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ORIGINAL ARTICLE

Clinical features and risk factors for early recurrence after esophagectomy following neoadjuvant chemotherapy for esophageal cancer

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Abstract

Purpose The purpose of this study was to clarify the clinical features and outcomes of patients with recurrence after esophagectomy following neoadjuvant chemotherapy (NAC) related to the timing of recurrence.

Methods We reviewed 240 consecutive patients who underwent NAC followed by esophagectomy for clinical stage II/III esophageal squamous cell carcinoma between 2009 and 2014. We compared the clinical features and survival after recurrence among groups of patients stratified by the timing of recurrence diagnosis and identified the risk factors for early recurrence (ER).

Results Recurrence was identified within 1 year in 61 patients and after 1 year in 23 patients. Significant differences were observed between the patients with recurrence within 1 year (early recurrence; ER) and those with recurrence after 1 year (late recurrence; LR). The ER patients had more advanced tumors and higher pretreatment serum squamous cell antigen (SCC-Ag) levels and less experienced downstaging than patients without recurrence (no recurrence; NR). Overall survival was significantly worse for the ER patients than for the LR patients. Multivariate analysis revealed that cN2-3, increased serum SCC-Ag levels, and clinical response to NAC were independent predictors of ER.

Conclusion The ER patients had distinctive clinical features from the LR and NR patients. Extensive lymph node metastasis, an elevated SCC-Ag, and inadequate response to NAC were identified as predictors of ER.

Keywords Esophageal cancer · Esophagectomy · Neoadjuvant chemotherapy · Early recurrence

Introduction

Recent progress in multidisciplinary strategies, including minimally invasive surgery [1] and perioperative treatment [2, 3], has improved the prognosis of patients with resectable esophageal squamous cell carcinoma (ESCC). Preoperative chemoradiotherapy has become the standard for resectable ESCC in Western countries [4], whereas that for locally advanced, resectable ESCC in Japan is neoadjuvant chemotherapy (NAC) followed by esophagectomy [5]. Although

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neoadjuvant strategies have improved long-term outcomes, recurrence after curative esophagectomy for ESCC is not uncommon.

The clinical features of recurrence related to timing after surgery, especially among patients treated with NAC followed by esophagectomy, have not been fully elucidated. Esophagectomy is considered highly invasive surgery that often impairs quality of life. Therefore, patients who suffer early recurrence (ER) after surgery might not benefit from esophagectomy. ER after esophagectomy often develops even when R0 resection has been achieved. Yoshida et al. reported recurrence within 6 months after curative esophagectomy in 17% of their patients [6]. Sugiyama et al. reported that recurrence developed within 1 year after esophagectomy in 71% of their patients, with a median recurrence time of 8.6 months [7]. Being able to identify the clinical features and risk factors of ER would enable us to choose a strategy other than the current standard treatment for those patients. Although several studies have investigated ER risk factors [8, 9], few have elucidated the risk factors of ER after NAC followed by esophagectomy for ESCC [6]. We conducted this study to clarify the clinical features and risk factors for ER among the preoperative variables and recurrence patterns.

Material and methods

Patients

A total 240 patients who underwent curative esophagectomy after NAC between 2009 and 2014 were eligible for inclusion in this study. Tumor stage was classified according to the UICC-TNM 7th staging system [10]. NAC followed by esophagectomy was indicated for patients with cStage II/III disease and those with cStage IV disease because of supraclavicular lymph node metastasis alone. Recurrence developed in 84 of these patients. The Institutional Review Board of JFCR approved the protocol of this study (No. 2016-1077).

Data collection and staging

Patient information was collected from the JFCR esophageal carcinoma database and the patients' records. The preoperative variables collected were age, sex, body mass index (BMI), Charlson comorbidity index (CCI), tumor location, cTNM stage, serum squamous cell carcinoma antigen (SCC-Ag), serum prealbumin, serum c-reactive protein (CRP), and the number of chemotherapeutic courses. BMI was calculated by the height and weight at the time of surgery. CCI was used as an indicator of patient comorbidities [11]. Lymph node metastases were evaluated by CT scans, with those larger than 10 mm in the short-axis diameter diagnosed as metastases. Lymph nodes were also considered metastatic positive if FDG uptake was detected on FDG-PET. CT scans and endoscopy were performed to assess the therapeutic effect of the chemotherapy 1–2 weeks after the completion of NAC. T-factor downstaging was diagnosed as positive only when the wall thickening had almost disappeared on CT scans, and an endoscopic good response was obtained. N-factor was interpreted as negative when lymph nodes had shrunk to 5 mm or less in the long-axis diameter. Prealbumin, CRP, and SCC-Ag were measured before NAC. The treatment-related variables included the operative approach, extent of lymph node dissection, operative time, blood loss, and postoperative morbidity. The pathologic variables included the pTNM stage, the number of metastatic nodes, vessel or lymphatic invasion, intramural metastasis, histologic grade, and pathologic response to chemotherapy. The pathologic evaluation was based on the Japanese classification of esophageal cancer (11th edition) [12], and the histologic grade was classified according to the World Health Organization (WHO) histological classification.

Neoadjuvant chemotherapy

The NAC regimen consisted of two courses of 5-fluorouracil (5-FU) and cisplatin. Cisplatin (80 mg/m2) was administered on day 1 and 5-FU (800 mg/m2) was administered from day 1 to day 5, with one course lasting for 28 days. If Grade 3 or more adverse events were observed, the dose was reduced by 25%. When adverse events, such as severe myelosuppression, renal dysfunction, or impaired liver function, were identified, treatment was halted midway through the course. Surgery was performed approximately 3 weeks after the completion of NAC. The pathologic response to NAC was evaluated according to the Japanese Classification of Esophageal Cancer [12]

Surgical procedures

All patients underwent esophagectomy, including esophageal subtotal resection, two- or three-field lymph node dissection, and reconstruction using a gastric tube. Thoracic procedures were performed via a right thoracotomy or by thoracoscopic surgery, whereas abdominal procedures were performed via laparotomy or by laparoscopic surgery. We began performing thoracoscopic surgery in our institute in 2010, and the percentage of patients who undergo thoracoscopic surgery increased during the study period. Esophageal reconstruction was performed via cervical esophagogastrostomy with a gastric pull-up through the retrosternal or posterior mediastinal route.

Follow-up

After surgery, the patients were followed up by physical examination, CT, and blood tests every 4 months for 1 year, and every 6 months thereafter. The duration until recurrence was defined as the period from the date of the surgery to the date of recurrence diagnosis. FDG-PET was done when there were suspicious or indefinite recurrent lesions on CT scans. The median follow-up was 5.2 years (range, 58 days–12.1 years) for all patients.

Recurrence pattern

The recurrence pattern was classified into four categories based on the site of recurrence, as distant organ recurrence, lymph node recurrence, local recurrence, and dissemination. Lymph node recurrence included both locoregional and distant lymph node recurrences. Patients with one of these recurrence patterns were classified as having a single-pattern recurrence, whereas those with two or more recurrence patterns were considered as having multiple-pattern recurrence. Patients with lymph node recurrence within one of the lymphatic fields, including the cervix, mediastinum, or abdomen, were classified as having a single-field recurrence, whereas those with metastases to two or three fields were classified as having a multiple-field recurrence.

Statistical analysis

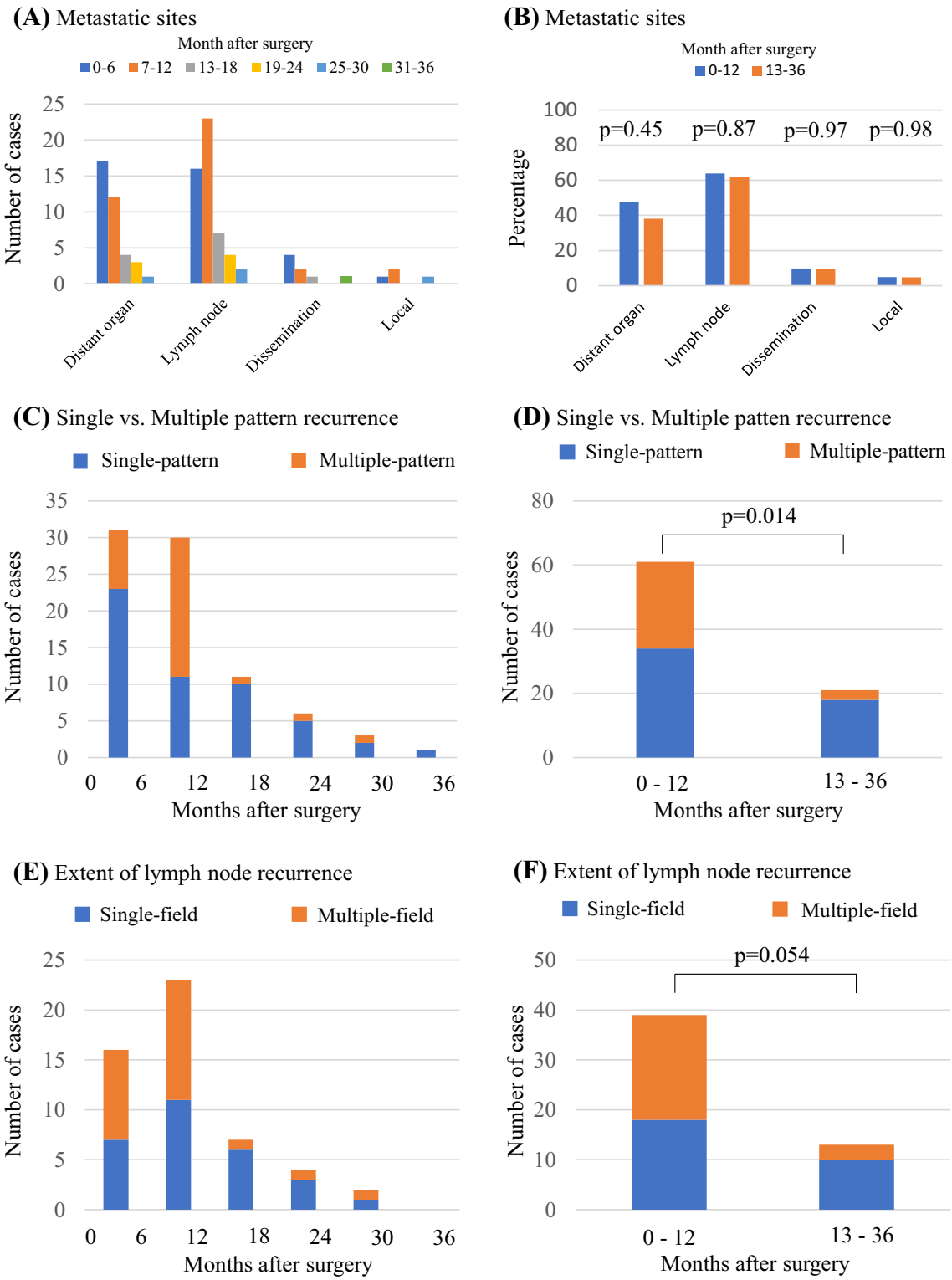
Statistical analyses were performed using JMP 12 (SAS Institute, Cary, NC, USA). Differences in clinical features were compared using Fisher's exact test and the Mann–Whitney *U* test. Survival curves after recurrence were calculated using the Kaplan–Meier method, and the statistical difference was calculated using the log-rank test. The logistic regression model was used for the multivariate analysis. Variables for multivariate analysis were selected using the stepwise regression procedure. A p value of less than 0.05 was considered significant.

Results

Recurrence was detected within 6 months in 31 patients, between 7 and 12 months in 30 patients, and after 12 months in 23 patients. We evaluated the difference in the recurrence patterns among the groups (Fig. 1A). Lymph node and distant organ recurrences were identified as the predominant patterns, and the timing of the recurrence diagnosis did not affect the recurrence pattern (Fig. 1B). Multiple-pattern recurrence was most frequently observed between 6 and 12 months, followed by within 6 months (Fig. 1C), but was rarely observed after 12 months, and the incidence was significantly higher in patients with recurrence within 1 year than in others (Fig. 1D). For lymph node recurrence, metastases to the multiple fields were often observed in patients with recurrence within 1 year; however, lymph node recurrence identified after 12 postoperative months was often limited to within the one field (Fig. 1E). Multiple-field lymph node recurrence was more common in patients with recurrence within 1 year (Fig. 1F). Lymph node recurrence was locoregional in 36 patients and distant in 17. The timing of recurrence and survival was similar in the locoregional and distant lymph node recurrence groups. (Supplementary Fig. 1). These findings indicate that patients with recurrence within 1 year have distinct clinical features from those with later recurrences. Therefore, we defined recurrence within 1 year as ER and recurrence after 1 year as late recurrence (LR).

We compared the preoperative variables among the ER, LR, and NR groups (Table 1). Both cT and cN stages were higher ($p=0.046$ and $p<0.001$, respectively), the SCC-Ag values before neoadjuvant chemotherapy were higher ($p<0.01$), and ycT and ycN stages were higher in the ER group than in the LR group. Downstaging was achieved in fewer of the ER patients than the LR patients ($p=0.034$). Among the treatment-related variables, no significant difference was observed among the groups for operative procedure, extent of lymph node dissection, operative time, or blood loss (Table 2). There were four cases of pT4. The pT4 organs included the pericardium in three patients and the mediastinal pleura in one. Curative combined resection was achieved in all patients. The incidence of postoperative complications did not differ among the groups. There were significant differences in all the pathologic variables evaluated, including pT, pN, pM, the number of metastatic nodes, vessel invasion, intramural metastasis, histologic grade, and pathologic response of NAC among the groups.

We compared the survival after recurrence between the ER and the LR groups (Fig. 2). Overall survival and cancer-specific survival were significantly worse in the ER group than in the LR group ($p=0.034$ and $p=0.0022$, respectively). These results indicate that strategies other than the current standard treatment should be considered for patients with a high risk of ER. Multivariate analysis, performed to predict the risk of ER, revealed that cN2/3, increased levels of serum SCC-Ag before chemotherapy, and lack of downstaging by NAC were independent risk factors (Table 3). Among the pathologic variables, the number of metastatic nodes and histologic grade were independent factors associated with ER (Supplementary Table 1).



Discussion

This study revealed that ER diagnosed within 1 year after surgery had distinct clinical features from LR or NR. ER occurred in approximately 25% of patients who underwent NAC followed by esophagectomy. Although the timing of recurrence did not affect the recurrence pattern, more frequent multiple metastases, including multiple-pattern recurrence and multiple-field lymph node metastases, were the features of ER. The ER group had significantly worse

◂**Fig.1** Differences in the clinical features of recurrence among the groups stratified by the timing of recurrence. **A** Metastatic sites: distant recurrence was observed most frequently in patients with recurrence detected 0–6 months after surgery, whereas lymph node recurrence was predominant in those with recurrence detected between 7 and 12 months after surgery. **B** Metastatic sites: no difference was observed in the recurrence site between the 0–12 M and 13–36 M groups. **C** Single- vs. multiple-pattern recurrence: multiple-pattern recurrence was observed most frequently in patients with recurrence detected between 7 and 12 months followed by those with recurrence at 0–6 M, and rarely in those with recurrence after 13 M. **D** Single- vs. multiple-pattern recurrence: the multiple-pattern recurrence was significantly more frequent in patients with recurrence detected within 1 year after surgery. **E** extent of lymph node recurrence: multiple-field recurrence was observed frequently in both the 0–6 M and 7–12 M groups, and its incidence decreased in patients with recurrence detected after 13 M. **F** Extent of lymph node recurrence: recurrence in the multiple-field lymph node was significantly more frequent in patients with recurrence detected within 1 year

survival after recurrence than the LR group. Based on the clinical features of ER, alternative treatment strategies are required to improve the long-term outcomes of patients at high risk of ER.

This study identified that cN2/3, increased levels of serum SCC-Ag before chemotherapy, and lack of downstaging by NAC were the independent risk factors of ER. Lymph node metastasis is a well-known powerful prognosticator for patients with ESCC. Akutsu et al. reported that the number of pathologic metastatic lymph nodes was the most reliable predictor of survival for patients who underwent neoadjuvant chemoradiotherapy for ESCC [13]. Sugimura et al. reported that distant recurrence developed more frequently in patients with three or more pathologically confirmed metastases after neoadjuvant docetaxel/cisplatin/5-fluorouracil [14]. The authors of these previous studies evaluated the lymph node metastases pathologically; however, clinical risk factors are more informative than pathologic results for the selection of alternative strategies for high-risk patients. Although it is difficult to make an accurate diagnosis of lymph node metastasis, it is not difficult to identify clinical N2 or N3 when using 18F-deoxyglucose positron emission tomography combined with computed tomography [15].

Serum SCC-Ag has been identified as a tumor marker that is often elevated in patients with squamous cell carcinoma of the cervix, vulva, head and neck, lung, and esophagus [16]. Shimada et al. reported that preoperative serum SCC-Ag concentrations might provide predictive information for tumor progression and survival for patients with esophageal SCC [17]. Recently, we found that a higher serum SCC-Ag level before neoadjuvant chemoradiotherapy was predictive of treatment failure and poor survival [18]. We also demonstrated that sensitivity to NAC was not high enough in patients with elevated pretherapeutic SCC-Ag, who were also found to have worse survival [19]. These findings indicate that elevated SCC-Ag is a predictor of poor response to NAC.

An inadequate response to NAC was another significant factor related to ER in this study. Histopathological tumor regression is a significant prognostic parameter for patients with complete resection following neoadjuvant chemoradiotherapy [20]. In contrast, the prognostic impact of tumor regression by neoadjuvant chemotherapy for ESCC remains controversial. Miyata et al. reported that nodal status, but not primary tumor regression, was an independent prognostic factor for patients treated with NAC [21]. However, only a few studies are investigating the importance of clinical downstaging after NAC for ESCC.

Among the pathologic findings, poorly differentiated histology, classified according to the WHO criteria, was an independent factor related to ER. Stiles et al. demonstrated that the risk factors predictive of early mortality after esophagectomy following neoadjuvant therapy included performance status, poorly differentiated histology, and clinical response [22]. For patients with ESCC who underwent NAC followed by surgery, Yoshida et al. reported that those with at least two factors of CRP $\geq$ 0.5 mg/dl, a poorly differentiated SCC component, and pathological vessel invasion were at high risk for ER [8].

All the patients included in this study underwent 5-FU plus cisplatin as NAC, which is the standard treatment for cStage II/III ESCC in Japan. The JCOG9907 trial suggested that 5-FU plus cisplatin may not have enough power as neoadjuvant therapy, especially for patients with cStage III or T3 tumors. Recently, the solid antitumor activities of docetaxel, cisplatin, plus 5-FU (DCF) or fluorouracil/leucovorin, oxaliplatin, plus docetaxel (FLOT) as neoadjuvant chemotherapy have been reported [23, 24, 25]. The efficacy of DCF or FLOT for ESCC patients with cN2-3 or those with elevated SCC-Ag should be investigated further. Meanwhile, additional treatments, including radiotherapy or immune checkpoint blockades, might be an alternative when NAC does not achieve downstaging. The efficacy of postoperative adjuvant therapy should also be investigated in patients with a high risk of ER.

This study has some limitations. First, it was a retrospective study in a single center with a relatively small case volume. Second, CRP, SCC-Ag, and prealbumin were analyzed based on blood data only from the first visit. Moreover, BMI was calculated based on height and weight taken at surgery as there were no data on height and weight at the first consultation. It may have been necessary to unify the timing of measurement of preoperative factors in the data analysis. Additionally, we could not identify the optimal cutoff value of SCC-Ag, although a higher SCC-Ag level before treatment was predictive of ER. Further large-scale analyses are required to elucidate the significance of pretreatment levels of SCC-Ag

Table 1 Association between preoperative variables and early recurrence

	ER $n=61$	LR $n=23$	NR $n=156$	p value
Age				
Mean ± SD	63.9 ± 0.9	65.5 ± 1.5	63.6 ± 0.6	0.41
Sex				
Male	51 (83.6)	21 (8.7)	120 (76.9)	0.16
Female	10 (16.4)	2 (91.3)	36 (23.1)	
BMI (kg/m^2)				
< 18.5	14 (22.9)	5 (21.7)	18 (11.5)	0.22
18.5 ≤ , < 25	37 (60.7)	15 (65.2)	116 (74.4)	
25 ≤	10 (16.4)	3 (13.1)	22 (14.1)	
CCI				
≤ 5	48 (78.7)	16 (69.6)	128 (82.1)	0.38
6 ≤	13 (21.3)	7 (30.4)	28 (79.5)	
Location				
Upper	6 (9.8)	2 (8.7)	21 (13.5)	0.88
Middle	31 (50.8)	12 (52.2)	82 (52.5)	
Lower	24 (39.4)	9 (39.1)	53 (34.0)	
cT				
1–2	18 (29.5)	11 (47.8)	74 (47.4)	0.046
3	43 (70.5)	12 (52.1)	82 (52.6)	
cN				
0–1	46 (75.4)	21 (91.3)	145 (93.0)	< 0.01
2–3	15 (24.6)	2 (8.7)	11 (7.0)	
cM				
0	56 (91.8)	21 (91.3)	152 (97.4)	0.14
1	5 (8.2)	2 (8.7)	4 (2.6)	
SCC-Ag (ng/ml)				
≤ 1.5	35 (57.4)	17 (73.9)	124 (79.5)	< 0.01
1.5 <	26 (42.6)	6 (26.1)	32 (20.5)	
Prealbumin (mg/dl)				
< 22	13 (21.3)	4 (17.4)	25 (16.0)	0.66
22 ≤	48 (78.7)	19 (82.6)	131 (84.0)	
CRP (mg/dl)				
≤ 0.5	55 (90.2)	21 (91.3)	143 (91.7)	0.94
0.5 <	6 (9.8)	2 (8.7)	13 (8.3)	
Cycles of NAC				
1	11 (18.0)	8 (34.8)	29 (18.6)	0.22
2	50 (82.0)	15 (65.2)	127 (81.4)	
ycT				
1–2	20 (32.8)	12 (52.2)	88 (56.4)	< 0.01
3	41 (67.2)	11 (47.8)	68 (43.6)	
ycN				
0–1	48 (78.7)	20 (87.0)	145 (93.0)	0.016
2–3	13 (21.3)	3 (13.0)	11 (7.0)	
ycM				
0	56 (91.8)	21 (91.3)	152 (97.4)	0.14
1	5 (8.2)	2 (2.6)	4 (2.6)	
Downstaging				
+	11 (18.0)	6 (26.1)	55 (35.3)	0.034
−	50 (82.0)	17 (73.9)	101 (4.7)	

ER early recurrence, *LR* late recurrence, *NR* no recurrence, *CCI* Charlson comorbidity index

Table 2 Association between treatment-related variables and early recurrence

	ER $n=61$	LR $n=23$	NR $n=156$	p value
Operative procedure				
MIE	12 (19.7)	8 (34.8)	55(35.3)	0.07
Open	49 (80.3)	15 (65.2)	101(64.7)	
Lymph node dissection				
2 field	11 (18.0)	5 (21.7)	30 (19.3)	0.62
3 field	50 (82.0)	19 (78.3)	126 (80.7)	
Operation time, min.				
Mean ± SD	556 ± 14.4	583 ± 23.5	566 ± 9.1	0.60
Blood loss, g				
Mean ± SD	505 ± 57	375 ± 44	534 ± 117	0.13
Morbidity				
Any	46 (75.4)	19 (82.6)	100 (64.1)	0.08
Pneumonia	16 (26.2)	10 (43.5)	46 (29.5)	0.31
Recurrent nerve palsy	7 (11.5)	4 (17.4)	28 (18.0)	0.48
Leakage	9 (14.8)	5 (21.7)	13 (8.3)	0.12
SSI	14 (23.0)	7 (30.4)	28 (17.9)	0.23
pT				
0–2	22 (36.0)	10 (43.5)	57 (36.5)	0.013
3–4	39 (64.0)	13 (34.8)	99 (63.5)	
pN				
0–1	30 (49.2)	15 (65.2)	136 (87.2)	< 0.01
2–3	31 (50.8)	8 (34.8)	20 (12.8)	
pM				
0	51 (83.6)	21 (91.3)	149 (95.5)	0.021
1	10 (16.4)	2 (8.7)	7 (4.5)	
No. of metastatic LNs				
0–2	28 (45.9)	15 (65.2)	132 (84.6)	< 0.01
3 or more	33 (54.1)	8 (34.8)	24 (15.4)	
Vessel or lymphatic invasion				
Present	53 (86.9)	19 (82.6)	93 (59.6)	< 0.01
Intramural metastasis	8 (13.1)	3 (13.0)	4 (2.6)	< 0.01
Histologic grade				
G3	19 (14.8)	4 (17.4)	94 (60.3)	0.020
Pathologic response				
1a	53 (86.9)	17 (73.9)	62 (39.7)	< 0.01
1b-3	8 (13.1)	6 (26.1)		

ER early recurrence, *LR* late recurrence, *NR* no recurrence, *LNs* lymph nodes

for determining treatment strategy. Third, we evaluated the downstaging clinically, although it is usually assessed by comparing clinical and pathologic stages, because we wanted to identify the preoperative factors affecting the occurrence of ER. The clinical diagnosis of both T and N stages is often inaccurate, and there is no consensus on the

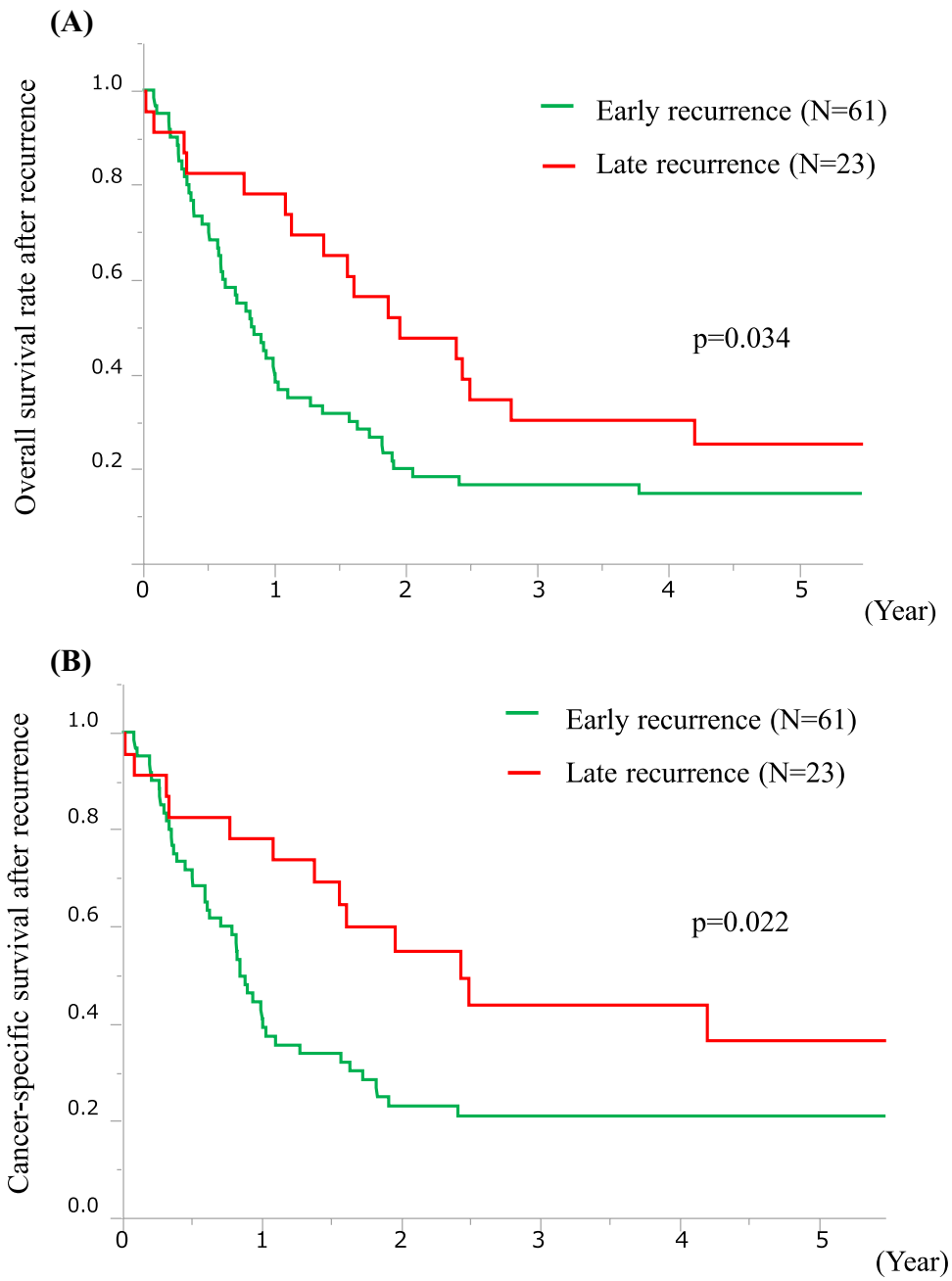


Fig.2 Overall survival (**A**) and cancer-specific survival (**B**) after the diagnosis of recurrence: the survival of the ER group was significantly worse than that of the LR group ($p=0.034$ and $p=0.0022$, respectively)

Table 3 Multivariate analysis of the preoperative factors related to early recurrence

Variables		Reference	OR	95% CI	*p* value
cT	cT3	cT1/2	1.51	0.76–3.03	0.24
cN	cN2/3	cN0/1	3.60	1.49–8.84	< 0.01
Downstaging	−	+	2.51	1.21–5.62	< 0.01
SCC-Ag before NAC (ng/ml)	1.5 <	< 1.5	2.28	1.17–4.44	0.016

OR odds ratio, *CI* confidence inflict, *NAC* neoadjuvant chemotherapy

clinical diagnosis of downstaging. In this study, downstaging positivity was diagnosed only when tumor shrinkage was evident, based on the criteria in our methods section; however, the efficacy of the criteria should be evaluated further.

In conclusion, ER within 1 year after esophagectomy had distinct clinical features. Extensive lymph node metastases, high pretreatment levels of serum SCC-Ag, and an inadequate response to NAC were identified as predictive factors for ER in patients treated with NAC followed by esophagectomy. To improve the outcomes of patients with these tumors, alternative strategies need to be established.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00595-021-02397-0.

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Declarations

Conflict of interest The authors have no conflicts of interest to declare.

References

1. Seesing MFJ, Gisbertz SS, Goense L, van Hillegersberg R, Kroon HM, Lagarde SM, et al. A propensity score matched analysis of open versus minimally invasive transthoracic esophagectomy in the Netherlands. Ann Surg. 2017;266:839–46.
2. Boonstra JJ, Kok TC, Wijnhoven BP, van Heijl M, van Berge Henegouwen MI, Ten Kate FJ, et al. Chemotherapy followed by surgery versus surgery alone in patients with resectable oesophageal squamous cell carcinoma: long-term results of a randomized controlled trial. BMC Cancer. 2011;11:181.
3. Kelsen DP, Winter KA, Gunderson LL, Mortimer J, Estes NC, Haller DG, et al. Long-term results of RTOG trial 8911 (USA Intergroup 113): a random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer. J Clin Oncol. 2007;25:3719–25.
4. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366:2074–84.
5. Ando N, Kato H, Igaki H, Shinoda M, Ozawa S, Shimizu 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.
6. Yoshida N, Baba Y, Shigaki H, Harada K, Iwatsuki M, Sakamoto Y, et al. Risk factors of early recurrence within 6 months after esophagectomy following neoadjuvant chemotherapy for resectable advanced esophageal squamous cell carcinoma. Int J Clin Oncol. 2016;21:1071–8.
7. Sugiyama M, Morita M, Yoshida R, Ando K, Egashira A, Takefumi O, et al. Patterns and time of recurrence after complete resection of esophageal cancer. Surg Today. 2012;42:752–8.
8. Zhu ZJ, Hu Y, Zhao YF, Chen XZ, Chen LQ, Chen YT, et al. Early recurrence and death after esophagectomy in patients with esophageal squamous cell carcinoma. Ann Thorac Surg. 2011;91:1502–8.
9. Kosugi S, Kanda T, Yajima K, Ishikawa T, Hatakeyama K. Risk factors that influence early death due to cancer recurrence after extended radical esophagectomy with three-field lymph node dissection. Ann Surg Oncol. 2011;18:2961–7.
10. Sobin LH, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours. 7th Edition. Hoboken: Wiley-Blackwell; 2009.
11. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373–83.
12. Japanese Classification of Esophageal Cancer. Japanese Classification of Esophageal Cancer, 11th Edition: part I. Esophagus. 2017;14:1–36.
13. Yamashita K, Watanabe M, Mine S, Kurogochi T, Okamura A, Hayami M, et al. Patterns and outcomes of recurrent esophageal cancer after curative esophagectomy. World J Surg. 2017;41:2337–44.
14. Akutsu Y, Shuto K, Kono T, Uesato M, Hoshino I, Shiratori T, et al. The number of pathologic lymph nodes involved is still a significant prognostic factor even after neoadjuvant chemoradiotherapy in esophageal squamous cell carcinoma. J Surg Oncol. 2012;105:756–60.
15. Sugimura K, Miyata H, Shinno N, Ushigome H, Asukai K, Yanagimoto Y, et al. Prognostic factors for esophageal squamous cell carcinoma treated with neoadjuvant Docetaxel/Cisplatin/5-Fluorouracil followed by surgery. Oncology. 2019;97:348–55.
16. Karashima R, Watanabe M, Imamura Y, Ida S, Baba Y, Iwagami S, et al. Advantages of FDG-PET/CT over CT alone in the preoperative assessment of lymph node metastasis in patients with esophageal cancer. Surg Today. 2015;45:471–7.
17. Torre GC. SCC antigen in malignant and nonmalignant squamous lesions. Tumour Biol. 1998;19:517–26.
18. Shimada H, Nabeya Y, Okazumi S, Matsubara H, Shiratori T, Gunji Y, et al. Prediction of survival with squamous cell carcinoma antigen in patients with resectable esophageal squamous cell carcinoma. Surgery. 2003;133:486–94.
19. Suzuki T, Okamura A, Watanabe M, Mine S, Imamura Y, Asari T, et al. Neoadjuvant chemoradiotherapy with cisplatin plus fluorouracil for borderline resectable esophageal squamous cell carcinoma. Ann Surg Oncol. 2019. https://doi.org/10.1245/s10434-019-08124-x.
20. Okamura A, Matsuda S, Mayanagi S, Kanamori J, Imamura Y, Irino T, et al. Clinical significance of pretherapeutic serum squamous cell carcinoma antigen level in patients with neoadjuvant chemotherapy for esophageal squamous cell carcinoma. Ann Surg Oncol. 2020. https://doi.org/10.1245/s10434-020-08716-y.
21. Schneider PM, Baldus SE, Metzger R, Kocher M, Bongartz R, Bollschweiler E, et al. Histomorphologic tumor regression and lymph node metastases determine prognosis following neoadjuvant radiochemotherapy for esophageal cancer: implications for response classification. Ann Surg. 2005;242:684–92.
22. Miyata H, Tanaka K, Makino T, Yamasaki M, Miyazaki Y, Takahashi T, et al. The impact of pathological tumor regression and nodal status on survival and systemic disease in patients undergoing neoadjuvant chemotherapy for esophageal squamous cell carcinoma. Ann Surg Oncol. 2018;25:2409–17.
23. Stiles BM, Salzler GG, Nasar A, Paul S, Lee PC, Port JL, et al. Clinical predictors of early cancer-related mortality following neoadjuvant therapy and oesophagectomy. Eur J Cardiothorac Surg. 2015;48:455–60 (**discussion 460–451**).
24. Yamashita K, Hosoda K, Moriya H, Katada C, Sugawara M, Mieno H, et al. Prognostic advantage of Docetaxel/Cisplatin/5-Fluorouracil neoadjuvant chemotherapy in clinical stage II/III esophageal squamous cell carcinoma due to excellent control of preoperative disease and postoperative lymph node recurrence. Oncology. 2017;92:221–8.
25. Al-Batran SE, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet. 2019;393:1948–57.