Papillary thyroid microcarcinoma with and without nodal metastasis

A comparative analysis

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ABSTRACT

الأهداف: تقييم التركيبة السكانية والعوامل السريرية لمرضى سرطان الغدة الدرقية الحليمي الصغير في المملكة العربية السعودية ومقارنة وتحليل الاختلافات مع المرضى الذين يعانون من انتشار الورم في العقد الليمفاوية . سرطان الغدة الدرقية الحليمي الصغير وهو سرطان شائع في الغدة الدرقية ولا يمكن اكتشاف سريريًا عادةً، ولكن يتم اكتشاف بالصدفة بعد فحص انسجة الغدة الدرقية عند إجراء عملية جراحية لاضطرابات الغدة الدرقية الحميدة.

المنهجية: تم ضم جميع مرضى سرطان الغدة الدرقية الحليمي الصغير الذين خضعوا لعملية جراحية في مستشفى الملك عبدالعزيز الجامعي ومدينة الملك فهد الطبية ومدينة الملك عبدالعزيز الطبية من عام 2012م إلى عام 2022م. وكان معدل الإصابة بانتشار الورم في العقد اللمفاوية 9.17% وكان متوسط عمر المرضى 44.05 . وكان معظم المرضى من الأناث.

النتائج: معدل انتشار الورم في العقد اللمفاوية لمرضى سرطان الغدة الدرقية الحليمي الصغير هو 9.17% (عدد=31). أظهر مرضى سرطان الغدة الدرقية الحليمي الصغير عوامل خطر مهمة للأنتشار في العقد اللمفاوية تشمل: فئة بيثيسدا العالية، ونوع الورم، والانتشار خارج الغدة الدرقية، والانتشار خارج الكبسولة، والانتشار في الأوعية اللمفاوية، والأورام المتبقية في المرضى الذين تلقوا اليود المشع. لم يكن وجود التهاب الغدة الدرقية، وتعدد البؤر، وتضخم الغدة الدرقية، والانتشار العصبي، وحجم الورم مرتبطًا بأنتشار الورم في العقد اللمفاوية.

الخلاصة: تم ربط فئة بيثيسدا العالية، ونوع الورم، والانتشار خارج الغدة الدرقية، والانتشار خارج الكبسولة، الانتشار اللمفاوي الوعائي، والأورام المتبقية المعالجة باليود المشع مرتبطة بقوة بأنتشار الورم في العقد اللمفاوية.

Objectives: To assess the demographics and clinical factors of papillary thyroid microcarcinoma (PTMC) patients in Saudi Arabia and compared and analyzed the differences between the patients with and without lymph node metastasis (LNM). Papillary thyroid microcarcinoma (PTMC) is a common thyroid cancer and is not usually detectable clinically but found incidentally after pathologic evaluation of thyroid tissue following surgery for benign thyroid disorders. However, these tumors have a significant risk of LNM.

Methods: All PTMC patients who underwent surgery at King Abdulaziz University Hospital, King Fahad Medical City, and King Abdulaziz Medical City from 2012 to 2022 were included. The incidence rate of LNM was 9.17%. The patients' average age was 44.05. Most of the patients were female.

Results: Prevalence of LNM among PTMC patients is 9.17% (n=31). The PTMC patients showed the following significant risk factors for LNM: higher Bethesda class, type of pathology, extrathyroidal extension, extracapsular extension, lymphovascular invasion, and residual tumors in patients who had received radioactive iodine. Presence of thyroiditis, multifocality, goitrous thyroid, neural invasion, and tumor size were unrelated to the LNM in the PTMC patients.

Conclusion: Higher Bethesda class, pathology type, extrathyroidal extension, extracapsular extension, lymphovascular invasion, and RAI-treated residual tumors were strongly linked to LNM.

Keywords: papillary thyroid microcarcinoma, lymph node metastasis, risk factor, thyroid cancer

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Thyroid cancer is considered the most common malignancy of the endocrine system, with an annual incidence of about 9/100,000. It exhibits a spectrum of activity: from clinically insignificant microcarcinomas that are discovered only incidentally, to aggressive and nearly incurable anaplastic malignant neoplasms.[1,2] According to the most recent cancer statistics, thyroid cancer is considered the second most common malignancy in women after breast cancer and the fourth most common malignancy in men in Saudi Arabia.[3] It has multiple risk factors, such as age, radiation exposure, alcohol consumption, genetic factors, smoking, pregnancy, oral contraceptives, high thyrotropin levels, and environmental and lifestyle changes.[4]

Most thyroid malignancies manifest as thyroid nodules that are asymptomatic or associated with adenopathy and local cervical compressive symptoms. Thyroid tumors rarely present at the beginning with signs of metastatic disease, such as a lung mass or bone ache.[1]

Thyroid cancer is classified as differentiated or undifferentiated. It has 4 types: papillary, follicular, medullary, and anaplastic.[5] The most common type of thyroid cancer is papillary thyroid carcinoma (PTC), which accounts for 70-90% of well-differentiated thyroid cancers. While the average age at diagnosis is 45 years, PTC can occur in pediatric age groups and increase in incidence as they grow in age.[1,6]

In most cases, papillary thyroid microcarcinoma (PTMC) is not detectable clinically and is discovered only incidentally after pathologic evaluation of thyroid tissue following surgery for benign thyroid disorders or during autopsy. It has distinctive cytologic characteristics that aid in its identification through fine needle aspiration (FNA) or after surgical resection. Among these characteristics are psammoma bodies, cleaved nuclei with an "orphan Annie" appearance caused by large nucleoli, and the development of papillary structures.[6,7]

A high number of PTC patients who were clinically negative for lymph node (LN) involvement during their preoperative evaluation were later discovered to have cervical lymph node metastases (LNM) during surgery and in the pathology tissue specimens.[8-10] Lymph node metastases have historically been recognized as among the most important factors linked to an increased rate of locoregional recurrence and distant metastasis.[11] The most common location of LNM is the central compartment. There is general agreement that when there are clinical LNM in the central compartment, therapeutic central neck dissection should be performed.[12] However, there is a debate over whether LN dissection is necessary for every PTC patient. Many surgeons in Japan routinely dissect the ipsilateral neck LN even in the absence of a palpable LN (called prophylactic LN dissection). On the other hand, in North America and Europe, only patients with a palpable LN undergo LN dissection (called therapeutic LN dissection), as few patients would experience clinical lymphadenopathy. Consequently, although therapeutic neck dissection is almost always recommended, the intended purpose of prophylactic neck dissection is not clear.[9] Therefore, in this study, we assess the demographics and clinical factors of PTMC patients in Saudi Arabia. Moreover, we compare and analyze the differences between the PTMC patients with and without LNM.

Methods. This retrospective comparative study was carried out at 3 tertiary care hospitals in Riyadh, Saudi Arabia: King Abdulaziz University Hospital (KAUH), King Fahad Medical City (KFMC), and King Abdulaziz Medical City (KAMC). The study focused on patients with PTMC whose tumor size was less than or equal to 1 cm and who underwent surgery between 2012 and 2022 at these hospitals.

Patients who were lost to follow-up, had missing records or pathology results, underwent hemithyroidectomy, subtotal, or near-total thyroidectomy, or were diagnosed with head and neck cancer other than PTMC were excluded from the study. The remaining patients were categorized into 2 groups based on the presence or absence of LNM on the final histopathology. In this study group, neck dissection is indicated when there is preoperative evidence of nodal metastasis through imaging or clinical assessment, as well as when intraoperative findings reveal involvement of central lymph nodes.

We carried out quantitative and descriptive analyses of various patient characteristics, including gender, height, weight, body mass index (BMI), age, Bethesda classification, type of pathology, presence of thyroiditis, goiter, extrathyroid extension (ETE), extracapsular extension (ECE), positive margin, lymphovascular invasion (LVI), perineural invasion, and tumor size. Approval for this study was obtained from the Research Ethics Committee of King Fahad Medical City (IRB Log Number: 20-072).

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Statistical analysis. We compared the categorical variables across the central or lateral LNM categories using a Pearson's Chi-squared test. When the expected sample size in a cell was smaller than 5, the *p*-values were computed using Fisher's exact test. The continuous variables were compared across the central and lateral LNM categories using independent sample t-tests. To study the effect of a demographic, physical, or clinical variable on the chances of a central or lateral LNM, we used univariate logistic regression for a single predictor variable at a time, and then, stepwise logistic regression to build a predictive model for the chances of central or lateral LNM using all the predictors. All the data were analyzed using SPSS version 23 (IBM Corp., Armonk, N.Y., USA).

Results. A total of 338 patients diagnosed with PTMC, ranging in age from 15 to 76, were included. Among these patients, 31 had central LNM, 11 had lateral LNM, and 10 had both central and lateral LNM. Notably, one patient presented with lateral LNM without histopathological evidence of central LNM.

Before the clinical factors that affect LNM are discussed, the demographic or physical characteristics of the patients grouped according to whether they had LNM or not are presented in Table 1. The gender proportions of the 2 groups did not significantly differ, with a *p*-value of 0.357, and neither did their average height, weight, BMI, and age, as all the *p*-values were more than 0.05.

Clinical factors that affect LNM are discussed in Table 2. The proportions of the different Bethesda classification among the patients with and without LNM significantly differed. Among the patients with LNM, 46.4% had a Bethesda class 6, compared to only 17.4% among those who did not have LNM. On the other hand, Bethesda class 1 and 2 had higher proportions in the patients without LNM than in those with LNM (p=0.003). There were 28 patients who have not done FNA preoperatively and none of them had LNM. Type of pathology was correlated with higher risk of LNM (p=0.003). There were no significant differences between the 2 groups in and presence of thyroiditis, multifocality, and presence of a goitrous thyroid. The proportions of ETE (58.1%) and ECE (43.5%) were significantly higher among the patients with LNM than in the other group. The margins did not significantly differ. The presence of LVI was also significantly higher

Table 1 - Demographic statistics by lymph node metastasis.

Factors	No (n= 307,90.8%)		Yes (n=31, 9.2%)		
Gender	n (Mean)	% (SD)	n (Mean)	% (SD)	*P*-value
Female	251	81.7	23	75	0.357
Male	56	18.3	8	25	
Height	1.6	0.1	1.6	0.1	0.897
Weight	81.4	20.0	76	13.8	0.141
Body mass index	31.5	7.1	29.6	6.2	0.15
Age	44.2	11.6	42.8	11.7	0.535

Table 2 - Clinical diagnostics by lymph node metastasis.

Factors	No		Yes		*P*-value
	n (Mean)	% (SD)	n (Mean)	% (SD)	
Bethesda classification					0.003**
1	1	0.4	2	7.1	
2	101	35.8	2	7.1	
3	80	28.4	7	25	
4	26	9.2	0	0	
5	25	8.9	4	14.3	
6	49	17.4	13	46.4	
Type of pathology					0.003**
Classical	246	80.4	28	87.5	
Follicular	34	11.1	1	3.1	
Hurthle cell variant	2	0.7	1	3.1	
Oncocytic	6	2	2	6.3	
Tall cell	18	5.9	0	0	
Thyroiditis	130	43.9	16	55.2	0.245
Multifocality					
Multifoci	103	33.7	13	40.6	0.430
Single focus	203	66.3	19	59.4	
Goitrous thyroid	197	70.4	12	48	0.055
ETE	28	10	18	58.1	<0.001**
ECE	27	12.7	10	43.5	<0.001**
Margin	52	18.1	10	31.3	0.094
LVI	3	1.2	9	29	<0.001**
Perineural invasion	3	2.2	1	4.5	0.450
Recurrence in the thyroid bed	15	5.5	1	3.4	0.640
Recurrence in the lymph nodes	3	1	1	3.1	0.332
Residual and received RAI	23	7.7	11	34.4	<0.001**
Residual needed completion surgery	5	1.7	2	6.3	0.099
Preoperative TSH level	2.2	2.2	2.6	2.2	0.1
FT4	15.4	11.1	13.7	2.8	0.1
FT3	5.1	4.6	5.5	4.4	0.1
Tumor size (largest in cm)	0.5	0.4	0.7	0.3	0.2

ETE: extrathyroidal extension, ECE: extracapsular extension, LVI: lymphovascular invasion, RAI: radio-active iodine, TSH: thyroid stimulating hormone, **Significant at p<0.05

among the patients with LNM (29%) than among those without (1.2%). The perineural invasion, recurrence in the thyroid bed, and recurrence in the LNs did not significantly differ between the 2 groups. The residual and received radioactive iodine (RAI) proportion was also significantly higher in the patients with LNM (34.4%) than in the other group (7.7%). The residual needed completion surgery did not significantly differ between the 2 groups. Likewise, among the continuous variables, the average preoperative Thyroid Stimulation Hormone number, free T4, free T3, and tumor size did not significantly differ.

Table 3 shows the results of the univariate and multivariate logistic regressions performed to predict the chances of LNM. The gender, height, weight, BMI, and age were not significant predictors. Among Bethesda classes, the reference category was class 1. From the results, we observed that the odds of having central LNM for all the Bethesda classes were lower than for class 1, and the odds for class 2 and 3 were significantly lower. The odds that the patients with a goitrous thyroid would have LNM were only 0.375, which is significant (p=0.019). This suggests that the patients with a goitrous thyroid had a significantly lower chance of having LNM. On the other hand, the odds of the patient having LNM were significantly predictors in ETE (12.412) and ECE (5.299). That is, patients with ETE and ECE have a significantly higher chance

Table 3 - Logistic regression to predict the chances of lymph node metastasis.

Factors	Univariate 95% CI				Multivariate 95% CI			
	OR	Lower	Upper	*P*-value	OR	Lower	Upper	*P*-value
Female	1							
Male	1.5	0.6	3.5	0.36				
Height	1.3	0.0	79.286	0.897				
Weight	1	1	1.005	0.141				
Body mass index	1	0.9	1.015	0.15				
Age	1	1	1.022	0.534				
Bethesda class 1	1	-	-	-				
Bethesda class 2	0.0	0.0	0.159	0.001**				
Bethesda class 3	0.0	0.0	0.545	0.015**				
Bethesda class 4	-	-	.	0.998				
Bethesda class 5	0.1	0.0	1.1	0.059				
Bethesda class 6	0.1	0.0	1.579	0.11				
Pathology: classical	1	-	-	-				
Pathology: follicular	0.3	0.0	1.961	0.191				
Pathology: Hurthle cell variant	4.4	0.4	50.002	0.233				
Pathology: oncocytic	2.9	0.6	15.209	0.201				
Pathology: tall cell	-	-	-	0.998				
Thyroiditis	1.6	0.7	3.384	0.248				
Multifocal	1.3	0.6	2.838	0.431				
Single focus	1	-	-	-				
Goitrous thyroid	0.4	0.2	0.852	0.019**	0.151	0.039	0.584	0.006**
ETE	12.4	5.5	27.993	<0.001**	7.724	1.859	32.102	0.005**
ECE	5.3	2.1	13.269	<0.001**	5.897	1.3	26.748	0.021**
Margin	1.9	1.0	3.486	0.036**				
LVI	33.5	8.5	133.009	<0.001**	25.817	2.461	270.806	0.007**
Perineural invasion	2.1	0.2	21.575	0.518				
Recurrence in the thyroid bed	0.6	0.1	4.827	0.643				
Recurrence in lymph nodes	3.2	0.3	31.956	0.317				
Residual and received RAI	6.3	2.7	14.625	<0.001**				
Residual needed completion surgery	3.8	0.7	20.224	0.123				
Preoperative TSH level	1.1	0.9	1.230	0.352				
FT4	0.9	0.8	1.06	0.221				
FT3	1	0.9	1.1286	0.766				
Tumor size (largest in cm)	1.8	0.9	3.859	0.109				

LNM: lymph node metastasis, ETE: extrathyroidal extension, ECE: extracapsular extension, LVI: lymphovascular Invasion, RAI: radio-active iodine, TSH: thyroid stimulating hormone, CI: confidence interval, OR: odds ratio, **Significantly at p<0.05.

of having LNM, as do patients with LVI and residual and received RAI.

In the multivariate logistic regression, we explored the effects of all the variables together on the chances of the patient having LNM; that is, the effect of one predictor was adjusted for the effects of the other variables. Due to the large number of predictor variables and the presence of multicollinearity among the predictors, we used a stepwise logistic regression model that fits the most significant variable at a time and stops entering a new variable in the model when there are no more significant predictors. Using this approach, the only significant predictors identified in the model are a goitrous thyroid, ETE, ECE, and LVI. While a goitrous thyroid has a negative effect, the other variables (ETE, ECE, and LVI) have a significant positive effect on the chances of having LNM. No other variable was significant in the presence of these variables.

Discussion. In this retrospective study, we investigated and analyzed the clinicopathological features of 338 PTMC patients and evaluated the risk factors for LNM. In recent years, there has been an increase in the incidence of PTC, which could be attributable to the greatly increasing incidence of PTMC.[13] In the literature, the incidence of LNM in PTMC ranges from 29.5% to 65%, and LNM is thought to be the most important predictor of local recurrence.[14-17]

We found that the incidence of LNM in PTMC patients reached 9.17%, which is lower than what was observed in previous studies.[14,15] This could be due to the underlying histologic subtype of the study group, the time from FNA to surgery, and other potential factors. Papillary thyroid microcarcinoma was more common in women than in men, as was LNM, which is similar to the findings in literature.[15,17]

Most studies agree with our finding and have shown that the type of pathology, specifically, tall cell, and the multifocality in thyroid carcinoma, are risk factors for LNM.[18-21] This may be because only 18 individuals had a tall cell subtype of PTMC. Our findings are in line with the literature, as ETE and ECE were found to be independent risk factors for LNM.[14,18,22,23] Moreover, LVI was found to be an independent risk factor, similar to the finding of Mao et al[18] that PTMC with capsular invasion exhibited a relatively high odds ratio for LNM.

In this study, no significant correlation was found between the size of the tumor and the risk for LNM, in contrast to the studies of Wang et al[18] and Mao et al[24] in which they found that a larger tumor size was linked to a higher chance of having LNM. Multiple studies have discovered that thyroiditis is one of the independent risk factors for LNM, although in this study, no significant correlation was found between thyroiditis and LNM.[25-27] Furthermore, it should be underlined that PTMCs with higher Bethesda class were associated with LNM, which could be attributed to the late presentation of the patients. Interestingly, we found that patients who received RAI had a higher chance of LNM, which could be attributed to the aggressiveness of PTMC.

Gu et al[14] found that a tumor size >0.5 cm in ultrasound was an independent risk factor for PTMC patients developing LNM. Zhao et al[15] described the role of ultrasound in PTMC and concluded that it may add valuable information and predict central LNM by identifying ECE and a tumor diameter >0.65.

It should be highlighted that one of the major changes in the new 2022 WHO classification of thyroid tumors is the removal of PTMC as a histologic subtype and the insistence that even for tumors <1 cm, the exact histologic subtype must be mentioned. This is imperative because, as mentioned in the literature, different histologic subtypes have different behaviors.[28]

Study limitation. This study had some limitations that should be addressed. First, this was a retrospective comparative study, and errors in retrospective studies are often higher than in prospective studies. Second, we did not address the need for lymph node dissection and the best treatment modality for those patients, as this is the first study in Saudi Arabia on this issue. Third, the sample size was limited, and larger-scale studies on PTMC are needed in the future.

In conclusion, this study highlighted the risk factors for lymph node metastasis in PTMC patients. Notably, higher Bethesda class, type of pathology, ETE, ECE, LVI, and RAI-treated residual tumors were correlated with an increased risk of metastasis. Conversely, presence of thyroiditis, multifocality, goitrous conditions, neural invasion, and tumor size showed no significant correlation with LNM. These findings contribute to a nuanced understanding of PTMC behavior. This study underscores the importance of accurate risk assessment in guiding clinical decisions for PTMC patients. Further research is needed to validate and extend these insights to refine patient management strategies.

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