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ORIGINAL ARTICLE

The impact of time to postoperative recurrence on the prognosis of patients with esophageal cancer post recurrence: exploratory analysis of OGSG 1003

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Abstract

Background The association between recurrence timing and prognosis in patients with locally advanced resectable esophageal cancer undergoing neoadjuvant chemotherapy (NAC) followed by esophagectomy remains unclear. This study aimed to clarify this association using multicenter prospective clinical trial data.

Methods Among 162 patients enrolled in a NAC phase II study comparing the efficacy of cisplatin and fluorouracil plus docetaxel with cisplatin and fluorouracil plus adriamycin, 64 patients with recurrence after R0 resection were included in this study. We evaluated the association between recurrence timing and overall survival after recurrence (OSr), along with clinicopathological factors associated with recurrence timing and OSr.

Results Among 64 patients, 46 (71.9%) and 59 (92.2%) experienced recurrence within 1 and 2 years after surgery, respectively. Groups based on recurrence timing, including ≤ 6, 6–12, and > 12 months, had median OSr of 3.6, 13.9, and 13.4 months, respectively. The prognosis was significantly poorer for patients with recurrence ≤ 6 months after surgery than for other patients ($P < 0.001$). Multivariate analysis revealed pathological lymph node staging as an independent factor associated with early recurrence (odds ratio: 3.46, 95% confidence interval: 1.47–8.02, $P = 0.0045$). On the other hand, multivariate analysis for factors associated with OSr revealed pT (hazard ratio [HR]: 1.91, 95%CI 1.26–2.88, $P = 0.0022$), early recurrence (HR: 6.88, 95%CI 2.68–17.6, $P < 0.001$), and treatment after recurrence, with both local treatment (HR: 0.47, 95%CI 0.22–0.98, $P = 0.043$) and chemotherapy (HR: 0.25, 95%CI 0.11–0.58, $P = 0.0011$) as independent prognostic factors.

Conclusion Patients with advanced esophageal cancer experiencing recurrence within 6 months after esophagectomy following NAC have an extremely poor prognosis, suggesting that an advanced pN stage is associated with early recurrence.

Keywords Esophageal cancer · Esophagectomy · Recurrence

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Introduction

Esophageal cancer is an aggressive malignant tumor. Multidisciplinary treatments, including chemoradiotherapy, chemotherapy, and esophagectomy, are performed in combination to achieve long-term survival in patients with locally advanced esophageal cancer. In Japan, neoadjuvant chemotherapy followed by esophagectomy is the standard treatment for resectable locally advanced esophageal cancer; however, the recurrence rate after curative surgery is as high as 36.8–64% [1–3]. In addition, approximately 80–90% of recurrences are observed in the early stage within 2 years after surgery [1, 4, 5], which is earlier than those compared to gastric and colorectal cancer [6, 7].

Some reports have addressed survival after recurrence, and most of them indicated a poor prognosis. The median survival after recurrence is usually less than 1 year [1, 2, 8]. Furthermore, in clinical practice, we often encounter cases of early recurrence after surgery with rapid disease progression and extremely poor prognosis; however, the relationship between the timing of recurrence and prognosis is not well known due to limited reports [9, 10].

We recently reported the results of a randomized controlled trial comparing two regimens of neoadjuvant chemotherapy (NAC) for locally advanced esophageal squamous cell carcinoma (OGSG1003) [11, 12]. In the present study, we aimed to investigate the association between the time to postoperative recurrence and prognosis after recurrence, as well as factors related to the time to recurrence using prospectively collected data from the OGSG1003.

Patients and methods

Patients

This study was an exploratory analysis of a multicenter randomized phase II study comparing cisplatin and fluorouracil (5-FU) plus docetaxel (DCF) with cisplatin and 5-FU plus adriamycin (ACF) as preoperative chemotherapy for resectable esophageal squamous cell carcinoma (OGSG1003) [12]. This randomized study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) of Japan (identification number: UMIN000004555/000004616).

In the OGSG1003 study, clinically and histologically confirmed cases of squamous cell carcinoma of the thoracic esophagus, according to the seventh edition of the Tumor Node Metastasis Classification of the International Union Against Cancer (UICC-TNM) [13] as T1-T4a, any N category, and M0 or M1LYM metastasis (confined to the supraclavicular lymph nodes) were defined. A total of 162 patients were enrolled in the study and randomly assigned to the two groups: ACF + surgery (81 cases) and DCF + surgery (81 cases).

This study included patients who underwent curative resection (R0) and developed postoperative recurrence. Eligible cases were categorized into three groups based on the timing of recurrence: patients with recurrence in ≤ 6, 6–12, and > 12 months after surgery.

This study was conducted in accordance with the Declaration of Helsinki and all applicable local laws and regulations. All patients provided written informed consent prior to enrollment. The study protocol was approved by the institutional review board of each participating hospital.

Study treatment

The ACF chemotherapy comprised administration of two cycles of adriamycin 35 mg/m^2 and cisplatin 70 mg/m^2 as a 1-h intravenous infusion and fluorouracil (5-FU) 700 mg/m^2/day as a continuous intravenous infusion for 7 days (days 1–7) every 4 weeks. The DCF chemotherapy comprised of administration of two cycles of docetaxel 70 mg/m^2 and cisplatin 70 mg/m^2 as a 1-h intravenous infusion and 5-FU 700 mg/m^2/day as a continuous intravenous infusion for 5 days (days 1–5) every 3 weeks.

Surgery, including subtotal esophagectomy with two- or three-field lymphadenectomy, was scheduled after the completion of the last cycle of chemotherapy in both groups.

None of the patients received adjuvant chemotherapy or radiotherapy, and there was no provision for treatment after tumor recurrence in the protocol.

Data collection

The data used in this study were obtained from the database registered in the OGSG1003 study.

Clinical tumor responses were evaluated using esophagoscopy and computed tomography after each cycle of chemotherapy in accordance with the criteria of the Japanese Society for Esophageal Disease (JSED) [14]. Patients with complete or partial responses were classified as responders, and those with stable or progressive diseases were classified as non-responders. Histopathological tumor response was evaluated according to the histological criteria of the JSED [15]. The histopathological evaluations were classified into five categories, according to the proportion of tumors affected by degeneration or necrosis, as follows: grade 0, "no discernible therapeutic effect"; grade 1a, "> 2/3 of the tumor contains viable cancer cells"; grade 1b, "> 1/3 of the tumor contains viable cancer cells"; grade 2, "< 1/3 of the tumor contains viable cancer cells"; and grade 3, "no viable cancer cells are present in the tumor."

Postoperative complications were graded in accordance with the Clavien–Dindo classification of surgical complications, version 2.0 [23], and identified as grade ≥ 2.

Outcomes and statistical analyses

The primary outcome was overall survival after recurrence (OSr). The secondary outcomes were risk factors for early recurrence.

OSr was calculated from the date of recurrence to the date of death or last follow up, and OSr curves were estimated using the Kaplan–Meier method and compared using the log-rank test. To compare the clinicopathological characteristics between groups categorized based on the timing of recurrence, Fisher's exact test for categorical data and the Student's t-test or the Mann–Whitney U test for continuous data were used. In addition, logistic regression analysis was performed to adjust for confounding factors and to identify factors related to the timing of recurrence. Furthermore, factors associated with OSr were examined using univariate and multivariate analyses with the Cox proportional hazards model. Multivariate analysis included variables with a P value < 0.1 in univariate analysis of clinicopathological findings.

All P-values were two-sided; a P value ≤ 0.05 was considered statistically significant. All statistical analyses were performed using the statistical software "R (ver.3.5.2)."

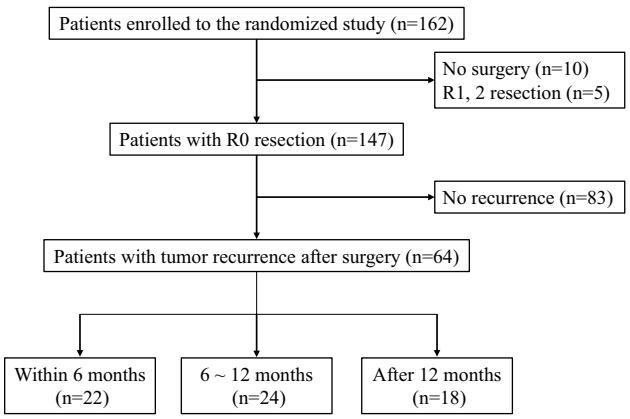

Fig. 1 Patient enrollment process

Results

Figure 1 illustrates the flow diagram of patient enrollment. A total of 162 patients from 10 institutions were enrolled in the randomized study between 2010 and 2012, and 147 patients underwent R0 resection. Among them, 64 patients (43.5%) experienced tumor recurrence (22, 24, and 18 patients experienced recurrence in ≤ 6, within 6–12, and > 12 months). Notably, 46 patients (71.9%) experienced recurrence within 1 year, and 59 patients (92.2%) developed recurrence within 2 years after surgery. The median time from surgery to recurrence was 276 (range 18–1233) days.

Survival and the timing of recurrence after surgery

Figure 2a depicts the OSr curve and at-risk population of all patients enrolled in this study. The median OSr was 9.2 months, and the 1-year survival rate after recurrence was 39.1%.

Figure 2b depicts the OSr curves for the three groups categorized based on the timing of recurrence. The median OSr was 3.6, 13.9, and 13.4 months and 1-year survival rate was 4.5%, 50.0%, and 66.7% in patients with recurrence in ≤ 6, 6–12, and > 12 months after surgery, respectively (P < 0.001).

Because of the similar prognosis of patients with recurrence within 6–12 and > 12 months, these two groups were

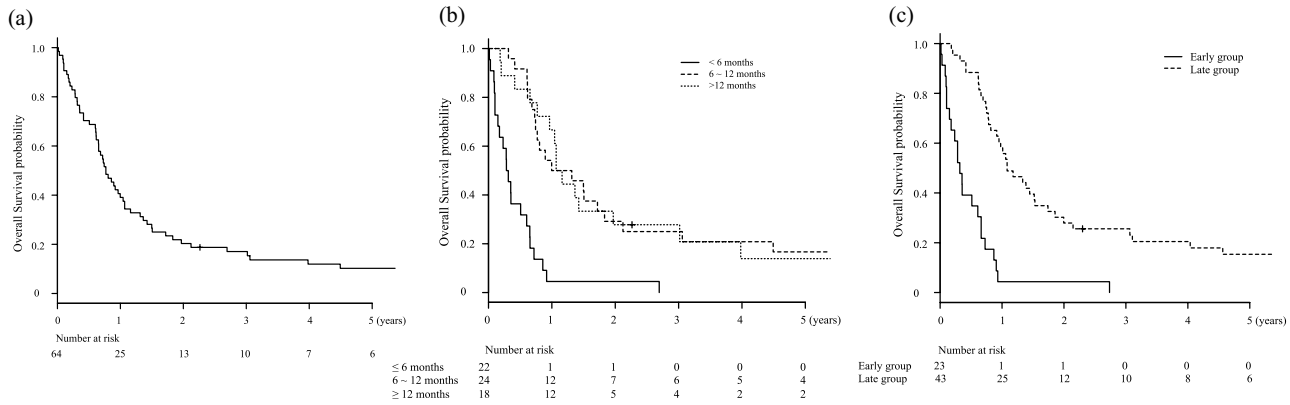

Fig. 2 OSr curves for **a** all patients, **b** three groups categorized based on the timing of recurrence, and **c** early and late recurrence groups (recurrence within and after 6 months after surgery, respectively). *OSr* overall survival after recurrence

combined as the late recurrence group. The following results were obtained by comparing the two groups: the early recurrence (ER) group (recurrence within 6 months after surgery) and the late recurrence (LR) group (recurrence 6 months after surgery). The OSr in the ER group was significantly poorer than that in the LR group (median OSr was 3.6 and 13.4 months, and the 1-year survival rate was 4.5% and 57.1% in the ER and LR groups, respectively; $P < 0.001$; Fig. 2c).

Relationship between the recurrence pattern and timing of recurrence

Table 1 shows the recurrence patterns based on the recurrence time after surgery. No significant differences were observed between the ER and LR groups in the number of organs in which esophageal cancer recurred simultaneously or in a pattern of lymph node metastasis. When comparing distant organ metastases, the incidence of lung metastasis tended to be higher for LR than that for ER (1 case of ER and 8 cases of LR, $P = 0.15$), and the incidence of liver metastasis was significantly higher for ER than that for LR (8 cases of ER and 3 cases of LR, $P = 0.0056$).

Relationship between clinicopathological characteristics and the timing of recurrence

Table 2 shows the relationship between clinicopathological characteristics and timing of recurrence. No differences in age, sex, tumor location, cT stage, or cN stage were observed between the two groups. Additionally, no statistically significant differences in the mean levels of tumor markers before treatment were observed between the groups.

When comparing NACs, although patients who received DCF had fewer recurrences than patients who received ACF (9 cases in the DCF group and 39 cases in the ACF group), no significant association was observed between the NAC regimen and timing of recurrence ($P = 0.79$). When comparing clinical responses to NAC, the number of primary lesions that responded was not statistically different between the two groups (15 cases [32.6%] in the ER and 31 cases [67.4%] in the LR groups [$P = 0.77$]), whereas the number of metastatic lymph node lesion that responded was significantly higher in the LR group (7 cases [31.8%]) than in the ER group (24 cases [57.1%]; $P = 0.050$).

Furthermore, no differences were observed between the two groups in terms of factors related to surgery or the incidence of postoperative complications.

Pathological findings revealed that the pathological tumor depth was not associated with the timing of recurrence ($P = 0.41$). In contrast, the number of patients with pathologically advanced nodal metastases was higher in the ER group than in the LR group ($P = 0.037$). Patients with lymphatic invasion were also more common in the ER group (19 cases [42.2%]) than in the LR group (26 cases [57.8%]; $P = 0.038$). Moreover, no differences were observed in histological evaluation between the two groups.

Table 1 Patterns of recurrence

	Early group (n = 22)	Late group (n = 42)	*P* value
Number of recurrent organ			
Single	17	36	0.49
Multiple	5	6	
Local recurrence	0	2	0.54
Lymph node recurrence			
All	13	25	1.0
Regional	10	24	0.60
Distant	4	4	0.43
Distant organ recurrence other than lymph node			
All	13	22	0.79
Lung	1	8	0.15
Liver	8	3	0.0056
Bone	3	2	0.33
Brain	0	1	1.0
Pleura	3	6	1.0
Other	1	4	0.65

Factors related to the timing of recurrence

Multivariate analysis with a logistic regression model was performed to investigate factors associated with early recurrence, including the clinical response of metastatic lymph nodes, pN, and lymphatic invasion as factors with p values < 0.1 in univariate analysis. "Clinical response of metastatic lymph node to NAC" and "ly" are binary variables, while "pN" is a multinomial variable, showing an odds ratio for a 1-unit increase in "pN" from 0, 1, 2, or 3. The result showed that only pN was an independent factor associated with early recurrence (odds ratio: 3.46, 95% confidence interval(CI): 1.47–8.02, $P = 0.0045$; Table 3).

Treatment after tumor recurrence

Among the 64 patients experiencing tumor recurrence, 51 out of 64 patients (79.7%) underwent at least one chemotherapy, (chemo)radiotherapy, or surgery. Specifically, chemotherapy was administered to 46 out of 64 patients (71.9%), (chemo)radiotherapy to 26 out of 64 (40.6%), and surgery to 5 out of 64 (7.8%).

When considering the timing of recurrence, it was noted that 14 out of 22 patients (63.6%) in the ER group and 37 out of 42 (88.1%) in the LR group underwent at least one

Table 2 Relationship between clinicopathological characteristics and the timing of recurrence

	Early group (n = 22)	Late group (n = 42)	*P* value
Age (mean [± SD]) (years)	64.3 [7.2]	65.9 [6.2]	0.37
Sex			
Male	20	38	1.0
Female	2	4	
BMI (mean [± SD]) (kg/m^2)	21.0 [3.3]	21.7 [3.0]	0.44
ECOG-PS			
0	18	34	1.0
1	4	8	
Location			
Ut	2	4	0.51
Mt	9	23	
Lt	11	15	
cT			
1	0	0	0.71
2	2	7	
3	20	35	
4	0	0	
cN			
0	2	5	0.17
1	11	21	
2	5	15	
3	4	1	
cStage (UICC 7th)			
I	0	1	0.47
II	4	10	
III	17	25	
IV	1	6	
Initial SCC (mean[± SD]) (ng/ml)	2.7 [3.6]	2.1 [3.7]	0.57
Initial p53 (mean[± SD]) (U/ml)	8.4 [12.6]	9.1 [29.2]	0.94
NAC regimen			
DCF	8	17	0.79
ACF	14	25	
Clinical response of primary lesion to NAC			
Responder	15	31	0.77
Non-responder	7	11	
Clinical response of metastatic lymph node to NAC			
Responder	7	24	0.050
Non-responder	13	13	
Operation time (median [range]) (min)	571 [344–772]	501 [467–960]	0.33
Blood loss (median [range]) (ml)	570 [200–1740]	605 [250–3460]	0.42
Postoperative complication (Clavien-Dindo grade ≥ 3)	1 (20.0)	4 (80.0)	0.65
pT			
0	1 (25.0)	3 (75.0)	0.41
1	1 (10.0)	9 (90.0)	
2	4 (33.3)	8 (66.7)	
3	14 (43.8)	18 (56.3)	
4	2 (33.3)	4 (66.7)	
pN			
0	2 (18.2)	9 (81.8)	0.037
1	3 (17.6)	14 (82.4)	

Table 2 (continued)

	Early group (n = 22)	Late group (n = 42)	*P* value
2	8 (36.4)	14 (63.6)	
3	9 (64.3)	5 (35.7)	
ly			
+	19 (42.2)	26 (57.8)	0.038
–	3 (15.8)	16 (84.2)	
v			
+	10 (43.5)	13 (56.5)	0.28
–	12 (29.3)	29 (70.7)	
Histological evaluation (Grade)			
0	3 (42.9)	4 (57.1)	0.81
1a	11 (40.7)	16 (59.3)	
1b	6 (30.0)	14 (70.0)	
2	1 (16.7)	5 (83.3)	
3	1 (25.0)	3 (75.0)	

SD standard deviation, *BMI* body mass index, *ECOG* Eastern Cooperative Oncology Group, *PS* performance status, *Ut* upper thoracic esophagus, *Mt* middle thoracic esophagus, *Lt* lower thoracic esophagus, *LYM* lymph node, *UICC* Union for International Cancer Control, *NAC* neoadjuvant chemotherapy, *DCF* Docetaxel + Cisplatin + Fluorouracil, *ACF* Adriamycin + Cisplatin + Fluorouracil, *ly* lymphatic invasion, *v* vascular invasion

Table 3 Factors related to early recurrence in multivariate analysis

Variables	Reference	odds ratio	95%CI		*P* value
			lower	upper	
Clinical responder of metastatic lymph node to NAC	Non-responder	0.29	0.08	1.07	0.063
pN[a]		3.46	1.47	8.20	0.0045
ly +	–	2.44	0.45	13.3	0.30

95%CI 95% confidence intervals, *NAC* neoadjuvant chemotherapy, *ly* lymphatic invasion

[a]"pN" is a multinomial variable, showing an odds ratio for a 1-unit increase in "pN" from 0, 1, 2, or 3

of chemotherapy, (chemo)radiotherapy, or surgery, with a significantly higher proportion observed in the LR group ($P = 0.046$).

Regarding specific treatments, chemotherapy was administered to 14 out of 22 patients (63.6%) in the ER group and 32 out of 42 (76.2%) in the LR group ($P = 0.38$). (Chemo) radiotherapy was administered to 6 out of 22 patients (27.3%) in the ER group and 20 out of 42 (47.6%) in the LR group ($P = 0.18$). Surgical intervention was performed in 0 out of 22 patients (0%) in the ER group and 5 out of 42 (11.9%) in the LR group ($P = 0.16$). Notably, local treatment comprising (chemo)radiotherapy and surgery was administered to 6 out of 22 patients (27.3%) in the ER group and 23 out of 42 (54.8%) in the LR group ($P = 0.063$) (Table 4).

The relationship between treatment administration after recurrence and OSr was additionally assessed by estimating OSr curves based on the timing of recurrence using the Kaplan–Meier method and comparing them using the log-rank test. The median survival time (MST) for patients with and without any chemotherapy, surgery, or (chemo) radiotherapy after relapse was 11.6 (95% confidence interval [CI]: 8.6–16.4) months and 2.8 (95%CI 1.0–5.0) months overall ($P < 0.001$); 6.7 (95%CI 3.4–8.6) months and 1.5 (95%CI 0.2–2.8) months in the ER group ($P < 0.001$); and 15.8 (95%CI 11.6–22.0) months and 7.4 (3.8-NA) months in the LR group, respectively ($P = 0.0596$) (Fig. 3a). The MST for patients with and without chemotherapy after relapse was 11.8 (95%CI 8.6–17.1) months and 4.6 (95%CI

Table 4 Treatment after tumor recurrence

	Early group (n = 22) (%)	Late group (n = 42) (%)	*P* value
Treatment after recurrence	14 (63.6%)	37 (88.1%)	0.046
Chemotherapy	14 (63.6%)	32 (76.2%)	0.38
(Chemo)radiotherapy	6 (27.3%)	20 (47.6%)	0.18
Surgery	0 (0%)	4 (11.9%)	0.29
Local treatment[a]	6 (27.3%)	23 (54.8%)	0.063

[a]Local treatment includes surgery and (chemo)radiotherapy

1.8–7.4) months overall ($P = 0.0056$); 6.7 (95%CI 3.4–8.6) months and 1.5 (95%CI 0.2–2.8) months in the ER group ($P < 0.001$); and 16.7 (95%CI 11.6–23.6) months and 8.1 (95%CI 3.8–12.8) months in the LR group, respectively ($P = 0.0859$) (Fig. 3b). The MST for patients with and without local treatment was 15.8 (95%CI 8.9–23.6) months and 7.3 (95%CI 3.7–9.2) months overall ($P = 0.0012$); 6.0 (95%CI 1.1-NA) months and 3.1 (95%CI 1.2–6.1) months in the ER group ($P = 0.0806$); and 18.0 (95%CI 11.6–25.5) months and 10.7 (95%CI 7.3–16.4) months in the LR group ($P = 0.037$), respectively (Fig. 3c).

Factors related to overall survival after recurrence

To determine the hazard ratio (HR) of clinicopathological factors for overall survival after recurrence, both univariate and multivariate analyses were performed using the Cox proportional hazards model, as outlined in Table 5. The results of the multivariate analysis, which included factors with a significance level of $P < 0.1$ in the univariate analysis, revealed several independent prognostic factors after recurrence. These included pT (HR: 1.91, 95%CI 1.26–2.88, P = 0.0022), early recurrence (HR: 6.88, 95%CI 2.68–17.6, $P < 0.001$), and treatment after recurrence, with both local treatment (HR: 0.47, 95%CI 0.22–0.98, $P = 0.043$) and chemotherapy (HR: 0.25, 95%CI 0.11–0.58, $P = 0.0011$) emerging as independent prognostic factors.

Discussion

This study revealed that patients with advanced esophageal cancer who experienced recurrence within 6 months after radical esophagectomy following NAC had extremely poor prognoses. The occurrence of liver metastasis was significantly higher in patients with early recurrence, and patients with pathologically more advanced lymph node metastases were found to be at a higher risk of early recurrence.

To our knowledge, two reports have retrospectively investigated the association between the timing of recurrence and prognosis after postoperative recurrence of esophageal cancer in a single-center setting [9, 10]. Compared to these reports, our study was based on data from a multicenter prospective study, which made our results more reliable because of the lack of missing data regarding prognostic analysis, minimal information bias, and high external validity.

In a report by Kurogochi et al., patients with cStage II/III (UICC 7th edition) esophageal cancer that recurred within 12 months after surgery following NAC had a poor prognosis. All patients in the study received NAC consisting of 5-FU and cisplatin. In another study by Hsu et al., patients with recurrence within 10 months of surgery were found to have a poor prognosis. None of the patients received preoperative neoadjuvant therapy, and adjuvant chemoradiotherapy was indicated for patients with pT3/4 and positive lymph node metastases. Despite differences in eligible patients and perioperative treatment between our study and the aforementioned studies, these reports are consistent with our results in terms of the poor prognosis associated with postoperative early recurrence.

The results of this study showed that the ER group had a very poor prognosis. The MST after recurrence was 3.6 months in the ER and 13.4 months in the LR groups. When comparing clinical factors between the ER and LR groups, there were significant differences in treatment opportunities after relapse, with significantly fewer cases in the ER group receiving treatment after relapse. These results indicate that although treatment had a certain positive effect on prognosis in the ER group, the MST in the group receiving any treatment was 6.7 months, shorter than the MST in the LR group without treatment (7.4 months). A similar trend was observed when focusing on the type of treatment (chemotherapy and local treatment). This may be due not only to the rapid disease progression after relapse in the ER group, limiting treatment opportunities for patients, but also to the poor response to treatment after recurrence, which may lead to a poorer prognosis. Shimada et al. reported that patients with recurrence within 1 year after surgery had a poor response to postoperative treatment and poor prognosis, which is consistent with our results [2].

Our results demonstrated that the occurrence of liver metastases was significantly high in patients with early recurrence. Although few reports are available on the relationship between the timing of recurrence after esophagectomy and the site of recurrence (organ), some reports indicate that recurrence in the lung after esophagectomy has a relatively good prognosis and long-term survival may be expected with surgical metastasectomy. Conversely, recurrence in another hematogenous organ, such as the liver, is associated with a poor prognosis [16, 17]. These results suggest that recurrence in the liver after esophagectomy tends to occur in the early postoperative period and progresses rapidly, resulting in poor prognosis, whereas recurrence in the lung tends to occur relatively late after surgery and progresses slowly, suggesting that metastasectomy may provide a long-term prognosis.

Several studies have investigated the risk factors for early recurrence [10, 18–24], and some have suggested pathological nodal metastasis as an independent risk factor for early recurrence [18, 19, 21, 24–27], which is consistent with the results of our study. However, most of these studies included patients who underwent surgery alone or in combination with neoadjuvant therapy, such as chemoradiotherapy. In recent years, especially in Japan, NAC followed by esophagectomy has been established as the standard of care for resectable advanced esophageal cancer [12, 28, 29], and

Table 5 Univariate and multivariate hazard ratios of clinicopathological factors for overall survival after recurrence

Variables		Reference	Univariate				Multivariate			
			Hazard ratio	95%CI		*P* value	Hazard ratio	95%CI		*P* value
				Lower	Upper			Lower	Upper	
Age (≥ 65 years)	≥65	<65	1.26	0.74	2.14	0.40				
Sex	Male	Female	1.02	0.41	2.56	0.96				
BMI (kg/m^2)	≥21	<21	0.84	0.49	1.43	0.52				
ECOG-PS	1	0	1.98	1.02	3.84	0.044	1.49	0.66	3.33	0.34
Location	Ut	Mt, Lt	0.87	0.33	2.29	0.77				
	Mt	Ut, Lt	1.45	0.84	2.50	0.19				
	Lt	Ut, Mt	0.76	0.45	1.29	0.31				
cT			2.02	0.91	4.50	0.085	1.37	0.51	3.68	0.53
cN			1.04	0.73	1.49	0.82				
cStage	1, 2	3, 4	0.81	0.44	1.51	0.51				
NAC regimen	DCF	ACF	1.22	0.72	2.08	0.47				
Clinical response of primary lesion to NAC	Responder	Non–responder	0.48	0.27	0.84	0.011	0.60	0.21	1.75	0.35
Clinical response of metastatic lymph node to NAC	Responder	Non–responder	0.37	0.21	0.65	<0.001	0.85	0.35	2.04	0.72
Surgical approach	Thoracoscopy	Thoracotomy	0.98	0.52	1.85	0.95				
Operation time (min)	≥500	<500	1.45	0.85	2.46	0.18				
Blood loss (ml)	≥600	<600	1.40	0.83	2.37	0.21				
Postoperative complication (Clavien-Dindo grade ≥ 3)	+	–	0.91	0.36	2.29	0.84				
pT			1.49	1.14	1.96	0.0039	1.91	1.26	2.88	0.0022
pN			1.39	1.05	1.84	0.021	0.73	0.49	1.10	0.14
ly	+	–	1.12	0.63	2.00	0.69				
v	+	–	1.26	0.73	2.16	0.40				
Histological evaluation (Grade)	0-1a	1b–3	0.90	0.54	1.51	0.68				
Timing of recurrence	Early	Late	4.81	2.68	8.64	<0.001	6.88	2.68	17.6	<0.001
Number of recurrent organs	Multiple	Single	1.28	0.66	2.47	0.47				
Local recurrence	+	–	0.79	0.19	3.24	0.74				
Lymph node recurrence										
All	+	–	1.05	0.62	1.79	0.85				
Regional	+	–	0.99	0.59	1.66	0.97				
Distant	+	–	0.93	0.44	1.98	0.85				
Distant organ recurrence other than lymph node										
All	+	–	1.07	0.64	1.80	0.79				
Lung	+	–	0.31	0.12	0.80	0.015	0.40	0.12	1.35	0.14
Liver	+	–	2.96	1.46	5.97	0.0025	1.03	0.35	3.06	0.96
Bone	+	–	1.32	0.52	3.31	0.56				

Table 5 (continued)

Variables		Reference	Univariate				Multivariate			
			Hazard ratio	95%CI		*P* value	Hazard ratio	95%CI		*P* value
				Lower	Upper			Lower	Upper	
Brain	+	–	1.79	0.24	13.2	0.57				
Pleura	+	–	1.35	0.66	2.75	0.42				
Other	+	–	1.62	0.64	4.09	0.31				
Treatment after recurrence	+	–	0.28	0.15	0.54	< 0.001				
Chemotherapy	+	–	0.45	0.25	0.81	0.0070	0.25	0.11	0.58	0.0011
(Chemo)radiotherapy	+	–	0.60	0.35	1.02	0.059				
Surgery	+	–	0.36	0.11	1.14	0.083				
Local treatment[a]	+	–	0.42	0.25	0.72	0.0017	0.47	0.22	0.98	0.043

SD standard deviation, *BMI* body mass index, *ECOG* Eastern Cooperative Oncology Group, *PS* performance status, *Ut* upper thoracic esophagus, *Mt* middle thoracic esophagus, *Lt* lower thoracic esophagus, *LYM* lymph node, *UICC* Union for International Cancer Control, *NAC* neoadjuvant chemotherapy, *DCF* Docetaxel + Cisplatin + Fluorouracil, *ACF* Adriamycin + Cisplatin + Fluorouracil, *ly* lymphatic invasion, *v* vascular invasion

[a]Local treatment includes surgery and (chemo)radiotherapy

our results can be extrapolated to current clinical practice in Japan. Patients with advanced pN are at high risk of early recurrence. Thorough imaging follow-up is necessary, and adjuvant therapy should be included in high-risk cases.

The long-term outcomes of the OGSG1003 trial revealed a notable difference in the 5-year relapse-free survival rates between the ACF and DCF groups, with rates of 40.7% and 59.9%, respectively. This indicates a significantly lower risk of relapse in the DCF group (HR: 0.55, 95%CI 0.35–0.86, $P = 0.012$). Similarly, the 5-year overall survival (OS) rates were 49.4% in the ACF group and 63.5% in the DCF group, with the DCF group exhibiting a significantly lower risk of death (HR: 0.61, 95%CI 0.38–0.96, $P = 0.034$) [11]. However, our findings indicate that the NAC regimen (ACF or DCF) did not correlate with the timing of recurrence or survival after recurrence (Table 5). These results imply that while intensifying NAC may effectively reduce recurrence rates and enhance overall prognosis, it may not necessarily influence the timing of recurrence or improve survival outcomes in cases where recurrence does occur.

It is important to establish further adjuvant therapy for patients at a high risk of recurrence, that is, those with poor prognosis. The CheckMate 577 trial demonstrated the efficacy of adjuvant nivolumab in patients with advanced esophageal cancer who underwent esophagectomy after neoadjuvant chemoradiotherapy [30]. To the best of our knowledge, this large-scale randomized controlled trial is the first to demonstrate the survival benefits of adjuvant therapy after neoadjuvant therapy. Postoperative adjuvant nivolumab may be effective in preventing recurrence, especially in patients at high risk of recurrence after esophagectomy following NAC; however, the indication for adjuvant nivolumab should be carefully considered because of insufficient evidence, immune-related adverse events, and high cost. A prospective observational study of adjuvant nivolumab in patients with esophageal cancer after esophagectomy following neoadjuvant chemotherapy or chemoradiotherapy was conducted by the Japan Esophageal Society, and a phase III randomized controlled trial of postoperative adjuvant therapy, including nivolumab, in patients with esophageal cancer undergoing esophagectomy after NAC was performed by the Japan Clinical Oncology Group (JCOG 2206 trial). To provide an appropriate treatment strategy for high-risk patients, evidence for adjuvant therapy should be established, and factors associated with patient prognosis, including clinicopathological and biological factors, should be explored.

In conclusion, patients with advanced esophageal cancer who develop recurrence within 6 months of esophagectomy following NAC have a poor prognosis, and advanced pN is an independent risk factor for early recurrence.

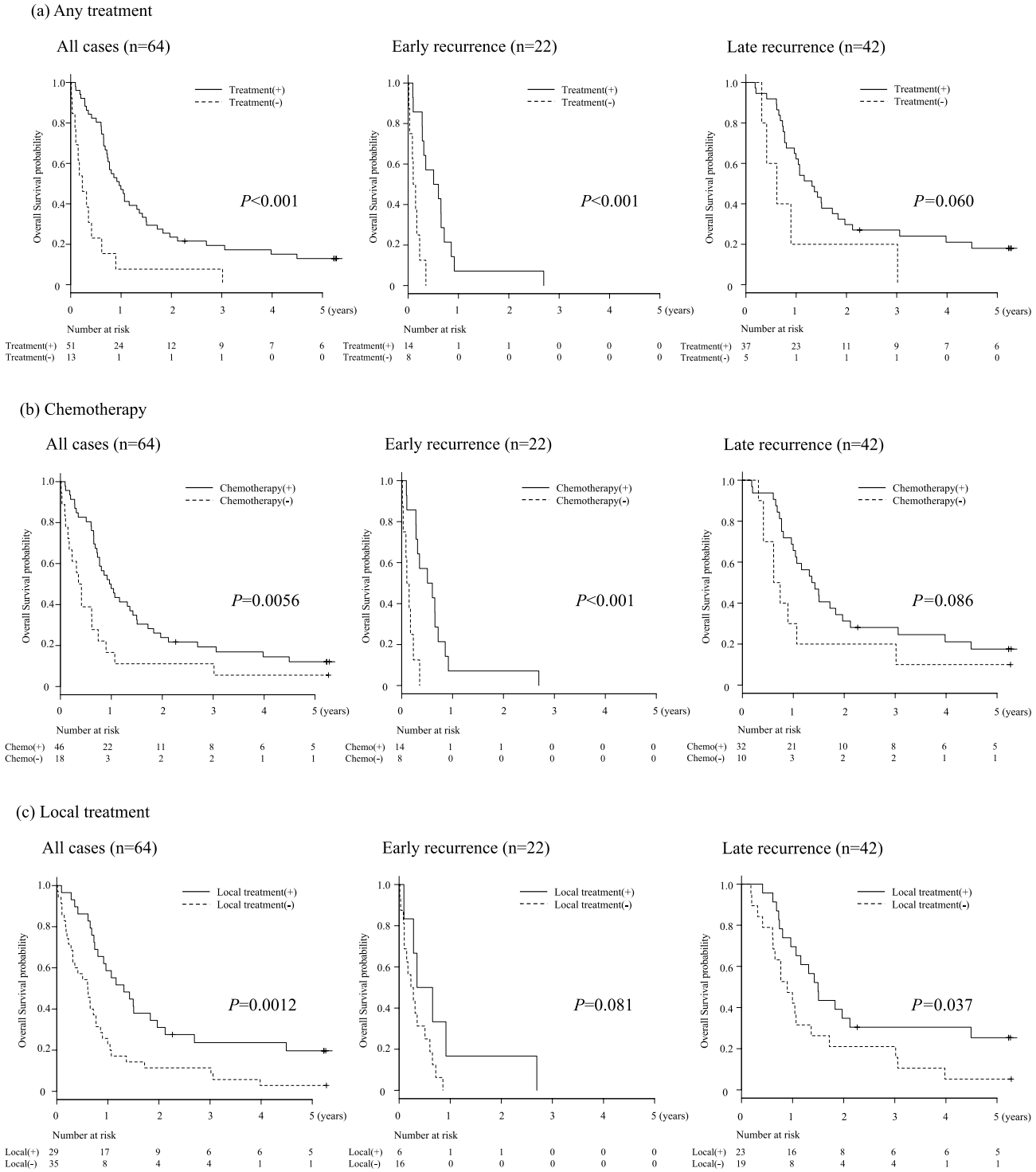

Fig. 3 Relationship between treatment administration after recurrence and OSr based on the timing of recurrence using Kaplan–Meier method and log-rank test. **a** Any treatment including chemotherapy, (chemo)radiotherapy and surgery, **b** chemotherapy, and **c** local treatment including (chemo)radiotherapy and surgery. *OSr* overall survival after recurrence

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Data availability The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Declarations

Conflict of interest None.

Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent was obtained from all patients to be included in the study.

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