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Skip Metastasis in Papillary Thyroid Cancer: Is it Predictable?

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Abstract

Background: Cervical lymph node metastasis is a prognostic factor in papillary thyroid carcinoma (PTC). Metastasizing PTC to cervical lymph nodes is very common and occurs in 30-80% of patients.
Aim: To investigate the risk factors of skip lateral lymph node metastasis in PTC patients.
Methods: This retrospective study was conducted at a single institution and included PTC patients treated in the period between 2018 and 2021. All patients with PTC who underwent total thyroidectomy with central and lateral block neck dissection were reviewed for skip metastases which was confirmed by histopathologic examination.
Results: During the study period, 267 patients with PTC underwent total thyroidectomy with central and/or lateral block neck dissection. Among them, only 64 patients matched the study inclusion criteria and their pathology was reviewed for skip metastases. Thirteen (20.3%) patients showed skip metastases. Their mean (±SD) age was 50.1 (±16.7) years and 8 (61.5%) were females. Only age ≥40 years and tumor size ≤0.5 cm differed significantly between patients with skip metastasis and those without.
Conclusions: The results support the conduction of a prospective multi-centric study with a larger sample size to better understand the risk factors for developing skip metastasis in PTC. This would help in selecting patients with a risk for skip metastasis.

Keywords: Cervical lymph nodes, Papillary thyroid carcinoma, Risk factors, Skip metastasis
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Introduction

Thyroid cancer detection is rapidly rising due to the increased use of different imaging modalities. In the USA, the incidence has increased four times. The last decades have seen notable advances in diagnosis as well as surgery for thyroid cancer [1]. Among the known types of thyroid cancer, papillary thyroid carcinoma (PTC) is an indolent disease that, generally, grows slowly and carries a good prognosis in most patients. The incidence of PTC has increased by threefold and makes up approximately 90% of all thyroid cancers [2-4].

The thyroid gland lymphatics drain into the central compartment (peritracheal, prelaryngeal, and paratracheal nodes) and lateral cervical nodes. The spread of PTC passes through the lymphatic system in a predictable stepwise pattern. Lymphatic metastasis in PTC involves firstly the ipsilateral central compartment then the contralateral central compartment, then the ipsilateral lateral compartment, and lastly the contralateral lateral compartment and the mediastinal lymph nodes (LNs) [5-6].

Metastasis from PTC to cervical LNs is quite common and occurs in 30-80% of patients. According to numerous studies on postoperative histology of metastatic LNs, the rate of central lymph node metastasis (LNM) ranges from 14.6% to 52%, and the rate of both lateral and central LNM is 42–65% [7-8].

Skip metastasis is noted in some patients in whom lateral LNM has developed in the absence of central LNs involvement and the frequency of skip metastasis in PTC is approximately 0.6– 37.5%. [9-11].

Despite the excellent prognosis, some PTC and papillary thyroid microcarcinoma may have an aggressive course, because of molecular biological alterations and other unknown reasons [11-12].

There are different surgical management approaches for LNs in the central as well as the lateral compartments in cases with PTC. However, lateral neck dissection is only done therapeutically in cases where there is confirmed nodal metastasis in the lateral compartment. Meanwhile, central compartment lymph node dissection (LND) is routinely performed in many institutions as a prophylactic measure to improve staging accuracy, reduce nodal recurrence risk, reduce thyroglobulin level postoperatively, and consequently avoid re-operation in the central neck [13]. Prophylactic neck dissection is limited only to the central compartment, and, on the other hand, therapeutic neck dissection is only performed when there is proof of metastatic lateral LNs involvement either radiologically or histopathologically [14].

Ultrasound (US) imaging features of the metastatic LNs include node enlargement, loss of the fatty hilum, hyperechogenicity, calcifications, a more rounded than oval shape, cystic change, and peripheral vascularity [15]. The false-positive and false-negative rates of US to palpable LNs range from 20% to 30%. In addition, the ultrasonic examination cannot identify abnormal LNs if their diameter is <5 mm [16-17].

It is suggested that skip metastases show different clinicopathological features when compared to continuous metastases and thus have a different prognosis. Since they are not uncommon, skip metastases' incidence and diagnostic methods should be identified in an attempt to avoid further locoregional recurrence and the complications of reoperation.

This study aimed to estimate the prevalence of skip metastasis in PTC patients in our institute and to investigate the risk factors of lateral LNM in PTC patients, which will contribute to assessing the optimal management of LNs in PTC patients.

Methods

A retrospective study was conducted at the Surgical Unit of the Oncology Centre of Mansoura University (OCMU) that included PTC patients treated during the period between 2018 and 2021.

Patients

All patients with PTC who underwent total thyroidectomy with central and lateral block neck dissection were reviewed for skip metastases which was confirmed by histopathologic examination (HPE) at the Pathology Department of OCMU.

For inclusion, patients should have pathologically proven PTC which is treated by both central and lateral LNs dissection after total thyroidectomy. Patients with only central LNs or lateral LNs removal or without neck dissection were excluded.

All patients underwent neck US, thyroid function tests, fine needle aspiration (FNA) biopsy, and indirect laryngoscopy before the procedure. In this study, all patients underwent total thyroidectomy plus central (level VI) and lateral block neck dissection (levels II to V).

The collected data included patients' demographics, sonographic and histopathological characteristics, and follow-up and survival data.

Statistical analysis

The expression of qualitative data was as absolute frequency (N) and percentage (%). Chi-Square / Fisher's exact test was used to compare categorical data. Initially, the quantitative data were tested for normality using Shapiro-Wilk's test. To test for the presence of significant outliers, inspecting boxplots was utilized. Quantitative data were expressed as mean ± standard deviation (SD) if normally distributed and as median and range if not normally distributed. Quantitative data between two groups were compared using independent samples *t*-test if normally distributed, or Mann-Whitney U-test if not.

The Cochran-Armitage test of trend is used to determine whether there is a linear trend between an ordinal independent variable (TIRAD) and a dichotomous dependent variable (skip metastasis). Binary logistic regression was used to predict the likelihood of the occurrence of skip metastasis.

Table 1: Comparisons between patients with and without skip metastasis

Variable	Total (*n*=64)	Skip metastasis		*p*-value
		Yes (*n* =13)	No (*n* =51)	
	***n* (%)**	***n* (%)**	***n* (%)**	
Sex				
Male	27 (42.2)	5 (38.5)	22 (43.1)	0.761
Female	37 (57.8)	8 (61.5)	29 (56.9)	
Age (years)				
<40	29 (45.3)	2 (15.4)	27 (52.9)	0.015
≥40	35 (54.7)	11 (84.6)	24 (47.1)	
Lymph nodes				
Normal	6 (9.4)	2 (15.4)	4 (7.8)	0.593
Suspicious	58 (90.6)	11 (84.6)	47 (92.2)	
Tumor size (cm)				
>0.5	61 (95.3)	10 (76.9)	51 (100)	0.007
≤0.5	3 (4.7)	3 (23.1)	0	
Bethesda				
B1	1 (1.6)	0	1 (2)	0.194
B2	1 (1.6)	0	1 (2)	
B3	4 (6.3)	1 (7.7)	3 (5.9)	
B4	11 (17.2)	4 (30.8)	7 (13.7)	
B5	36 (56.3)	4 (30.8)	32 (62.7)	
B6	11 (17.2)	4 (30.8)	7 (13.7)	
Intraoperative residuals	10 (15.6)	0	10 (19.6)	0.107
Papillary thyroid carcinoma subtype				
Typical	57 (89.1)	11 (84.6)	46 (90.2)	0.437
Follicular	3 (4.7)	1 (7.7)	2 (3.9)	
Insular	1 (1.6)	0	1 (2)	
Solid	1 (1.6)	0	1 (2)	
Tall	1 (1.6)	0	1 (2)	
Micro	1 (1.6)	1 (7.7)	0	
Site				
Upper	20 (31.3)	4 (30.8)	16 (31.4)	0.544
Middle	22 (34.4)	3 (23.1)	19 (37.3)	
Lower	22 (34.4)	6 (46.2)	16 (31.4)	
Side				
Right	25 (39.1)	4 (30.8)	21 (41.2)	0.782
Left	26 (40.6)	6 (46.2)	20 (39.2)	
Bilateral	13 (20.3)	3 (23.1)	10 (19.6)	
Extra-thyroid extension	26 (40.6)	7 (53.8)	19 (37.3)	0.277
Tumor capsule infiltration	33 (51.6)	8 (61.5)	25 (49)	0.420
Perineural invasion	4 (6.3)	0 (0)	4 (7.8)	0.574
Lymphovascular extension	29 (45.3)	6 (46.2)	23 (45.1)	0.946
Multicentricity	33 (51.6)	8 (61.5)	25 (49)	0.420
Thyroiditis	17 (26.6)	5 (38.5)	12 (23.5)	0.305
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Age (years)	44 ± 16.3	50.1 ± 16.7	42.4 ± 16	0.133
Tumor size by ultrasound (cm)	3.2 ± 1.6	2.8 ± 1.6	3.3 ± 1.6	0.376
Tumor size by histopathology (cm)	3.1 ± 1.7	3.2 ± 1.7	3.1 ± 1.7	0.865
	Median (range)	**Median (range)**	**Median (range)**	
Dissected central lymph nodes	5 (0-35)	2 (0-6)	6 (0-35)	0.003
Positive central lymph nodes	2 (0-14)	0 (0-0)	3 (0-14)	<0.001
Dissected lateral lymph nodes	18 (3-60)	22 (9-27)	15 (3-60)	0.345
Positive lateral lymph nodes	2 (0-25)	2 (1-15)	2 (0-25)	0.438

The Kaplan-Meier curve was used to describe survival characteristics (time-to-tumor recurrence). Log-rank test was used for the comparison between the survival curves. Also, restricted mean survival time (RMST) was compared between groups. The RMST is the average event-free survival time up to a pre-specified time point (2 years). The selected time point must lie between the first and last event in every group; if not, then the software will reset it to the lowest time point of the last event among the different groups. For all of the used tests, results were considered statistically significant if $p < 0.05$.

The data were analyzed using IBM SPSS Statistics for Windows, version 26.0. (Armonk, NY: IBM Corp) and MedCalc® Statistical Software version 20 (MedCalc Software Ltd, Ostend, Belgium).

Results

During the study period, 267 PTC patients underwent total thyroidectomy with central and/or lateral block neck dissection. Among them, only 64 patients matched the criteria, and their pathology was reviewed for skip metastases. Among them, 13 (20.3%) patients showed skip metastases including 5 males and 8 females and their average age was 50.1 (± 16.7) years.

The comparison between patients with skip metastases and those without is illustrated in Table 1. The prevalence of skip metastasis differed significantly according to age and tumor size. There was no statistically significant difference for other examined parameters. On univariate binary logistic regression, age ≥ 40 years has 6.2-times higher odds to exhibit skip metastasis (crude odds ratio = 6.2, 95% CI = 1.2 – 30.8, P = 0.026).

A Cochran-Armitage test of the trend was run to determine whether a linear trend exists between TIRAD and the proportion of patients who had skip metastasis. The TIRADs were T0 (n = 2), T2 (n = 1), T3 (n = 6), T4 (n = 36) and T5 (n = 19), and the proportion of patients with skip metastasis was 1.000, 1.000, 0.167, 0.194 and 0.105, respectively. The Cochran-Armitage test of trend showed a statistically significant linear trend, p = 0.002, with lower TIRADs associated with a higher proportion of patients with skip metastasis.

Table 2 and Figure 1 show that recurrence occurred in 25% of cases. As the survival curve did not drop to 0.5 or below for all cases and the studied factors, the median time was not computed. The RMST was statistically significantly shorter in tumors >0.5 cm vs. smaller tumors. For this risk factor, HR was not calculated (zero recurrences in those with size ≤0.5 cm). All other risk factors did not achieve statistical significance.

Table 3: Time-to-recurrence (TTR) analysis

Variable	N	Log-rank test		HR (95% CI)	RMST (2 years) in weeks		
		χ^2	*p*-value		Mean (SE)	95% CI	*p*-value
Sex							
Male	27	0.198	0.656	1.3 (0.46-3.5)	83 (6.9)	69.5-96.5	0.714
Female	37			Reference	86.3 (5.6)	75.3-97.3	
Age (years)							
<40	29	0.415	0.519	Reference	87.3 (6)	75.5-99.2	0.633
≥40	35			1.4 (0.51-3.7)	83.2 (6.1)	71.2-95.3	
Thyroiditis							
Absent	47	0.009	0.926	1.1 (0.34-3.2)	83.8 (5.2)	73.6-93.9	0.576
Present	17			Reference	89 (7.9)	73.6-104.4	
Tumor size (cm)							
>0.5	61	0.741	0.389	-	69.9 (3.5)	63.1-76.7	<0.001
≤0.5	3			-	84 (0.0)	84-84	
Skip metastasis							
No	51	0.303	0.582	Reference	85.8 (4.7)	76.7-95	0.788
Yes	13			1.4 (0.41-4.9)	82.7 (10.8)	61.6-103.8	

RMST: Restricted mean survival time, **SE:** Standard error, **CI:** Confidence interval, **HR:** Hazard ratio

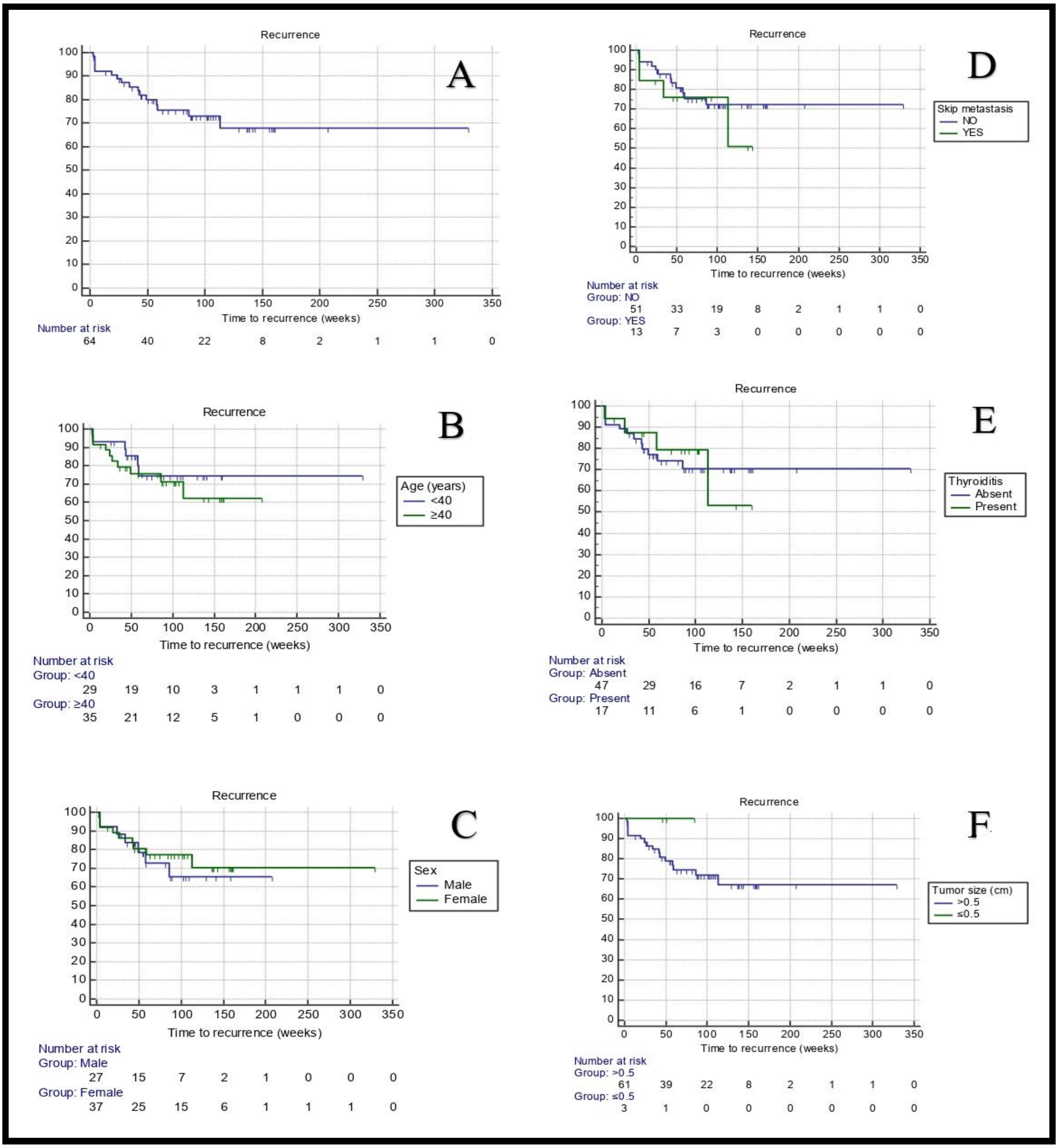

Figure 1: Time-to-recurrence (TTR) Kaplan-Meier Curves. 1A: TTR of all patients; **1B:** TTR, age >40 years vs <40; **1C:** TTR, males vs. females; **1D:** TTR, skip metastasis vs. no skip metastasis; **1E:** TTR, thyroiditis versus no thyroiditis; **1F:** TTR, tumor size >0.5 cm vs. <0.5 cm

Discussion

The prevalence of skip metastases in our study was nearly 20% which is higher than that found in most of the published studies. For example, Nie et al. reported a prevalence of 14.8% (in 30 out of 203 patients) and other studies reported further lower rates ranging from 7.4% to 12.4%. [12, 19-21] On the other hand, our results are matching with Feng et al. [22] and Park et al. [23] who reported a prevalence of 22.5% (20/89) and 21.8% (32/147) respectively.

Multiple factors had been studied for their association with skip metastasis development in PTC patients including gender, age, thyroiditis, bilaterality, multifocality, presence of psammoma bodies, tumor site and size, capsular invasion, extrathyroid extension, number of harvested central LNs and number of harvested/metastatic lateral LNs.

In the current study, an age of 40 years or older and a tumor size of 0.5 cm or less were the only parameters demonstrating a statistically significant association with skip metastasis. There was no statistically significant difference for other examined parameters including tumor size/site, US criteria, multicentricity, extra-thyroid extension, Bethesda type, PTC subtype, capsule infiltration, perineural invasion, lymphovascular extension, and intra-operative residue. By univariate binary logistic regression, age ≥40 years and tumor size >0.5 cm are independent factors for skip metastases in PTC patients.

Age was associated with an increased risk of skip metastasis in some studies. Zhan et al. [24] emphasized the importance of the association between the age of patients (>45 years) and the development of skip metastases. This was supported by several other studies like those of Lei et al. [12], Jin et al. [19], Chung et al. [25], and Zhang et al. [26]

Tumor size is inversely related to skip metastasis. Tumors ≤1 cm were more likely to be associated with skip metastasis in many studies. [12, 16, 20, 24] In addition, Nie et al. [18] reported that tumors ≤0.5 cm tend to metastasize to lateral LNs instead of central LNs. This appears counterintuitive, but this result was concordant with Machens et al. [9] who concluded that skip metastasis was observed to be more recurrent in less aggressive forms of PTC. The direct relation of older age and smaller tumor size to skip metastasis in PTC is supported in our study.

Primary tumor location in the upper pole of the thyroid was significantly associated with skip metastases. [27] This is supported by nearly all studies searching for predisposing factors for skip metastasis in PTC. [12, 17, 18, 21, 22, 24] Although, many studies supported the direct relation between tumor location in the upper pole and PTC skip metastasis, this was not the case in our study. Similarly, Wada et al. [28] and Noguchi et al. [29] have denied this relation. The significant association of Lateral LNM with primary tumor location could be explained by the hypothesis that cancer cells at the upper thyroid pole are more likely to be carried to the lateral LNs by the lymphatic flow along the superior thyroid artery. [30] Lymph node metastasis arising from a primary tumor located in the upper part of the thyroid lobe was more frequent in level II than in other levels. This suggests that the lymphatic drainage system is different from that in other parts of the thyroid lobe. [31]

There was no association between tumor multifocality and skip metastasis in a metanalysis done by Qiu et al. [17] However, it had been reported as a risk factor for PTC skip metastasis by Lei et al. [12] and Koo et al. [32] On the other hand, unifocality was reported as a risk factor for developing skip metastasis in the studies done by Park et al. [23] and Zhao et al. [20] However, unilaterality may increase the risk of skip metastasis according to a study by Hu et al. [21] Neither multifocality/multicentricity nor unifocality was supported to be as a risk factor for PTC skip metastasis in our study.

Regarding US criteria, skip metastasis was common in tumors without a well-circumscribed margin. [19] Unfortunately, this was not investigated in our retrospective study.

The capsular invasion was considered as a possible risk factor for the development of skip metastasis in PTC patients. [12, 25, 26, 24] Lim and Koo [33] found that extra-thyroid extension (ETE) is an important predictor of skip metastasis in PTC patients. This was supported by Lin et al. who considered ETE as a risk factor for skip metastasis. [19] But in other studies, ETE was not considerably associated with skip metastasis. However, ETE has a higher incidence of nodal metastasis to the central as well as the lateral LNs. PTC with ETE is thought to be more likely to spread to central LNs due to its shorter distance. So, when lateral LNM occurs, central LN had already been affected. [17, 21]

The results of this study showed that when compared to patients with no skip metastases PTC, those with skip metastasis had a lower number of dissected lateral LNs [22 (9-27) vs. 15 (3-60)] and dissected central LNs [2 (0-6) vs 6 (0-35)]. While the number of dissected lateral LNs doesn't reach a statistical significance; the number of dissected central LNs does show statistical significance (0.003). This is supported by the results of Zhao et al. [20] and Hu et al. [21] who reported that fewer central LNs were dissected among patients with skip metastasis than those with no skip metastasis (9.5 ± 6.4 vs 13.4 ± 6.4, P < .001), and the number of dissected central LNs was negatively associated with skip metastasis (OR: 0.89, *p*<0.001). However, neglected LNs may become the source of local recurrence and distant metastasis. Patients with skip metastasis had a smaller number of metastatic lateral LNs and vice versa, the number of metastatic LNs in the lateral compartment was inversely associated with skip metastasis. [20]

Extracapsular spread is considered a risk factor for developing skip metastasis as per a study done by Lim and Koo. [33] On the other hand, lymphovascular invasion was found to be inversely related to PTC skip metastasis, as emphasized by Qiu et al in their metanalysis. [17]

In two large meta-analyses done by Qiu et al. [17] and Nie et al. [18], gender, age, bilaterality, multifocality, thyroiditis, and presence of psammoma bodies were not significantly associated with skip metastasis.

Multivariate analysis done by Zhao et al. [20] in 2019 showed that the female sex was an independent risk factor for skip metastasis. But this is not consistent with our results and those of other studies conducted by Qui et al. [17] and Lei et al. [12]

Three hypotheses for skip metastasis were proposed: the first hypothesis supports the idea that existing anatomical lymphatic channels are enabling skip metastasis. This can be applied to upper pole tumors which spread directly to level II and III lateral LNs before central LNs. A second hypothesis proposed that normal anatomical lymphatic pathways could be altered by surgeries on the neck, infection, or radiotherapy. The third hypothesis suggests the presence of false negative lymph node samples. [33]

The significance of skip metastasis in PTC is still unclear. Previous studies have found that skip metastasis could be found more frequent in less aggressive PT microcarcinoma. [22, 23] Having said that, Qiu et al. [17] found no significant impact of skip metastasis on tumor-free survival of PTC patients, which is supported by our findings.

Patients with skip metastases had a lower number of harvested central LNs. Additionally, the PTC skip metastasis presented at the lower lateral LNM. In PTC, skip metastases affects most frequently Level III and to a fewer extent Levels II, IV, and level V. The PTC skip metastases showed much higher-Level II metastasis and lower Level III, IV, and V metastases. Also, PTC skip metastases showed a higher number of single-level and comparable amounts of double-level spread but much lower triple- and quadruple-level spread in the lateral compartment. [10-12, 21-23, 34] This might be explained by the role of lymphatics running close to the superior thyroid artery from the primary tumor at the upper thyroid pole which tends to spread to the upper levels rather than to the other levels. [14]

It has been indicated that disease recurrence and distant metastasis are significantly more frequent in PTC patients with lateral LNs compared to those with central LNM and clinically negative for LNs. [35] Also, redo surgery for PTC recurrence may significantly increase the surgical time, complications, and costs and in addition affect the patient's quality-of-life. [36]

Our study enrolled only PTC patients who underwent therapeutic lateral LND (US-reported or FNA biopsy-proven metastasis). Both US scan and FNA biopsy have false negative results, while latent lateral LNM is detected in >50% of the patients who received prophylactic lateral compartment dissection. [30] Additional predictive factors and more accurate detection methods are required to predict skip metastasis after prophylactic LND, which is not recommended by many guidelines.

Our study has limitations. It is a retrospective study conducted in a single institution; hence the collected data represents a relatively small sample size, which carries inevitable inherent features of non-randomization. Additionally, patients' follow-up interval was relatively short (the average follow-up period was 18 months). Also, the thyroidectomy/LND were performed by different surgeons of different level of training and years of experience, in addition to other surgeon-related factors that might have an impact on the outcomes. Moreover, since LND is not recommended as a prophylactic practice, there may be undetected lateral LNM.

Conclusion

Our study results can serve as a proof of concept for conducting a prospective multi-centric study with a larger sample size, which would explain and give us a better understanding of the risk factors for developing skip metastasis in PTC, thus predicting its occurrence and helping to select patients at risk of skip metastasis.

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Authors' contribution

Conception or design: MTH, SA; Acquisition, analysis, or interpretation of data: AZ, OB, MA; Drafting the manuscript: AMZ, ME; Revising the manuscript: MTH; Approval of the manuscript version to be published: All authors; Agreement to be accountable for all aspects of the work: All authors

Conflict of interest
The authors declare that they have no conflict of interest to disclose.

Data availability
Deidentified individual participant data used to produce the results of this study are available from the corresponding author (MTH) on request.

Ethical considerations
The study has been approved by the Institutional Research Board of Mansoura University.

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Study registration
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