Incidence and Clinical Significance of Delphian Lymph Node Metastasis in Unilateral Papillary Thyroid Carcinoma

Wei Liu
Zhongshan Hospital Fudan University
Zhenglin Wang
Zhongshan Hospital Fudan University
Cong Wang
Zhongshan Hospital Fudan University
Zhilong Ai (ai.zhilong@zs-hospital.sh.cn)
Zhongshan Hospital Fudan University https://orcid.org/0000-0002-3452-721X

Research

Keywords: Papillary thyroid carcinoma, Delphian lymph node, Metastasis, Central lymph node

Posted Date: June 8th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-33260/v1

Abstract

Background: Some studies have reported that Delphian lymph node (DLN) metastasis is associated with a poor prognosis of papillary thyroid carcinoma (PTC), but the number of the available studies is limited and the results are inconsistent. The aim of this investigation was to study the incidence and clinical significance of DLN metastasis in patients with unilateral PTC.

Methods: This was a cross-sectional study from January 2016 to December 2019. The data were obtained from the department of general surgery in Shanghai Zhongshan Hospital affiliated to Fudan University. This study included 522 patients with unilateral PTC and had DLN harvested. The associations between DLN metastasis and the clinical characteristics of the patients, i.e. age, sex, tumor size, multifocality, capsular invasion, extrathyroidal extension, central lymph nodes (CLN) metastasis (excluding DLN), and lateral lymph nodes (LLN) metastasis was analyzed.

Results: Among all the 522 patients, 133 (25.5%) patients had metastasized DLN lymph nodes. DLN metastasis was significantly associated with age ($p = 0.047$), male ($p < 0.001$), larger tumor size ($p < 0.001$), capsular invasion ($p < 0.001$), extrathyroidal extension ($p = 0.004$), tumor location in upper third ($p = 0.003$), other CLN metastasis ($p < 0.001$), number of positive CLN (excluding DLN) ($p < 0.001$), LLN metastasis ($p = 0.036$), number of positive LLN ($p = 0.004$) and number of DLN removed ($p = 0.043$). No association was found between DLN metastasis and multifocality, number of CLN removed and number of LLN removed.

Conclusions: DLN metastasis is associated with some adverse prognostic markers of PTC. If the DLN is positive on intraoperative frozen section, careful dissection of CLN and careful evaluation of LLN are essential, and intensive follow-up should be warranted.

Background

Thyroid cancer is the most common malignancy of the endocrine system, which accounts for approximately 1% of all cancer cases every year. The dominant (> 90.3%) histopathology of thyroid cancer is papillary thyroid carcinoma (PTC). The most common metastasis of PTC is metastasis of the central lymph nodes (CLN), which occurs among approximately 30–80% of the PTC patients[1–3]. CLN metastasis has previously been reported to be associated with tumor size, thyroid capsular invasion, and extrathyroidal extension (ETE)[4–6]. Almost half of the patients with unilateral PTC whose CLN was clinically negative (cN0) before the surgery have ipsilateral CLN metastases proved by pathology after the surgery, suggesting the need of prophylactic ipsilateral CLN dissection[7]. But prophylactic ipsilateral CLN dissection is also related to a risk of hypoparathyroidism and recurrent laryngeal nerve injury[8–10]. Thus, it is important to identify unilateral PTC patients with high risks of ipsilateral CLN metastases who would benefit most from prophylactic dissection.

The Delphian lymph node (DLN), also known as prelaryngeal lymph node, is a part of the CLN. The name “Delphian” originated from the “Oracle of Delphi” because the metastasis of this node could foretell a

terrible end-result from the thyroid cancer, just like the Oracle could foretell terrible events[11].Over the past three decades, studies have proved that DLN metastasis in laryngeal cancer is an independent adverse prognostic factor that predicting higher rates of recurrence, extensive metastasis of lymph nodes and increased mortality[12–16]. The status of DLN metastasis has been shown to be important in deciding the extent of operation, estimating prognosis after the operation and planning radiotherapy[16]. However, there is no consensus on the value of DLN metastasis in the management of thyroid cancer and the number of studies evaluating the role of DLN metastasis in the prognosis of unilateral PTC is still very limited[17–23]. Therefore, the present study was designed to determine whether DLN metastasis is associated with any prognostic factors of unilateral PTC.

Methods

Study design

This was a single-center cross-sectional study between January 2016 and December 2019. All patients and their related individual data were collected from in Shanghai Zhongshan Hospital affiliated to Fudan University. All patients who underwent thyroidectomy as their primary treatment for suspicious unilateral thyroid malignancy during the study period were potential eligible for the study. These patients accepted standardized treatment and operation under the care of the same surgical team leading by one senior surgeon specialized in thyroid disease. The operation was conducted by the same senior surgeon for all the patients. Lobectomy plus isthmusectomy plus unilateral CLN dissection was the standard operation method for all patients. However, if the patient met any of the following criteria, total thyroidectomy was conducted: preoperative tumor stage > T2 (according to the 7th Edition AJCC Staging Guide for Thyroid Cancer), multifocality in one lobe, distant metastasis and extra-thyroid extension (determined by preoperative examination and frozen section during the operation). Lateral lymph nodes (LLN) were dissected if there were confirmed or suspected metastasis by fine needle aspiration or ultrasound preoperatively.

After review of the post-operative histopathology records, only patients with histopathologically confirmed unilateral PTC and had successful harvest of at least one DLN were enrolled. The exclusion criteria were: a) Previous history of thyroid-related surgery; b) Patients who had accepted other treatment, e.g. radio frequency ablation, as their primary treatment for PTC; c) thyroid cancer of the other histopathology type; d) metastasis in lymph nodes originated from tumors other than thyroid; f) tumor location in the thyroid isthmus. After exclusion, a total number of 522 patients were enrolled in the study. Individual-level data on patients' age at operation, sex, PTC tumor size, multifocality of the tumor, the existence of capsular invasion (yes or no), ETE (yes or no), tumor location (upper third, middle third or lower third), number of CLN removed (excluding DLN), number of metastasized nodes of CLN (excluding DLN), number of LLN removed, number of metastasized nodes of LLN and number of DLN removed were also obtained from the surgery records and histopathology records.

Statistical Analysis

Associations between DLN metastasis (yes or no) and patients' age at operation (continuous) and PTC tumor size (continuous) were analyzed by Student *t* test. Associations between DLN metastasis and numbers of removed CLN (excluding DLN) (continuous), metastasized nodes of removed CLN (excluding DLN) (continuous), removed LLN (continuous), metastasized nodes of removed LLN (continuous), and removed DLN (continuous) were analyzed by Mann-Whitney U test. Associations between DLN metastasis and sex, multifocality of the tumor (yes or no), the existence of capsular invasion (yes or no), ETE (yes or no), tumor location (upper third, middle third or lower third), CLN (excluding DLN) metastasis (yes or no) and LLN metastasis (yes or no) were analyzed by Chi-square test. All analyses were conducted using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). A P value < 0.05 was considered as statistically significant.

Results

Among all 522 unilateral PTC patients who had DLN harvested, 416 (79.7%) of them underwent lobectomy plus isthmusectomy and the rest 106 (20.3%) underwent total thyroidectomy. All the 522 patients underwent CLN dissection and 46 patients (8.8%) underwent LLN dissection. Of all the included patients, 133 (25.5%) had at least one metastasized DLN. The median number of harvested DLN was 2 (range: 1–10). The demographics and clinical characteristics of patients by their DLN metastasis status were presented in Table 1.

Table 1
Demographic and clinical characteristics of patients with unilateral PTC who had the DLN Removed

Characteristics	DLN+ (n = 133)	DLN- (n = 389)	p-value
Age (mean ± SD)	41.0 ± 12.3	43.4 ± 11.7	0.047[a]
Gender (F/M)	64/69	261/128	< 0.001[b]
Size of tumor (mean ± SD)	1.27 ± 0.68	0.92 ± 0.57	< 0.001[a]
Capsular invasion (%)	84 (63.2)	177 (45.5)	< 0.001[b]
Extrathyroidal extension (%)	18 (13.5)	21 (5.4)	0.004[b]
Multifocality (%)	22 (16.5)	58 (14.9)	0.676[b]
Location			0.003[b]
Upper third (%)	60 (45.1)	121 (31.1)	
Middle third (%)	35 (26.3)	160 (41.1)	
Lower third (%)	38 (28.6)	108 (27.8)	
Number of *CLN removed	133	389	
Median number of CLN removed (interquartile range)	5 (2–7)	4 (2–6)	0.140[c]
*CLN metastasis (%)	108 (81.2)	161 (41.4)	< 0.001[b]
Median number of positive nodes of *CLN (quartile)	2 (1–4)	0 (0–2)	< 0.001[c]
Number of *LLN removed	30	16	
Median number of LLN removed (quartile)	21 (15–27)	20 (13.25–23.75)	0.267[c]
LLN metastasis (%)	29 (96.7)	11 (68.8)	0.036[b]
Median number of positive nodes of LLN (quartile)	4.5 (2–7.25)	1.5 (0.25–3.75)	0.004[c]
Median number of DLN removed (quartile)	2 (1–3)	2 (1–2)	0.043[c]

Characteristics	DLN+ (n = 133)	DLN- (n = 389)	p-value

All size in cm. DLN+, positive for metastatic disease; DLN-, negative for metastatic disease; SD, standard deviation; No, number; CLN, central lymph nodes; *CLN, central lymph nodes excluding Delphian lymph node; LLN, lateral lymph nodes;
a Student's t-test
b Chi-square test
c Mann-Whitney U test

Overall, the metastasis of DLN was more prevalent among men than that among women ($p < 0.001$). DLN metastasis was significantly associated with tumor location in upper third. Patients with metastasized DLN was younger, and had larger tumor size, higher rates of capsular invasion and ETE, more metastasized CLN (excluding DLN) and LLN compared with patients with normal DLN (Table 1). Besides, presence of DLN metastasis was also associated with a higher rate of metastasis in LLN and the resting CLN. (Table 1).

Discusssion

The results of this study showed that DLN metastasis is associated with some poor prognostic factors of PTC, including male sex, lager tumor size, other CLN metastasis, and LLN metastasis.

The strength of this study lies in the inclusion of only unilateral PTC patients as the study population. Besides, the relationship between DLN metastasis and tumor locations was also analyzed in this study. Moreover, the number of patients in the DLN positive group is the biggest compare with previous studies. There are also some limitations in the present study. First, this is a cross-sectional study without follow-up, which makes it impossible to determine whether DLN is a direct prognostic factor for unilateral PTC patients. Secondly, we are unable to know the state of lymphatic vessel invasion, which makes it impossible to analyze whether DLN metastasis is associated with lymphatic vessel invasion. Finally, we did not collect data of DLN size. Thus, it is impossible to analyze whether there exists a relationship between DLN size and DLN metastasis.

In previous studies, among patients with PTC, the detection rate of DLN and the rate of metastasis to DLN varies a lot (detection rate: 23% -74.6%, metastasis rate 8.2%-24.8%) [17–23]. In the present study, the detection rate of DLN was 31.5% and the rate of metastasis to DLN was 25.5%. Several studies have reported that DLN metastasis is associated with a poor prognosis of thyroid cancer[17–23]. The first published study evaluating the associations between DLN metastasis and prognosis of thyroid cancer found that DLN metastasis was significantly associated with larger tumor size and was highly predictive of metastasis in other lymph nodes[17]. Similarly, another study also reported that DLN metastasis was associated with extra-thyroid extension, and higher frequency of concomitant metastases in the lymph nodes[18]. A cohort study in 2012 reported that DLN metastasis was associated with multifocality of the tumor, lager tumor size, and higher frequency of lymphvascular invasion, capsular invasion, central metastasis and lateral metastasis[19]. In the present study, DLN metastasis was found to be associated

with several adverse prognostic factors of PTC, including male sex, larger tumor size, higher proportion of positive lymph nodes in CLN (excluding DLN), higher rate of ETE and capsular invasion. All the results of the previous studies on DLN in thyroid cancer were summarized in supplementary table.

The DLN receives afferent lymphatic drainage from the isthmus and the upper lobes of the thyroid[24]. Therefore, there may exist an association between different tumor locations and DLN metastasis. Two previous studies have reported that tumors in the upper third and isthmus are related to DLN metastasis, but the sample size of DLN positive groups in these two studies is small and may affect the validity of the results [20, 25]. In this study, there were 133 DLN positive patients among all 522 included patients. Our results showed that PTC located in upper third thyroid was significantly associated with DLN metastasis. Previous studies have reported PTC in upper third thyroid as a risk factor of LLN metastasis [26, 27]. In this study, we found that DLN metastasis was associated with the existence of LLN metastasis, and patients with metastasized DLN had more metastasized LLN compared with patients with normal DLN. These findings further confirmed the links between DLN metastasis, location of PTC, and LLN metastasis.

Previous study seldom separate patients with unilateral and bilateral PTC. The present study narrowed down the study population to patients with unilateral PTC, which is the most commonly diagnosed type of PTC. Patients with unilateral PTC generally have a good prognosis with a five-year survival rate over 95% according to the SEER database. Despite the good prognosis, the locoregional recurrence rate of these patients is between 15–30% and the central compartment recurrence rate is between 5–20% in 5–10 years [28–30]. Lymph nodes metastasis is the most common pathway for metastasis in PTC. Prior studies have reported the metastasis rate of CLN was almost 50% for cN0 PTC patients, and it is 48.3% in our study. Although some reports suggested that CLN metastasis had no effect on the prognosis of PTC, others indicated that PTC patients with CLN metastasis have a poor prognosis, including higher rates of recurrence and distant metastasis, worse disease-free survival, and higher mortality [3, 31]. Thus, it is still under debate for CLN resection as an operation routine for all PTC patients. An optional challenge is to select patients who may benefit from the resection of CLN. The stepwise process of lymph node metastasis of PTC has been revealed by several studies, firstly to the tracheoesophageal groove nodes and pretracheal nodes, and subsequently to the lateral neck nodes [32, 33]. Paratracheal lymph node is usually the most common metastasis sites for PTC, followed by DLN and pretracheal lymph node [7]. DLN is located in the fascia above the isthmus of the thyroid gland between the cricoid and thyroid cartilage, so that the resection of DLN could be done at the early stage of the operation. Moreover, the resection of DLN is easy and safe and could hardly result in complications. Moreover, the fast-pathological feedback of DLN could be achieved within 30 minutes by frozen section examination during the operation. Given these advantages and the high frequency of concomitant metastasis in other CLNs when DLN is positive, it has been suggested that total thyroidectomy and CLN dissection should be the first-line treatment in PTC patients with DLN metastasis. The finding of the present study showed that among all patients with DLN metastasis, 81.2% of them were detected with metastases to the other central compartment lymph nodes, adding supportive evidence to this suggestion. The PPV of

metastasized DLN for metastasized CLN is up to 81.2% in the present study. However, more observational studies are needed to further confirm the role of DLN in predicting CLN metastasis.

Conclusion

This is the first study to determine the clinical significance of DLN metastasis in unilateral PTC patients and the sample size of DLN positive group in this study is large enough to reach solid associations. In unilateral PTC patients, DLN metastasis is associated with lots of poor prognostic factors of PTC. We recommend that the DLN should be removed first during the surgery procedure, and the metastasis status of DLN may provide meaningful information for surgeons to determine the scope of the surgery and improve the assessment of the prognosis.

List Of Abbreviations

papillary thyroid carcinoma, PTC

Delphian lymph node, DLN

central lymph node, CLN

lateral lymph node, LLN

extrathyroidal extension, ETE

Declarations

Ethics approval and consent to participate

This study was approved as a retrospective study by the Institutional Review Board in our hospital.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

Not applicable

Authors' contributions

Zhenglin Wang and Cong Wang helped collected patients' data. Wei Liu collected patients' data and analyzed the data. Zhilong Ai was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Acknowledgements

Not applicable

References

1. Shaha AR, Shah JP, Loree TR: **Patterns of nodal and distant metastasis based on histologic varieties in differentiated carcinoma of the thyroid.** *Am J Surg* 1996, **172:**692-694.
2. Schoppy DW, Holsinger FC: **Management of the neck in thyroid cancer.** *Otolaryngol Clin North Am* 2014, **47:**545-556.
3. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, et al: **2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer.** *Thyroid* 2016, **26:**1-133.
4. Mercante G, Frasoldati A, Pedroni C, Formisano D, Renna L, Piana S, Gardini G, Valcavi R, Barbieri V: **Prognostic factors affecting neck lymph node recurrence and distant metastasis in papillary microcarcinoma of the thyroid: results of a study in 445 patients** *Thyroid* 2009, **19:**707-716.
5. Lee YS, Lim YS, Lee JC, Wang SG, Kim IJ, Lee BJ: **Clinical implication of the number of central lymph node metastasis in papillary thyroid carcinoma: preliminary report.** *World J Surg* 2010, **34:**2558-2563.
6. So YK, Son YI, Hong SD, Seo MY, Baek CH, Jeong HS, Chung MK: **Subclinical lymph node metastasis in papillary thyroid microcarcinoma: a study of 551 resections.** *Surgery* 2010, **148:**526-531.
7. Roh JL, Kim JM, Park CI: **Central lymph node metastasis of unilateral papillary thyroid carcinoma: patterns and factors predictive of nodal metastasis, morbidity, and recurrence.** *Ann Surg Oncol* 2011, **18:**2245-2250.

8. Cavicchi O, Piccin O, Caliceti U, De Cataldis A, Pasquali R, Ceroni AR: **Transient hypoparathyroidism following thyroidectomy: a prospective study and multivariate analysis of 604 consecutive patients.** *Otolaryngol Head Neck Surg* 2007, **137:**654-658.
9. Mazzaferri EL, Doherty GM, Steward DL: **The pros and cons of prophylactic central compartment lymph node dissection for papillary thyroid carcinoma.** *Thyroid* 2009, **19:**683-689.
10. Gyorki DE, Untch B, Tuttle RM, Shaha AR: **Prophylactic central neck dissection in differentiated thyroid cancer: an assessment of the evidence.** *Ann Surg Oncol* 2013, **20:**2285-2289.
11. Means J: **The thyroid and its diseases. 2nd Edit.** JB Lippincott Co., Philad-elphia; 1948.
12. Resta L, Micheau C, Cimmino A: **Prognostic value of the prelaryngeal node in laryngeal and hypopharyngeal carcinoma.** *Tumori* 1985, **71:**361-365.
13. Olsen KD, DeSanto LW, Pearson BW: **Positive Delphian lymph node: clinical significance in laryngeal cancer.** *Laryngoscope* 1987, **97:**1033-1037.
14. Szmeja Z, Kaczmarek J, Szyfter W, Malinowska B: **[Metastases in the prelaryngeal (delphian) lymph nodes in the course of the laryngeal cancer].** *Otolaryngol Pol* 1995, **49:**422-425.
15. Gawlak-Prycka A: **[Prelaryngeal lymph node (Delphian) in patients with laryngeal cancer].** *Otolaryngol Pol* 2001, **55:**35-41.
16. Ferlito A, Shaha AR, Rinaldo A: **Prognostic value of Delphian lymph node metastasis from laryngeal and hypopharyngeal cancer.** *Acta Otolaryngol* 2002, **122:**456-457.
17. Isaacs JD, Lundgren CI, Sidhu SB, Sywak MS, Edhouse PJ, Delbridge LW: **The Delphian lymph node in thyroid cancer.** *Ann Surg* 2008, **247:**477-482.
18. Iyer NG, Kumar A, Nixon IJ, Patel SG, Ganly I, Tuttle RM, Shah JP, Shaha AR: **Incidence and significance of Delphian node metastasis in papillary thyroid cancer.** *Ann Surg* 2011, **253:**988-991.
19. Kim WW, Yang SI, Kim JH, Choi YS, Park YH, Kwon SK: **Experience and analysis of Delphian lymph node metastasis in patients with papillary thyroid carcinoma.** *World J Surg Oncol* 2012, **10:**226.
20. Lee YC, Shin SY, Kwon KH, Eun YG: **Incidence and clinical characteristics of prelaryngeal lymph node metastasis in papillary thyroid cancer.** *Eur Arch Otorhinolaryngol* 2013, **270:**2547-2550.
21. Oh EM, Chung YS, Lee YD: **Clinical significance of Delphian lymph node metastasis in papillary thyroid carcinoma.** *World J Surg* 2013, **37:**2594-2599.
22. Tan Z, Ge MH, Zheng CM, Wang QL, Nie XL, Jiang LH: **The significance of Delphian lymph node in papillary thyroid cancer.** *Asia Pac J Clin Oncol* 2017, **13:**e389-e393.
23. Zheng G, Zhang H, Hao S, Liu C, Xu J, Ning J, Wu G, Jiang L, Li G, Zheng H, Song X: **Patterns and clinical significance of cervical lymph node metastasis in papillary thyroid cancer patients with Delphian lymph node metastasis.** *Oncotarget* 2017, **8:**57089-57098.
24. Nakayama M, Seino Y, Okamoto M, Mikami T, Okamoto T, Miyamoto S: **Clinical significance of positive Delphian node in supracricoid laryngectomy with cricohyoidoepiglottopexy.** *Jpn J Clin Oncol* 2011, **41:**987-991.

25. Chai YJ, Kim S-j, Choi JY, Koo DH, Lee KE, Youn Y-K: **Papillary Thyroid Carcinoma Located in the Isthmus or Upper Third is Associated with Delphian Lymph Node Metastasis.** *World Journal of Surgery* 2014, **38:**1306-1311.
26. Kwak JY, Kim EK, Kim MJ, Son EJ, Chung WY, Park CS, Nam KH: **Papillary microcarcinoma of the thyroid: predicting factors of lateral neck node metastasis.** *Ann Surg Oncol* 2009, **16:**1348-1355.
27. Zhang L, Wei WJ, Ji QH, Zhu YX, Wang ZY, Wang Y, Huang CP, Shen Q, Li DS, Wu Y: **Risk factors for neck nodal metastasis in papillary thyroid microcarcinoma: a study of 1066 patients.** *J Clin Endocrinol Metab* 2012, **97:**1250-1257.
28. Lundgren CI, Hall P, Dickman PW, Zedenius J: **Clinically significant prognostic factors for differentiated thyroid carcinoma: a population-based, nested case-control study.** *Cancer* 2006, **106:**524-531.
29. Al-Saif O, Farrar WB, Bloomston M, Porter K, Ringel MD, Kloos RT: **Long-term efficacy of lymph node reoperation for persistent papillary thyroid cancer.** *J Clin Endocrinol Metab* 2010, **95:**2187-2194.
30. Schlumberger MJ: **Papillary and follicular thyroid carcinoma.** *N Engl J Med* 1998, **338:**297-306.
31. Podnos YD, Smith D, Wagman LD, Ellenhorn JD: **The implication of lymph node metastasis on survival in patients with well-differentiated thyroid cancer.** *Am Surg* 2005, **71:**731-734.
32. Gimm O, Rath FW, Dralle H: **Pattern of lymph node metastases in papillary thyroid carcinoma.** *Br J Surg* 1998, **85:**252-254.
33. Qubain SW, Nakano S, Baba M, Takao S, Aikou T: **Distribution of lymph node micrometastasis in pN0 well-differentiated thyroid carcinoma.** *Surgery* 2002, **131:**249-256.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarytable.docx