Title

LYMPH NODE CHARACTERISTICS OF 6,279 N1 DIFFERENTIATED THYROID CANCER PATIENTS

Suggested running title: Chengqiu Sui et al.: Lymph node features and DTC.

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Acknowledgements: This study was supported by the National Nature Science Foundation of China (81702651, 81972499), the Jilin Province Science and Technology Development Program (20180520123JH, 20190201275JC), the Program from the education department of Jilin Province (JJKH20190075KJ), the Program of Jilin provincial finance department (2018SCZ007).

Word count of the full article : 2,775 words
ABSTRACT

Purpose. This study examined the clinicopathological characteristics of 6,279 N1 differentiated thyroid cancer (DTC) patients who underwent operations in our center.

Methods. This was a retrospective longitudinal analysis. We categorized the DTC 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 3,693 (58.8%) N1a patients and 2,586 (41.1%) 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 ($P < 0.05$). Male sex, tumor located in inferior lobe, maximal tumor diameter (MTD) < 1cm, and nodular goiter were independent predictors for skip metastases ($P < 0.05$). MTD > 1cm, central neck metastasis and advanced 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 et al.

KEY WORDS

Differentiated thyroid cancer, lymph node metastases, lymph node ratio, location, neck dissection
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, 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 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 6,279 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., 3,500 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 old 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 computed tomography 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), 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 standard deviations (SD) 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 < 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 8,621 patients (57.4%) without neck metastasis and 5 patients (0.03%) with incomplete information were excluded. A total of 6,279 N1 consecutive patients were included in the final analysis (Figure 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 3,693 (58.8%) patients had N1a disease, and 2,586 (41.2%) had N1b disease. We further found that 1,956 patients (31.1%) had both central and lateral LN metastases. Only 5 (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 2012 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).

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 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 were 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 NR is approximately equal to the weighted sum of the NRs of three LNDs: $r_M \approx r_{\text{sum}} = \sum (rf/n) = r_1f_1/n + r_2f_2/n + r_3f_3/n$ (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 (26.1%, vs. 20.5%, $P = 0.002$). Most patients were in the middle-aged or elderly groups (35.4% and 33.7%, $P < 0.001$). MTD $< 1$ cm and nodular goiter were associated more with skip metastasis [352 (55%) and 495 (77.3%), respectively] ($P < 0.001$). Capsular infiltration ($P = 0.002$) were rare in this subgroup analysis. Multifocality ($P = 0.233$), and thyroiditis ($P = 0.554$) were not found to be different between two groups. In multivariate analysis, male sex,
advanced age, inferior lobe of the thyroid, MTD < 1cm, 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 1,548 patients with DTC located in one lobe, 1,509 patients had unilateral lateral neck metastasis (ULNM) and 39 had BLNM. Younger age had a higher rate of BLNM \((31 \text{ vs. } 39, P < 0.001)\). MTD > 1 cm, multifocality, and thyroiditis were associated more with BLNM \([31 (79.5%), 15 (38.5%) \text{ and } 14(35.9%), \text{ respectively}] \(P < 0.05)\). 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 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 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 is, 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 N1a 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 an increased NR (Table 3). Male sex, tumor size, multifocality, capsular infiltration, and nodular goiter were independent risk factors with significant odds ratios (Tables 4, 5, 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).

Skip metastasis

Subsequently, we noted that male sex, advanced age, inferior lobe of the thyroid, MTD < 1cm, 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 > 1cm, central neck metastasis and advanced 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, and nodular goiter et al, 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.

DECLARATION OF INTEREST, FUNDING AND ACKNOWLEDGEMENTS

Declaration of interest There are no disclosures or conflicts of interest to disclose.

Funding This work was supported by the National Nature Science Foundation of China (81702651, 81972499), the Jilin Province Science and Technology Development Program (20180520123JH, 20190201275JC), the Program from the education department of Jilin Province (JJKH20190075KJ), the Program of Jilin provincial finance department (2018SCZ007).
Acknowledgements We sincerely thank for the support from all clinicians in the division. They are Guang Zhang, Le Zhou, Xuehai Bian, Xiaoli Liu, Shijie Li, Lina Zhao, Jingting Li, Qingfeng Fu, Hongbo Li, Yishen Zhao, Gaofeng Xue, Xueyan Zhang, Tie Wang, Changlin Li, Jiao Zhang, Jingwei Xin, Tianyu Yu, etc.

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FIGURE LEGENDS

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×). ▲ means the metastatic tumor foci.

Figure 2. Flowchart for inclusion and exclusion criteria. TC, Thyroid Cancer, MTC, Medullary Thyroid Cancer; ATC, Anaplastic Thyroid Cancer; DTC, differentiated thyroid cancer.

Table 1. The diagnostic value of lymph nodes metastasis in thyroid cancer. LNs, lymph nodes; NR, lymph node ratio; Location of positive LNs, N1a and N1b; DSM, disease-specific mortality; CSM, cancer-specific mortality; OS, overall survival; DSS, disease-specific survival; EFS, event free survival.

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

*Tumor size, maximum meridian of tumor.

Table 4. The related factors of the size of positive lymph nodes*. *We evaluated the size of positive lymph nodes (LNs) using the maximum diameter (MD) of the metastatic tumor foci within a LN. **Tumor size, Maximum meridian of tumor.

Table 5. The related factors of the NR*. NR, lymph node ratio, number of positive lymph nodes (LNs) / number of sampled LNs. **Tumor size, maximum meridian of tumor.

Table 6. The weighted calculation of lymph node ratio (NR). n, number of patients with neck metastasis per year; f, the number of patients underwent three lymph node dissections (LNDs), separately; \( r_M \), 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 (lymph node ratio) of patients underwent therapeutic LLND with neck metastasis per year; 

\[
r_{\text{sum}} = \sum (rf/n) = r_1f_1/n + r_2f_2/n + r_3f_3/n.
\]

Table 7. Comparison of clinicopathologic characteristics between two groups (patients with skip metastasis or not). Skip metastasis, 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 node metastases. BLNM, Bilateral lateral neck metastasis; ULNM, Unilateral lateral neck metastasis; MTD, maximum tumor diameter.

Supplementary Table. Time trends of lymph node characteristics. 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.
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×). ▲ means the metastatic tumor foci.
Figure 2. Flowchart for inclusion and exclusion criteria. TC, Thyroid Cancer; MTC, Medullary Thyroid Cancer; ATC, Anaplastic Thyroid Cancer; DTC, differentiated thyroid cancer.
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         | +                         |

LN values, lymph nodes; NR, lymph node ratio; Location of positive LNs, N1a and N1b; DSM, disease-specific mortality; CSM, cancer-specific mortality; OS, overall survival; DSS, disease-specific survival; EFS, event free survival.
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** |                   |         |
| No             | 1                 |         |
| Yes            | 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   |

*Tumor size, maximum meridian of tumor.*
Table 4. The related factors of the size of positive lymph nodes*.

| Variates             | Unstandardized Coefficients | Std.Error | 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**         | 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   |

*We evaluated the size of positive lymph nodes (LNs) using the maximum diameter (MD) of the metastatic tumor foci within a LN.

**Tumor size, Maximum meridian of tumor.
Table 5. The related factors of the NR*.

| Variates                   | Unstandardized Coefficients | Std. Error | 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                 | -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   |

*NR, lymph node ratio, number of positive lymph nodes (LNs) / number of sampled LNs.

**Tumor size, maximum meridian of tumor.
| Years | Number of patients with LNM (n) | CLND  | Prophylactic LLND | Therapeutic LLND | r_{sum} |
|-------|-------------------------------|-------|-------------------|------------------|---------|
|       |                               | r_{1} | r_{2} f_{2}/n     | r_{3} f_{3}/n    |         |
|       |                               | f_{1} | r_{1} f_{1}/n     |                  |         |
| 2008  | 43                            | 21.4  | 7                 | 17.7             | 36.7    |
|       |                               |       |                   | 6                | 30      |
|       |                               |       |                   | 2.5              | 25.6    |
|       |                               |       |                   |                   | 31.6    |
| 2009  | 196                           | 28.6  | 50.0              | 11.5             | 24.0    |
|       |                               |       | 75                | 21               | 100     |
|       |                               |       |                   | 1.2              | 12.3    |
|       |                               |       |                   |                   | 32.6    |
| 2010  | 294                           | 18.2  | 18.2              | 9.1              | 21.4    |
|       |                               |       | 47                | 70               | 177     |
|       |                               |       |                   | 2.2              | 12.9    |
|       |                               |       |                   |                   | 18.0    |
| 2011  | 313                           | 12.0  | 11.8              | 7.7              | 13.6    |
|       |                               |       | 16                | 88               | 209     |
|       |                               |       |                   | 2.2              | 9.1     |
|       |                               |       |                   |                   | 11.9    |
| 2012  | 399                           | 14.0  | 14.3              | 7.7              | 20.0    |
|       |                               |       | 13                | 113              | 273     |
|       |                               |       |                   | 2.2              | 13.7    |
|       |                               |       |                   |                   | 16.3    |
| 2013  | 735                           | 17.9  | 16.7              | 8.3              | 20.0    |
|       |                               |       | 111               | 228              | 396     |
|       |                               |       |                   | 2.6              | 10.8    |
|       |                               |       |                   |                   | 15.9    |
| 2014  | 961                           | 24.1  | 33.3              | 8.3              | 22.7    |
|       |                               |       | 399               | 165              | 397     |
|       |                               |       |                   | 1.4              | 9.4     |
|       |                               |       |                   |                   | 24.6    |
| 2015  | 1032                          | 25.7  | 25.5              | 8.3              | 24.1    |
|       |                               |       | 531               | 89               | 412     |
|       |                               |       |                   | 0.7              | 9.6     |
|       |                               |       |                   |                   | 23.5    |
| 2016  | 1089                          | 33.3  | 33.3              | 8.7              | 28.6    |
|       |                               |       | 760               | 27               | 302     |
|       |                               |       |                   | 0.2              | 7.9     |
|       |                               |       |                   |                   | 31.4    |
| 2017  | 1217                          | 33.3  | 33.3              | 8.7              | 29.8    |
|       |                               |       | 911               | 27               | 291     |
|       |                               |       |                   | 0.2              | 7.1     |
|       |                               |       |                   |                   | 32.3    |

{n}, number of patients with neck metastasis per year;

{f}, the number of patients underwent three lymph node dissections (LNDs), separately;

*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 (lymph node ratio) of patients underwent therapeutic LLND with neck metastasis per year;

\[ r_{sum} = \sum (rf/n) = r_{1} f_{1}/n + r_{2} f_{2}/n + r_{3} f_{3}/n. \]
Table 7. Comparison of clinicopathologic characteristics between two groups (patients with skip metastasis or not).

| Skip metastasis | Present | Absent | P value | OR[CI]         | P value |
|-----------------|---------|--------|---------|----------------|---------|
| Total           | 629(24.3) | 1956(75.7) |         |                |         |
| **Sex**         |         |        |         |                |         |
| Male            | 163(20.2) | 642(79.8) | 0.001   | 2.195[1.617-2.979] | <0.001  |
| Female          | 466(26.2) | 1314(73.8) | Ref.    | NA             |         |
| **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             | NA      |
| Isthmus         | 2(33.3) | 4(66.7) | NA      | NA             | NA      |
| Bilaterlity     | 228(22.1) | 803(77.9) | NA      | 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 < 1cm       | 350(55.6) | 774(39.6) | <0.001  | Ref. | NA |
| Multifocality               | 279(44.4) | 1182(60.4) | 0.620[0.602-0.639] | <0.001 |
|---------------------------|-----------|------------|-------------------|--------|
| Yes                       | 311(49.4) | 1046(53.5) | 0.078             | NA     |
| No                        | 318(50.6) | 910(46.5)  | NA                | NA     |

| Capsular infiltration     | 119(18.9) | 492(25.2)  | 0.001             | 0.750[0.723-0.778] | <0.001 |
|---------------------------|-----------|------------|-------------------|-------------------|--------|
| Yes                       | 510(81.1) | 1464(74.8) | Ref.              | NA                |        |

| Thyroiditis present       | 133(21.1) | 432(22.1)  | 0.619             | NA                | NA     |
|---------------------------|-----------|------------|-------------------|-------------------|--------|
| No                        | 496(78.9) | 1524(77.9) | NA                | NA                |        |

| Nodular goiter present    | 487(77.4) | 1373(70.2) | <0.001            | 1.398[1.351-1.447] | <0.001 |
|---------------------------|-----------|------------|-------------------|-------------------|--------|
| Yes                       | 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 node 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               | 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               | 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               | 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               | NA      |
| Superior lobe        | 4(10.3)  | 227(15)    | NA      | NA               | NA      |
| **Tumor size**       |      |            |         |                  |         |
| MTD < 1cm            | 8(20.5)  | 680(45.1)  | 0.002   | Ref.             | NA      |
| MTD > 1cm            | 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               | NA      |
| **Capsular infiltration** |   |            |         |                  |         |
| Yes                  | 12(30.8) | 316(20.9)  | 0.138   | NA               | NA      |
|                      | No            | Thyroiditis present | Nodular goiter present | Central neck metastasis |
|----------------------|---------------|---------------------|------------------------|-------------------------|
|                      | 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; **ULNM**, Unilateral lateral neck metastasis; **MTD**, maximum tumor diameter.
**Supplementary Table. Time trends of lymph node characteristics.**

| Years | Total | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | P value |
|-------|-------|------|------|------|------|------|------|------|------|------|------|---------|
| Number of LNs involved (median) | 2 | 2 | 2 | 3 | 2 | 2 | 3 | 3 | 3 | 3 | 2 | > 0.05 |
| Number of LNs sampled (median) | 14 | 6.5 | 10 | 21 | 21 | 19 | 20 | 15 | 13 | 8 | 7 | < 0.001 |
| LNR (median) | 25.0 | 28.6 | 28.6 | 18.2 | 12.0 | 14.0 | 17.9 | 24.1 | 25.7 | 33.3 | 33.3 | < 0.001 |
| Size of LNs involved (median, cm) | 0.2 | — | 0.3 | 0.3 | 0.3 | 0.25 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | > 0.05 |

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.