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Clinical impact of splenic hilar dissection with splenectomy for gastric stump cancer

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ABSTRACT

Background: Splenectomy for advanced gastric stump cancer (GSC) is performed in Japan, based on the concept that lymphatic flow toward the splenic hilum is dominant following initial gastrectomy. However, little has been reported on the therapeutic impact of complete splenic hilar dissection with splenectomy.

Material and methods: A total of 184 patients who underwent R0 total gastrectomy with or without splenectomy for GSC between 1998 and 2015 were included in this retrospective analysis. Patients were divided into subgroups: patients with tumors involving the greater curvature (Gre group) and tumors without greater curvature involvement (non-Gre group), and each group was further divided into those with and without splenectomy. The incidence of lymph node (LN) metastasis, index of the estimated benefit from LN dissection in each station, and survival curves were compared.

Results: The incidence of No.10 LN metastasis was higher in the Gre group than in the non-Gre group (16.7% vs. 2.0%, $P = 0.036$). The index of No.10 LN dissection was higher in the Gre group than in the non-Gre group (6.3 vs. 0). However, there was no tendency that splenectomy was superior to spleen preservation for survival outcomes in either group, although selection bias certainly existed.

Conclusions: In advanced GSC, similar to primary advanced proximal gastric cancer, splenectomy can be omitted unless the tumor infiltrates the greater curvature. Complete splenic hilar dissection may be expected to be beneficial for some patients with tumors infiltrating the greater curvature.

Introduction

Gastric stump cancer (GSC) is a rare disease that accounts for 1%–2% of all gastric cancers [1,2]. GSC following distal gastrectomy for benign disease used to be predominant. However, gastrectomy is no longer a standard treatment for peptic ulcer disease, and thus a future decrease in the incidence of GSC following benign disease would have been anticipated. However, GSC following gastrectomy for cancer could become more common in the future, because longer survival is expected following surgical resection, especially for early gastric cancer.

GSC following distal gastrectomy arises anatomically from the upper third of the original stomach, hence treatment strategy is generally determined following the guidelines for primary proximal third gastric cancer (PGC) [3]. Accordingly, in advanced GSC, splenectomy had been regarded as a mandatory procedure, as in advanced PGC, especially in Japan. Some researchers have more strongly recommended splenectomy for GSC regardless of circumferential tumor location because initial surgery for GSC might have altered lymphatic flow toward the splenic hilum. Sasako et al. [4] and Imada et al. [5] showed that the incidence of metastatic LNs along the greater curvature, splenic artery and splenic hilum was higher in GSC than in PGC.

However, splenectomy is no longer a standard treatment for advanced PGC in Japan unless the tumor infiltrates the greater

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curvature line, because the JCOG 0110 trial clearly demonstrated the noninferiority of spleen-preservation procedures to splenectomy [6]. The JCOG 0110 trial did not include patients with GSC; hence the clinical question was raised as to whether splenectomy is necessary in all cases of GSC. In the present study, we retrospectively reviewed the clinical data of surgically resected GSC using the reliable clinical database of two high-volume centers in Japan. We aimed to elucidate the survival impact of splenectomy for patients with GSC.

Material and methods

Patients

We enrolled 184 patients with GSC following distal gastrectomy who underwent R0 total gastrectomy between 1998 and 2015 at the National Cancer Center Hospital and National Cancer Center Hospital East, Japan. We excluded patients who received neoadjuvant chemotherapy (n = 4), those with tumors that directly invaded the pancreas or spleen (n = 13), and those with bulky metastatic LNs at No. 10 station (around the splenic hilum) (n = 1). The patients were divided into two groups: those with gastric cancer involving a cross-sectional quarter part of the greater curvature site (Gre group, n = 44); and those with gastric cancer not involving the greater curvature site (non-Gre group, n = 140). Each group was divided into splenectomy (A group in Gre and C group in non-Gre) and spleen-preservation (B group in Gre and D group in non-Gre) groups. The patient flow diagram is shown in Fig. 1. This study was approved by the Institutional Review Board (IRB) of the National Cancer Center, Japan (IRB file No. 2017–456, approval date: February 21, 2018).

During the study period, in principle, total gastrectomy with splenectomy was performed for cT2–4 GSC irrespective of circumferential tumor location, as long as patients were medically and physically fit for radical surgery. In patients with early stage GSC and in patients who did not seem to fit for splenectomy, such as those with severe comorbidity or poor performance status, spleen-preservation was selected. However, decision was basically made according to physician preference.

Operation was performed by surgeons experienced in gastric cancer surgery. Basically, at least one or more than drainage tubes were placed in the abdominal cavity during surgery. Amylase levels of drain were measured to monitor pancreatic leakage. In patients with pStage II or III tumor, postoperative adjuvant chemotherapy with S-1 has been considered since 2007 [7].

The patient characteristics, pathological and surgical findings were collected from the clinical database. The location of regional LNs was categorized according to the Japanese Gastric Cancer Association classification [8]. Clinical and pathological stage and T stage followed the 8th TNM classification [9].

Incidence of LN metastasis and index of estimated benefit of LN dissection

Incidence of metastasis at each LN station including No.10 was investigated in the splenectomy patients (A + C group, n = 74), because in these patients No.10 nodes were completely resected. In addition, the distribution of LN metastasis and therapeutic value index was compared between the Gre (A group, n = 24) and non-Gre (C group, n = 50) groups. The therapeutic value index, proposed by Sasako et al. [10], was adopted to estimate the benefit of each LN dissection. The therapeutic value index was calculated by multiplication of the incidence of metastasis and rate of 5-year overall survival in patients with metastasis for each station.

Splenectomy versus spleen preservation

Clinicopathological factors as well as surgical outcomes were compared between splenectomy (A + C group, n = 74) and spleen-preservation (B + D group, n = 110) groups. Postoperative complications within 30 days were classified using the Clavien–Dindo grading system [11], and grade III or higher complications were defined as severe. We compared survival outcomes between splenectomy and spleen-preservation groups who had pT2 or deeper tumors.

Statistical analysis

All statistical analyses were performed using JMP version 11 (SAS Institute, Cary, NC, USA). Fisher's exact test and Wilcoxon's signed-rank test were used for comparison of categorical valuables. Survival curves were constructed by the Kaplan–Meier method, and

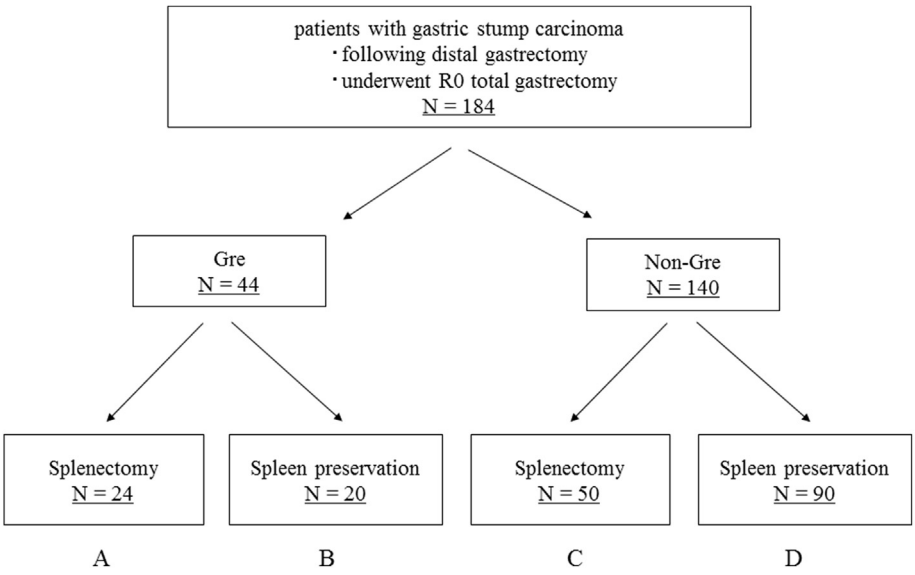

Fig. 1. Patient flow diagram.

the log-rank test was used to compare survival outcomes between groups. A P value < 0.05 was considered as statistically significant.

Results

The clinicopathological characteristics of all the patients are summarized in Table 1. In 33% (124/184) of the patients, the initial surgery was performed for cancer. Eleven patients (6%) had pT4b cancer, infiltrating liver (n = 4), jejunum (n = 3), diaphragm (n = 3), and transverse colon (n = 2). Postoperative adjuvant chemotherapy was given to 49% (21/49) of the patients with pStage II/III cancer who underwent surgery between 2007 and 2015.

Incidence of LN metastasis and therapeutic value index of each station (in A and C groups)

The incidence of No. 10 LN metastasis (16.7 vs. 2.0%, respectively; $P = 0.036$) and the therapeutic value index (6.3 vs 0, respectively) were higher in the Gre than non-Gre group (Table 2). Similarly, the incidence of metastasis and the index of the No. 2, 4sa and 4sb LNs, which are located along the greater curvature side of the stomach, were also higher in the Gre than non-Gre group. The incidence of LN metastasis at No.3 station was high in both groups, but higher in the non-Gre group (25.0 vs. 43.8%), and the index (0 vs. 12.5) was also higher in the non-Gre group.

Splenectomy versus spleen preservation (A + C vs. B + D)

The operating time was longer and blood loss volume was higher in the splenectomy group than the spleen-preservation group. Morbidity (grade III or higher) was more frequent in the splenectomy group than spleen-preservation group (35 vs. 16%; $P = 0.0021$) (Table 3). The details of morbidity were as follows: grade IIIa, 18 (24%) vs. 10 (9%); grade IIIb, 5 (7%) vs. 5 (5%); grade IVa, 2 (3%) vs. 1 (1%); grade V, 1 (1%) vs. zero. Pancreatic fistula was observed more often in the splenectomy than spleen-preservation group (20% vs. 3%). Regarding details of severe complication with grade IV or more, two patients in the splenectomy group experienced sepsis due to anastomotic leakage required re-operation for drainage, and one patient in the spleen-preservation group had pulmonary embolism requiring management with ventilator. One patient in the splenectomy group died from aspiration pneumonia.

pT2 or deeper tumor was found in 53 patients in the splenectomy group and 40 in the spleen-preservation group. The 5-year overall survival of these patients was not significantly different between the splenectomy and spleen-preservation groups (Fig. 2), even when divided into Gre invasion (+) and Gre invasion (−).

Discussion

The optimal extent of lymphadenectomy for GSC remains uncertain because of the rarity of the disease, and the therapeutic

Table 1
Clinicopathological factors.

	All n = 184	Gre		non-Gre		*P* (A vs. B)	*P* (C vs. D)
		A n = 24	B n = 20	C n = 50	D n = 90		
Sex						1.00	0.65
Male	146 (80)	17 (71)	15 (75)	42 (84)	72 (80)		
Female	38 (20)	7 (29)	5 (25)	8 (16)	18 (20)		
Age, years, median (range)	68 (34–85)	68 (52–81)	68 (37–83)	67 (42–84)	69 (34–85)	1.00	0.19
Initial surgery						0.55	0.85
Benign	60 (33)	11 (46)	7 (35)	14 (28)	28 (31)		
Malignant	124 (67)	13 (54)	13 (65)	36 (72)	62 (69)		
Interval[a], years, median (range)	30 (1–59)	26 (3–51)	17 (3–50)	13 (1–50)	12 (1–59)	0.085	0.63
Reconstruction at initial surgery						0.56	0.47
Billroth-I	118 (64)	12 (50)	13 (65)	34 (68)	59 (66)		
Billroth-II	54 (29)	11 (46)	6 (30)	11 (22)	26 (29)		
Roux-en-Y	12 (7)	1 (4)	1 (5)	5 (10)	5 (5)		
Year of surgery for GSC						0.015	<0.0001
1998–2006	88 (48)	14 (58)	4 (20)	37 (74)	33 (37)		
2007–2015	96 (52)	10 (42)	16 (80)	13 (26)	57 (63)		
Clinical depth of invasion						0.033	<0.0001
cT2 or greater	69 (38)	16 (66)	6 (30)	32 (64)	15 (17)		
Clinical LN metastasis						0.65	0.022
present	11 (6)	2 (8)	3 (15)	5 (10)	1 (1)		
Operating time, min, median (range)	243 (99–727)	264 (111–520)	251 (148–465)	260 (132–727)	234 (99–488)	0.49	0.037
Intraoperative blood loss, ml, median (range)	415 (54–2820)	472 (72–2820)	369 (97–1605)	575 (119–2493)	350 (54–2803)	0.732	<0.0001
Morbidity, n (%)	42 (23)	9 (38)	1 (5)	17 (34)	15 (17)	0.013	0.023
Tumor size, mm, median (range)	35 (3–160)	50 (11–160)	35 (8–90)	39.5 (11–140)	30.5 (3–105)	0.089	0.018
Pathological depth of invasion						0.029	0.0002
T2 or greater	93 (51)	19 (79)	9 (45)	34 (68)	31 (34)		
Pathological LN metastasis						0.76	0.032
Present	40 (22)	10 (42)	7 (35)	13 (26)	10 (11)		
Pathological stage						0.21	0.002
I	113 (61)	8 (33)	12 (60)	24 (48)	69 (77)		
II	46 (25)	10 (42)	5 (25)	16 (32)	15 (17)		
III	25 (14)	6 (25)	3 (15)	10 (20)	6 (6)		
Histological type						0.33	0.033
Differentiated	91 (50)	5 (21)	7 (35)	22 (44)	57 (63)		
Undifferentiated	93 (50)	19 (79)	13 (65)	28 (56)	33 (37)		
Postoperative chemotherapy (2007–2015, pStage II or higher)	49%	33%	33%	30%	44%	0.67	0.69

Pathological stage and T numbers were defined using the 8th TNM classification.
[a] Time interval between the initial operation and resection of GSC.

Table 2
Comparison of incidence of LN metastasis and therapeutic value index[a] between the Gre (A group) and non-Gre group (C group) in the splenectomy group.

LN station	Incidence of metastasis, % (n)			*P* value	Index	
	All n = 74	Gre n = 24	non-Gre n = 50		Gre	non-Gre
No. 1	8.1 (3/37)	6.7 (1/15)	9.1 (2/22)	1.00	0	0
No. 2	7.6 (5/66)	8.3 (2/24)	7.1 (3/42)	1.00	8.3	0
No. 3	35.7 (10/28)	25.0 (3/12)	43.8 (7/16)	0.43	0	12.5
No. 4sa	8.3 (6/72)	20.8 (5/24)	2.1 (1/48)	0.014	7.8	0
No. 4sb	7.7 (3/38)	23.1 (3/13)	0 (0/25)	0.034	11.6	0
No. 8a	6.9 (2/29)	7.7 (1/13)	6.3 (1/16)	1.00	0	0
No. 9	12.5 (4/32)	7.7 (1/13)	15.8 (3/19)	0.63	0	0
No. 10	6.8 (5/74)	16.7 (4/24)	2.0 (1/50)	0.036	6.3	0
No. 11p	9.1 (5/54)	16.7 (3/18)	5.6 (2/36)	0.64	0	0
No. 11d	13.0 (3/23)	22.2 (2/9)	7.1 (1/14)	0.54	0	0

The number of LN station was categorized according to the Japanese Gastric Cancer Association classification (3rd English edition).
[a] Index of estimated benefit obtained from dissecting a particular LN station, which is calculated by multiplying the incidence of metastasis to the site (%) by the 5-year survival rate of patients with metastasis to the site.

Table 3
Details of postoperative complications (Clavien–Dindo classification grade III or higher).

	All n = 184	Splenectomy (A + C) n = 74	Spleen-preservation (B + D) n = 110	*P*
All	42 (23)	26 (35)	16 (15)	0.0021
Infectious complications	32 (87)	21 (28)	11 (10)	
Pancreatic fistula	18 (43)	15 (20)	3 (3)	
Anastomotic leakage	10 (24)	3 (4)	7 (6)	
Intra-abdominal abscess	2 (5)	1 (1)	1 (1)	
Pneumonia	2 (5)	2 (2)	0	
Ileus	3 (7)	1 (1)	2 (2)	
Intra-abdominal bleeding	2 (5)	2 (2)	0	
Others	5 (12)	2 (2)	3 (3)	

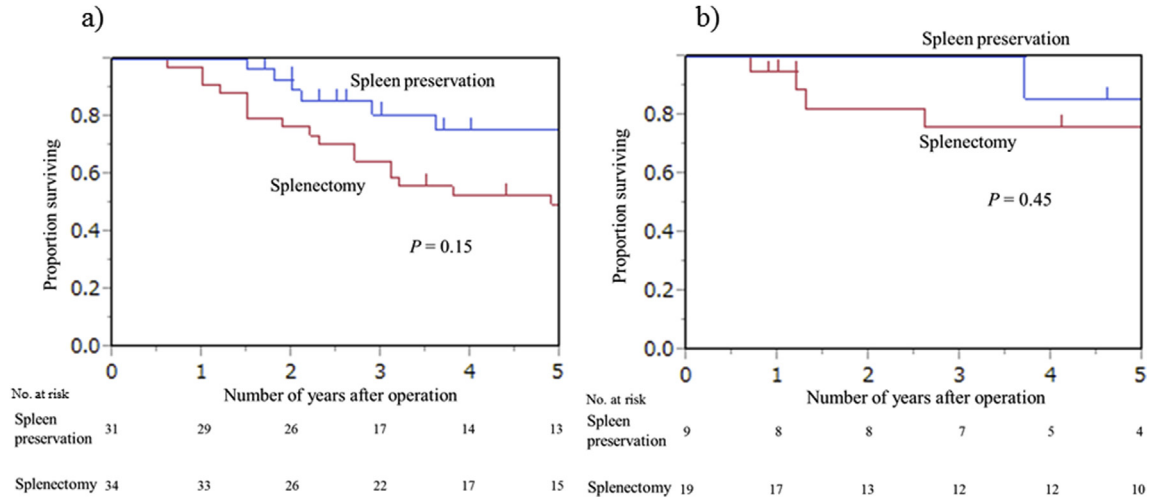

Fig. 2. Survival curves for patients with pT2 or deeper GSC who underwent splenectomy or spleen preservation. (a) Survival curve for patients in the non-Gre group with and without splenectomy. There was no significant difference between the two groups. (b) Survival curve for patients in the Gre group with and without splenectomy. There was no significant difference between the two groups.

value of splenectomy is also controversial. One of the main goals of this study was to investigate the possibility of avoiding splenectomy when carrying out adequate extend of LN dissection for GSC.

The incidence of No.10 LN metastasis in GSC has been reported as 10%–27% [4,12–14]. In the present study, the overall incidence of No.10 metastasis was 6.8%, and that in Gre-invasion (+) was 16.7% and that in Gre invasion (−) was only 2.0%. Patients with far-advanced tumors, such as those directly invading the pancreas or spleen, or with bulky metastatic LNs at No. 10 or No. 11d, were excluded from the present study because splenectomy is necessary to achieve R0 resection in such cases. This may explain the low incidence of overall No.10 metastasis in the present study cohort. However, what is more important is the low incidence of No.10 metastasis in the tumors not involving the greater curvature, as well as nearly zero therapeutic value. These results strongly suggest the unnecessity of prophylactic splenectomy in patients with tumors not involving the greater curvature, even in GSC. Several studies have pointed out that the circumferential location of the tumor is closely correlated with splenic hilar LN metastasis in PGC [15,16]. However, to the best of our knowledge, the present study is

the first to explore the tendency of LN metastasis distribution in GSC according to circumferential tumor location.

Splenectomy is an undoubtedly invasive procedure that is associated with high incidence of postoperative pancreatic fistula, possibly resulting from full splenopancreatic mobilization from the retroperitoneal bed. The JCOG 0110 trial clearly demonstrated higher morbidity rate following splenectomy (30.3%) than spleen preservation (16.1%) [6]. The same trend would be expected for total gastrectomy for GSC; moreover, further adhesions in the abdominal cavity are likely to cause postoperative complications. The possible adverse outcomes of short- and long-term postoperative complications [17] suggest that it is important to carefully select candidates for splenectomy, so as to prevent needless procedures.

The therapeutic impact of splenectomy for GSC was previously investigated by Sugita et al. [18], and better survival outcomes following splenectomy in patients with pT3/4 GSC were reported. In the present study, we compared the survival outcomes between splenectomy and non-splenectomy, but no superiority of splenectomy was observed. It seems difficult to explain the discrepancy. The difference from the present study was that circumferential tumor location was not taken into account in the previous study. We separated the patients into Gre invasion (+)/(−), or excluded pT1 cases to adjust the conditions but, nevertheless, the results were similar without statistical difference. These results might be due to a limited statistical power from small sample size. In addition, it should be noted that both studies were retrospective, with potential patients' selection bias, thus, we cannot reach final conclusions. However, in the present study, the therapeutic index of No.10 dissection in the Gre group was high. Given these facts, it is likely that some patients with tumors invading the greater curvature actually obtain survival benefit from complete splenic hilar dissection as a local control procedure. However, splenectomy is not necessary for all patients. At least, for patients with tumors not invading the greater curvature, prophylactic splenectomy can be omitted.

The effect of initial surgery on lymphatic flow has been investigated previously [19], with a change in dominant lymphatic flow toward the splenic hilum following gastrectomy even for benign disease being indicated [4,5,20]. However, in the present study, patients whose initial surgery was for benign disease did not have No. 10 LN metastasis (data not shown), as long as their tumors did not infiltrate the greater curvature line, and we could not support the above-mentioned hypothesis. Therefore, it seems reasonable that indications for splenectomy should depend mainly on circumferential tumor location rather than type of initial surgery, even in GSC. Moreover, considering the expected future decrease in GSC following distal gastrectomy for benign disease, stratification of surgical procedure by initial disease would be less meaningful.

Although the present study included the largest number of patients to date, its retrospective nature was a limitation. We could not have completely excluded potential selection bias for splenectomy group; that is, patients who underwent splenectomy could have more advanced GSC. A prospective study, ideally a multi-institutional randomized controlled trial, of splenectomy versus non-splenectomy, needs to be carried out to obtain conclusive results. However, considering the rarity of the disease, randomization of the patients seems unrealistic; thus, some well-designed prospective cohort study with adjustment for confounding factors may be an alternative.

In conclusion, splenectomy for prophylactic splenic hilar LN dissection has less therapeutic value and should be omitted, even for GSC, unless the tumor invades the greater curvature line. In contrast, the incidence of No.10 LN metastasis and therapeutic impact of splenectomy or splenic hilar lymphadenectomy cannot be ignored once the tumor infiltrates the greater curvature line. The indication for splenectomy for patients with GSC should be carefully decided according to the circumferential tumor location, as in upper-third PGC.

Conflicts of interest

All authors declare that they have no conflicts of interest.

Ethical standards

The Institutional Review Board (IRB) of the National Cancer Center approved this study. All procedures followed the standards of the Declaration of Helsinki and current ethical guidelines. Written informed consent for participation in this study was not obtained from the patients because identifying information was not included in this article.

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