

Prognostic Impact of Splenectomy in Patients with Esophagogastric Junction Carcinoma

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Abstract. *Background/Aim:* We evaluated the survival benefit of splenectomy in patients with esophagogastric junction (EGJ) carcinoma. *Patients and Methods:* We retrospectively examined clinicopathological and survival data for 60 surgically-treated patients with ECJ carcinoma. *Results:* The 5-year overall survival (OS) rate was 47%. Splenectomy was performed in 20 patients (30%). Multivariate Cox regression analysis revealed splenectomy (odds ratio (OR), 2.70; 95% confidence interval (CI)=1.06-7.17; $p=0.04$) and venous invasion (OR=3.03; 95%CI=1.20-9.27; $p=0.02$) as significant independent predictors of poorer OS. Splenic hilar lymph node metastasis was not observed. Multivariate logistic regression analysis identified perioperative blood transfusion (BTF) as a significant independent factor associated with splenectomy. *Conclusion:* The survival benefit of splenectomy in ECJ carcinoma patients may decrease with increasing frequency of perioperative BTF for blood loss. We recommend that splenectomy should be performed carefully when indicated by the extent or invasion of EGJ carcinoma.

The incidence of adenocarcinoma of the oesophagogastric junction (EGJ) is increasing in both Western and Eastern countries (1). The Siewert classification of EGJ adenocarcinomas has been widely accepted (2), while the current classification system in Japan designates a tumor as an EGJ carcinoma, regardless of its histological type, when its

epicentre is located within 2 cm proximal or distal to the EGJ (3). Moreover, though in these EGJ carcinomas are less than 4 cm in diameter, the algorithm was established to provide a tentative standard for lymphadenectomy based on the results of a retrospective multi-institutional study in Japanese guidelines (4). However, the final results of this study did not alter the recommendations, and the optimal surgical procedures for EGJ carcinoma, including the surgical approach (transthoracic or transhiatal), range of lymphadenopathy and type of gastrectomy remain controversial.

The European Society for Medical Oncology clinical practice guidelines recommend D2 gastrectomy for curable gastric cancer. However, splenectomy is not recommended unless the tumor is directly infiltrating the spleen (5, 6). In contrast, Japanese guidelines include splenectomy in D2 total gastrectomy (3). A recent randomised trial reported that splenectomy should be avoided because it increased operative morbidity without improving survival in patients undergoing total gastrectomy for proximal gastric cancer not invading the greater curvature (7). Moreover, a previous study reported that splenic hilar lymph node dissection could be omitted from EGJ carcinoma surgery without decreasing curability, based on the index of estimated benefit from lymph node dissection (8). However, this study did not establish the value of splenectomy or not in patients with EGJ carcinoma.

Further information regarding the survival benefits of splenectomy will help determine the optimal surgical procedure in patients with ECJ carcinoma. We retrospectively examined clinicopathological and survival data for surgically treated patients with ECJ carcinoma, to determine the benefits of splenectomy.

Patients and Methods

Patients. We retrospectively reviewed a database of 60 patients with EGJ carcinoma who had undergone macroscopically complete resection (R0 or R1) at Saitama Medical Center, Saitama Medical University, or Gunma Chuo Hospital between July 2005 and

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August 2017. The selection criteria for the type of surgical procedure and techniques were the same at the two institutions, and splenectomy was performed purely for oncological reasons. We excluded 10 patients with stage IA ECJ carcinoma who were treated without splenectomy, but who remained alive with no recurrence. This retrospective study was approved by the local ethics committee of Saitama Medical Centre of Saitama Medical University (No. 613- III).

ECJ carcinoma was defined as a tumor with a center located within 2 cm proximal or distal to the EGJ, according to the Japanese Gastric Cancer Association (JGCA) classification (9). T tumor staging was performed according to the Union for International Cancer Control pTNM staging guidelines, 7th edition (10). Surgical complications were assessed by the Clavien–Dindo classification (11). Terminology defined by the JGCA classification was used to avoid unnecessary confusion (9).

Statistical analysis. Continuous variables are expressed as medians and ranges. Categorical and continuous variables were grouped according to standard thresholds. Univariate and multivariate survival analyses were carried out using the Cox proportional hazard regression model. Significant factors associated with splenectomy were investigated using univariate and multivariate logistic regression analyses. Factors with a *p*-value <0.05 according to univariate analysis were assessed by multivariate analysis. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for the univariate and multivariate analyses. Survival curves were drawn by the Kaplan–Meier method and compared with the log-rank test. All statistical analyses were performed using JMP 5.0 software (SAS Institute, Cary, NC, USA).

Results

Patient characteristics. The characteristics of 60 patients with ECJ carcinoma are presented in Table I. There were 51 male and 9 female patients with a median age of 70 years. The tumors were located in the GE region in 45 patients, and the median tumor size was 60 mm. The thoracoabdominal and transhiatal approaches were used in 31 and 29 patients, respectively. Splenectomy was performed in 20 patients (30%). The median numbers of dissected and involved nodes were 36 and three, respectively. The median intraoperative blood loss (IBL) was 530 ml, and perioperative blood transfusion (BTF) was performed in 15 patients (25%). Grade II or higher complications occurred in 18 patients. Fifty-three patients underwent R0 resection and seven underwent R1 resection. Thirty-four patients received adjuvant chemotherapy, predominantly with S-1 agents.

Survival. The 5-year overall survival (OS) rate of all patients was 47%, with a median follow-up time of 31 months (range=2-116 months). We selected the following 22 variables for univariate analysis with regard to OS: age (<70 vs. ≥70 years), gender (male vs. female), location (EG vs. E=G/GE), tumor size (<60 vs. ≥60 mm), histological type (differentiated vs. undifferentiated), tumor depth (T1b, 2 or 3 vs. T4a or 4b), nodal stage (N0, 1 or 2 vs. N3), TNM stage

Table I. *Clinicopathological characteristics of 60 patients with esophagogastric junction carcinoma.*

Characteristics	
Median age (range), years	70 (33-75)
Gender, n	
Male/female	51/9
Location, n	
EG/E=G/GE	12/3/45
Median tumor size (range), mm	60 (15-105)
Histological type, n	
Differentiated/undifferentiated	33/27
Tumor depth, n	
T1b/2/3/4a/4b	1/7/32/17/3
Nodal stage, n	
N0/1/2/3	18/10/16/16
TNM stage, n	
IB/II/III/IV	5/15/33/7
Median esophageal invasion (range), mm	20 (2-54)
Median gastric invasion (range), mm	34 (10-90)
Lymphatic invasion, n	
ly0/1/2/3	15/17/18/10
Venous invasion, n	
v0/1/2/3	10/13/29/8
Approach, n	
Thoracoabdominal/transhiatal	31/29
Type of gastrectomy, n	
Total/proximal	42/18
Splenectomy, n	
No/yes	40/20
Lymphadenectomy, n	
D1/2	28/32
Median dissected nodes (range), n	36 (9-96)
Median involved nodes (range), n	36 (9-96)
Median operating time (range), min	275 (139-580)
Median perioperative blood loss (range), ml	530 (50-3100)
Intraoperative transfusion, n	
No/yes	45/15
Complications*, n	
Grade I/II/III/IV	8/10/7/1
Residual tumor, n	
R0/1	53/7
Neoadjuvant chemotherapy, n	
No/Yes	57/3
Adjuvant chemotherapy, n	
No/Yes	26/34

*Based on the Clavien-Dindo classification.

(IB or II vs. III or IV), esophageal invasion (<20 vs. ≥20 mm), gastric invasion (<34 vs. ≥34 mm), type of approach (thoracoabdominal vs. transhiatal), type of gastrectomy (total vs. proximal), splenectomy (yes vs. no), lymphadenectomy (D1 vs. D2), lymphatic invasion (ly0 or 1 vs. ly2 or 3), venous invasion (v0 or 1 vs. v2 or 3), operating time (<275 vs. ≥275 min), IBL (<530 vs. ≥530 ml), perioperative BTF (yes vs. no), toxicity grade (grade 0 or I vs. grade II, III or

Table II. Univariate and multivariate Cox regression analyses for overall survival.

Variables	N	Univariate		Multivariate	
		Odds ratio (95%CI)	p-Value	Odds ratio (95%CI)	p-Value
Nodal stage					
N0, 1, 2	44	1		1	
N3	16	3.62 (1.56-7.98)	<0.01	2.27 (0.79-7.00)	0.13
TNM stage					
IB, II	20	1		1	
III, IV	40	2.51 (1.02-7.52)	0.04	1.25 (0.31-5.15)	0.76
Lymphatic invasion					
ly0, 1	32	1		0.57 (0.16-1.91)	0.36
ly2, 3	28	2.83 (1.09-5.47)	0.03	1	
Venous invasion					
v0, 1	23	1		1	
v2, 3	37	3.19 (1.30-9.55)	0.01	3.03 (1.20-9.27)	0.02
Splenectomy					
No	40	1		1	
Yes	20	3.03 (1.40-6.79)	0.01	2.70 (1.06-7.17)	0.04
Adjuvant chemotherapy					
No	26	1		1	
Yes	34	2.54 (1.14-6.22)	0.02	1.83 (0.56-6.62)	0.32

CI: Confidence interval.

Table III. Univariate and multivariate logistic regression analyses for splenectomy.

Variables	N	Univariate		Multivariate	
		Odds ratio (95%CI)	p-Value	Odds ratio (95%CI)	p-Value
Gastric invasion; mm					
<34	30	1		1	
≥34	30	3.50 (1.15-11.7)	0.03	2.94 (0.67-14.5)	0.16
TNM stage					
IB, II	20	1		1	
III, IV	40	4.19 (1.17-20.0)	0.04	4.72 (0.85-36.6)	0.10
Lymphadenectomy					
D1	28	1		1	
D2	32	4.06 (1.30-14.5)	0.02	4.40 (1.03-23.1)	0.06
Residual tumor					
R0	53	1		1	
R1	7	6.33 (1.22-47.7)	0.04	2.74 (0.34-28.7)	0.36
Intraoperative blood loss; ml					
<530	29	1		1	
≥530	31	4.50 (1.43-16.2)	0.01	3.71 (0.79-19.9)	0.10
Perioperative blood transfusion					
No	45	1		1	
Yes	15	7.00 (2.02-27.3)	<0.01	5.45 (1.15-30.7)	0.04

CI: Confidence interval.

IV), residual tumor (R0 vs. R1) and adjuvant chemotherapy (yes vs. no). According to univariate analysis, nodal stage ($p<0.01$), TNM stage ($p=0.04$), lymphatic invasion ($p=0.01$), venous invasion ($p=0.01$), splenectomy ($p=0.01$)

and adjuvant chemotherapy ($p=0.02$) were significantly associated with poorer OS. Multivariate Cox regression analysis identified venous invasion (OR, 3.03; 95%CI, 1.20-9.27; $p=0.02$) and splenectomy (OR, 2.70; 95%CI, 1.06-

7.17; $p=0.04$) as significant independent predictors of poorer OS (Table II). The 40 patients treated with spleen preservation exhibited a 5-year OS rate of 63%, and the 20 patients treated with splenectomy exhibited a 5-year OS rate of 25%. Patients treated with spleen preservation had a significantly longer OS than those treated with splenectomy ($p<0.01$) (Figure 1).

Factors associated with splenectomy. We examined the factors significantly associated with the performance of splenectomy for EGJ carcinoma by logistic regression analysis. Univariate analysis revealed gastric invasion, TNM stage, lymphadenectomy, residual tumor, IBL and perioperative BTF as significantly associated with splenectomy, while perioperative BTF was the only significant independent factor associated with splenectomy according to multivariate analysis (Table III). No incidental splenic hilar lymph node metastasis was observed in the present study (data not shown).

Discussion

The results of this study identified splenectomy and venous invasion as independent factors associated with poorer OS in patients with ECJ carcinoma undergoing macroscopically complete resection. Our data also indicated that splenectomy for EGJ carcinoma was significantly associated with an increasing frequency of perioperative BTF.

In terms of the impact of splenectomy on surgical outcome, a recent randomised trial reported that it failed to improve survival in patients with proximal gastric cancer not invading the greater curvature (7). Moreover, another study reported that splenectomy with splenic hilar lymph node dissection had no survival benefit in patients with EGJ carcinoma (8). In the current study, patients treated with spleen preservation had a significantly longer OS than those treated with splenectomy. Moreover, splenectomy itself was an independent unfavourable factor in patients with ECJ carcinoma, and no splenic hilar lymph node metastasis was observed. It may, thus, be important for splenectomy to be performed carefully when indicated by the extent or invasion of EGJ carcinoma.

The present analysis identified venous invasion as an unfavourable prognostic factor in patients with EGJ carcinoma. Several previous studies have identified a number of prognostic factors for gastric cancer, with lymph node metastasis being the strongest prognostic factor after curative resection (5), and venous invasion only reported as an unfavourable prognostic factor in patients with IB stage gastric cancer without lymph node metastasis (12). ECJ carcinoma patients with venous invasion may thus have a poor prognosis compared with gastric cancer, and may benefit from the effective use of adjuvant chemotherapy.

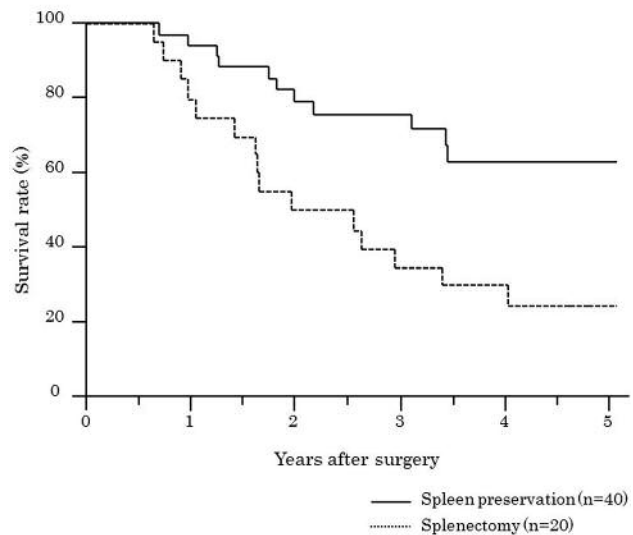


Figure 1. Cumulative overall survival (OS) of 60 patients with esophagogastric junction carcinoma treated with or without splenectomy. The cumulative OS of 40 patients treated with spleen preservation was significantly better than that of 20 patients treated with splenectomy ($p<0.01$).

In another study, splenectomy was significantly associated with a higher rate of infectious complications in patients with gastric or EGJ carcinoma (13). In the present study, perioperative BTF was a significant factor associated with splenectomy in patients with EGJ carcinoma. BTF is required when performing complex surgery with a large IBL; however, BTF may adversely cause dysfunction of the immune system and malignant transformation of neoplastic cells (14, 15). Several studies have attempted to evaluate the influence of perioperative BTF on the prognosis of gastric cancer patients, but the results have varied. Ojima *et al.* (16) and Kanda *et al.* (17) explored prognostic factors in patients with stage I-IV and II/III gastric cancer, respectively, and identified perioperative BTF as an independent unfavourable factor. In contrast, Zhou *et al.* (18) found that perioperative BTF was not an independent prognostic factor in patients with stage I-III gastric cancer, and Pacelli *et al.* (19) reported no significant difference in survival of stage I-IV gastric cancer patients in relation to the receipt of BTF, regardless of splenectomy. Based on these previous findings, the prognostic effect of BTF in gastric cancer patients remains unclear. The surgical procedure for EGJ carcinoma may be more complex than that for gastric cancer, because of its approach or the extent of lymphadenectomy, and BTF for excessive IBL may thus be more common during surgery for EGJ carcinoma compared with gastric cancer (20). However, our current results suggest that BTF for excessive IBL associated with complex surgery, in addition to splenectomy, may lead to poor outcomes in patients with ECJ carcinoma.

Conclusion

In conclusion, the survival benefits of splenectomy in patients with ECJ carcinoma may decrease in line with the increasing frequency of perioperative BTF for blood loss. Splenectomy should thus be performed carefully when indicated by the extent or invasion of the EGJ carcinoma. Although the current retrospective study was performed in a small patient population and was therefore subject to selection bias, the findings warrant further prospective studies with larger sample sizes to determine the optimal surgical treatment strategy in patients with ECJ carcinoma.

Conflicts of Interest

Minoru Fukuchi and the other co-authors have no conflict of interest.

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