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ORIGINAL

Impact of superior mediastinal metastasis on the prognosis of papillary thyroid carcinoma

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Abstract. The impact of lymph node (LN) metastasis on survival or tumor recurrence in patients with papillary thyroid carcinoma (PTC) is controversial. The objective of this study was to investigate the effect of superior mediastinal metastasis on the prognosis of patients with PTC and to identify any correlations between such metastasis and clinical indicators. Medical records of PTC patients who underwent surgery as their initial treatment between 1981 and 2008 at our institution were retrospectively reviewed. Patients with or without superior mediastinal metastasis were selected. Prognosis was determined using the Kaplan-Meier method and Cox-hazard regression model with the forward stepwise method. Correlations between multiple factors and superior mediastinal metastasis were investigated using a binary logistic regression analysis. The study cohort included 488 patients of whom 75 (15.4%) had superior mediastinal metastasis. The survival differences between patients with superior mediastinal metastasis dissected *via* the transcervical approach and patients without metastasis were not significant. The prognosis of patients with superior mediastinal metastasis dissected by sternotomy was significantly poorer. As for disease-free survival, significant differences were found between patients with superior mediastinal metastases dissected by either method and patients without metastases. The main variables predicting superior mediastinal metastasis were an age of 45 years or older and the total number of cervical LN metastases. Superior mediastinal metastasis was an independent predictive factor for recurrence-free survival in PTC patients. The main variables predicting superior mediastinal metastasis were being 45 years of age or older, and having a greater total number of cervical LN metastases.

Key words: Papillary thyroid carcinoma, Superior mediastinal metastasis, Prognosis, Clinical indicators, Mediastinal dissection

PAPILLARY THYROID CARCINOMA (PTC) is known for its relatively indolent course, despite its high incidence of cervical lymph node (LN) metastases. Although several studies have identified clinicopathological indicators that may potentially predict prognosis and recurrence in PTC patients, the role of nodal metastases on disease progression and prognosis is unclear. The spread of LN metastases occurs in a predictable pattern beginning in the perithyroidal LNs of the central compartment and progressing to the LNs of the lateral cervical compartments and the superior mediastinum [1, 2].

Although LN metastases in PTC patients are most commonly found in the central compartment where they first arise [3], the advantage of comprehensive central neck dissection remains uncertain [4–6]. The lower anatomic border of the central compartment, and whether it includes the superior mediastinal node compartment, is not clearly defined in the literature [7, 8].

In this study, we investigated whether an association exists between various clinical indicators and superior mediastinal metastasis, and also determined the impact of superior mediastinal metastasis on the prognosis of patients with PTC.

Materials and Methods

Patients

The charts of PTC patients who underwent surgical treatment at Kyoto Medical Center and Kusatsu General Hospital between 1981 and 2008 were retrospectively reviewed. Selected patients were categorized into 2 groups according to whether or not they had superior mediastinal metastasis. Data on patient characteristics were collected and compared between the 2 groups.

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Mediastinal LNs

The mediastinum lies between the right and left pleurae within the median sagittal plane that extends from the sternum anteriorly to the vertebral column posteriorly. It contains all the thoracic organs except the lungs.

The superior mediastinal LN compartment is the region extending from the upper level of the pericardium, with its upper limit at the superior thoracic aperture and its lower limit at the thoracic plane that runs from the sternal angle to the intervertebral discs between T4 and T5. This compartment is divided into 3 types of sections: those containing the thoracic paratracheal LNs, thoracic pretracheal LNs, and tracheobronchial LNs. Thoracic paratracheal LNs are located between the upper manubrium and intersection of the caudal margin of the brachiocephalic vein with the trachea on the right and the superior border of the aortic arch on the left. The thoracic pretracheal LNs are located in the prevascular compartment of the mediastinum overriding the upper portions of the pericardium. The tracheobronchial LNs lie around the bifurcation of the trachea and are contiguous with the thoracic paratracheal nodes proximally (Fig. 1). The boundaries between cervico-paratracheal nodes and superior mediastinal nodes define the superior thoracic aperture under the neck extension position.

Surgical methods

Following routine central compartment neck dissection, superior mediastinal LN dissection (SMD) was performed with or without sternotomy for patients suspected of having a superior mediastinal metastasis. A transcervical approach was used for SMD without sternotomy, while SMD with sternotomy was performed by reversed-T upper mini-sternotomy or partial resection of the manubrium and sternoclavicular joint.

Reversed-T upper mini-sternotomy involved a midline incision from the manubrium to the third intercostal level and transverse sectioning at the third intercostal level without damaging the penetrating branch of the internal thoracic artery. Partial segmental resection of the manubrium and sternoclavicular joint was defined as partial or subtotal resectioning of the manubrium and partial resectioning of the ipsilateral sternoclavicular joint without dislocating the clavicle.

Reversed-T upper mini-sternotomy ensured visualization from a cranial oblique direction, while partial

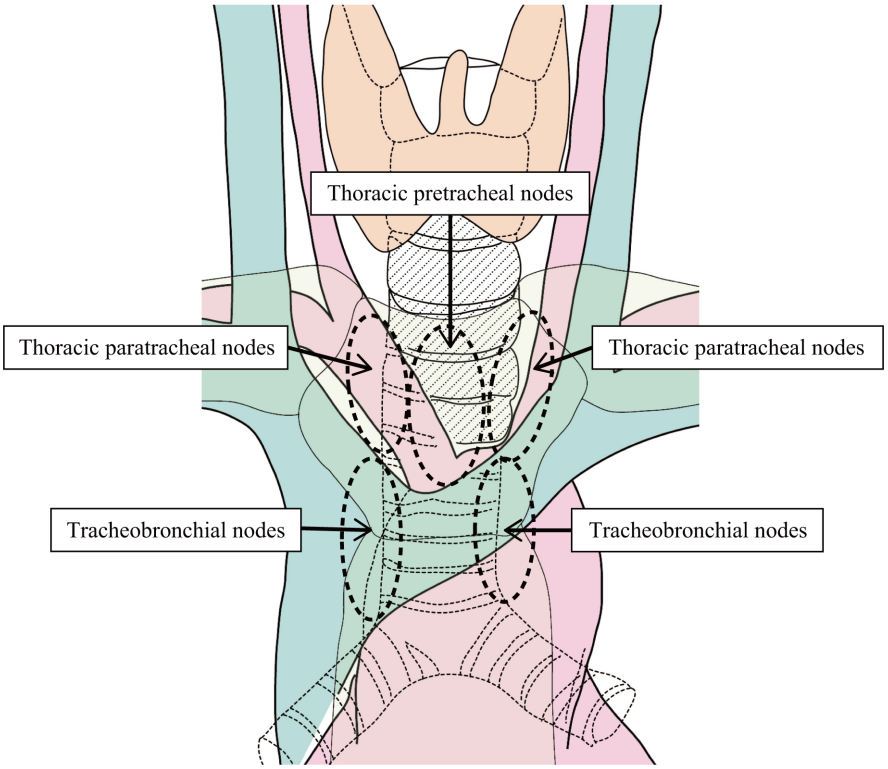

Fig. 1 Superior mediastinal lymph nodes

segmental resection of the manubrium and sternoclavicular joint exposed the view from the frontal direction. Although the visual fields differ from each other, the same surgical field can be obtained using these 2 approaches with sternotomy. Reaching the surgical field of the superior mediastinum by partial segmental resection of the manubrium and sternoclavicular joint is straightforward. Reversed-T upper mini-sternotomy facilitates operating on a mediastinal tumor suspected of peripheral organ invasion.

SMD with sternotomy was performed for patients suspected of having a large superior mediastinal metastasis, surrounding organ invasion in the superior mediastinal compartment, or tracheobronchial LN metastasis. Prophylactic SMD with sternotomy was not performed. For patients with successive superior mediastinal metastases in the paratracheal region detected intraoperatively, SMD *via* the transcervical approach was performed.

Preoperative diagnosis and postoperative follow up

Superior mediastinal LN metastases, cervico-central, or cervico-lateral LN metastases were evaluated by preoperative diagnostic imaging and intraoperative clinical or pathological findings. The total number of superior mediastinal metastases and cervico-central or cervico-lateral LN metastases were evaluated by pathological examination. For all patients with thyroid carcinoma, cervical ultrasonographic examination was routinely performed. For high-risk patients suspected of having a large thyroid tumor (≥4 cm), extrathyroidal extension, multiple cervical metastases, or distant metastasis prior to initial treatment, contrast enhanced computed tomography or magnetic resonance imaging was employed for preoperative evaluation.

Ablation of the remnant thyroid or radioactive iodine (RAI) treatment was performed in few patients. Postoperative assessments with cross-sectional imaging were performed every 6 months to detect locoregional or distant recurrence. For patients with locoregional recurrence that was surgically resectable, additional surgical treatment was performed.

Extrathyroidal extension was defined as tumor invasion of the larynx, trachea, esophagus, recurrent laryngeal nerve, mediastinal vessels, or carotid artery from the thyroid primary tumor site (excluding invasion into the sternothyroid or sternohyoid muscle). Invasive extranodal extension was defined as the intraoperative detection of gross invasion by LN metastasis into the surrounding organs or intraoperative cryosection analysis showing LN metastasis in the organs [9]. Table 1 lists the times at which each condition was diagnosed (Table 1).

The study was enacted on the basis of the Code of Ethics of the hospital. Patients' privacy was strictly maintained, and informed consent was obtained.

Statistical analysis

Groups were compared using the Mann-Whitney *U* test or chi-square test as appropriate. Factors that were significant by univariate analysis subsequently underwent binary logistic regression analysis using the forward stepwise method to determine the correlation between these different variables and superior mediastinal metastasis.

Kaplan-Meier survival curves were compared for statistical significance using the log-rank test, and a Cox-hazard regression model with the forward stepwise method was used for multivariate analysis. Commercially available software (Ekuseru-Toukei 2015; SSRI Co., Ltd., Tokyo, Japan) was used for all statistical analyses. Significance was defined by a p value of less than 0.05.

Table 1 Time of diagnosis for each pathologic condition

Condition	Time of diagnosis
Superior mediastinal metastasis	Preoperative diagnostic imaging, intraoperative clinical or pathological findings
CCNM	Preoperative diagnostic imaging, intraoperative clinical or pathological findings
CLNM	Preoperative diagnostic imaging, intraoperative clinical or pathological findings
Total number of CCNM	Postoperative pathological findings
Total number of CNM	Postoperative pathological findings
Presentation	Intraoperative or postoperative pathological findings
Extrathyroidal extension	Preoperative diagnostic imaging, intraoperative clinical or pathological findings
Invasive extranodal extension	Preoperative diagnostic imaging, intraoperative clinical or pathological findings

CCNM, cervico-central node metastases; CLNM, cervico-lateral node metastases; CNM, cervical node metastases.

Results

During the study period, 488 PTC patients underwent primary thyroid surgery. The study cohort included 114 men (23.4%) and 374 women (76.6%). The patients' mean age at initial treatment was 51 years (range: 9–92 years). The mean ± standard deviation follow-up period after surgery for surviving patients was 10.5 ± 7.1 years.

Seventy-five (15.4%) patients with and 413 (84.6%) without superior mediastinal metastasis were enrolled. Of the former 75 patients, 46 were referred from other institutions for advanced thyroid surgery including upper mediastinal dissection. Patients with superior mediastinal metastasis had a higher frequency of LN metastasis in the central compartment ($p = 0.0000$, chi-square test), ipsilateral neck ($p = 0.0000$, chi-square test) or contralateral neck ($p = 0.0002$, chi-square test). Patients with superior mediastinal metastasis also had a higher frequency of extrathyroidal extension ($p = 0.0018$, chi-square test), invasive extranodal extension ($p = 0.0029$, chi-square test) and distant metastasis prior to initial treatment ($p = 0.0078$, chi-square test), as shown in Table 2.

Of 75 patients with superior mediastinal LN metastasis, 57 underwent transcervical SMD, while 18 underwent SMD by sternotomy; of the latter patients, 15 underwent partial segmental resection of the manubrium and sternoclavicular joint while 3 underwent reversed-T upper mini-sternotomy. With respect to superior mediastinal LN metastases, 53 patients (93%) who underwent transcervical SMD had thoracic paratracheal LN metastasis and 5 (9%) had thoracic pretracheal LN metastasis. Furthermore, 18 patients (100%) who underwent SMD by sternotomy had thoracic paratracheal LN metastasis, 2 patients (11%) had thoracic pretracheal LN metastasis, and 3 (17%) had tracheobronchial LN metastasis. All patients with tracheobronchial LN metastasis also had thoracic paratracheal LN metastasis.

The mean number of superior mediastinal LNs and LN metastases in patients who underwent transcervical SMD were 3.6 (range: 1–14) and 1.8 (range: 1–5) respectively. Those in patients who underwent SMD by sternotomy were 8.3 (range: 1–29) and 3.7 (range: 1–21) respectively. The number of superior mediastinal LNs were significantly different between patients who underwent transcervical SMD *vs*. those who underwent SMD by steronotomy ($p = 0.004$, Mann Whitney *U* test), but the number of superior mediastinal metastases between 2 groups were not significantly different ($p = 0.084$, Mann Whitney *U* test).

Invasion into surrounding organs was detected in 30 patients (52.6%) who underwent transcervical SMD; 23 had extrathyroidal extension and 10 had invasive extranodal extension. In patients who underwent SMD

Table 2 Baseline patient characteristics

	Superior mediastinal metastasis		*p*-value
	Positive (n = 75)	Negative (n = 413)	
Mean age (SD), y	52.6 (12.6)	51.9 (16.8)	0.6851
Sex			
Female	51 (68%)	323 (78%)	0.0614
Male	24 (32%)	90 (22%)	
Presentation			
Well differentiated	72 (96%)	397 (96%)	0.9385
Poorly differentiated	3 (4%)	14 (4%)	
LN metastasis			
No metastatic nodes		142 (34.4%)	
CCNM	60 (80%)	219 (53%)	0.0000 *
Ipsilateral CLNM	60 (80%)	188 (45.5%)	0.0000 *
Contralateral CLNM	18 (24%)	38 (9.2%)	0.0002 *
Extrathyroidal extension	34 (45.3%)	113 (27.4%)	0.0018 *
Invasive extranodal extension	17 (22.7%)	43 (10.4%)	0.0029 *
Distant metastasis prior to intial treatment	7 (9.3%)	10 (2.4%)	0.0078 *

* denotes statistical significance. SD, standard deviation; y, years; CCNM, cervico-central node metastases; CLNM, cervico-lateral node metastases.

by sternotomy, there were 15 (83.3%) with invasion; 11 had extrathyroidal extension and 7 had invasive extranodal extension. The rates of extrathyroidal invasion and invasive extranodal extension were significantly different between patients who underwent transcervical SMD *vs*. those who underwent SMD by sternotomy (p = 0.0018 and 0.0205, chi-square test, respectively). Of the 18 patients who underwent SMD with sternotomy, 10 had surrounding organ invasion in the superior mediastinal compartment (tracheal invasion: 5, great vein: 3, recurrent laryngeal nerve: 1, pleura: 1), 4 had a primary tumor extension into the mediastinum, 3 had a large superior mediastinal metastasis, and 3 had tracheobronchial LN metastasis.

Postoperative complications occurred in 5 patients who underwent SMD with sternotomy and in 2 who underwent SMD *via* the transcervical approach. Lymphorrhea and partial tracheal necrosis, which was involved and resected with the tumor, occurred in 5 and 3 patients, respectively. Two patients with lymphorrhea after SMD with sternotomy experienced massive bleeding from the innominate artery due to infection.

A comparison of prognoses in patients with and without superior mediastinal metastasis indicated that the 10-year disease-specific survival was shorter for patients with such metastasis than for those without; this difference was significant (p = 0.0318, log-rank test). However, the survival difference between patients with superior mediastinal metastasis dissected by the transcervical approach and those without was not significant (92.0% *vs*. 95.6%, p = 0.467, log-rank test). The prognosis for patients with superior mediastinal metastasis dissected by sternotomy was significantly poorer (66.7%; Fig. 2).

The distant recurrence rates for patients with and without superior mediastinal metastasis were 21.3% and 7.5%, respectively. In a comparison of distant-free survival between patients with superior mediastinal metastasis that was dissected either by the transcervical approach or by sternotomy, as well as patients without superior mediastinal metastasis, there was no significant different between patients with superior mediastinal metastasis dissected transcervically and those without metastasis (p = 0.076, log-rank test). However, the distant-free survival for patients with superior mediastinal metastasis dissected by sternotomy was poorer than the 2 other categories (p = 0.000, log-rank test; the median distant-free survival was 1317 days (Fig. 3).

The locoregional recurrence rates for patients with

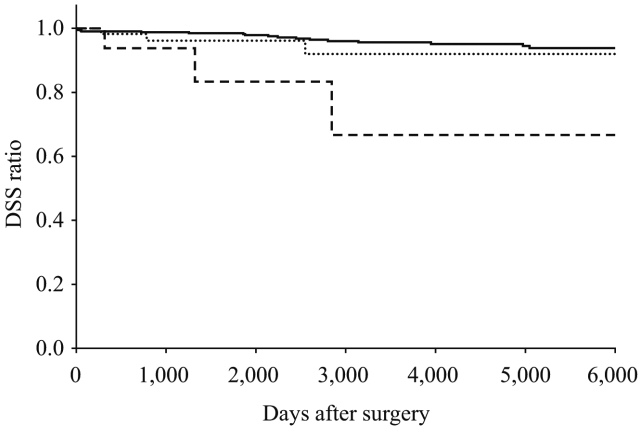

Fig. 2 Comparison of disease-specific survival (DSS) rates among patients.
The 10-year DSS rates for patients with mediastinal metastasis dissected by the transcervical approach (dotted line ⋯ ; n = 57), those dissected by sternotomy (dashed line --- ; n = 18), and those without superior mediastinal metastasis (solid line — ; n = 413) were 92.0%, 66.7%, and 95.6%, respectively. The survival differences between patients with superior mediastinal metastasis dissected by the transcervical approach and those without were not significant (p = 0.467, log-rank test). The prognosis for patients with superior mediastinal metastasis dissected by sternotomy was significantly poorer (p = 0.0005, log-rank test). DSS, disease specific survival.

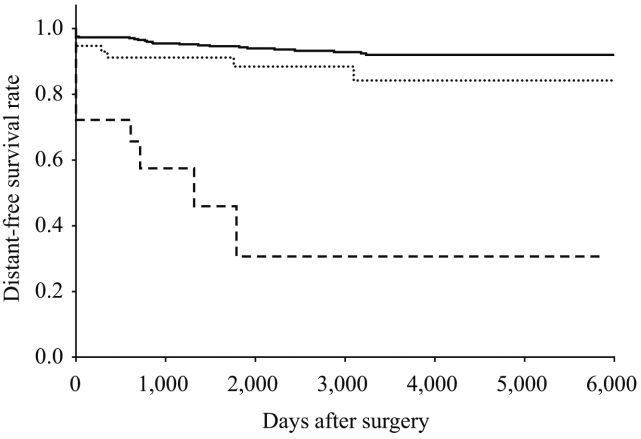

Fig. 3 Comparison of distant-free survival rates among patients.
The distant-free survival differences between patients with superior mediastinal metastasis dissected by the transcervical approach (dotted line ⋯ ; n = 57) and those without (solid line — ; n = 413) were not significant (p = 0.076, log-rank test). The distant-free survival for patients with superior mediastinal metastasis dissected by sternotomy (dashed line --- ; n = 18) was significantly poorer (p = 0.000, log-rank test; median distant-free survival, 1317 days).

and without superior mediastinal metastasis were 14.7% and 5.3%, respectively. Recurred lesions were detected in the superior mediastinal components in 3 patients, all of whom originally had metastases in that location. These patients were managed with additional SMD with sternotomy. A comparison of disease-free survival for the 3 patient groups revealed a significant difference between the superior mediastinal metastasis group that underwent SMD *via* the transcervical approach *vs*. the group without mediastinal metastasis ($p = 0.037$, log-rank test), as well as between the group that underwent SMD with sternotomy *vs*. the group without mediastinal metastasis ($p = 0.000$, log-rank test; the median disease-free survival was 715 days (Fig. 4). Multivariate analysis was performed on the recurrence factors that were deemed significant by univariate analysis. The results indicated that an age of 45 years or older, male sex, extrathyroidal extension, poor differentiation, contra cervico-lateral node metastasis, and superior mediastinal metastasis were independent predictive factors for recurrence-free survival in PTC patients (Table 3).

Various clinical, operative, and pathological variables were analyzed to determine their association with superior mediastinal metastasis. Based on univariate analysis, significant factors included an age of 45 years or older; extrathyroidal extension; invasive extranodal extension; central compartment node metastasis; ipsilateral and contralateral node metastases; total number of central compartment, ipsilateral, and cervical LN metastases; and the maximum diameter of cervical LN metastasis. The main variables predicting superior mediastinal metastasis according to multivariate analysis were an age of 45 years or older and a greater total number of cervical LN metastases (Table 4).

Discussion

We found that superior mediastinal metastasis was not associated with poor prognosis in our series; however, it was associated with recurrence. Although the prognosis for patients with superior mediastinal metastases that were dissected by sternotomy was poor, that for patients with superior mediastinal metastases dissected by the transcervical approach was comparable

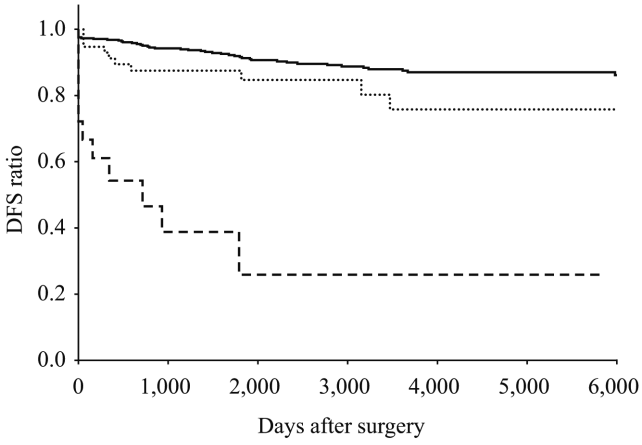

Fig. 4 Comparison of disease-free survival rates among patients. The disease-free survival differences between patients with superior mediastinal metastasis dissected by the transcervical approach (dotted line ⋯ ; n = 57) and those without (solid line — ; n = 413) were significant ($p = 0.037$, log-rank test). The distant-free survival for patients with superior mediastinal metastasis dissected by sternotomy (dashed line --- ; n = 18) was the significantly poorer ($p = 0.000$, log-rank test: median distant-free survival, 715 days). DFS, disease-free survival.

Table 3 Multivariate analysis of prognostic factors for disease-free survival in 488 papillary thyroid carcinoma patients

Variables	*p*-value	Hazard ratio	95% CI
Age ≥45 year	0.0438	1.9911	1.019 - 3.890
Male gender	0.0154	1.9790	1.139 - 3.438
Extrathyroidal extension	0.0074	2.0192	1.207 - 3.378
Presence of poorly differentiated lesions	0.0101	2.8678	1.285 - 6.397
Contra CLNM	0.0174	2.0737	1.137 - 3.783
Superior mediastinal metastasis	0.0008	2.6175	1.495 - 4.582
Large nodal metastasis (≥3 cm)	0.1133	1.6260	0.891 - 2.968

Superior mediastinal or cervico-lateral lymph node metastases were evaluated by preoperative diagnostic imaging and intraoperative clinical or pathological analysis. Tumor presentation was evaluated by intraoperative clinical or pathological analysis and postoperative pathological analysis. CI, confidence interval; CLNM, cervico-lateral node metastases.

Table 4 Multivariate analysis of the main variables predicting superior mediastinal metastasis

Variables	B	Wald	*p*-value	Odd's ratio	95% CI
Distant metastasis prior to initial treatment	0.8449	1.9763	0.1598	2.3278	0.7167 - 7.5603
Age 45 years or older	0.9760	7.2283	0.0072	2.6538	1.3028 - 5.4058
Total number of CCNM	0.6484	3.1051	0.0780	1.9124	0.9298 - 3.9336
Total number of CNM	0.0785	12.7821	0.0003	1.0816	1.0361 - 1.1292
Maximum diameter of CNM (mm)	0.0191	2.7958	0.0945	1.0192	0.9967 - 1.0423

Total number of CCNM, total number of CNM and maximum diameter of CNM were evaluated by postoperative pathological analysis. B, partial regression coefficient; CI, confidence interval; CCNM, cervico-central node metastases; CNM, cervical node metastases.

to the prognosis of patients without superior mediastinal metastases. The main variables predicting superior mediastinal metastasis were an age of 45 years or older and a greater total number of cervical LN metastases.

The effect of LN metastasis, including superior mediastinal LN metastasis, on survival or recurrence in PTC patients is unclear. Some studies investigating the impact of LN metastasis on the survival of PTC patients indicated that large nodal metastases (≥3 cm) in older patients (age ≥50 years), extranodal invasion, LN involvement in patients ≥45 years of age, LN metastases (N1 status) with T1–T3 status, N1b status with a carcinoma of ≥3.0 cm, a ratio of metastatic LNs to total LNs of ≥0.42, and lateral/mediastinal cervical involvement in patients ≥45 years of age were associated with a poor prognosis [3, 10–15]. Furthermore, lateral/mediastinal nodal metastasis is reported to be associated with recurrence [16].

Superior mediastinal LN metastasis is classified as lateral cervical node metastasis (N1b) under the AJCC/UICC TNM system. The lymphatic flow in the thyroid gland, as described below, drains into the central mediastinal compartment. This direction of flow suggests that the superior mediastinal LNs are the next metastasis target in the central compartment. It is therefore appropriate that superior mediastinal LN metastasis is classified as lateral cervical node metastasis. In our series, there were no significant survival differences between patients with superior mediastinal metastasis dissected by the transcervical approach and those without. Moreover, the survival difference between patients with superior mediastinal metastasis dissected by the transcervical approach and the patients with cervical metastasis under the N1b category without superior mediastinal metastasis (n = 198) was not significant (92.0% *vs*. 93.3%, respectively; $p = 0.778$, log-rank test).

The lymphatic pathways in the thyroid gland are intricate, and are interconnected with those of the larynx, trachea, recurrent laryngeal nerve, and cervical great vessels. The periglandular lymph network is primarily drained in 2 ways: the primary lymph drainage system comprises LNs and lymph vessels in the central compartment, which stretches down pre- and paratracheally. From that location, lymph drainage can connect to the superior mediastinal nodes. The secondary lymph drainage system is located in the lateral region and includes the lymph vessels and nodes along the jugular vein. There are also direct lymphatic communications in the lateral cervical nodes, which drain into the superior mediastinal nodes *via* central compartment nodes [7, 17].

The route for metastases from the contralateral cervical node to the superior mediastinal node has been hypothesized to follow a downward retrograde route to the mediastinum following an interruption of lymphatic circulation to the ipsilateral nodes. The route may also flow adjacent to the contralateral nodes and through the central nodes. This ultimately results in mediastinal LN metastasis [18, 19].

Consistent with previous reports, patients with superior mediastinal metastases in this study had higher frequencies of central compartment, ipsilateral, and contralateral nodal metastases. However, these variables were not predictive factors for superior mediastinal metastasis. Machenes *et al*. [20] examined the risk factors that may trigger mediastinal LN metastasis and reported that poor tumor differentiation and distant metastasis represented the sole significant factors. Although some predictive factors in our study were consistent with theirs as determined by univariate analysis, the significant factors we determined using a multivariate logistic regression model (age of 45 years or older and a greater total number of cervical LN metastases) did not correspond to those in their report. Since all patients with tracheobronchial LN metastasis also

had thoracic paratracheal LN metastasis, it is likely that these LN metastases were seeded through common pathways.

The incidence of mediastinal metastasis has been reported to range from 2.7% to 22% [3, 7, 19–21]. The frequency of mediastinal metastases in patients with clinical cervical metastasis was higher [5, 7, 22]. Although not an uncommon procedure, there is no consensus on the indication for SMD, including for prophylactic dissection. It has been suggested that the superior mediastinal LNs should be completely removed during central compartment LN resection because these nodes are in direct anatomic continuity with the paratracheal region, and SMD through a cervical incision can be undertaken safety [7, 23, 24]. It has also been suggested that the superior mediastinal LNs should be removed if radiologic evidence of a tumor in the compartment is present [20, 25]. We adopted the latter indication for SMD. Locoregional recurrences in the superior mediastinal components occurred in only 3 patients (0.6%), all of whom belonged to the original superior mediastinal metastasis group.

In conclusion, superior mediastinal metastases were independent predictive factors for recurrence-free survival in PTC patients. The main variables predicting superior mediastinal metastasis were being 45 years of age or older, and having a greater total number of cervical LN metastases.

Author Disclosure Statement

No competing financial interests exist.

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