

Lymphatic Invasion in Bethesda VI Papillary Thyroid Microcarcinomas: A Single-Center Retrospective Analysis

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Abstract

Aim: Although small size in papillary thyroid microcarcinomas is generally associated with low risk, it may not reflect the biological behavior of the tumor. In this study, the effect of lymphatic invasion on metastatic risk and the metastatic characteristics of microcarcinomas with lymphatic invasion compared to macrocarcinomas were evaluated in a cohort with Bethesda VI diagnosis.

Methods: A total of 116 patients with Bethesda VI cytology were categorized into papillary microcarcinoma (n=35) and papillary macrocarcinoma (n=81) groups. Lymphatic and vascular invasion were evaluated separately. Risk factors for central lymph node metastasis and inter-group metastatic burden were compared.

Results: Vascular invasion was significantly more frequent in papillary macrocarcinomas (p=0.035), whereas lymphatic invasion rates were similar between the groups (p=0.385). In the papillary microcarcinoma group undergoing lymph node dissection, a significant association was detected between the presence of lymphatic invasion and central metastasis (p<0.001). Tumor size and multifocality were found to be non-significant in predicting metastasis. In the analysis performed, no difference was observed between the number of metastatic lymph nodes in lymphatic invasion-positive papillary microcarcinomas and macrocarcinomas (5.2 vs 4.9; p=0.597). A metastatic case with a 5 mm tumor size supported the independence of the aggressive phenotype from tumor size.

Conclusions: Since the presence of lymphatic invasion in papillary microcarcinomas suggests that the tumor's metastatic potential may be elevated to a level similar to that of macrocarcinomas, considering a more cautious strategy in the clinical management of these cases may be beneficial. However, due to the limited sample size, these findings are hypothesis-generating rather than definitive and should be validated in larger cohorts.

Keywords: Papillary thyroid microcarcinoma; Bethesda VI; lymphatic invasion; central lymph node metastasis

1. Introduction

The global incidence of papillary thyroid carcinoma (PTC) has shown a significant increase over the past three decades.^{1,2} However, the absence of a parallel increase in mortality despite the rising incidence suggests that a substantial proportion of these small lesions may be clinically insignificant.³ These epidemiological findings have drawn attention to the risk of overdiagnosis and overtreatment in PTMC management and have led to the emergence of conservative approaches such as active surveillance in low-risk cases.^{4,5} Current guidelines suggest that close follow-up protocols can be implemented instead of surgery in selected low-risk PTMC cases.⁶

However, microcarcinoma size does not definitively indicate indolent biological behavior. Clinical series and meta-analyses demonstrate that approximately 30-65% of PTMC cases develop central lymph node metastasis at the time of diagnosis or during follow-up.⁷⁻⁹ Although mortality is low in PTMC, lymph node metastasis increases recurrence rates. This leads to an increased need for reoperation and directly affects patient morbidity.

Lymphatic Invasion (LI) is defined by the presence of tumor cells

within lymphatic endothelium and is a critical parameter that plays a role in the pathway to nodal metastasis.¹⁰ While LI is a strong predictor of nodal metastasis in macrocarcinomas, its clinical impact in microcarcinomas remains controversial.^{11,12} While most PTMC series in the literature include incidentally detected tumors in postoperative pathology, this study consists of patients with preoperative Bethesda VI cytology.

The aim of this pilot study is to evaluate the relationship between lymphatic invasion and central lymph node metastasis in the PTMC subgroup within a PTC series with Bethesda VI diagnosis and to characterize the metastatic features of LI-positive microcarcinomas. Due to the limited sample size, this study aims to present hypothesis-generating findings rather than definitive conclusions.

2. Materials and Methods

Study Design and Ethics Approval

This study is a single-center, retrospective cohort consisting of patients who underwent total thyroidectomy with Bethesda VI cy-

Corresponding Author: Burak Aydoğan, baydogan1902@gmail.com, Received: 13.01.2026, Accepted: 17.02.2026, Available Online Date: 15.03.2026.

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tology between January 2015 and November 2025 at Çukurova University Medical Faculty Balçalı Hospital, General Surgery Clinic. The study protocol was approved by the Çukurova University Medical Faculty Clinical Research Ethics Committee (Decision No: 28, Date:09.01.2026).

Patient Selection

Inclusion criteria: Patients whose preoperative Fine Needle Aspiration Biopsy (FNAB) was performed at our hospital and reported as Category VI according to the Bethesda System (TBSRTC), with a final histopathological diagnosis of Papillary Thyroid Carcinoma (PTC) after total thyroidectomy, were included in the study.

Exclusion criteria: Non-PTC thyroid malignancies (Medullary, Anaplastic), patients with previous thyroid surgery history, and patients whose FNAB was performed at an external center and/or whose FNAB results were from an external center were defined as exclusion criteria.

Preoperative Evaluation

All patients underwent high-resolution cervical ultrasonography (USG) by experienced radiologists during the preoperative period. The decision for FNAB was made based on ultrasonographic malignancy risk features, including nodule size criteria. Dominant nodules (including size <1 cm) with high-risk features such as solid structure, marked hypoechogenicity, microcalcification, irregular margins, and lymph nodes showing suspicious cervical lymphadenopathy were selectively biopsied. This approach ensured that the microcarcinoma cases in the study represent a high-risk subgroup.

Surgical Procedure and Lymph Node Approach

The surgical approach was determined according to the patient's risk profile, bilaterality of nodules showing high-risk features, and current guidelines. The lymph node sampling strategy was as follows: Central and/or lateral neck dissection was performed in the presence of metastasis proven by preoperative USG and/or FNAB in lymph nodes, while intraoperative lymph node sampling was performed in cases of intraoperative suspicion (hard, enlarged, or macroscopically suspicious lymph nodes palpated in the operative field).

Histopathological Evaluation

Patients were divided into two main groups according to the largest diameter of the tumor in accordance with World Health Organization (WHO) classification: Microcarcinoma Group (PTMC): Tumor diameter ≤ 10 mm (n=35), Macrocarcinoma Group (PTC): Tumor diameter > 10 mm (n=81).

All surgical specimens were examined by pathologists specialized in thyroid pathology. Tumor size, histological variant, multifocality, tumor capsule invasion, and extrathyroidal extension (ETE) were recorded. The presence of Lymphovascular Invasion (LVI) was determined by detailed examination of routine Hematoxylin-Eosin (H&E) stained sections. LVI diagnosis was based on clear visualization of tumor cell clusters within vascular spaces or lymphatic channels; in suspicious cases that could be confused with retraction artifacts (shrinkage spaces), the final decision was made with senior pathologist opinion or consensus.

Statistical Analysis: Data analysis was performed using SPSS (Statistical Package for the Social Sciences) version 25.0 software (IBM Corp., Armonk, NY, USA). The normality distribution of continuous variables was evaluated by the Kolmogorov-Smirnov test, and variance homogeneity by the Levene test. Mann-Whitney U test was used for inter-group comparisons; Chi-square test was used for comparison of categorical variables. Fisher's Exact Test was applied in subgroup analyses with limited sample size (cells with expected value <5). Univariate and multivariate logistic regression analyses were performed to determine independent risk factors for central lymph node metastasis. A p-value < 0.05 was considered statistically significant for all tests.

3. Results

Comparison of General Demographic and Histopathological Data

A total of 116 papillary thyroid carcinoma patients included in the study were examined in two groups as Microcarcinoma (PTMC, n=35) and Macrocarcinoma (Macro-PTC, n=81) according to tumor size. The comparison of group data is presented in Table 1. No statistically significant difference was found between PTMC and Macro-PTC groups in terms of age (45.1±11.2 vs 46.8±14.3; p=0.612) and gender distribution (p=0.785). The mean tumor size was 7.6±1.9 mm in the PTMC group, while it was measured as 26.5±12.1 mm in the Macro-PTC group (p<0.001).

When tumor invasion characteristics were examined, extrathyroidal extension (ETE) and capsular invasion rates were found to be significantly higher in the Macro-PTC group compared to the PTMC group (p=0.048 and p=0.002, respectively). While Vascular Invasion was observed at a rate of 17.2% in the Macro-PTC group, it was detected in only 1 patient (2.8%) in the PTMC group, and this difference was statistically significant (p=0.035). In contrast, no statistically significant difference was observed between PTMC (22.9%) and Macro-PTC (30.8%) groups in terms of Lymphatic Invasion rates (p=0.385). The frequency of Central Lymph Node Metastasis (CLNM) was found to be 17.1% in the PTMC group and 34.6% in the Macro-PTC group (p=0.061).

Table 1
Demographic and histopathological characteristics of the study cohort: Comparison of Papillary Thyroid Microcarcinoma (PTMC) and Macrocarcinoma (Macro-PTC)

Characteristic	PTMC (n=35)	Macro-PTC (n=81)	p-value
Age (years), mean±SD	45.1±11.2	46.8±14.3	0.612
Gender (Female/Male)	28/7	63/18	0.785
Tumor Size (mm), mean±SD	7.6±1.9	26.5±12.1	<0.001*
Multifocality	12 (34.3%)	31 (38.3%)	0.684
Extrathyroidal Extension (ETE)	4 (11.4%)	23 (28.4%)	0.048*
Capsular Invasion	9 (25.7%)	46 (56.8%)	0.002*
Invasion Type			
Lymphatic Invasion (LI)	8 (22.9%)	25 (30.8%)	0.385
Vascular Invasion (VI)	1 (2.8%)	14 (17.2%)	0.035*
Central LN Metastasis (CLNM)	6 (17.1%)	28 (34.6%)	0.061

Table 2
Relationship between Lymphatic Invasion (LI) presence and metastatic outcomes in the PTMC subgroup undergoing lymph node dissection or lymph node sampling (n=16).

Feature	Lymphatic Invasion (+) (n=6)	Lymphatic Invasion (-) (n=10)	p-value
Central LN Metastasis			<0.001*
Present	6 (100%)	-	
Absent	-	10 (100%)	
Tumor Focality			0.315
Unifocal	4 (66.7%)	7 (70.0%)	
Multifocal	2 (33.3%)	3 (30.0%)	
Mean Metastatic LN Count	5.2±5.2	0	<0.001*

Table 3

Comparison of Microcarcinomas and Macrocarcinomas with positive Lymphatic Invasion in terms of metastatic burden

Table 3. Comparison of Microcarcinomas and Macrocarcinomas with positive Lymphatic Invasion in terms of metastatic burden

Variable	LI (+) PTMC (n=8)	LI (+) Macro-PTC (n=25)	p-value
Tumor Size (mm)	7.6±1.9	26.5±12.1	<0.001*
Total LN Removed	11.5±6.8	13.2±8.4	0.621
Metastatic LN Count	5.2±5.2	4.9±6.0	0.597
Max Metastatic LN (Range)	1-15	1-21	-
LN Metastasis Ratio (LNR)	45.2%	37.1%	0.563

Table 4

Analysis of preoperative USG findings and histopathological invasion types (Lymphatic/Vascular) of aggressive microcarcinoma cases (n=5)

Case No	Age/Sex	Preop USG Features	Pathological Size	Lymphatic Inv.	Vascular Inv.	Metastatic LN
1	45/F	Microcalcification, Irregular Margin	8.0 mm	(+)	(-)	2
2	52/F	Solid, Markedly Hypoechoic	8.2 mm	(+)	(-)	1
3	29/F	Irregular Margin, 'Taller-than-Wide'	7.0 mm	(+)	(-)	4
4	31/M	Suspicious LAP, Microcalcification	5.0 mm	(+)	(+)	6
5	48/F	Dominant Nodule, Hypoechoic	9.0 mm	(+)	(-)	15

Table 5

Analysis of risk factors associated with Lymph Node Metastasis development in the microcarcinoma group (n=16) undergoing Lymph Node Sampling or Central/Lateral neck dissection.

Risk Factor	Metastasis PRESENT (n=6)	Metastasis ABSENT (n=10)	p-value
Lymphatic Invasion			
Positive (+)	6 (100%)	0 (0%)	<0.001*
Negative (-)	0 (0%)	10 (100%)	
Vascular Invasion			
Positive (+)	1 (16.7%)	0 (0%)	0.375
Negative (-)	5 (83.3%)	10 (100%)	
Tumor Size			
> 5 mm	5 (83.3%)	8 (80.0%)	1.000
≤ 5 mm	1 (16.7%)	2 (20.0%)	
Multifocality			
Present	2 (33.3%)	3 (30.0%)	1.000
Absent (Unifocal)	4 (66.7%)	7 (70.0%)	
Age			
< 45 years	4 (66.7%)	4 (40.0%)	0.315
≥ 45 years	2 (33.3%)	6 (60.0%)	

Relationship Between Lymphatic Invasion and Metastasis in Microcarcinomas

Data from 16 patients in the PTMC group who underwent central neck dissection or lymph node sampling were analyzed according to the presence of Lymphatic Invasion in Table 2. While central lymph node metastasis was detected in all 6 patients with Lymphatic Invasion, no metastasis was observed in any of the 10 patients without Lymphatic Invasion. This difference was found to be statistically highly significant ($p<0.001$). Additionally, the mean number of metastatic lymph nodes was 5 in the Lymphatic Invasion positive group and 0 in the negative group ($p<0.001$). No significant relationship was found between tumor focality (unifocal/multifocal) and Lymphatic Invasion ($p=0.315$).

Evaluation of the Effect of Lymphatic Invasion on Metastasis

To evaluate the effect of Lymphatic Invasion development on metastatic burden, PTMC (n=8) and Macro-PTC (n=25) cases with positive Lymphatic Invasion were compared in Table 3. Despite a

significant difference in tumor size between the two groups (7.6 mm vs 26.5 mm; $p<0.001$), no statistically significant difference was found in terms of total number of lymph nodes removed ($p=0.621$), number of metastatic lymph nodes detected (5.2±5.2 vs 4.9±6.0; $p=0.597$), and Lymph Node Metastasis Ratio (LNR, 45.2% vs 37.1%; $p=0.563$). This biological equivalence is visualized in Figure 1, showing the metastatic burden distribution.

Characteristics of Aggressive Microcarcinoma Cases

The radiological and pathological features of 5 cases in the PTMC group showing aggressive course and lymph node metastasis are summarized in Table 4. Preoperative ultrasonographic examination of all cases showed the presence of risk findings such as microcalcification, irregular margins, hypoechoic, or suspicious lymphadenopathy (LAP). Pathological examination revealed Lymphatic Invasion positivity in all 5 cases. In the 31-year-old male patient (Case 4) with the smallest tumor size (5.0 mm) in

the series, a total of 6 metastatic lymph nodes were detected along with simultaneous Lymphatic and Vascular Invasion.

Univariate Analysis of Risk Factors for Central Lymph Node Metastasis

Risk factors associated with the development of central lymph node metastasis in the microcarcinoma group (n=16) undergoing intraoperative lymph node sampling or central/lateral neck dissection were examined by Univariate analysis using Fisher's Exact Test (Table 5). As a result of the analysis, Lymphatic Invasion was determined to be the only parameter showing a statistically significant relationship with the presence of metastasis ($p<0.001$). No statistically significant relationship was found between central metastasis development and tumor size being greater or less than 5 mm ($p=1.000$), multifocality ($p=1.000$), age ($p=0.315$), and presence of Vascular Invasion ($p=0.375$). One patient in the metastasis-detected group had a tumor size of 5 mm.

4. Discussion

An important methodological feature of this study is that it includes patients with preoperatively known malignancy diagnosis who underwent SLND and lymph node sampling, rather than incidental microcarcinomas. In our cohort, some cases had lymph node metastasis or suspicion preoperatively; in other cases, suspicious lymph nodes were sampled during intraoperative central compartment exploration. In both situations, metastasis was histopathologically confirmed in the removed lymph nodes. However, postoperative histopathological examination revealed that the primary tumor size causing metastatic disease was ≤ 1 cm in some cases. These cases represent a subgroup showing clinically aggressive behavior despite being microcarcinomas. This reduces the potential selection bias resulting from the natural indolent course of incidental tumors seen in many PTMC series in the literature. However, performing dissection only in the presence of clinically or intraoperatively suspicious lymph nodes creates another selection bias leading to selection of high-risk patients. This limits the generalizability of our findings to the entire PTMC population.

A significant relationship was found between the presence of Lymphatic Invasion (LI) and nodal metastasis in the PTMC subgroup undergoing intraoperative lymph node sampling or central neck dissection ($p<0.001$). While lymph node metastasis was detected in all LI-positive PTMC cases, no metastasis was observed in any LI-negative cases, indicating that the presence of lymphatic invasion is a histopathological marker associated with metastatic potential in our study. However, the strength of this relationship may be affected by selection bias due to lymph node sampling being performed only in the presence of intraoperatively suspicious lymph nodes. This consistent relationship between Lymphatic invasion and nodal spread shown in this study has also been reported in larger PTC series.^{10,13}

Meta-analyses have revealed that lymph node metastasis prevalence in PTMC is at clinically significant levels (20-60%), and in these studies, age, gender, multifocality, capsular invasion, and extrathyroid extension have been defined as independent risk factors.¹⁴⁻¹⁶ Contrary to previous studies showing multifocality as one of the main determinants of pathological aggressiveness in PMTC, in this study, the majority of our microcarcinoma group with LI positivity and metastatic course consists of unifocal tumors. This finding shows that metastatic potential is independent of multifocality; even a single focus of 8 mm can cause widespread lymph node metastasis. This finding suggests that, as in similar studies in the literature, ≤ 1 cm tumor size and unifocal involvement are not sufficient safety parameters alone in conservative treatment

indication.¹³

The second main finding of the study is the similarity of metastatic burden parameters between the two groups. PTMC and Macro-PTCs showed no significant difference in terms of lymph node metastasis rate and number of metastatic lymph nodes. As detailed in Table 3, when comparing Lymphatic Invasion positive microcarcinomas (mean 7.6 mm) with macrocarcinomas (mean 26.5 mm), no statistical difference was observed in mean number of metastatic lymph nodes (5.2 vs 4.9, $p=0.597$) and lymph node ratio (LNR). The distribution analysis presented in Figure 1 shows that the metastatic burden in the microcarcinoma group is similar to that of macrocarcinomas. These findings put forward the hypothesis that the metastatic potential of the tumor may increase independently of size in the presence of lymphatic invasion. However, this comparison includes only 16 patients (6 PTMC, 10 macrocarcinomas) and the statistical power is very low. This should be evaluated as a hypothesis for future studies rather than a definitive conclusion and should be investigated in larger series.

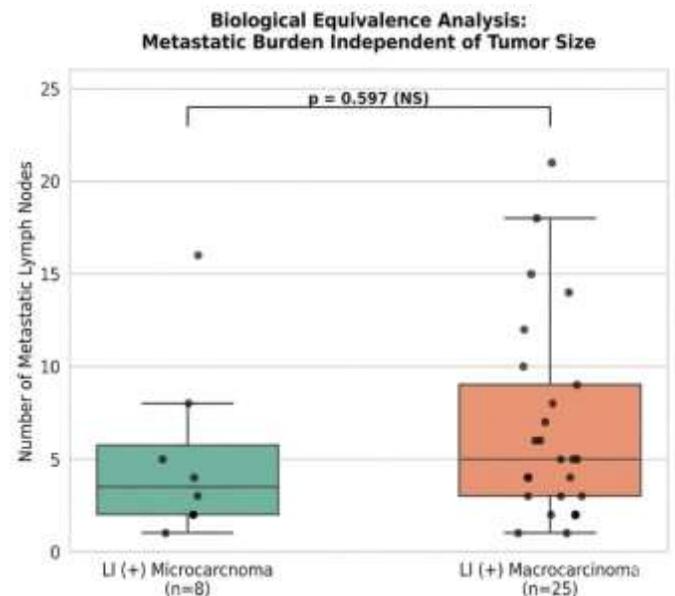


Figure 1

Comparison of Papillary Thyroid Microcarcinomas (n=8) with Lymphatic Invasion (LI) positivity and Macrocarcinomas (n=25) in terms of metastatic burden. Horizontal lines within boxes represent median values, and black dots represent individual patient data. No statistically significant difference was found between the two groups in terms of number of metastatic lymph nodes ($p=0.597$, Mann-Whitney U Test)

Current management guidelines (ATA) recommend avoiding aggressive surgical approaches in Papillary Thyroid Microcarcinomas (PTMC) and prioritizing conservative strategies such as Active Surveillance.¹⁷ This approach is largely based on the acceptance of tumor size as a prognostic marker. The findings presented in this study suggest that this approach focusing on tumor size may be insufficient in a "high-risk" microcarcinoma subgroup harboring critical histopathological risk factors such as Lymphatic Invasion (LVI).

These pilot findings suggest that the presence of lymphatic

invasion may be an important risk indicator in microcarcinomas with preoperative malignancy diagnosis. Detection of LI in lobectomy material may indicate the biological aggressiveness of the tumor, independent of size criteria. Despite the limited sample size, the consistent relationship between LI and metastasis can be evaluated as a clinically meaningful signal regarding the invasive biology of the tumor.

Limitations

The main limitation of this study is its single-center and retrospective design, which may limit the generalizability of the results. Secondly, the relatively small sample size (n=16) especially in the microcarcinoma subgroup undergoing central dissection and lymph node sampling is a factor that may affect statistical power. Thirdly, performing “therapeutic” dissection only in clinically suspicious cases instead of routine prophylactic dissection in our clinic may create a selection bias leading to biological selection of more aggressive cases. Additionally, since the study is cross-sectional, it does not include follow-up data on the effects of lymphatic invasion on long-term recurrence and survival.

5. Conclusions

The findings of this study suggest that in the clinical management of papillary thyroid microcarcinomas, in addition to tumor size, the presence of lymphatic invasion (LI) reflecting the biological behavior of the tumor is also an important prognostic indicator. Our analyses indicate that microcarcinomas with lymphatic invasion positivity may exhibit a metastatic burden similar to macrocarcinomas. The example case in our series with a size of 5 mm but with detected metastasis also supports that aggressive course potential should not be overlooked even in sub-centimetric tumors. In conclusion, while size is an important criterion in the clinical decision-making process, adopting a more careful evaluation and management strategy may be beneficial in cases with LI presence, especially independent of tumor diameter.

Statement of ethics

This retrospective study was approved by the Çukurova University Medical Faculty Clinical Research Ethics Committee (Decision No: 28, Date:09.01.2026).

genAI

No artificial intelligence-based tools or generative AI technologies were used in this study. The entire content of the manuscript was originally prepared, reviewed, and approved by both authors.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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