

# Clinicopathological characteristics of papillary thyroid cancer located in the isthmus with Delphian lymph node metastasis

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## Abstract

Papillary thyroid carcinomas (PTC) arising from the isthmus have aggressive clinical and pathological features, especially regarding the Delphian lymph node (DLN), which are associated with poor overall and disease-specific survival of patients with head and neck cancer. In the present study, we evaluated clinicopathological characteristics in 195 DLN-positive isthmus PTCs (14.9%) and their lymph node metastatic pattern in 1305 isthmus PTC patients in our hospital between January 2016 and July 2019. Furthermore, a multivariate analysis was conducted to investigate independent risk factors for isthmus PTC with a positive DLN. The results showed that a positive DLN was significantly related to tumour size, extrathyroid extension, median number of DLN, and metastasis to the central, bilateral central, lateral, and pretracheal lymph nodes. Meanwhile, patients with DLN-positive PTC had a significantly increased incidence of suspected preoperative lymph node status than patients with DLN-negative PTC. Multivariate logistic regression of DLN metastasis in PTC located in the isthmus showed that tumour size, extrathyroid extension, and metastasis to the central, bilateral central, lateral, and pretracheal lymph nodes, were independent risk factors.

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**Keywords:** Papillary thyroid carcinoma; Isthmus; Lymph node metastasis; Delphian lymph node

## Introduction

The thyroid isthmus is the part of the thyroid gland that connects the lower third of the right and left thyroid lobes. It is usually located at the second and third rings of the trachea and is covered by skin, fascia, and strap muscles.<sup>1</sup> The incidence of papillary thyroid carcinoma (PTC) located in the isthmus ranges from 2.5% - 9.2%.<sup>2</sup> Previous studies have demonstrated that isthmus PTC exhibits more aggressive features, such as extrathyroidal extension (ETE), multifocality, and lymphovascular invasion, than those located in other parts of the thyroid,<sup>3,4</sup> so total thyroidectomy and bilateral central neck dissection are considered a better choice in these

cases. The surgical strategy for isthmus PTC, however, is still controversial, and the American Thyroid Association (ATA) and National Comprehensive Cancer Network (NCCN) do not specify clear guidelines for treatment.<sup>5</sup> It was therefore necessary to figure out the appropriate surgical treatment for different types of PTC.

The central lymph nodes (LN) that are mainly involved are the prelaryngeal, pretracheal, and right and left paratracheal nodes. The prelaryngeal lymph node, also called the Delphian node (DLN), which is a single node or group of nodes located along the fascia above the isthmus of the thyroid gland between the cricoid and thyroid cartilage, has been considered to be a gate that predicts widespread nodal metastasis of head and neck cancer.<sup>6</sup> We know of few data, however, regarding DLN positivity in patients with PTC and its relation with adverse factors. Thus the aims of this study were to assess the risk factors for DLN metastasis in PTC

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located in the isthmus, and to evaluate its clinicopathological significance. Prediction of DLN positivity may help to plan the extent of neck dissection and improve data on the treatment of DLN-positive PTC.

## Material and methods

### Patients

We enrolled 1305 patients with isthmus PTC who underwent total thyroidectomy with bilateral central lymph node dissection in our hospital between January 2016 and July 2019. It is worth mentioning that 103 patients underwent lateral neck lymphadenectomy because of a suspicion of metastasis to the lateral cervical lymph nodes. All patients underwent preoperative high-resolution ultrasonography and PTCs were diagnosed by fine-needle aspiration biopsy. All the patients had ultrasonography and fine-needle aspiration biopsy classification of thyroid imaging reporting and data system (TI-RAD) 4a, 4b, 4c, or above, and Thy4, Thy5, or above, respectively. Patients with a history of previous treatment for head and neck cancer or other thyroid malignancies, or who had undergone other surgical treatments, were excluded from the study. All 1305 patients' DLN were harvested. Patients were then divided into two groups: DLN-positive ( $n = 195$ ) and DLN-negative ( $n = 1110$ ). Gender, age, extent of surgery, and tumour characteristics including tumour size, multifocality, ETE, lymphovascular invasion, and lymph node metastasis, were reviewed.

### Surgery and pathological examination

The boundaries of the central LN compartment were defined: superiorly by the hyoid bone, inferiorly by the innominate artery, laterally by the carotid sheath, and dorsally by the prevertebral fascia. The central lymph nodes were divided into left or right using the median line of the trachea, which was further separated into prelaryngeal, pretracheal, and ipsilateral/bilateral paratracheal compartments. It is worth mentioning that all patients underwent fibre electronic laryngoscopy before surgery.

Intraoperative nerve monitoring was done to evaluate nerve function and protect the nerve from disturbance. Tumour and patient clinical pathological data were analysed by multivariate analysis, including age at diagnosis, gender, tumour size, tumour bilaterality, multifocality, and ETE. The amount of harvested and metastatic LNs was presented as a mean value.

### Delphian lymph node removal

The prelaryngeal area was evaluated intraoperatively in all patients, and lymph nodes and soft tissue between the thyroid cartilage and the cricoid cartilage were excised. Lymph nodes in this area and those attached to the pyramidal lobe were called DLN.

### Statistical analysis

Continuous data are presented as mean (SD). Student's independent samples  $t$  test, chi squared test, and Fisher's exact test were used to compare the differences between isthmus PTC and non-isthmus PTC. Binary logistic regression was used to conduct the multivariate analysis, including Student's independent samples  $t$  test, chi squared test, and Fisher's exact test. Differences were considered statistically significant at a  $p$  value of less than 0.05. All data were analysed using SPSS for Windows version 16.0 (SPSS Inc).

## Results

Comparison of clinicopathological characteristics between the DLN-positive and DLN-negative groups is shown in [Table 1](#). Of the 1305 patients, 195 (14.9%) had DLN metastasis while 1110 (85.1%) had no DLN metastasis ([Table 1](#)). The mean (SD) patients' age at surgery was 48.4 (9.1) in the DLN-positive group and 51.5 (8.4) in the DLN-negative group ( $p = 0.09$ ). The proportion of patients older than 55 years did not differ significantly ( $p = 0.91$ ) between the groups, and there was no significant difference in gender ( $p = 0.42$ ). On the other hand, the mean (range) size of the isthmus PTC was 1.16 (0.3–2.0) cm in the DLN-positive, and 0.8 (0.2–1.4) cm in the DLN-negative group. Several clinicopathological characteristics differed extremely significantly between the groups, including tumour size, ETE, central lymph node metastasis (CLNM), lateral lymph node metastasis (LLNM), and bilateral CLNM ( $p < 0.001$  in each). Furthermore, the DLN-positive group had a significantly higher pretracheal LN positive ratio (+) than the DLN-negative group ( $p = 0.018$ ).

To further evaluate the relation between the DLN and suspected lymph node metastasis, all 1305 patients had an ultrasound investigation. The incidence of metastasis to the central, lateral, and central or lateral compartments in DLN-positive and DLN-negative cases is shown in [Table 2](#). The lateral compartment ratio was significantly higher in the DLN-positive group than in the DLN-negative group ( $p = 0.047$ ). Meanwhile, the central compartment and central or lateral compartment had an extremely significantly higher ratio in the DLN-positive group than in the DLN-negative group ( $p < 0.001$ ), which means that a positive DLN may be strongly involved with the preoperative lymph node status on ultrasonic investigation of PTC.

Univariate analysis was done to investigate the relation between the clinicopathological characteristics of PTC and the DLN. Results are shown in [Table 3](#). Univariate analysis revealed that a tumour size of  $\geq 1.0$  cm, ETE, and bilateral CLNM and LLNM, were significantly associated with a positive DLN ( $p < 0.001$ ). Pretracheal LNM was also common in the DLN-positive group ( $p = 0.018$ ). These factors were included in the multivariate analysis and were found to be independent risk factors of DLN metastasis ([Table 3](#)).

**Table 1**  
Comparison of clinicopathological characteristics between the Delphian lymph node (DLN)-positive and DLN-negative group.

Clinicopathological characteristic	DLN (+) (n = 195)	DLN (-) (n = 1110)	p value	t or $\chi^2$
Mean (SD) age (years)	48.4 (9.1)	51.5 (8.4)	0.09	3.140
Age $\geq 55$ / $<55$ years	67/128	386/724	0.91	0.153
Sex (M/F)	39/156	251/859	0.42	0.795
Mean (SD) tumour size (cm)	1.16 (0.8)	0.8 (0.59)	<0.001**	9.211
Tumour size $\geq 1.0$ / $<1.0$	119/76	475/635		
Multifocality (+/-)	56/139	248/862	0.052	3.852
Extrathyroid extension (+/-)	179/16	688/422	<0.001**	11.345
Lymphovascular invasion (+/-)	30/165	122/988	0.08	2.912
Median (range) DLN	3 (1.0- 8.0)	1(1.0 - 5.0)	0.03*	17.535
No. (%) CLNM (+)	195 (100)	394 (35.5)	<0.001**	11.143
No. (%) bilateral CLNM (+)	96 (49.2)	303 (27.3)	<0.001**	12.549
No. (%) LLNM (+)	32 (16.4)	67 (6.0)	<0.001**	10.645
No. (%) pretracheal LN (+)	106 (54.4)	502 (45.2)	0.018*	6.722
No. (%) recurrence	8 (4.1)	22 (2.0)	0.07	3.016
No. (%) thyroiditis (+)	124 (63.6)	711 (64.1)	0.9	0.281

CLNM: central lymph node metastasis; LLNM: lateral lymph node metastasis; LN: lymph node; \* statically significant; \*\* extremely statically significant.

**Table 2**  
Preoperative lymph node status on ultrasound.

Metastasis type	DLN (+) (n = 195)	Suspected incidence in DLN (+)	DLN (-) (n = 1110)	Suspected incidence in DLN (-)	p value	t or $\chi^2$
Central compartment: (No evidence/suspected)	127/68	34.9%	990/120	10.8%	<0.001**	12.017
Lateral compartment: (No evidence/suspected)	171/33	16.9%	1030/70	6.3%	0.047	3.357
Central or lateral compartment: (No evidence/suspected)	123/72 (36.9%)	36.0%	976/134	12.1%	<0.001**	12.831

DLN: Delphian lymph node; \* statistically significant; \*\* extremely statistically significant.

**Table 3**  
Multivariate logistic regression of Delphian lymph node (DLN) metastasis in papillary thyroid carcinoma (PTC) located in the isthmus.

Variables	Odds ratio	95% CI	p value	t or $\chi^2$
Suspected lymph node metastasis on ultrasound	0.88	0.57 to 1.35	0.44	0.682
Tumour size ( $\geq 1.0$ cm)	2.42	1.19 to 4.91	0.014	6.527
Multifocality	1.17	0.81 to 1.68	0.404	4.351
Extrathyroid extension	3.94	2.78 to 5.97	<0.001	11.389
Lymphovascular invasion	1.14	0.81 to 1.59	0.452	0.474
Median No. of DLN	1.45	0.61 to 3.45	0.400	18.338
Bilateral CLNM	4.78	3.25 to 7.04	<0.001	15.086
LLNM	1.88	1.24 to 2.84	0.003	7.815
Pretracheal LNM	2.47	1.05 to 5.78	0.038	5.035
Recurrence	1.07	0.72 to 1.6	0.727	0.282

CLNM: central lymph node metastasis; LLNM: lateral lymph node metastasis; \* statically significant; \*\* extremely statically significant.

**Discussion**

As previous studies have reported, isthmic PTC was more aggressive clinically and had more pathological features including ETE and invasion of adjacent tissue than PTCs that were not located on the isthmus.<sup>3,4</sup> Researchers have demonstrated that prelaryngeal LN involvement is associated with tumours located in the isthmus; patients with isthmus thyroid carcinoma tended to have higher rates of LN involvement.<sup>7-9</sup> The explanation for this phenomenon may be that isthmus tumours are located in a thin space enclosed by solid struc-

tures, such as the trachea and strap muscles, which could facilitate the invasion of adjacent tissues.<sup>10</sup> A positive DLN in patients with laryngeal cancer is an independent adverse prognostic factor, and is associated with an increased frequency of lateral and bilateral lymph node metastasis, as well as reduced survival.<sup>11,12</sup> To our knowledge, however, the effects of a positive DLN in PTC patients undergoing prophylactic central and lateral lymph node neck dissection has not yet been characterised. Isthmus PTC patients were therefore chosen in the present study, as they all had DLN and pretracheal lymph node dissection. All 1305 patients'

preoperative ultrasonographic investigations were reviewed and isthmus thyroid carcinoma was defined as a tumour in which the median line was located between the lateral margins of the trachea.

In the present study the incidence of DLN metastasis was 14.4% (195/1350). Meanwhile, comparison of the clinicopathological characteristics between the groups showed that the median number of DLN, the tumour size, and pretracheal LN, ETE, CLNM, and bilateral CLNM and LLNM frequency, were significantly higher in the DLN-positive group than in the DLN-negative group, indicating that a positive DLN may increase risk in isthmus PTC patients.<sup>12,13</sup> Furthermore, ultrasonic photographs of the 1305 patients showed that no matter whether in the central, lateral, central or lateral compartment, the suspected frequency was higher in the DLN-positive group than in the DLN-negative group, indicating that a positive DLN may bring more potential risks.<sup>12</sup> Our results are consistent with a previous study.<sup>6</sup>

As shown in Table 3, a positive DLN correlated significantly with a larger tumour size ( $\geq 1.0$  cm), ETE of the primary tumour, bilateral CLNM, LLNM, and pretracheal LN, especially ETE of the primary tumour and bilateral CLNM (both  $p < 0.001$ ). All DLN-positive patients had CLNM, LLNM, pretracheal LN, and bilateral central LN metastasis were also highly prevalent in DLN-positive patients. All the results mentioned above are consistent with previous studies.<sup>11,12</sup>

Although the isthmus has poor lymphatic channels, lymphatics from here usually drain into the prelaryngeal and pretracheal regions.<sup>14</sup> Our results showed that DLN-positive isthmus PTC and pretracheal LN involvement have a strong correlation.

The results in Table 3 show that patients with a positive DLN tend to have a higher incidence of bilateral CLNM (the incidence of bilateral CLNM in the DLN-positive group and DLN-negative groups was 49.2% and 27.3%, respectively,  $p < 0.001$ ). In a recent retrospective study, the presence of DLN metastasis was associated with a 4.4-fold higher incidence of lateral neck lymph node metastasis.<sup>12</sup> A positive DLN increased the probability of additional nodal metastasis including lateral lymph node metastasis and bilateral central lymph node metastasis. Thus, the intraoperative findings combined with the preoperative evaluation could provide important information to optimise surgical management. We therefore suggest that preoperative ultrasound should be used to evaluate the DLNs and their location. Frozen pathological examination of these nodes and surrounding tissues is recommended. If a positive DLN is found, total thyroidectomy and bilateral central lymph node dissection are strongly recommended. Furthermore, it is important to carefully examine the prelaryngeal and cricothyroid area during thyroidectomy to remove any obvious lymphoid tissue.

Bilateral central lymph node dissection could be considered for patients with isthmus PTC and a positive DLN, a tumour size of  $\geq 1.0$  cm, and ETE.

### Conflict of interest

We have no conflicts of interest.

### Ethics statement/confirmation of patients' permission

Not required.

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