Surgical indications for upper mediastinal dissection by sternotomy in patients with papillary thyroid carcinoma

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Abstract. Papillary thyroid carcinoma (PTC) is a relatively indolent disease, despite the high incidence of lymph node metastases. Although less frequent, some upper mediastinal metastases of PTC cannot be removed without sternal resection. In this study, we investigated the prognostic impact of upper mediastinal dissection (UMD) by sternotomy on patients with mediastinal metastases of PTC. Charts of patients with PTC who underwent surgical treatment at our institution between 2006 and 2018 were retrospectively reviewed. Fifty-eight patients with upper mediastinal metastases were enrolled. Kaplan–Meier survival curves were compared, and Cox hazard regression models were used for analyses. Of the 58 patients with mediastinal metastasis, 12 (20.7%) underwent dissection of the prevascular nodes, 51 (87.9%) underwent dissection of the upper paratracheal nodes, and 14 (24.1%) underwent dissection of the lower paratracheal node. The preferred site of mediastinal metastasis was the upper paratracheal nodes. The 5 and 10-year disease-specific survival rates for patients after UMD were 74.6% and 58.7%, respectively. Among 25 patients (43.1%) with locoregional recurrence, 12 (20.7%) had mediastinal recurrence and 7 were eligible for additional UMD. Although distant metastasis was the predominant poor prognostic factor, mediastinal recurrences were more frequently unresectable than cervical recurrences, suggesting that mediastinal recurrence is a poor prognostic factor. Mediastinal metastases larger than 30 mm or metastases to the lower paratracheal nodes are considered a risk factor for mediastinal recurrence. UMD by sternotomy for patient with upper mediastinal metastases which are difficult to resect via the transcervical approach is an effective treatment option to improve patient prognosis.

Key words: Mediastinal metastasis, Upper mediastinal dissection, Sternotomy, Papillary thyroid carcinoma, Prognosis

THE FREQUENCY of mediastinal metastasis of papillary thyroid carcinoma (PTC) ranges from 0.7% to 27% [1-5]. Most reports on upper mediastinal dissection (UMD) for differentiated thyroid carcinoma have been concerned with UMD outcomes via the transcervical approach consecutive to central neck dissection [1-4, 6, 7]. There are few reports on UMD using sternotomy [5, 8]. The frequency of mediastinal metastases requiring sternotomy is low, and surgical treatment of UMD via sternotomy requires more invasive surgery. Therefore, the fact that such metastases are not considered an indication for surgery may be one of the major reasons for the lack of reports.

In our previous study on prognosis and recurrence in patients with PTC with upper mediastinal metastases, the prognosis of patients with upper mediastinal metastasis dissected via the transcervical approach was no different from that of patients without mediastinal metastases. However, the prognosis of patients with upper mediastinal metastasis dissected by sternotomy was significantly poorer compared to the other two groups [9]. In this study, we investigated which patients with mediastinal metastases would benefit from UMD by sternotomy.

Materials and Methods

The medical records of PTC patients who underwent surgical treatment at the Oumi medical center between 2006 and 2018 were retrospectively reviewed. Patients who underwent UMD by sternotomy, including those treated for recurrence, were enrolled in the study. We examined clinicopathological features, reasons for sternotomy, survival outcomes, and the risk factors for recurrence in the mediastinum for patients with mediastinal metastasis and dissected by sternotomy.

Surgical methods

Three surgical methods for approaching upper...
mediastinum were utilized in this study, reversed-T upper mini-sternotomy, total sternotomy or partial resection of the manubrium and the sternoclavicular joint. Reversed-T upper mini-sternotomy involved a midline incision from the manubrium to the level of transverse sectioning, which was made at the second or third intercostal level without damaging the penetrating branch of the internal thoracic artery. Partial segmental resection of the manubrium and the sternoclavicular joint was defined as partial or subtotal resection of the manubrium and partial resection of the ipsilateral sternoclavicular joint without dislocation of the clavicle.

**Surgical indications**

Surgical indications for UMD were existence of metastases in the prevascular, upper or lower paratracheal nodes in the mediastinum. For patients with successive upper mediastinal metastases in the upper paratracheal nodes, UMD was performed via the transcervical approach. UMD using sternotomy was performed for patients suspected of having a large upper mediastinal metastasis, surrounding organ invasion in the upper mediastinal compartment, lymph node (LN) metastasis in the brachiocephalic vein or artery proximal side, lower paratracheal LN metastasis. Only mediastinal nodes suspected of metastasis on preoperative imaging were dissected, and prophylactic UMD using sternotomy was not performed.

**Preoperative diagnosis and postoperative follow-up**

Upper mediastinal LN metastases were evaluated by enhanced computed tomography. Upper mediastinal LN swelling larger than 1 cm, suspected surrounding organ invasion in the mediastinal compartment, or those continued from the cervical lesion were diagnostic criteria for mediastinal LN metastasis by preoperative imaging. Ablation of the remnant thyroid or radioactive iodine treatment was performed in patients with distant metastasis but not as adjuvant therapy for patients after UMD. 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.

**Definitions**

The upper mediastinal LN compartment extends 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 classified into three categories, those containing the prevascular nodes (#3a), upper paratracheal nodes (#2R, #2L), lower paratracheal nodes (#4R, #4L), according to the international association for the study of lung cancer lymph node map [10] (Fig. 1). The boundaries between the cervico-paratracheal nodes and upper mediastinal nodes define the superior thoracic aperture under the neck extension position.

Extrathyroidal invasion 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).

Extranodal invasion (LN-Ex) was defined as the intraoperative detection of gross invasion by LN metastasis into the surrounding organs.

**Ethical considerations**

The study was conducted according to the Code of Ethics of the hospital (2021-0063). Patient privacy was strictly maintained, and informed consent was obtained.

**Statistical analyses**

Groups were compared using the Mann–Whitney U test or the chi-square test, as appropriate. Kaplan–Meier survival curves were compared for statistical significance using the log-rank test. A Cox hazard regression model with the forward stepwise method was used for the multivariate analysis to determine their association with mediastinal recurrence. Commercially available software (BellCurve for Excel; SSRI Co., Ltd., Tokyo, Japan) was used for all statistical analyses. Significance was defined as a p-value < 0.05.

**Results**

Over the study period, out of 645 patients who underwent surgery for PTC, 58 patients with mediastinal metastases who underwent UMD using sternotomy were enrolled in this study. Fifty-three (91.4%) patients were referred to our hospital for surgical treatment. The follow-up duration (mean ± standard deviation) after surgery was 5.9 ± 4.4 years. The patients with mediastinal metastases included 28 (48.3%) men and 30 (51.7%) women. Among the 58 patients, mediastinal metastasis was identified at initial PTC diagnosis in 22 (37.9%) patients. In the other 36 (62.1%) patients, mediastinal metastasis was diagnosed as relapsing PTC. The median age of the patients at the time of surgery was 63.9 years (range, 29–92 years, Table 1).

Surgical indications for UMD using sternotomy were large upper mediastinal LN metastasis in 14 (24.1%, all patients had LN metastasis larger than 4 cm) patients, suspicion of surrounding organ invasion in the mediastinal compartment in 35 (60.3%) patients, LN metastasis in the proximal side of a brachiocephalic vein or artery in 7 (12.1%) patients, suspicion of the lower paratracheal LN metastasis in 14 (24.1%) patients. Among the 58 patients with mediastinal metastasis, 21 (36.2%) underwent UMD by reversed-T upper mini-sternotomy, and 36 (62.1%) underwent partial resection of the manubrium and sternoclavicular joint. Only 1 patient underwent UMD by total sternotomy (Table 2).

Forty-five patients (77.6%) underwent cervical surgery, including 23 patients with cervical recurrence and mediastinal recurrence and 22 initially treated patients. The patients without metastases in the lateral neck (8.6%) did not receive lateral neck dissections. Fifteen initially treated patients had an extrathyroidal invasion. Thirty patients (51.7%) had LN-Ex in the neck. Of the 58 patients with mediastinal metastasis, 12 (20.7%) underwent dissection of the prevascular nodes, 51 (87.9%) underwent dissection of the upper paratracheal nodes, and 14 (24.1%) underwent dissection of the lower paratracheal nodes (Table 3).

**Table 1** Baseline patient characteristics

| Age, y | 63.9 (29–92) |
| Sex   | Male 28 (48.3%) | Female 30 (51.7%) |
| Initial treatment | Stage I 6 (10.3%) | Stage II 5 (8.6%) | Stage III 5 (8.6%) | Stage IVA 1 (1.7%) | Stage IVB 5 (8.6%) |
| Recurrent treatment | 36 (62.1%) |
| DM before UMD | 16 (27.6%) |

Abbreviations: y, years; UMD, upper mediastinal dissection; DM, distant metastasis

**Table 2** Surgical indications for UMD using sternotomy

| UMD indication                          | Large mediastinal metastasis | 14 (24.1%) |
|----------------------------------------|------------------------------|------------|
| Suspicion of mediastinal organ invasion |                              | 35 (60.3%) |
| LN metastasis in the proximal side of brachiocephalic vein or artery | 7 (12.1%) |
| Suspicion of the lower paratracheal metastasis | 14 (24.1%) |

| Surgical approach for upper mediastinum | Partial segmental resection of the manubrium and the sternoclavicular joint 36 (62.1%) | Reversed-T upper mini-sternotomy 21 (36.2%) | Total sternotomy 1 (17%) |

Abbreviations: UMD, upper mediastinal dissection; LN, lymph node
The mean number (range) of dissected LNs and the mean number (range) of metastatic LNs in the prevascular nodes, the upper paratracheal nodes, or the lower paratracheal nodes were 3.4 (1–7) and 2.0 (1–6), 4.1 (1–12) and 1.9 (1–10), 4.3 (1–7) and 2.2 (1–6). All patients with metastases in the lower paratracheal nodes had metastases in the upper paratracheal or prevascular nodes. LN-Ex in the prevascular nodes, the upper paratracheal nodes, or the lower paratracheal nodes was noticed in 1 patient, 23 patients, 3 patients. LN metastasis larger than 30 mm in the prevascular nodes, the upper paratracheal nodes, or the lower paratracheal nodes was noticed in 1 patient, 28 patients, 3 patients (Table 4).

The 5 and 10-year disease-specific survival (DSS) rates for patients after UMD were 74.6% and 58.7%, respectively (Fig. 2). Median disease-free survival for 42 patients excluded 16 patients with distant metastasis before UMD was 55.9 months (Fig. 3). Median locoregional free survival for 58 patients was 72.3 months (Fig. 4). Distant metastases were found during the postoperative observation period in 18 patients (31.0%). More than 50% of the patients had distant metastases when combined with distant metastases before UMD. Twenty-seven patients (46.6%) died, among whom 15 (25.9%) died owing to distant metastases, 3 (5.1%) owing to locoregional disease progression, 2 (3.4%) had early death due to mediastinitis or injury to the brachiocephalic artery following clavicular resection and mediastinal dissection, and 7 (12.1%) died owing to other diseases. Eleven patients with distant metastases were alive at the end of the observation.

Table 3  Dissected regions in the neck or mediastinum

| Dissected regions in the neck | None | 13 (22.4%) |
|------------------------------|------|------------|
|                              | Central compartment | 5 (8.6%) |
|                              | Lateral neck (affected side) | 24 (41.4%) |
|                              | Lateral neck (bilateral sides) | 16 (27.6%) |

| Dissected region in the mediastinum | Prevascular region | 12 (20.7%) |
|-------------------------------------|--------------------|------------|
| Upper paratracheal region           | 51 (87.9%)         |
| Lower paratracheal region           | 14 (24.1%)         |

Table 4  The mean number of dissected LNs and the mean number of metastatic LNs in the upper mediastinal nodes

| Dissected region in the mediastinum | Mean No. of metastatic LNs | Mean No. of dissected LNs | LN-Ex in the mediastinum | LN metastasis >30 mm |
|-------------------------------------|---------------------------|---------------------------|--------------------------|----------------------|
| Prevascular nodes                   | 2                         | 3.4                       | 1                        | 1                    |
| Upper paratracheal nodes            | 1.9                       | 4.1                       | 23                       | 28                   |
| Lower paratracheal nodes            | 2.2                       | 4.3                       | 3                        | 3                    |

Abbreviations: No., number; LN-Ex: extranodal invasion; LN, lymph node

Locoregional recurrences were found in 25 patients (43.1%). Thirteen (22.4%) and 12 (20.7%) had a cervical recurrence and mediastinum recurrence, respectively. Among the 13 patients with cervical recurrence, one was inoperable due to extensive invasion with suspected anaplastic transformation, but the other 12 patients...
underwent surgery for recurrence. In contrast, among the 12 patients with mediastinal recurrence, 7 were eligible for additional mediastinal dissection. Compared with the rate of salvage surgery for patients with cervical recurrence, that for patients with mediastinal recurrence was low.

Complications associated with mediastinal dissection were observed in 12 patients (20.7%). Pleural effusion was observed in 4 patients (6.9%), lymphatic leakage in 3 (5.2%), postoperative bleeding in 2 (3.4%), postoperative infection in 4 (6.9%), and pneumothorax in 1 (1.7%). All four patients with postoperative infections underwent tracheostomy. Serious complications (mediastinitis: 1, brachiocephalic artery rupture: 1) occurred in two patients.

Various clinical, operative and pathological variables such as age, previous surgery, distant metastasis at the time of mediastinal surgery, number of mediastinal metastases, mediastinal metastasis larger than 30 mm, LN-Ex in the mediastinum, or presence of metastasis in the lower paratracheal nodes were analyzed to determine their association with mediastinal recurrence. The predictors of mediastinal recurrence according to multivariate analysis were mediastinal metastasis larger than 30 mm and the presence of metastasis in the lower paratracheal nodes (Table 5).

**Discussion**

In this study, we examined the preferred sites of mediastinal metastasis in patients with PTC and their prognosis after mediastinal dissection. We investigated which patients with mediastinal metastases would benefit from UMD by sternotomy. The preferred site of mediastinal metastasis was the upper paratracheal nodes. The 5- and 10-year DSS after UMD was 74.6% and 58.7%, respectively. Although distant metastasis was the predominant poor prognostic factor, tumors of patients with mediastinal recurrence were more unresectable than those of patients with cervical recurrence, suggesting that mediastinal recurrence is a poor prognostic factor. Mediastinal metastases larger than 30 mm or metastases to the lower paratracheal nodes are considered a risk factor for mediastinal recurrence. Although surgical indication in patients with these factors on preoperative evaluation should be carefully considered, UMD by sternotomy for patient with upper mediastinal metastases which are difficult to resect via transcervical approach is an effective treatment option to improve patient prognosis.

The lymphatic pathways in the thyroid gland are complex and interconnected with those of the larynx, trachea, recurrent laryngeal nerve, and cervical great vessels. The peri-glandular lymph network primarily has two drainage pathways. The primary lymph drainage system comprises the lymph vessels in the central compartment, which stretch down along the pre-and para-trachea to the upper mediastinal nodes. The secondary lymph drainage system consists of lateral lymph vessels along the jugular
There are also direct lymphatic communications in the lateral cervical nodes, which have lymphatic communications to the upper mediastinal nodes via central compartment nodes. The lymphatic flow associated with the thyroid gland indicates that the most favorable site for mediastinal metastasis of PTC is the upper mediastinum [11].

In our series, surgical indications for UMD were metastases in the prevascular, upper and lower paratracheal-tracheal nodes in the mediastinum. All patients with metastases in the lower paratracheal nodes had metastases in the upper paratracheal or prevascular nodes in the mediastinum. There was no skip metastasis to the lower paratracheal nodes without metastasis in the upper paratracheal or prevascular nodes. The frequency of metastasis in the lower paratracheal nodes was also lower than that in the other two nodes. Based on the distribution of mediastinal LN metastases and mediastinal lymphatic flow, UMD using total sternotomy is rarely indicated, and most mediastinal metastases can be dissected by reversed-T upper mini-sternotomy or partial resection of the manubrium and sternoclavicular joint.

Risk factors for mediastinal metastasis include LN metastases in the pre-tracheal, paraesophageal, and lateral regions of the neck, especially in the lateral region, including the contralateral neck [8, 12-14]. Other reports depict tumors larger than 15 mm, extrathyroidal extension, lymphovascular invasion, recurrent surgery, and distant metastasis as the risk factors at the time of surgery [1, 15]. However, most of these reports are related to UMD via the transcervical approach, and few are related to the efficacy of therapeutic mediastinal metastases requiring sternotomy [8, 9, 16]. Although this study was about UMD by sternotomy, both lateral neck metastases and extrathyroidal invasion or LN-Ex were frequently observed, as described above.

Our results showed that the 5, 10-year DSS rate after UMD by sternotomy was 74.6% and 58.7%, respectively. The main cause of death was distant metastasis. Death owing to locoregional disease progression was noticed in 3 (5.1%) patients. Conversely, the locoregional recurrence rate in the neck or mediastinum was high (43.1%). More patients with mediastinal recurrences failed salvage surgery compared to those with cervical recurrences. These results indicate that salvage surgery for mediastinal recurrence is more difficult than for cervical recurrence, and uncontrolled locoregional recurrence leads to death. Surgery for recurrence after UMD is more difficult in disease progression due to delayed recurrent tumor detection or the risk of mediastinal organ damage during salvage surgery. In this study, the main variable predicting mediastinal recurrence according to multivariate analysis was mediastinal metastases larger than 30 mm or metastases to the lower paratracheal nodes.

Table 5  Multivariate analysis of the main variable predicting mediastinal recurrence

| Variable                        | B     | Wald  | p-value | Hazard ratio | 95% CI            |
|---------------------------------|-------|-------|---------|--------------|-------------------|
| Recurrent treatment             | 0.9449| 1.9351| 0.1642  | 2.5724       | 0.6795–9.7387     |
| Lower paratracheal metastasis   | 1.3339| 3.9377| 0.0472  | 3.7958       | 1.0165–14.1739    |
| Mediastinal metastasis larger than 30 mm | 1.5093 | 4.7393 | 0.0295  | 4.5236       | 1.1624–17.6047    |

Abbreviations: B, partial regression coefficient; CI, confidence interval

In conclusion, PTC patients who underwent UMD by sternotomy could expect a 10-year survival prognosis of approximately 60%. However, locoregional recurrences were common; especially mediastinal recurrences were more frequently unresectable than cervical recurrences. Mediastinal metastases larger than 30 mm or metastases to the lower paratracheal nodes are considered a risk factor for mediastinal recurrence. UMD by sternotomy for patients with upper mediastinal metastases which are difficult to resect via transcervical approach is an effective treatment option to improve patient prognosis.

Disclosure

No competing financial interests exist.
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