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Clinical and Pathological Factors that Affecting the Lymph Node Metastasis in Papillary Thyroid Carcinoma

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ABSTRACT

Background: Papillary thyroid carcinoma (PTC) is the most common form of thyroid cancer, characterized by its indolent growth and propensity to metastasize to lymph nodes, understanding the factors affecting metastasis in PTC is crucial for improving patient outcomes. **Aim of the Study:** To evaluate the influence of various clinical and pathological factors on the occurrence of lymph node metastasis (LNM) in patients with PTC. **Methodology:** A prospective interventional study was conducted at Safeer Al-Imam Al-Hussain Surgical Hospital, Imam Hussain medical city, Zain Al-Abedin surgical hospital and Al-Kafeel specialized hospital / Karbalaa/ Iraq over 13 years from 2011-2024, involving 40 patients diagnosed with PTC that underwent total thyroidectomy, and data on demographic, clinical, and pathological variables were collected and evaluated to identify correlations between these variables and N. **Results:** The mean age of patients was 42.4 ± 12.3 years, with a predominance of females (75%). LNM was observed in 50% of the patients. Significant correlations were found between N and age ($p = 0.036$), nodule site ($p = 0.004$), tumor type ($p = 0.012$), and adjacent lymphatic and vascular invasion ($p < 0.001$). Older patients, males, patients with nodules in the isthmus or bilateral nodules, and those with multinodular tumors or adjacent lymphatic and vascular invasion had a higher likelihood of LNM. **Conclusions:** Age, nodule site, tumor type, and adjacent lymphatic and vascular invasion significantly influence N in papillary thyroid carcinoma.

Keywords: Papillary Thyroid Carcinoma, Lymph Node Metastasis (LNM), Thyroidectomy.

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INTRODUCTION

Thyroid carcinoma, a cancer that affects the thyroid gland, has seen a significant rise in incidence over the past 30 years, now representing around 3.8% of all newly diagnosed cancer cases (Cabanillas et al., 2016). In general, thyroid cancer is classified into four main types: anaplastic thyroid carcinoma (ATC), medullary thyroid carcinoma (MTC), papillary thyroid carcinoma (PTC), and follicular thyroid carcinoma (FTC), with PTC and FTC being differentiated types (Carling & Udelsman, 2014). PTC is the most common form, accounting for 80% of all cases. Despite the increase in thyroid cancer diagnoses, the mortality rate has remained stable (Asa, 2019; Jamal et al., 2024).

Additionally, 87% of the rise in PTC is due to tumors measuring 2 cm or less. This surge is attributed to the enhanced accuracy of diagnostic techniques, including advancements in ultrasonography and fine needle aspiration (FNA) biopsy (Chen et al., 2023; Al Qurani. 2024).

The observed increase is present across tumors of varying sizes, suggesting the involvement of other contributing factors. PTC is more prevalent in females, Men, however, face a significantly higher mortality from PTC, with a two-fold increase in mortality compared to women. The disease typically affects individuals in their 30s or 40s, with an average age of diagnosis of 48 years. While death rates are notably lower for those under 40, they gradually rise with age. Factors like familial predisposition and exposure to ionizing radiation during childhood or adolescence can also influence susceptibility to thyroid cancer. Hereditary non-modular thyroid cancer may appear as part of various family cancer syndromes or as familial non-medullary thyroid cancer (FNMTC) (Pellegriti et al., 2013).

PTC is the most common form of thyroid cancer, while the follicular variant of PTC (FNMTC) accounts for 3.2-6.2% of all thyroid cancer cases (Seib & Sosa, 2019). The American Thyroid Association (ATA) advocates for the use of fine-needle aspiration biopsy (FNAB) as the primary method for distinguishing between benign and malignant thyroid nodules and determining the need for surgery. When combined with ultrasound (US) or computed tomography (CT), FNAB significantly improves the accuracy of cytological assessments and helps confirm the presence of nodal metastases, reducing the likelihood of false-negative results (Bible et al., 2021).

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Although PTC typically grows slowly and has a low mortality rate, it tends to metastasize to nearby lymph nodes and other organs, leading to a relatively high frequency of local and distant recurrence (Agrawal et al., 2014). Furthermore, identifying risk factors related to PTC helps surgeons evaluate lymph node status and decide if prophylactic central lymph node dissection (CLND) is warranted (Guo & Wang, 2014). LNM is a strong predictor of both local recurrence and distant spread in PTC. However, clinical indicators for conventional papillary thyroid cancer (CPTC) with lateral lymph node metastases (LLNM) have yet to be established (Liu et al., 2019).

Aim of the Study

To evaluate the influence of several clinical and pathological factors, such as age, gender, presence of multiple tumor foci, size and location of the tumor, invasion of the thyroid capsule, and spread outside the thyroid gland, on the occurrence of LNM in PTC.

METHODOLOGY

Study design: prospective interventional study

Methodology: the study was conducted in Safeer Al-Imam Al-Hussain Surgical Hospital, Imam Hussain medical city, Zain Al-Abedin surgical hospital and Al-Kafeel specialized hospital / Karbalaa/ Iraq over 13 years from 2011-2024.

The study involved 40 patients that were treated for PTC.

Inclusion criteria:

1. Adult patients that were diagnosed with PTC.
2. Tumor size ≥1 cm.
3. Agreed to participate in the study.

Exclusion criteria:

1. Other types of thyroid cancer (Aplastic, medullary, follicular, lymphoma)
2. Tumor size <1 cm (micro papillary carcinoma, TX or T0)
3. Cases of recurrence thyroid cancer that were treated before.
4. Patient who refused to participated in the study.

Data collection

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A prepared paper form is prepared by the researcher was filled after verbal consent is taken from each patient prior to surgery, containing the demographic variables of the patients including age, gender, and residency and family history of thyroid cancer.

And the clinical variables that including past medical history, past surgical history, drugs history and physical examination and document findings related to thyroid cancer like nodule size and site.

Outcome measures that were recorded during the intraoperative treatment were:

- Wither the tumor is multinodular or single nodule
- The presence of capsular invasion
- Adjacent lymphatic invasion
- Adjacent vascular invasion
- Cervical lymph nodes metastasis

Patients were then followed up after the surgery with periodic ultrasound examinations, serum thyroglobulin (Tg) measurements, and other imaging studies like CT scan if necessary.

Then the outcome of surgical treatment and the state of LNM of each patient is included in the prospective questionnaire, data from the questioners is then transformed into an excel format sheet and sent for statistical analysis.

Procedure

After admission to the surgical ward preoperative preparation for general anesthesia is done by performing the required investigations (CBC, viral screen, CXR, ECG, RFT, LFT), Medical consultation for GA fitness is also established.

The diagnosis relied on comprehensive assessment histopathological examination after biopsy to evaluate the extent of the tumor and lymph nodes invasion and establish the type of tumor and type of thyroid cancer.

PTC was treated with total thyroidectomy which is the standard treatment for most cases of PTC, especially for tumors larger than 1 cm, multifocal disease, or when there is evidence of extrathyroidal extension or distant metastasis.

Central compartment (level VI) neck dissection is performed in conjunction with thyroidectomy to remove lymph nodes around the thyroid gland if required when there is clinical or radiographic or intraoperative evidence of lymph node involvement.

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After surgery patients were followed up at various intervals to detect any complications or recurrence and to receive the treatment.

Statistical analysis

Data analysis was performed using SPSS-27 for Windows 10. The results were presented using basic statistical measures such as frequency, percentage, mean, range, and standard deviation. To assess differences between means of quantitative data, the Student's t-test was used for comparing two independent groups, while the chi-square test was applied to analyze categorical variables. A p-value of less than 0.05 was considered statistically significant for all variables.

RESULTS

The study involved 40 patients with PTC their mean age was 42.4 ± 12.3 years ranging from 22 to 73 years.

The sample was predominantly females, with 30 out of 40 patients (75%) being women, and the remaining 10 patients (25%) being men,

A small portion of the sample has a positive family history of thyroid cancer, with 3 out of 40 patients (7.5%) reporting a positive family history, whereas the majority, 37 out of 40 (92.5%), do not have any family history of the disease.

Table 1: *Demographic variables of the study sample (n=40)*

Variable		n	%
Age years	20-29	5	12.5
	30-39	14	35
	40-49	11	27.5
	50-59	4	10
	≥60	6	15
	Mean ± SD	42.4 ± 12.3	
	Range	22-73	
Gender	Male	10	25
	Female	30	75
Family History of Thyroid Cancer	Positive	3	7.5
	Negative	37	92.5

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Nodule size varies among the patients, with the majority having nodules between 2 and 4 cm, representing 60% of the sample (24 patients). Smaller nodules, less than 2 cm, are present in 35% of the patients (14 patients), and larger nodules, greater than 4 cm, are found in 5% of the patients (2 patients), the mean nodules size was 2.2 ± 1.07 cm, and the sizes range from 1 to 5.5 cm.

The right side of the thyroid was the most common site for nodules, with 45% of the patients (18 patients) having nodules there, the left side has nodules in 37.5% of the patients (15 patients), while bilateral nodules are found in 10% (4 patients), and nodules in the isthmus are present in 7.5% (3 patients), most patients have a single nodule, with 55% (22 patients), the remaining 45% (18 patients) have multinodular tumors, intraoperatively capsular invasion was present in 25% of the patients (10 patients) and absent in the remaining 75% (30 patients) and adjacent lymphatic and vascular invasion is observed in 22.5% of the patients (9 patients), while it is absent in 77.5% (31 patients).

Table 2: *Thyroid carcinoma characteristics among the study sample patients*

Variable		n	%
Nodule Size (cm)	<2	14	35
	2-4	24	60
	>4	2	5
	Mean ± SD	2.2 ± 1.07	
	Range	1-5.5	
Nodule Site	right	18	45
	left	15	37.5
	bilateral	4	10
	isthmus	3	7.5
Tumor Type	Single Nodule	22	55
	Multinodular	18	45
Capsular Invasion	Present	10	25
	Absent	30	75
Adjacent Lymphatic Vascular Invasion	Present	9	22.5
	Absent	31	77.5

After surgery patients were periodically followed up and send for the required investigations half of the patients (20 out of 40) have LNM that was discovered either during the operation or at the follow up, while the other half (20 out of 40) did not any evidence of lymph nodes involvement.

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Recurrence of thyroid carcinoma is observed in 12.5% of the patients (5 patients), whereas the majority, 87.5% (35 patients), do not experience recurrence and distant metastasis was observed in one of them.

Table 3: *Postoperative Outcomes among the study sample patients (n=40)*

Variable		n	%
LNM	Yes	20	50
	No	20	50
Recurrence	Yes	5	12.5
	No	35	87.5
Distant Metastasis (M)	Yes	1	2.5
	No	39	97.5

There was a significant correlation between age and LNM (p-value = 0.036). In the 20-29 age group, 60% (3 out of 5) are N0, and 40% (2 out of 5) are N1. In the 30-39 age group, 57.2% (8 out of 14) are N0, and 42.8% (6 out of 14) are N1. For the 40-49 age group, 36.4% (4 out of 11) are N0, and 63.6% (7 out of 11) are N1. In the 50-59 age group, 75% (3 out of 4) are N0, and 25% (1 out of 4) are N1. Among those aged 60 and above, 33.3% (2 out of 6) are N0, and 66.7% (4 out of 6) are N1. This trend indicates that younger patients are less likely to have LNM compared to older patients, particularly those aged 40-49 and 60 and above.

Gender shows a near-significant correlation with LNM (p-value = 0.051). Among males, 30% (3 out of 10) are N0, and 70% (7 out of 10) are N1. Among females, 56.7% (17 out of 30) are N0, and 43.3% (13 out of 30) are N1. This suggests that males are more likely to have LNM compared to females yet the correlation was not statistically significant.

Family history of thyroid cancer does not show a statistically significant correlation with LNM (p-value = 0.177). Among those with a family history, 66.7% (2 out of 3) are N0, and 33.3% (1 out of 3) are N1. Among those without a family history, 48.6% (18 out of 37) are N0, and 51.4% (19 out of 37) are N1. This indicates a slight tendency for those with no family history of thyroid cancer to have LNM, but the correlation is not strong.

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Table 4: *The statistical correlation between demographic variables and lymph nodes metastasis.*

Correlation with LNM		N0 n (%)	N1 n (%)	Total N	P Value
Age years	20-29	3 (60)	2 (40)	5	0.036
	30-39	8 (57.2)	6 (42.8)	14	
	40-49	4 (36.4)	7 (63.6)	11	
	50-59	3 (75)	1 (25)	4	
	≥60	2 (33.3)	4 (66.7)	6	
Gender	Male	3 (30)	7 (70)	10	0.051
	Female	17 (56.7)	13 (43.3)	30	
Family History of Thyroid Cancer	Yes	2 (66.7)	1 (33.3)	3	0.177
	No	18 (48.6)	19 (51.4)	37	
Total		20 (50)	20 (50)	40	-

The correlation between nodule size and LNM is not statistically significant (p-value = 0.171). Among those with nodules less than 2 cm, 35.7% (5 out of 14) are N0, while 64.3% (9 out of 14) are N1. For nodules sized 2-4 cm, 58.3% (14 out of 24) are N0, and 41.7% (10 out of 24) are N1. For nodules larger than 4 cm, 50% (1 out of 2) are N0, and 50% (1 out of 2) are N1. This indicates a tendency for smaller nodules (<2 cm) to have a higher likelihood of metastasis.

Nodule site shows a statistically significant correlation with LNM (p-value = 0.004). Among those with right-sided nodules, 55.6% (10 out of 18) are N0, and 44.4% (8 out of 18) are N1. For left-sided nodules, 53.3% (8 out of 15) are N0, and 46.7% (7 out of 15) are N1. For nodules in the isthmus, 25% (1 out of 4) are N0, and 75% (3 out of 4) are N1. For bilateral nodules, 33.3% (1 out of 3) are N0, and 66.7% (2 out of 3) are N1. This indicates that nodules located in the isthmus and bilaterally are more likely to be associated with LNM.

Tumor type shows a statistically significant correlation with LNM (p-value = 0.012). Among those with a single nodule, 63.6% (14 out of 22) are N0, while 36.4% (8 out of 22) are N1. For those with multinodular tumors, 33.3% (6 out of 18) are N0, and 66.7% (12 out of 18) are N1. This suggests that multinodular tumors have a higher likelihood of metastasis compared to single nodules.

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The correlation between capsular invasion and LNM is not statistically significant (p-value = 0.135). Among those with capsular invasion, 40% (4 out of 10) are N0, while 60% (6 out of 10) are N1. For those without capsular invasion, 53.3% (16 out of 30) are N0, and 46.7% (14 out of 30) are N1. This indicates a trend where capsular invasion is associated with a higher likelihood of metastasis, though the correlation is not strong.

Adjacent lymphatic and vascular invasion show a statistically significant correlation with LNM (p-value <0.001). Among those with adjacent lymphatic and vascular invasion, none are N0, while all 100% (9 out of 9) are N1. For those without invasion, 64.5% (20 out of 31) are N0, and 35.5% (11 out of 31) are N1. This indicates a very strong correlation between adjacent lymphatic and vascular invasion and LNM.

Table 5: *The statistical correlation between thyroid cancer variables and LNM*

Correlation with LNM		N0 n (%)	N1 n (%)	Total N	P Value
Nodule Size cm	<2	5 (35.7)	9 (64.3)	14	0.171
	2-4	14 (58.3)	10 (41.7)	24	
	>4	1 (50)	1 (50)	2	
Nodule Site	right	10 (55.6)	8 (44.4)	18	0.004
	left	8 (53.3)	7 (46.7)	15	
	isthmus	1 (25)	3 (75)	4	
	bilateral	1 (33.3)	2 (66.7)	3	
Tumor Type	Single Nodule	14 (63.6)	8 (36.4)	22	0.012
	Multinodular	6 (33.3)	12 (66.7)	18	
Capsular Invasion	Present	4 (40)	6 (60)	10	0.135
	Absent	16 (53.3)	14 (46.7)	30	
Adjacent Lymphatic and Vascular Invasion	Present	0	9 (100)	9	<0.001
	Absent	20 (64.5)	11 (35.5)	31	
Total		20 (50)	20 (50)	40	_

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DISCUSSION

The current demographic findings are consistent with the other studies about thyroid cancer epidemiology, showing a higher prevalence of thyroid carcinoma in females and middle-aged individuals, family history prevalence vary among studies and that might be due to different population samples or study sizes.

For instant a study on 931 patients with thyroid carcinoma found that differentiated thyroid carcinoma was more common in the 40-49 age group with average age of 43 years and that females were more commonly affected (70%), they also found that 10% had a positive family history of thyroid cancer, which is slightly higher than the current study. They also concluded that A total of 731 patients had PTC, while 200 patients were diagnosed with follicular carcinoma. Among these patients, 153 had lesions larger than 4 cm. Extrathyroidal extension was observed in 71 patients, and multifocal lesions were found in 159 patients. At the time of admission, 451 patients had regional LNM, and 45 patients had distant metastases (Shah et al., 1992).

The current study results show that the majority of patients (60%) have nodules between 2-4 cm and that nodules are present most commonly on the right side (45%) with single nodules being more common (55%), Capsular invasion was present intraoperatively in 25% of patients and adjacent lymphatic or vascular invasion in 22.5%.

Another study found the similar with most nodules <2 cm and higher proportion of single nodules, they also found that capsular invasion rate was (20%) and adjacent lymphatic and vascular invasion incidence of (15%) (Ito et al., 2014).

Another study by Akbulut et al., 2021 on 823 thyroidectomy specimens with PTC found that capsular invasion was present in 12.75% of thyroid cancer patients, 62% were unifocal, they also concluded that the status of capsular invasion is crucial in assessing papillary-patterned encapsulated PTC to predict LNM (Akbulut et al., 2021).

The current study results show that LNM was found in 50% of patients (20 patients) and nodal involvement was found either during surgery or during the follow up period recurrence of thyroid nodules was noted in 12.5% of patients during follow up among them 2.5% of patients had distant metastasis

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A study by Shaha et al., 1994 on series of 1,038 previously untreated patients with differentiated thyroid carcinoma found that LNM was present in 45% of cases, they reported higher rate of recurrence (15%) and distant metastasis, yet their follow up period was longer (median follow-up o20 years), they also concluded that the low-risk group achieved a 99% survival rate, while the high-risk group had only a 57% survival rate (Shaha et al., 1994).

The current results show significant correlation between the patients age and lymph nodes involvements with older patients being a higher risk (P value = 0.036), males also have higher likelihood of having LNM compared to females but the correlation was near-significant (P value = 0.051), our results also show no significant correlation between the family history of thyroid cancer and lymph nodes involvements (p-value = 0.177).

Similarly, a study by Wu et al., 2020 found that risk factors for lymph node involvement in PTC include older age, male gender, larger tumor size and specific tumor location (with the isthmus being at higher risk), multifocality, bilaterality, extrathyroidal extension, and the presence of abnormal lymph nodes on ultrasound (Wu et al., 2020).

The current study results show no significant correlation with nodule size (P value = 0.171) and capsular invasion (P value = 0.135), but significant correlation with nodule site with nodules at the isthmus and located bilaterally carry higher risk (p-value = 0.004), significant correlation was also found with tumor type and multifocal nodules have higher risk compared to single nodules (P value = 0.012).

Adjacent lymphatic and vascular invasion have statistically high significant correlation (p-value <0.001).

Another study by XU et al., 2018 on 3607 cases of papillary thyroid microcarcinoma (PTMC) concluded that age of less than 45 years ($P < 0.01$), male gender ($P < 0.01$), tumor diameter greater than 0.7 cm ($P < 0.01$), and multifocality ($P < 0.01$) significantly increase the risk of central LNM. However, clinical factors such as LNM, age, gender, multifocality, and the extent of the operation do not impact the 10-year disease-free survival rate ($P > 0.05$). [(29)] Yet their study is not conclusive with our results in term of age but the only included nodules of <1 cm in size (thyroid microcarcinoma) (Xu et al., 2018).

A Study by Sessa et al., 2018 compared micro and macro-PTC in 186 patients and their results show that 82 patients exhibited central neck metastasis (44%) extracapsular invasion and

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multifocality were identified as independent risk factors for lymph nodes involvement (Sessa et al., 2018).

Risk factors for LNM in PTC can vary across studies depending on sample size, demographic, and clinical characteristics. In a study by Tang et al., 2018 which included 180 patients with PTC the incidence of LNM was found to be 67.8% (122/180). The study identified multifocality ($p = 0.002$), Hashimoto's thyroiditis (HT) ($p < 0.001$), and lymphovascular invasion (LVI) ($p < 0.001$) as significant factors associated with LNM. However, no significant associations were observed between factors such as age, gender, tumor size, and extrathyroidal extension (Tang et al., 2018).

CONCLUSIONS

The majority of the patients in these studies were women, and about half had LNM at the time of surgery. Factors such as age, nodule site, tumor type, and adjacent lymphatic and vascular invasion were found to significantly influence LNM in PTC.

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