

# Investigating the Involvement of Mediastinal Lymph Nodes in Patients with Papillary Thyroid Carcinoma

Sayed Abbas Tabatabaei<sup>1</sup>, Mohsen Kolaheidouzan<sup>2</sup>, Sayed Esmaeil Tabatabaei<sup>3</sup>

<sup>1</sup>Department of Thoracic Surgery, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran, <sup>2</sup>Department of Thoracic Surgery, Al Zahra University Hospital, Isfahan University of Medical Sciences, Isfahan, Iran, <sup>3</sup>Department of Surgery, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

## Abstract

**Background:** Papillary thyroid carcinoma (PTC) is also the most common endocrine malignancy. In the present study, we aimed to evaluate the metastasis pattern of upper mediastinal lymph node involvement in patients with PTC.

**Materials and Methods:** This is a descriptive cross-sectional study that was performed in 2020 in Isfahan, Iran, on 73 patients with PTC who were candidates for total thyroidectomy. Demographic data including age and gender were collected. The frequency distribution of upper mediastinal lymph node involvements and their relationships with mass size, gender, and age, location of tumor in the thyroid gland and involvement of lateral lymph nodes in the neck were evaluated.

**Results:** The mean mass size was 17.27 mm. The most involved thyroid lobe in patients with upper mediastinal lymph node involvement was the right lobe (16.5%). In terms of mediastinal lymph node involvement, there were no significant relationships between the two sexes ( $P = 0.161$ ), primary mass size ( $P = 0.151$ ), and thyroid mass location ( $P = 0.739$ ) with mediastinal lymph node involvement. There was a significant relationship between lateral lymph node involvement of the neck ( $P = 0.007$ ) and age groups ( $P = 0.042$ ) with involvement of the upper mediastinal lymph nodes. Based on our results, the upper mediastinal lymph node involvement was more frequent among patients under 40 years of age.

**Conclusion:** Upper mediastinal lymph node metastasis in PTC was significantly more frequent in cases with younger ages (lower than 40 years) and involvements of lateral lymph nodes in the neck.

**Keywords:** Lymph node metastasis, papillary thyroid carcinoma, thyroidectomy

**Address for correspondence:** Dr. Sayed Esmaeil Tabatabaei, School of Medicine, Al-Zahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran.

E-mail: ses.tabatabaei@gmail.com

**Submitted:** 22-May-2021; **Revised:** 20-Nov-2021; **Accepted:** 01-Jan-2022; **Published:** 27-Apr-2024

## INTRODUCTION

Thyroid cancer is associated with a high and growing incidence in women. It is currently the sixth most common cancer in women and the second most common cancer in women under 45 years of age.<sup>[1]</sup> Papillary thyroid carcinoma (PTC) is also the most common endocrine malignancy. It accounts for 80% of all thyroid malignancies in areas with insufficient iodine, and thyroid cancer is predominant in children and people who have been exposed to external radiotherapy.<sup>[2,3]</sup> Papillary carcinoma is more common in women and the ratio of women to men is

2:1 and the average age at the time of referral is 20–30 years.<sup>[4]</sup> The incidence of thyroid cancer in the United States is growing at a rapid rate of 4% per year for 20 years. In 2016, 44,670 new cases and 1690 deaths were reported from thyroid cancer.<sup>[4,5]</sup>

Cervical lymph node metastasis is very common in PTC and is seen in 20%–90% of patients.<sup>[6]</sup> About 17.4% of these metastases are on the opposite side of the PTC. On the other hand, most PTC patients, especially latent PTC, show benign behavior and patients are usually treated with thyroidectomy, although some end in death. Studies have shown that total

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10.4103/abr.abr\_128\_21

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**How to cite this article:** Tabatabaei SA, Kolaheidouzan M, Tabatabaei SE. Investigating the involvement of mediastinal lymph nodes in patients with papillary thyroid carcinoma. Adv Biomed Res 2024;13:26.

thyroidectomy is the treatment of choice for PTC.<sup>[7]</sup> On the other hand, studies have confirmed that micrometastasis has been seen in 80% of patients who have had lymph node resection for prophylaxis. Involvement in the Delphian lymph node is also a predictive factor for central and lateral lymph node involvements.<sup>[8]</sup> Other studies have shown that the presence of lymph node metastases that can be detected by touch and ultrasound (other than micrometastases below 2 mm) has been associated with lower survival and a higher chance of recurrence.<sup>[9]</sup>

Thyroid cancer typically presents with lymphatic metastases in the surrounding area. The lymph nodes in the area to which thyroid carcinoma metastasizes are classified into three areas: (1) central, (2) lateral, and (3) mediastinal. Clinical and surgical characteristics for the treatment of the first and second groups are well defined.<sup>[10,11]</sup> As mediastinal lymph node metastases have not been studied as much as these groups, surgery of these nodes requires more extensive surgery, which increases the potential risk of various complications and can subsequently affect a person's quality of life.<sup>[12]</sup> Therefore, careful selection of patients at high risk of mediastinal metastasis is crucial, both financially and medically.

Numerous prognostic indicators have been integrated into classification systems to enable patients to be classified into low-risk and high-risk groups. Unfortunately, all of these classification systems require information that is not available before surgery. Therefore, in order to balance the risks and benefits of lymph node dissection, careful consideration of treatment options for these patients should be considered. In order to understand this issue and the extent of lymph node dissection, it is crucial to examine the patterns of upper mediastinal lymph node involvement in cases of PTC. Furthermore, examining the predictive features in upper mediastinal lymph node involvement and the control of lymph node metastasis can be a more selective approach for the patients. Based on the above information, it is necessary to determine the pattern of upper mediastinal lymph node involvement and related factors in this type of thyroid cancer. For this purpose, we considered it necessary to conduct a study to investigate the upper mediastinal lymph node involvement pattern of PTC.

## MATERIALS AND METHODS

This is a descriptive cross-sectional study that was performed in 2020 in Al-Zahra, Imam Reza, and Amiralmomenin hospitals affiliated to Isfahan University of Medical Sciences in Iran. The current study was conducted on patients with PTC who were candidates for open total thyroidectomy. The study protocol was approved by the Research Committee of Isfahan University of Medical Sciences and the Ethics committee has confirmed it (Ethics code: IR.MUI.MED.REC.1398.504).

The inclusion criteria were diagnosis of PTC, being a candidate for open total thyroidectomy in our medical centers using the classic method, undergoing thyroidectomy for the first time,

referral cases from endocrine specialists to the surgeons, and signing the written informed consent to participate in this study. The exclusion criteria were previous surgery in this area and damage to lymph nodes, presence of other types of cancers, history of cancer, patients' death during the operation, and patients will to exit the study.

A total number of 73 patients were entered the study based on the sample size calculation formula and underwent total thyroidectomy done by two surgeons. Demographic data of patients including age and gender were collected. Lymph node dissection at the parathyroid and mediastinal site was also performed for all patients. Dissection of suprasternal lymph nodes was done to the level of the innominate artery. During the surgery, three patients were considered to have lymph node involvements.

The mass size was measured prior to surgery with the use of ultrasonics as an examination tool. The removed lymph nodes were separately labeled and sent for pathology to be examined for involvements. The samples were processed and evaluated by two expert pathologists for the presence of metastasis and its grading. Data regarding the mass size and location of involvements were gathered and their relationships with age of patients were determined using SPSS software. The frequency distribution of upper mediastinal lymph node involvements and their relationships with mass size, gender, and age, location of tumor in the thyroid gland and involvement of lateral lymph nodes in the neck were evaluated.

The obtained data were entered into the Statistical Package for the Social Sciences (SPSS) version 24 SPSS Inc., 233 South Wacker Drive, 11<sup>th</sup>. Floor, Chicago, IL 60606-6412. Patent No. 7,023,453. We used independent t-test and repeated measure tests to compare data between different time lines and also different groups.  $P < 0.05$  was considered as a significance threshold.

## RESULTS

In the present study, documents of 73 patients with PTC undergoing total thyroidectomy were reviewed. Our study population consisted of 63 females (86.3%) and 10 males (13.7%). The mean age of the patients was  $41.38 \pm 11.65$  years, with the range of 22 years to 70 years.

**Table 1: Evaluation of the relationship between the mean age of patients with mass size and also the relationship between mass size and patients' age**

	Mean±SD		P
	Age (years)	Mass size (mm)	
Total	41.38±11.65	17.27±12.36	0.843
Female	41.63±11.40	17.16±12.73	
Male	39.80±13.66	18.0±10.23	
P	0.187		

SD: Standard deviation

According to Table 1, the mean mass size was 17.27 mm, which had no significant relationship with patients' age ( $P = 0.187$ ). The mean of mass size in women was  $17.16 \pm 12.81$  and in men was  $18 \pm 10.23$  mm. According to the independent t-test, there were no significant differences between the two genders in terms of mass size ( $P = 0.843$ ).

The number of women with upper mediastinal lymph node involvement was 18 (57.28%) and the number of men with upper mediastinal lymph node involvement was 5 (50%). According to Chi-square test, there was no significant difference between the two sexes in terms of upper mediastinal lymph node involvement ( $P = 0.175$ ). This finding was also confirmed by Fisher's exact test ( $P = 0.161$ ) [Table 2].

Table 3 examines the relationship between upper mediastinal lymph node involvement and primary mass size by independent t-test. According to the results of this table, the mean mass size in patients with upper mediastinal lymph node involvement was  $20.35 \pm 16.18$  mm and in patients who did not have involvement of these glands was  $15.86 \pm 10.02$  mm. The difference between the two values was not significant according to the independent t-test ( $P = 0.151$ ).

Tables 4 and 5 show the relationship between upper mediastinal lymph node involvement and thyroid mass location with Chi-square test. In these two tables, the frequency of involvement of each of upper-lower dimension, the upper side conflict alone, and the upper and lower side conflict were the same. Furthermore, the relationship between upper mediastinal

lymph node involvement and thyroid mass location was not significant ( $P > 0.05$ ).

Table 6 examines the relationship between upper mediastinal lymph node involvement and lateral cervical lymph node involvement. In this table, the frequency of lateral lymph node involvement in the presence or absence of upper mediastinal lymph nodes is expressed. According to this table, there is a significant relationship between lateral lymph node involvement of the neck and involvement of the upper mediastinal lymph nodes (odds ratio [OR] = 4.11, confidence interval [CI] = 1.44–11.75,  $P = 0.007$ ).

Table 7 examines the relationship between upper mediastinal lymph node involvement and age. In this regard, patients were divided into two age groups under 40 years and 40 years or older. The number of patients under 40 years of age who had upper mediastinal lymph node involvement was 16 and the number of patients 40 years and older who had upper mediastinal lymph node involvement was 7. According to this table, the relationship between these two variables was significant (OR = 0.34, CI = 0.12–0.98,  $P = 0.042$ ).

## DISCUSSION

Involvements of mediastinal lymph node in PTC could result in dissection of the lymph nodes. Therefore, estimation of the mediastinal lymph node involvement during the surgical procedure could have beneficial effects. In the present study, 73 patients with PTC undergoing total thyroidectomy were examined. Based on our results, the mean mass size was 17.27 mm. We also showed that the most involved thyroid lobes in patients were the right lobe and the least were the left lobe and isthmus.

We showed that the mass size had no significant relationship with patients' age and gender. In terms of mediastinal lymph node involvement, we showed that there were no significant relationships between the two sexes, primary mass size, and thyroid mass location with mediastinal lymph node involvement. There was a significant relationship between lateral lymph node involvement of the neck (OR = 4.11) and age groups (OR = 0.34) with involvement of the upper mediastinal lymph nodes. Based on our results, the upper mediastinal lymph node involvement was more frequent among patients with patients under 40 years of age.

These data emphasize the involvement of upper mediastinal lymph nodes in patients with involvement of lateral lymph

**Table 2: Investigation of the relationship between upper mediastinal lymph node involvement and patients' gender**

	Patients with upper mediastinal lymph node involvement, <i>n</i> (%)	<i>P</i> ( $\chi^2$ )	<i>P</i> (Fisher's exact test)
Female	18 (57.28)	0.175	0.161
Male	5 (50)		

**Table 3: Investigating the relationship between upper mediastinal lymph node involvement and primary mass size**

Involvement of the upper mediastinal lymph nodes	Mass size, mean $\pm$ SD	<i>P</i>
Yes	20.35 $\pm$ 16.18	0.151
No	15.86 $\pm$ 10.02	

SD: Standard deviation

**Table 4: Investigation of the relationship between involvements of the upper mediastinal lymph nodes with the lobe involved in the thyroid**

Involvement of the upper mediastinal lymph nodes	Location of the thyroid mass (lobe)						<i>P</i>
	Right	Left	Isthmus	Right and left	Right and isthmus	Left and isthmus	
Yes	12	5	2	2	1	1	0.739
No	26	15	3	4	2	0	
Total	38	20	5	6	3	1	

**Table 5: Investigation of the relationship between upper mediastinal lymph node involvement and the area involved in the thyroid**

Involvement of the upper mediastinal lymph nodes	Thyroid involvement (area)			P
	Upper	Lower	Upper and lower	
Yes	8	5	8	0.876
No	19	13	15	

**Table 6: Investigation of the relationship between upper mediastinal lymph node involvement and lateral cervical lymph node involvement**

Involvement of the upper mediastinal lymph nodes	Involvement of lateral lymph nodes in the neck		P
	Yes	No	
Yes	13	10	0.007
No	12	38	
Total	25	48	

**Table 7: Investigating the relationship between upper mediastinal lymph node involvement and age of patients**

Involvement of the upper mediastinal lymph nodes	Patient's age		P
	Lower than 40 years	Higher than 40 years	
Yes	16	7	0.042
No	22	28	

nodes in the neck and age under 40 years. Similar studies have been conducted on the importance of upper mediastinal lymph node involvement in PTC. In 2011, a study was conducted by Kikumori and Imai in China on 33 patients undergoing total thyroidectomy due to PTC. They showed that upper mediastinal lymph node metastases were more frequent in patients with lower ages and involvement of lateral lymph nodes in the neck and could have a significant relationship to the tumoral mass size. It was also mentioned that prophylactic dissection of upper mediastinal lymph nodes could be unnecessary in patients with higher ages.<sup>[13]</sup>

Another study was performed by Smith *et al.* in 2012. They evaluated documents of 11,453 cases of PTC and showed that the mean mass size in patients was 15.3 mm and the right thyroid lobe was the most frequent involved area. Considering the metastasis of upper mediastinal lymph nodes, they showed that this condition could be observed more often in younger patients but the mortality rate of patients older than 45 years was higher if the upper mediastinal lymph node metastasis was observed.<sup>[14]</sup> The results of our study were in line with these findings showing the higher probability of upper mediastinal lymph node metastasis in younger patients and also in those patients with involvement of lateral lymph nodes in the neck.

In 2017, a study was conducted by Lei *et al.* on 450 PTC patients. In this study, they showed that upper mediastinal lymph node metastasis was significantly correlated with smaller tumoral size, younger ages, and capsule invasion and recommended that dissection of the upper mediastinal lymph nodes should be performed in these patients.<sup>[15]</sup> In another study by Ito *et al.*, it was indicated that the most important predictive factor for upper mediastinal lymph node metastasis is tumor size of more than 20 mm. They also showed that the risk of upper mediastinal lymph node metastasis was higher if a larger tumor was diagnosed in younger patients.<sup>[16]</sup> Park *et al.* mentioned that the upper mediastinal lymph node metastasis in PTC could be dependent on various factors including age and ethnic. The rate of metastasis varies among different populations.<sup>[17]</sup> We believe that these differences in the results of various studies could be due to variations in the study population size and characteristics.

In the present study, we observed no significant relationships between upper mediastinal lymph node metastasis and factors such as age, gender, and tumor mass size, but the metastasis was more frequent in cases with involvements of lateral lymph nodes in the neck and younger ages. To date, few studies have been conducted in our region evaluating the metastasis of upper mediastinal lymph nodes and related factors. As Song *et al.* indicated, dissection of these lymph nodes should be considered based on the epidemiologic results and also in patients with higher risk factors.<sup>[18]</sup> Liu *et al.* also calculated various risk factors for mediastinal lymph nodes metastasis in PTC and showed that younger age is one of these risk factors.<sup>[6]</sup> The same results were reported by Liu *et al.* in 2020. They showed that the risks of lymph node metastasis increase in patients with younger ages.<sup>[19]</sup> Our data were consistent with these findings.

The procedure done in this study may cause complications such as pneumothorax or hypothyroidism or nerve damage. Fortunately, none of these complications were seen in our patients.

An important point of our study was that we assessed various epidemiologic data and their relationships to upper mediastinal lymph node metastasis. Association of tumoral mass size with lymph node metastasis was mentioned in some previous studies, while we observed no significant relationships. These results could be justified by our restricted study population size. The limitations of this study were that this study could have unknown potential confounders, we used the data that were originally collected for these purposes, not all the relevant information, and we had also inferior level of evidence compared with prospective studies. Therefore, we suggest that more studies on larger populations considering the potential confounders should be performed.

## CONCLUSION

Taken together, in the present study, we showed that upper mediastinal lymph node metastasis in PTC was significantly



more frequent in cases with younger ages (lower than 40 years) and involvements of lateral lymph nodes in the neck. These findings were in line with most previous studies; however, some surveys have considered other variables to be connected to upper mediastinal lymph node metastasis. We believe that more studies in our region are required to determine the possible risk factors for upper mediastinal lymph node metastasis in PTC in the Iranian population.

### Financial support and sponsorship

This study was granted by Isfahan University of Medical Sciences.

### Conflicts of interest

There are no conflicts of interest.

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