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ORIGINAL ARTICLE

Risk factors of early recurrence within 6 months after esophagectomy following neoadjuvant chemotherapy for resectable advanced esophageal squamous cell carcinoma

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Abstract
Background Esophagectomy following neoadjuvant chemotherapy (NAC) is a standard treatment for resectable advanced esophageal cancer in Japan. However, approximately 10 % of patients with resectable advanced esophageal cancer experience recurrence within 6 months.
Methods One hundred twenty-eight patients with resectable advanced esophageal cancer underwent NAC between October 2008 and July 2015 in Kumamoto University Hospital. Among them, 82 patients with esophageal squamous cell carcinoma (SCC), who underwent curative esophagectomy without adjuvant treatment, were eligible. Clinicopathological factors correlated with early recurrence were retrospectively analyzed.
Results Of 82 patients, 14 (17 %) recurred within 6 months after surgery. The logistic regression analysis suggested that CRP before NAC $\geq$ 0.5 mg/dl [hazard ratio (HR) 33.8, 95 % confidence interval (CI) 2.767–413.9; $p = 0.006$), presence of poorly differentiated SCC component (HR 138, 95 % CI 5.339–3576; $p = 0.003$), and pathological vessel invasion (HR 16.3, 95 % CI 1.960–136.1; $p = 0.010$) were candidates for independent risk factors of early recurrence. Patients with at least two factors frequently recurred (82 %). Of 14 patients with early recurrence, 13 (93 %) had a distant metastasis.
Conclusions Patients with resectable advanced esophageal cancer with at least two factors of CRP before NAC $\geq$ 0.5 mg/dl, presence of poorly differentiated SCC component, and pathological vessel invasion might be at high risk for early recurrence after esophagectomy following NAC. These patients might be considered for additional treatment and should be meticulously followed up after treatment.

Keywords Early recurrence · Esophageal cancer · Esophagectomy · Neoadjuvant chemotherapy

Introduction

Although esophageal cancer remains a refractory neoplasm, treatment results have been improving in the recent decade [1]. Regarding resectable advanced esophageal cancer, the 5-year overall survival (OS) rate was reported to be 17–52 % when treated with surgery alone [2–4]. Recent randomized controlled trials (RCTs) proved that additional treatment with esophagectomy significantly improved the 5-year OS compared with those after surgery alone [2–5]. The standard treatment for resectable advanced esophageal cancer differs between Western and Eastern countries. In Western countries, neoadjuvant chemoradiotherapy (CRT) is common. However, in Japan, neoadjuvant chemotherapy (NAC) is usually considered before esophagectomy [6].

In patients with resectable advanced esophageal cancer, early recurrence sometimes occurs after these standard treatments. In previous studies on NAC, approximately 10 % of patients with resectable advanced esophageal cancer were noted to recur within 6 months after surgery [6–9]. Although these patients might require further treatment or meticulous follow-up after surgery, it is unclear as to which

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cohort might recur in such an early period. Although there are several studies on the risk factors of early recurrence after surgery alone or neoadjuvant treatment including CRT [10–13], to our knowledge, the risk factors of early recurrence after only NAC for resectable advanced esophageal cancer have never been investigated.

In the present study, we retrospectively examined the clinicopathological factors in patients with resectable advanced esophageal cancer, which correlate with early recurrence within 6 months after esophagectomy following NAC. In addition, we also investigated the pattern of early recurrences to estimate the ideal additional treatment.

Materials and methods

Patients

Between October 2008 and July 2015, 128 patients with resectable advanced esophageal cancer received NAC, which consisted of docetaxel, cisplatin, and 5-FU (DCF), or 5-fluorouracil (FU) and cisplatin (FP), followed by surgery at the Department of Gastroenterological Surgery, Kumamoto University. Among these patients, 6 who underwent surgery other than subtotal esophagectomy, 4 who had remnant cancer after esophagectomy, 6 who were followed up not more than 6 months after surgery, and 8 who had a cancer histologically different from squamous cell carcinoma (SCC) were excluded from this study. Moreover, 22 patients who received additional treatment after surgery were also excluded because such treatments certainly affect the timing of recurrence. Consequently, 82 patients were eligible for this study. Clinical, surgical, and pathological data were collected from among the prospectively entered data in the clinical database. The pretreatment tumor stage was classified according to the Union for International Cancer Control (UICC) TNM staging, version 7 [14]. Our institutional ethics committee approved this study (Registry No. 1067). Documented comprehensive consent was obtained from all the patients.

Treatment strategy

The treatment strategy for esophageal cancer was as follows: for patients with T1, node-negative tumors, we performed esophagectomy without preoperative treatment. For patients with T2/T3, node-negative tumors, or non-T4, node-positive tumors, which indicate resectable advanced esophageal cancer, NAC was administered before esophagectomy. For patients with T4 tumors, induction CRT was indicated. Definitive CRT was considered when patients preferred nonsurgical treatment, regardless of the tumor stage. When the use of CRT failed to locally control the carcinoma, we recommended salvage esophagectomy.

Neoadjuvant chemotherapy

The applied DCF regimen consisted of docetaxel (60 mg/m^2), administered intravenously (IV) on day 1, followed by cisplatin (6 mg/m^2), administered IV on days 1–5, and 5-FU (350 mg/m^2), administered continuously IV on days 1–5. This regimen cycle was repeated every 3 weeks [15]. The applied FP regimen consisted of cisplatin (80 mg/m^2), administered IV on day 1, followed by 5-FU (800 mg/m^2), administered continuously IV on days 1–5. This regimen cycle was repeated every 4 weeks. Although DCF was principally administered, FP was considered when patients had an allergy to docetaxel. Most patients received two cycles of each regimen and underwent elective subtotal esophagectomy at 3–4 weeks after the last round of NAC.

Subtotal esophagectomy

Esophagectomy in this study was defined as a subtotal esophagectomy with two- or three-field regional lymph node dissection that required three incisional manipulations (neck, chest, and abdomen). When tumors were located in the upper or middle thoracic esophagus, three-field lymph node dissection was performed. For lower esophageal tumors, dissection of the cervical lymph nodes was omitted when tumor depth could be classified as within clinical stage T1. Minimally invasive esophagectomy (MIE) was defined as surgery performed using only thoracoscopy, regardless of the use of laparoscopy in the abdomen. MIE for clinical T1 and T2 cases was adopted after May 2011.

Definition of morbidities

We applied the definitions of risk-adjusted morbidity and mortality for esophagectomy for cancer in accordance with the Society of Thoracic Surgeons General Thoracic Surgery Database guidelines [16]. Pulmonary morbidity was defined as the presence of one or more of the following postoperative conditions: initial ventilatory support for more than 48 h or reintubation for respiratory failure, need for tracheostomy, and pneumonia. Pneumonia was defined as the presence of new infiltrates as seen on chest radiographs and a positive culture result from bronchoalveolar lavage. Furthermore, any pulmonary morbidity requiring intervention or surgical treatment was included. Surgical site infection (SSI) was defined as an infection that occurred within 30 days of surgery in the area of the body affected by the surgery, including superficial incisional, deep incisional, and organ/space SSIs. Anastomotic leak was defined based on signs of clinical leakage such as rubefaction, skin

edema, emission of digestive fluid or pus from the wound or drain, or a radiographically apparent leak confirmed by using esophagography or computed tomography (CT). Cardiovascular morbidity was defined as the presence of any cardiac disorders such as arrhythmia, ischemic heart disease, and pericardial fluid collection requiring pharmacological, electrical, or interventional treatment, as well as the presence of any thrombosis in accordance with the Common Terminology Criteria for Adverse Events, version 4.03 [17]. Morbidity was defined as morbidity with a Clavien–Dindo classification (CDc) ≥II [18]. Severe morbidity was defined as morbidity with a CDc ≥IIIb, which indicates the need for surgical, endoscopic, or radiological intervention under general anesthesia.

Follow-up evaluation

The patients were followed up at 3-month intervals. Recurrence was confirmed by performing clinical examinations, including CT and endoscopy. Tumor marker levels were measured every 3 months until 5 years after surgery. CT scanning from the neck to the upper abdomen was performed at least twice a year for 3 years after surgery. When recurrence was strongly suggested as observed on CT, [^{18}F]-fluorodeoxyglucose–positron emission tomography CT (FDG-PET CT) was considered. Patients who had recurrence within 6 months after esophagectomy were defined as having early recurrence in this study.

Statistical analyses

Statistical analyses were performed by using the software program StatView version 5.0 (Abacus Concepts, Berkeley, CA, USA). Statistical comparisons between the groups were performed by using the chi-square test. When the matrix contained fewer than five patients, Fisher's exact test was used. The Mann–Whitney *U* test was used for unpaired samples. Linear regression analysis between two variables was carried out using a simple regression method. The following clinical factors were adopted for analyses of risk factors of early recurrence: age, sex, performance status, American Society of Anesthesiologists Performance status, Brinkman index, body mass index (BMI), tumor location, clinical T, clinical N, number of lymph node metastases, type of NAC regimen, effect of NAC, presence of diabetes mellitus, respiratory comorbidity, cardiovascular comorbidity, pretreatment and preoperative value of albumin, C-reactive protein (CRP), SCC, width of dissection field, use of MIE, incidence of any morbidity, pneumonia, pulmonary morbidity, leak, surgical site infection, cardiovascular morbidity, severe morbidity, reoperation, presence of poorly SCC component, pathological T, pathological N, number of pathological lymph node metastases, presence of lymphatic invasion, and vessel invasion. BMI was divided into two groups (<18.5 kg/m^2, or ≥18.5 kg/m^2) according to the BMI as recommended by the World Health Organization [19]. Number of lymph node metastases was divided into two groups (0–2, ≥3) according to the median value. Pretreatment and preoperative value of albumin and CRP were divided in two groups (<3.5 g/dl, ≥3.5 g/dl, and <0.5 mg/dl, ≥0.5 mg/dl) based on each standard value. Clinical response (effect of NAC) was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 [20]. Valuables with a probability level ≤0.1 (clinical T, albumin before NAC, CRP before NAC, reoperation, presence of poorly SCC component, pathological T, number of pathological lymph node metastases, lymphatic invasion, and vessel invasion) were considered to be possibly associated with early recurrence and adopted for the subsequent multivariate analysis. However, if clinical T and pathological T were closely associated with each other, we deleted clinical T according to the hazard ratio in univariate analysis. In the logistic regression analysis, factors for which the *p* value was <0.05 were considered to be independent risk factors.

Results

A total of 82 patients received NAC with the DCF (74 patients) or FP (8 patients) regimen and subsequent esophagectomy. Of these patients, 14 patients (17 %) recurred within 6 months after esophagectomy following NAC. Of 14 recurrences, 5 were detected by planned CT at 6 months. Six recurrences with metastasis in the skin or cervical LN or bone or local recurrence were discovered by CT or PET CT for examination of patient symptoms from postoperative day (POD) 58 to POD 140. Two recurrences of dissemination or abdominal LN was detected by PET CT to scrutinize the cause of elevation of tumor marker at 3 months. One recurrence of mediastinal LN was discovered by CT at the time of two-stage surgery for reconstruction in POD 70. Of 82 patients, 11 patients received only one cycle of NAC because of adverse events (enteritis, 2 patients; ischemic colitis, 1; diverticulitis, 1; pleurisy, 1; aneurysmal inflammation, 1 patient) or patient refusal to undergo the next cycle (5 patients). Patient backgrounds are listed in Table 1. Patients with early recurrence had significantly more advanced clinical T stage. Albumin level before NAC was significantly lower and CRP level before NAC was significantly higher in patients with early recurrence.

Surgical outcomes are listed in Table 2. Any postoperative morbidity did not affect the incidence of early

Table 1 Association between patient background and early recurrence

Variables		Early recurrence ($n = 14$)	Non-early recurrence ($n = 68$)	p value
Age (years)		66.1 ± 6.9	67.4 ± 7.5	0.555
Sex (male:female)		12:2	59:9	0.999
Performance status	0:1:2	11:3:0	54:11:3	0.668
ASAP	1:2:3	5:8:1	14:50:4	0.445
Brinkman index	Number/day × year	785 ± 489	921 ± 784	0.536
Body mass index	kg/m/m	21.4 ± 3.1	22.0 ± 3.0	0.514
	<18.5:≥18.5	3:11	6:62	0.178
Location	Ut:Mt:Lt	2:7:5	14:37:17	0.679
Clinical T	T1:T2:T3	0:1:13	11:15:42	0.072
	T1–T2:T3	1:13	26:42	0.024
Clinical N	N0:N1:N2:N3	1: 8: 5:0	9:37:21:1	0.883
	N0:N1–N3	1:13	9:59	0.999
Number of clinical LN metastases	Number	2.5 ± 1.9	2.0 ± 1.5	0.302
	0–2:≥3	9:5	46:22	0.999
NAC regimen	DCF:FP	12:2	62:6	0.619
Number of courses	1:2	2:12	9:59	0.999
Effect of NAC	CR:PR:SD:PD	0:7:6:1	2:42:23:1	0.480
	CR, PR:SD, PD	7:7	44:24	0.301
Comorbidity				
Diabetes mellitus	Present:absent	2:12	11:57	0.999
Respiratory	Present:absent	4:10	24:44	0.762
Cardiovascular	Present:absent	6:8	37:31	0.431
Blood chemistry				
Albumin before NAC	g/dl	3.8 ± 0.5	4.1 ± 0.4	0.021
	<3.5:≥3.5	4:10	6:62	0.040
Albumin before surgery	g/dl	3.6 ± 0.5	3.8 ± 0.4	0.174
CRP before NAC	mg/dl	1.5 ± 2.5	0.4 ± 0.6	0.001
	<0.5:≥0.5	5:9	55:13	<0.001
CRP before surgery	mg/dl	0.5 ± 0.7	0.3 ± 0.6	0.223
SCC before NAC	ng/ml	2.3 ± 1.6	2.1 ± 2.7	0.782
SCC before surgery	ng/ml	1.6 ± 1.0	1.5 ± 2.2	0.988

Data are expressed as number of cases or mean number ± standard deviation

ASAP American Society of Anesthesiologists Performance status, *LN* lymph node, *NAC* neoadjuvant chemotherapy, *DCF* docetaxel/5-fluorouracil/CDDP, *FP* 5-fluorouracil/CDDP, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NAC* neoadjuvant chemotherapy, *CRP* C-reactive protein, *SCC* squamous cell carcinoma

recurrence within 6 months. Reoperation was considered possibly relevant to early recurrence. Pathological outcomes are shown in Table 3. Presence of poorly differentiated SCC component, advanced T stage (T3, T4), three or more lymph node metastases, and presence of vessel invasion were significantly associated with early recurrence. Lymphatic invasion was also considered possibly relevant to early recurrence. Pathological response grade did not correlate with early recurrence (data not shown). The logistic regression analysis suggested that CRP before NAC at ≥0.5 mg/dl [hazard ratio (HR) 33.8, 95 % confidence interval (CI) 2.767–413.9; $p = 0.006$], presence of poorly differentiated SCC component (HR 138, 95 % CI 5.339–3576; $p = 0.003$), and presence of pathological vessel invasion (HR 16.3, 95 % CI 1.960–136.1; $p = 0.010$) have the possibility of becoming independent risk factors of early recurrence (Table 4). As for these potential risk factors, 28 % of patients with one factor recurred within 6 months after esophagectomy. On the other hand, patients with at least two factors frequently recurred, with an incidence of 82 % (9/11).

Table 5 shows the pattern of early recurrence. Thirteen patients (93 %) had a distant metastasis; only 1 patient had a local recurrence.

Table 2 Association between surgical outcomes and early recurrence

Variables		Early recurrence ($n = 14$)	Non-early recurrence ($n = 68$)	p value
Dissection field	2:3	3:11	14:54	0.999
Minimally invasive esophagectomy	Present:absent	1:13	13:55	0.445
Morbidity				
Any morbidity (CDc ≥ II)	Present:absent	8:6	29:39	0.321
Pneumonia	Present:absent	2:12	7:61	0.647
Pulmonary	Present:absent	5:9	14:54	0.222
Leak	Present:absent	2:12	5:63	0.342
Surgical site infection	Present:absent	5:9	24:44	0.976
Cardiovascular	Present:absent	1:13	3:65	0.534
Severe morbidity (CDc ≥ IIIb)	Present:absent	4:10	8:60	0.205
Reoperation[a]	Present:absent	3:11	4:64	0.092

Data are expressed as number of cases, *CDc* Clavien–Dindo classification

[a] Leak from colonic conduit (4), peritonitis from leak from gastrostomy (2), bleeding from intercostal artery (1)

Table 3 Association between pathological outcomes and early recurrence

Variables		Early recurrence ($n = 14$)	Non-early recurrence ($n = 68$)	p value
Poorly differentiated SCC component	Present:absent	4:10	3:65	0.014
Pathological T	T0:T1:T2:T3:T4	0:1:2:10:1	7:21:14:26:0	0.018
	T0–T2:T3–T4	3:11	42:26	0.006
Pathological N	N0:N1:N2:N3	3:5:4:2	29:28:8:3	0.137
	N0:N1–N3	3:11	29:39	0.228
Number of pathological LN metastases	Number	3.0 ± 3.8	1.3 ± 2.0	0.019
	0–2:≥3	8:6	57:11	0.025
Lymphatic invasion	Present:absent	11:3	35:33	0.080
Vessel invasion	Present:absent	10:4	19:49	0.004

Data are expressed as the number of cases or mean number ± standard deviation

SCC squamous cell carcinoma, *LN* lymph node

Table 4 Multivariate analysis of factors associated with early recurrence

Variables	Objective variables	Control	Hazard ratio	95 % confidence interval	p-value
Albumin before NAC	<3.5 g/dl	≥3.5 g/dl	36.7	0.797–55.62	0.080
CRP before NAC	≥0.5 mg/dl	<0.5 mg/dl	33.8	2.767–413.9	0.006
Reoperation	Present	Absent	10.6	0.081–1382	0.344
Poorly differentiated SCC component	Present	Absent	138	5.339–3576	0.003
Pathological T	T3–T4	T0–T2	1.14	0.113–11.55	0.912
Number of pathological LN metastases	≥3	0–2	1.69	0.158–18.09	0.664
Lymphatic invasion	Present	Absent	5.69	0.503–64.47	0.160
Vessel invasion	Present	Absent	16.3	1.960–136.1	0.010

SCC squamous cell carcinoma, *LN* lymph node

Discussion

We retrospectively analyzed the clinicopathological factors of patients with resectable advanced esophageal cancer who had an early recurrence within 6 months after esophagectomy following NAC. In this study, 17 % of patients recurred during this early period. This rate is slightly higher than that seen in the JCOG 9907 study [6], which might be caused by the differences in cancer stage and NAC regimen. This study included cases of more

Table 5 Pattern of early recurrence within 6 months after esophagectomy

Pattern	Number (%)
Local	1 (7)
Regional LN	0
Distant LN[a]	6 (43)
Distant metastasis other than LN	5 (36)
Pleural dissemination	0
Mixed	2 (14)

LN lymph node

[a] Distant LN means metastatic LN according to the Union for International Cancer Control (UICC) TNM staging, version 7

advanced esophageal cancer, which consisted of 53 % of clinical stage III and 10 % of stage IVA, whereas the patients in the JCOG 9907 study consisted of 50 % in clinical stage III and none in stage IVA (6th UICC). Moreover, although several studies reported that the response rate of NAC with DCF is higher than that of NAC with FP, the long-term outcome is still unclear [21].

As for the difference in chemotherapy regimen, the incidence of early recurrence was same between DCF and FP. Relapse-free survival (RFS) was also same (data not shown). Nomura et al. reported the same results on RFS after NAC with DCF and FP [9]. Unfortunately, this study did not contain a sufficient number of patients to clarify the definitive difference between DCF and FP.

The current analyses contained multiple variables of different time phases. It is unclear which timing is best to predict those patients who would recur such an early period, before initial treatment or after NAC just before surgery or after surgery. We believe that we should select those patients after surgery for two reasons. One reason is that pathological findings are certainly integral for prediction of prognosis. The other reason is that at least, as of now, patients with resectable advanced esophageal cancer should be treated with the best strategy currently performed (NAC and subsequent surgery). Therefore, we conducted multivariate analysis with multiple variables of different phases that could be obtained after surgery.

In this study, CRP before NAC $\geq$0.5 mg/dl, presence of poorly differentiated SCC component, and pathological vessel invasion were associated with early recurrence. To date, several retrospective studies have been conducted to confirm risk factors of early death within 1 year after surgery for esophageal cancer. Kosugi et al. reported that the presence of intramural metastasis was the only risk factor of early death after extended radical esophagectomy [11]. Zhu et al. and Davies et al. reported that grade of differentiation and number of lymph node metastases were valuable prognostic factors predicting early death [12, 13]. Zhu et al. also suggested that depth of invasion, lymph node metastasis, and marginal status of specimen resected become prognostic factors. However, these studies included patients without NAC, total or partial. There was only one study of early cancer-related mortality after neoadjuvant therapy [10]. In this article, Stiles et al. suggested that performance status, poor tumor differentiation, and clinical response of NAC were independent risk factors of early mortality within 1 year. Additionally, they also reported that 29 % of patients with at least two of these risk factors would die within 1 year after surgery. However this study also contained 31 % of neoadjuvant CRT. To date, studies of early recurrence for patients who underwent surgery following only NAC were not available.

In this study, pathological factors associated with early recurrence were consistent with those in previous studies. Common in most studies, poorly differentiated SCC was a strong risk factor for poor prognosis. Several key enzymes, such as fatty acid synthase and pyruvate kinase M2, were reported to correlate with the differentiation of esophageal SCC, and these were also associated with the prognosis of esophageal cancer [22, 23]. It is already confirmed that vessel invasion of esophageal SCC correlated with poor prognosis because of the high incidence of metastasis [24, 25]. Elevated CRP is established as a risk factor of poor prognosis of advanced or inoperable esophageal SCC [26–28]. The Glasgow Prognostic Score (GPS) or novel inflammation-based prognostic score, which includes CRP level as a parameter, could also predict the prognosis of esophageal SCC [29–31]. In this study, because albumin <3.5 g/dl before NAC was close to being the independent risk factor of early recurrence with a probability level of 0.084, we also examined the usefulness of GPS and modified GPS as the indicator for early recurrence. Consequently, both scores could also be the predictive indicator (data not shown) in this cohort. Production of CRP is induced by interleukin (IL)-6, IL-1, tumor necrosis factor-α, and transforming growth factor-β [32]. These cytokines could induce tumor progression or invasion and are correlated with poor prognosis in esophageal cancer [33–36]. Moreover, cancer cells could also produce CRP by themselves; positive findings of tumoral CRP expression in immunohistochemistry are reported to be associated with a poor outcome in esophageal SCC [37].

Among these three risk factors in this study, patients with at least two factors frequently recurred, with an incidence of 82 %. Such patients should certainly be considered for additional treatment and should be followed up carefully. Regarding additional treatment, systemic chemotherapy might be appropriate, as most of the recurrences were distant metastases (Table 5) as in a previous report [38]. However, an optimal treatment regimen for such patients was not established. We believe that both the development

of novel agents and advance in treatment strategy are necessary for patients at high risk of early recurrence. In addition, a reliable method to predict such patients before treatment should be established to avoid unprofitable treatment, especially highly invasive esophagectomy.

This study has certain limitations. This is a retrospective study that was conducted at a single institute. Moreover, the sample size was not sufficiently large. Therefore, the present results remain undefined. We believe that a multicenter study with a larger cohort is desirable to establish definitive risk factors of early recurrence after surgery following NAC for resectable advanced esophageal cancer.

In conclusion, for resectable advanced esophageal cancer, CRP before NAC ≥0.5 mg/dl, presence of poorly differentiated SCC component, and pathological vessel invasion might be correlated with early recurrence within 6 months after esophagectomy following NAC. Particularly, for patients with at least two factors, additional treatment and cautious follow-up might be necessary after surgery.

Compliance with ethical standards

Conflict of interest Naoya Yoshida and coauthors have no conflict of interest in relation to this article.

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