Prognoses of advanced esophago-gastric junction cancer may be modified by thoracotomy and splenectomy

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Abstract. Globally, the incidence of esophago-gastric junction (EGJ) cancer is rapidly increasing. However, the proposed strategies for the treatment of these types of cancer are so diverse that there is no established consensus on the optimal treatment. The aim of the present study was to identify independent prognostic factors to delineate the optimal strategies for the treatment of EGJ cancer. The medical records of 150 patients with EGJ cancer who underwent curative surgery at the Kitasato University were retrospectively reviewed. The median follow-up period was 48 months. The patients with tumors that were classified as post-treatment primary tumor stage 3 [(y)pT3] or higher had a 5-year disease-specific survival (DSS) rate of 53%, whereas those with tumors that were classified as (y)pT0-2 had a 5-year DSS rate of 90%. Therefore, prognostic analysis was restricted to those tumors that were designated (y)pT3 or higher. A multivariate Cox's proportional hazards model identified the following independent prognostic factors that negatively influenced the DSS: i) Presence of tumors classified as post-treatment regional lymph node stage 1-3 [(y)pN1-3] [hazard ratio (HR), 3.62; 95% confidence interval (CI), 1.39-12.36]; ii) not undergoing treatment with splenectomy (HR, 2.40; 95% CI, 1.15-5.15); and iii) undergoing treatment with thoracotomy (HR, 2.07; 95% CI, 1.02-4.23). In patients with (y)pN0 tumors, the DSS rate was significantly improved for those who underwent splenectomy than for those who did not (P=0.024). In patients with (y)pN1-3 tumors, the DSS rate was significantly worse for those who underwent thoracotomy compared with those who did not (P=0.004). Splenectomy and thoracotomy may critically affect prognosis in locally advanced EGJ cancer that are classified as (y)pN0 and (y)pN1-3, respectively. Surgical treatments require optimization in order to improve prognoses in advanced EGJ cancer.

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Introduction

The incidence of adenocarcinoma of the esophago-gastric junction (EGJ) is increasing in Western (1,2) and Eastern (3-5) countries. By contrast, the prevalence of squamous cell carcinoma (SCC) remains increased in Japan compared with Western countries.

Siewert *et al* (6) proposed a classification system for adenocarcinoma of the EGJ, and discussed the characteristics and treatments of these according to the individual type of disease. The authors proposed that patients with type I cancer should be treated similarly to those with distal esophageal cancer, whereas patients with type II and III cancer should undergo transhiatal total gastrectomy, lower esophagectomy, lower mediastinal lymph node dissection and extended (D2) lymph node dissection similar to that performed in patients with gastric cancer. Conversely, a previous study in which >50% of the patients had Siewert type II adenocarcinoma of the EGJ identified that treatment with esophagectomy was associated with improved patient outcomes compared with treatment with gastrectomy (7). In Japan, Sasako *et al* (8) reported that a left thoracoabdominal approach does not improve survival rate following an abdominal-transhiatal approach and leads to increased morbidity in patients with predominantly Siewert type II and III EGJ adenocarcinoma. As aforementioned, the treatment strategies for these types of cancer are so diverse that the optimal treatment strategy has not yet been well established. Furthermore, the aforementioned studies included only patients with adenocarcinoma and did not include patients with SCC, although SCC occurs at a high incidence in Eastern countries.

In Western countries, the standard treatment modality, other than surgery, for patients with esophageal or EGJ cancer is preoperative chemoradiotherapy (9-11). In Japan, a randomized controlled trial by the Japan Clinical Oncology Group (JCOG9204) which compared postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil with surgery alone for treatment of patients with esophageal SCC demonstrated superior disease-free survival rates in the group of patients who received postoperative chemotherapy (12). Furthermore,

another study by the same group (JCOG9907) demonstrated that patients with esophageal SCC who received preoperative adjuvant chemotherapy had superior overall survival rates compared with those that received postoperative adjuvant chemotherapy (13). In the JCOG9204 study, locoregional recurrences were observed in <50% of patients who experienced recurrences. In Japan, the performance of aggressive surgeries for the treatment of esophageal cancer is hypothesized to be one reason for the lower rates of local recurrences and, therefore, the eradication of systemic micrometastases by chemotherapy followed by surgery is standard therapy in Japan. However, these treatment strategies did not allow for appropriate control of distant recurrences in locations including the liver.

In the present study, patients with EGJ cancer, including those with SCC, were investigated to identify independent prognostic factors and to clarify the patterns of recurrences for those with poor prognoses. Additionally, a treatment strategy for EGJ cancer is proposed.

Materials and methods

Definition of EGJ cancer. EGJ cancer was defined as cancer that invaded the EGJ and exhibited tumor epicenters that were located ≤5 cm from the EGJ. Tumors were classified as follows: Type I, tumor epicenters located between 1 and 5 cm above the EGJ; type II, tumor epicenters located between 1 cm above and 2 cm below the EGJ; and type III, tumor epicenters located between 2 and 5 cm below the EGJ. The locations of the epicenters were comprehensively evaluated on the basis of results obtained by upper gastrointestinal series and upper gastrointestinal endoscopy. In patients who received preoperative chemotherapy, tumors were classified on the basis of their characteristics prior to receiving chemotherapy.

Patients and clinicopathological evaluations. Between January 1997 and December 2012, a total of 3,004 patients underwent surgery for esophageal or gastric cancer at the Kitasato University School of Medicine (Sagamihara, Kanagawa, Japan). Of these patients, 191 (6.4%) underwent surgical resections for EGJ adenocarcinoma or SCC. Of these, 41 patients who had undergone R1 or R2 resections were excluded. The medical records of the remaining 150 patients who underwent curative (R0) surgery were retrospectively reviewed in order to identify the independent prognostic factors and clarify recurrence patterns. The median follow-up period was 48 months (interquartile range, 26-68 months).

Tumor depths and lymph node metastases were classified according to the International Union Against Cancer Tumor Node and Metastases staging system, 7th edition (14).

Perioperative transfusion (POT) was defined as the allogeneic blood transfusion performed during surgery or within the first 2 postoperative days, as previously reported (15).

The present study was conducted in accordance with The Declaration of Helsinki and was approved by the Research Ethics Committee of the Kitasato University School of Medicine. The requirement for informed consent was waived due to the retrospective nature of the study.

Surgical procedures and morbidity. Surgical procedures were determined based on the tumor locations and the lengths of esophageal invasions. A right thoracic approach (RTA) was used to perform subtotal esophagectomy and mediastinal lymph node dissections through right thoracotomy, and gastric conduit reconstructions were performed through laparotomy. A left thoracic approach (LTA) through left thoracotomy and laparotomy and a transhiatal approach (THA) following wide-splitting of the esophageal hiatus were used to perform total gastrectomy, distal esophagectomy, D2 lymph node dissections including splenectomy and lower mediastinal lymph node dissections. For clinical T1 cancer, proximal gastrectomy and jejunal interposition or esophago-gastric anastomosis were performed, wherever possible. Video-assisted thoracoscopic esophagectomy was performed through an RTA in only 5 patients; therefore, these patients were included in the RTA group for analysis.

Surgical complications were classified by the surgical approach using the Clavien-Dindo classification (16,17).

Chemotherapy. Of the patients who received preoperative chemotherapy (n=29), 18 had marginally resectable disease and 11 had stage IV disease. For these patients, the combination of docetaxel, cisplatin and S-1 (tegafur, gimeracil and oteracil potassium) (DCS), cisplatin and 5-fluorouracil (CF), or cisplatin and S-1 (CS) were commonly used for chemotherapy. The treatment schedules for DCS, CF and CS have been described previously (13,18,19). The most commonly used regimen was DCS (in 11/18 patients with marginally resectable disease and 3/11 patients with cStage IV disease). All the patients who received DCS had adenocarcinoma. The second most commonly used regimen was CF (in 5/18 patients with marginally resectable disease). All the patients who received CF had SCC.

A number of patients also received postoperative adjuvant chemotherapy (n=56). The most commonly used regimen was S-1 monotherapy (in 30/56 patients) (20,21). All the patients who received S-1 monotherapy had adenocarcinoma.

Statistical analysis. Disease-specific survival (DSS) was measured from the date of surgery or from the date of starting chemotherapy in patients who received preoperative chemotherapy, to the date of mortality from EGJ cancer or date of last follow-up. The causes of mortality were identified from the hospital medical records. Patients who succumbed to causes other than EGJ cancer were regarded as censored at the time of mortality. Patients who were alive at their last visit were also regarded as censored. Student's t-test was used to analyze continuous variables and a χ^2 test or Fisher's exact test was used to analyze categorical variables. Survival rates were calculated by the Kaplan-Meier estimator method (22). Univariate analyses of prognostic factors for DSS were performed using log-rank tests. Factors with P<0.10 on univariate analyses were subjected to multivariate analysis using Cox's proportional hazards model to identify independent prognostic factors. All calculations were performed using JMP® 10 software (SAS Institute Inc., Cary, NC, USA). P<0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics and stage distributions. The characteristics of patients included in the present study are listed

in Table I. The proportion of patients with type I, II and III cancer was 14% (21/150), 62% (93/150) and 24% (36/150), respectively. The median number of dissected lymph nodes was 37 (range, 5-96). A number of patients received preoperative chemotherapy (n=29; 19%) and pathologically complete responses in primary tumors (ypT0) were obtained in 6 patients; 4 of these received DCS and 2 received CS.

Surgical approach, morbidity and mortality. Surgery was performed via an RTA in 81% (17/21) of the patients with type I tumors. A THA was used in 74% (69/93) and 89% (32/36) of the patients with type II and III tumors, respectively (Fig. 1A-C).

The frequency of Clavien-Dindo Grade IIIa or IIIb surgical complications was higher with the RTA, followed by the LTA and the THA. Clavien-Dindo Grade IVb surgical complications were identified in only 1 patient who underwent an RTA (Table II). In-hospital mortalities occurred in 3 patients (2%). Of these, 1 had undergone an RTA and the others had undergone a THA.

Survival rate analysis. The 5-year DSS rate for all patients with EGJ cancer was 72%. Patients with tumors classified as post-treatment primary tumor stage 3 [(y)pT3] or higher had a 5-year DSS rate of 53% and those with tumors classified as (y)pT0-2 had an 5-year DSS rate of 90%. Therefore, only patients with tumors classified as (y)pT3 or higher were analyzed further. In the univariate analysis, the following factors were identified as potential predictors of poor survival rate: a pathological nodal stage of post-treatment regional lymph node stage 1-3 [(y)pN1-3] (P=0.038), splenectomy not performed (P=0.005), thoracotomy performed (P=0.005) and POT (P=0.093) (Table III). The multivariate Cox's proportional hazards model revealed that a pathological tumor nodal stage of (y)pN1-3 [hazard ratio (HR), 3.62; 95% confidence interval (CI), 1.39-12.36; P=0.006], splenectomy not performed (HR, 2.40; 95% CI, 1.15-5.15; P=0.020) and thoracotomy (HR, 2.07; 95% CI, 1.02-4.23; P=0.044) were independent prognostic factors for poor DSS (Table III; Fig. 2).

Combination analysis of independent prognostic factors in patients with tumors classified as (y)pT3 or higher. Combination analyses were conducted using independent prognostic factors, namely, thoracotomy and splenectomy, according to the (y)pN stage. In the patients with (y)pN0 tumors, the 5-year DSS rate is presented according to their status of treatment with thoracotomy and splenectomy (Fig. 3A). Notably, the 5-year DSS rate was 100% in patients who underwent splenectomy (Fig. 3B); the DSS was significantly improved for patients who underwent splenectomy compared with for those who did not (P=0.024). On the other hand, in the patients with (y)pN1-3 tumors, the 5-year DSS rate of patients who underwent thoracotomy without undergoing splenectomy was as low as 18% (Fig. 3C); the DSS was significantly worse for patients who underwent thoracotomy compared with for those who did not (P=0.004; Fig. 3D).

Initial recurrence site in patients with tumors classified as (y)pT3 or higher. The proportion of patients whose tumors recurred initially at locoregional sites was only 6% (5/91). Patients who underwent thoracotomy and splenectomy and those

Table I. Patient characteristics (n=150).

Characteristic	No.	Proportion, %	Range
Median age, years	68		31-87
Sex			
Male	124	83.	
Female	26	17	
ASA			
I	47	31	
II	91	61	
III	12	8	
Histological type			
Adenocarcinoma	130	87	
Squamous cell carcinoma	20	13	
Tumor type			
I	21	14	
II	93	62	
III	36	24	
Tumor depth (histological)			
(y)pT0	6	4	
(y)pT1a	7	5	
(y)pT1b	27	18	
(y)pT2	19	13	
(y)pT3	91	61	
Nodal stage (histological)			
(y)pN0	62	41	
(y)pN1	31	21	
(y)pN2	31	21	
(y)pN3	26	17	
Splenectomy			
Yes	58	39	
No	92	61	
POT			
Yes	40	27	
No	110	73	
Approach			
Right thoracic	30	20	
Left thoracic	16	11	
Transhiatal	104	69	
Preoperative chemotherapy			
Yes	29	19	
No	121	81	
Postoperative chemotherapy			
Yes	56	37	
No	94	63	
Dissected lymph nodes			
Median	37		5-96
Metastatic lymph nodes			
Median	1		0-25

ASA, Physical status classification of American Society of Anesthesiologists. POT, perioperative allogeneic blood transfusions; (y)pT, post-treatment primary tumor; (y)pN, post-treatment regional lymph node.

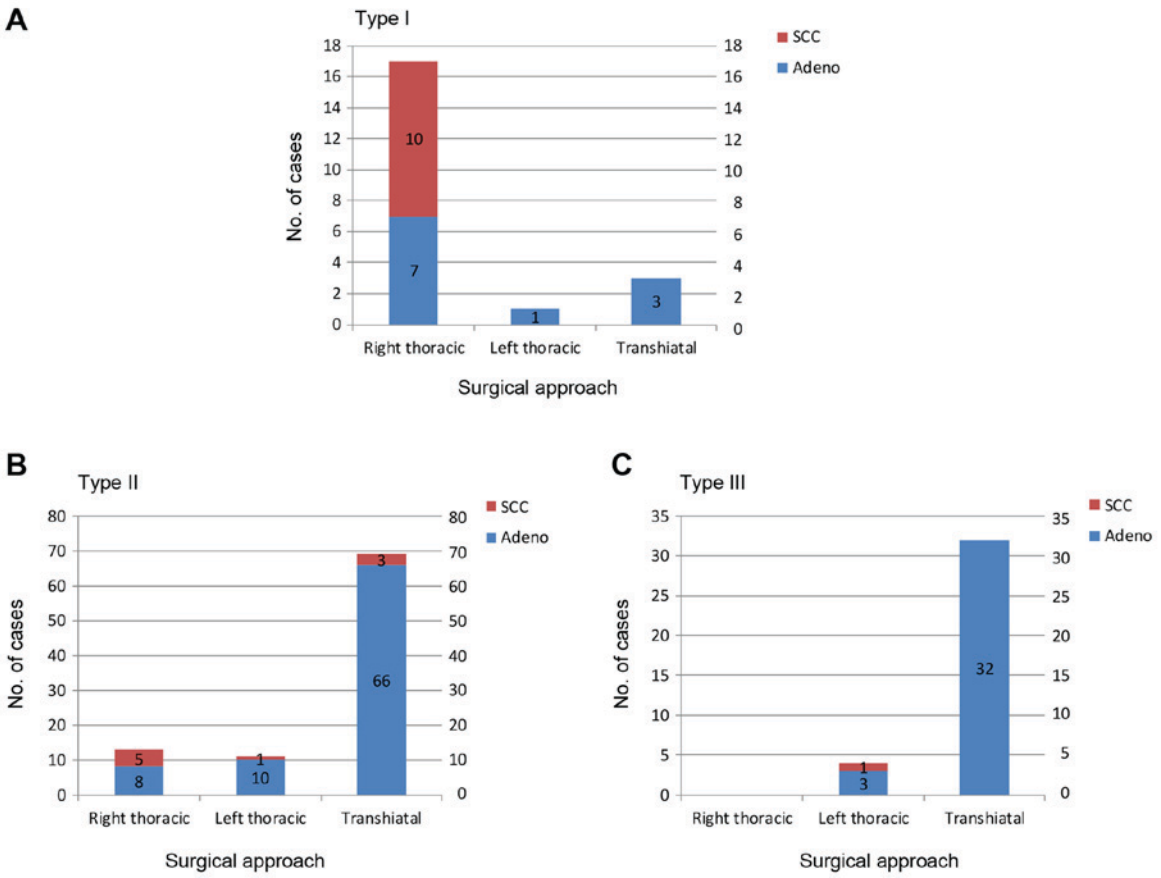

Figure 1. Distribution of surgical approaches according to the tumor type, (A) I, (B) II and (C) III, and the histological type. SCC, squamous cell carcinoma; adeno, adenocarcinoma.

who did not undergo either procedure were analyzed further for their initial sites of tumor recurrence. The proportion of patients with initial liver recurrences tended to be larger in the group of patients who underwent thoracotomy compared with those that underwent laparotomy only (P=0.21; Fig. 4A). The corresponding proportion of patients was significantly larger in the group that did not undergo splenectomy compared with the group that did (P=0.016; Fig. 4B). In the patients with adenocarcinoma, the proportion of patients with initial liver recurrences was larger among those who underwent thoracotomy compared with those who underwent laparotomy only (19 vs. 10%; P=0.29). This corresponding proportion was also significantly larger in the group of patients that did not undergo splenectomy compared with the group that did (24 vs. 6%; P=0.024; data not shown).

Sub-analysis of patients with tumors classified as (y)pT3 or higher with initial recurrence sites in the liver. Patients with initial recurrences in the liver were analyzed further. Patients with type I cancer tended to exhibit initial recurrences in the liver (P=0.091; Fig. 5A). Of the 4 patients with type I cancer who had initial recurrences in the liver, 3 had SCC (Fig. 5B). Of the 7 patients in the thoracotomy group who experienced initial recurrences in the liver, 3 patients had type I SCC (Table IV). In the group that did not undergo splenectomy, 3/10 patients who had initial recurrences in the liver had type I SCC. These 3 patients were the same individuals aforementioned (Table IV) and only 1 of them had received preoperative chemotherapy (CF).

Discussion

The prognostic analyses of EGJ cancer identified that undergoing thoracotomy and splenectomy may affect the DSS in patients. Patients who underwent thoracotomy and did not undergo splenectomy tended to experience initial recurrences in the liver. In addition, patients whose tumors initially recurred in the liver tended to have type I SCC. The patients with type I SCC usually underwent thoracotomy, not splenectomy, and data revealed that such patients are prone to tumor recurrences in the liver. This may indicate that type I SCC possesses biological behavior differing from that of other EGJ cancer. In the institute where the present study was conducted, type I SCC is included with thoracic esophageal SCC, with respect to therapeutic strategy. Nevertheless, 2/3 type I SCC which exhibited recurrence in the liver were not treated with preoperative chemotherapy. Thus, potent preoperative chemotherapy may be required for patients with type I SCC to improve their survival rates. However, in patients with adenocarcinoma, the same effects of thoracotomy and splenectomy were observed, in terms of initial liver recurrences.

Thoracotomy was one of the independent factors for poor prognosis. The incidence rate of liver recurrences in patients who underwent thoracotomy tended to be increased compared with the corresponding rate in patients who did not undergo thoracotomy. In patients undergoing surgery for non-small cell lung cancer, compared with video-assisted thoracic surgery (VATS), thoracotomy is reportedly associated with more

Table II. Morbidity classified by surgical approach and Clavien-Dindo classification.

	THA (n=104)					LTA (n=16)				RTA (n=30)				
Cause of morbidity	IIIa	IIIb	IVa	IVb	V	IIIa	IIIb	IVa	IVb	IIIa	IIIb	IVa	IVb	V
Pulmonary complications[a]	1 (1)	0	2 (2)	0	1 (1)	0	0	0	0	3 (10)	1 (3)	0	1 (3)	0
Anastomotic leakage	4 (4)	2 (2)	0	0	0	1 (6)	0	0	0	6 (20)	0	0	0	1 (3)
Recurrent nerve palsy	0	0	0	0	0	0	0	0	0	0	2 (7)	0	0	0
Diaphragmatic hernia	0	0	0	0	0	0	0	0	0	0	1 (3)	0	0	0
Chylous leakage	1 (1)	0	0	0	0	0	0	0	0	0	0	0	0	0
Pancreatic fistula	7 (7)	0	0	0	0	2 (13)	0	0	0	0	0	0	0	0
Abdominal abscess	3 (3)	0	0	0	0	0	0	0	0	0	0	0	0	0
Small bowel obstruction	0	1 (1)	0	0	0	0	1 (6)	0	0	0	0	0	0	0
Cholecystitis	0	0	0	0	0	1 (6)	0	0	0	0	0	0	0	0
Wound infection	0	0	0	0	0	0	0	0	0	0	1 (3)	0	0	0
Wound dehiscence	0	0	0	0	0	0	0	0	0	0	1 (3)	0	0	0
Postoperative hemorrhage	1 (1)	1 (1)	0	0	1 (1)	0	0	0	0	0	0	0	0	0
Total	17 (16)	4 (4)	2 (2)	0	2 (2)	4 (25)	1 (6)	0	0	9 (30)	6 (20)	0	1 (3)	1 (3)

Values are n, with percentages in parentheses. [a]Pulmonary complications included pleural effusion, thoracic empyema, pulmonary edema, pneumonia and atelectasis. THA, transhiatal approach; LTA, left thoracic approach; RTA, right thoracic approach.

Table III. Prognostic analysis in patients with (y)pT3 EGJ cancer.

	Univariate analysis				Multivariate analysis		
Characteristic	Number	Proportion, %	5-year DSS, %	P-value	HR	95% CI	P-value
Age, years							
≤65	51	56	59	0.46			
<65	40	44	59				
Sex							
Male	72	79	54	0.21			
Female	19	21	77				
Tumor type							
I	11	12	55	0.68			
II	49	54	60				
III	31	34	59				
Esophageal invasion, cm							
≤3	73	80	62	0.12			
>3	18	20	46				
(y)pN							
(y)pN0	21	23	89	0.038[a]	1.00		0.006[a]
(y)pN1-3	70	77	50		3.62	1.39-12.36	
Histology							
Adeno	77	85	58	0.52			
SCC	14	15	64				
Preoperative chemotherapy							
Yes	17	19	57	0.85			
No	74	81	60				
Postoperative chemotherapy							
Yes	46	51	66	0.34			
No	45	49	53				
POT							
Yes	28	31	43	0.093	1.28	0.61-2.59	0.50
No	63	69	66		1.00		
Splenectomy							
Yes	50	55	68	0.005[a]	1.00		0.020[a]
No	41	45	49		2.40	1.15-5.15	
Thoracotomy							
Yes	32	35	40	0.005[a]	2.07	1.02-4.23	0.044[a]
No	59	65	71		1.00		

[a]P<0.05. EGJ, esophagogastric junction; DSS, disease-specific survival; HR, hazard ratio; CI, confidence interval; POT, perioperative allogeneic blood transfusion; (y)pT, post-treatment primary tumor; (y)pN, post-treatment regional lymph node.

marked decreases in the numbers of circulating natural killer cells and more marked increases in the plasma levels of matrix metalloproteinase-9 (23). In an experimental model, the excessive surgical stress of undergoing a thoracolaparotomy was revealed to markedly enhance tumor metastasis, by a mechanism that involved immunosuppression (24). The results of the present study may also reflect a subset of immunosuppression. VATS may compensate for this drawback of thoracotomy.

Splenectomy was also identified to be an independent prognostic factor. However, the treatment of gastric cancer or EGJ cancer with splenectomy is controversial. Numerous studies on treatment of cancer with splenectomy have been published describing the high morbidity rates and low survival rate benefits of such treatment (25). However, Huang *et al* (26) reported that splenectomy is beneficial for splenic hilar lymph node dissections in patients with advanced proximal gastric cancer and is associated with improved survival rates. In the present study, 4 patients exhibited metastatic splenic hilar lymph nodes. Of these, 1 patient, whose tumor had widely invaded the greater curvature of the stomach, survived for

Table IV. List of patients with Siewert type I squamous cell carcinoma who had initial recurrence in the liver following thoracotomy.

Age, years	Sex	(y)pT	(y)pN	(y)p stage TNM 7th	Preoperative chemotherapy	Esophageal invasion, mm	PM, mm	POT	Splenectomy	Adjuvant regimen
58	M	3	3	IIIC	N	51	78	N	N	5FU, cisplatin, MMC
74	M	3	3	IIIC	N	60	87	Y	N	Radiation
66	M	3	0	IIA	CF	40	85	N	N	N

PM, proximal margin; POT, perioperative blood transfusion; LN, lymph node; 5FU, 5-fluorouracil; MMC, mitomycin C; CF, cisplatin and 5-fluorouracil; Y, yes; N, no; TNM, tumor-node-metastasis; (y)pT, post-treatment primary tumor; (y)pN, post-treatment regional lymph node.

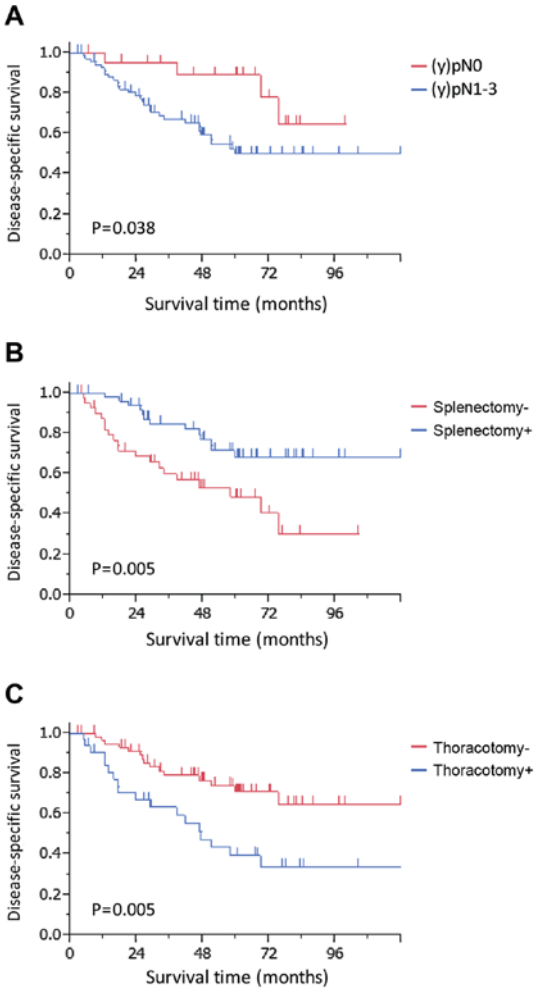

Figure 2. Disease-specific survival rates according to the independent prognostic factors, namely the (A) presence of tumors classified as (y)pN, (B) performance of splenectomy and (C) performance of thoracotomy.

5 further years without experiencing any recurrence of the tumor.

Splenectomy has been reported to serve an important role in the antitumor immune response in an experimental model (27-29). Higashijima *et al* (28) reported that splenectomy enhances liver metastasis through an increase in forkhead box P3 mRNA in the liver. On the other hand, Sonoda *et al* (29) reported that the metastatic lung nodules were significantly smaller in size and number in the subject group that underwent splenectomy compared with the control group in a mouse metastasis model and concluded that this occurred due to splenectomy-induced decreases in serum levels of vascular endothelial growth factor and basic fibroblast growth factor. In the present study, patients with (y)pT3N0 EGJ cancer who underwent splenectomy had improved DSS compared with those who did not undergo splenectomy. Splenectomy may exert a negative impact on the recurrence of tumors by enhancing antitumor immunity. Furthermore, patients with (y)pT3N1-3 EGJ cancer who underwent thoracotomy without splenectomy had poorer prognostic outcomes (5-year DSS, 18%), which may be the result of the negative impact on antitumor immunity caused by the combination of undergoing thoracotomy without undergoing splenectomy. Patients

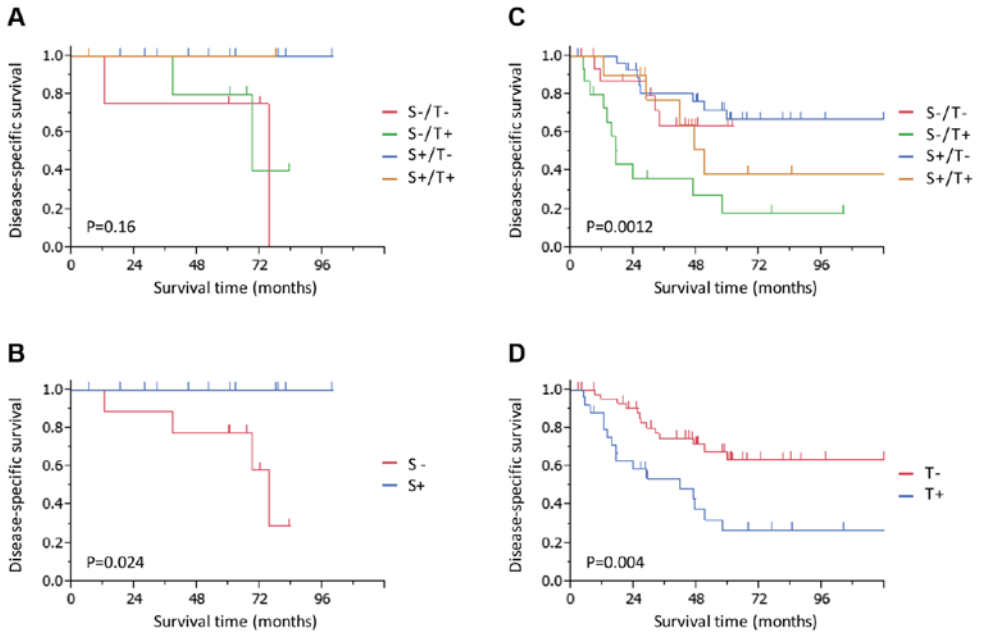

Figure 3. (A) Disease-specific survival rates stratified by the combination of splenectomy and thoracotomy in patients with tumors classified as (y)pN0. (B) Disease-specific survival rates according to the performance of splenectomy in patients with tumors classified as (y)pN0. (C) Disease-specific survival rates stratified by the combination of splenectomy and thoracotomy in patients with tumors classified as (y)pN1-3. (D) The performance of thoracotomy in patients with tumors classified as (y)pN1-3 (D). S, splenectomy; T, thoracotomy.

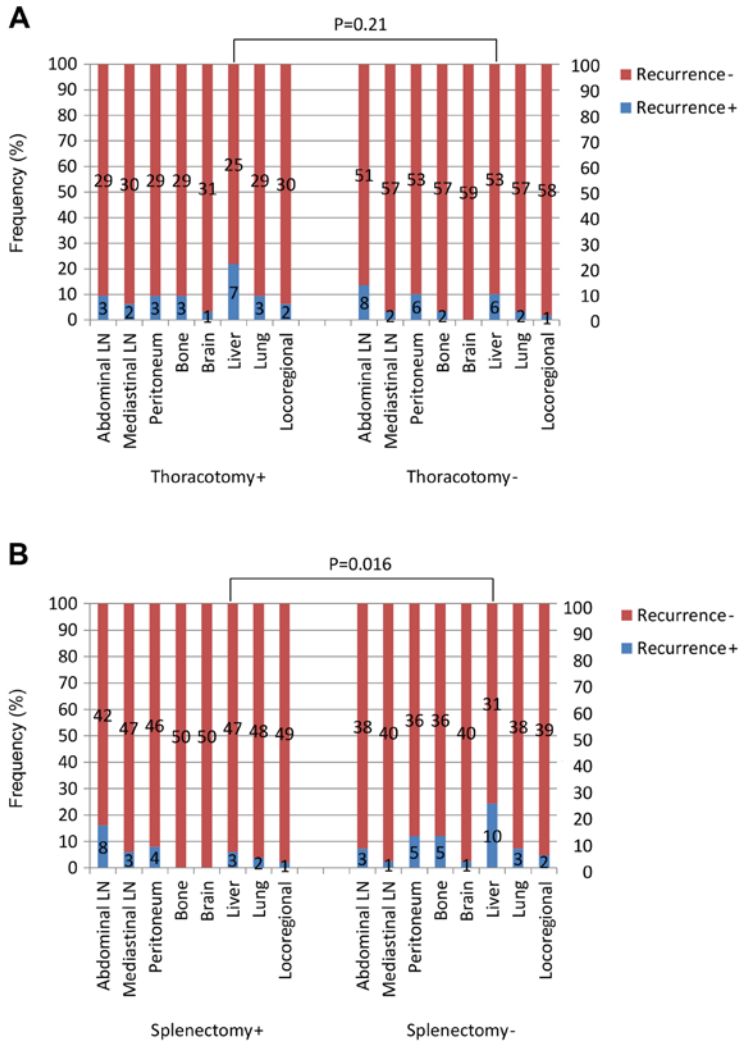

Figure 4. Frequency of sites of initial recurrences according to the performance status of (A) thoracotomy and (B) splenectomy. LN, lymph node.

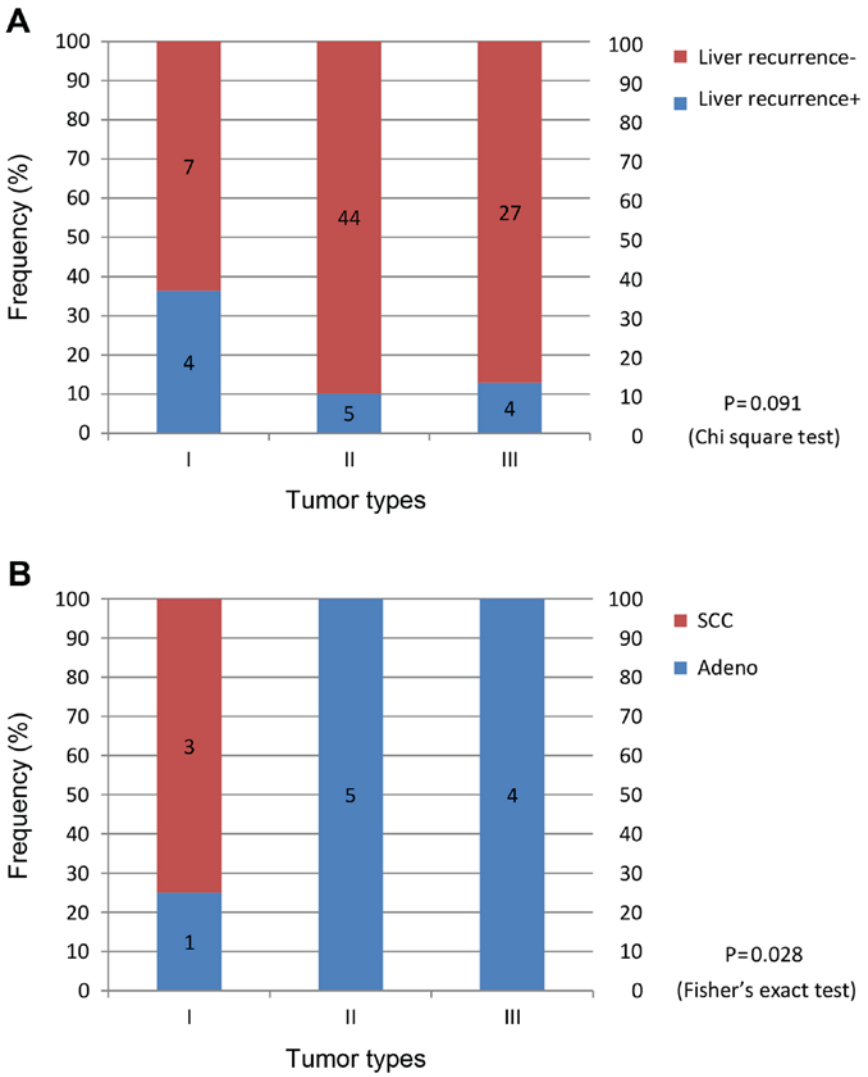

Figure 5. (A) Frequency of recurrences in the liver, as a site of initial recurrence, according to the tumor type. (B) Ratio of patients with liver recurrences who had adenocarcinoma and those who had squamous cell carcinoma. SCC, squamous cell carcinoma; adeno, adenocarcinoma.

who underwent thoracotomy had significantly more severe complications compared with those who did not; therefore, the immunosuppression caused by the complications may be associated with the negative impact on survival rate.

In Western countries, the standard therapy for patients with esophageal or EGJ cancer is preoperative chemoradiotherapy (9-11). However, the rate of locoregional recurrences in patients who received preoperative chemoradiotherapy was reported to be as high as 12.3 and 5.2% in patients with SCC and adenocarcinoma, respectively (10). The use of chemotherapeutic drugs, including carboplatin and paclitaxel, or 5-fluorouracil and cisplatin did not appear to limit hematogenous recurrences. On the other hand, locoregional recurrences were observed in only 6% of patients in the series, although none of the patients received preoperative chemoradiotherapy. In patients with EGJ adenocarcinoma, the most frequent type of recurrence was reported to be hematogenous spread to the liver and lungs (30,31). In Korea, a randomized controlled trial evaluating the addition of radiation therapy to postoperative chemotherapy with capecitabine plus cisplatin for gastric or EGJ tumors following D2 dissections did not identify any significant benefits with the inclusion of radiation in the therapeutic regimen (32). That study indicated that the addition of radiation to preoperative or postoperative chemotherapy, which is commonly performed in Western countries, may not be effective against EGJ cancer in Eastern countries where the majority of surgeons are able to perform extensive lymph node dissections that lead to good local control of tumors. Therefore, rather than chemoradiotherapy, more aggressive preoperative chemotherapy and R0 surgery with adequate lymph node dissections was able to influence improved oncological outcomes for patients with EGJ cancer.

The combination DCF has been used to treat unresectable and recurrent SCC of the esophagus and is well tolerated with high response rates (33,34). Recently, preoperative chemotherapy using DCF was reported to have increased survival rate benefits for patients with resectable and advanced esophageal cancer (35). In that study, significantly fewer distant metastases were observed in the patients treated with DCF (23%; 7/30 patients) compared with those treated with CF (52%; 13/25 patients; P=0.048). In the present study, preoperative chemotherapy with DCS was preferred in patients with EGJ adenocarcinoma. However, there is little evidence

supporting the use of DCS as preoperative chemotherapy for patients with esophageal or esophago-gastric cancer (in adenocarcinoma and SCC) and certain patients were not able to receive oral drugs, including S-1, due to the stenosis caused by their EGJ cancer. Therefore, preoperative chemotherapy using DCF may be a reasonable treatment strategy for patients with EGJ cancer.

In the present study, patients with (y)pT0-2 tumors were identified to have a 5-year DSS rate of 90%. However, 8 patients experienced recurrences and 3 had complete responses of their primary tumors to preoperative chemotherapy. Of the 3 patients, 2 had initial recurrences in the brain. In the present study, 29 patients underwent preoperative chemotherapy and 6 experienced complete responses of their primary tumors to chemotherapy, i.e., of the 6 patients with complete responses of primary tumors to preoperative chemotherapy, 3 experienced recurrences and 2 experienced initial recurrences in the brain. Patients who experience complete responses of their primary tumors or metastatic lymph nodes to preoperative chemotherapy have been reported to exhibit improved prognoses (36,37). However, in cases where patients experience micrometastases in the brain, these metastases may survive even if the cells themselves are susceptible to chemotherapeutic agents as the blood-brain barrier precludes the entry of chemotherapeutic agents into the brain. Thus, recurrences in the brain become evident. Therefore, in patients with complete responses to preoperative chemotherapy, the regulation of brain metastases is important.

The present study has several important limitations. First, the analysis was based on retrospective data collected at a single center and the number of patients included was low. Secondly, treatment strategies were not necessarily specified. For example, an LTA has rarely been used since the results of the JCOG9502 study were reported (8). The regimens and indications for preoperative chemotherapy were also heterogeneous. Thirdly, the choice of surgical approach and performance of splenectomy included numerous selection biases.

In conclusion, splenectomy and thoracotomy may critically affect prognoses in patients with (y)pT3 EGJ cancer classified as (y)pN0 and (y)pN1-3 respectively, and the prognostic differences may result from a distinct distribution of liver recurrences. These results also suggested that careful attention must be paid to improving surgical maneuvers, by means including the use of less invasive surgery and splenectomy, to improve prognoses in EGJ cancer with pT3 invasion.

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