 11,7$ yıl; $p=0,001$) gruplarındaki hastalara göre anlamlı olarak daha yaşlıydı. Tümör boyutu, NM-PTMK ($4,8 \pm 2,5$ mm) ve NonInc-PTMK ($5,3 \pm 2,2$ mm) gruplarında, Inc-PTMK grubuna ($3,4 \pm 2,4$ mm; $p<0,0001$) kıyasla daha büyüktü. Çoklu lojistik regresyon analizinde, NM-PTMK'ların servikal lenf nodu metastazı açısından hem Inc-PTMK'lara [olasılık oranı (OR): 36,04; %95 güven aralığı (GA): 6,02-215,59; $p=0,001$] hem de NonInc-PTMK'lara (OR: 8,68; %95 GA: 1,15-65,22; $p=0,036$) kıyasla belirgin şekilde daha yüksek risk taşıdığı saptandı. NM-PTMK grubunda ayrıca Inc-PTMK grubuna göre pozitif cerrahi sınır riski daha yüksekti (OR: 5,08; %95 GA: 1,57-16,39; $p=0,006$). Buna karşılık, yalnızca NonInc-PTMK grubunda ekstrasitroidal yayılım riski daha yüksekti (OR: 3,19; %95 GA: 1,48-8,84; $p=0,003$). Saptama yöntemi ile multifokalite arasında ilişki bulunmadı.

Sonuç: Nükleer tıp yöntemleriyle saptanan PTMK'lar, klinikopatolojik profilleri açısından diğer PTMK alt gruplarından farklılık gösterebilir ve Inc-PTMK ile NonInc-PTMK'lar arasında ara bir fenotipi temsil edebilir.

Anahtar Kelimeler: Papiller tiroid mikrokarsinomu, insidental, non-insidental, nükleer tıp, ^{18}F -FDG PET/BT

Introduction

Incidental papillary thyroid microcarcinomas (Inc-PTMCs) generally have a favorable prognosis, with low recurrence and long-term mortality rates in large cohorts and meta-analyses, compared with non-Inc-PTMCs (NonInc-PTMCs) (1,2,3,4,5). One possible explanation is that the two groups have distinct clinicopathological characteristics, with NonInc-PTMC showing larger tumor size and higher rates of multifocality, cervical lymph node involvement, and capsular invasion (2,3,5).

Nuclear medicine modalities, including ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT), are increasingly used for indications ranging from malignancies to benign inflammatory conditions, and have become important methods in the detection of thyroid lesions, with papillary thyroid carcinoma (PTC) rates ranging from 20% to 30% (6,7,8,9). In addition, studies have shown that nuclear medicine imaging methods used for parathyroid imaging, such as $^{99\text{m}}\text{Tc}$ -methoxyisobutylisonitrile ($^{99\text{m}}\text{Tc}$ -MIBI) single-PET/CT (SPECT/CT) and ^{18}F -florokolin (^{18}F -FCH) PET/CT, have high specificity and accuracy for detecting concurrent thyroid carcinoma (10,11). Importantly, PTCs detected by ^{18}F -FDG PET/CT may exhibit more aggressive features than PTCs in general (12,13,14). Whether these observations extend to PTMCs, however, remains unknown. No studies to date have investigated whether PTMCs detected by nuclear medicine imaging show distinct clinical and pathological characteristics compared with those of Inc-PTMC and Non-Inc-PTMC. While many classification systems categorize

tumors detected on imaging performed for unrelated indications as "incidental," PTMCs detected by nuclear medicine may represent a functionally and metabolically distinct subgroup whose clinicopathological profile has not been characterized separately. PTMCs are increasingly managed with active surveillance protocols in selected patients, making accurate risk stratification at the time of detection particularly important. Clinicopathological features that indicate a higher likelihood of nodal involvement or aggressive histological variants may influence the decision between immediate surgery and observation. In this context, the modality through which a PTMC is first identified may carry prognostic implications that extend beyond those established for PTCs in general, and cannot be assumed to mirror findings derived from larger tumor cohorts. This study therefore aimed to compare the clinicopathological features of PTMCs detected by nuclear medicine imaging with those of Inc-PTMC and Non-Inc-PTMC to determine whether the method of detection may serve as an additional consideration in risk stratification.

Materials and Methods

This retrospective cohort study included 407 patients diagnosed with PTMC at Hacettepe University Faculty of Medicine, Ankara, Türkiye between January 2008 and December 2020, who were identified through a comprehensive review of thyroidectomy pathology reports. Only patients who underwent surgery at our institution were included; cases referred from external centers for pathological consultation were excluded. Tumors were classified and subtyped according to the

World Health Organization (WHO) criteria (15). Although the most recent WHO classification no longer uses the term PTMC, it remains widely used in clinical practice and contemporary literature; therefore, the term was retained for clarity and comparability. PTMC was defined as a PTC measuring <10 mm in greatest dimension, regardless of focality. Tumors were considered multifocal if two or more distinct tumor foci were identified in one or both lobes. Bilobar involvement was defined as the presence of tumor foci in both thyroid lobes. For multifocal tumors, the largest tumor focus was used for size-based analyses. Extrathyroidal extension was defined as microscopic or gross invasion beyond the thyroid capsule. Vascular invasion was recorded when tumor emboli were present within blood vessels located in the tumor capsule or in the adjacent thyroid parenchyma. Cervical lymph node metastasis was histologically confirmed in resected nodes. Positive surgical margins were identified in pathology reports and were defined as the presence of tumor cells at the inked margin or within <1 mm of the surgical margin. This study was performed in accordance with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Hacettepe University (approval no: SBA 25/813, date: 23.09.2025).

Patients were categorized into three groups according to the detection method:

Group 1 - Inc-PTMC

Tumors were incidentally detected in thyroidectomy specimens removed for benign thyroid disease (e.g., multinodular goiter) or for non-thyroidal head and neck pathology, with no preoperative suspicion of thyroid malignancy. These cases fulfilled all of the following criteria (n=249):

- The PTMC was not the index lesion leading to surgery.
- Surgery was not performed for suspected thyroid cancer or its metastasis.
- The surrounding thyroid tissue was histologically benign, except for the PTMC.

Group 2 - NonInc-PTMC

Tumors detected following preoperative suspicion of malignancy based on at least one of the following (n=134):

- Fine-needle aspiration biopsy showing malignant or suspicious cytology.
- Preoperative ultrasound suggestive of thyroid malignancy.
- Preoperative evidence or suspicion of regional lymph node or distant metastasis.

Group 3 - Nuclear medicine-detected PTMCs (NM-PTMC)

Tumors identified after a thyroid lesion was detected on nuclear medicine imaging performed for unrelated clinical indications, including (n=24):

- ^{18}F -FDG PET/CT (n=16): oncologic staging or surveillance in 15 patients, and evaluation of vasculitis in the remaining patient.
- ^{18}F -FCH PET/CT (n=2): evaluation of hyperparathyroidism.
- $^{99\text{m}}\text{Tc}$ -MIBI SPECT/CT (n=6): evaluation of hyperparathyroidism.

Representative examples of NM-PTMC are shown in Figures 1 and 2. All patients undergoing ^{18}F -FCH PET/CT or $^{99\text{m}}\text{Tc}$ -MIBI imaging also received a thyroid ultrasound during the same session as part of our institutional protocol. Given the small sample size, nuclear medicine imaging modalities were grouped a priori; post-hoc subgroup analyses were also performed.

For each patient, data were collected, including age at PTMC diagnosis, sex, tumor size (mm), multifocality, bilobar involvement, extrathyroidal extension, vascular invasion, cervical lymph node metastasis, concurrent lymphocytic thyroiditis, details of the surgical procedure and LND, the indication for surgery, and preoperative imaging results.

Statistical Analysis

Continuous variables were expressed as mean $\pm$ standard deviation or median (range), as appropriate. Differences among the three groups were assessed using ANOVA for

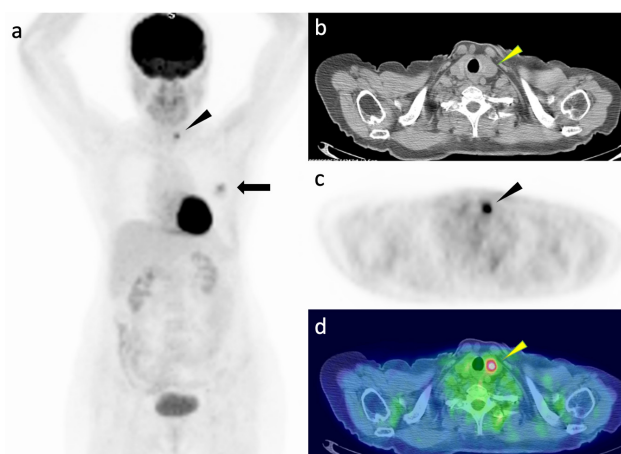


Figure 1. Maximum intensity projection image of ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) (a); axial CT (b), PET (c), and fused PET/CT (d) slices at the level of the thyroid gland. The case represents a female patient who was referred for ^{18}F -FDG PET/CT for staging of left breast cancer (a, arrow). An incidental sub-centimetric thyroid nodule with intense FDG uptake was also identified and later confirmed as papillary thyroid carcinoma (a-d, arrowhead)

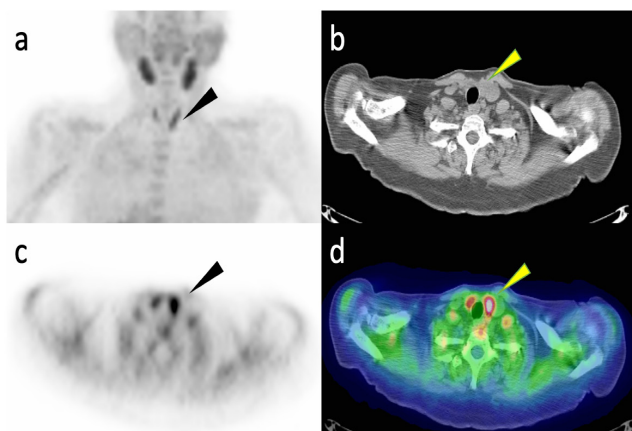


Figure 2. Maximum intensity projection image of ^{18}F -florokolin (^{18}F -FCH) PET (a); axial computed tomography (CT) (b), positron emission tomography (PET) (c), and fused PET/CT (d) slices at the level of the thyroid gland. This case concerns a female patient referred for ^{18}F -FCH PET/CT to evaluate hyperparathyroidism. An incidental sub-centimetric thyroid nodule with intense ^{18}F -FCH uptake was also detected and subsequently confirmed to be a 6-mm papillary thyroid carcinoma (a-d, arrowhead)

variables that were normally distributed. The Kruskal-Wallis test was used for non-normally distributed variables.

Categorical variables were summarized as frequencies and percentages, and group differences were compared using Pearson's chi-square test or Fisher's exact test, as appropriate.

To identify independent predictors of pathological tumor characteristics (extrathyroidal extension, positive surgical margins, multifocality, vascular invasion, and cervical lymph node metastasis), univariate logistic regression analyses were initially performed. Variables with a p -value <0.05 in univariate analyses and clinically relevant covariates (age at diagnosis, sex, tumor size, multifocality, and detection method) were included in multiple logistic regression models. Results were presented as odds ratios (ORs) with 95% confidence intervals (CIs).

All statistical analyses were performed using IBM SPSS Statistics version 21 (IBM Corp., Armonk, NY, USA). A two-tailed p -value <0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics

The main characteristics of the patients are presented in Table 1. Patients in NM-PTMC group were the oldest on average (54.7 ± 11.2 years), significantly older than those in NonInc-PTMC but not significantly different from those in

Inc-PTMC group. In contrast, sex distributions were similar across cohorts, with no significant pairwise differences in the proportions of male patients.

Thyroid functional status differed markedly among the groups ($p < 0.001$ overall). The Inc-PTMC group had the highest proportion of hyperthyroid patients (21.3%), followed by the NonInc-PTMC group (5.2%) and the NM-PTMC group (4.2%). The remaining patients in each group were predominantly euthyroid (Inc-PTMC: 73.1%, NonInc-PTMC: 85.1%, NM-PTMC: 91.7%), with a small proportion hypothyroid (Table 1).

The extent of surgical treatment varied significantly according to detection method ($p < 0.001$ overall). Total thyroidectomy (with or without completion thyroidectomy) was the primary surgical procedure in the majority of cases in all groups. Concurrent central compartment lymph node dissection (LND) was markedly more common in the NM-PTMC group than in the NonInc-PTMC group. Only 2.0% of patients with Inc-PTMC had an initial cervical lymph node excision as part of a total thyroidectomy. The NM-PTMC group had a significantly higher LND rate than the NonInc-PTMC group.

A total of 145 patients received radioactive iodine following thyroid surgery: 62 in the incidental group (24.9%), 72 in the non-incidental group (53.7%), and 11 in the nuclear medicine group (45.8). These differences were statistically significant ($p < 0.001$). The median dose of RAI was 100 mCi (range, 21-175 mCi).

The prevalence of additional malignancies (synchronous non-thyroidal cancers) differed between groups. More than half of the patients in the NM-PTMC group had a concomitant malignancy (62.5%), a rate significantly higher than that in both the Inc-PTMC and NonInc-PTMC groups. The Inc-PTMC group also had a higher incidence of coexisting malignancy than the NonInc-PTMC group (12.9% vs 6.0%, $p = 0.036$). However, the presence of a non-thyroidal malignancy was not a risk factor for adverse tumoral characteristics in multiple regression analyses.

In the NM-PTMC group, all thyroïdal uptakes identified on nuclear medicine imaging were focal. In patients detected by ^{18}F -FDG PET/CT, the median maximum standardized uptake value (SUV_{max}) was 3.3 (range, 1.2-21.2). Among patients undergoing ^{18}F -FCH PET/CT or $^{99\text{m}}\text{Tc}$ -MIBI imaging, suspicious sonographic features were identified in both patients who underwent ^{18}F -FCH PET/CT and in two of the six patients who underwent $^{99\text{m}}\text{Tc}$ -MIBI imaging.

Pathological Characteristics

The main pathological features of PTMCs across the three groups are presented in Table 2, while independent

predictors identified through multivariable analyses are shown in Table 3.

Mean tumor size differed significantly among the three groups ($p < 0.001$ overall). Tumors in NonInc-PTMC group were the largest, with a mean diameter of 5.35 ± 2.28 mm, followed by those in NM-PTMC group (4.82 ± 2.57 mm) and then Inc-PTMC group (3.43 ± 2.40 mm).

Histopathological subtypes also showed a distinct distribution (overall $p < 0.001$). The classical papillary subtype predominated in the Inc-PTMC and NonInc-PTMC groups, with smaller proportions of the follicular variant and other aggressive variants, including tall cell, diffuse sclerosing, hobnail, and columnar. The NM-PTMC group exhibited a more heterogeneous pattern, with classical,

Table 1. The main characteristics of papillary thyroid microcarcinoma (PTMC) patients

	Inc-PTMC (n=249)	NonInc-PTMC (n=134)	NM-PTMC (n=24)	p-value	p ¹	p ²	p ³
Age at diagnosis (years $\pm$ SD)	51.1 $\pm$ 11.3	46.9 $\pm$ 11.7	54.7 $\pm$ 11.2	0.001	0.001	0.14	0.003
Gender (M, %)	62 (24.9%)	26 (19.4%)	2 (8.3%)	0.11			
Type of thyroid surgery (n, %)							
Total thyroidectomy	211 (84.7%)	107 (79.9%)	12 (50.0%)				
Subtotal thyroidectomy	25 (10.0%)	4 (2.9%)	2 (8.3%)				
Subtotal thyroidectomy + completion thyroidectomy	8 (3.2%)	2 (1.5%)	2 (8.3%)				
Total thyroidectomy + cervical LND	5 (2%)	21 (15.6%)	8 (33.3%)				
Preoperative thyroid hormone status (n, %)							
Euthyroid	182 (73.1%)	114 (85.1%)	16 (66.7%)	<0.001	0.004	0.55	0.014
Hypothyroid	6 (2.4%)	4 (3.0%)	4 (16.7%)				
Hyperthyroid	53 (21.3%)	12 (9.0%)	4 (16.7%)				
Unknown	8 (3.2%)	4 (3.0%)	-				
Additional malignancy (n, %)	32 (12.9%)	8 (6%)	15 (62.5%)	<0.001	0.036	<0.001	<0.001

Inc-PTMC: Incidental PTMC, NonInc-PTMC: Non-incidental PTMC, NM-PTMC: PTMC detected by nuclear medicine imaging methods, SD: Standard deviation, LND: Lymph node dissection
p¹: Comparison between groups Inc-PTMC and NonInc-PTMC
p²: Comparison between groups Inc-PTMC and NM-PTMC
p³: Comparison between groups NonInc-PTMC and NM-PTMC

Table 2. The main pathological characteristics of PTMCs

	Inc-PTMC (n=249)	NonInc-PTMC (n=134)	NM-PTMC (n=24)	p-value			
				p	p ¹	p ²	p ³
Tumor size (mm $\pm$ SD)	3.43 $\pm$ 2.40	5.35 $\pm$ 2.28	4.82 $\pm$ 2.57	<0.001	<0.001	0.009	0.32
Variant (n, %)							
Classical	194 (78.2%)	102 (76.1%)	8 (33.3%)	<0.001	0.51	<0.001	<0.001
Follicular	44 (17.7%)	21 (15.7%)	8 (33.3%)				
Other	10 (4.0%)	11 (8.2%)	8 (33.3%)				
Multifocality (yes, %)	70 (28.1%)	66 (49.3%)	10 (41.7%)	<0.001	<0.001	0.16	0.49
Capsule invasion (yes, %)	2 (0.8%)	5 (3.7%)	2 (8.3%)	0.02	0.042	0.003	0.31
Extrathyroidal extension (yes, %)	13 (5.2%)	27 (20.1%)	3 (12.5%)	<0.001	<0.001	0.14	0.39
Surgical margins (positive, %)	18 (7.3%)	25 (18.7%)	7 (29.2%)	<0.001	0.001	0.001	0.36
Vascular invasion (yes, %)	1 (0.4%)	3 (2.2%)	0	0.19	0.09	0.76	0.47
Cervical LN involvement (yes, %)	4 (1.6%)	20 (14.9)	6 (25.0%)	<0.001	<0.001	<0.001	0.22
Lymphocytic thyroiditis (yes, %)	45 (18.1%)	43 (32.1%)	6 (25.0%)	0.008	0.002	0.40	0.49

PTMC: papillary thyroid microcarcinoma, Inc-PTMC: Incidental PTMC, NonInc-PTMC: Non-incidental PTMC, NM-PTMC: PTMC detected by nuclear medicine imaging methods, LN: Lymph node, Group 1: Incidental PTMCs, group 2: Non-incidental PTMCs, group 3: PTMCs detected by nuclear medicine imaging methods
p¹: Comparison between groups Inc-PTMC and NonInc-PTMC
p²: Comparison between groups Inc-PTMC and NM-PTMC
p³: Comparison between groups NonInc-PTMC and NM-PTMC

Table 3. Independent predictors of adverse pathological features in PTMC (multivariable logistic regression)

Outcome	Significant predictors	OR (95% CI)	p-value
ETE	Non-incidental vs. incidental PTMCs	3.19 (1.48-8.84)	0.003
	Tumor size	1.24 (1.07-1.43)	0.004
Multifocality	Tumor size	1.18 (1.08-1.30)	<0.001
Positive surgical margins	PTMCs detected by nuclear medicine imaging methods	5.08 (1.57-16.39)	0.006
	Multifocality	2.07 (1.03-4.15)	0.039
	Tumor size	1.32 (1.14-1.52)	<0.001
Cervical LN metastasis	PTMCs detected by nuclear medicine imaging methods vs. incidental PTMCs	36.04 (6.02-215.59)	0.001
	PTMCs detected by nuclear medicine imaging methods vs. non-incidental PTMCs	8.68 (1.15-65.22)	0.036
	Non-incidental vs. incidental PTMCs	5.64 (1.58-20.11)	0.004
	ETE	8.31 (2.40-28.81)	0.001
	Vascular invasion	74.91 (1.31-4285.91)	0.037
	Age	0.94 (0.90-0.99)	0.017
	Male gender	6.01 (2.00-18.01)	0.001

PTMC: Papillary thyroid microcarcinoma, ETE: Extrathyroidal extension, LN: Lymph node, OR: Odds ratio, CI: Confidence interval

follicular, and other aggressive variants each occurring in equal proportions (Table 2).

Tumor multifocality and bilaterality were more common in the NonInc-PTMC and NM-PTMC groups than in the Inc-PTMC group. However, in the multiple logistic regression analysis, the detection method for PTMC was not associated with multifocality; only tumor size was associated with multifocality (Table 3).

Several markers of local tumor invasion differed significantly between groups. Capsular invasion was rare in the Inc-PTMC group but more frequent in the NonInc-PTMC and NM-PTMC groups, with an overall group difference of $p=0.02$ (Table 2). However, the detection method was not identified as a risk factor for capsular invasion in the multiple logistic regression analysis. Extrathyroidal extension was more common in Inc-PTMC and Non-Inc-PTMC. This difference was mainly driven by the contrast between the NonInc-PTMC and Inc-PTMC groups. Multiple logistic regression analysis confirmed that Non-Inc-PTMCs had a significantly higher risk of extrathyroidal extension than Inc-PTMCs. Tumor size was also an independent risk factor for extrathyroidal extension, whereas multifocality was not an independent risk factor (Table 3). Positive resection margins were more common in the NonInc-PTMC and NM-PTMC groups (Table 2). Multiple logistic regression analysis confirmed that only the NM-PTMC group had a significantly increased risk of positive surgical margins compared with the Inc-PTMC group, whereas the NonInc-PTMC group showed no comparable increase in risk. In

addition, tumor size and multifocality were independent risk factors for positive surgical margins. Vascular invasion was exceedingly uncommon in all three groups, with no statistically significant differences among the groups.

Cervical lymph node metastasis differed markedly among groups, with the highest rates in the NM-PTMC group, followed by the NonInc-PTMC group, and very low rates in the Inc-PTMC group (Table 2). Both the NonInc-PTMC and NM-PTMC groups had significantly higher rates of lymph node involvement than the Inc-PTMC group, whereas the difference between the NonInc-PTMC and NM-PTMC groups was not significant (Table 2). Multiple logistic regression analysis revealed that patients in the NonInc-PTMC and NM-PTMC groups had a significantly increased risk of cervical lymph node metastasis compared with the Inc-PTMC group. The NM-PTMC group also had a significantly higher risk than the NonInc-PTMC group. Younger age, male sex, and features of invasive disease (extrathyroidal extension and vascular invasion) emerged as significant predictors of nodal involvement (Table 3). However, the wide CI for vascular invasion suggests limited precision of this estimate, likely due to the low number of cases.

Coexisting lymphocytic thyroiditis was most prevalent in Non-Inc-PTMCs, but was not associated with adverse pathological characteristics in multivariable models.

Patients in the NM-PTMC group were further subdivided according to whether they were detected incidentally via PET/CT or other nuclear medicine imaging modalities

because the likelihood of secondary malignant tumors is already higher in patients with known malignancies. No significant differences were observed between these subgroups with respect to age at diagnosis (53.81 ± 11.35 vs 56.63 ± 11.63 years, respectively), tumor size (5.06 ± 2.56 vs 4.28 ± 2.69 mm, respectively), or other pathological characteristics, including multifocality, cervical lymph node metastasis, and extrathyroidal extension (all $p > 0.1$).

Discussion

In this study, we demonstrated that NM-PTMC displayed distinct clinicopathological features compared with both Inc-PTMC and Non-Inc-PTMC. Patients in this group were older at diagnosis, had larger tumors, and had a disproportionately high prevalence of aggressive histological variants. They also underwent LND more frequently and had markedly higher rates of positive surgical margins and cervical lymph node metastases. In contrast, Non-Inc-PTMCs were characterized by larger tumor size and an increased risk of extrathyroidal extension, whereas Inc-PTMCs generally showed the most favorable pathological profile. Logistic regression confirmed that NM-PTMC were independently associated with a higher risk of positive margins and nodal metastasis, whereas extrathyroidal extension was more strongly linked to non-incidental tumors. Additional predictors of aggressiveness across the cohort included younger age, male sex, and the presence of extrathyroidal extension or vascular invasion, although the latter was rare and associated with imprecise estimates due to small numbers. Taken together, these findings suggest that the mode of detection may be an important determinant of the biological behavior of PTMCs.

Studies have shown that during ^{18}F -FDG PET/CT, the chance of detecting thyroid uptake is 2%-3%. Patients with focal uptake seem to be particularly at risk, and when cytopathological confirmation is available, a 20%-30% risk of thyroid malignancy has been reported (7,8,9,13). SUV_{max} has been investigated as a potential predictor of malignancy, but no consensus exists regarding an optimal cutoff value. In our cohort, the median SUV_{max} of incidental PTMCs was 3.3 (range, 1.2-21.2). Pagano et al. (16) proposed a cutoff of 5.0 (positive predictive value 50%, negative predictive value 92.3%), whereas Demir et al. (8) suggested 5.5 (sensitivity 82%, specificity 65%). Others have also reported higher SUV_{max} values in malignant than in benign lesions (17,18,19). Conversely, Makis et al. (20) and Toyoshima et al. (21) found no correlation, highlighting that subsequent thyroid ultrasound findings were more reliable. These findings further emphasize that incidental focal uptake should be corroborated by

dedicated thyroid ultrasonography, as metabolic activity alone may be insufficient to characterize malignancy risk. Notably, in our cohort, all patients undergoing ^{18}F -FCH PET/CT or $^{99\text{m}}\text{Tc}$ -MIBI imaging also received thyroid ultrasound during the same session (a "one-stop-shop" approach), which strengthens the reliability of lesion assessment.

PTCs detected by ^{18}F -FDG PET/CT may show less favorable pathological characteristics than PTCs in general. An earlier paper by Are et al. (12) suggested that PTCs detected by ^{18}F -FDG PET/CT showed aggressive features such as the tall cell variant and extrathyroidal extension, although no control group was included. Law and Lang (14) later compared Inc-PTMCs according to detection method (^{18}F -FDG PET/CT, $n=22$, and ultrasound, $n=11$) and found that multifocality, bilaterality, and cervical lymph node metastasis may be more frequent in the ^{18}F -FDG PET/CT group. Although this study included patients with PTMCs, the exact number was not specified. Piccardo et al. (22) reported that intense focal uptake in differentiated thyroid carcinomas detected by ^{18}F -FDG PET/CT ($\text{SUV}_{\text{max}} \geq 3$) was associated with persistent or progressive disease. On the other hand, Pak et al. (23) found no difference in multifocality, extrathyroidal extension, surgical margins, or cervical lymph node metastasis between Inc-PTMC patients detected by ^{18}F -FDG PET/CT ($n=48$) and those detected by other imaging methods ($n=48$), except that patient in the ^{18}F -FDG PET/CT group were older and had a higher tumor stage at diagnosis. Nonetheless, clinical and pathological data on PTCs detected by ^{18}F -FDG PET/CT remain limited, likely because patients undergoing ^{18}F -FDG PET/CT often have another primary malignancy, and not all individuals with thyroidal uptake proceed to fine-needle aspiration or thyroid surgery. Furthermore, prognosis and survival are predominantly determined by the primary malignancy rather than by the thyroid lesion itself. Regarding other modalities, including $^{99\text{m}}\text{Tc}$ -MIBI SPECT/CT and ^{18}F -FCH PET/CT, a limited number of studies have suggested that incidental focal thyroidal uptake may indicate malignancy (10,11). However, there are no data on their clinical or pathological significance.

PTMCs represent a different clinical context. Although previous studies have compared Inc-PTMC and Non-Inc-PTMC (4), the potential impact of detection by nuclear medicine imaging on PTMC clinicopathological features has not been investigated previously. Definitions of incidental thyroid carcinoma vary across studies. In many reports, thyroid cancers detected during imaging performed for unrelated indications, including nuclear medicine imaging, are also classified as incidental. However, in our study, we deliberately categorized NM-PTMC as a separate group

because their detection pathways, patient characteristics, and clinical contexts differ substantially from those of surgically incidental tumors.

NM-PTMC occupied an intermediate clinicopathological position between Inc-PTMCs and Non-Inc-PTMCs. Their mean tumor size resembled that of non-incidental PTMCs, and they displayed a higher frequency of aggressive histological variants, consistent with a previous report on PTC (12). In contrast, only Non-Inc-PTMCs were independently associated with extrathyroidal extension. A potential explanation for the larger tumor size and higher rate of positive surgical margins observed in NM-PTMCs is the limited spatial resolution of nuclear medicine imaging. Both PET and SPECT have substantially lower spatial resolution than high-resolution ultrasound, so lesions generally must reach a sufficient size or demonstrate significant radiotracer avidity to be detectable. Accordingly, the tumors in the NM-PTMC group may represent a biologically selected subset whose members have already achieved a size or metabolic activity threshold necessary for detection, rather than a random sample of all PTMCs. This detection threshold effect could enrich the nuclear medicine-detected group with tumors exhibiting more aggressive biological behavior, including tumors with higher proliferative activity or greater metabolic demand, features that may independently contribute to incomplete resection and positive margins.

The most prominent and clinically relevant finding was a significantly increased risk of cervical lymph node metastasis in NM-PTMC. This association persisted after adjustment for potential confounders. Notably, extrathyroidal malignancy had no significant impact on any clinicopathological characteristics. However, patients in the NM-PTMC group underwent LND at a significantly higher rate than those in the other groups, particularly the Inc-PTMC group, in which LND was performed in only 2.0% of cases. Because lymph node metastasis can only be confirmed histologically in dissected specimens, the higher LND rate in the NM-PTMC group may have increased the likelihood of identifying microscopic nodal involvement that would otherwise have remained undetected. This could have artificially inflated the observed nodal metastasis rate in the NM-PTMC group relative to the Inc-PTMC group and this should be considered when interpreting the large OR for lymph node metastasis in the NM-PTMC group. The decision to perform LND in the NM-PTMC group was likely influenced by preoperative suspicion of nodal disease based on imaging or intraoperative findings; nonetheless, the possibility of ascertainment bias cannot be excluded in this retrospective cohort.

We also evaluated pathology reports according to the presence of concomitant Hashimoto's thyroiditis (HT), as previous studies have suggested that coexisting HT may influence the clinicopathological features of both PTC and PTMC, either favorably (24,25) or unfavorably (26). In our series, HT was more prevalent in the non-incidental and nuclear medicine-detected groups than in incidental PTMCs. However, no significant association was observed between the presence of HT and tumor characteristics in our analysis.

This study has several strengths. It represents one of the largest series focusing exclusively on PTMCs and, to our knowledge, is the first to investigate their clinicopathological features by detection method. Second, all cases were evaluated within a single tertiary center, ensuring standardized pathological assessment and uniform reporting. Third, Inc-PTMC and Non-Inc-PTMCs were defined carefully to avoid misclassification and overlap between the groups. The inclusion of three distinct cohorts (Inc-PTMC and Non-Inc-PTMC, and NM-PTMC) facilitated a comprehensive comparative analysis.

Study Limitations

The study also has several limitations. The relatively small number of NM-PTMC (n=24) and the retrospective design should be acknowledged as limitations. Although only 24 patients in the nuclear medicine-detected PTMC group underwent surgery and were included in the analysis, the total number of PTMCs identified by nuclear medicine imaging is likely to be higher, as not all such lesions necessarily proceed to surgery. In clinical practice, thyroid foci identified on imaging performed for non-thyroid malignancies are often not investigated further, leading to possible underdiagnosis, rather than true rarity, in this subgroup. Therefore, our findings should be interpreted as indicating a strong association rather than as a precise estimate of effect size; this is reflected by the large ORs and wide CIs resulting from the limited number of events in the nuclear medicine-detected group. Furthermore, long-term data on overall survival and disease-free survival were not available. An additional limitation warranting explicit discussion is the potential for detection bias in assessing cervical lymph node metastasis (see above).

Conclusion

In this retrospective cohort, PTMCs detected by nuclear medicine imaging were associated with less favorable pathological features than Inc-PTMCs and Non-Inc-PTMCs identified through conventional diagnostic methods. Despite their small size, these tumors showed a significantly higher frequency of cervical lymph node metastasis. While

the underlying mechanisms remain uncertain and selection bias cannot be excluded, our findings suggest that NM-PTMC may differ in their clinicopathological profiles from other PTMC subgroups. Accordingly, the context in which a PTMC is detected may provide additional information during risk assessment. Further prospective multicenter studies are required to validate these observations and clarify their potential implications for clinical decision-making.

Ethics

Ethics Committee Approval: This study was performed in accordance with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Hacettepe University (approval no: SBA 25/813, date: 23.09.2025).

Informed Consent: This retrospective cohort study included 407 patients diagnosed with PTMC at Hacettepe University Faculty of Medicine, Ankara, Türkiye between January 2008 and December 2020, who were identified through a comprehensive review of thyroidectomy pathology reports.

Footnotes

Authorship Contributions

Surgical and Medical Practices: C.S., Concept: S.H.O., G.K., J.K., M.F.B., A.G., Design: A.G., Data Collection or Processing: İ.Ç., B.E., G.K., Analysis or Interpretation: J.K., M.F.B., A.G., Literature Search: S.H.O., Writing: S.H.O., A.G.

Conflict of Interest: Murat Fani Bozkurt is the Editor-in-Chief of Molecular Imaging and Radionuclide Therapy. However, he was not involved in any stage of the editorial evaluation or decision-making process for this manuscript. The manuscript was evaluated by editors from institutions different from those of the authors. The remaining authors declared no conflicts of interest.

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