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ORIGINAL ARTICLE

How does presurgical chemotherapy influence the efficiency of treatment for esophageal cancer recurrence after curative esophagectomy?

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Abstract

Background: The effectiveness of treatments for recurrent esophageal squamous cell carcinoma (ESCC), particularly chemotherapy and chemoradiotherapy (CRT), remains unclear in patients who have previously been administered the same drugs during neoadjuvant chemotherapy.

Methods: In this retrospective study, 117 patients with recurrent thoracic ESCCs who had undergone curative resection were included. Patients were divided into two groups based on presurgical treatment: no presurgical treatment (n = 74), and neoadjuvant chemotherapy (n = 43). Prognosis after recurrence was analyzed differently in the group of patients who received CRT and chemotherapy for a recurrent site because of differences in recurrence patterns.

Results: There were no differences in patterns and times to recurrence between the patients who underwent each presurgical treatment. For treatment of recurrence, CRT was administered to 66 patients, chemotherapy to 32, surgical resection to 5, and best supportive care to 14. In patients who underwent CRT for local recurrence, the survival rates of those administered neoadjuvant chemotherapy were similar to those who did not receive any presurgical treatment (P = 0.706). In patients who underwent chemotherapy for distant metastasis, the survival rates of those administered neoadjuvant chemotherapy were worse than in those who did not receive any presurgical treatment (P = 0.028).

Conclusions: The effects of CRT for recurrent cancers are not influenced by neoadjuvant chemotherapy, even when using the same anticancer agent. Chemotherapy is an acceptable treatment for patients who do not receive presurgical treatment.

Introduction

Esophagectomy with lymph node dissection is the standard treatment for patients with resectable thoracic esophageal squamous cell carcinomas (ESCC). Unfortunately, more than 40% of patients develop recurrence, even after undergoing curative resection.[1–6] For such patients, chemotherapy or chemoradiotherapy (CRT) are the main treatments for recurrence.[6–8] However, patients have often previously been treated with these anticancer agents before undergoing treatment for recurrence.

Presently, presurgical therapies, such as neoadjuvant chemotherapy (NAC), neoadjuvant CRT, or definitive CRT, have become common for ESCC because of their effectiveness.[9–13] The main anticancer agents for presurgical therapy are 5-fluorouracil (5FU) and platinum agents, which remain the key drugs for postoperative chemotherapy or CRT for recurrence. However, the effectiveness of these treatments for recurrence in patients who have previously been treated with these drugs remains unclear. Therefore, in this study we evaluated ESCC patients who underwent curative resection but developed recurrence to

analyze if the presurgical treatments administered to these patients influenced their treatment for recurrence.

Methods

Patients

Between January 2001 and August 2015, 513 patients with ESCCs were treated via subtotal esophagectomy at our institution, and 484 patients underwent curative resection, both clinically and pathologically. Among these, ESCC recurrence was detected in 184 patients. To exclude the treatment effects resulting from radiation, 21 patients administered neoadjuvant CRT and 32 administered definitive CRT followed by esophagectomy were excluded. Nine patients administered adjuvant chemotherapy or CRT were excluded because the effects of recurrence treatment would be modified in these patients. Additionally, five cases for which appropriate treatment and prognostic records could not be obtained were excluded. A total of 117 patients who developed ESCC recurrence were included in this retrospective study. The characteristics of the patients are shown in Table 1.

The study protocol was reviewed and approved by the Tohoku University Institutional Review Board (2017–1-458) and informed consent was obtained from all patients before enrollment. The study was conducted in accordance with the Declaration of Helsinki (1975).

Presurgical treatment

Patients diagnosed with stage II or III ESCC according to 2017 tumor node metastasis (TNM) criteria were administered NAC according to previously reported protocols.[12] This chemotherapy regimen used 5FU and cisplatin as anticancer agents. Patients who had undergone esophagectomy before 2007 or patients who were not indicated for chemotherapy, such as those with renal failure, underwent surgery without neoadjuvant therapy.

Surgery

All patients underwent subtotal esophagectomy with radical lymphadenectomy, either with fifth intercostal thoracotomy or a thoracoscopic procedure (Table 1). In most cases, the stomach is used for reconstruction; however, in cases in which the use of the stomach was not feasible, such as after gastrectomy or in cases of gastric cancer, we used the colon or jejunum. All specimens were pathologically diagnosed at the Tohoku University Department of Pathology. The seventh edition Union for International Cancer Control was used for TNM classification, and pathology results determined the T and N scales.

Follow-up

Patients were mainly followed up at our outpatient clinic; those who lived far from our hospital were followed up at a cooperative hospital. To check for recurrence, contrasted computed tomography scans with blood tests were routinely performed once every four months for two years after esophagectomy, and once every six months for the next three years. Additionally, in cases where the presence of recurrence was suspected, positron emission tomography scans or ultrasound examinations were performed for extensive examination.

Table 1 Characteristics of patients with ESCC who experienced recurrence after curative resection

Characteristics	Total	Non-presurgical treatment	NAC	*P*
Number of patients	117	74	43	
Age in years (mean, average)	66, 65.4	66, 65.5	66, 65.3	0.773
Gender (male, female)	102, 15	63, 11	39, 4	0.568
Clinical stage of original ESCC				0.016
I	13	13	0	
II	32	21	11	
III	65	35	30	
IV	7	5	2	
Type of surgery				0.297
McKeown	114	71	43	
Ivor–Lewis	3	3	0	
Pathological ESCC stage				0.145
I	11	10	1	
II	26	16	10	
III	71	41	30	
IV	9	7	2	

ESCC, esophageal squamous cell carcinoma; NAC, neoadjuvant chemotherapy.

Treatment for recurrence

CRT was administered to patients with recurrence in localized areas. If the recurrence lesions were detected in multiple areas, chemotherapy was indicated as an alternative treatment. Surgical resection was considered if the recurrence was solitary or localized and believed to be completely resectable. Best supportive care was provided to patients who could not tolerate CRT or chemotherapy, or to patients who did not wish to undergo additional treatment.

Details of the CRT regimen have been described previously.[8,14] Briefly, 700 mg/m^2 of 5FU was administered continuously for four days on days 1 and 28, with 70 mg/m^2 of cisplatin or nedaplatin on days 1 and 28, respectively. Radiation therapy was commenced on the same day as the anticancer agents, and 1.8–2.0 Gy daily fraction doses and 60–66 Gy total doses were used for irradiation.

Chemotherapy was performed by administering 700 mg/m^2 of 5FU from days 1 to 5 and 70 mg/m^2 of cisplatin on day 1 for four weeks. Additionally, 70 mg/m^2 of docetaxel was administered to five patients every three weeks.[15] When toxicity of grade 3 or higher was observed, we suspended or discontinued chemotherapy entirely or reduced the dose of anticancer agents in the subsequent cycle.

Patients in whom treatment for recurrence failed may have a chance to continue chemotherapy, either with the same regimen or modified to docetaxel. However, none of the patients who failed initial treatment for recurrence could achieve a complete response by subsequent treatment.

Statistics

The Wilcoxon test was used for intergroup comparisons of continuous variables, and the Pearson test to compare categorized data. Overall survival was calculated from the day of the start of treatment for recurrence to the time of death or last follow-up. The survival rate was analyzed using the Kaplan–Meier method, and all causes of death were included. Patients who were alive for more than five years after recurrence were censored. The statistical significance of the survival differences was compared by the log rank test. These analyses were performed electronically using JMP Pro 11.0 statistical software (SAS, Cary, NC, USA). Values of $P < 0.05$ were considered to indicate statistical significance.

Results

The clinical and pathologic characteristics of the study population are summarized in Table 1. All stage IV patients had metastases in the supraclavicular lymph node (LN), which is considered distant metastasis per the current TNM criteria. LN recurrence was observed in 60 patients, organ recurrence in 29, peritoneal or pleural recurrence in 11, and combined metastases in 17. CRT was selected as the treatment for recurrence in more than half of the cases, and chemotherapy in less than a third of the cases in this study.

The median day until recurrence was 258 among all patients, and ESCC recurrence was usually detected within one year after surgery, as shown in Table 2. There were no differences in patterns and times to recurrence between patients who underwent each presurgical treatment.

CRT was administered in 66 patients and chemotherapy in 32. Five patients who underwent surgical resection for recurrence received CRT or chemotherapy before or after surgery; however, they were not categorized into the CRT or chemotherapy groups because it is well known that patients who can undergo surgical resection for recurrence have good prognoses,[4–6] which can modify the effects of recurrence treatment. In the patients who underwent CRT to treat recurrence, the survival of patients who did not receive any presurgical treatment and of patients

Table 2 Differences in recurrence patterns and treatments according to the different types of presurgical treatments administered

Variables	Non presurgical treatment (n = 74)	NAC (n = 43)	P
Time to recurrence after surgery			0.183*
Median days	247.5	261	
Average days (95th percentile)	401 (316–485)	261 (209–312)	
Recurrence within 1 year (%)	48 (64.9)	34 (79.1)	0.143**
Recurrence location			0.871**
Lymph node (%)	38 (51.4)	22 (51.2)	
Organ (%)	17 (23.0)	12 (27.9)	
Peritoneum and/or pleura (%)	8 (10.8)	3 (7.0)	
Combined (%)	11 (14.9)	6 (14.0)	
Initial treatment for recurrence			0.227*
CRT	39 (52.7)	27 (62.8)	
Chemotherapy	19 (25.7)	13 (30.2)	
Surgical resection	4 (5.4)	1 (2.3)	
BSC	12 (16.2)	2 (4.7)	
Outcome			0.648*
Alive	12	10	
Death from cancer	60	32	
Death from other reasons	2	1	

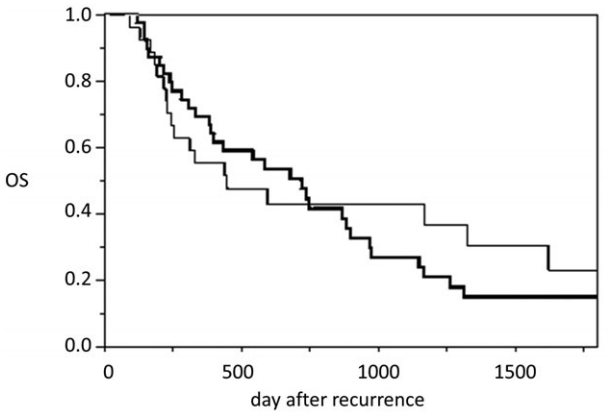
P value was evaluated by *Wilcoxon or **Pearson test. BSC, best supportive care; CRT, chemoradiotherapy; NAC, neoadjuvant chemotherapy.

administered NAC were similar (Fig 1). However, in the patients who underwent chemotherapy to treat recurrence, the survival of the patients administered NAC was worse than those who did not receive any presurgical treatment (Fig 2).

We also analyzed the survival data classified as early and late recurrence using the mean duration from esophagectomy to recurrence (258 days). In the patients administered CRT to treat recurrence, patients with late recurrence showed better survival than patients with early recurrence in each presurgical treatment group (Fig 3). Conversely, the time to recurrence did not affect the survival of patients administered chemotherapy to treat recurrence in any presurgical treatment group (Fig 4).

Discussion

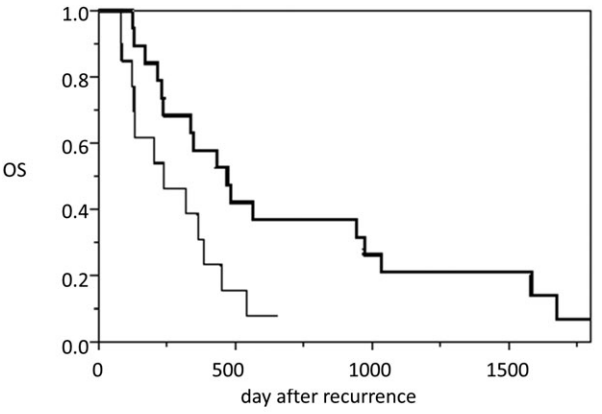
The rate of recurrence after curative resection of ESCC is reported as 31–47%.[1–6] For patients who experience recurrence, it is still possible to treat the recurrent site, regardless of whether they have been administered neoadjuvant therapy. However, as far as we know, few reports have evaluated how presurgical treatment affects treatment for ESCC recurrence. Although an evaluation of treatment for recurrence is necessary, a randomized trial to answer this question is difficult to perform because each case of recurrence has a different background. For these reasons, we adapted a retrospective approach because it is suitable for analyzing the cohort, which has many potential biases.



No. at risk

day	0	300	600	900	1200	1500
Non pre-treatment	39	30	20	13	8	3
Neo adjuvant	27	16	10	8	7	5

Figure 1 Survival curves following recurrence in patients administered chemoradiotherapy (CRT) as second-line treatment according to presurgical treatment type (P = 0.706). (——) Non pretreatment, and (——) neoadjuvant chemotherapy (NAC). OS, overall survival.



No. at risk

day	0	300	600	900	1200	1500
Non pre-treatment	19	14	8	8	4	4
Neo adjuvant	13	9	2	-	-	-

Figure 2 Survival curves following recurrence in patients administered chemotherapy as second-line treatment according to the presurgical treatment type (P = 0.028). (——) Non pretreatment, and (——) neoadjuvant chemotherapy (NAC). OS, overall survival.

Among the patients who underwent CRT for recurrence, the group of patients administered NAC showed similar survival to patients that did not receive any presurgical treatment. This suggests that CRT can provide similar treatment effects for patients, including those who have had prior treatment with the same anticancer agents, as patients who have not been treated previously with anticancer agents. Clinically, the repeat use of previously administered anticancer agents during CRT for recurrence is a pertinent issue. Previous reports have shown that platinum agents can biologically enhance the effects of radiation on cancer cells;[16] therefore, we assumed that treatment with CRT using previously administered anticancer agents is effective for recurrent cancer. Our results suggest that 5FU and platinum agents are effective drugs to treat patients who have undergone prior treatment, but need further administration of these drugs during CRT for recurrence.

Conversely, chemotherapy for recurrence in patients administered NAC was less effective than in patients who did not receive previous treatment with anticancer agents. This does not mean that NAC does not have overall advantages compared to non-neoadjuvant therapy; this is specific to patients who experience recurrence. Thus, treatment for patients administered NAC that experience recurrence after surgery poses a problem. If resistance to anticancer agents is a barrier to chemotherapy in the patients who have already been treated with an anticancer

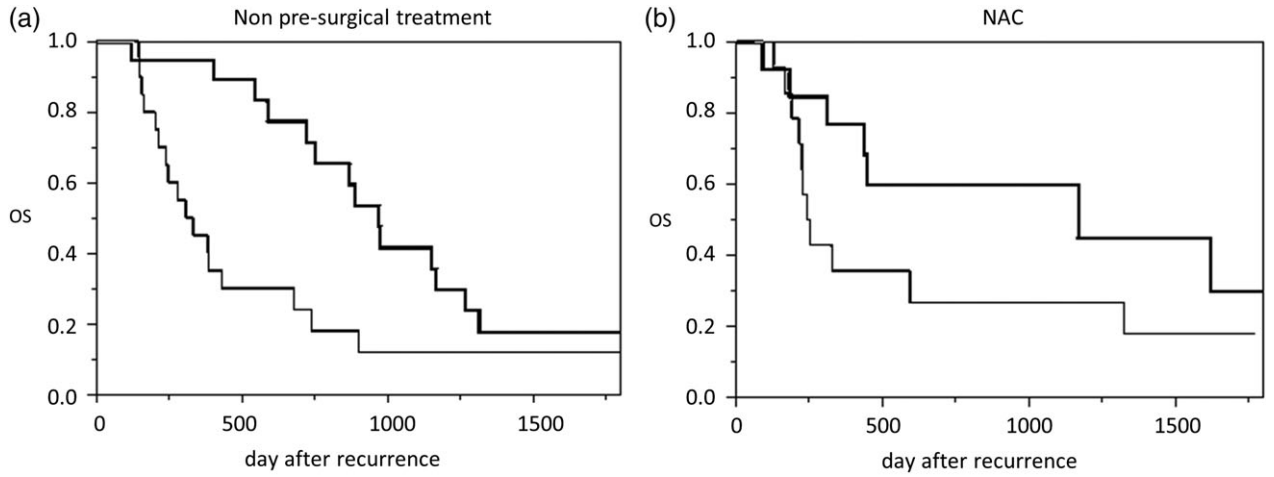


Figure 3 Survival curves following recurrence in patients administered chemoradiotherapy (CRT) as second-line treatment according to presurgical treatment type, classified on the basis of the mean time to recurrence from the day after surgery (262 days): (**a**) no presurgical treatment ($P = 0.010$), (**b**) neoadjuvant chemotherapy (NAC) ($P = 0.134$). (——) Late recurrence, and (——) Early recurrence. OS, overall survival.

agent, then different types of anticancer agents may be more effective in these patients. Unfortunately, our study included a small number of patients who had been treated with agents other than 5FU and cisplatin; therefore, an appropriate solution requires further evaluation.

In the patients treated by CRT in both presurgical treatment groups, patients with early recurrence had poorer prognoses than those with late recurrence (Fig 3).[17] This suggests that local treatments, like CRT, are not as effective for early recurrence, because undetected multiple metastases may already have spread at the time of surgery in these cases, and detectable metastasis would be evident after undergoing CRT at the primary recurrence lesion. In contrast, recurrence lesions detected after a longer duration after surgery would comprise metastases that would have had sufficient time to propagate. In those cases, local treatments, such as CRT, would be expected to be effective for recurrence.

However, in patients treated with chemotherapy, the time to recurrence did not affect survival in any presurgical treatment group (Fig 4). Patients who underwent chemotherapy for recurrence may be developing systemic metastases, regardless of the time to recurrence. Conversely, patients who receive CRT for late recurrence may only develop recurrence in local areas. This resulted in survival differences between patients undergoing these different treatments for early or late recurrence.

Our study has several potential limitations: it was a retrospective single-center study covering 15 years with a

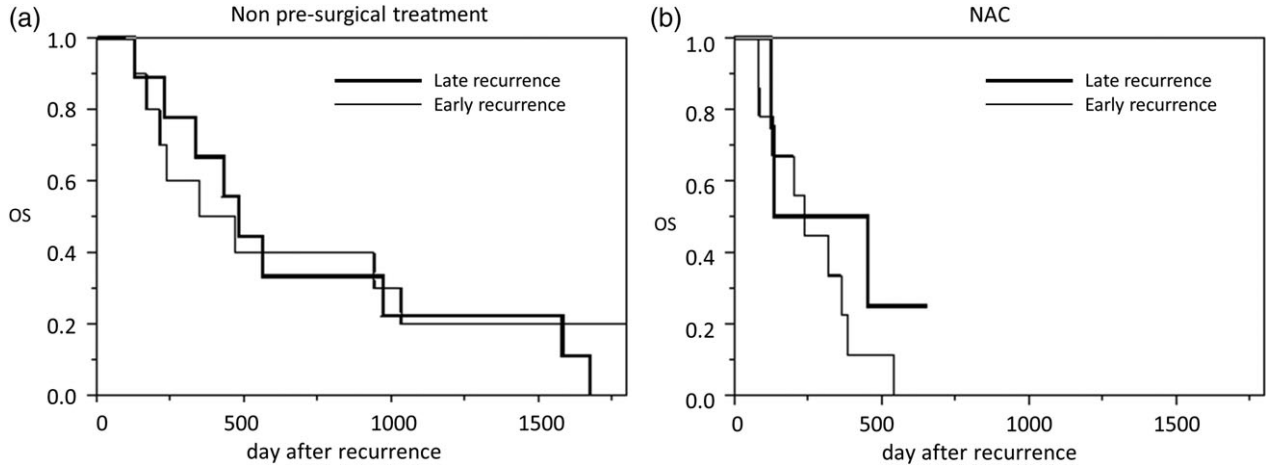


Figure 4 Survival curves following recurrence in patients administered chemotherapy as second-line treatment according to the presurgical treatment type, classified on the basis of the mean time to recurrence from the day after surgery (262 days): (**a**) no presurgical treatment ($P = 0.850$), (**b**) neoadjuvant chemotherapy (NAC) ($P = 0.336$). (——) Late recurrence, and (——) Early recurrence. OS, overall survival.

relatively small sample size. The actual number of patients with ESCC recurrence after curative esophagectomy was also small. Our results provide significant data and could promote further investigation, such as a multicenter study. Furthermore, the backgrounds between the NAC and non-presurgical groups differed, especially regarding the clinical features of the original ESCC. However, this cohort was limited to only patients with recurrence, and survival analysis was calculated from the point when they developed recurrence. Although the number of patients who match this cohort might differ between the two groups, the prognoses should not be affected by the original clinical stage of ESCC.

In conclusion, the efficiency of CRT treatment is not affected by neoadjuvant therapy. If patients who have not received any prior presurgical treatment do not meet the criteria for CRT, chemotherapy is also a good treatment option. The prognoses of patients already administered neoadjuvant therapy that require chemotherapy to treat recurrence are less favorable. Further development of new anticancer agents is anticipated.

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Disclosure

No authors report any conflict of interest.

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