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Evaluation of the risk factors of metastasis to central cervical lymph nodes in patients with papillary thyroid carcinoma

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Background: Papillary thyroid cancer, comprising 80% of thyroid malignancies in iodine-sufficient areas, can be effectively treated if detected early before metastasis. Cervical lymph nodes are a common site of metastasis, prompting some surgeons to suggest prophylactic dissection in all patients. To minimize potential side effects, this study aims to identify patients benefiting from this procedure by assessing risk factors for central lymph node metastasis.

Methods and materials: This descriptive-analytical study was conducted on 150 patients with papillary thyroid cancer. The samples included cases in which central lymph node involvement was ruled out clinically and radiologically. After proving papillary cancer in the pathology sample, the variables of age, sex, frequency of central lymph node involvement, tumor size, location of thyroid involvement, multi-centric involvement, multi-focal involvement, presence of microcalcification, capsular invasion, lymphovascular invasion, and pathology were analyzed. The results were presented with descriptive statistics.

Results: The percentage of central lymph node involvement in this study was reported as 9.3%. In the analysis, capsular invasion ($P = 0.01$), lymphovascular invasion ($P = 0.0001$) and involvement of the upper thyroid pole ($P = 0.001$) were identified as risk factors for central lymph node involvement. There was no significant relationship between the variables of age, sex, tumor size, pathology, multi-centricity and multifocality and central lymph node involvement.

Conclusion: Involvement of central lymph nodes in patients with capsular invasion, lymphovascular invasion, and involvement of the upper thyroid bridge is far more common than in other patients, and central lymph node dissection is recommended in patients with several of the above risk factors.

Keywords: capsular invasion, central lymph nodes, lymphovascular invasion, papillary thyroid cancer, prophylactic lymph node dissection, upper pole involvement

Introduction

Thyroid cancer is the most common malignancy in the endocrine system, constituting ~1% of all cancers and around 33% of malignant neck tumors. Among thyroid cancers, papillary thyroid carcinoma accounts for 80% of all thyroid malignancies in iodine-sufficient regions and is the most prevalent cancer in children and individuals exposed to radiation[1]. Papillary carcinoma is about 2 times more common in females than males, with an average age of onset between 30 and 40 years[2]. The most common route of metastasis for this type of cancer is to the lymph nodes in the region[3]. These lymph nodes are divided into two compartments: central lymph nodes (CLN) and lateral lymph nodes (LLN)[4]. The central compartment includes lymph nodes between the two carotid sheaths, while the lateral compartment refers to lymph nodes outside this area[5].

Papillary thyroid cancer can metastasize to both compartments, but typically involves the central compartment initially and then extends to the lateral lymph nodes[6]. Distant metastasis is uncommon in the early stages of this disease, but eventually, it can be observed in 20% of cases, with the most common sites being the lungs, bones, liver, and brain[7]. Lymph node involvement in papillary thyroid cancer occurs in ~20–90% of patients, indicating

HIGHLIGHTS

- Papillary thyroid cancer, comprising 80% of thyroid malignancies in iodine-sufficient areas, can be effectively treated if detected early before metastasis.
- Cervical lymph nodes are a common site of metastasis, prompting some surgeons to suggest prophylactic dissection in all patients.
- Involvement of central lymph nodes in patients with capsular invasion, lymphovascular invasion.
- -Involvement of the upper thyroid bridge is far more common than in other patients, and central lymph node dissection is recommended in patients with several of the above risk factors.

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a significant independent factor for local recurrence and potential survival determinant, particularly in elderly individuals[8].

Given that central lymph node involvement is common in papillary thyroid cancer (20–50%), prophylactic dissection of central lymph nodes plays a crucial role in disease staging, determining postoperative radioactive iodine dosage, and eliminating a significant source of disease recurrence[9]. Therefore, prophylactic central neck dissection can be considered a strategy in the treatment of all patients with papillary thyroid cancer[2]. Currently, according to the American Thyroid Association guidelines, prophylactic central lymph node dissection is recommended only in patients with advanced papillary cancer (T3 and T4) or those with involvement of lateral neck lymph nodes[10]. On the other hand, the American Head and Neck Society's comprehensive guidelines suggest prophylactic neck lymph node dissection in all patients with high risk (using any risk assessment method)[11]. Considering the above factors and the common occurrence of central neck lymph node involvement in papillary thyroid cancer, disease recurrence can negatively impact patient survival[12]. Additionally, the potential for complications in subsequent surgeries, such as nerve damage, parathyroid gland injury, and impact on adjacent structures, warrants a rational consideration of prophylactic central neck lymph node dissection[10]. However, the increased risks associated with lymph node dissection, including nerve damage, parathyroid gland injury, and subsequent hypocalcemia postoperatively, necessitate the development of a precise protocol for selecting suitable patients who benefit from prophylactic central neck dissection. This study aims to examine the risk factors for central neck lymph node involvement to predict in which patients the benefits of prophylactic central neck dissection outweigh its drawbacks.

Methods

In this descriptive-analytical study, a total of 150 patients diagnosed with papillary thyroid cancer and undergoing total thyroidectomy were included in the study population. It should be noted that preoperative clinical and radiological assessments did not reveal any evidence of central neck lymph node involvement.

Patients suspected of having papillary thyroid cancer, based on preoperative fine-needle aspiration biopsy results, underwent central neck lymph node dissection in addition to thyroidectomy during surgery. After obtaining postoperative pathology results, patients confirmed to have papillary thyroid cancer remained in the study, while those with different pathology were excluded.

Additionally, criteria for study exclusion include a history of radiation, neck surgery, and concurrent cancer in the patients. Patient information entered into the study was extracted from preoperative ultrasound and postoperative pathology. For all patients, the surgical procedure and potential complications were explained before surgery, and an informed consent form was completed by all patients before the commencement of the procedure. Factors such as age, gender, tumor size, lobe involvement, unilateral or bilateral tumor occurrence, preoperative microcalcifications on ultrasound, multi-centricity, capsular involvement, and vascular and lymphatic involvement were collected from the patients. The relationship between these factors and central lymph node involvement was then studied. Additionally, the percentage of positive cases of central lymph node metastasis in these patients was also investigated. The obtained data were subjected to statistical analysis, and the results were then presented.

Study population and sample size

Sampling is done through an accessible (convenient) method. In this comprehensive study, the study population consists of 150 patients diagnosed with PTC who have undergone total thyroidectomy. It should be noted that preoperative clinical assessments did not show any evidence of central lymph node involvement.

Based on the study by Jiru *et al*.[13] and according to the formula below, the sample size was calculated to be 135 individuals. To enhance the precision of the results over the course of sampling, a larger number of samples was collected whenever possible, ultimately gathering 150 samples for the study.

$$n = \frac{Z1 \quad - \alpha^2/2pq}{d^2} \alpha = 0.05, \quad d = 0.08,$$

$$P = 0.66, Z1 - a/2 = 1.961150826, \quad n = 35$$

Data analysis

In analyzing the data, descriptive statistics such as frequency, mean, and standard deviation were calculated using SPSS version 26 software, considering the variable types involved. To explore the relationship between quantitative and qualitative variables, independent t-tests were utilized, while the association between qualitative variables was examined using the Chi-square test. A significance level of less than 0.05 was deemed statistically significant, ensuring a stringent criterion for identifying meaningful results. These statistical methods provided a robust framework for analyzing the data and drawing valid conclusions from the study results.

This study was approved by the Research Ethics Board of Qazvin University of Medical Sciences, Qazvin, Iran (IR.QUMS.REC.1399.445).

The methods were reported in accordance with STROCC 2021 guideline[14].

Results

This study was conducted on 150 patients diagnosed with papillary thyroid cancer. After the confirmation of papillary thyroid cancer through fine-needle aspiration, patients underwent central lymph node dissection during surgery, and the samples were sent to pathology for final confirmation. The confirmed samples were subjected to statistical analysis, and various variables were examined regarding the presence of papillary thyroid cancer.

In this study, central lymph node involvement was observed in 14 out of 150 patients examined, accounting for 9.3%. In the remaining cases, no involvement was observed (Table 1).

Out of 150 patients in the study, 111 were female (74%), and 39 were male (26%). In postoperative examinations, no significant relationship was found between the gender of the patients and the absence of central lymph node involvement ($P = 0.68$) (Table 2).

The mean age of the participating patients in this study is 33.06 ± 10.95 years, with the patients' ages ranging from 17 to 65 years. In postoperative examinations, no significant relationship was found between the age of the patients and the absence of central lymph node involvement ($P = 0.06$) (Table 3).

Table 1

Frequency of involvement of central lymph nodes.

Involvement of central lymph nodes	Frequency, *n* (%)
Positive	14 (9.3)
Negative	136 (90.7)
Total	150 (100)

The average size of the masses in the studied patients is reported as 2 ± 0.8, with the mass sizes ranging from 1 to 4 centimeters. In postoperative examinations, no significant relationship was found between the size of the masses and the absence of central lymph node involvement ($P = 0.07$).

In 55 patients, involvement of the right thyroid lobe was reported, accounting for 36.7%. In postoperative examinations, no significant relationship was found between the involvement of the right thyroid lobe and the absence of central lymph node involvement ($P = 0.61$).

Out of 150 study patients, involvement of the left thyroid lobe was observed in 75 patients (50%). In postoperative examinations, no significant relationship was found between the involvement of the left thyroid lobe and the absence of central lymph node involvement ($P = 0.26$).

In 37 out of 150 study patients, isthmus involvement was reported, accounting for 24.7%. In postoperative examinations, no significant relationship was found between thyroid isthmus involvement and the absence of central lymph node involvement ($P = 0.31$).

In total, involvement in the superior thyroid pole was observed in 33 patients (22%), and among them, central lymph node involvement was observed in 10 cases. In postoperative examinations, a significant relationship was found between the involvement of the superior thyroid pole and central lymph node involvement ($P = 0.001$).

Among the 150 study patients, involvement in the isthmus was observed in 43 patients (28.7%). In postoperative examinations, no significant relationship was found between isthmus involvement and the absence of central lymph node involvement ($P = 0.06$).

In 54 out of 150 patients, involvement in the inferior thyroid pole was observed (36%). In postoperative examinations, out of 14 cases with central lymph node involvement, only 1 case was involved in the inferior thyroid pole. Therefore, it can be inferred that involvement in the inferior thyroid pole can be used as a negative predictive factor for central lymph node involvement ($P = 0.01$).

Multi-centricity was considered in cases where involvement occurred in more than one lobe. In 15 cases out of 150, multicentric involvement was observed (10%). In postoperative examinations, no significant relationship was found between multi-centric involvement and central lymph node involvement ($P = 0.57$).

Multifocality was defined as involvement in more than one nodule within a lobe. Out of 150 study patients, multi-focal involvement was observed in 10 patients (6.7%). In postoperative examinations, no significant relationship was found between multi-focal involvement and the absence of central lymph node involvement ($P = 0.23$).

Table 2

Frequency and gender relationship with central lymph node involvement.

Sex	Frequency, *n* (%)
Male	39 (26)
Female	111 (74)
Total	150 (100)
P value	0.68

Table 3

Frequency and gender relationship with central lymph node involvement.

Age (mean)		
33.06 ± 10.95		
Frequency		
45 years <	45 years >	Total
130	20	150
P value	*P* value	*P* value
0.2	0.07	0.06

In the postoperative examination of 150 samples, microcalcifications were identified in 85 cases (56.7%). However, no significant relationship was found between the presence of microcalcifications and the absence of central lymph node involvement ($P = 0.59$).

In 5 cases out of 150 study samples, invasion of the thyroid capsule was observed (3.3%). In the postoperative examination, a significant relationship was found between central lymph node involvement and tumor invasion into the thyroid capsule ($P = 0.01$).

In 21 cases out of 150 study samples, vascular invasion was observed (14%). In the postoperative examinations, there was a significant relationship was found between the presence of vascular invasion and central lymph node involvement ($P = 0.0001$).

Out of 150 study patients, lymphatic invasion was observed in 26 cases (17.3%). In the postoperative examinations, there was a significant relationship between vascular invasion and central lymph node involvement ($P = 0.0001$).

In the postoperative examination of 150 patients, 9 samples had follicular pathology (6%), and 141 samples had classical pathology. In the postoperative examinations, no significant relationship was found between the type of pathology and central lymph node involvement ($P = 0.85$) (Table 4).

In the analysis performed on the patients, metastasis was not observed in any of the 150 study patients.

Discussion

The main objective of this study is to investigate the relationship between various variables and the involvement of central lymph nodes in patients who, clinically and radiologically, do not show any signs of lymph node involvement. The aim is to identify high-risk cases and prevent the need for reoperation and its associated complications.

The analysis revealed a significant relationship between the variables of age, sex, tumor size, involvement of the right and left lobes, thyroid isthmus involvement, central involvement, focal involvement, presence of microcalcification, and pathology type.

On the other hand, in this study, a significant relationship was found between involvement of the superior thyroid pole, capsule invasion, vascular invasion, and lymphatic invasion. This relationship was particularly clear for the variable of lymphovascular invasion ($P = 0.0001$).

Regarding the variable of involvement of the infra-thyroid isthmus, it was shown that only 1 case out of 14 cases with central lymph node involvement had infra-thyroid isthmus involvement.

Table 4

Frequency and relationship of variables related to mass with involvement of central lymph nodes.

Variables	Frequency	*P* value
Right lobe involvement	55	0.61
	Positive lymph node	Negative lymph node
	6	49
Left lobe involvement	75	0.26
	Positive lymph node	Negative lymph node
	5	70
Isthmus involvement	37	0.31
	Positive lymph node	Negative lymph node
	5	32
Upper bridge involvement	33	0.001
	Positive lymph node	Negative lymph node
	10	23
Middle bridge involvement	43	0.06
	Positive lymph node	Negative lymph node
	1	42
Lower bridge involvement	54	0.01
	Positive lymph node	Negative lymph node
	1	53
Multi-centric involvement	15	0.57
	Positive lymph node	Negative lymph node
	2	13
Multi-focal involvement	10	0.23
	Positive lymph node	Negative lymph node
	2	8
Microcalcification	85	0.59
	Positive lymph node	Negative lymph node
	8	78
capsular invasion	5	0.01
	Positive lymph node	Negative lymph node
	2	3
Vascular invasion	21	0.0001
	Positive lymph node	Negative lymph node
	10	11
Lymphatic invasion	26	0.0001
	Positive lymph node	Negative lymph node
	10	16

Considering this, it can be concluded that infra-thyroid isthmus involvement could be considered a negative predictive factor for central lymph node involvement ($P = 0.01$).

Regarding the variable of tumor size, in multiple studies conducted by Chenxi *et al.*[15], Seyed *et al.*[16], and Suresh *et al.*[17] in India, all reported tumor sizes above 1 centimeter as a risk factor for central lymph node involvement. The difference in results with our study can be attributed to the fact that in the current study, all samples had sizes above 1 centimeter, with an average tumor size of 2 centimeters. However, a significant relationship with central lymph node involvement has not been demonstrated. Nevertheless, considering the *P* value of 0.07, it might be predicted that with a larger sample size, this significant relationship could have been observed in the current study as well.

In studies conducted by El Seyed and colleagues[17], Hui *et al.*[18], and Young Woo Chang and colleagues[19], capsule invasion and extranodal involvement, which can be considered analogous to capsule involvement, have been introduced as risk factors for central lymph node involvement. Regarding lymphovascular invasion, not many studies have been conducted, but in a study by El Seyed and colleagues in Egypt[16] and Debashish Mukherjee and colleagues in India[19], lymphovascular invasion has been identified as a risk factor, aligning with the results of this study. Considering the *P* value of 0.0001, lymphovascular invasion and capsule involvement can be considered as major risk factors for central lymph node involvement.

In none of the studies conducted, upper pole involvement has been introduced as a risk factor for central lymph node involvement. Only in a study conducted by Wen Liu and colleagues in China[20], a significant relationship between central lymph node involvement and thyroid isthmus involvement was observed. Considering these contradictions and the limited information in this regard, it is advisable to conduct further studies with a larger sample size to investigate this variable in the future.

In numerous studies conducted by Wei *et al.*[21], Young *et al.*[22], and HuanHuan *et al.*[23], male sex has been reported as a risk factor for central lymph node involvement. However, this factor was not observed in the current study, which may be attributed to the smaller sample size and the low percentage of cases with central lymph node involvement in the present study.

In studies conducted by Wei *et al.*[21], Young *et al.*[22], and HuanHuan *et al.*[23], age below 45 years has been mentioned as a risk factor for central lymph node involvement. However, this factor was not observed in the current study, which may be attributed to the small number of patients over the age of 45 in this study. Only 20 out of 150 patients (13.3%) were above 45 years old. Conducting future studies with a larger number of patients in this age group may lead to more accurate results in this regard.

This study also demonstrated that involvement of the subcapsular area can be used as a negative predictive factor for central lymph node involvement. However, considering that this finding has not been reported in similar studies, further investigation of this matter is warranted in the future, particularly in studies with larger sample sizes.

Conclusion

Based on the results obtained from this study and considering that the only significant relationship was found between central lymph node involvement and capsular invasion, lymphovascular invasion, and superior pole involvement, and given the potential complications of prophylactic central lymph node dissection (such as nerve damage, hypocalcemia, etc.), it might not be logical to recommend this procedure for all patients. It may be advisable to perform prophylactic central lymph node dissection only in patients with capsular or lymphovascular invasion.

Overall, these findings underscore the importance of individualized risk assessment in determining the necessity of prophylactic central lymph node dissection for patients with papillary thyroid cancer. By considering specific tumor characteristics and patient factors, clinicians can tailor treatment strategies to optimize outcomes and minimize unnecessary interventions.

limitations

The greatest challenge and difference in this study compared to similar studies can be seen in the lower percentage of central lymph node involvement (9.3%) compared to similar studies (38–63%), which may lie in the existing difference between the results of this study and similar studies on this subject. Therefore, under these circumstances, it is suggested that a study with a larger sample size and a broader range of variables such as age, sex, and tumor size be conducted to obtain more accurate results in this regard.

Furthermore, by examining the incidence of complications resulting from surgery, patients who benefit from prophylactic central lymph node dissection can be identified with greater precision.

Ethical approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the Alborz University of Medical Sciences and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Research Ethics Board of Qazvin University of Medical Sciences, Qazvin, Iran (IR.QUMS.REC.1399.445).

Consent

Written consent was obtained from all the patients.

Source of funding

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Author contribution

L.H.M.: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. H.P.: designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. M.D.: coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

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Guarantor

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Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Provenance and peer review

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