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Clinical analysis of cervical lymph node metastasis patterns and multivariate factors in differentiated thyroid carcinoma

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Abstract. The incidence rate of thyroid cancer is rising rapidly in numerous parts of the world, but the mortality rate is relatively stable or even declining. The aim of the present study was to analyze the risk factors of cervical lymph node metastasis (LNM) in differentiated thyroid carcinoma (DTC). The clinical data of 846 patients with DTC were collected from the Department of General Surgery of Chifeng Municipal Hospital of Inner Mongolia Medical University (Chifeng, China) from June 2018 to June 2022. The relationship between central LNM (CLNM) and lateral LNM (LLNM) was explored in terms of sex, age, tumor diameter, multifocality, capsular invasion and Hashimoto's thyroiditis. It was revealed that male sex, age <35 years, tumor size >1 cm, multifocality and capsular invasion were associated with CLNM and LLNM (P<0.001), while there was no relationship between Hashimoto's thyroiditis, CLNM and LLNM (P>0.05). The number of positive lymph nodes in CLNM dissection, accounting for ≥50% of the total number of lymph nodes dissected, was significantly associated with LLNM (P<0.0001). In conclusion, there was no correlation between Hashimoto's thyroiditis and CLNM and LLNM. The present study revealed that patients with the characteristics of sex, age <35 years, tumor size >1 cm, multifocality and capsular invasion were associated with cervical LNM. The proportion of the number of central lymph node metastases to the total number of lymph nodes cleared during surgery is more than or equal to 50%, indicating a susceptibility to external cervical lymph node metastasis. The results of multivariate logistic analysis showed that male sex, multifocality, capsular invasion and CLNM were risk factors for LLNM, and age was a protective factor for LLNM in DTC.

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Introduction

In 2020, the incidence rate of thyroid cancer ranked ninth among malignant tumors, with ~586,000 patients worldwide (1). The global incidence rate of women is three times higher compared with that of men, and the mortality rate is 5:3 of that of men (2). The incidence rate of thyroid cancer is rising rapidly in numerous parts of the world, but the mortality rate is relatively stable or even declining (3). Thyroid cancer tends to progress very slowly, allowing for a good prognosis in the majority of patients.

However, the cancer is prone to regional lymph node metastasis (LNM), and cervical LNM is the main factor for its recurrence and reoperation (4). The risk of permanent hypocalcemia may increase after central lymph node dissection (CLND). The cervical lymph node metastasis of thyroid cancer usually begins with central lymph node metastasis (CLNM) and gradually extends to the lateral lymph node metastasis, which leads to a significant increase in the incidence of complications related to parathyroid and recurrent laryngeal nerves caused by repeated or multiple neck surgeries, bringing enormous pain and economic burden to patients (5). At the same time, it has been revealed that even individuals with intralobar thyroid microcarcinoma have a risk of developing LLNM, which often indicates the high biological invasion of the tumor (6).

There is no consensus on how to evaluate the risk of LLNM before surgery, the selection of the intraoperative surgical plan or the extent of lymph node dissection (LND). Additionally, efforts are needed to explore high-risk factors of cervical LNM and whether a protective factor for LNM exists. The aim of the present retrospective study was to analyze the risk factors that affect CLNM and LLNM in order to develop an optimized surgical plan for such patients.

Materials and methods

Clinical data. Informed consent was obtained from the patients before the study. The data were collected at the Chifeng Municipal Hospital of Inner Mongolia Medical University (Chifeng, China) from June 2018 to June 2022. A total of 846 patients were collected. Inclusion criteria included: i) DTC was confirmed by intraoperative and postoperative pathology; and ii) complete and reliable clinical statistical data were available.

Excluded specimens include: i) DTC family members refusing to apply their data to clinical studies; and ii) unclear pathological results. Participants consisted of 154 males and 692 females in a ratio of 1:4.49 (mean age 46.57±10.21 years; range, 13 to 73 years). All patients with DTC underwent ipsilateral central LND. If LLNM was confirmed according to preoperative or intraoperative pathology, external neck dissection should be performed. The method of cervical lymph node division was selected according to the American Society of Head and Neck Surgery in 2008 (7). The patients were followed up until November 2022, with no death and serious postoperative complications. A total of 52 patients were treated by I^{131}; four underwent reoperation due to contralateral thyroid nodules; and two had reoperation owing to abnormal lateral cervical lymph node (LLN).

Analysis indicators. Tumor diameter was divided into three groups: <1.0 cm; 1-2 cm; and >2 cm. For multifocal patients, the maximum tumor diameter served as the criterion. Patients were divided into three groups according to their ages: <35; 35 to 55; and >55 years. Antithyroglobulin antibodies (TGAb) and or thyroid peroxidase (TPOA) were used to diagnose Hashimoto's thyroiditis; those with TGAB (0-115 IU/ml) and/or TPOA (0-34 IU/ml) exceeding the normal value were assumed to have Hashimoto's thyroiditis. The sex, age, tumor diameter, multifocality, capsule invasion, Hashimoto's thyroiditis, the rate of CLNM and LLNM were analyzed.

Statistical analysis. Measurement data were expressed as mean ± standard deviation, and count data were expressed as frequency or percentage. The data was double checked and confirmed to be correct before being entered into the table. The age, sex, tumor diameter, single lesion or multiple lesions, Hashimoto's thyroiditis, capsule invasion, the proportion of positive CLNM and LLNM were analyzed. The data were analyzed using χ^2 test using SPSS 17.0 (SPSS, Inc.) statistical software. Univariate logistic regression analysis and multivariate logistic regression analysis were performed using R language (R studio version 1.2.5033).

Results

Risk factors for CLNM. The central neck lymph nodes are defined as those located within the region bordered laterally by the carotid sheath, medially by the trachea, superiorly by the hyoid bone and inferiorly by the sternal notch, where is IV level (5). Features of LLNM cases are presented in Table I. Overall, 846 patients underwent central lymph node (CLN) dissection on the affected side, with 329 positive cases (38.89%) and 517 negative cases (61.11%). The age of onset was mostly between 35 and 55 years old (579 cases, accounting for 68.44%), and the tumor diameter was mostly <1 cm (584 cases, accounting for 69.03%). Patients were composed of 692 (81.80%) females and 154 males (18.20%). Male sex was significantly associated with CLNM (P<0.0001). The probability of developing CLNM increased in patients aged <35 years, remained unchanged in patients between 35 and 55 years of age, and decreased in patients aged >55 years (P<0.0001). Patients with tumor diameters of 1-2 cm and >2 cm had a higher probability of developing CLNM over LLNM (P<0.0001). Multifocality and capsular invasion were significantly associated with CLNM (P<0.0001). There was no significant difference in CLNM rates between patients with and without Hashimoto's thyroiditis (P>0.05).

Risk factors for LLNM. Features of LLNM cases are presented in Table II. Among 846 patients, 75 patients (8.87%) underwent external neck dissection, including 9 patients undergoing bilateral external neck dissection. Compared with female patients, there was a notable association between male patients and LLNM (P<0.001). Compared with patients aged ≥35 years, patients aged <35 years had a higher probability of developing LLNM (P<001). Compared with patients with tumor diameter <1 cm, patients with tumor diameter 1-2 cm and >2 cm were more likely to develop LLNM (P<0.01). Multifocality and capsular invasion were significantly associated with LLNM (P<0.0001). No significant difference was revealed in LLNM rates between patients with and without Hashimoto's thyroiditis (P>0.05). In patients with LLNM, 48 cases (64%) had positive central lymph metastasis accounting for ≥50% of the total lymph nodes dissected. The proportion of positive CLNs was significantly associated with LLNM (P<0.001).

Characteristics of LLNM. Overall, 30 cases developed II level of LNM and 23 cases presented with III level. Among them, 45 cases underwent VB LND, with 12 cases being positive. There were 12 cases of skip metastasis without CLNM. A total of 10 patients had 1/1 or 1/2 metastasis of the external neck by intraoperative frozen pathology, with an LNM rate of 0%. A previous study has demonstrated that unilateral or bilateral comprehensive LND can be performed secondarily in some cases, if necessary, after obtaining pathology results of the initial surgery, since massive involvement of CLNs increases the rate of positive LND. Metastases commonly start by involving the central nodes and subsequently spread to lateral nodes (7).

Logistic regression analysis results. In Table III, univariate logistic analysis demonstrated that age, sex, tumor diameter, multifocality, capsule invasion, the proportion of positive CLNM and Hashimoto's thyroiditis were associated with LLNM. In Table IV, multivariate logistic regression analysis indicated that age was a protective factor for LLNM. Male sex, multifocality, capsular invasion and CLNM were demonstrated to be risk factors for LLNM. Hashimoto's thyroiditis tended to be a protective factor for LLNM, but the difference was not statistically significant.

Discussion

DTC has low malignant potential and slow progress, with a 10-year survival rate of >90% (8); however, a study has revealed that it is prone to early LNM, with a metastasis rate of 40-90% (9). Reoperation significantly increases the incidence of surgical complications and injuries to the recurrent laryngeal nerve and parathyroid gland, thus seriously affecting the quality of life of patients (9). Intraoperative prevention of central LND is widely used, but there is controversy over whether LLNM should be dissected and the scope of LLNM (10).

Table I. Characteristics of central LNM cases.

Clinical case characteristics	Central LNM		χ^2	P-value
	Present	Absent		
Age, years			46.79	10^{-4}
<35	73 (22.19)	42 (8.12)		
35-55	222 (67.48)	357 (69.05)		
>55	34 (10.33)	118 (22.83)		
Sex			19.42	10^{-4}
Male	84 (25.53)	70 (13.54)		
Female	245 (74.47)	447 (84.46)		
Tumor diameter, cm			107.25	10^{-4}
<1.0	161 (48.94)	423 (81.82)		
1-2	127 (39.60)	80 (15.47)		
>2	41 (12.46)	13 (2.51)		
Capsule invasion			49.586	10^{-4}
Present	245 (74.47)	84 (25.53)		
Absent	259 (50.10)	258 (49.90)		
Multifocality			21.185	10^{-4}
Present	127 (38.60)	123 (23.79)		
Absent	202 (61.40)	394 (76.21)		
Hashimoto's thyroiditis			2.824	0.09
Present	71 (21.58)	138 (26.69)		
Absent	258 (78.42)	379 (73.31)		
LLNM			75.16	10^{-4}
Present	64 (19.51)	264 (80.49)		
Absent	11 (2.12)	507 (97.88)		

Values are expressed as n (%). LNM, lymph node metastasis; LLNM, lateral LNM.

Levels II, III and IV are frequently involved, with level III having the highest rate of lymph node metastasis, which was consistent with the results of the present study (11). However, Roh *et al* (12) showed that the lymph node metastasis rate in level IV is the highest (34.8%). Due to the lower metastasis rate of grade I and grade V lymph nodes in DTC compared to other lymph node metastases, some researchers have proposed superselective neck dissection to reduce unnecessary surgical procedures and complications (12).

In the present study, there were 10 cases with 1/1 or 1/2 metastasis of the external neck by intraoperative frozen pathology, with the lymph node metastasis rate being 0%. It was hypothesized that super-selective lymph node dissection requires preoperative high-precision positioning and qualitative diagnosis, as well as a combination of color Doppler ultrasound, CT diagnosis and pathology. If positive lymph nodes are missed during the operation, then the reoperation will significantly increase the incidence of complications. Additionally, its feasibility needs further study. Occasionally, there may be skip transfers without CLNM in DTC, with a reported incidence of 11.1-19.7%, while there were 12 skip transfers in the present group, with an incidence of 16%, which is consistent with previous reports (13). It is hypothesized that skip metastasis may be associated with the location of the tumor.

The tumors of nine patients with skip metastasis of lymph nodes were located in the upper end or isthmus of the gland, which is probably due to lymph reflux (14). This study failed to identify whether the location of the tumor is related to LLNM levels and skip metastasis, which was not elaborated in detail in the paper.

The follow paragraphs detail the risk factors for cervical lymph node metastasis in DTC.

The incidence of DTC in women was significantly higher compared with that in men. The ratio of males to females was 1:4.49 (154/692), suggesting that women were more susceptible to thyroid cancer. The reason for this requires further study. However, the effect of sex on cervical lymph node metastasis of DTC is different. A study has suggested that LNM in male patients has a higher incidence compared with that in female patients (15). Another study has suggested that CLNM has a sex tendency and male sex is a risk factor (16). In the present study, male patients with DTC were more likely to have CLNM and LLNM compared with female patients, which was statistically significant. Further study is required to explore the specific reason.

Whether age is associated with cervical lymph node metastasis in patients with DTC is also controversial. Ito *et al* (17) analyzed 1,231 cases of papillary thyroid carcinoma (PTC)

Table II. Features of LLNM cases.

Clinical case Characteristics	LLNM		χ^2	P-value
	Present	Absent		
Age			33.84	10^{-3}
<35	26 (34.7)	88 (11.5)		
35-55	44 (58.7)	535 (69.4)		
>55	5 (6.7)	147 (19.1)		
Sex			17.51	10^{-3}
Male	27 (36.0)	127 (16.5)		
Female	48 (64.0)	644 (83.5)		
Tumor diameter, cm			102.82	10^{-3}
<1.0	22 (29.3)	563 (73.0)		
1-2	30 (40.0)	177 (23.0)		
>2	23 (30.7)	31 (4.0)		
Capsule Invasion			30.26	10^{-4}
Present	67 (89.3)	437 (56.7)		
Absent	8 (10.7)	334 (43.3)		
Multifocality			24.94	10^{-4}
Present	41 (54.7)	209 (27.1)		
Absent	34 (45.3)	562 (72.9)		
Hashimoto's thyroiditis			3.35	0.07
Present	12 (16.0)	197 (25.6)		
Absent	63 (84.0)	574 (74.4)		
Proportion of lymph node metastasis/total number of dissections in six zones			77.08	10^{-3}
Present (≥50%)	48 (64.0)	148 (15.4)		
Absent (<50%)	27 (36.0)	623 (85.6)		

Values are expressed as n (%). LLNM, lateral lymph node metastasis.

Table III. Univariate logistic regression analysis.

Clinical case characteristic	Risk ratio	95% Confidence interval		P-value
		Lower	Upper	
Age (<35 vs. 35-55 vs. >55 years)	1.00	0.75	1.33	0.8
Sex (female vs. male)	0.85	0.66	1.09	0.2
Tumor diameter (stepwise 1-cm increment)	1.73	1.76	2.66	$2x10^{-5}$
Multifocality	1.76	1.17	2.25	$1.60x10^{-6}$
Capsule invasion	0.19	0.14	0.25	$1.11x10^{-6}$
Hashimoto's thyroiditis	1.32	1.065	1.64	0.01
CLNM	0.75	0.61	0.92	$0.6x10^{-2}$

CLNM, central lymph node metastasis.

with clinically negative cervical lymph nodes (cN0). This revealed that age >55 years is a risk factor for cervical lymph node metastasis and affects the disease-free survival rate post-surgery. A total of 108 patients with cN0 PTC who underwent neck dissection were analyzed (17). This revealed that lymph node metastasis is more likely to occur in patients

Table IV. Multivariate logistic regression analysis.

Clinical case characteristics	Risk ratio	95% Confidence interval		P-value
		Lower	Upper	
Age (<35 vs. 35-55 vs. >55 years)	0.37	1.64	4.52	10^{-4}
Sex (male vs. female)	1.77	0.31	1.06	0.07
Tumor diameter (stepwise 1-cm increment)	3.28	0.20	0.46	3.80×10^{-8}
Multifocality (N vs. Y)	4.181	0.13	0.43	2.24×10^{-6}
Capsule invasion (Y vs. N)	2.69	0.15	0.83	0.02
Hashimoto's thyroiditis (Y vs. N)	0.78	0.63	2.77	0.52
CLNM (Y vs. N)	4.04	0.12	0.499	10^{-4}

Y, present; N, absent; CLNM, central lymph node metastasis.

<45 years old. It is also indicated that age ≤45 years is an independent risk factor for CLNM (17).

The present study showed that the probability of CLNM increased in patients aged <35 years, was unchanged in patients aged 35-55 and decreased in those >55 years. In addition, patients <35 years old have a higher probability of developing LLNM compared with patients in other age groups. The results of multivariate logistic analysis showed that age was a protective factor for LLNM and that older individuals were less likely to develop the disease.

At present, it is considered that there is a positive correlation between tumor size and cervical lymph node metastasis; the larger the tumor diameter, the more obvious the cervical lymph node metastasis (14). Related research demonstrated that tumor size >1 cm is an independent risk factor for lymph node metastasis in PTC (18). In the present study, the tumor size was divided into three groups: <1, 1-2 and >2 cm. The results revealed that in patients with tumor diameter 1-2 and >2 cm, the probability of CLNM was higher and increased with tumor diameter; the probability of LLNM was also higher.

A study has shown that multifocality of thyroid tumors is closely associated cervical LNM (19). Moreover, a previous study has revealed that the multifocality of tumors is the main cause of LLNM (20). The present study showed that patients with multifocal thyroid cancer had a higher probability of central and external cervical lymph node metastases compared with those with single thyroid cancer. Multivariate logistic regression analysis also showed that multifocal thyroid cancer was a high-risk factor for cervical LNM.

In a previous study of 76 patients, 45 patients (59.2%) with PTC complicated by local invasion had cervical LNM, which is significantly more compared with those without local invasion (41.7%). This indicates that local invasion is a risk factor for LLNM (21). Capsular invasion has also been associated with cervical LNM (14). In the present study, patients with capsular invasion had a higher risk of CLNM and LLNM. Multivariate logistic regression analysis also showed that capsule invasion was a risk factor for cervical LNM.

Whether Hashimoto's thyroiditis affects cervical LNM is controversial. It is suggested that Hashimoto's thyroiditis may reduce cervical LNM in DTC, and has a protective effect on LNM (22). Another study suggests that Hashimoto's thyroiditis is considered an autoimmune disease, and it is unclear whether it affects cervical LNM (23). In the present study, TGAb and TPOA exceeding the normal value was the diagnostic criterion of Hashimoto's thyroiditis, and 209 cases (24.70%) were diagnosed with Hashimoto's thyroiditis. The results showed that there was no significant difference in CLNM rates between PTC patients with and without Hashimoto's thyroiditis; there was also no significant difference in LLNM rates between patients with PTC with and without Hashimoto's thyroiditis. Hashimoto's thyroiditis was not associated with cervical LNM in DTC. According to the multivariate logistic regression analysis, Hashimoto's thyroiditis was a protective factor for LLNM, but the difference was not statistically significant, therefore, conclusions cannot be drawn from the present data (24).

The majority of DTCs first metastasize to the CLN and then to the external neck through lymphatic reflux. The present study showed that patients with LLNM had a higher probability of CLNM, but DTC occasionally had skip metastasis of LLNM without metastasizing to the central neck lymph node. A total of 12 cases had skip metastasis with an incidence of 16%. In the presence of CLNM, it is unclear to doctors whether LLNM occurs simultaneously and if there is a need for external neck dissection. It is still controversial whether CLNM can be used to predict LLNM (14). A previous study divided the number of CLNs into none, 1-3 and >3, which demonstrated that the risk of LLN increases significantly with the number of CLNs (14). In the study, the number of CLNs with metastasis/total number of dissected CLNs was divided into ≥50 and <50%. The results showed that patients with the proportion ≥50% were more likely to have external neck metastasis; the proportion of positive CLNs was significantly associated with external neck metastasis. When LLNM occurs, the metastasis rate of level III is the highest, and the metastasis rate of level I and that of level V is relatively low. Level II, III and IV LND are recommended for LLNM, and level VB LND is recommended for level III and IV LNM. Super-selective neck dissection needs further research and demonstration.

In conclusion, there is no association between Hashimoto's thyroiditis and CLNM and LLNM. Male sex, age <35 years, tumor diameter >1 cm, multifocality and capsule invasion

are risk factors of cervical LNM. If the ratio (the number of CLNM/the total number of dissected lymph nodes) is over 50%, LLNM should be considered, and it is necessary to conduct LLN biopsy according to the preoperative evaluation of the LLN, so as to develop the optimal treatment plan for patients. Therefore, the present study concludes that all patients with thyroid cancer should undergo CLN dissection. In addition, patients with lateral cervical lymph nodes should undergo lateral cervical lymph node dissection.

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Availability of data and materials

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

Authors' contributions

JL designed the research scheme, collected data and wrote the manuscript. MG made statistical analysis and contributed the paper. All authors read and approved the final manuscript. JL and MG confirm the authenticity of all the raw data.

Ethics approval and consent to participate

This study was approved by Chifeng Hospital Ethics Committee. This data is retrospective in nature. The study exempted the requirement of informed consent and was approved by the Ethics Committee of Chifeng Hospital.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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