



# Lymph Node Progression and Optimized Node Dissection of Middle Thoracic Esophageal Squamous Cell Carcinoma in the Latest Therapeutic Surgical Strategy

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## ABSTRACT

**Purpose.** The aim of this study is to elucidate the optimized lymph node dissection range in middle thoracic (Mt) esophageal squamous cell carcinoma (ESCC) requiring surgery.

**Patients and Methods.** We retrospectively analyzed 165 ESCC patients who underwent surgery with curative intent between 2009 and 2016, including 99 (60%) with MtESCC. Preoperative chemotherapy was administered in more than 80% of cStage II/III MtESCC patients. The rates of pathological and potential metastasis (representing recurrences) to lymph nodes and prognosis (median follow-up 52 months) were clarified. Lymph node dissection efficacy was assessed by calculating the efficacy index (EI) for each lymph node.

**Results.** No. 2R had the highest rate of metastasis, with frequencies of 13/38/46% in cStage I/II/III, respectively, with the highest EI in MtESCC. Recurrences were seen in about 2–10% in the regional (nos. 1, 2L, 4R, and 10) and extraregional lymph nodes (paraaortic lymph node). The EI of lymph nodes was found to exhibit the highest score of 15

for no. 2R, followed by 11.5 for no. 17. The 5-year overall survival (OS) in MtESCC patients who underwent no. 2R lymph node dissection was 73.8%, while those who did not undergo no. 2R dissection did never reach 5-year OS ( $P = 0.002$ ).

**Conclusions.** Meticulous lymph node dissection of no. 2R is the most important for long-term survival, and mandatory with the highest priority in MtESCC.

Esophageal cancer is the eighth most common cancer and the sixth leading cause of cancer-related death worldwide.<sup>1</sup> The patterns of regional lymph node recurrence are related to the tumor location.<sup>2</sup> In Japan, esophageal cancer requiring esophagectomy is located most dominantly in the middle thoracic (Mt) esophagus (45.2%),<sup>3</sup> but there have been few reports on the distribution of lymph node metastasis (LNM) limited to MtESCC.

MtESCC is surrounded by critical organs such as the left main bronchus, aorta, and bronchial veins. Moreover, the absence of intramuscular lymphatic vessels in the middle mediastinal zone causes skip LNM in thoracic ESCC,<sup>4</sup> which exhibit poor prognosis compared with adjacent LNM.<sup>5,6</sup> Subcarinal LNM also indicated poor survival rate,<sup>7</sup> and its dissection might have little value in patients with thoracic ESCC, especially for superficial carcinoma.<sup>8</sup>

In addition to lymphadenectomy in the middle and lower posterior mediastinum, extension along the right side of trachea and upper mediastinum is termed extended lymphadenectomy, and the benefit of extended versus standard lymphadenectomy has been debated between advocates<sup>9,10</sup> and opponents.<sup>11</sup> In particular, extended lymphadenectomy

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is likely to significantly affect prognosis for patients with MtESCC.<sup>10,11</sup> On the other hand, there have also been no reports limited to MtESCC patients describing that three-field lymph node dissection (3-FLD) improved 5-year overall survival (OS) as compared with two-field lymph node dissection (2-FLD). Nevertheless, clinical practice often includes cervical lymph node dissection, as short-term outcome was not deteriorated by 3-FLD in thoracic ESCC patients.<sup>12</sup>

We have developed novel potent chemotherapeutic regimens to control early treatment failure in clinical stage (cStage) II/III ESCC by neoadjuvant chemotherapy (NAC) with a docetaxel (DTX)/cisplatin (CDDP)/5-FU (DCF) regimen,<sup>13,14</sup> showing better prognosis than standard CDDP/5-FU (CF) NAC.<sup>15</sup> Clarification of the LNM recurrence pattern with such latest treatment strategies will be useful for developing future considerations of new treatments, as recently reported in lower thoracic (Lt) ESCC.<sup>16</sup>

In this study, patients with MtESCC were assessed with regard to the rates of LNM allowing for recurrence in the context of the latest multimodality treatments, as well as their influence on patient prognosis. These data could be important for determining the optimal range of lymph node dissection in MtESCC.

## PATIENTS AND MATERIALS

### Patients

A prospective database of 464 patients with thoracic ESCC, provided by the esophageal cancer board of Kitasato University Hospital between 2009 and 2016, was analyzed. Among 165 patients who had initially undergone surgery, 98 were diagnosed with MtESCC, excluding 1 with cStage IV cancer. Median follow-up was 51.8 months (range 12.1–108.1 months). This study was conducted in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee of Kitasato University School of Medicine. Tumor stage was classified according to the 7th edition of the Union for International Cancer Control (UICC) TNM. The definition of positive LNM was a short diameter of 1 cm on computed tomography (CT), as previously described.<sup>16</sup> Sensitivity was excellent, while specificity was unsatisfactory. To supplement this unsatisfactory specificity, maximum standardized uptake value (SUVmax) on positron emission tomography (PET)-CT was also considered in the multidisciplinary tumor board (MTB) for esophageal cancer, while it was not mandatory.

### NAC Treatments in cStage II/III ESCC

Patients received three cycles of DCF NAC every 3 weeks, consisting of DTX 70–75 mg/m<sup>2</sup>, CDDP 70–75 mg/m<sup>2</sup>, and 5-FU 750 mg/m<sup>2</sup>, as described previously.<sup>14</sup> CF NAC is a standard treatment described elsewhere in Japan.<sup>15</sup>

### Surgical Treatment

Standard esophagectomy was performed according to the McKeown method (i.e., right thoracotomy followed by laparotomy and neck incision with cervical anastomosis), and three-field (thoracoabdominal and cervical) lymph node dissection was also performed if the attending physician considered it feasible, as previously described.<sup>16</sup>

### Efficacy Index (EI)

The efficacy index of lymph node dissection was defined to evaluate the contribution of dissection at each lymph node to the survival rate. The EI was calculated by multiplying the rate of metastases at each lymph node and the 5-year overall survival rate of patients with metastases to that lymph node, as previously described.<sup>9,17</sup>

### Statistical Analysis

All statistical analyses were performed using JMP<sup>®</sup> 14 software (SAS Institute Inc., Cary, NC). Frequency tables were analyzed using the  $\chi^2$  test, with the likelihood ratio or Fisher's exact test used to determine significance of differences between categorical variables. Overall survival (OS) was measured from date of death or censored at date of last follow-up evaluation, as described previously.<sup>16</sup>

## RESULTS

### Prognosis of MtESCC Patients Who Underwent Surgery with Curative Intent

Surgery was initially performed with curative intent in 165 thoracic ESCC patients. Thoracotomy was considered as surgical treatment, but excluded from analyses with regard to LNM. Five-year OS was 60.8, 68.3, and 65.3% in upper thoracic (Ut) ( $n = 19$ ), Mt ( $n = 99$ ), and Lt ESCC ( $n = 47$ ), respectively ( $P = 0.9229$ ; Fig. 1a).

The characteristics of the MtESCC patients are presented in Table 1 after excluding  $n = 1$  cStage IV case. The 98 MtESCC patients were distributed in cStage I ( $n = 48$ ), cStage II ( $n = 22$ ), and cStage III ( $n = 28$ ), and included 2/1/4 patients who had thoracotomy in cStage I/II/

III, respectively. Thoractomy in cStage I was due to sticky pleural adhesion, and definitive CRT was applied in such cases. Video-assisted thoracic surgery (VATS) esophagectomy was performed more frequently in earlier than more advanced stage ( $P < 0.0001$ ). The median number of lymph nodes resected at surgery was 44 (range 9–96). The 43 MtESCC patients in cStage II/III received neoadjuvant chemotherapy (NAC). The response to NAC was as follows: complete response (CR) in 2, partial response (PR) in 23, stable disease (SD) in 16, and progressive disease (PD) in 2. The two patients with CR both survived. Those with PD did not reach 5-year OS. However, there was no statistically significant difference in prognosis according to chemotherapy response ( $P = 0.5152$ ) (Supplementary Fig. 1).

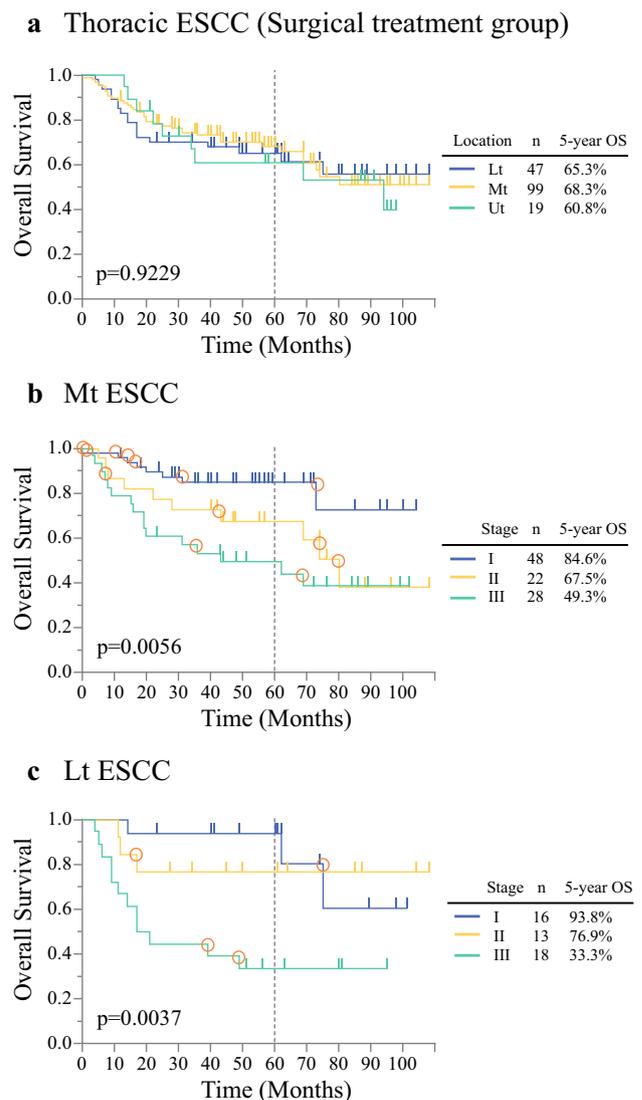
In MtESCC patients, the 5-year OS rate was 84.6% in cStage I, 67.5% in cStage II, and 49.3% in cStage III ( $P = 0.0056$ ), and OS decreased with higher cStage (Fig. 1b). In LtESCC patients, these percentages were 93.8% in cStage I, 76.9% in cStage II, and 33.3% in cStage III ( $P = 0.0037$ ) (Fig. 1c). Circles in Fig. 1b, c indicate deaths due to other disease. The features of prognosis differed between MtESCC and LtESCC according to cStage. Death due to other disease occurred more among MtESCC patients (13, 13.3%) than among LtESCC patients (4, 8.5%) ( $P = 0.4049$ ).

Regarding the range of lymph node dissection, 3-FLD was almost always performed (82/91, 90.1%). Either CF or DCF NAC was applied in 43/50 (86.0%) with cStage II/III MtESCC. Some of the patients with cStage II/III MtESCC did not receive NAC; the reasons included age over 75 years, renal dysfunction, significant weight loss, and other diseases with steroid treatment at high dose. DCF NAC was performed in 59.1% (13/22) and 60.7% (17/28) of patients with cStage II and III MtESCC, respectively. Unexpectedly, lymph node recurrence was recognized even in cStage I, so there was no statistical significance of LNM recurrence rates according to cStage.

The lymph node dissection rates of MtESCC and LtESCC patients are compared in Fig. 2a, b. The lymph node dissection range was similar between MtESCC and LtESCC, but there were statistically different rates of dissection of lymph node no. 16 (100% versus 95.6%,  $P = 0.0428$ ), no. 18 (9.9% versus 31.1%,  $P = 0.0026$ ), no. 19 (2.19% versus 22.2%,  $P = 0.0002$ ), and no. 20 (31.9% versus 51.1%,  $P = 0.0298$ ) (Fig. 2a, b).

#### Distribution of LNM and Metastatic Rates (Including Recurrences) in Patients with MtESCC and Esophagectomy

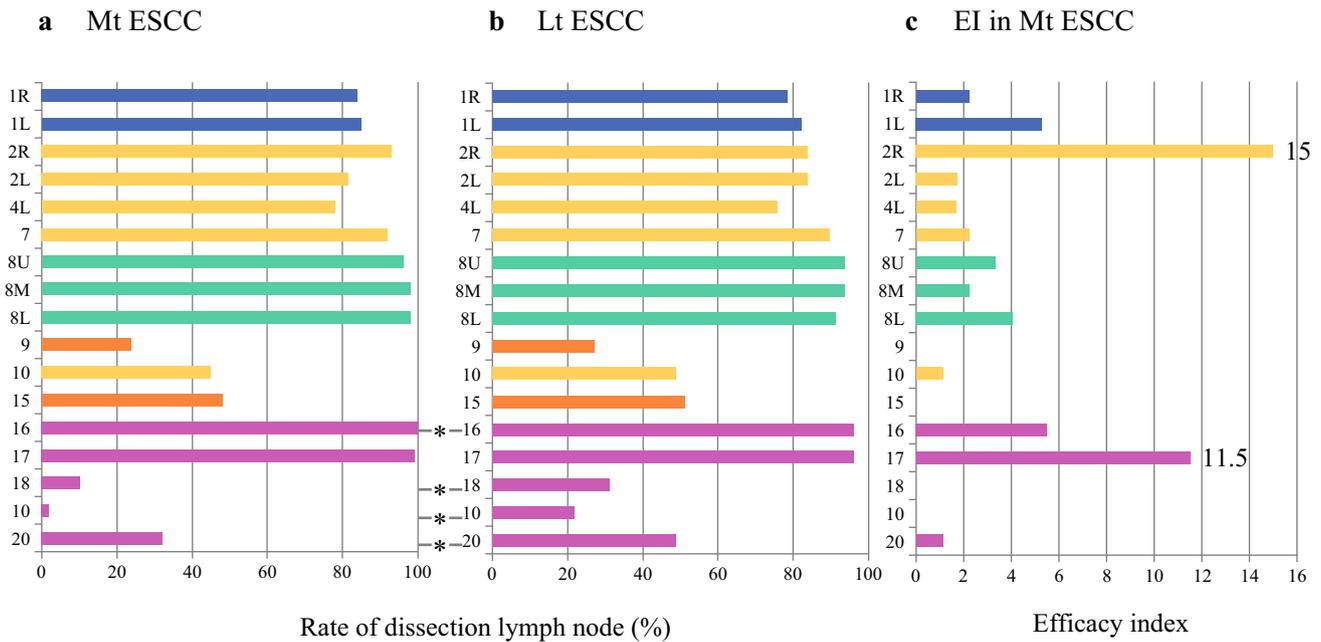
Allowing for lymph node recurrences in combination with pathological LNM was defined as potential LNM



**FIG. 1** a Five-year OS rates for patients who underwent surgical treatment according to tumor location (Ut, upper thoracic; Mt, middle thoracic; Lt, lower thoracic). Five-year OS rates for patients with (b) middle thoracic esophageal squamous cell carcinoma (MtESCC) in cStage I/II/III and (c) lower thoracic esophageal squamous cell carcinoma (LtESCC) in cStage I/II/III

(Fig. 3). Blue circles represent LNM with recurrence, and the rate of the potential LNM was calculated in contrast to the yellow circle (LNM with no recurrence).

The rate of metastasis for each lymph node, according to cStage, is shown in Fig. 3a (cStage I), 3B, (cStage II), and 3C (cStage III). In cStage I MtESCC patients, metastases to lymph node were rather frequent in skip lymph node areas, e.g., no. 2R and abdominal no. 17, compared with the adjacent lymph node area (no. 8M and 8L), and this tendency was preserved from cStage I to cStage III. Unexpectedly, LNM in the subcarinal region (nos. 7 and 10L) was infrequent, occurring in 2.2, 4.8, and 16.7% in



**FIG. 2** Frequency of lymph node dissection in (a) MtESCC and (b) LtESCC. Blue, cervical and supraclavicular lymph node; yellow, paratracheal lymph node; green, paraesophageal lymph node; orange, lower mediastinal lymph node; purple, abdominal lymph node. The marks indicate statistically significant difference

lower mediastinal lymph node; purple, abdominal lymph node. The marks indicate statistically significant difference

cStage I, II, and III patients, respectively. The upper mediastinal area, especially no. 2R, is always the most dominant for LNM in MtESCC, while the abdominal area also became dominant as disease progressed. The efficacy index (EI) of the individual lymph nodes was calculated in MtESCC with esophagectomy (Fig. 2c). The highest EI was 15 for no. 2R, followed by 11.5 for no. 17.

Differently from LtESCC,<sup>16</sup> recurrences of regional LNM were recognized in cStage I MtESCC (Fig. 3a). Among the adjacent LNM around Mt tumor location, recurrences of left subcarina were unique, because this was never seen in LtESCC.<sup>16</sup> Although abdominal LNM became dominant in MtESCC as cStage progressed, recurrence was limited to only extraregional LNM [paraaortic lymph node (PALN)]. On the other hand, recurrences in the upper mediastinal and cervical area were sparsely found in cStage II (Fig. 3b) and cStage III MtESCC (Fig. 3c).

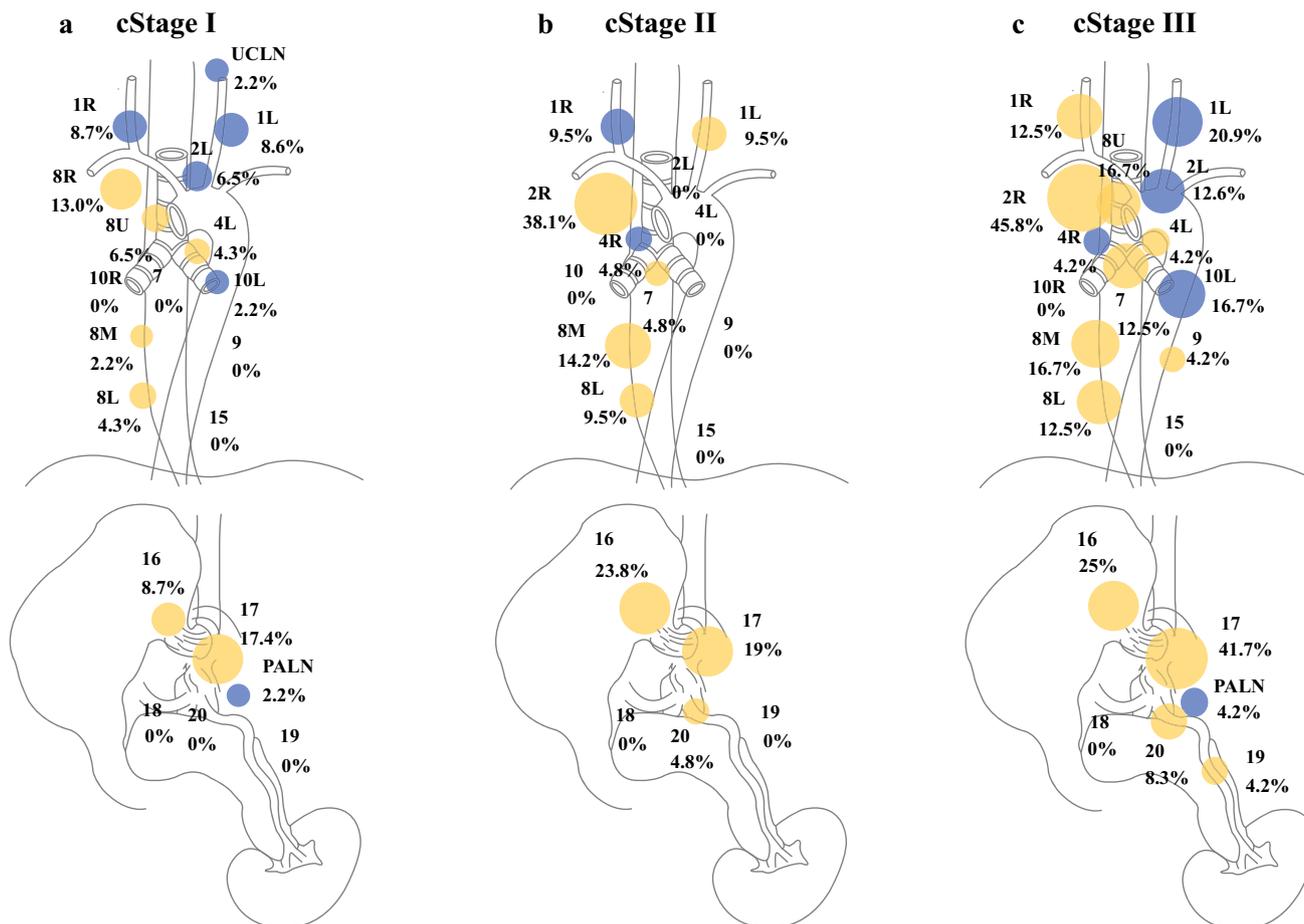
*Lymph Node Dissection Along No. 2R, 2L, and 4L and Prognosis in MtESCC*

The prognostic relevance of lymph node dissection around the recurrent laryngeal nerve (RLN) was then examined in 91 MtESCC patients with esophagectomy. The 5-year OS for cases undergoing lymph node dissection of no. 2R ( $n = 85$ ) was 73.8%, while that for those who did not undergo dissection ( $n = 6$ ) was 33.3% ( $P = 0.002$ ;

Fig. 4a). The 5-year OS for cases undergoing lymph node dissection of no. 2L ( $n = 75$ ) was 77.1%, while that for those who did not undergo dissection ( $n = 16$ ) was 43.8% ( $P = 0.002$ ; Fig. 4b). The 5-year OS rate for cases undergoing lymph node dissection of no. 4L ( $n = 71$ ) was 77.2%, while that for those who did not undergo dissection ( $n = 20$ ) was 50.0% ( $P = 0.003$ ; Fig. 4c).

There were 50 patients with cStage II/III MtESCC, of whom 45 underwent esophagectomy. We analyzed whether NAC contributed to prognosis in the no. 2R dissection group or no. 2R nondissection group in cStage II/III MtESCC. The 5-year OS rate for cases undergoing no. 2R lymph node dissection was 61.4% with NAC ( $n = 37$ ), in contrast to 66.7% with no NAC ( $n = 6$ ) ( $P = 0.8181$ ). The remaining two patients who did not undergo no. 2R dissection and received NAC were dead due to disease progression. There were no patients who did not undergo no. 2R and did not receive NAC. Therefore, no. 2R dissection might contribute to prognosis rather than NAC.

The characteristics of patients who underwent or did not undergo no. 2R dissection are presented in Supplementary Table 1, as well as for no. 2L. These results show that age and field of lymph node dissection were significantly associated with lymph node dissection for both no. 2 nodes. We then analyzed the prognosis for two groups (those who underwent no. 2R dissection versus those who did not, and the same for no. 2L) in elderly patients (aged 69 years or over). The 5-year OS rate for cases undergoing no. 2R



**FIG. 3** Rates of lymph node metastases (yellow) and lymph node recurrence (blue) by cStage in patients with MtESCC: **a** cStage I, **b** cStage II, and **c** cStage III. Yellow spheres represent the pathological lymph node metastases positive rate after esophagectomy. Blue spheres represent the recurrence rate of lymph node metastases after esophagectomy. The size of each ball represents the ratio. PALN, paraaortic lymph nodes. The relation between lymph nodes for the UICC 7th edition and the Japan Esophageal Society (JES) is as follows: UCLN = upper cervical lymph nodes = 102; 1R = right lower cervical and supraclavicular nodes = 101R and 104R; 1L = left lower cervical and supraclavicular nodes = 101L and

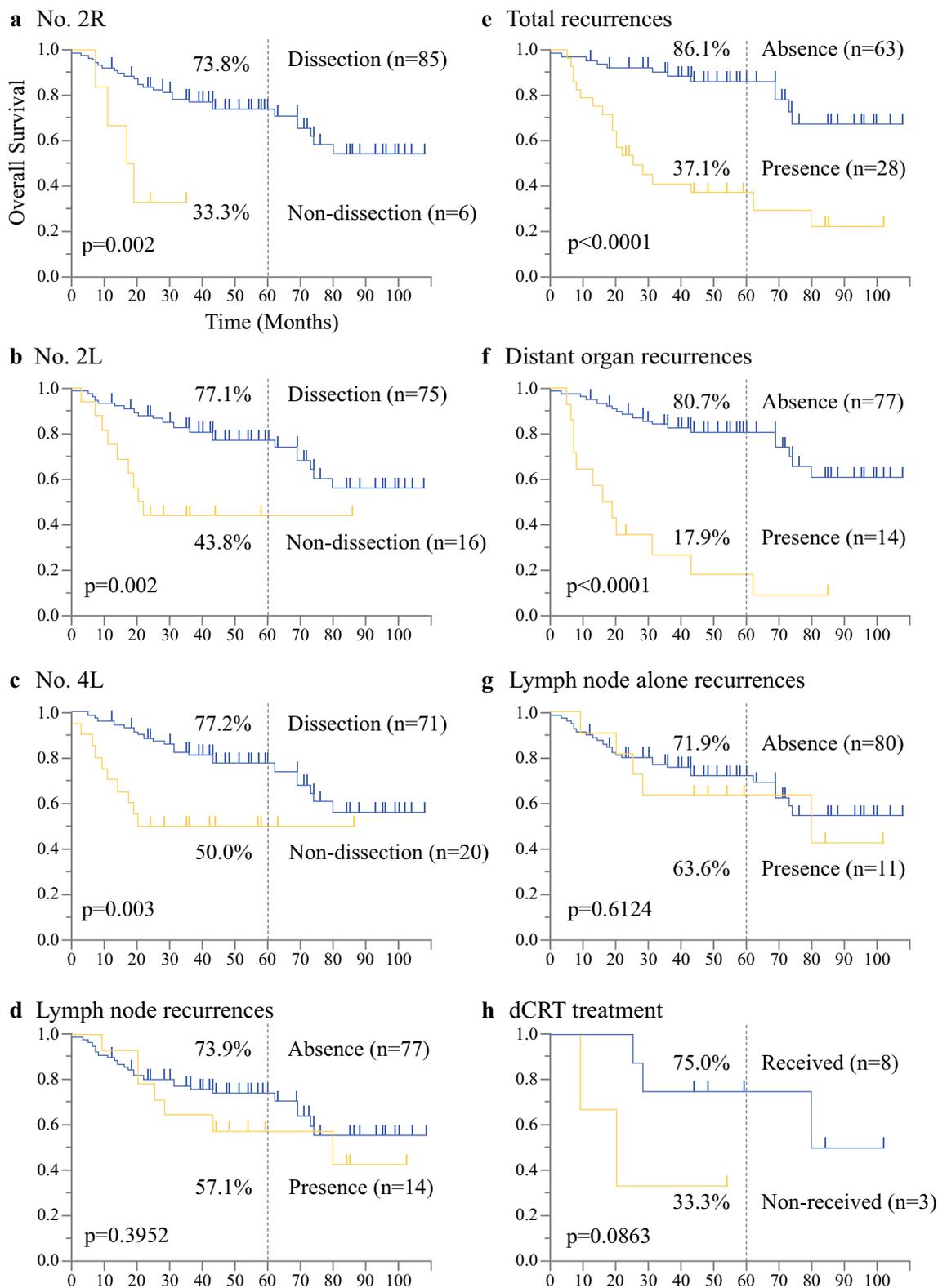
104L; 2R = right upper tracheal nodes = 106recR; 2L = left upper tracheal nodes = 106recL; 4L = left lower paratracheal nodes = 106tbl; 7 = subcarinal nodes = 107; 8U = upper thoracic paraesophageal nodes = 105; 8M = middle thoracic paraesophageal nodes = 108; 8L = lower thoracic paraesophageal nodes = 110; 9 = pulmonary ligament nodes = 112pul; 10 = tracheobronchial nodes = 109; 15 = diaphragmatic nodes = 111; 16 = paracardial nodes = 1 and 2; 17 = left gastric nodes = 3 and 7; 18 = common hepatic nodes = 8; 19 = splenic nodes = 10 and 11; 20 = celiac nodes = 9; PALN = paraaortic lymph nodes = 16

dissection ( $n = 39$ ) was 71.5%, while for those who did not undergo no. 2R dissection ( $n = 6$ ) it was 33.3% ( $P = 0.0186$ ). The 5-year OS rate for cases undergoing no. 2L dissection ( $n = 33$ ) was 78.3%, while for those who did not undergo no. 2L dissection ( $n = 12$ ) it was 33.3% ( $P = 0.0015$ ) (Supplementary Fig. 2). As a result, no. 2R/L dissections were likely to affect prognosis.

#### Curative Treatment after Lymph Node Recurrence in MtESCC

Among the 91 MtESCC patients with esophagectomy, recurrences of lymph nodes were seen in 14 cases (15.4%).

Intriguingly, MtESCC with esophagectomy did not show significantly differential prognosis, irrespective of lymph node recurrences (Fig. 4d,  $P = 0.3952$ ). This excellent outcome is very unique, because MtESCC with any type of recurrence showed significantly poorer prognosis than other cases (Fig. 4e,  $P < 0.0001$ ), when limited to that at distant organ (Fig. 4f,  $P < 0.0001$ ). Among the 14 recurrences of lymph nodes, recurrences of lymph node alone were found in 11 cases, and they showed relatively good prognosis (Fig. 4g), putatively due to definitive CRT (dCRT) having therapeutic potential to cure them (Fig. 4h,  $P = 0.0863$ ).



**FIG. 4** Five-year OS rates for patients who had dissection of lymph nodes (a) 2R, (b) 2L, and (c) 4L and those who did not in MtESCC. Five-year OS rates for patients with (d) lymph node recurrences, (e) total recurrences, (f) distant organ recurrences, and (g) lymph node

alone recurrences. (h) Five-year OS rates for patients with lymph node recurrences alone who received definitive chemoradiotherapy (dCRT) and those who did not

**TABLE 1** Patient characteristics of Mt ESCC with surgery according to UICC 7th edition

Variable	Number***	Total <i>n</i> = 98(91)	cStage I <i>n</i> = 48(46)	cStage II <i>n</i> = 22(21)	cStage III <i>n</i> = 28(24)	<i>P</i> value
Age (years)						0.0767
< 69		49	19	15	15	
≥ 69		49	29	7	13	
Gender						0.5938
Male		79	39	19	21	
Female		19	9	3	7	
Pathological T factor (pT)						< 0.0001
pT0		3	0	2	1	
pT1		52	40	9	3	
pT2		12	4	4	4	
pT3		24	2	6	16	
pT4		0	0	0	0	
Lymphatic invasion						0.2013
Presence		42	17	12	13	
Absence		49	29	9	11	
Venous invasion						0.5749
Presence		41	19	9	13	
Absence		50	27	12	11	
pStage						< 0.0001
IA		34	29	3	2	
IB		5	3	1	1	
IIA		6	0	4	2	
IIB		18	9	7	2	
IIIA		10	1	2	7	
IIIB		6	1	1	4	
IIIC		7	1	1	5	
IV		3	2	1	0	
X		7	2	1	4	
Complete response		2	0	1	1	
Procedure of esophagectomy						< 0.0001
Open esophagectomy		30	2	10	18	
VATS esophagectomy		61	44	11	6	
Thoracotomy		7	2	1	4	
Field of lymph node dissection						0.2230
Two		9	6	0	3	
Three		82	40	21	21	
Preoperative therapy						< 0.0001
Surgery alone (SA)		50	43	4	3	
Cisplatin + 5-FU (CF)**		14(13)	1	5	8	
Docetaxel + cisplatin + 5-FU (DCF)**		34(30)	4	13	17	
Histological response after neoadjuvant therapy ( <i>n</i> = 48)						0.4012
Complete response (CR)**		3(2)	1	1	1	
Partial response (PR)**		26(23)	3	11	12	
Stable disease (SD)**		17(16)	1	6	10	
Progressive disease (PD)**		2(2)	0	0	2	
Reccurrence of lymph node						0.6837

TABLE 1 continued

Variable	Number***	Total <i>n</i> = 98(91)	cStage I <i>n</i> = 48(46)	cStage II <i>n</i> = 22(21)	cStage III <i>n</i> = 28(24)	<i>P</i> value
Presence*		14(9)	6(4)	3(2)	5(3)	
Absence		77	40	18	19	

There were two, one and four patients had inoperable cancer in cStage I/II/III, respectively

\*The inside of ( ) is the number of regional lymph node recurrences

\*\*The inside of ( ) is the number that received neoadjuvant chemotherapy (NAC) in cStageII/III

\*\*\*The inside of ( ) is the number that underwent esophagectomy

## DISCUSSION

Among thoracic ESCC patients, those with MtESCC showed the best OS (Fig. 1a), and the 5-year OS of MtESCC reached the best score of 68.3%. Nevertheless, prognostic analysis according to cStage suggested insufficient lymph node dissection in cStage I MtESCC compared with cStage I LtESCC, because there was no recurrence at lymph nodes in cStage I LtESCC.<sup>16</sup> Lymph node recurrences were sometimes experienced in cStage I MtESCC. Recurrent sites of all MtESCC after surgery for cStage I were at regional lymph nodes (no. 1L, 2L, and 10L) and extraregional lymph nodes [upper cervical lymph nodes (UCLN)], occurring rather frequently compared with in cStage II/III MtESCC (Fig. 3b/c). In cStage II/III ESCC, NAC was performed in about 80% of our cases, and DCF NAC significantly suppressed lymph node recurrences in our experience.<sup>14</sup> Conversely, only surgery can completely dissect invisible lymph node disease,<sup>18</sup> especially in cStage I ESCC patients, in whom NAC was never applied. Recurrence of regional lymph nodes in our cases resulted from omission of lymph node dissection due to various clinical reasons, especially for lymph nodes around the left laryngeal nerve (no. 1L and 2L).

No. 10L lymph node recurrence was also seen in cStage I MtESCC. This result is amazing, because patients with subcarinal LNM also had a significantly lower survival rate than those without,<sup>7</sup> and its dissection might have little value in patients with upper and lower thoracic ESCC and could be omitted, especially for superficial carcinoma.<sup>8</sup> Actually, there was no subcarinal LNM in LtESCC in our early study.<sup>16</sup> In MtESCC, however, LNMs in the subcarinal region and recurrences of no. 10L were surely found more frequently than in LtESCC. No. 10L is the most deeply located in the operative field, and its meticulous dissection could risk tracheal injury. According to our current results, however, it may be considered critical to dissect lymph nodes in this area from an oncological point of view in MtESCC.

Miyata et al. reported that cardiac and recurrent nerve lymph nodes showed high efficacy index (EI) using 3-year OS irrespective of tumor location.<sup>9</sup> The EI in our current

study, calculated using 5-year OS with sufficient follow-up duration, supports their report. The highest EI was 15 for no. 2R, followed by 11.5 for no. 17, in MtESCC. Lymph node dissection may be safely omitted for patients in the low-risk subgroup,<sup>19</sup> however dissection of lymph nodes no. 2R/L could not be safely omitted in MtESCC. We did not experience recurrences of no. 2R in MtESCC, suggesting that our lymph node dissection of no. 2R was technically sufficient. On the other hand, we sometimes experienced no. 2L lymph node recurrences, and in such cases the lymph node dissection was omitted due to various clinical reasons, largely aiming at avoidance of bilateral paralysis of the recurrent laryngeal nerve for elderly patients. With regard to omission of no. 2L dissection, the clinical debate is difficult to resolve at present. For no. 4L lymph nodes, on the other hand, metastasis was infrequent.

In the current study, the definition of positive LNM was a short diameter of 1 cm on CT, and preoperative diagnosis of LNM permitted high sensitivity of 100% (8/8) but relatively low specificity of 68.5% (37/54).<sup>16</sup> Nodal size was reported to be significantly associated with hematological recurrence ( $P = 0.007$ ), but not lymphatic relapse ( $P = 0.272$ ).<sup>20</sup> Reflected these findings, lymph node recurrences in our current study were not so biased according to cStage, while distant organ recurrences showed a different tendency between cStage II and cStage III ( $P = 0.079$ ). We therefore believe that our original definition of LNM by size is not very accurately predictive of pathological lymph node metastasis, but reflects prognosis, representing the distant metastatic ability of MtESCC.

Our data also support a recent report describing that solitary lymph node recurrence developed inside and outside of the surgical field, showing relatively favorable prognosis with local treatment regardless of location, concluding that localized disease may even lie outside of the surgical field in ESCC.<sup>21</sup> Our current prognostic analysis of recurrences at lymph nodes reveals that metastasis at lymph nodes alone is prognostically different from that at distant organs. Our clinical outcomes with regard to

recurrences of lymph nodes alone were excellent, putatively due to emerging dCRT for recurrences, which could cure even such risky cases.

### Limitations

During the study period, our hospital decided treatment policy using the 6th UICC stage for esophageal cancer treatments, while a prospective database using the 7th UICC stage was also obtained. This explains why some of the patients who received NAC in 6th UICC cStage II were in 7th UICC cStage I. Subanalysis of the current study results resulted in such small patient numbers that statistical results should be considered with care.

### CONCLUSIONS

Meticulous surgical dissection of lymph nodes around both the right and left laryngeal recurrent nerves should be tried for local disease control, and their control even after recurrences may be mandatory with the highest priority to obtain the best prognostic outcome in Mt ESCC.

**DISCLOSURES** The authors have no conflicts of interest to declare.

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