RESEARCH

Lymph node characteristics of 6279 N1 differentiated thyroid cancer patients

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Abstract

Purpose: This study examined the clinicopathological characteristics of 6279 N1 differentiated thyroid cancer (DTC) patients who underwent operations in our center.
Methods: This was a retrospective longitudinal analysis. We categorized the DTC patients on the basis of various lymph node (LN) characteristics. Logistic regression models and multiple linear regression models were used for the correlation analysis.
Results: A total of 3693 (58.8%) N1a patients and 2586 (41.2%) N1b patients were included. Patients with N1b disease had larger metastatic foci (0.5 vs 0.15 cm), a greater number of metastatic LNs (5 vs 2), a greater number of dissected LNs (25 vs 7), and a smaller lymph node ratio (NR, number of positive LNs/number of sampled LNs) (23.1% vs 28.6%) than patients in stage N1a. Comparing the clinicopathological features, we found that male, increased tumor size, multifocality, and thyroiditis increased the risk of stage N1b disease ($P < 0.05$). Sex, multifocality, capsular infiltration, and tumor size were associated with the size of the metastatic LNs ($P < 0.05$). Sex, capsular infiltration, and nodular goiter were associated with the NR ($P < 0.05$). Female sex, tumor located in inferior lobe, maximal tumor diameter (MTD) < 1 cm, and nodular goiter were independent predictors for skip metastases ($P < 0.05$). MTD > 1 cm, central neck metastasis and age were independent predictors for bilateral lateral neck metastasis (BLNM) ($P < 0.05$).
Conclusion: The LN characteristics of stage N1a and N1b disease were associated with significantly different features, such as sex, tumor size, multifocality, capsular infiltration, and nodular goiter.

Introduction

According to the current 8th edition of the American Joint Committee on Cancer staging system, the N stage in TC is determined by the location of positive LNs, and other LNs features (i.e., the number of positive LNs, number of sampled LNs, size of the largest positive LN, size of the largest metastatic focus within a LN, and lymph node ratio (NR)) were considered as potential prognostic factors (1). The size and number of positive LNs have been included in the risk stratification system in the American Thyroid Association (ATA) guidelines (2). In recent years, LN metastasis has attracted more and more attention (3, 4), which could significantly affect the prognosis of TC (Table 1). In patients with inappropriately dissected cervical nodes, however, a discrepancy may exist between the absolute number of positive nodes and the substantive extent of differentiated thyroid cancer (DTC) node metastasis (1, 2, 6). Therefore, the NR, defined as the absolute number of positive nodes/number of

Table 1 The diagnostic value of lymph nodes metastasis in thyroid cancer.

References	LN values	Outcomes	Predictive validity (+/−)
Randolph GW (5)	Number of positive LNs	Risk stratification	+
Schneider DF (6)	NR	DSM	+
Beal SH (7)	NR	Survival	−
Wu MH (8)	Number of positive LNs	Risk stratification	+
Kim HI (9)	Number of positive LNs	CSM	+
	Size of positive LNs	CSM	+
Ito Y (10)	Size of positive LNs	Recurrence	+
Adam M (11)	Number of positive LNs	OS	+
Kim M (12)	Size of positive LNs	DSS	+
Jeon MJ (13)	Location of positive LNs	DSM	+
Vrachimis A (14)	Location of positive LNs	EFS	+

CSM, cancer-specific mortality; DSM, disease-specific mortality; DSS, disease-specific survival; EFS, event free survival; LNs, lymph nodes; Location of positive LNs, N1a and N1b; NR, lymph node ratio; OS, overall survival.

excised nodes, has been suggested to address this discrepancy (15, 16). However, no consensus has been reached regarding the appropriate criteria to discriminate between low- and high-risk groups of NR values for TC (15, 16).

In the current study, we examined the clinicopathological characteristics of 6279 consecutive stage N1 DTC patients. To the best of our knowledge, the present study is the largest study to examine the characteristics of LNs in patients with DTC.

Materials and methods

Study design

A retrospective study was conducted in line with the STROCSS criteria (17).

Setting

The Thyroid Surgery Division in China-Japan Union Hospital of Jilin University is the largest referral and academic endocrine surgery center in the northeastern region of China. Surgical treatment was performed by dedicated surgeons who belonged to the same high-volume TC surgical unit and who have extensive experience in endocrine surgery (i.e. 3500 thyroidectomies/year and 100,000 outpatients/year).

Study population

We retrospectively analyzed patients with stage N1 DTC. The time frame of 2008–2017 was selected. Patients older than 18 years, who had received surgical treatment, and a pathologically confirmed diagnosis of N1 DTC were included in the study. The exclusion criteria were as follows: patients for whom the number of examined or positive regional LNs was 0 or unknown (Nx), N0 patients, patients with occult cancer, patients who had the surgery outside our hospital, patients with recurrent TC cancer or a history of TC, patients with incomplete follow-up and non-primary TC, and patients with known secondary cancers. All patients qualified for surgical treatment underwent preoperative thyroid stimulating hormone (TSH), free thyroxine-4 (fT4), and free thyroxine-3 (fT3) tests and neck ultrasonography (2). Fine-needle aspiration biopsy (FNAB) and preoperative CT were not routinely employed. All patients after surgical treatment required L-tyrosine supplementation (2). The follow-up period was from the date of surgery to the date of the last clinical follow-up.

Data source, collection and variables

The institutional electronic database of the Thyroid Surgery Division in China-Japan Union Hospital of Jilin University was searched to identify N1 DTC patients who were treated between 2008 and 2017. Information on patients treated in the unit is prospectively collected for the continuous monitoring of quality indicators. The deidentified data include histology, information about the preoperative work-up, surgery details, multidisciplinary management, and follow-up. The local database was reviewed to identify patients who underwent surgery for primary N1 DTC. The data collection was carried out by completing a data sheet that included the clinical-histopathological nature of the tumors and LN-related information.

Definitions

The ATA consensus statement regarding the terminology and classification of the central neck defines the central compartment LNs as all perithyroidal and paratracheal soft tissue and LNs with borders extending superiorly

to the hyoid bone, inferiorly to the innominate artery, and laterally to the common carotid arteries. Whereas, the lateral neck includes submandibular and submental LNs (level I), the high (level IIA), mid- (level III), and lower jugular (level IV), and the supraclavicular (level V) and the upper deep jugular and spinal accessory LNs (level IIB) (1, 2, 18).

Surgery

Patients in this study underwent open or endoscopic surgeries. The primary lesion was excised at the same time that the cervical LNs were dissected. Ipsilateral lobe and isthmus resection was performed for unilateral primary lesions. Total thyroidectomy was performed for unilateral primary lesions requiring iodine 131 treatment. We generally performed the LN dissection (LND) of ipsilateral cervical central VI, which is recommended in China (19, 20). For all bilateral primary lesions, total thyroidectomy and bilateral cervical central VI LND were performed. Additional lateral compartment neck dissections, including levels II, III, and IV, were performed if metastases were present in the lateral compartment, and no level I or V LND was performed unless lymph node metastasis to level I or V.

Pathological evaluation

For all patients with TC, formalin-fixed, paraffin-embedded tissue was centralized (China-Japan Union Hospital of Jilin University). All clinical specimens were examined by pathologists, whose observations were recorded. TC diagnosis was based on histopathology reports from surgical specimens. The tumor and LN were completely dissected. All the tumors and LNs were serially sectioned into slices that were 1 mm thick and submitted for histologic examination. Figure 1 shows the positive LNs in histological and gross specimens.

Postoperative staging system

The tumors were staged according to the tumor-node-metastasis (TNM) classification system (1). Staging was performed based on the data collected using the American Joint Committee on Cancer (AJCC) guidelines (1).

Outcomes analysis

We retrieved baseline and clinical characteristics, including age at diagnosis, sex, maximum tumor diameter (MTD),
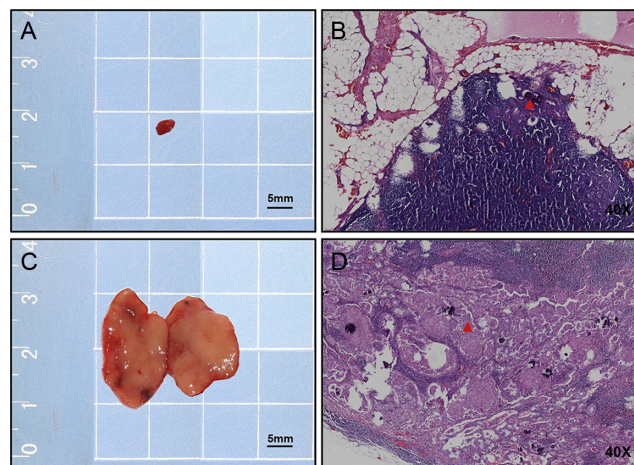
Figure 1
Positive lymph nodes (LNs) in histological and gross specimens. (A) microscopic foci of metastatic LN in gross specimens; (B) microscopic foci of metastatic LN in histological specimens (40×), maximum diameter of the metastatic tumor foci was 0.05 cm; (C) macroscopic foci in gross specimens, maximum diameter of the metastatic tumor foci was 2.0 cm; (D) macroscopic foci in histological specimens (40×). Red arrowheads: metastatic tumor foci.

multifocality, capsular invasion, thyroiditis, and nodular goiter. We categorized patients based on various LN characteristics, including location, size (maximum diameter of the metastatic tumor foci within a LN), number of positive and sampled LNs, and NR. The location and number of metastatic LNs were obtained from operative and pathologic reports. The NR was calculated as the number of positive LNs divided by the number of sampled LNs. Finally, the features of skip metastasis (i.e. lateral LN metastases without involvement in central compartment nodes) and bilateral lateral neck metastasis (BLNM) were examined.

Location and classification of LN status

According to the location of the positive LNs, LNs were classified as N1a or N1b. N1a: cancer has spread to the LNs around the thyroid (called the central compartment; the pretracheal, paratracheal, prelaryngeal LNs, and upper mediastinal LNs) (1, 2, 18). N1b: cancer has spread beyond the central compartment, including unilateral cervical (LNs on 1 side of the neck), bilateral cervical (LNs on both sides of the neck), contralateral cervical (the opposite side of the tumor), or mediastinal (the chest) LNs (1, 2, 18).

Bias

The selection bias was reduced by including all the N1 DTC patients.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approval of the Research Ethics Committee of China-Japan Union Hospital of Jilin University was obtained.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Statistical analysis

We summarized continuous variables by arithmetic means and s.d. or medians and categorical values by weighted frequencies and percentages (%). Data were analyzed using Student's t-test, the Mann–Whitney U test, and the Kruskal–Wallis H test for continuous variables and the chi-square test for categorical variables. A binary logistic regression model and a multiple linear regression model were used for the correlation analysis. A P value of <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS version 19.0.

Results

Population

In the period between June 2008 and December 2017, 15,005 patients with TC underwent primary surgery at our center (thyroid surgery in China-Japan Union Hospital of Jilin University). A total of 8621 patients (57.4%) without neck metastasis and five patients (0.03%) with incomplete information were excluded. A total of 6279 N1 consecutive patients were included in the final analysis (Fig. 2).

Clinicopathological characteristics of patients

All DTCs were confirmed to be N1 by the postoperative pathologic examination of resected tumor and LN tissues. A total of 3693 (58.8%) patients had N1a disease and 2586 (41.2%) had N1b disease. We further found that 1956 patients (31.1%) had both central and lateral LN metastases. Only five (0.8%) patients had contralateral N1b metastasis. The median number of positive LNs per

procedure was 2 (1–44). The median maximum diameter (MD) of the metastatic foci within the LNs was 0.2 cm (0.005–8 cm).

Time trend analysis of lymph node pathological evaluation

In the 10-year period, the total numbers of positive and sampled LNs were 26,784 and 108,885, respectively. The number of sampled LN increased from 6.5 (2008) to 21 (2010) and remained stable from 2010 to 2013 but decreased from 20 in 2013 to 7 in 2017. The NR decreased from 28% in 2008 to 12% in 2011, while it increased from 14% in 2012 to 33% in 2017 (Supplementary Table 1, see section on supplementary materials given at the end of this article).

Features of lymph node metastasis based on the LN location

Patients with N1b disease had larger metastatic foci (0.5 vs 0.15 cm, $P<0.001$), a greater number of metastatic
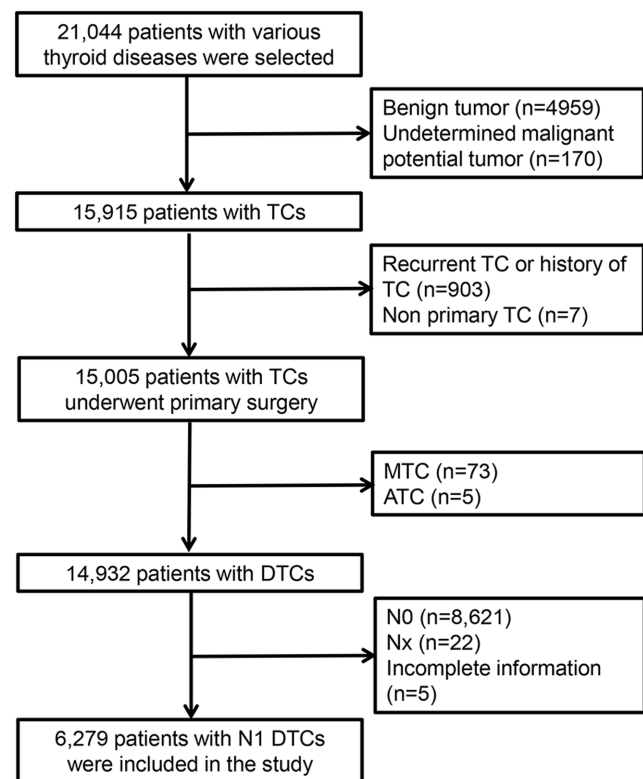
Figure 2
Flowchart for the inclusion and exclusion criteria. TC, thyroid cancer; MTC, medullary thyroid cancer; ATC, anaplastic thyroid cancer; DTC, differentiated thyroid cancer.

LNs (5 vs 2), a greater number of dissected LNs (25 vs 7, $P<0.001$), and a smaller NR (23.1% vs 28.6%, $P<0.001$) (Table 2).

Comparing the clinicopathological features of patients with N1a and N1b disease, we found that men had a 1.249 times higher risk of stage N1b disease than women. For every 1 cm increase in T size, the risk of stage N1b disease increased by 3.1%. Multifocality (OR=1.443, 95%CI: 1.289–1.615) and thyroiditis (OR=1.197, 95%CI: 1.034–1.410) increased the risk of stage N1b disease. Capsular infiltration (OR=0.820, 95%CI: 0.713–0.944) and nodular goiter (OR=0.839, 95%CI: 0.732–0.962) decreased the risk of stage N1b disease (Table 3).

Logistic regression model

As shown in Table 4, male sex, multifocality, capsular infiltration, and tumor size were positively associated with the size of positive LNs, whereas advanced age and nodular goiter were negatively associated with the size of positive LNs ($P<0.05$) in the multivariate logistic regression (except for thyroiditis). Male sex, capsular infiltration, and nodular goiter were associated with a higher NR, while advanced age, multifocality, and thyroiditis were associated with a lower NR ($P<0.05$) (Table 5).

Our previous studies have found that trends of the central neck dissection (CND) and CND+lateral neck dissection (LND) changed dramatically between 2008 and 2017, as a result of the revision of the guidelines. And we noted that more extensive prophylactic LND of treating TCs was gradually giving way to therapeutic LND. The percentage of prophylactic LND increased from 13.9% ($n=6$) in 2008 to 31.0% ($n=228$) in 2013 and decreased to 1.3% ($n=16$) in 2017. Meanwhile, we also found that the NR was related to three different LNDs (including central LND, prophylactic LLND, and therapeutic LLND). After further statistical verification, the following formula was obtained: the median

Table 2 The lymph node characteristics of the location of lymph node metastasis (N1a vs N1b).

	N1a	N1b	*P* value
Size of LNs involved (median)	0.15	0.5	<0.001
Number of LNs involved (median)	2	5	<0.001
Number of LNs sampled (median)	7	25	<0.001
NR (median, %)	28.6	23.1	<0.001

NR, lymph node ratio, number of positive lymph nodes (LNs)/number of sampled LNs; Size of positive LNs, maximum diameter (MD) of the metastatic tumor foci within a LN.

Table 3 The related factors of the location of lymph node metastasis (N1a vs N1b).

	OR (95%CI)	*P* value
Sex		
Female	1	
Male	1.249 (1.106–1.420)	<0.001
Tumor size[a]	3.126 (2.859–3.418)	<0.001
Multifocality		
No	1	
Yes	1.443 (1.289–1.615)	<0.001
Capsular infiltration		
No	1	
Yes	0.820 (0.713–0.944)	0.006
Thyroiditis		
No	1	
Yes	1.197 (1.034–1.410)	0.016
Nodular goiter		
No	1	
Yes	0.839 (0.732–0.962)	0.012

[a]Tumor size, maximum meridian of tumor.

NR is approximately equal to the weighted sum of the NRs of three LNDs: $r_M \approx r_{sum} = \sum(rf/n) = r_1 f_1/n + r_2 f_2/n + r_3 f_3/n$ (Table 6). These LN features were affected by several factors, such as sex, age, tumor size, multifocality, capsular infiltration, and nodular goiter.

N1b skip metastasis

Females had a higher rate of skip metastases than males (26.2%, vs 20.2%, $P=0.001$). Most patients were in the middle-aged or elderly groups (35.7% and 34.6%, $P<0.001$). MTD<1 cm and nodular goiter were associated more with skip metastasis (350 (55.6%) and 487 (77.4%), respectively) ($P<0.001$). Capsular infiltration ($P=0.001$) were rare in this subgroup analysis. Multifocality ($P=0.078$) and thyroiditis ($P=0.619$) were not found to be different between two groups. In multivariate analysis, female sex, advanced age, inferior lobe of the thyroid, MTD<1 cm, and nodular goiter were positively associated with the incidence of skip metastases ($P<0.05$), whereas capsular infiltration ($P<0.05$) was negatively associated with skip metastases. (Table 7).

BLNM

Of the 1548 patients with DTC located in one lobe, 1509 patients had unilateral lateral neck metastasis (ULNM) and 39 had BLNM. Younger age had a higher rate of BLNM (31 vs 39, $P<0.001$). MTD>1 cm, multifocality, and thyroiditis were associated more with BLNM (31 (79.5%), 15 (38.5%), and 14 (35.9%), respectively) ($P<0.05$).

Table 4 The related factors of the size of positive lymph nodes.[a]

Variates	Unstandardized coefficients	s.e.	Standardized coefficients	P value
Constant	0.232	0.04		<0.001
Sex	0.082	0.015	0.069	<0.001
Age	−0.005	0.001	−0.087	<0.001
Multifocality	0.09	0.014	0.082	<0.001
Capsular infiltration	0.117	0.017	0.085	<0.001
Tumor size[b]	0.197	0.009	0.27	<0.001
Thyroiditis	0.032	0.018	0.023	0.075
Nodular goiter	−0.047	0.017	−0.038	0.005

[a]We evaluated the size of positive lymph nodes (LNs) using the maximum diameter (MD) of the metastatic tumor foci within a LN; [b]Tumor size, maximum meridian of tumor.

Central neck metastasis ($P=0.003$) was predominated in patients with BLNM. Sex, tumor location, capsular infiltration, and nodular goiter ($P>0.05$) were not found to be different between the two groups. In addition, MTD>1 cm and central neck metastasis were positively associated with BLNM ($P<0.05$), whereas advanced age was negatively associated with BLNM ($P<0.05$) in the multivariate logistic regression (Table 8).

Discussion

TC is a tumor with indolent behavior but with an early tendency to locoregional lymphatic spread (21, 22). The presence of LN metastases in the setting of TC is a poor prognostic factor, and the importance of LN characterization is clear (21, 22). Furthermore, LN dissection is a surrogate for adequate staging, and it can be expected that the lower the lymph nodes harvested, the higher the probability that metastatic nodal disease will remain. The present study is the largest study to examine the characteristics of positive LNs in patients with DTC. The profiles of positive LN distribution and histological findings in the neck are depicted. LNs were stratified into N1a or N1b according to the current 8th edition of the AJCC staging system (1).

N1a vs N1b

Our results showed that the LN characteristics of N1a and N1b were associated with significantly different features.

An interesting finding for the N1b subgroup was the larger number of dissected LNs and small NR. Many patients with LN sampled from N1a would have DTC with a very small primary tumor size.

After the integral analysis of N1a DTC, we studied the characteristics of N1b DTC. Our analysis showed that N1b was significantly associated with larger metastatic foci, a greater number of positive LNs, and a decreased NR (Table 3). Male sex, tumor size, multifocality, capsular infiltration, and nodular goiter were independent risk factors with significant odds ratios (Tables 4, 5 and 6).

As reported previously for DTCs, the spread of the tumor into the surrounding normal tissue and vascular invasion were the most significant features predictive of nodal involvement (15, 23). In contrast, peritumoral thyroiditis correlated with a lack of nodal metastases, possibly reflecting an immunological reaction against the cancer and a suppressive function against the development of regional LN metastases (15, 23).

Table 5 The related factors of the NR.[a]

Variates	Unstandardized coefficients	s.e.	Standardized coefficients	P value
Constant	0.49	0.019		<0.001
Sex	0.061	0.007	0.108	<0.001
Age	−0.003	0	−0.134	<0.001
Multifocality	−0.033	0.006	−0.064	<0.001
Capsular infiltration	0.02	0.008	0.031	0.015
Tumor size[b]	−0.004	0.004	−0.012	0.339
Thyroiditis	−0.077	0.008	−0.121	<0.001
Nodular goiter	0.024	0.008	0.04	0.003

[a]NR, lymph node ratio, number of positive lymph nodes (LNs)/number of sampled LNs; [b]Tumor size, maximum meridian of tumor.

Table 6 The weighted calculation of lymph node ratio (NR).

Years	Number of patients with LNM (*n*)	NR(r_M)	CLND			Prophylactic LLND			Therapeutic LLND			r_sum
			r_1	f_1	r_1f_1/n	r_2	f_2	r_2f_2/n	r_3	f_3	r_3f_3/n	
2008	43	28.6	21.4	7	3.5	17.7	6	2.5	36.7	30	25.6	31.6
2009	196	28.6	50.0	75	19.1	11.5	21	1.2	24.0	100	12.3	32.6
2010	294	18.2	18.2	47	2.9	9.1	70	2.2	21.4	177	12.9	18.0
2011	313	12.0	11.8	16	0.6	7.7	88	2.2	13.6	209	9.1	11.9
2012	399	14.0	14.3	13	0.5	7.7	113	2.2	20.0	273	13.7	16.3
2013	735	17.9	16.7	111	2.5	8.3	228	2.6	20.0	396	10.8	15.9
2014	961	24.1	33.3	399	13.8	8.3	165	1.4	22.7	397	9.4	24.6
2015	1032	25.7	25.5	531	13.1	8.3	89	0.7	24.1	412	9.6	23.5
2016	1089	33.3	33.3	760	23.3	8.7	27	0.2	28.6	302	7.9	31.4
2017	1217	33.3	33.3	911	24.9	17.9	16	0.2	29.8	291	7.1	32.3

f, the number of patients underwent three lymph node dissections (LNDs), separately; *n*, number of patients with neck metastasis per year; r_M, the median NR of patients with neck metastasis per year; r_1, the median NR of patients underwent central LND (CLND) with neck metastasis per year; r_2, the median NR of patients underwent prophylactic lateral LND (LLND) with neck metastasis per year; r_3, the median NR of patients underwent therapeutic LLND with neck metastasis per year; $r_{sum}=\sum(rf/n)=r_1f_1/n + r_2f_2/n + r_3f_3/n$.

Table 7 Comparison of clinicopathologic characteristics between two groups (patients with skip metastasis or not).

	Skip metastasis		*P* value	**OR** (CI)	*P* value
	Present	Absent			
Total	629 (24.3)	1956 (75.7)			
Sex					
Male	163 (20.2)	642 (79.8)	0.001	Ref.	NA
Female	466 (26.2)	1314 (73.8)		2.195 (1.617–2.979)	<0.001
Age groups					
Median	43	38		1.069 (1.066–1.072)	<0.001
Children (<18 years)	2 (7.7)	24 (92.3)	<0.001	Ref.	NA
Youth (19–44 years)	340 (19.4)	1412 (80.6)		5.648 (3.851–8.284)	<0.001
Middle age (45–59 years)	260 (35.7)	469 (64.3)		3.000 (2.704–3.328)	<0.001
Elderly (60+ years)	27 (34.6)	51 (65.4)		2.426 (2.248–2.618)	<0.001
Tumor lobe					
Left lobe	195 (27)	527 (73)	0.117	NA	NA
Right lobe	204 (24.7)	622 (75.3)		NA	NA
Isthmus	2 (33.3)	4 (66.7)		NA	NA
Bilaterlity	228 (22.1)	803 (77.9)		NA	NA
Tumor location					
Inferior lobe	228 (29.8)	536 (70.2)	<0.001	Ref.	NA
Middle lobe	262 (19.6)	1076 (80.4)		0.839 (0.758–0.923)	<0.001
Superior lobe	79 (19.1)	334 (80.9)		0.956 (0.916–0.998)	0.042
Tumor size					
MTD < 1 cm	350 (55.6)	774 (39.6)	<0.001	Ref.	NA
MTD > 1 cm	279 (44.4)	1182 (60.4)		0.620 (0.602–0.639)	<0.001
Multifocality					
Yes	311 (49.4)	1046 (53.5)	0.078	NA	NA
No	318 (50.6)	910 (46.5)		NA	NA
Capsular infiltration					
Yes	119 (18.9)	492 (25.2)	0.001	0.750 (0.723–0.778)	<0.001
No	510 (81.1)	1464 (74.8)		Ref.	NA
Thyroiditis present					
Yes	133 (21.1)	432 (22.1)	0.619	NA	NA
No	496 (78.9)	1524 (77.9)		NA	NA
Nodular goiter present					
Yes	487 (77.4)	1373 (70.2)	<0.001	1.398 (1.351–1.447)	<0.001
No	142 (22.6)	583 (29.8)		Ref.	NA

Skip metastasis, lateral LN metastases without involvement in central compartment nodes; MTD, maximum tumor diameter.

Table 8 Comparison of clinicopathologic characteristics between patients with unilateral and bilateral lateral neck metastases.

	BLNM	ULNM	*P* value	**OR** (CI)	*P* value
Total	39 (2.5)	1509 (97.5)			
Sex					
Male	15 (38.5)	479 (31.7)	0.374	NA	NA
Female	24 (61.5)	1030 (68.3)		NA	NA
Age					
Median	31	39	<0.001	0.959 (0.925–0.994)	0.023
<45 years	33 (84.6)	1063 (70.4)	0.055	NA	NA
>45 years	6 (15.4)	446 (29.6)		NA	NA
Tumor lobe					
Left lobe	18 (46.2)	704 (46.7)	0.951	NA	NA
Right lobe	21 (53.8)	805 (53.3)		NA	NA
Tumor location					
Inferior lobe	8 (20.5)	522 (34.6)	0.066	NA	NA
Middle lobe	27 (69.2)	760 (50.4)		NA	NA
Superior lobe	4 (10.3)	227 (15)		NA	NA
Tumor size					
MTD < 1 cm	8 (20.5)	680 (45.1)	0.002	Ref.	NA
MTD > 1 cm	31 (79.5)	829 (54.9)		2.288 (1.176–4.452)	0.015
Multifocality					
Yes	15 (38.5)	311 (20.6)	0.006	1.142 (0.876–1.490)	0.326
No	24 (61.5)	1198 (79.4)		Ref.	NA
Capsular infiltration					
Yes	12 (30.8)	316 (20.9)	0.138	NA	NA
No	27 (69.2)	1193 (79.1)		NA	NA
Thyroiditis present					
Yes	14 (35.9)	328 (21.7)	0.035	1.911 (0.966–3.782)	0.063
No	25 (64.1)	1181 (78.3)		Ref.	NA
Nodular goiter present					
Yes	30 (76.9)	1280 (84.8)	0.177	NA	NA
No	9 (23.1)	229 (15.2)		NA	NA
Central neck metastasis					
Yes	37 (94.9)	1112 (73.7)	0.003	5.204 (1.217–22.253)	0.026
No	2 (5.1)	397 (26.3)		Ref.	NA

BLNM, bilateral lateral neck metastasis; MTD, maximum tumor diameter; ULNM, unilateral lateral neck metastasis.

Skip metastasis

Subsequently, we noted that female sex, advanced age, inferior lobe of the thyroid, MTD<1 cm, and nodular goiter were positively associated with the incidence of skip metastases, while capsular infiltration was negatively associated with skip metastases in multivariate analysis. Similar to these results, Jin *et al.* and Nie *et al.* also found that small TCs (MTD<1 cm) are more likely to have skip metastases (24, 25).

BLNM

Finally, we found that MTD>1 cm, central neck metastasis, and age were significantly associated with BLNM in the multivariate analysis. Additionally, another study indicated that males, and patients with a primary tumour size >2 cm, aggressive subtype of PTC, central node metastasis, and Delphian node metastasis are more likely to have BLNM (4).

Limits

The limitations of the study should be acknowledged. In the present study, histopathological features, such as sex, tumor size, multifocality, capsular infiltration, nodular goiter and so on, differed significantly between N1a and N1b diseases, but this information was available only after surgery and was not useful for planning surgery. Second, because this analysis was conducted retrospectively with data from a single institution, the registration information, patient volume, and inspection items could not be designed beforehand. Third, lateral compartment LN dissection was not performed on a part of patients in the lateral compartment clinical LN-negative group. Subclinical lateral compartment LN metastases may exist. The follow-up and disease recurrence information were not included in the current report. Prospective and multicenter clinical trials should be performed to provide more supporting evidence with greater reliability.

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