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Papillary thyroid microcarcinomas that metastasize to lymph nodes

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ABSTRACT

Purpose: We aimed to determine clinicopathological features that can predict lymph node metastasis (LNM) in papillary thyroid microcarcinomas (PTMC).
Methods: Medical records of 872 patients with papillary thyroid cancer >1 cm (PTC > 1 cm) and 1184 patients with papillary thyroid microcancer (PTMC) (≤1 cm) were reviewed retrospectively. Demographical, clinical and histopathological features of (PTC > 1 cm) and PTMC were compared. Association between clinicopathological features and LNM in PTMC was investigated.
Results: The median age of patients with PTMC was significantly higher than patients with PTC > 1 cm (49 vs 46 years old, $p < 0.001$). Multifocality, capsular invasion, vascular invasion, extrathyroidal extension (ETE) and LNM were more frequent in patients with PTC > 1 cm compared to patients with PMTC ($p < 0.001$ for each). In PTMC group, those with LNM had significantly higher proportion of multifocality, capsular invasion, vascular invasion and ETE compared to those without LNM ($p = 0.007$, <0.001, $p = 0.011$ and $p < 0.001$, respectively). Multifocality and ETE were significant factors for LNM with logistic regression analysis. Multifocality increased the risk of LNM by 1.737 times (95% CI: 1.079–2.979) and ETE increased the risk by 3.528 times (95%: 1.914–6.503). Primary tumor diameter ≥ 5.75 mm was predictive for LNM with a sensitivity of 0.782 and a specificity of 0.517 in PTMC.
Conclusions: LNM should be investigated more carefully in patients with PTMC in the presence of tumor diameter ≥ 5.75 mm, multifocality or ETE.

1. Introduction

There is a gradual increase in the incidence of thyroid carcinoma in recent decades [1]. This is most probably related with the growing use of sensitive diagnostic methods such as high-resolution ultrasonography (US) and fine-needle aspiration biopsy (FNAB) [2]. Another contributing factor is detection of small tumors with improved pathological methods and detailed examination of specimens. Papillary thyroid cancers measuring 1 cm or smaller are defined as papillary thyroid microcarcinomas (PTMC). Although the upward trend in the incidence of PTMC continues, there are still controversies regarding the optimal treatment of these patients [3]. One of the most controversial issue is the extent of surgery. Preoperative assessment of risk factors is generally not enough to guide the surgical approach. In the presence of some histopathological features that are related with poor prognosis, a more radical treatment might be needed to achieve a better prognosis [4]. It is not uncommon to encounter such histopathological features in a tumor that is preoperatively thought to be low risk.

It is suggested that majority of PTMCs have an indolent clinical course, however similar to papillary thyroid carcinomas (PTC), they can also present with lymph node metastasis (LNM), recurrence, distant metastasis and even death [3,5]. The rate of LNM was reported to change between 17% and 64% in previous reports, the most common site being the central compartment [6]. In the study by Chow et al. [7] the 10-year recurrence rate of PTMC in lymph nodes was 5%. Since the management of PTMC is affected by the presence of LNM, it is important to detect it preoperatively or during follow-up.

Routine prophylactic central neck dissection is generally avoided in PTMC due to the risk of recurrent laryngeal nerve injury and hypoparathyroidism. However, PTMC is not homogeneous [3] and this

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approach may cause metastatic lymph nodes to remain and requirement of a second surgery in high-risk patients. Even aggressive tumors appear as microcarcinomas at an early stage and if not treated properly, they can present with extrathyroidal extension (ETE), LNM and distant metastases [8]. Therefore, high risk patients who need prophylactic lymph node dissection should be selected. This can partially be done by identifying predictive factors for LNM in patients with PTMC [9]. In this study, we aimed to determine potential risk factors related with LNM in PTMC patients.

2. Methods

Medical records of patients operated between December 2006 and January 2019 and diagnosed with PTC histopathologically were reviewed retrospectively. Pregnant patients, patients with a previous history of thyroid surgery, history of radiotherapy to head and neck region and patients with unilateral resection were excluded.

Age, sex, presence of lymphocytic thyroiditis, tumor number (unifocal/multifocal), primary tumor diameter, presence of LNM, vascular invasion, capsular invasion and ETE were determined. Patients with a tumor diameter 1 cm or lower were classified as PTMC and patients with a tumor diameter higher than 1 cm were classified as PTC > 1 cm. Multifocality was defined as presence of two or more tumor foci. Central lymph node dissection is not routinely performed in our center for patients undergoing thyroidectomy. It is performed when there is suspicion or diagnosis of LNM in preoperative evaluation or during intraoperative assessment. In the preoperative period, suspicious lymph nodes are evaluated both cytologically and by fine needle aspiration thyroglobulin washout procedure to detect metastasis. Intraoperatively, a lymph node exceeding 5 mm in diameter which is palpable, hard, conglomerated and dark in color is evaluated as suspicious by surgeon and dissected after sending for frozen biopsy.

Demographical and histopathological features of patients with PTC > 1 cm and PTMC were compared. Risk factors possibly related with LNM in PTMC patients were investigated.

Written informed consent was obtained from all patient before thyroidectomy. Local ethical committee approval was obtained in accordance with the ethical standards of Helsinki declaration.

2.1. Statistical analysis

All analyses were performed via IBM SPSS Statistics 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). The distributions of the quantitative variables were examined by both Shapiro-Wilk's test and normality graphs. Quantitative and categorical variables were assessed by median (IQR: 25th–75th percentiles) and frequency (%), respectively. The age was compared by Mann-Whitney *U* test with respect to the largest tumor diameter and the LNM. Pearson chi-square test, Yates' chi-square test and Fisher exact test were applied for the comparison of the categorical characteristics, where appropriate. The related factors to the LNM in patients with PTMC were determined by multivariate logistic regression analysis. The main effect model was specified by the factors having a p-value<0.250 in the univariate analyses. Since none of the interaction effects contributed significantly to the multivariate model, further evaluations were proceeded by the main effect model. The model fit was assessed by Hosmer-Lemeshow statistics, and the graphs of $\Delta\chi^2$, ΔD and ΔB versus predicted probabilities. Some of the covariate patterns were found to have poor fit due to the low frequency distribution. Then the factors resulting this problem were excluded from the main effect model step by step. The odds ratio and its 95% confidence interval (CI) were reported for the final model. The receiver-operating characteristic (ROC) analysis and Youden index were used to identify the cut-off point of primary tumor diameter for defining the LNM. A p-value<0.05 was considered as statistically significant.

3. Results

There were 1184 patients with PTMC and 872 patients with PTC > 1 cm. The median age was significantly higher in PTMC group compared to PTC > 1 cm group (49 years vs 46 years, $p < 0.001$) (Table 1). The distribution of sex was similar in two groups ($p = 0.942$). Patients with PTC had higher proportion of multifocality, LNM, central LNM, lateral LNM, capsular invasion, vascular invasion and ETE ($p < 0.001$ for each).

Clinical and histopathological features of PTMC patients with and without LNM were compared (Table 2). The age, sex distribution and lymphocytic thyroiditis were similar in two groups ($p = 0.115$, $p = 0.332$ and $p = 0.316$, respectively). The primary tumor diameter, proportion of multifocality, capsular invasion, vascular invasion and ETE were significantly higher in patients with LNM ($p < 0.001$, $p = 0.007$, <0.001, $p = 0.011$ and p < 0.001, respectively).

Factors related with LNM in PTMC patients were multifocality and ETE after further analyses (Table 3). The multifocality increased the risk of LNM by 1.737 times (95% CI: 1.079–2.979). The risk of LNM was 3.528 times (95%: 1.914–6.503) higher in patients with ETE compared to those without ETE.

The area under ROC curve was determined as 0.681 ± 0.027 to identify the LNM by tumor diameter in PTMC (Fig. 1). The highest Youden index was obtained for tumor diameter ≥ 5.75 mm with a sensitivity of 0.782 and a specificity of 0.517.

4. Discussion

Although PTMCs have generally an indolent biological behaviour, some might show aggressive clinical features. In a large national cancer database study including 18,445 PTMC patients, the 10-year and 15-year overall survivals were 94.6% and 90.7%, respectively. These rates were similar with the PTC patients. In addition, albeit low, disease specific mortality was 0.5% which means that it is not a totally innocent disease [3]. Poor outcomes seen in PTMC are mainly related with the presence of LNM [10]. Cervical LNM has a significant impact on both the local recurrence and survival of PTC patients [11]. In the study by Cho et al. [12], during a follow-up period of 5.3 years, recurrence was

Table 1
Clinical and histopathological features in patients with papillary thyroid cancer >1 cm and papillary thyroid microcarcinoma.

	Total (n = 2056)	PTMC (n = 1184)	PTC > 1 cm (n = 872)	p
Age[a] (years)	48 (39–56)	49 (40–57)	46 (36–56)	**<0.001**
Sex (male)	400 (19.5%)	231 (19.5%)	169 (19.4%)	0.942
Primary tumor diameter	9.0 (5.0–15.0)	6.0 (3.0–8.0)	16.0 (13.0–25.0)	**<0.001**
Multifocality	704 (34.2%)	348 (29.4%)	356 (40.8%)	**<0.001**
LNM	232 (11.3%)	78 (6.6%)	154 (17.7%)	**<0.001**
Central LNM[b]	188 (9.2%)	58 (4.9%)	130 (15.0%)	**<0.001**
Lateral LNM[b]	82 (4.0%)	26 (2.2%)	56 (6.4%)	**<0.001**
Capsular invasion	444 (21.6%)	166 (14.0%)	278 (31.9%)	**<0.001**
Vascular invasion	87 (4.2%)	14 (1.2%)	73 (8.4%)	**<0.001**
Extrathyroidal extension	275 (13.4%)	84 (7.1%)	191 (21.9%)	**<0.001**
Lymphocytic thyroiditis[c]	649 (31.7%)	375 (31.9%)	274 (31.5%)	0.850

PTMC: papillary thyroid microcarcinoma, PTC > 1 cm: Papillary thyroid cancer >1 cm, LNM: Lymph node metastasis.
Bold indicates p value&0.05 for statistical significance.
Quantitative and categorical variables are summarized by median (IQR: 25th–75th percentiles) and frequency (%), respectively.
[a] n = 1182 (PTMC), 871 (PTC > 1 cm).
[b] n = 1182 (PTMC), 869 (PTC > 1 cm).
[c] n = 1176 (PTMC), 870 (PTC > 1 cm).

Table 2
Clinical and histopathological features of papillary thyroid microcarcinoma patients with and without lymph node metastasis.

	LNM - (n = 1106)	LNM + (n = 78)	p
Age[a] (years)	49 (41–57)	45 (37–58)	0.115
Sex (male)	212 (19.2)	19 (24.4)	0.332
Primary tumor diameter	5.0 (3.0–8.0)	7.0 (6.0–9.0)	**<0.001**
Multifocality	314 (28.4)	34 (43.6)	**0.007**
Capsular invasion	141 (12.7)	25 (32.1)	**<0.001**
Vascular invasion	10 (0.9)	4 (5.1)	**0.011**
Extrathyroidal extension	68 (6.1)	16 (20.5)	**<0.001**
Lymphocytic thyroiditis[b]	355 (32.2)	20 (26.7)	0.316

Quantitative and categorical variables are summarized by median (IQR: 25th–75th percentiles) and frequency (%), respectively.
LNM: Lymph node metastasis.
Bold indicates p value&0.05 for statistical significance.
[a] n = 1105 (LNM -), 77 (LNM+).
[b] n = 1101 (LNM -), 75 (LNM+).

Table 3
The results of the logistic regression analysis examining the factors related to lymph node metastasis in patients with papillary thyroid microcarcinoma.

	b ± SE	OR (%95 GA)	p
Constant	−3.001 ± 0.161	–	**<0.001**
Multifocality	0.552 ± 0.243	1.737 (1.079–2.797)	**0.023**
Extrathyroidal extension	1.261 ± 0.319	3.528 (1.914–6.503)	**<0.001**

b: Regression coefficient, SE: Standard error, OR: Odds Ratio, CI: Confidence interval.
Bold indicates p value&0.05 for statistical significance.

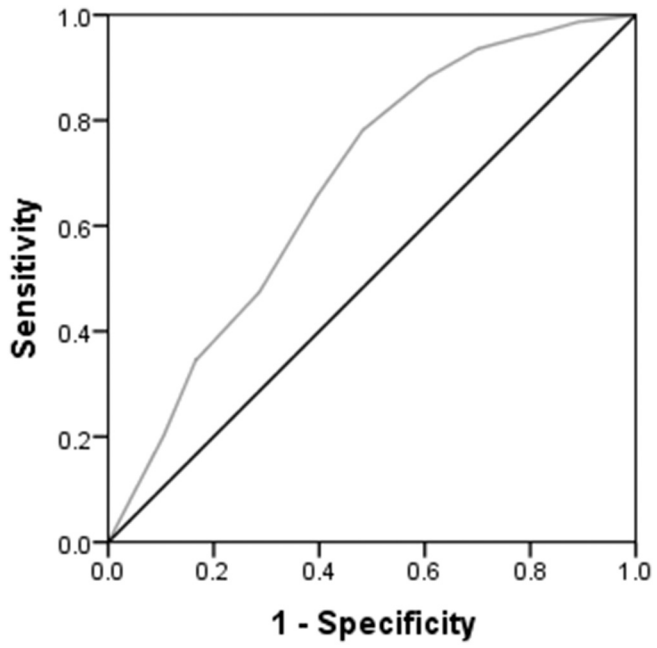

Fig. 1. ROC curve of tumor diameter to identify lymph node metastasis in patients with papillary thyroid microcarcinoma.

observed in 16 (4.8%) of 336 patients with PTMC. The authors reported that among several clinicopathologic factors, LNM was the most potent risk factor for recurrence. In another study, the risk of cervical lymph node recurrence was 6.2 fold and 5.6-fold higher when LNM and multifocal disease were present at diagnosis, respectively. In addition, the rate of distant metastasis increased by 11.2 times in the presence of LNM [7]. In a long term follow up study, Hay et al. [13]. reported significantly higher rate of recurrence in patients with lymph node positive PTMC patients (16% vs. 0.8%) at 20 years. Recurrent surgeries for PTC not only confer an increased risk for surgical complications but also affect the patient's quality of life [14]. So, in terms of the overall prognosis of patients, it is very important to identify predictors for LNM and removal of metastatic lymph nodes in the initial operation.

Although age is a well-known risk factor for LNM in PTMCs, the age threshold varies between studies. In general, younger age lower than <45 years is suggested to be related with higher risk of LNM. In a study including 1031 patients with PTMC, age ≤ 40 years was found to be a risk factor for central LNM [10]. Patients younger than 45 years of age were more likely to have central LNM in another study of 2129 PTMC patients [6]. The cut-off age at diagnosis with respect to the mortality risk was increased to 55 years from 45 years in the last edition (8th) of the AJCC staging system [15]. Cheng et al. [16] [14] used this new cut-off and found that younger age (<55 years old) was still an independent risk factor for LNM and central LNM. We also observed that patients with LNM were younger than those without LNM, but the difference was not significant.

While the incidence of PTMC is higher in women than men, male sex was defined as a risk factor for LNM [9]. In contrast to studies indicating for higher risk of LNM and central LNM in male patients with PTMC [10,17], some others did not find a correlation between sex and LNM [18]. In our study, the rate of LNM was similar in male and female patients with PTMC.

Multifocal tumors can be observed in approximately 20–40% of patients with PTMC [9,19]. Whether they develop as independent tumors or occur due to the intraglandular spread of a primary focus is not clear [20]. Multifocality was reported to increase the risk of cervical LNM by 17.9 times in a study including 933 patients with PTMC [21]. Zhao et al. [19] found the rate of multifocality as 34.0% in PTMCs, and 51.4% of them had LNM. In accordance with the literature, there was a significant association between multifocality and LNM in patients with PTMC in both univariate and multivariate analysis in our study. We observed that multifocality increased the risk of LNM by 1.737 times.

ETE is another risk factor for LNM in PTMCs. In the study by Varshney et al. [22], ETE was reported in 16 (9.4%) of 170 PTMCs and it was the only tumoral feature that was significantly associated with LNM. In another study, ETE was a risk factor for central LNM in addition to age < 45 years old and multifocality. Additionally, in multivariate analysis, it was the only risk factor for lateral LNM [18]. ETE was also a significant risk factor for LNM in our study and it was associated with 3.528 times higher risk.

Tumor diameter is an important component of TNM staging system and higher tumor diameter is suggested to be related with LNM. Variable cutoff values for tumor diameter was presented in previous studies, while a tumor size of 5 mm was the most commonly used size threshold [6,16]. In a meta-analysis of 19 studies including 8345 PTMC patients, central LNM was associated with a tumor size >5 mm [23]. Jiang et al. [24] reported a nearly linear correlation between central LNM and tumor size in 10 groups based on the maximum diameter of the tumor. Central LNM rate was 8.93% in patients with PTMC and a 5 mm threshold was suggested also in that study. The authors concluded that the tumor size was one of the most important risk factors for central LNM and even extremely small tumors might present with LNM. In another study, Zheng et al. [25] found that a tumor size of >6 mm was significantly correlated with LNM in PTMC. In the present study, we included a huge number of patients with PTMC and found the size threshold for LNM as ≥5.75 mm.

Despite these findings, prophylactic central lymph node dissection is still a matter of debate. Kim et al. [26] followed 164 PTMC patients for a mean duration of 73.4 months and reported no oncological benefit of prophylactic ipsilateral central node dissection for patients with clinically negative lymph nodes. In contrary, in the metaanalysis by Su et al. [27], prophylactic central neck dissection was shown to reduce recurrence rates in patients with PTMC. The guidelines are also discordant regarding the recommendations for prophylactic central lymph node

dissection. American Thyroid Association (ATA) guidelines recommend routine dissection only in patients with advanced T3 and T4 primary tumors [28]. However, considering that metastasis can also be seen in T1 or T2 tumors, this recommendation is debatable. The European Society of Endocrine Surgeons suggests that prophylactic central neck dissection should be performed considering risk factors such as large tumors (T3 or T4), age, male sex, bilaterality or multifocality, and involvement of lateral lymph nodes [29]. Routine prophylactic central lymph node dissection is recommended by The Japanese Association of Endocrine Surgeons (JAES) [30]. The rationale for recommending this procedure routinely by some authors depends on the role of it to prevent future recurrence, the high risk of positive lymph nodes, reduced postoperative thyroglobulin levels, and a lower morbidity rate associated with the first operation. On the opposite side, others call attention for increased risk of injury to parathyroid glands and recurrent laryngeal nerves, while there is no demonstrable benefit in terms of long-term survival. Unilateral instead of bilateral central lymph node dissection was presented as an alternative method to decrease the risk of postoperative complications. Although this approach seems to be safe and effective, there is not enough data yet to support this approach.

Our study has some limitations. Firstly, although the sample size was high, it was a retrospective study conducted in a single center. Secondly, routine prophylactic lymph node dissection is not performed in our center. However, as we have already mentioned, the rationale of such an approach is questionable. Lastly, we are aware of the possible limitations of US in the detection of metastatic lymph nodes in the neck region [19]. This might have caused detection of LNM lower than its actual rate, although the rates in our study were similar with previous studies [31,32].

In conclusion, despite majority of patients with PTMC has a favorable outcome, some may experience negative consequences of the disease. Identification of high-risk patients will contribute to the optimal management of these patients. In the presence of multifocality and ETE, and a tumor diameter of $\geq$5.75 mm, PTMC patients should be carefully assessed in terms of LNM during the management and follow-up.

CRediT authorship contribution statement

Ahmet Dirikoc: Study design, analysis, data interpretation, and writing of the manuscript. Abbas Ali Tam: Study design, analysis, data interpretation, and writing of the manuscript. Nurcan Ince: Data collection and writing of the manuscript. Didem Ozdemir: Study design, data collection, analysis, data interpretation, and writing of the manuscript. Oya Toplaoglu: Data collection and writing of the manuscript. Afra Alkan: Formal analysis, methodology, data collection, and writing of the manuscript. Aylin Kılıcyazgan: Data collection and writing of the manuscript. Reyhan Ersoy: Study design, data collection, and writing of the manuscript. Bekir Cakır: Study design, data collection and writing of the manuscript.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Declaration of competing interest

There is no conflict of interest and nothing to declare in this paper.

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