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# Histopathological Evidence of Lymph Node Metastasis in Papillary Thyroid Carcinoma

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**Abstract** Prophylactic lymph node dissection is still controversial due to the potentially surgery-related morbidity in management of papillary thyroid carcinomas. So, some histopathological predictors for lymph node metastasis in thyroidectomy specimens may reveal importance. The objective of this study was to define histomorphological indicators of lymph node metastasis in the patients who had been performed thyroidectomy without lymph node dissection. Clinicopathological features of patients archived in Department of Pathology at Trakya University Medical Faculty were reviewed. A total of 211 patients who had been diagnosed as papillary carcinoma and had been performed total thyroidectomy/lobectomy with central/cervical lymph node dissection were included in the study. Clinical features (age, gender, preoperative/postoperative clinical, and laboratory findings) and histopathological features (histological variant, tumor size, focality, extrathyroidal extension, tumor border, lateral tubular growth, intraglandular dissemination, stromal and lymphocytic tumor response, lymphocytic thyroiditis, lymphovascular invasion, lymph node metastasis, number of metastatic lymph nodes, extranodal extension, size of the metastatic foci) were evaluated. Male gender, conventional variant, tumor size greater than 10 mm, multifocality, extrathyroidal extension, lateral tubular growth, intraglandular dissemination, lymphocytic and stromal tumor response, and absence of lymphocytic thyroiditis were predictive, and older age (≥45 years) and follicular variant PTC were protective for lymph node metastasis. In order to optimize the management

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of papillary thyroid carcinomas, pathologists should search for the clues of lymph node metastasis particularly intraglandular dissemination, lateral tubular growth, tumor border and lymphocytic/stromal tumor response, multifocality, concomitant lymphocytic thyroiditis besides the actual prognostic criteria especially in younger aged male patients.

**Keywords** Papillary thyroid carcinoma · Clinicopathological predictors · Lymph node metastasis · Stromal tumor reaction · Lymphocytic tumor reaction

## Introduction

Incidences of papillary thyroid carcinoma (PTC), the most common malignancy of the thyroid gland, have been increasing over the past two decades [1–3]. Although PTC generally follows an indolent course, patients with certain clinicopathological features may have a poor prognosis. Accordingly, 18 classification systems have been proposed for defining the characteristics of aggressive tumor behaviors, beginning with the European Organization for Research and Treatment of Cancer (EORTC) [4] (1979), and including the systems proposed by the Mayo Clinic (Age, Grade, Extent, Size or AGES) [5]; the Lahey Clinic (Age, Metastases, Extent, Size or AMES) [6]; the Mayo Clinic (Metastases, Age, Complete resection, Invasion, Size or MACIS) [7]; the Ankara Oncology Training and Research Hospital, Ankara, Turkey (Ankara) [8]; and most recently, the system designed by the American Joint Committee on Cancer, 7th Edition (AJCC) [2]. Furthermore, the management guidelines adopted by the American Thyroid Association (ATA) [9], the American Association of Clinical Endocrinologists [10], the American Association of Endocrine Surgeons [10], the British Thyroid Association [11], and the National Cancer Center Network (NCCN) [12] have been based on these characteristics. Total thyroidectomy/lobectomy specimens can provide the suggested prognostic criteria, aside from lymph node status; however, lymph node metastasis is common in PTC, with approximately 40 % of patients having positive nodes at initial presentation [13], with higher rates of regional recurrence [14, 15] and distant metastasis [16]. It has been reported that 50–60 % of patients without clinical and radiological evidence of metastatic nodes have lymph node metastasis [17, 18]. Although AJCC [2] stratifies pN1 into pN1a and pN1b according to the compartment of the metastatic lymph nodes, neither the number of positive nodes or the size of the metastatic foci in the nodes are considered for tumor staging. That said, a number of recent studies have reported that the number of metastatic nodes [19], the extranodal extensions [1], and the size of the metastatic foci are independent risk factors indicating recurrence [20]. Moreover, the practice of prophylactic central lymph node dissection is still controversial due to the potential for surgery-related morbidity. Since PTC has a favorable prognosis according to the tumor node metastasis (TNM) classification and optimal management of the tumor, recent studies have attempted to define some histopathological features of thyroidectomy specimens that can be used to predict lymph node metastasis [21, 22], which have included the pattern of the tumor border, lateral tubular growth, intraglandular dissemination, extrathyroidal extension (ETE) [23], and stromal tumor response [22]. Some authors have suggested that immune response presenting as tumor-associated lymphocytes or lymphocytic thyroiditis (LT) affects the prognosis of PTC [23, 24] and with a low incidence of central nodal metastasis in LT-associated PTC [25, 26]. However, the AJCC TNM classification system does not consider multifocality to be a feature of the TNM stage [2], and it has been reported that multifocal PTCs have higher recurrence rates and a higher incidence of postoperative disease progression [27–29].

The aim of this study is to identify a histomorphological indicator or indicators of lymph node metastasis in patients undergoing a thyroidectomy/lobectomy without lymph node dissection, and also an indicator of a more disseminated disease in patients undergoing only a lobectomy. To this end, the intention is to evaluate the relationships between potential histological reasons behind lymph node metastasis, including the pattern of the tumor border, lateral tubular growth, intraglandular dissemination, stromal tumor response, lymphocytic tumor response, concomitant LT, and the prognostic criteria proposed by AJCC [2], and also to investigate the associations between these features and the features of metastatic nodes and tumor focality.

## Patients and Methods

### Patient Selection

The medical reports of patients who presented at the Department of Pathology of the Trakya University Medical Faculty (Edirne, Turkey) were reviewed (between August 2007 and August 2014). The study protocol was approved by the local Ethics Committee of the University Hospital of Trakya University, Edirne (TUTF-BAEK 2014/167). The patients were selected according to the following criteria: (1) patients diagnosed with PTC and (2) patients who had undergone total thyroidectomy/lobectomy with central/cervical lymph node dissection. In all, 211 patients who fulfilled the criteria were included in the study. Patient data regarding age at the time of diagnosis, sex, serum levels of antithyroglobulin antibodies (anti-TG) and antithyroid peroxidase antibodies (anti-TPO), presence/absence of preoperative suspected lymph nodes, as revealed by ultrasound (USLAP), status of radioactive iodine therapy (RAI), and data from clinical follow-ups (recurrence of disease, reoperation, retreatment of RAI) were obtained

from the records of the Department of Clinical Endocrinology and Metabolism Diseases and the Department of General Surgery. Data on the number and size of tumors was obtained from the hospital database. Hematoxylin and eosin-stained slides obtained from paraffin-embedded blocks of the total thyroidectomy/lobectomy specimens and lymph node dissections were re-evaluated by two pathologists (N.C and E.T). The histopathological features were evaluated in the largest tumor focus in cases in which multifocal tumors were present.

### Definitions of Clinicopathological Criteria

Cases exhibiting no metastatic foci in the lymph nodes in an evaluation of two serial slides were classified as "lymph node negative." Tumor border, lateral tubular growth, and intraglandular dissemination were interpreted in line with the approach of Jung et al. [21]. Tumors exhibiting an irregular spiculated margin or more than three penetrating structures, including tumor follicles, into an adjacent thyroid were accepted as infiltrative tumors (Fig. 1a). Regardless of the presence of fibrous tumor capsules, well-circumscribed tumors with no infiltration into the surrounding thyroid tissue were defined as smooth bordered tumors; tumors encircled by a fibrous capsule were regarded as encapsulated (Fig. 1b); lateral tubular growth was defined as an elongated tubular follicle (not more than one follicle) extending perpendicular to the invasive tumor border (Fig. 1c); and intraglandular dissemination was defined as clusters of tumoral follicles measuring less than 1 mm and located at least 500 μm away from the primary tumor (Fig. 1d).

The clinical features considered in the statistical analyses included age at the time of diagnosis (<45 and ≥45 years), sex (male or female), serum levels of anti-TG (positive, negative), serum levels of anti-TPO (positive, negative), USLAP (present, absent), and RAI therapy (present, absent). Histopathological features considered in the statistical analyses were the histological variant (conventional variant PTC [CVPTC], follicular variant PTC [FVPTC]), tumor size (≤10 mm, >10 mm), tumor focality (unifocal, multifocal), extrathyroidal extension (ETE) (absent, present), tumor border (TB) (smooth bordered/encapsulated, infiltrative), lateral tubular growth (LTG) (absent, present), intraglandular dissemination (IGD) (absent, present), stromal tumor response (STR) (absent, mild, severe) (Fig. 1e), lymphocytic tumor response (LTR) (in three grades, according to the severity of infiltration and regardless of concomitant LT, being absent, mild, severe) (Fig. 1f), tumor surrounding LT (absent, present), lymphovascular invasion (LVI) (absent, present), lymph node metastasis (absent, present), number of metastatic lymph nodes (<5, ≥5) [19], extranodal extension (absent, present) [19], and the size of the metastatic foci (<2 mm; micrometastasis, ≥2 mm; macrometastasis) [20].

### Statistical Analysis

The statistical analysis was carried out using SPSS v20.0 (IBM SPSS Inc., Chicago, IL, USA). A chi-square test

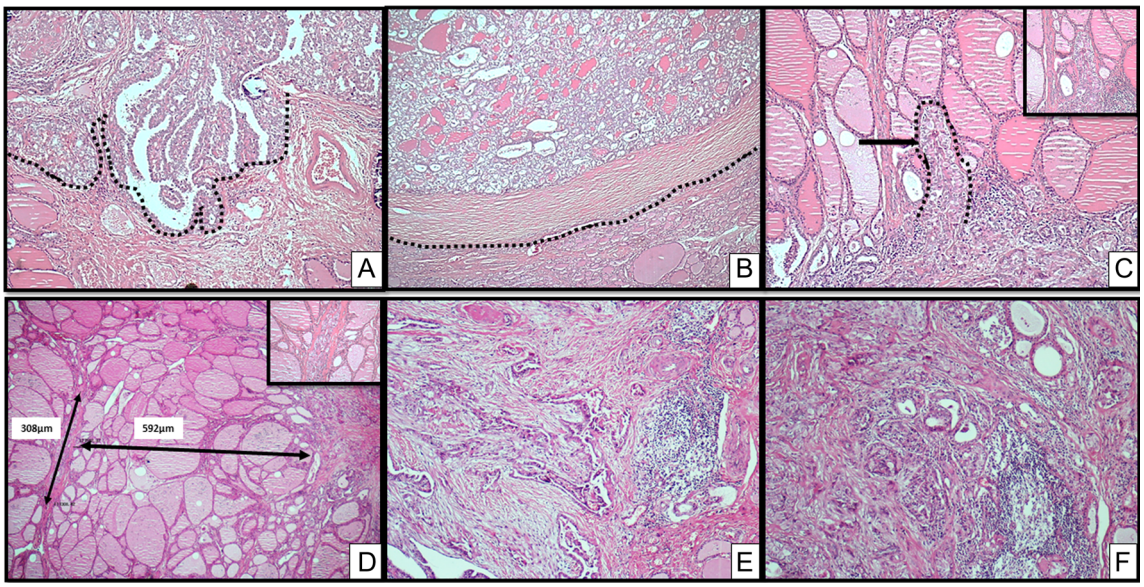


**Fig. 1** **a** Infiltrative tumor border defined as more than three follicles penetrating through the adjacent thyroid (*dashed lines*) (hematoxylin and eosin ×100), **b** encapsulated tumor border (*dashed lines*) (hematoxylin and eosin ×100), **c** a tumor follicle spreading perpendicular to the route of lateral tumor border accepted as lateral tubular growth (*arrow, dashed lines*) (closer view in the inset) (hematoxylin and eosin ×200), **d** intraglandular dissemination, note the distance (more than 500 μm) between the tumor and tumoral follicle measuring smaller than 1 mm (*black arrows*, closer view in the inset) and also, disseminated small tumor islands accepted as intraglandular dissemination (*yellow arrows*) (hematoxylin and eosin ×50), **e** severe stromal tumor response within the tumor (hematoxylin and eosin ×100), **f** lymphocytic tumor response around the tumor (hematoxylin and eosin ×200)

(Pearson, Yates, or Fisher) was used to compare the clinicopathological features in terms of the lymph node metastasis (present vs absent), the number of metastatic lymph nodes (<5 vs ≥5), the size of the nodal metastatic foci (<2 vs ≥2 mm), and extranodal extension (present vs absent), with the results expressed in numbers and percentages. In addition, possible relationships between the lymph node status and clinicopathological features were evaluated in microcarcinomas and carcinomas sized >10 mm. Also, other clinicopathological features related to tumor size (≤10 vs >10 mm), multifocality (present vs absent), LVI (present vs absent), and ETE (present vs absent) were compared using a chi-square test. The effects of clinicopathological features on lymph node metastasis were examined using a logistic regression analysis. The odds ratio and a 95 % confidence interval of the clinicopathological features were calculated. A $p$ value of <0.05 was considered statistically significant.

## Results

### Clinicopathological Features of Patients in the Study Group

The mean age of the patients was 46.6±13.2 years. Those aged <45 years numbered 86 (40.7 %) while those ≥45 years numbered 125 (59.3 %). Of the 211 patients, 172 (81.5 %) were female, and 39 (18.5 %) were male. Lymph node metastasis was present in 61 (29 %) of the patients, while 150 (71 %) of the patients exhibited no lymph node metastasis. Among all cases, the histological variant of the tumor was CVPTC in 153 (72.5 %) of the patients and FVPTC in 58 (27.5 %) of the patients. When the patients were grouped according to tumor size, 112 (57.3 %) had microcarcinoma, while the tumor size was larger than 10 mm in 99 (42.7 %) of the cases. Multifocality of the tumor was present in 99 (47 %) of the cases, and 112 (53 %) had unifocal tumors. The tumor was limited to the thyroid in 146 (69.2 %) of the patients, while an extrathyroidal extension was present in 65 (30.8 %). In 110 (52.1 %) patients, the pattern of tumor border was infiltrative. Lateral tubular growth was present in 146 (69.2 %) cases, and the tumor revealed IGD in 73 (34.6 %) patients. While LTR was observed in 126 (59.7 %), STR was seen in 193 (91.5 %) of the cases, and LT accompanied PTC in 89 (42.2 %) of the patients.

The mean follow-up was 31.6±21.1 months (range 10–97 months). The preoperative serum levels of anti-TG were positive in 37 (28.5 %) of 130 patients, anti-TPO were positive in 39 (31.2 %) of 125 patients. USLAP was present in 31 (14.7 %) of the patients in the entire group. RAI therapy was given to 141 (66 %) of the patients and recurred in three (1.4 %) of the patients in the study group, who underwent reoperation and retreatment with RAI. At the time of the initial diagnosis, all of these female patients had positive serum anti-TG and positive serum anti-TPO, and their tumors revealed IGD and TSR. Furthermore, two of them were in the younger age group (<45 years), with LTG, TLR, concomitant LT, LVI, CVPTC, multifocality, microcarcinoma, and ETE. Only one had a metastatic lymph node at the time of the initial diagnosis. None of the patients had a distant metastasis.

### Comparisons of Clinicopathological Features and Lymph Node Metastasis

The relationships between the clinicopathological features and the lymph node metastasis, obtained through a statistical analysis and the rate of lymph node metastasis according to clinicopathological criteria, are summarized in Table 1. A younger age (<45 years, $p$=0.005) had a significant relationship with lymph node metastasis (mean age for lymph node metastasis was 43±14.5). An evaluation of the age at the time of diagnosis in decades gave results that were similar to the age of the patients when evaluated in years and exhibited a significant association, indicating that lymph node metastasis was more common in younger patients (<40 years, $p$=0.023), particularly those in the fourth decades of their lives (Fig. 1). According to the results, the male gender ($p$=0.001), CVPTC ($p$<0.001), tumor size greater than 10 mm ($p$<0.001), infiltrative tumor border ($p$=0.003), LTG ($p$<0.001), IGD ($p$<0.001), STR ($p$<0.001), ETE ($p$<0.001), and USLAP ($p$<0.001) were associated significantly with lymph node metastasis. Lymphocytic tumor response ($p$=0.058) and multifocality ($p$=0.052) exhibited close to a statistically significant association with lymph node metastasis, indicating that the rate of lymph node metastasis was higher in cases with multifocal tumors and tumors with lymphocytic tumor response than in cases with unifocal tumors and tumors without lymphocytic tumor response. No association was identified in univariate analyses between concomitant LT, preoperative serum levels of anti-TG and anti-TPO antibodies, and lymph node status.

### Comparisons of Clinicopathological Features and Lymph Node Metastasis According to Tumor Size

The relationships between clinicopathological features and lymph node status were evaluated in groups differentiated by tumor size (≤10 vs >10 mm), as presented in Supplemental Table 1. In the microcarcinoma group, lymph node metastasis

**Table 1** Comparisons of clinicopathological features by lymph node metastasis

| Variables | | Lymph node metastasis | | *p* | OR (95 % CI) |
|---|---|---|---|---|---|
| | | *Present* n (%) | *Absent* n (%) | | |
| Age | *<45 years* | 34 (55.7) | 52 (34.7) | **0.005** | 1.6(1.1–2.2) |
| | *≥45 years* | 27 (44.3) | 98 (65.3) | | 0.6(0.4–0.9) |
| Sex | *Male* | 20 (32.8) | 19 (12.7) | **0.001** | 2.5 (1.4–4.4) |
| | *Female* | 41 (67.2) | 131(87.3) | | 0.7 (0.6–0.9) |
| Variant | *CVPTC* | 55 (90.2) | 98 (65.3) | **<0.001** | 1 *(Reference category)* |
| | *FVPTC* | 6 (9.8) | 52 (34.7) | | 0.7(0.6–0.8) |
| Size | *<10 mm* | 19 (31.1) | 102(68.0) | **<0.001** | 0.2 (0.1–0.4) |
| | *≥10 mm* | 42 (68.9) | 48 (32.0) | | 1 *(Reference category)* |
| Tumorfocality | *Unifocal* | 26 (42.6) | 86 (57.3) | 0.052 | 0.5 (0.3–1.0) |
| | *Multifocal* | 35 (57.4) | 64 (42.7) | | 1 *(Reference category)* |
| TB | *S/E* | 19 (31.1) | 82 (54.7) | **0.003** | 0.3 (0.2–0.7) |
| | *Infiltrative* | 42 (68.9) | 68 (45.3) | | 1 *(Reference category)* |
| ETE | *Absent* | 24 (39.3) | 123 (82) | **<0.001** | 1 *(Reference category)* |
| | *Present* | 37 (60.7) | 28 (18.7) | | 6.7 (3.4–12.9) |
| LTG | *Absent* | 3 (4.9) | 62 (41.3) | **<0.001** | 0.1 (0.1–0.2) |
| | *Present* | 58 (95.1) | 88 (58.7) | | 1 *(Reference category)* |
| IGD | *Absent* | 26 (42.6) | 112(74.7) | **<0.001** | 0.2 (0.1–0.4) |
| | *Present* | 35 (57.4) | 38 (25.3) | | 1 *(Reference category)* |
| LTR | *Absent* | 17 (27.9) | 68 (45.3) | 0.058 | 1 *(Reference category)* |
| | *Mild* | 29 (47.5) | 57 (38.0) | | 2.0 (1.0–4.0) |
| | *Severe* | 15 (24.6) | 25 (16.7) | | 2.4 (1.0–5.5) |
| STR | *Absent* | 2 (3.3) | 16 (10.7) | **<0.001** | 1 *(Reference category)* |
| | *Mild* | 14 (23.0) | 69 (46.0) | | 1.6 (0.3–7.8) |
| | *Severe* | 45 (73.8) | 65 (43.3) | | 5.5 (1.2–25.2) |
| LT | *Absent* | 41 (67.2) | 81 (54.0) | 0.108 | 1 *(Reference category)* |
| | *Present* | 20 (32.8) | 69 (46.0) | | 0.5 (0.3–1.0) |
| Anti-TG | *Negative* | 51(83.6) | 123(82.0) | 0.937 | 0.8 (0.4–1.9) |
| | *Positive* | 10(16.4) | 27(18.0) | | 1 *(Reference category)* |
| Anti-TPO | *Negative* | 26 (72.2) | 60 (67.4) | 0.755 | |
| | *Positive* | 10 (27.8) | 29 (32.6) | | 1 *(Reference category)* |
| USLAP | *Absent* | 38 (62.3) | 142 (94.7) | **<0.001** | 10.7 (4.4–25.9) |
| | *Present* | 23 (37.7) | 8 (5.3) | | 1 *(Reference category)* |

*CVPTC* conventional variant papillary thyroid carcinoma, *FVPTC* follicular variant papillary thyroid carcinoma, *TB* tumor border, *ETE* extrathyroidal extension, *LTG* lateral tubular growth, *IGD* intraglandular dissemination, *LTR* lymphocytic tumor response, *STR* stromal tumor response, *LT* lymphocytic thyroiditis, *S/E* smooth bordered/encapsulated, *Anti-TG* antithyroglobulin antibodies, *Anti-TPO* antithyroid peroxidase antibodies, *USLAP* preoperative suspicious lymph nodes by ultrasound, *OR* odds ratio, *CI* confidence interval

was associated with ETE ($p$=0.049), LTG ($p$=0.038), and USLAP ($p$<0.001). There was a possibly close statistically significant association between the male gender ($p$=0.06), severe LTR ($p$=0.053), and severe STR ($p$=0.065). In the group of tumors sized >10 mm, a significant association was identified between lymph node metastasis and a younger age (<45 years) ($p$=0.041), CVPTC ($p$<0.001), infiltrative tumor border ($p$=0.001), presence of ETE ($p$<0.001), LTG ($p$<0.001), IGD ($p$=0.001), severe STR ($p$=0.004), and USLAP ($p$=0.009). A comparison of the results of two groups showed that a younger age, CVPTC, infiltrative tumor border, IGD, and STR had significant associations with lymph node metastasis, particularly in tumors sized >10 mm.

## Effects of clinicopathological features on lymph node metastasis

Principally, the effects of clinicopathological features on lymph node metastasis were analyzed in the entire study

sample through logistic regression analyses, and subsequent logistic regression analyses were carried out to evaluate the impacts of these features on tumor size, tumor focality, and ETE (Table 2).

*In the Entire Study Sample*

In the logistic regression analyses applied to the entire study sample, younger age (<45 years), male gender, tumor size ≥10 mm, multifocality, presence of ETE, LTG, IGD, severe LTR, and an absence of a tumor surrounding LT were found to be predictive of a lymph node metastasis.

*According to Tumor Size*

The logistic regression analyses revealed that while the male gender was a predictor of lymph node metastasis in microcarcinomas, a younger age, male gender, multifocality, and presence of ETE were predictors of tumors sized ≥10 mm.

*According to Tumor Focality*

Younger age, male gender, and LTG were predictors of unifocal tumors, while male gender, larger tumor size (≥10 mm), presence of ETE, presence of IGD, presence of LTR, presence of STR, and absence of LT predicted lymph node metastasis in multifocal tumors.

*According to ETE*

Lymph node metastasis was affected by younger age, the presence of LTG, and the presence of IGD in tumors limited to the thyroid, while male gender, larger tumor size (≥10 mm), multifocality, and an absence of LT were predictors of lymph node metastasis in tumors exhibiting ETE.

**Comparisons of Clinicopathological Features According to the Number of Metastatic Lymph Nodes/Size of the Nodal Metastatic Foci/Extranodal Extension in the Lymph Node-Positive Group**

The association between the clinicopathological features and the number of metastatic lymph nodes/size of the nodal metastatic foci/extranodal extension was evaluated in the lymph node-positive group (data not shown). No significant relationship was identified between the clinicopathological features and number of metastatic lymph nodes or the size of the metastatic foci, and none of these clinicopathological features, except male gender ($p$=0.048), was found to be associated with an extranodal tumor extension. There was a possibly close significant association between serum level of anti-TPO and the number of metastatic lymph nodes ($p$=0.076).

**Comparisons of Clinicopathological Features According to Tumor Size, Multifocality, Lymphovascular Invasion, and Extrathyroidal Extension**

An evaluation was made of the associations between such prognostic histopathological features as tumor size, ETE and multifocality, and LVI and other clinicopathological features (Table 3). A greater tumor size (≥10 mm) was found to be significantly and statistically related with the male gender ($p$=0.014), intraglandular dissemination ($p$=0.045), and stromal tumor response ($p$=0.004). In contrast, no significant association was identified between multifocality and clinicopathological features. A significant relationship was noted between LVI and younger age (<45 years, $p$=0.007), male gender ($p$=0.003), CVPTC ($p$<0.001), infiltrative tumor border ($p$<0.001), lateral tubular growth ($p$<0.001), intraglandular dissemination ($p$<0.001), and severe stromal tumor response ($p$<0.001). Although there was no significant association in the groups, the frequency of LVI increased in line with the severity of lymphocytic tumor response ($p$= 0.059). The presence of ETE was seen to be related significantly with CVPTC ($p$=0.001), infiltrative tumor border ($p$<0.001), lateral tubular growth ($p$<0.001), intraglandular dissemination ($p$<0.001), severity of stromal tumor response ($p$<0.001), and lymphocytic tumor response ($p$<0.001).

## Discussion

In the molecular age of the tumors bearing too many questions to be answered, the present study attempts to identify the numerous histological clues hidden in the primary tumor (lateral tubular growth, tumor size greater than 10 mm, conventional variant PTC), in the patterns of tumor extension (ETE, multifocality, intraglandular dissemination), and in the tumor surrounding events (lymphocytic tumor response, severe stromal tumor response, and absence of concomitant lymphocytic thyroiditis) as the predictors of lymph node metastasis, as a whole rather than in fragments. The most remarkable feature identified in this study can be said to be the younger age of the patient (<45 years) as an indicator of lymph node metastasis, which is also one of the most current issues in the management of PTC. Unfortunately, the results were unable to reflect the signs of the properties of metastatic nodes, which are narrated as prognostic features of PTC. This study revealed that predictors of lymph node metastasis can vary according to tumor size, tumor focality, and tumor extension, and also that dual combinations, such as multifocality/tumor size >10 mm for tumors showing extrathyroidal extension; multifocality/extrathyroidal extension for tumors larger than 10 mm; and tumor size >10 mm/extrathyroidal extension for multifocal tumors in male patients should be regarded as indicators of a high risk of lymph node metastasis.

**Table 2** Effects of clinicopathological features on lymph node metastasis according to tumor size/tumorfocality/extrathyroidal extension and in the entire study sample

| Variables | | According to tumor size | | According to tumor focality | | According to ETE | | All groups |
|---|---|---|---|---|---|---|---|---|
| | | ≤10 mm | >10 mm | Unifocal | Multifocal | Absent | Present | |
| Age | *p* | 0.078 | **0.044** | **0.014** | 0.087 | **0.05** | 0.262 | **0.003** |
| *<45 years* | OR (95 % CI) | 3.5 (0.8–14.1) | 4.1 (1.0–15.8) | 5.9 (1.4–25.0) | 4.2 (0.8–21.9) | 3.5 (1.0–11.9) | 2.6 (0.5–13.5) | 3.9 (1.6-9.9) |
| Sex | *p* | **0.036** | **0.049** | **0.014** | **0.037** | 0.121 | **0.01** | **0.003** |
| *Male* | OR (95 % CI) | 6.6 (1.1–38.8) | 4.9 (1.0–23.5) | 7.8 (1.5–40.1) | 7.0 (1.1–44.2) | 3.5 (0.7–17.4) | 44.9(2.5-808.7) | 5.1 (1.7-15.1) |
| Variant | *p* | 0.859 | 0.079 | 0.968 | 0.146 | 0.345 | 0.973 | 0.305 |
| *CVPTC* | OR (95 % CI) | 1.2 (0.2–6.2) | 0.1 (0.01–1.3) | 0.9 (0.1–5.9) | 0.1 (0.0–1.7) | 0.5 (0.1–2.2) | 1.0 (0.07–13.9) | 0.5 (0.2-1.8) |
| Size | *p* | | | 0.279 | **0.001** | 0.130 | **0.021** | **0.002** |
| *≥10 mm* | OR (95 % CI) | | | 2.1 (0.5–8.4) | 20.0(3.3-119.2) | 2.6 (0.8–9.1) | 14.7 (1.5-145.3) | 4.2 (1.7–10.5) |
| TumorFocality | *p* | 0.542 | **0.016** | | | 0.207 | **0.025** | **0.009** |
| *Multifocal* | OR (95 % CI) | 1.5 (0.4–5.7) | 7.3 (1.5–37.1) | | | 2.1 (0.7–6.9) | 16.7 (1.4–196.0) | 3.4 (1.4–8.4) |
| TB | *p* | 0.338 | 0.841 | 0.923 | 0.875 | 0.390 | 0.699 | 0.420 |
| *Infiltrative* | OR (95 % CI) | 0.2 (0.1–1.9) | 0.8 (0.2–4.3) | 0.9 (0.2–4.0) | 0.8 (0.1–5.3) | 0.6 (0.1–2.1) | 1.7 (0.1–25.7) | 0.6 (0.2–1.9) |
| ETE | *p* | 0.271 | **0.041** | 0.416 | **0.020** | | | **0.009** |
| *Presence* | OR (95 % CI) | 2.7 (0.5–15.6) | 4.8 (1.1–21.8) | 1.9 (0.3–9.7) | 6.0 (1.3–27.1) | | | 3.9 (1.4–10.6) |
| LTG | *p* | 0.106 | 0.07 | **0.026** | 0.217 | **0.039** | 0.590 | **0.009** |
| *Presence* | OR (95 % CI) | 7.2 (0.7–79.4) | 9.3(0.8-104.0) | 29.8(1.5-592.2) | 4.1 (0.4–40.7) | 9.0 (1.1–72.8) | 2.6 (0.7–90.7) | 8.6 (1.7–43.5) |
| IGD | *p* | 0.186 | 0.104 | 0.281 | **0.012** | **0.009** | 0.971 | **0.024** |
| *Presence* | OR (95 % CI) | 2.8 (0.6–13.3) | 3.2 (0.8–12.1) | 2.0 (0.5–7.9) | 8.6 (1.6–46.2) | 6.6 (1.6–27.1) | 0.9 (0.2– 4.6) | 2.9 (1.2–7.4) |
| LTR | *p* | 0.707 | 0.252 | 0.254 | **0.005** | 0.322 | 0.063 | **0.020** |
| LTR, *severe* | OR (95 % CI) | 0.7 (0.1–5.8) | 5.5 (0.3-103.0) | 5.4 (0.2–98.6) | 88.7(3.7-2077.0)) | 3.3 (0.3–35.2) | 107.2 (0.7–147) | 7.7 (1.4–43.0) |
| STR | *p* | 0.687 | Could not be be calculated | 0.163 | **0.035** | 0.105 | 0.826 | 0.081 |
| STR, *severe* | OR (95 % CI) | 0.5 (0.1–11.3) | | 0.07 (0.0-2.8) | 0.01 (0.0–0.7) | 0.1 (0.01–1.6) | 0.7 (0.05–10.0) | 0.1 (0.01–1.3) |
| LT | *p* | Could not be be calculated | 0.178 | 0.084 | **0.016** | 0.111 | **0.020** | **0.003** |
| *Absence* | OR (95 % CI) | | 3.4 (0.5–28.5) | 7.9 (0.7–84.7) | 11.4 (1.5-84.0) | 4.7 (0.7–31.7) | 27.2 (1.6–446.1) | 7.1 (1.9–26.5) |

Reference categories: ≥45 years for age, female for sex, conventional variant papillary carcinoma for variant, smooth/encapsulated growth pattern for tumor border, absence for ETE, absence for lateral tubular growth, absence for intraglandular dissemination, absence for lymphocytic tumor response, absence for stromal tumor response, presence for LT, unifocality for focality, <10 mm for tumor size

*CVPTC* conventional variant papillary thyroid carcinoma, *FVPTC* follicular variant papillary thyroid carcinoma, *TB* tumor border, *ETE* extrathyroidal extension, *LTG* lateral tubular growth, *IGD* intraglandular dissemination, *LTR* lymphocytic tumor response, *STR* stromal tumor response, *LT* lymphocytic thyroiditis, *OR* odds ratio, *CI* confidence interval

**Table 3** Comparisons of other clinicopathological features by tumor size, multifocality, lymphovascular invasion, and extrathyroidal extension

| Variables | | Tumor size | | *P* | Tumorfocality | | *P* | LVI | | *P* | ETE | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | ≤10 mm | >10 mm | | Unifocal | Multifocal | | Absent | Present | | Absent | Present | *P* |
| Sex | Male | 15 (12.4) | 24 (26.7) | 0.014 | 23 (20.5) | 16 (16.2) | 0.523 | 19 (12.9) | 20 (31.2) | 0.003 | 22 (15.1) | 17(26.2) | 0.085 |
| | Female | 106 (87.6) | 66 (73.3) | | 89 (79.5) | 83 (83.8) | | 128 (87.1) | 44 (68.8) | | 124 (84.9) | 48(73.8) | |
| Age | <45 years | 48 (39.7) | 38 (42.2) | 0.709 | 48 (42.9) | 38 (38.4) | 0.509 | 51 (34.7) | 35 (54.7) | 0.007 | 59 (40.4) | 27(41.5) | 0.878 |
| | ≥45 years | 73 (60.3) | 52 (57.8) | | 64 (57.1) | 61 (61.6) | | 96 (65.3) | 29 (45.3) | | 87 (59.6) | 38(58.5) | |
| Variant | CVPTC | 85 (70.2) | 68 (75.6) | 0.485 | 80 (71.4) | 73 (73.7) | 0.708 | 95 (64.6) | 58 (90.6) | <0.001 | 95 (65.1) | 58 (89.2) | 0.001 |
| | FVPTC | 36 (29.8) | 22 (24.4) | | 32 (28.6) | 26 (26.3) | | 52 (35.4) | 6 (9.4) | | 51 (34.9) | 7 (10.8) | |
| TB | S/E | 60 (49.6) | 41 (45.6) | 0.562 | 59 (52.7) | 42 (42.4) | 0.137 | 82 (55.8) | 19 (29.7) | <0.001 | 91 (62.3) | 10 (15.4) | <0.001 |
| | Infiltrative | 61 (50.4) | 49 (54.4) | | 53 (47.3) | 57 (57.6) | | 65 (44.2) | 45 (70.3) | | 55 (37.7) | 55 (84.6) | |
| LTG | Absent | 41 (33.9) | 24 (26.7) | 0.331 | 37 (33.0) | 28 (28.3) | 0.456 | 61 (41.5) | 4 (6.2) | <0.001 | 61 (41.8) | 4 (6.2) | <0.001 |
| | Present | 80 (66.1) | 66 (73.3) | | 75 (67.0) | 71 (71.7) | | 86 (58.5) | 60 (93.8) | | 85 (58.2) | 61 (93.8) | |
| IGD | Absent | 86 (71.1 | 52 (57.8) | 0.045 | 74 (66.1) | 64 (64.6) | 0.828 | 110 (74.8) | 28 (43.8) | <0.001 | 108 (74.0) | 30(46.2) | <0.001 |
| | Present | 35 (28.9) | 38 (42.2) | | 38 (33.9) | 35 (35.4) | | 37 (25.7) | 36 (56.2) | | 38 (26.0) | 35 (53.8) | |
| LTR | Absent | 54 (44.6) | 31 (34.4) | 0.062 | 44 (39.3) | 41 (41.4) | 0.822 | 67 (45.6) | 18 (28.1) | 0.059 | 72 (49.3) | 13 (20) | <0.001 |
| | Mild | 41 (33.9) | 45 (50.0) | | 45 (40.2) | 41 (41.4) | | 55 (37.4) | 31 (48.4) | | 47 (32.2) | 39 (60.0) | |
| | Severe | 26 (21.5) | 14 (15.6) | | 23 (20.5) | 17 (17.2) | | 25 (17.0) | 15 (23.4) | | 27 (18.5) | 13 (20.0) | |
| STR | Absent | 17 (14.0) | 1 (1.1) | 0.004 | 11 (9.8) | 7 (7.1) | 0.320 | 16 (10.9) | 2 (3.1) | <0.001 | 18 (12.3) | 0 (0.0) | <0.001 |
| | Mild | 44 (36.4) | 39 (43.3) | | 48 (42.9) | 35 (35.4) | | 68 (46.3) | 15 (23.4) | | 69 (47.3) | 14 (21.5) | |
| | Severe | 60 (49.6) | 50 (55.6) | | 53 (47.3) | 57 (57.6) | | 63 (42.9) | 47 (73.4) | | 59 (40.4) | 51 (78.5) | |
| LT | Absent | 65 (53.7) | 57 (63.3) | 0.162 | 46 (41.1) | 43 (43.4) | 0.729 | 79 (53.7) | 43 (67.2) | 0.096 | 84 (57.5) | 38 (58.5) | 0.900 |
| | Present | 56 (46.3) | 33 (36.7) | | 66 (58.9) | 56 (56.6) | | 68 (46.3) | 21 (32.8) | | 62 (42.5) | 27 (41.5) | |
| AntiTG | Negative | 97 (80.2) | 77 (85.6) | 0.404 | 92 (82.1) | 82 (82.8) | 1.000 | 121 (82.3) | 53 (82.8) | 1.000 | 121 (82.9) | 53 (81.5) | 0.968 |
| | Positive | 24 (19.8) | 13 (14.4) | | 20 (17.9) | 17 (17.2) | | 26 (17.7) | 11 (17.2) | | 25 (17.1) | 12 (18.5) | |
| AntiTPO | Negative | 44 (64.7) | 42 (73.7) | 0.376 | 47 (71.2) | 39 (66.1) | 0.673 | 59 (67.8) | 27 (71.1) | 0.881 | 60 (67.4) | 26 (72.2) | 0.755 |
| | Positive | 24 (35.3) | 15 (26.3) | | 19 (28.8) | 20 (33.9) | | 28 (32.2) | 11 (28.9) | | 29 (32.6) | 10 (27.8) | |

*TB* tumor border, *LTG* lateral tubular growth, *IGD* intraglandular dissemination, *LTR* lymphocytic tumor response, *STR* stromal tumor response, *LT* lymphocytic thyroiditis, *Anti-TPO* anti-thyroid peroxidase antibodies, *USLAP* preoperative suspicious lymph nodes by ultrasound, *CVPTC* conventional variant papillary thyroid carcinoma, *FVPTC* follicular variant papillary thyroid carcinoma, *MFCPTC* Mixt follicular-conventional variant papillary thyroid carcinoma, *S/E* smooth bordered/encapsulated, *LVI* lymphovascular invasion, *ETE* extrathyroidal extension

Several recent papers have reported that there may be some histopathological signs of lymph node status in thyroidectomy/lobectomy specimens [21, 22]. Addressing this issue, Jung et al. [21] presented definitions of tumor growth patterns, lateral tubular growth, and intraglandular dissemination and suggested that infiltrative tumor border, lateral tubular growth, and intraglandular dissemination all induce lymph node metastasis. In this study, all of the results concurred with criteria reported by authors [21]. The authors suggested that intraglandular dissemination and lateral tubular growth might be signs of lymphatic spread or tumor dissemination presenting as multifocality and highlighted the need for new studies to clarify the associations between these features [21]. In our study, based on the results of the logistic regression analyses, lateral tubular growth, intraglandular dissemination, and multifocality were found to be predictive factors for lymph node metastasis, in consistent with previously reported data. Although our results are unable to provide a clear explanation of the interactions between lymphovascular spread and intraglandular dissemination or lateral tubular growth, significant associations were identified between these criteria and LVI, while no relationship was found between the criteria and multifocality. Further studies evaluating these interactions through molecular analyses and immunohistochemical studies should be carried out. While an infiltrative tumor border was not a significant predictor, it was found to be associated significantly with lymph node metastasis in the univariate analyses, particularly in tumors sized >10 mm.

That said, AJCC [2] does not require tumor multifocality as a prognostic factor, as it seemed to be a predictive factor for lymph node metastasis particularly in tumors sized >10 mm and those that spread beyond the thyroid in our study. Similar results, indicating that multifocal tumors show lymph node metastasis more frequently than unifocal tumors, have been found by Karatzas et al. [30] and Kuo et al. [27]. Molecular studies may explain the nature of multifocal tumors, and whether they are de novo tumors or an intrathyroidal dissemination of the primary tumor.

Koperek et al. [22] suggest that a stromal tumor reaction is an indicator of lymph node metastasis and also has relationships with LVI, ETE, and a larger tumor size in microcarcinomas. Mai et al. [31] found that "infiltrating" PTCs with a sclerotic stroma are more frequently associated with lymph node metastasis than encapsulated tumors. In the present study, the percentage of lymph node-positive cases was correlated with an increase in the severity of the stromal tumor response, while astromal tumor response was associated with larger tumor size, LVI, and ETE in the present study, concurring with the findings of Koperek et al. [22]. The hypothesis that a stromal tumor response leads to local extension and dissemination via the lymphatic network should be investigated.

French et al. [24] identified a correlation between a prognosis of PTC and tumor-associated lymphocytes (TAL) and showed that $FoxP3^+$ regulatory T cells (Tregs) were correlated with lymph node metastasis in particular. Although we did not score lymphocytic infiltration as numerical value and did not consider possible coexistence of background LT in consistent with the previously reported data in the literature, the univariate analyses revealed a nonsignificant but close to significant ($p$=0.058) inverse relationship between the number of lymph node-negative cases and the significance of lymphocytic tumor response, and a similar ($p$=0.059) relationship between LVI and the severity of the lymphocytic tumoral response. In addition, severe lymphocytic tumor response was found to be a significant predictive factor of lymph node metastasis in the logistic regression analyses, as reported previously [24]. Tumors surrounding LT have been reported as a protective factor of lymph node metastasis in many studies [25, 26, 32], although Jeong et al. [33] demonstrated no difference in the frequency of lymph node metastasis between PTC associated LT and LT negative groups. In the present study, we showed in the logistic regression analyses that the absence of concomitant LT was a predictive factor in lymph node metastasis, particularly in multifocal tumors and tumors that extend beyond the thyroid, as reported in many previous papers [25, 26, 32]. However, no relationship was identified between concomitant LT and lymph node metastasis and other prognostic criteria in the univariate analyses, as described by Jeong et al. [33]. Although lymphocytic tumor response may be a predictive factor for tumor aggressiveness in PTC, as is the case in some other organ tumors, such as breast and ovarian carcinomas [34, 35], concomitant LT may be a protective factor. Accordingly, this type of tumor response may be a goal in the treatment of PTCs in the future, and a typing of lymphocytic response (LT or intra/peritumoral lymphocytic infiltration or lymphocytes) may be required. In this issue, detailed studies supported by molecular analyses are required.

Furthermore, certain variants of PTC, including the tall cell variant, columnar cell variant, and diffuse sclerosing variant, have been reported to be aggressive tumors [36, 37]. In our study, the univariate analyses showed that lymph node metastasis was significantly more frequent in CVPTC than FVPTC. Also, CVPTC was found to have a significant association with ETE and LVI, while FVPTCs had lower rates of lymph node metastasis and LVI. This result can be interpreted as the requirement of defining the real tumor variant in pathology reports and may be a reflection of the aggressiveness of tumors exhibiting a BRAF mutation, based on the knowledge of the molecular pathway of carcinogenesis in PTC [21, 38].

Although current staging systems accept an older age (>45 years) [9] as a worse prognostic criterion, in the present study, a younger age (<45 years) at the time of diagnosis, particularly in the fourth decade of life, was found to have a significant relationship with lymph node metastasis and LVI in the univariate analyses and was also a predictor of lymph node metastasis. Karatzas et al. [30] identified no association between the age of the patient and lymph node status, and Jung et al. [21] reported similar results in their study. In this regard, younger aged male patients, particularly those in their fourth decade of life with unifocal tumors limited to the thyroid, should be managed in an attentive manner.

A preoperative neck ultrasound is a useful tool for the staging of thyroid carcinomas, as suggested by ATA [9], and so, preoperative ultrasound findings and also preoperative serum anti-TG and anti-TPO levels were evaluated where possible from the limited data of some patients in the group. Although no relationship could be found between the serum levels of the two antibodies, the presence of a suspected lymphadenopathy in a neck ultrasound had a significant association with a histological lymph node metastasis, similar to previous reports [19, 39]. However, in the presence of definitive data regarding the risk categories [9], two of the patients showing a local recurrence were <45 years old female patients with smooth-bordered microcarcinomas exhibiting intraglandular dissemination and lateral tubular growth with lymphocytic/stromal tumor response. Concomitant lymphocytic thyroiditis was absent, and a preoperative ultrasound was unable to define any suspicious lymph node, while preoperative serum antibody levels were positive. Despite no statistical analysis being made due to the small sample size, these findings suggest that the relationships between these criteria, particularly in microcarcinomas, should be sought in larger series.

In conclusion, our results suggest that there may be some signs of lymph node metastasis in hematoxylin- and eosin-stained slides, which can be interpreted in ordinary pathology laboratories without the need for special studies. With the aim of optimizing the management of PTCs, particularly in patients undergoing a lobectomy/thyroidectomy without lymph node dissection, pathologists should search for evidence of lymph node metastasis in and around the primary tumors, particularly lateral tubular growth and intraglandular

dissemination for pT1a tumors, besides the prognostic criteria proposed by several staging systems, particularly in younger male patients.

**Conflict of interest** The authors have nothing to disclose.

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