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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Clinicopathologic Characteristics of Oligometastases from Esophageal Cancer and Long-Term Outcomes of Resection

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ABSTRACT

Background. Recurrent esophageal cancer after radical therapy usually is thought to be incurable and treated with palliative-intent systemic therapy. However, it is empirically known that surgical resection may be effective for selected patients, although no consensus exists on the efficacy of surgery for recurrent esophageal cancer. This study sought to identify a group of patients for whom surgical resection is considered effective.

Methods. The study enrolled 206 patients at a single center who had recurrence after radical therapy for esophageal cancer. Prognostic factors after recurrence were identified, and efficacy of surgery was analyzed according to whether the recurrent lesions were oligometastases (i.e., $\leq$ 5 lesions in a single domain) or not.

Results. In the multivariate analysis, oligometastatic presentation was the only factor associated with survival after recurrence (hazard ratio 6.29; 95% confidence interval, 4.10–9.71). The actuarial survival rates for the patients with oligometastases were 59.5% at 3 years and 51.7% at 5 years. The survival rates at 3 and 5 years were significantly higher for the patients who underwent resection (64.3% and 55.6%, respectively) than for those who did not (both 100%) and for the patients with multiple metastases (9.8% and 0%, respectively). The survival rates for the patients who had oligometastases without resection were comparably lower than for the patients with multiple metastases.

Conclusion. Oligometastatic presentation at recurrence was associated with better survival outcomes for the patients who experienced recurrence after radical treatment for esophageal cancer, and surgical resection could be a choice of treatment for this group of patients.

Esophageal cancer is one of the most life-threatening forms of gastrointestinal cancer. The efficacy of chemotherapy and chemoradiotherapy for this disease has been demonstrated, and both methods are widely used. However, despite increasing use of neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy, approximately half of patients who undergo curative esophagectomy for esophageal cancer experience recurrence, and the prognosis remains poor.[1–5]

The median survival for patients with locoregional and/or distant postoperative recurrence of esophageal cancer is reported to be 6.0–8.2 months.[6–8] These patients usually are referred for systemic therapy with palliative intent, but potentially curative definitive treatment has historically been offered to patients with a limited number of metastases.[9–11] No consensus exists on the best treatment for patients with recurrent esophageal cancer or the effectiveness of resection of oligometastases. This study therefore aimed to identify predictors of better survival for

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patients who have esophageal cancer with recurrence after curative treatment and to clarify the prognostic impact of resection of oligometastases.

MATERIALS AND METHODS

Definition of Oligometastases

Oligometastases is a disease concept defined as a limited number of systemic metastatic tumors for which local ablative therapy could be curative. Although most past studies vary in the number of metastatic lesions considered to represent oligometastases, the common range is one to five lesions in various fields.[5,12] In this study, we defined oligometastases as metastatic lesions fewer than six in number, assumed to share the same pattern of metastasis and located in a single organ or domain. Six or more metastatic lesions located in multiple organ or domain or showing multiple different patterns of metastases (e.g., lymphatic and hematogenous) are considered to be multiple metastases.

Study Population

From a database prospectively constructed between January 2011 and June 2017, 910 consecutive patients with esophageal cancer were identified. These 910 patients included 206 patients with recurrence. Of these 206 patients, 177 had undergone R0 esophagectomy with two- or three-field lymphadenectomy, 9 patients had undergone endoscopic submucosal dissection, and 20 had a complete response after definitive chemoradiotherapy, whereas 87 of the 206 patients had recurrence with multiple metastases, and the remaining 119 patients had oligometastases.

Neoadjuvant Therapy

In Japan, neoadjuvant chemotherapy is a standard treatment,[13–15] especially for patients with stage 2 or 3 disease. In our hospital, we tend to select neoadjuvant chemoradiotherapy for patients with bulky T3 or nearly T4 esophageal cancer.

The chemotherapy regimens used for the patients in this study were either 5-fluorouracil 800 mg/m^2 and cisplatin 80 mg/m^2 (FP) or docetaxel 75 mg/m^2, cisplatin 75 mg/m^2, and 5-fluorouracil 750 mg/m^2 (DCF). The total neoadjuvant radiation dose was 50 Gy or less. No patient received additional radiation therapy after esophagectomy.

Definitive Chemoradiotherapy

Definitive chemoradiotherapy generally is accepted to consist of chemotherapy combined with 50.4 Gy of radiation or more to the main tumor and any metastases as well as more than 40 Gy of prophylactic radiation to the regional lymph nodes. In this study, the clinical response was assessed by endoscopy with esophageal biopsy, computed tomography (CT) (with positron emission tomography-CT in some cases), and ultrasonography of the abdomen and neck.

The clinical response was determined using the Response Evaluation Criteria In Solid Tumors (RECIST) guidelines[16,17] and the 11th edition of the Japanese Classification of Esophageal Cancer, parts 2 and 3.[18] The clinical response for the main lesions was defined as disappearance of endoscopic findings suggesting the presence of a tumor, negative endoscopic biopsy findings from the area of the primary tumor, observation of the entire esophagus possible using endoscopy, and no endoscopic findings of active esophagitis. The response for lymph node metastases was defined as a reduction in the short axis of the affected lymph nodes to less than 10 mm on CT and on ultrasonography of the abdomen and neck.

Post-treatment Follow-up Evaluation

Post-treatment follow-up evaluation included clinical examination, testing for tumor markers, contrast-enhanced CT, intra-esophageal endoscopic examination with or without biopsy, and abdominal and neck ultrasonography every 4 months for the first 3 years after endoscopic submucosal dissection (ESD), then definitive chemoradiotherapy (DCRT), every 6 months thereafter. Subsequent follow-up evaluation was determined on the basis of individual risk and likelihood of recurrence. Similarly, frequent examinations were performed for patients after esophagectomy, except that fewer endoscopic examinations were performed.

In all the recurrent cases, we decided on the management of therapy at a multidisciplinary conference. We tended to choose resection of metastases basically when R0 resection was thought possible. Finally, the management of therapy was the patient's self-decision-making after detailed informed consent regarding the risks and benefits of each treatment option.

Statistical Analysis

We investigated long-term outcomes for patients with oligometastases from esophageal cancer after radical therapy and the effectiveness of resection in oligometastic disease. Overall survival was defined as the interval

between the day the first recurrence was detected and the day of death from esophageal cancer. Disease stage was classified according to the Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) grading system, 7th edition.[19] The study was approved by the Institutional Review Board of Toranomon Hospital (approval no. 1907). Informed consent was obtained from all the participants.

Pairwise comparisons of proportions and median values were performed using the χ^2 test, Fisher's exact test, or Mann–Whitney *U* test as appropriate. Cumulative overall, disease-specific, and recurrence-free survival rates were analyzed using the Kaplan–Meier method. Factors identified to be significant in simple Cox proportional hazards models were entered into the multiple Cox proportional hazards model. The disease-free interval (DFI) was defined as the time between the date of resection or the date of complete response (CR) entry of the primary tumor and the date of detection of disease recurrence. All statistical analyses were performed using SPSS for Windows (version 19.0J; IBM Corp., Armonk, NY, USA). A p value lower than 0.05 was considered statistically significant.

RESULTS

Characteristics of Patients with Recurrence After Radical Treatment

The 206 patients with recurrence after radical therapy had a median age of 66 years, and 86.4% were male (Table 1). Among the 119 patients who experienced oligometastases, 53 experienced pulmonary metastases, 41 experienced lymph node metastases, 5 experienced kidney metastases, 7 experienced liver metastases, 6 experienced local recurrences, and 7 experienced other (brain, muscle, bone, skin) metastases. Of these 119 patients with oligometastases, 109 underwent resection of these tumors, and 10 did not despite suspected resectability of their tumors. The treatment strategies and alternative treatments for these latter 10 patients are shown in Table S1. We describe the difference in type of recurrence between the patients who had oligometastases and those who had multiple metastases in Table 2. The data showed that 64 patients (73.6%) in the multiple metastases group had multiple organ metastases, and about 23 (26.4%) of the remaining patients had more than six metastatic lesions in one organ, lymph node metastases located in multiple domains, or multiple different patterns of metastases (lymphatic and hematogenous).

All the managements of therapy were determined by the patient's self-decision after detailed informed consent regarding the risks and benefits of each treatment option. The median DFI was 13.2 months. The median follow-up duration was 55.4 months for all 206 patients (Kaplan–Meier estimate). No patients slipped out of the follow-up evaluation in this study.

Predictors of Better Survival of Esophageal Cancer and Overall Survival

The factors identified as predictors of overall survival for the patients who experienced recurrent esophageal cancer are shown in Table 3. Univariate analysis showed a significant difference in overall survival according to clinical stage of the primary tumor, type of recurrence (i.e., oligometastasis or not), and DFI.

In the multivariate analysis, only oligometastasis was an independent predictor of overall survival (hazard ratio [HR], 6.289; 95% confidence interval [CI], 4.098–9.709). The actuarial 3- and 5-year survival rates after recurrence for patients with oligometastases (59.5% and 51.7%, respectively) were significantly better than for the patients with multiple metastases (9.8% and 0%; $p < 0.001$; Fig. 1).

Predictor of Overall Survival for Patients with Oligometastasis and Effectiveness of Resection

Survival curves for the patients with esophageal cancer who did or did not undergo resection of oligometastases compared with multiple metastases are shown in Fig. 2. The actuarial 3- and 5-year survival rates after recurrence were significantly higher for the patients who underwent resection of oligometastases (64.3% and 55.6%, respectively) than for the patients who did not (both 10%) or for the patients with multiple metastases (9.8% and 0%, respectively).

Among the 119 patients with oligometastases, 109 underwent resection of these tumors. The demographic and clinical characteristics of the patients with oligometastases are shown in Table 4. The site of oligometastases differed significantly between the two groups ($p = 0.007$). The median follow-up duration was 61.5 months in the resection group and 75.6 months in the non-resection group ($p = 0.570$, Kaplan–Meier estimate). The survival rates for the patients who had oligometastases without resection were comparably lower than for the patients with multiple metastases.

The advantages of predicting overall survival after oligometases are shown in Table 5. In the multivariate analysis, only resection of oligometastases (HR, 7.407; 95% CI, 3.497–15.63) was an independent predictor of better overall survival.

TABLE 1 Demographic and clinical characteristics of the patients with recurrence of esophageal cancer

Variable	n = 206
Age (years)	
Median	66.0
Range	29–86
Sex	
Male	178
Female	28
cT factor	
T1a/T1b	10/54
T2	28
T3	90
T4a/T4b	14/10
cN factor	
N0	69
N1	46
N2	53
N3	38
cM factor	
M0	171
M1	35
cStage (7th ed)	
1 (1A, 1B)	31/10
2 (2A, 2B)	19/29
3 (3A, 3B, 3C)	25/21/36
4	35
Initial treatment of primary tumor	
Esophagectomy	177
ESD	9
DCRT	20
Type of recurrence	
Multiple recurrence	87
Oligometastases ($\leq$ 5 metastatic tumors in a single domain)	119
Site of oligometastases	
Total	119
Lung	53
Lymph node	41
Kidney	5
Liver	7
Local	6
Other (brain, muscle, bone, skin)	7
Organs resected for oligometastases (109 patients, 144 cases)	
All	144
Lung	70
Lymph node	44
Kidney	5
Liver	9
Local	3
Other (brain, muscle, bone, skin)	13
No. of resections for metastatic tumors (109 patients)	
1	82
$\geq$ 2	27
DFI	
Median	13.2
Range	0–229.5

ESD Endoscopic submucosal dissection, *DCRT* definitive chemoradiotherapy, *DFI* disease-free interval

Survival Data After Resection of Oligometastases by Metastatic Organs

The treatment patterns for primary tumors and oligometastases are shown in Table S2. We also describe DFI after resection of oligometastases by metastatic organs. The median DFI was 16.9 months for the lung, 15.5 months for the lymph node, 8.1 months for the kidney, 7.4 months for the liver, 39 months for the local recurrence, and 14.2 months for the others (Table S2). The survival curves for each organ of the patients with esophageal cancer who had resection of oligometastases are shown in Fig. 3a. The 3-year overall survival rate was 60.6% for the lung, 67.0% for the lymph node, 100% for the kidney, 68.6% for the liver, 100% for the local tumor, and 38.1% for the others.

We also compared the data between regional lymph node recurrence and distant lymph node recurrence (Fig. 3b), as well as between cervical lymph node recurrence and the others (Fig. 3c). As a result, the actuarial 3-year survival rates for the patients who underwent resection of regional lymph nodes were significantly higher than for the patients who underwent resection of distant lymph nodes (74.7% and 0%, respectively; $p = 0.042$). On the other hand, the 3-year overall survival rate was 72.5% for the patients with cervical lymph node resection and 55.6% for the patients with resection of other lymph nodes. These two groups did not differ significantly ($p = 0.315$).

DISCUSSION

Historically, potentially curative definitive treatment has been offered on an individual basis for patients with various types of cancer but a limited number of metastases.[9–11] However, the evidence base needed to guide decision-making is limited, and no consensus exists on the best treatment for patients with recurrence of esophageal cancer or on the effectiveness of resection of oligometastases.

TABLE 2 Difference in the type of the recurrence between the patients who had oligometastases and those who had multiple metastases

Site of metastases	Oligometastases *n* (%)	Multiple metastases *n* (%)
Total	119	87
Lung	53 (44.5)	7 (8.0)
Lymph node	41 (34.5)	12 (13.8)
Kidney	5 (4.2)	–
Liver	7 (5.9)	4 (4.6)
Local	6 (5.0)	–
Other (brain, muscle, bone, skin)	7 (5.9)	–
Multiple organs	–	64 (73.6)
Pleural dissemination		29
Lymph node		22
Lung		17
Bone		15
Liver		11
Local		11
Carcinomatous lymphangiosis		3
Kidney		2
Muscle		2
Other (brain, skin, pancreas, adrenal grand)		

TABLE 3 Results of uni- and multivariate analyses of prognostic factors in the patients with recurrence of esophageal cancer

	n = 206	Univariate *p* value	Multivariate *p* value	HR (95% CI)
Age (years)		0.420		
< 65	88			
≥ 65	118			
Sex		0.606		
Male	28			
Female	178			
cT factor		0.063		
T1 or T2	92			
T3 or T4	114			
cN factor		0.039		
N-Negative	69			
N-Positive	137			
cM factor		0.745		
M0	171			
M1	35			
cStage (7th ed)		0.030		
1 (1A, 1B)	31/10			
2 (2A, 2B)	19/29			
3 (3A, 3B, 3C)	25/21/36			
4	35			
Type of recurrence		< 0.001	< 0.001	6.289 (4.098–9.709)
Multiple	87			
Oligometastases	119			
DFI		0.002	0.071	
< 12	91			
≥ 12	115			

HR Hazard ratio, *CI* confidence interval, *DFI* disease-free interval

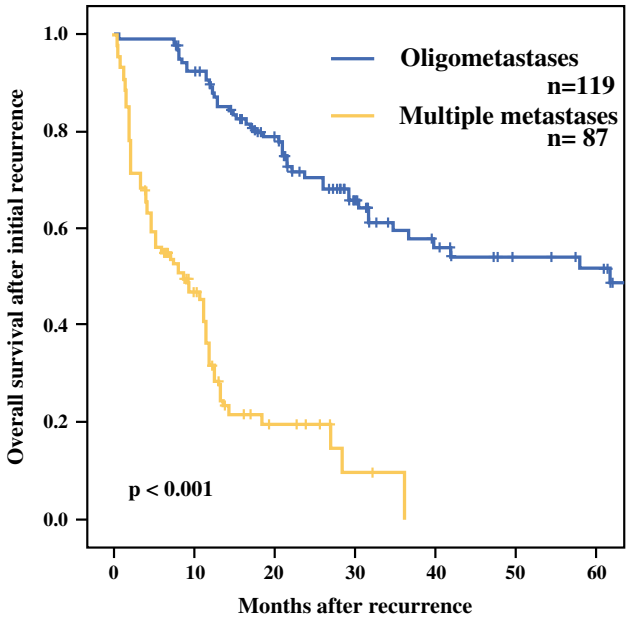

FIG. 1 Survival curves for the patients with esophageal cancer who experienced multiple metastases and for those who experienced oligometastases

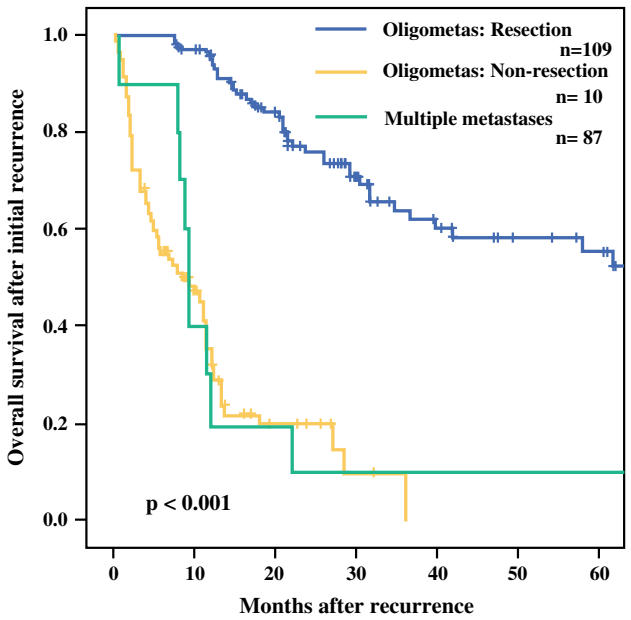

FIG. 2 Survival curves for the patients with esophageal cancer who did and did not undergo resection of oligometastases compared with multiple metastases

In this study we attempted to clarify predictors of better survival for esophageal cancer patients with recurrence and to clarify the prognostic impact of resection of oligometastases. Reports show that approximately half of patients with esophageal cancer who undergo curative esophagectomy experience a recurrence and a poor prognosis.[1–5] Generally, these patients are referred for systemic therapy with palliative intent. Ghaly et al.[10] found no statistically significant difference in survival according the method used for definitive treatment of oligometastases (surgery vs. definitive chemoradiotherapy). However, in our experience, pulmonary metastasectomy has been effective for selected patients, although we could not reach a conclusion on the indications for pulmonary metastasectomy in patients with esophageal carcinoma due to the small number of cases treated.[11]

In this study, the outcomes for resection of tumor recurrence were significantly better for the patients who had five or fewer metastatic tumors in a single domain than for the patients with more metastatic lesions or with a comparable number of tumors in multiple domains who underwent nonsurgical treatment. Furthermore, overall survival was significantly better for the patients who underwent resection of oligometastases than for those who did not. These findings suggest that surgery for oligometastases of esophageal cancer confers a better prognosis and that resection of these tumors could be offered more widely. At the same time, given that several studies have reported favorable outcomes after resection of more than five metastatic tumors or tumors in multiple domains,[20,21] our result does not exclude the possibility of other conditions in which even patients with multiple metastases could benefit by surgery.

Regarding the timing of resection of oligometastasis, we found no significant difference in 5-year survival rates between 37 patients with a DFI shorter than 12 months and 72 patients with a DFI of 12 months or longer (cumulative survival at 5 years, 53.6% vs. 57.4%; $p = 0.878$). This result indicates that a short DFI after radical treatment of esophageal cancer should not be considered an unfavorable prognostic factor and that surgeons should not hesitate to resect oligometastases.

The survival rates for the patients with different metastatic organs showed no significant difference in this study. In lymph node metastases, although the 3-year overall survival rates did not differ significantly between the patients with cervical lymph node resection and those with resection of other lymph nodes, the actuarial 3-year survival rates for the patients who underwent resection of regional lymph nodes were significantly higher than for the patients who underwent resection of distant lymph nodes. As a result, in cases of distant lymph node metastases, the resection of oligometastases may not be beneficial for survival even if the metastatic tumors are fewer than six lesions and located in a single organ or domain.

The major limitations of our study were its single-center and retrospective design. However, the study data were obtained during a relatively short period from a prospectively constructed database containing information on consecutive patients. The largest bias of this study was that

TABLE 4 Demographic and clinical characteristics of the patients with oligometastases

Variable	Resection (n = 109)	Non-resection (n = 10)	P value
Age (years)			0.206
Median	66.2	68.5	
Range	34–80	59–81	
Sex			0.739
Male	94	9	
Female	15	1	
cT factor			0.086
T1a/T1b	8/30	0/0	
T2	17	2	
T3	45	6	
T4a/T4b	4/5	2/0	
cN factor			0.756
N0	43	3	
N1	29	2	
N2	25	3	
N3	12	2	
cM factor			0.148
M0	89	10	
M1	19	0	
cStage (7th edition)			0.442
I (IA, IB)	25/5	0/1	
II (IIA, IIB)	8/19	2/0	
III (IIIA, IIIB, IIIC)	13/9/11	2/1/4	
IV	19	0	
Initial treatment of primary tumor			0.580
Esophagectomy	85	9	
ESD	9	0	
DCRT	15	1	
Site of oligometastases			0.007
Total	109	10	
Lung	50	3	
Lymph node	37	4	
Kidney	5	0	
Liver	7	0	
Local	3	3	
Other (brain, muscle, bone, skin)	7	0	
DFI			0.294
Median	15.8	13.1	
Range	0–229.5	5.8–24.5	
Median follow up periods (months)	61.5	75.6	0.570

DCRT Definitive chemoradiotherapy, *DFI* disease-free interval, *ESD* endoscopic submucosal dissection

the patients who underwent surgical resection were selected patients. However, we think this selected bias decreases as much as possible by conducting a multidisciplinary conference for all recurrent patients. In this study, all the patients with oligometastases considered in the multidisciplinary conference had resectable tumors of oligometastases. Therefore, we suggested choices of treatments to these patients including resection.

Finally, the management of therapy was determined by the patient's self-decision-making after detailed informed consent regarding the risks and benefits of each treatment option. Also, we showed and compared the difference in

TABLE 5 Advantageous factors in predicting overall survival after oligometases

	$n = 119$	Univariate p value	Multivariate p value	HR (95% CI)
Age (years)		0.904		
< 65	47			
≥ 65	72			
Sex		0.169		
Male	16			
Female	103			
cT factor		0.280		
T1 or T2	57			
T3 or T4	62			
cN factor		0.149		
N-Negative	46			
N-Positive	73			
cM factor		0.228		
M0	99			
M1	19			
cStage (7th ed)		0.206		
1 (1A, 1B)	25/6			
2 (2A, 2B)	10/19			
3 (3A, 3B, 3C)	15/10/15			
4	19			
Resection of oligometastases		< 0.001	< 0.001	7.407 (3.497–15.63)
Yes	109			
No	10			
DFI		0.761		
< 12	40			
≥ 12	79			

HR Hazard ratio, *CI* confidence interval, *DFI* disease-free interval

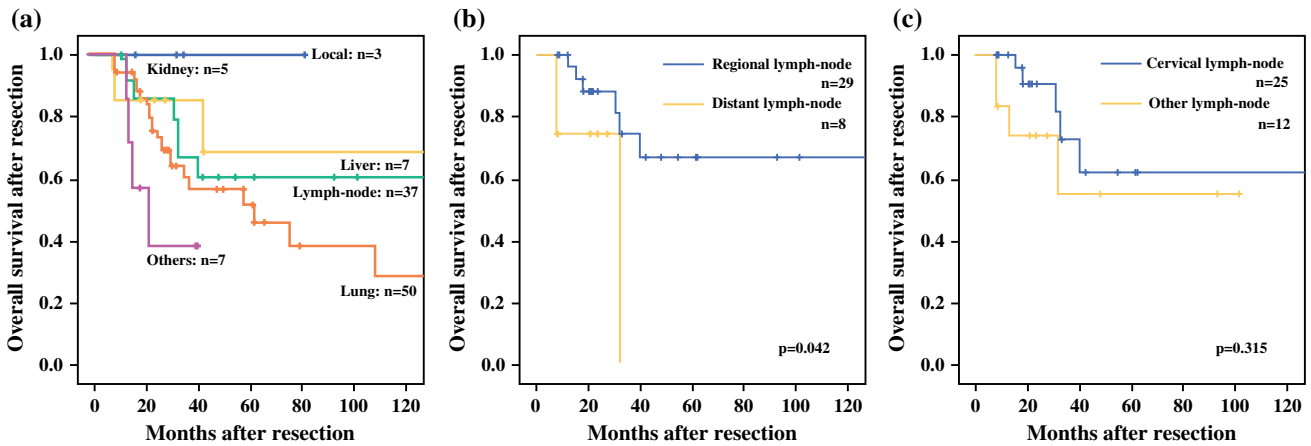

FIG. 3 Survival curves for each organ of the patients with esophageal cancer who had resection of oligometastases. **a** Survival curves for the patients with regional lymph node recurrence and distant lymph node recurrence. **b** Survival curves for the patients with cervical lymph node recurrence and for the others

background between the patients who had oligometastases with or without resection (Table 4). Almost none of the background showed a significant difference between the two groups. A multicenter external validation study with a larger group of patients is needed to confirm our observations.

CONCLUSIONS

In this study, the overall survival rate was significantly better for the patients who underwent resection of oligometastases than for those who did not. Recurrence of esophageal cancer in the form of oligometastases could be an independent predictor of overall survival for patients who have undergone radical treatment.

DISCLOSURE There are no conflicts of interest.

REFERENCES

1. Abate E, DeMeester SR, Zehetner J, et al. Recurrence after esophagectomy for adenocarcinoma: defining optimal follow-up intervals and testing. *J Am Coll Surg.* 2010;210:428–35.
2. Lee DH, Kim HR, Kim DK, Park SI, Kim YH. Outcomes of cervical lymph node recurrence in patients with esophageal squamous cell carcinoma after esophagectomy with 2-field lymph node dissection. *J Thorac Cardiovasc Surg.* 2013;146:365–71.
3. Hsu PK, Wang BY, Huang CS, Wu YC, Hsu WH. Prognostic factors for post-recurrence survival in esophageal squamous cell carcinoma patients with recurrence after resection. *J Gastrointest Surg.* 2011;15:558–65.
4. Port JL, Nasar A, Lee PC, et al. Definitive therapy for isolated esophageal metastases prolongs survival. *Ann Thorac Surg.* 2012;94:413–9.
5. Ghaly G, Kamel M, Nasar A, et al. Locally advanced esophageal cancer: what becomes of 5-year survivors? *J Thorac Cardiovasc Surg.* 2016;151:726–32.
6. Miyata H, Yamasaki M, Kurokawa Y, Takiguchi S, Nakajima K, Fujiwara Y, et al. Survival factors in patients with recurrence after curative resection of esophageal squamous cell carcinomas. *Ann Surg Oncol.* 2011;18:3353–61.
7. Bhansali MS, Fujita H, Kakegawa T, Yamana H, Ono T, Hikita S, et al. Pattern of recurrence after extended radical esophagectomy with three-field lymph node dissection for squamous cell carcinoma in the thoracic esophagus. *World J Surg.* 1997;21:275–81.
8. Yamashita H, Jingu K, Niibe Y, Katsui K, Matsumoto T, Nishina T, Terahara A. Definitive salvage radiation therapy and chemoradiation therapy for lymph node oligo-recurrence of esophageal cancer: a Japanese multi-institutional study of 237 patients. *Radiat Oncol.* 2017;12:38.
9. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med.* 1990;322:494–500.
10. Ghaly G, Sebron H, Mohamed KK, Mohamed R, Abu N, Jeffrey L, et al. Predictors of survival after treatment of oligometastases after esophagectomy. *Ann Thorac Surg.* 2018;105:357–362.
11. Kobayashi N, Kohno T, Haruta S, et al. Pulmonary metastasectomy secondary to esophageal carcinoma: long-term survival and prognostic factors. *Ann Surg Oncol.* 2014;21:365–9.
12. Diane KR, Kenneth JP. The biology and treatment of oligometastatic cancer. *Oncotarget.* 2015;6:8491–8524.
13. Allum WH, Stenning SP, Bancewicz J, et al. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. *J Clin Oncol.* 1987;27:5062–7.
14. Ando N, Kato H, Igaki H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). *Ann Surg Oncol.* 2012;19:68–74.
15. Nakamura K, Kato K, Igaki H, et al. Three-arm phase III trial comparing cisplatin plus 5-FU (CF) versus docetaxel, cisplatin plus 5-FU (DCF) versus radiotherapy with CF (CF-RT) as preoperative therapy for locally advanced esophageal cancer (JCOG1109, NExT study). *Jpn J Clin Oncol.* 2013;43:752–5.
16. Therasse P, Arbuck S, Eisenhauer E, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst.* 2000;92:205–16.
17. Eisenhauer E, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45:228–47.
18. Japanese Esophageal Society. Japanese classification of esophageal cancer, 11th edition: parts II and III. *Esophagus.* 2017;14:37–65.
19. Sobin LH, Gospodarowicz MK, Wittekind C (eds). Oesophagus including oesophagogastric junction. In: TNM classification of malignant tumours. International union against cancer. West Sussex: Wiley-Blackwell; 2009. p. 66–72.
20. Kaneda H, Saito Y. Oligometastases: defines by prognosis and evaluated by cure. *Cancer Treat Commun.* 2015;3:1–6.
21. Mao YS, Suntharalingam M, Krasna MJ. Management of late distant metastases after trimodality therapy for esophageal cancer. *Ann Thorac Surg.* 2003;76:1742–3.