



The impact of thyroid tumor features on lymph node metastasis in papillary thyroid carcinoma patients in head and neck department at KAMC: A retrospective cross-sectional study

Amjad O. Aljohani^a, Reyhan H. Merdad^b, Anas I. Alserif^c, Layan S. Alhemayed^d, Noor Z. Farsi^d, Thamer A. Alsufyani^e, Haddad H. Alkaf^f, Ameen Z. Alherabi^g, Sherif K. Abdelmonim^h, Mohammad A. Alessa^{f,*}

^a Al-Farabi Private College for Dentistry and Nursing, Jeddah, Saudi Arabia

^b College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia

^c Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

^d Umm Al-Qura University, Makkah, Saudi Arabia

^e Taif University, Taif, Saudi Arabia

^f Department of Head and Neck Surgery, Head and Neck and Skull Base Health Center, King Abdullah Medical City, Makkah, Saudi Arabia

^g Department of Otolaryngology-Head & Neck Surgery, College of Medicine, Umm Al-Qura University, Saudi Arabia

^h Department of Otolaryngology Head and Neck Surgery, Faculty of Medicine, Ain Shams University, Cairo, Egypt

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ABSTRACT

Introduction: Papillary thyroid carcinoma (PTC) is the most prevalent type of thyroid cancer. It is one of the most common types of malignancy of the thyroid that spreads to cervical lymph nodes. Lymph node metastasis (LNM) is an important factor when determining recurrence risk, and determining the extent of lymph node involvement can guide treatment. Our main objective is to evaluate the association between the size of the tumor and the number of lymph node metastases in patients with PTC. **Methods:** We conducted an electronic retrospective chart review of 125 patients with PTC followed in the Head and Neck Department at KAMC from 2009 to 2020. Twenty-two patients included in our study were pathologically and clinically diagnosed and confirmed to have LNM of PTC. **Results:** The study included 22 PTC patients who had undergone lymph node dissections. Patients had a median age of 38.8 years (IQR = 32.2–54.5), and the median tumor size was 20.5 mm. The most commonly affected level of the neck was IV (76.2%). Distant metastasis M1 was seen in only two patients (9.1%). Tumor sizes >30mm (75%) had ≥ 5 LNM. Most cases were the classic subtype PTC. For the site of the tumor, the site had a significant impact on the number of LNM ($p = 0.004$). Multifocality had a high impact on LNM ($p = 0.019$). **Conclusions:** This study showed no association between the size of PTC and the number of LNMs. The bilaterality of PTC was significantly associated with a high number of LNMs.

1. Introduction

Papillary thyroid carcinoma (PTC) is the most prevalent type of thyroid cancer. It is one of the most common types of malignancy of the thyroid that spreads to cervical lymph nodes [1]. In Saudi Arabia, the incidence of PTC has been increasing [2]. Thyroid cancer is the second most common type of cancer among women in Saudi Arabia, and PTC makes up 82.7% of all thyroid carcinomas [3]. Generally, the prognosis

of patients with PTC is very good, and it has a very low postoperative mortality risk [4]. However, recurrence is common and occurs in up to 32% of patients [5]. LNM is an important factor when determining recurrence risk, and determining the extent of lymph node involvement can guide treatment [6]. Thyroidectomy is the treatment of PTC along with central and lateral lymph node dissection depending on whether the lymph nodes are affected or not. The tumor spreads to central lymph nodes first and then to lateral lymph nodes. In some cases, the lateral

* Corresponding author. Head and Neck and Skull Base Health Center, King Abdullah Medical City, Mecca, 24246, Saudi Arabia.

E-mail addresses: Amjadaljahani8@gmail.com (A.O. Aljohani), reyhanmerdad@gmail.com (R.H. Merdad), Abu.naif1235@gmail.com (A.I. Alserif), layansaad@gmail.com (L.S. Alhemayed), noorfarsi@hotmail.com (N.Z. Farsi), moony2tm@gmail.com (T.A. Alsufyani), Abuhusseini@hotmail.com (H.H. Alkaf), Herabi@hotmail.com (A.Z. Alherabi), dr.sherif@med.asu.edu.eg (S.K. Abdelmonim), Alessa.mohammad@gmail.com (M.A. Alessa).

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nodes can be affected without the central lymph nodes, which is called skip metastasis known to happen in small upper lobe tumors [7]. Determining whether the lymph nodes are affected or not is an important factor in determining the extent of surgery [8]. One way to determine the risk of LNM is by assessing the patient's risk factors and using fine needle aspiration (FNA) to identify features that may suggest a chance of LNM [9]. There is a relationship between primary tumor features and the histopathological component of lymph node metastasis, which is linked to tumor invasiveness [10]. Male gender, age under 45, and absence of Hashimoto's thyroiditis are all risk factors for central lymph node metastasis (CLNM) [11]. Tumor characteristics such as multifocality, size, extrathyroidal extension, capsular invasion, and lymphovascular invasion are also risk factors for LNM [12]. In all previous studies, LNM was classified as CLNM and lateral lymph node metastasis (LLNM) without elaborating on the number and exact lymph nodes affected. In our study, we aimed to investigate the impact of thyroid tumor histopathological and clinical features on LNM.

2. Materials and methods

We conducted an electronic retrospective chart review of 125 patients with PTC followed in a single-center "King Abdullah Medical City Hospital in Makkah-Head and Neck and Skull Base Health Center" (a tertiary public referral center) between 2009 and 2020.

Patients were identified through the operative database. Twenty-two patients met the inclusion criteria, which were pathologically confirmed to have lymph node metastasis of papillary thyroid carcinoma, and 103 were excluded because no neck dissection was performed or the lymph node was negative for metastasis.

After receiving the ethical approval from the Institutional Review Board at King Abdullah Medical City in Makkah, the following data were collected from patients' medical records: gender, age at diagnosis, family history, laboratory findings, tumor stage and size at diagnosis, tumor histological details, and lymph node characteristics.

This study was registered at <https://www.researchregistry.com/> (unique identifying number: researchregistry6633) and work has been reported in line with the STROCSS criteria [13].

All statistical data were produced using SPSS (version 23.0, SPSS, Inc., Chicago, Ill., USA). Numerical data were presented as the mean \pm SD or as the median and range according to the type of distribution of each variable. For categorical variables, percentages were used. Comparisons between two qualitative variables were made using the chi square test. To determine association between variables, Non-parametric tests were used. P-values were considered significant if < 0.05 .

3. Results

3.1. Patients

The study included 22 patients with PTC who had undergone lymph node dissections. There were 11 males (50%) and 11 females (50%), with a median age of 38.8 years (IQR = 32.2–54.5 years). The majority of patients were Saudi Arabian 17 (77%) and lived in Makkah 18 (81.8%).

3.2. Clinicopathologic characteristics

The median tumor size was 20.5 mm (IQR 14.25–43.5 mm). Multifocality was found in 10 (45.5%) patients, extrathyroidal extension in 8 (36%), extranodal extension in 12 (54.5%), and lymphovascular invasion in 12 (54%). The location of the tumor varied: 6 (27.3%) were right, 7 (31.8%) were on the left side of the thyroid and 9 (40.9%) were bilateral. Only one patient (4.5%) had Hashimoto's thyroiditis. The largest ultrasound nodule size had a median of 25 mm (IQR 11.5–40 mm) (Table 1). The most commonly affected levels of the neck were IV

Table 1
Baseline clinicopathological characteristics.

Characteristics	Value
Age at diagnosis, years	
Average (range)	38.8 (12.5–78.44)
≤ 45	14 (63.6%)
> 45	8 (36.4%)
Gender (male)	11 (50%)
LMN number	
< 5	8 (36.4%)
≥ 5	14 (63.6%)
Tumor size (mm)	
0–5 mm	3 (13.6%)
6–30 mm	11 (50%)
> 30 mm	8 (36.4%)
Thyroid size	
Not affected	7 (36.8%)
Affected	12 (63.2%)
Multifocality	
No	12 (54.5%)
Yes	10 (45.5%)
Bilaterality	
No	13 (59.1%)
Yes	9 (40.9%)
Extrathyroidal extension (Radiological)	
No	16 (88.9%)
Yes	2 (11.1%)
Extrathyroidal extension (Histological)	
No	14 (63.6%)
Yes	8 (36.4%)
Extranodal extension	
No	10 (45.5%)
Yes	12 (54.5%)
Lymphovascular invasion	
No	10 (45.5%)
Yes	12 (54.5%)
Distant metastasis	
Yes	2 (9.1%)
Hashimoto's thyroiditis	
No	15 (93.8%)
Yes	1 (6.3%)
Tumor site	
Right	6 (27.3%)
Left	7 (31.8%)
Bilateral	9 (40.9%)
TI-RADS classification	
2	4 (25%)
3	3 (18.8%)
4	6 (37.5%)
5	3 (18.8%)
Bethesda classification	
Category 2	1 (4.5%)
Category 5	3 (13.6%)
Category 6	18 (81.8%)
TNM stage	
T stage	
T 1a	3 (13.6%)
T 1b	6 (27.3%)
T 2	7 (31.8%)
T 3a	6 (27.3%)
N stage	
N 1a	3 (13.6%)
N ab	19 (86.4%)
M stage	
M 0	20 (90.9%)
M 1	2 (9.1%)
Thyroid nodule number	
Single	7 (46.7%)
Multiple	8 (53.3%)
Additional Therapeutic Intervention	
No	1 (5.6%)
Yes	15 (82.8%)
Not yet (COVID-19 Period)	2 (11.1%)

Values are presented as n (%) or median (IQR).

(76.2%), III (71.4%), IIa (61.9%), and IIb (57.1%) (Fig. 1). The TI-RADS classification was 1 in none of the patients, 2 in four patients (25%), 3 in three patients (18.8%), 4 in six patients (37.5%), and 5 in three patients (18.8%). The TNM stage was T1a in three patients (13.6%), T1b in six patients (27.3%), T2 in seven patients (31.8%), and T3a in six patients (27.3%). In addition, N1a was seen in three patients (13.6%), and N1b was seen in nineteen patients (86.4%). Distant metastasis M1 was seen in only two patients (9.1%) (Table 1).

3.3. Lymph node metastasis

For patients with tumor size 0–5 mm, (66.7%) had ≥ 5 LNM, and for size 6–30 mm, (54.5%) had ≥ 5 LNM, and sizes >30 mm (75%) had ≥ 5 LNM ($p = 0.653$). Most cases were the classic subtype, as 40% had <5 LNM and 60% had ≥ 5 LNM. One case had a follicular variant and one case with tall cell subtypes, both had ≥ 5 LNM ($p = 0.533$). For the site of the tumor, the site had a significant impact on LNM, as right-sided tumors (16.7%) had ≥ 5 LNM, left-sided tumors (57.1%) had ≥ 5 LNM, and (100%) of bilateral tumors had ≥ 5 LNM ($p = 0.004$). Multifocality had a high impact on LNM, as (90%) had ≥ 5 LNM ($p = 0.019$) (Table 2). The tumor marker thyroglobulin (Tg) postoperatively was measured for all patients, and it did not have a significant impact on LNM, as low Tg (66.7%) had ≥ 5 LNM, normal Tg (62.5%) had ≥ 5 LNM, and high Tg (66.7%) had ≥ 5 LNM ($p = 0.982$) (Table 3).

4. Discussion

In this study, there were 11 males and 11 females, unlike other studies where the females predominated. And in terms of age, (63.6%) were below 45 years with median age of 38.8 years (IQR = 32.2–54.5), unlike another study performed on 159 patients where (64.8%) were older than 45 years with median age of 48.4 years [14]. The median tumor size was 20.5 mm which is comparable to a recent study reported from Saudi Arabia, where the mean size was 21.5 mm [15]. Multifocality was found in (45.5%), which is similar to a previous study where multifocality was (44.3%) [16]. In our study, 9 patients had bilaterality (40.9%). When compared to a large pool study (3296 patients) from Korea, only 983 (29.8%) had bilaterality [17]. We found that (36.4%) of the patients had histological extrathyroidal extension. When we compared it to a similar study, we found that the rate of extrathyroidal extension was (34.1%) [7]. Our extranodal extension was higher than expected (54.5%) when we compared it to another study with 152 patients; only 56 had extranodal extension (approximately 37%) [18]. Lymphovascular invasion was higher than expected (54.5%); a similar study published in 2017 reported it to be (9.3%) [19]. Only 2 patients (9.1%) had distant metastasis; compared to another study with 966

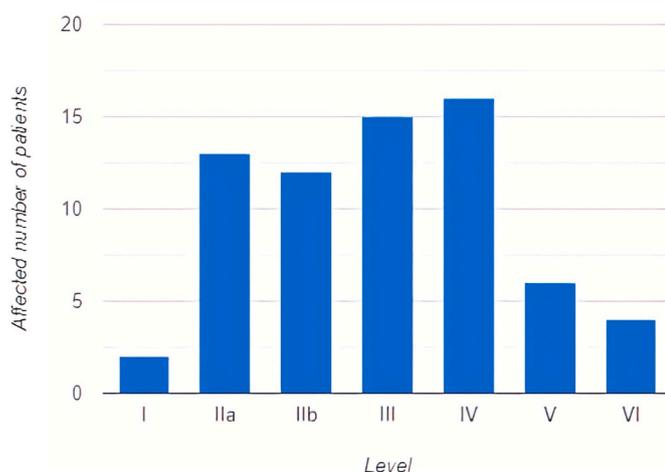


Fig. 1. Most affected level of lymph nodes.

Table 2

Association between clinicopathological characteristics and number of lymph node metastasis.

	Number of Lymph Node Metastasis n (%)		P-value
	<5	≥ 5	
Tumor Size			
0–5 mm	1 (33.3%)	2 (66.7%)	0.653
6–30 mm	5 (45.5%)	6 (54.5%)	
>30 mm	2 (25.0%)	6 (75.0%)	
Gender			
Male	4 (36.4%)	7 (63.6%)	1
Female	4 (36.4%)	7 (63.6%)	
Age at diagnosis			
≤ 45	5 (35.7%)	9 (64.3%)	0.933
>45	3 (37.5%)	5 (62.5%)	
Histology			
Conventional	8 (40%)	12 (60%)	0.533
Follicular	0 (0%)	1 (100%)	
Tall cell	0 (0%)	1 (100%)	
Extrathyroidal extension			
Histological	3 (37.5%)	5 (62.5%)	0.933
Radiological	1 (50%)	1 (50%)	
Multifocality	1 (10%)	9 (90%)	0.019
Tumor site			
Right	5 (83.3%)	1 (16.7%)	0.004
Left	3 (31.8%)	4 (57.1%)	
Bilateral	0 (0%)	9 (100%)	

Table 3

Association between lymph node number and lab results.

	Number of Lymph Node Metastasis n (%)		P-value
	<5	≥ 5	
Thyroid-Stimulating Hormone (TSH) pre-operative			
Low	0 (0%)	2 (100%)	0.469
Normal	6 (35.3%)	11 (64.7%)	
High	0 (0%)	1 (100%)	
Thyroid-Stimulating hormone (TSH) post-operative			
Low	1 (20%)	4 (80%)	0.533
Normal	3 (33.3%)	6 (66.7%)	
High	4 (50%)	4 (50%)	
Thyroglobulin (Tg) post-operative			
Low	3 (33.3%)	6 (66.7%)	0.982
Normal	3 (37.5%)	5 (62.5%)	
High	1 (33.3%)	2 (66.7%)	

Reference ranges were TSH: 0.45–4.50 mIU/L; Tg: 3.5–77.0 ng/mL.

patients, only 5 patients had distant metastasis (approximately 0.5%) [16]. Out of 16 patients, Hashimoto's thyroiditis was detected in only one patient (6.3%), which is lower than expected. A study published in 2017 showed that Hashimoto's thyroiditis was found in (31.3%) [20]. In the Bethesda classification, patients classified with the 6th category (malignant) were very high (18 patients 81.8%). A study of 560 male and 1974 female patients with 5784 nodules showed that only 160 nodules out of 5784 were malignant; however, the results aren't comparable, since the study was performed on all types of thyroid cancers [21]. In this study, the median tumor size was 20.5 mm (2.05 cm) (IQR 14.25–43.5). Similar results have also been reported in a previous study. One study reported that primary tumor size less than or equal to 1 cm (10 mm) was significantly related to lymph node metastasis pathological features, which are related to tumor invasiveness [10]. Additional studies performed in Saudi Arabia have shown that the primary tumor size is 2.3 cm (23 mm), and the other tumor size is 2.15 cm (21.5 mm) [2]. Earlier studies showed that females were affected more often than males; the cause behind the females' higher incidence is not well understood [2,22]. However, in this study, both genders were equal. Whether age is associated with LNM, the present findings are not consistent. Several studies found a significantly decreased risk of CLNM in older patients >45 years [23]. However, few studies reported that CLNM was not associated with age [24]. In this study, we did not find an

association between age and LNM ($p = 0.933$). Previous studies in Jeddah, Riyadh, Aseer and our study in Makkah reported the same histological subtype of the global data regarding thyroid cancer, which is papillary followed by follicular thyroid carcinoma [2,3,22,25]. Many studies have investigated ETE associated with lymph node metastasis in PTC to assess disease prognosis. It has been reported that LNM in patients with PTC is associated with extrathyroidal extension [26]. However, our results did not associate ETE (histological) with LNM ($p = 0.933$). Generally, most of the studies in PTC referred to multifocality without separation between unilateral and bilateral multifocality [27, 28]. Only a few studies described the effect of unilateral and bilateral multifocality tumors on LNM [29]. In line with previous studies [12,28], we observed that bilaterality and multifocality were associated with aggressive features such as LNM. This is in concordance with our results; both bilateral and multifocal PTC were significantly associated with a high number of LNMs. We confirmed that bilateral tumors are slightly different from multifocal tumors in comparison with LNM ≥ 5 (90.9% vs 90%) ($P = 0.003$, $P = 0.019$). In a retrospective study by Han et al., bilateral multifocal tumor was considered an independent risk factor for ≥ 5 LNM. However, there were results where evaluating the predictors of ≥ 5 LNM on bilateral solitary and bilateral multifocal ($P = 0.014$, $P < 0.001$) had a significant association. Additionally, it has been reported that predicting LNM is more correlated with bilaterality than multifocality [29]. Considering the tendency of PTC to be multifocal (often bilateral), some studies showed a low risk of recurrence after complete thyroidectomy compared with thyroid lobectomy [9].

Thyroid-stimulating hormone (TSH) was compared before and after the operation to determine if there was a difference according to LNM. The number of LNMs was not affected by TSH values before surgery ($p = 0.469$) or after surgery ($p = 0.533$). This is consistent with what Liu et al. reflected in their results, as the mean TSH value for patients with CLNM was 2.13 $\mu\text{IU/mL}$ compared to 2.10 $\mu\text{IU/mL}$ of patients without CLNM [15]. In addition, Lang et al. concluded that TSH values were not affected by tumor size, ($p = 0.595$) [30]. However, Jin et al. used logistic regression and determined that TSH was a risk factor for LLNM; for every 1 $\mu\text{IU/mL}$ increase in TSH, the risk of LLNM increased 0.975 times [31]. Thyroglobulin (Tg) is a vital tumor marker to monitor response to treatment, and it is used to detect recurrence or metastasis. Post-operative Tg results showed that LNM number did not affect Tg levels, ($p = 0.982$). This result shows that the number of affected nodes does not affect Tg levels; however, the presence of LNM has already been confirmed to be related to higher Tg levels in other studies. Liu et al.'s results revealed that intrathyroidal tumors had a mean Tg of 24.9 ± 11.2 ng/mL, while tumors with LNM had 68.6 ± 18.1 ng/mL, ($p = 0.0001$) [32]. Additionally, So et al. and Korkmaz et al. demonstrated that patients with neck dissections along with total thyroidectomy (TT) had lower Tg levels than patients who had only undergone TT, which indicates that subclinical LNM is responsible for the higher Tg levels in the second group [33,34]. Our study had the limitations that it was retrospective in design and the sample size was small. Future researchers should try to get a larger sample size which might reveal further significant relations in the data.

5. Conclusion

In conclusion, histopathological characteristics can be a predictor of the extent of LNM. Bilateral and multifocal PTC indicate that the disease has probably spread to more lymph nodes. So, patients should undergo careful evaluations for LNM when they have multifocal or bilateral PTC. Also, Lymph nodes in level IV were the most common metastasis site for PTC.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amsu.2021.102217>.

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Provenance and peer review

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Ethical approval

This study was approved by the Institutional Review Board at King Abdulla Medical City in Holy Capital.

Consent

Not applicable.

Author contribution

Amjad Obaid Aljohani: Collected and processed the data and wrote the final manuscript.

Reyan Hatem Merdad: Performed the statistical analysis and wrote the final manuscript.

Anas Ibrahim Alsefri: Performed the statistical analysis and wrote the final manuscript.

Layan Saad Alhemayed: Collected and processed the data and wrote the final manuscript.

Noor Ziyad Farsi: Collected and processed the data and wrote the final manuscript.

Thamer Abdulrahim Alsufyani: Performed the statistical analysis and wrote the final manuscript.

Haddad Hussein Alkaf: Reviewed and approved the final manuscript.

Ameen Ziyed Alherabi: Reviewed and approved the final manuscript.

Sherif Abdelmonim:: Reviewed and approved the final manuscript.

Mohammad Ali Alessa: Planned and supervised the work.

Registration of research studies

2. Unique Identifying number or registration ID:

1. Name of the registry:

3. Hyperlink to your specific registration (must be publicly accessible and will be checked):

Not applicable.

Guarantor

Dr. Mohammad Ali Alessa.

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