Risk factors for lateral lymph node metastasis in patients with papillary thyroid cancer: a retrospective analysis

Hossam R. Moussa, Amir F. Abdelhamid, Salah E.A. Elgohary, Waleed Y. El Sherpiny

Department of General Surgery, Faculty of Medicine, Tanta University, Tanta, Egypt

Correspondence to Hossam Ramadan Moussa, MD, Surgical Oncology Unit, Department of General Surgery, Faculty of Medicine, Tanta University, Tanta 31527, Egypt
Tel:+20403337544; fax: +20403337544;
e-mail: hossam.ramdan2019@gmail.com

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Background

There is still a great controversy among oncologic surgeons regarding the role of lateral lymph node dissection in patients with papillary thyroid cancer, although tumors spread to this compartment have been established. To optimize the management of such patients, we intended to study the predictors for lateral lymph node metastasis (LLNM) in patients with papillary thyroid cancer.

Patients and methods

This study included 63 patients whose data were retrospectively reviewed. All of them underwent total thyroidectomy with central and lateral lymph node dissection. They were divided into two groups based on the final histopathological analysis: group A (LLNM +ve) and group B (LLNM –ve).

Results

The incidence of LLNM was 41.27%, making 26 patients included in group A, and the remaining 37 patients included in group B. Group A expressed younger age and higher prevalence of male sex. Operative time was statistically comparable between the two groups. Although group A had significantly larger tumors, other tumor criteria, including number, bilaterality, capsular, and extracapsular spread, showed no significant difference between the two groups. Nonetheless, upper-pole lesions, lymphovascular invasion, and the number of harvested and infiltrated central lymph nodes were significantly increased in group A. Although most of the significant factors maintained their significance on univariate analysis, only the central lymph node status remained significant on the multivariate one.

Conclusion

Younger age, male sex, larger tumors, upper-pole lesions, lymphovascular invasion, concomitant thyroiditis, and increased metastatic central lymph nodes are strongly associated with LLNM.

Keywords:
lateral lymph nodes, metastasis, papillary cancer, predictors

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Introduction

Papillary thyroid carcinoma (PTC) is a differentiated form of epithelial thyroid malignancies. It shows follicular cell differentiation along with some distinctive nuclear features. It is the most common type of thyroid cancer, as it accounts for about 80% of follicular-derived thyroid malignancies [1].

It is characterized by its tendency to spread through the lymphatic channels [2]. About half of PTC patients have central lymph node metastasis when prophylactic central neck dissection is performed [3,4]. Although the lymphatic behavior of PTC is supposed to affect the central lymph node compartment prior to the lateral one [5], some patients may have lateral lymph node metastasis (LLNM) with a free central compartment, and this is known as skip metastasis [6].

According to multiple previous reports, the rate of LLNM in such patients ranges between 28 and 80% [7,8]. Multiple studies have reported that LLNM in patients with PTC is associated with an increased risk of local recurrence and distant metastasis. Therefore, it is associated with poor patient survival [9–11].

Currently, PTC patients are managed by surgical excision of the thyroid gland with prophylactic central lymph node dissection if the patient has advanced primary tumor (T3 or T4) even in the absence of clinical lymphatic involvement [12]. However, lateral neck dissection is only performed therapeutically. Lateral neck dissection is suggested to be done only in patients with pathologically proved LLNM [13].

If we could determine the risk factors for LLNM before the operation, this would enable us to provide better management plans for PTC patients. This would help us to perform lateral neck dissection in high-risk patients to enhance their oncological outcomes and to avoid it in low-risk patients to decrease its associated morbidity. Therefore, in the current study, we intended to study the incidence and predictors for LLNM in patients with PTC in our tertiary care center.

Patients and methods

This retrospective study was conducted at Tanta University Surgical Oncology Unit. We retrospectively reviewed the data of consecutive 63 patients who underwent surgery for PTC during the period between January 2018 and December 2021. We collected the data of adult patients who were suspected of having LLNM based on preoperative and intraoperative findings. On the contrary, we excluded cases with the following criteria: other thyroid tumors rather than PTC, recurrent tumors, previous neck surgery, previous neck radiation, or free lateral neck nodes on preoperative or intraoperative assessment.

Before data collection, we gained ethical approval from the local ethical committee of our university. In addition, all patients have routinely signed informed written consent before the operation, despite the retrospective nature of the study. Before that, the benefits and possible complications of the surgical procedure were simply explained for them.

All participants received the standard preoperative assessment parameters, including history taking, general and local neck examination, and neck ultrasonography (US), in addition to neck and chest computed tomography (CT). Moreover, routine preoperative laboratory investigations were also ordered, including thyroid-function tests. Fine-needle aspiration for the suspected lymph node was not routinely done for all patients.

LLNM was suspected by US when the radiologist reported round shape, cystic changes, microcalcifications, or heterogeneous inner structure [14]. The same criteria also raised suspicion during CT imaging along with enhancement and necrotic changes [15]. Regarding nodal size, metastasis was suspected if its size was larger than 15 mm for submandibular and jugulodigastric lymph nodes or when larger than 10 mm for the remaining nodes [16].

All patients underwent total thyroidectomy with central lymph node dissection, and this is the routine management plan for such patients in our center. Therapeutic lateral lymph node dissection was performed if the patient had any one of the following criteria: suspicious LLNM on preoperative imaging, fine-needle aspiration, or positive malignant lateral nodes on intraoperative frozen biopsy. This included dissection of cervical lymph node levels from II to V.

After surgery, the surgical specimen, including the thyroid gland and excised labeled lymph nodes, was sent to the histopathology laboratory for examination. The results of lateral node examination were taken as the final conclusive result regarding involvement of lateral nodes by thyroid metastasis. Based on that perspective, the included patients were assigned into two groups: group A included patients with +ve LLNM, and group B included the remaining cases with –ve LLNM.

The collected data in our study included patient age, sex, systemic comorbidities, operative time, tumor location, laterality, size, number, capsular invasion, extracapsular involvement, lymphovascular invasion, number of harvested and infiltrated central lymph nodes, and the presence of concomitant thyroiditis.

Statistical analysis

We used SPSS software (SPSS inc., Chicago, IL, USA) for Mac for data collection and analysis. Data were either expressed in the form of number and percentage (for categorical data), while the quantitative data were expressed as mean±SD with parametric data or median and range for nonparametric data. We used χ^2 or Fisher's exact tests to compare two independent groups of categorical data. While comparing the quantitative data within two independent groups, independent samples t test was used for parametric data and Mann–Whitney U test for nonparametric data. Univariate and multivariate regression analyses were used to assess the dependent and independent predictors of binary outcomes. For all used statistical tests, the cutoff point below 0.05 for P value was considered to be statistically significant.

Results

According to the final pathological examination of the excised specimen, 26 patients showed positive LLNM, with an incidence rate of 41.27%.

Starting with the demographic criteria of the included participants, their ages had mean values of 38.15 and 46.44 years in groups A and B, respectively. The prevalence of patients younger than 40 years was significantly increased in group A (P=0.038). Although women were more predominant in both study groups, there was a significant tendency toward increased male sex in group

A (*P*=0.01). The prevalence of both hypertension and diabetes was statistically comparable between the two groups (*P*>0.05). Table 1 shows the previous data.

As shown in Table 2, the duration of operation had mean values of 197.63 and 194.52 min in groups A and B, respectively (*P*=0.597). Tumors more than or equal to 2 cm showed a significant increase in group A (76.9 vs. 51.35% in group B – *P*=0.04). Nevertheless, both tumor number and laterality were statistically comparable between the two study groups.

Upper-pole tumors were significantly increased in group A (53.85 vs. 24.32% in group B – *P*=0.017). However, the incidence of capsular invasion and extracapsular extension showed no significant difference between the two groups (*P*=0.978 and 0.891, respectively). Lymphovascular invasion was detected in 34.62 and 13.51% of patients in groups A and B, respectively, which was significantly increased in association with LLNM (*P*=0.047).

Concomitant thyroiditis was encountered in 42.3 and 18.92% of patients in the same groups, respectively (*P*=0.043). The number of dissected and infiltrated central lymph nodes showed a significant increase in association with group A (*P*<0.001). The former had median values of 9 and 5 nodes, while the latter had median values of 4 and 1 in groups A and B, respectively.

On univariate analysis, young age, male sex, tumors equal to or larger than 2 cm, concomitant thyroiditis, and increased number of dissected and infiltrated central lymph nodes were risk factors for LLNM. However, only the last two parameters remained significant on multivariate analysis (*P*=0.001). The previous data are shown in Table 3.

Discussion

The current study was conducted to estimate the incidence and risk factors of LLNM in patients with PTC. First of all, we suspected the tumor spread to the

Table 1 Demographic characteristics of the study population

Items	Group A (*N*=26) [*n* (%)]	Group B (*N*=37) [*n* (%)]	*P* value
Age (years)	38.15±4.29	46.44±8.09	0.019
Age groups			
<40 years	16 (61.54)	13 (35.14)	0.038*
>40 years	10 (38.46)	24 (64.86)	
Sex			
Male	11 (42.3)	5 (13.5)	0.010*
Female	15 (57.7)	32 (86.5)	
Comorbidity			
Diabetes mellitus	4 (15.38)	4 (10.81)	0.658
Hypertension	2 (7.69)	3 (8.11)	0.924

*Statistically significant (*P*<0.05).

Table 2 Operative time, tumor, and pathological characteristics of the study population

Items	Group A (*N*=26) [*n* (%)]	Group B (*N*=37) [*n* (%)]	*P* value
Operative time (min)	197.63±21.71	194.52±19.68	0.597
Tumor size			
<2 cm	6 (23.1)	18 (48.65)	0.040*
≥2 cm	21 (76.9)	19 (51.35)	
Tumor number			
Single	18 (69.23)	28 (75.68)	0.334
Multiple	8 (30.77)	9 (24.32)	
Laterality			
Unilateral	20 (76.92)	31 (83.78)	0.670
Bilateral	6 (23.08)	6 (16.22)	
Location			
Upper pole	14 (53.85)	9 (24.32)	0.017*
Middle or lower pole	12 (46.15)	28 (75.68)	
Capsular invasion	7 (26.92)	10 (27.03)	0.978
Extracapsular extent	6 (23.08)	8 (21.62)	0.891
Lymphovascular invasion	9 (34.62)	5 (13.51)	0.047*
Concomitant thyroiditis	11 (42.3)	7 (18.92)	0.043*
Number of dissected central lymph nodes	9 (4–15)	5 (4–9)	<0.001*
Number of infiltrated central lymph nodes	4 (1–7)	1 (0–4)	<0.001*

*Statistically significant (*P*<0.05).

Table 3 Univariate and multivariate regression analysis of the risk of lateral lymph node metastasis (*N*=26)

Variables	Univariate analysis	Multivariate analysis		
		OR	95% CI for OR	*P* value
Age	0.026*	0.758	0.643–1.102	0.168
Male sex	0.013*	1.251	0946–1.564	0.124
DM	0.736			
HTN	0.894			
Operative time	0.946			
Large tumor size	0.044*	0.687	0.525–1.909	0.183
Multiple tumors	0.436			
Bilateral tumors	0.520			
Upper-pole tumors	0.009*	1.113	0.937–1.332	0.211
Capsular invasion	0.993			
Extracapsular extent	0.891			
Lymphovascular invasion	0.054			
Concomitant thyroiditis	0.047*	0.746	0.646–1.106	0.068
Number of dissected central lymph nodes	<0.001*	2.426	1.782–3.620	0.001*
Number of infiltrated central lymph nodes	<0.001*	3.114	2.054–3.874	0.001*

CI, confidence interval; DM, diabetes mellitus; HTN, hypertension; OR, odds ratio.
*Statistically significant (*P*<0.05).

lateral cervical lymph nodes via clinical examination, US, CT examination, as well as a frozen biopsy. Although Amin *et al.* [17] reported that clinical assessment together with US examination of cervical lymph nodes were the most important and reliable factors to define LLNM, both of them have their own drawbacks. It is not necessary to find significantly enlarged nodes in the lateral compartment even in the presence of metastasis. Also, US is highly dependent on operator experience and machine quality [18]. Even CT can miss micrometastasis in such nodes, along with the side effects of intravenous contrast injection [18,19]. Furthermore, the intraoperative frozen section could not be available in some centers, and it could miss lymph node metastasis as pathologists often make it in a single lymph node [20].

In the current study, the incidence of LLNM was 41.27% in the current series, and this lies with the range reported in the literature (28 and 80%) as previously stated in the 'introduction' section.

Our findings showed a significant association between younger age and the occurrence of LLNM (*P*=0.019). Patients aged less than 40 years were more prevalent in the LLNM group (*P*=0.038). Young age was a significant risk factor in univariate analysis. In line with our findings, Song *et al.* [13] reported that the mean age of PTC patients was 37.93 and 42.63 years in the LLNM and non-LLNM groups, respectively. Young age was a significant risk factor for LLNM on univariate analysis in that study (*P*<0.001). Moreover, Zhao *et al.* [7] showed that the prevalence of patients aged less than 55 years showed a significant increase in the LLNM group, as about 80% of this age group had LLNM (*P*=0.04).

In our study, the male sex was a significant risk factor for LLNM on univariate analysis (*P*=0.013), although its significance faded with the multivariate one. Likewise, another study reported a significantly higher prevalence of male sex in the LLNM group (32.8 vs. 24.03% in the non-LLNM group – *P*=0.038). Nevertheless, that significance faded on multivariate analysis (*P*=0.630) [7]. Another study also showed similar findings [21]. Contrarily, Jin *et al.* [18] reported that the male sex was not associated with an increased risk of LLNM, as men formed 22.7 and 25.8% of patients in the LLNM and non-LLNM groups, respectively (*P*=0.729). Nie *et al.* [15] confirmed the previous findings regarding sex (*P*=0.359).

Our findings showed that a larger tumor size (≥2 cm) was significantly associated with LLNM (*P*=0.04). It was also a significant risk factor on univariate analysis. Nie *et al.* [15] confirmed our findings regarding tumor size. Larger tumors (>1.5 cm) were detected in 52.81 and 29.21% of patients in the LLNM and non-LLNM groups, respectively (*P*<0.001).

In the current study, tumor number did not have a significant impact on LLNM (*P*=0.334). Similarly, Nie *et al.* [15] reported that single tumors were detected in 84.64 and 86.55% of LLNM and non-LLNM groups, respectively, with no significant difference between the two groups (*P*=0.668). The remaining patients had multifocal tumors. On the other hand, another study reported a significant increase in tumor multifocality in the LLNM group (41.3 vs. 19.4% in the non-LLNM group – *P*=0.031) [18].

In the current study, unilobar or bilobar affection with tumor did not have a significant association with LLNM (P=0.67). Another study confirmed our perspective regarding the insignificant impact of tumor bilaterality on the risk of LLNM (P=0.456) [7]. Nie *et al.* [15] also confirmed the previous findings.

Our study showed a significant association between upper-pole tumors and LLNM (P=0.017). It was a significant factor for the lateral spread on univariate analysis. Another recent study reported that upper-lobe PTC is a significant predictor of LLNM (odds ratio 2.127 – P=0.037) [13]. Besides, other studies reported that upper-pole PTCs were also positively associated with LLNM risk [3,22]. This could be explained by the spread of tumor cells from this region directly to the lateral compartment along lymphatics accompanying the superior thyroid artery [23,24]. Jin *et al.* [18] negated the previous findings as upper-pole tumors were detected in 84 and 71% of patients in the LLNM and non-LLNM groups, respectively (P=0.219).

In the current study, the capsular invasion was not significantly associated with LLNM (P=0.978). Song *et al.* [13] agreed with our findings regarding the impact of capsular invasion on LLNM. It was detected in 35.05 and 31.22% of patients in the LLNM and non-LLNM groups, respectively (P=0.348). On the other hand, Jin *et al.* [18] reported a significant increase of the same parameter in association with LLNM (P=0.03). It was detected in 29.3 and 9.7% of patients in the LLNM and non-LLNM groups, respectively.

The extracapsular extension was not a risk factor for LLNM in our study (P=0.891). Another study confirmed the previous findings regarding the insignificant association between extracapsular extension and LLNM [13]. On the other hand, Zhao *et al.* [7] reported that extracapsular extension showed a significant increase in association with LLNM (P=0.003). The authors reported that LLNM was present in 87% of patients with extracapsular extension.

In our study, the lymphovascular invasion was strongly associated with LLNM (P=0.043). However, it lost its significance in regression analysis. In agreement with our findings, Kim *et al.* [25] reported that the same variable was significantly associated with LLNM. Also, the significance persisted after adjusting other risk factors, which was not encountered in the current study. Another study also confirmed the association between lymphovascular invasion and LLNM [26].

Our study showed a significant association between thyroiditis and LLNM, and it was a significant risk factor for that finding on univariate analysis. In accordance with our findings, Zeng *et al.* [27] reported a significant increase in the prevalence of thyroiditis in the LLNM group (34.9 vs. 13.3% in the non-LLNM group – P=0.003). Nonetheless, Hu *et al.* [21] negated any significant impact of concomitant thyroiditis on LLNM (P=0.592). It was detected in 12.4 and 11.2% of cases in the LLNM and non-LLNM groups, respectively.

In the current study, the number of dissected and infiltrated central lymph nodes showed a significant increase in association with LLNM. Both of them were significant on both univariate and multivariate analyses. Song *et al.* [13] also reported that the increased number of harvested and infiltrated lymph nodes was more significantly encountered in the LLNM group (P<0.001). The former had mean values of 7.69 and 5.47, while the latter had mean values of 4.61 and 1.79 in the LLNM and non-LLNM groups, respectively.

Although Zhao *et al.* [7] reported almost similar findings between the LLNM and non-LLNM groups regarding the number of dissected central lymph nodes (13.1 vs. 12.2 – P=0.11), the number of metastatic central nodes showed a significant rise in association with LLNM (6.1 vs. 1.8 – P<0.001). That difference even persisted on multivariate analysis. Jin *et al.* [18] also confirmed the strong association between the metastatic rate of central cervical lymph nodes and the occurrence of LLNM (odds ratio 1.407 – P=0.001). Therefore, the presence of extensive metastasis in central lymph nodes should warrant surgeons to strictly follow up or perform subsequent lateral lymph node dissection following the primary procedure if not performed [15].

While looking at the previous comparisons with the literature reports, one could see a great diversity in the results. Nearly most of the study variables showed agreement and disagreement with multiple studies. This could be explained by different sample size, tumor criteria, and inclusion criteria. However, this should encourage surgical oncologists to create prediction scores for LLNM.

Our study has some limitations: it was retrospective in nature, and the included sample size was relatively small and collected from a single surgical center. The upcoming studies should cover these drawbacks.

Conclusion

According to the previous findings, younger age, male sex, larger tumors, upper-pole lesions, lymphovascular invasion, concomitant thyroiditis, and increased metastatic central lymph nodes are strongly associated with LLNM. Patients showing one or more of the previous criteria should undergo a preoperative and intraoperative assessment to avoid missed metastasis in such a compartment.

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Conflicts of interest
There are no conflicts of interests.

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