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Original Article

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Limited Clinical Significance of Splenectomy and Splenic Hilar Lymph Node Dissection for Type 4 Gastric Cancer

Aina Kunitomo, Kazunari Misawa, Yuichi Ito, Seiji Ito, Eiji Higaki, Seiji Natsume, Takashi Kinoshita, Tetsuya Abe, Koji Komori, Yasuhiro Shimizu

Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Nagoya, Japan

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Correspondence to
Kazunari Misawa
Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan.
E-mail: misawakzn@aichi-cc.jp

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ORCID iDs
Aina Kunitomo
https://orcid.org/0000-0002-8019-4858
Kazunari Misawa
https://orcid.org/0000-0002-2047-3919

Author Contributions
Conceptualization: K.A., M.K.; Data curation: K.A., M.K., I.Y., I.S.; Formal analysis: K.A., M.K.; Investigation: K.A.; Methodology: K.A., M.K.; Project administration: K.A., M.K.; Supervision: M.K., I.S., S.Y.; Validation: M.K., I.Y., I.S., H.E., N.S., K.T., A.T., K.K., S.Y.; Writing - original draft: K.A.; Writing - review & editing: K.A., M.K., I.Y., I.S., H.E., N.S., K.T., A.T., K.K., S.Y.

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

ABSTRACT

Purpose: Type 4 gastric cancer (GC) has a very poor prognosis even after curative resection, and the survival benefit of splenectomy for splenic hilar lymph node (LN; #10) dissection in type 4 GC remains equivocal. This study aimed to clarify the clinical significance of splenectomy for #10 dissection in patients with type 4 GC.
Materials and Methods: The data of a total of 56 patients with type 4 GC who underwent total gastrectomy with splenectomy were retrospectively analyzed. Postoperative morbidity, state of LN metastasis, survival outcomes, and therapeutic value index (TVI) of each LN station were evaluated. TVI was calculated by multiplying the incidence of LN metastasis at each nodal station and the 5-year overall survival (OS) of patients who had metastasis to each node.
Results: Overall, the postoperative morbidity rate was 28.6%, and the incidence of #10 metastasis in the patients was 28.6%. The 5-year OS rate for all patients was 29.9%, and most patients developed peritoneal recurrence. Moreover, the 5-year OS rates with and without #10 metastasis were 6.7% and 39.1% (median survival time, 20.4 vs. 46.0 months; P=0.006). The TVI of #10 was as low as 1.92.
Conclusions: The clinical significance of splenectomy in the dissection of #10 for type 4 GC is limited and splenectomy for splenic hilar dissection alone should be omitted.

Keywords: Splenectomy; Stomach neoplasms; Linitis plastica; Lymph node excision

INTRODUCTION

The standard treatment for advanced gastric cancer (GC) in Japan is gastrectomy with D2 lymph node (LN) dissection according to the guidelines of the Japanese Gastric Cancer Association (JGCA) [1]. Because 15%–20% of GC involving the upper third of the stomach metastasizes to the splenic hilum LNs (#10) even without direct invasion to the spleen or pancreas [2], total gastrectomy with simultaneous splenectomy for complete dissection of splenic hilum LNs is the standard surgery for D2 dissection. However, spleen-preserving D2 dissection is recommended in Western countries [3,4] because splenectomy increases postoperative morbidity and mortality. In addition, several other studies [5-10] have reported that splenectomy for GC involving the proximal stomach increased postoperative

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complications but demonstrated no long-term survival benefit compared with spleen-preserving dissection, suggesting that splenectomy should be omitted.

The Japan Clinical Oncology Group (JCOG) conducted a phase III randomized controlled trial (JCOG0110 study) to clarify the role of splenectomy in total gastrectomy for proximal advanced GC with no invasion into the greater curvature. The results showed non-inferiority of spleen preservation to splenectomy in terms of overall survival (OS), whereas splenectomy was associated with greater blood loss and significantly higher rates of postoperative morbidities, particularly pancreatic fistulas [11]. Therefore, spleen-preserving total gastrectomy is the standard treatment for proximal advanced GC that does not invade the greater curvature [1].

In general, type 4 GC frequently results in peritoneal recurrence even after radical gastrectomy and has an extremely poor prognosis [12-14]. In the JCOG0110 study, "Borrmann type 4 GC (linitis plastica, LP)" was excluded from the eligibility criteria because of poor prognosis regardless of the operative procedure [11], and the role of splenectomy for type 4 GC was not clarified in the study. Thus, in Japan, total gastrectomy with splenectomy is customarily performed for type 4 GC to date. Further, only few studies have investigated the role of splenectomy in type 4 GC, and the significance of splenectomy remains unclear.

Therefore, the aim of the present study was to clarify the clinical significance of splenectomy for splenic hilar LN dissection in patients with type 4 GC. We investigated the short- and long-term outcomes of total gastrectomy with splenectomy for type 4 GC and evaluated the benefits of splenic hilar LN dissection.

MATERIALS AND METHODS

Patients

Between April 2003 and March 2018, 86 patients with type 4 GC underwent total gastrectomy at the Aichi Cancer Center Hospital and were enrolled in this retrospective study. Type 4 GC was defined based on the JGCA classification [15], which was synonymous with that of Borrmann type 4 GC. During this period, our standard treatment was total gastrectomy with splenectomy for curatively resectable type 4 GC with proximal stomach invasion. Eight patients with remnant GC were excluded from the present study. A total of 22 patients underwent total gastrectomy without splenectomy in the same period because of R2 resection (n=9), malignancy in other organs (n=3), conversion surgery (n=2), and other reasons (n=8), including old age, multiple comorbidities, and poor general condition. The data of a total of 56 patients with primary type 4 GC, who underwent curative total gastrectomy and D2 lymphadenectomy with simultaneous splenectomy, were analyzed in the present study (**Fig. 1**). Preoperative chemotherapy was not performed fundamentally because it is not the standard treatment for advanced GC in our country. However, neoadjuvant chemotherapy was administered to the patients assigned to the preoperative chemotherapy group in clinical trials or for cases with tumors that were resectable but showed severe local invasion, and these patients were included in this study.

Surgical procedure

After laparotomy and confirmation of the resectability of the tumor, peritoneal lavage for cytological examination was performed and 100 ml of saline was introduced into the

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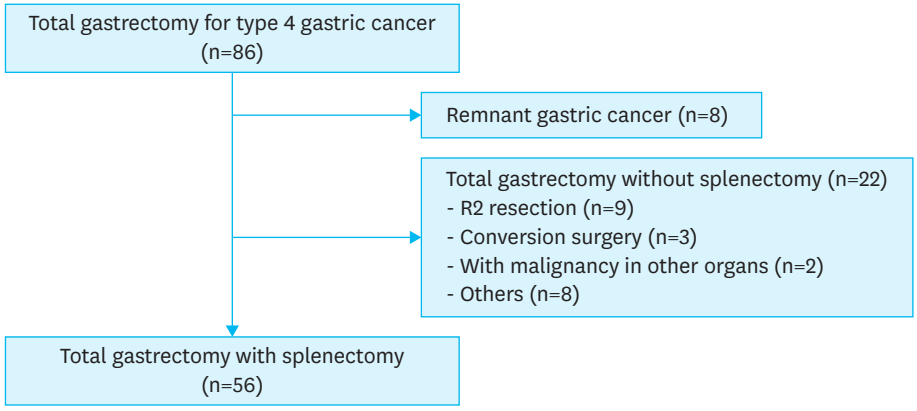

Fig. 1. Patient flow diagram.

pouch of Douglas, which was then aspirated. The results were not necessarily confirmed by intraoperative rapid diagnosis. Total gastrectomy (D2) with splenectomy was performed with full mobilization of the body and tail of the pancreas and spleen. The LNs around the splenic artery were dissected, and the spleen was excised using en bloc removal technique with the splenic hilar LNs. The pancreas was preserved unless direct invasion of the organ was identified. All patients underwent Roux-en-Y reconstruction.

Clinical and pathological factors

Macro- and microscopic classification of primary tumors, curability of resection, and final pathological stage were assessed based on the 14th edition of the JGCA classification [15]. Histopathological diagnosis was performed by experienced pathologists. Perioperative complications were evaluated using the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) [16].

Postoperative therapy and follow-up

Based on the results of the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) in Japan, S-1 (a combination of tegafur, gimeracil, and oteracil) has been the standard postoperative chemotherapy regimen since 2007 [17]. Postoperative adjuvant chemotherapy with S-1 was therefore performed for patients with pathological stage II–III since 2007, and most patients in the present study also underwent adjuvant chemotherapy before 2007 in a clinical trial or as part of clinical practice. The schedule, dose, and indication of S-1 were performed according to the ACTS-GC protocol [17]. For pathological stage IV cases, most patients underwent S-1 monotherapy, although some patients were administered S-1 combined with cisplatin or oxaliplatin.

Outpatient follow-up evaluations involved physical examination and blood tests, including tumor marker evaluation every 3 months for the initial postoperative 2 years. Chest and abdominal computed tomography (CT) was performed every 6 months for the first 3 years and then annually until postoperative 5 years. When peritoneal recurrence was suspected based on clinical signs, symptoms, or CT evidence, attempts were made to confirm the diagnosis with additional imaging (barium enema or positron emission tomography).

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Therapeutic value index (TVI) of LN dissection

TVI presented by Sasako et al. [18] was used to evaluate the efficacy of nodal dissection at each LN station. TVI was calculated by multiplying the incidence of LN metastasis at each LN station with the 5-year survival rate of patients with positive nodes and was calculated independently for each LN station. The incidence of LN metastasis was defined as the rate of metastasis-positive patients for each station, determined using the final pathological reports. Relapse-free survival (RFS) was defined as the interval between the date of surgery and the first recurrence or death from any cause. OS was defined as the interval between the date of surgery and date of death due to any cause. Data for patients who did not experience an adverse event were censored as of the date of the final observation. Survival data were obtained from hospital records.

Statistical analysis

The χ^2 test was performed for categorical data and the Mann-Whitney U test for continuous data. Survival curves were estimated using the Kaplan-Meier method, and the significance of the differences in survival was determined using the log-rank test. Differences were considered statistically significant at a P-value of <0.05. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan [19]) and a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). This study was approved by the Review Board of Aichi Cancer Center Hospital (approval number: 2019-1-251).

RESULTS

Clinicopathological features

The clinicopathological features of the 56 patients are summarized in **Table 1**. Females accounted for the majority of patients (38/56, 67.9%), the median maximum diameter of the tumor was 13.8 cm (interquartile range: 11.0-15.0 cm), and 45 patients (80.4%) had encircling tumors. Tumors involved 3 sections in 33 cases (58.9%) and 2 sections in 21 cases (37.5%). Fifty-three tumors (94.5%) penetrated the serosa (pathological T3 [pT3] and pT4), and 44 tumors (76.8%) were diagnosed to be pT4. Three cases were diagnosed as P0 preoperatively but were identified as showing resectable perigastric peritoneal deposits intraoperatively and were resected completely. Two patients with para-aortic LN metastasis showed swollen LNs intraoperatively and underwent sampling resection. R0 resection was achieved in these 5 cases. Seven patients underwent R1 resection, of whom 5 were positive cytology findings (CY1), one showed pathologically positive proximal margins, and one showed pathologically positive distal margins. There were no cases of R2 resection in this cohort. Adjuvant chemotherapy was administered to 48 patients, with most treatments involving S-1 monotherapy.

Morbidity and mortality

Postoperative complications occurred in 16 patients (28.6%) in this cohort (n=56) (**Table 2**). The incidence of pancreatic fistula was 10.7%, and grade II or higher postoperative complications occurred in 12 patients (21.4%). No in-hospital deaths were observed postoperatively.

LN metastasis

The incidence of metastasis to #10 was 28.6% (16/56). The incidence of metastasis to the regional LN stations is shown in **Table 3**. Metastasis was more often recognized in the upper perigastric LN stations (#1, 2, 3, 4) and #7, with metastatic rates of over 30%. The incidence of #10 metastasis was similar to that of #6, #9, and #11 metastases, with metastatic rates of 20%–30%.

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Table 1. Clinicopathological factors of all patients and comparison between patients with and without #10 metastasis

Clinicopathological factors	All patients (n=56)	#10 (+) (n=16)	#10 (–) (n=40)	P-value
Sex				0.752
Male	18 (32.1)	6 (37.5)	12 (30.0)	
Female	38 (67.9)	10 (62.5)	28 (70.0)	
Age (yr)	65 (21–86)	60 (30–70)	68 (21–86)	0.015
Extent of gastric involvement				0.879
UML, MUL	33 (58.9)	9 (56.3)	24 (60.0)	
UM, MU	21 (37.5)	7 (43.7)	14 (35.0)	
U	2 (3.6)	0	2 (5.0)	
Tumor size	13.8 (5.5–20)	13.3 (6–20)	13.8 (5.5–18)	0.899
≥10 cm	44 (78.6)	13 (81.3)	31 (76.3)	1.000
<10 cm	12 (21.4)	3 (18.7)	9 (23.7)	
Circumferential localization				1.000
Encircling	45 (80.4)	13 (81.3)	32 (80.0)	
Non-encircling	11 (19.6)	3 (18.7)	8 (20.0)	
Greater curvature invasion (+/–)	7/4	3/0	4/4	
Preoperative chemotherapy	11 (19.6)	2 (12.5)	9 (22.5)	0.483
Combined resection of other organs (excluding the spleen)				0.094
Present/absent (Pancreas: 5; transverse colon: 3; adrenal: 2 [overlap])	7/49	4/12	3/37	
Histological type				0.193
Differentiated/undifferentiated	3/53	2/14	1/39	
Pathological depth of invasion†				0.117
T1/T2/T3/T4a/T4b	1/2/9/40/4	0/0/0/14/2	1/2/9/26/2	
Pathological nodal stage†				0.097
N0/N1/N2/N3a/N3b	5/11/6/18/16	0/1/1/6/8	5/10/5/12/8	
Peritoneal lavage cytology (CY)				0.020*
CY0/CY1	51/5	12/4	39/1	
Pathological stage†				0.031*
I/II/IIIA/IIIB/IIIC/IV	1/7/9/9/20/10	0/0/1/1/8/6	1/7/8/8/12/4	
Residual tumor				0.016*
R0/R1	49/7	11/5	38/2	
Adjuvant chemotherapy	48 (85.7)	15 (93.8)	33 (82.5)	0.416

Values are presented as median (interquartile range) or number (%).
*P-values of <0.05 were considered significant; †Japanese Classification of Gastric Carcinoma, 14th edition.

Table 2. Postoperative complications in all patients as evaluated with CTCAE v3.0

Postoperative complications	Any grade	>Grade 2
Postoperative morbidity (any)*	16 (28.6)	12 (21.4)
Pancreatic fistula	6 (10.7)	2 (3.6)
Intraabdominal abscess	4 (7.2)	4 (7.2)
Paralytic ileus	1 (1.8)	1 (1.8)
Mechanical ileus	1 (1.8)	1 (1.8)
Wound infection	2 (3.6)	2 (3.6)
Ascites (chylous ascites)	2 (3.6)	0
Pneumonia	2 (3.6)	2 (3.6)
Stroke	1 (1.8)	1 (1.8)

Values are presented as number (%).
CTCAE v3.0 = Common Terminology Criteria for Adverse Events version 3.0.
*Some patients had multiple complications.

Survival outcomes

Median follow-up was 34.3 months (range, 5.6–126.4 months). The 5-year RFS rate for all 56 patients was 15.0% (95% confidence interval [CI], 6.8%–26.2%), and median survival time (MST) was 21.6 months. The 5-year OS rate was 29.9% (95% CI, 18.0%–42.7%), and MST was 36.5 months. During follow-up, 51 patients developed recurrence or died, and only 5 patients remained alive without recurrence. In 45 of the 51 patients with recurrence, recurrent sites were identified, with peritoneal recurrence in 43 patients and skin recurrence and distant LN recurrence in one patient each. Of the 43 patients who showed peritoneal recurrence, 39

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Table 3. TVI* of lymph nodes at each station

Station No.	Incidence of lymph node metastasis (%)	5-year overall survival (%)†	TVI
1	39.3	42.9	16.9
2	42.9	26.2	11.2
3a	71.4	28.8	20.6
3b	44.6	36.7	16.4
4sa	44.6	36.4	16.2
4sb	35.7	24.1	8.60
4d	51.8	27.3	14.1
5	14.3	14.3	2.04
6	23.2	21.0	4.87
7	33.9	25.5	8.64
8a	17.9	11.3	2.02
9	23.2	25.0	5.80
10	28.6	6.7	1.92
11p	25.0	7.7	1.93
11d	19.6	10.1	1.98
12a	3.6	0	0

TVI = therapeutic value index.
*TVI = estimated by multiplying the incidence of lymph node metastasis at that station by 5-year overall survival (%); †5-year survival (%) = 5-year overall survival rate of patients with metastasis to that nodal station.

had peritoneal metastasis alone, whereas 4 had other concomitant metastases in addition to peritoneal metastases.

Comparison of clinicopathological features and survival outcomes in patients with and without #10 metastasis

The clinicopathological features of patients with and without #10 metastasis are summarized in **Table 1**. In patients with #10 metastasis, the depth of tumor invasion was T4 in all cases, the incidence of CY1 (P=0.020) and that the of R1 cases were significantly higher than those in patients without #10 metastasis. Further, 5-year RFS rates with and without #10 metastasis were 6.2% (MST, 10.6 months) and 18.2% (MST, 29.5 months), respectively, and showed a significant difference (P=0.005) (**Fig. 2**). Five-year OS rates with and without #10 metastasis were 6.7% (MST, 20.4 months) and 39.1% (MST, 46.0 months), respectively, and showed a significant difference (P=0.006) (**Fig. 3**).

Estimated benefit of LN dissection

Five-year OS rates with LN metastasis at each station and the TVI, as an index of the estimated benefit of LN dissection for each station are shown in **Table 3**. The 5-year OS rate of patients with #10 metastasis was 6.7%. The TVI of #10 was 1.92, which is the lowest other than that of #12a. TVIs for upper perigastric LN stations (#1–4 except #4sb) were high, with TVIs exceeding 10.0. Otherwise, the TVIs of #4sb, #6, #7, and #9 were approximately 5.0, all higher than those of #5, #8a, #10, #11p, #11d, and #12a that had TVIs of approximately 2.0.

Survival outcomes and TVI in patients without pathological stage IV

In the present study, 10 patients had pathological stage IV, including 5 with CY1, 3 with peritoneal dissemination who achieved R0 resection, and 2 with para-aortic LN metastasis. These patients could be diagnosed as stage IV by intraoperative rapid histopathological diagnosis and cytology and may have the option to omit splenectomy. Therefore, we excluded 10 patients with pathological stage IV disease and evaluated long-term outcomes in 46 patients with stage I–III disease. Overall, the incidence of #10 metastasis was 21.7% (10/46). Five-year OS rates with and without #10 metastasis were 10.0% (MST, 33.6 months) and 43.9% (MST, 50.7 months), respectively (P=0.054). Moreover, the TVI of #10 was 2.17.

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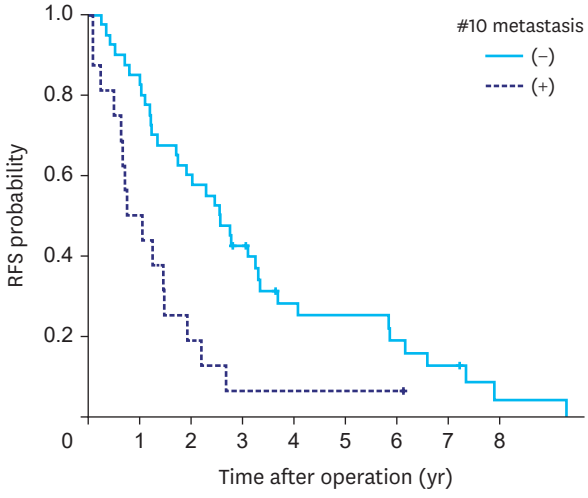
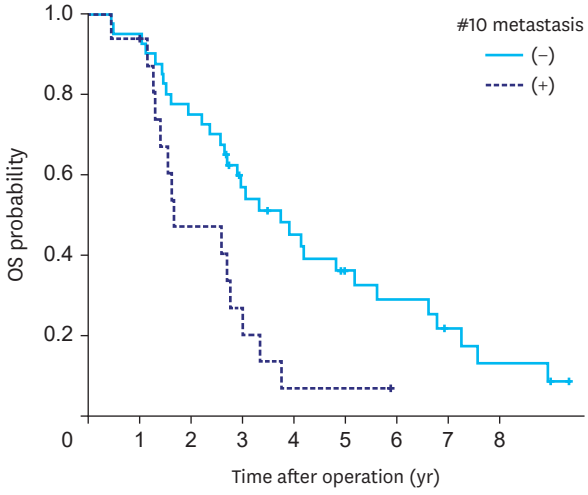


No. at risk									
(−)	40	33	23	16	8	8	6	4	1
(+)	16	8	3	1	1	1	1	0	0

Fig. 2. Kaplan-Meier curve depicting RFS for patients with and without #10 metastasis; survival differed significantly between the 2 groups (P=0.005).
RFS = relapse-free survival.
#10 = splenic hilar lymph node.



No. at risk									
(−)	40	38	30	22	15	12	8	6	3
(+)	16	15	7	4	1	1	1	0	0

Fig. 3. Kaplan-Meier curve depicting OS for patients with and without #10 metastasis; survival differed significantly between the 2 groups (P=0.006).
OS = overall survival.
#10 = splenic hilar lymph node.

DISCUSSION

This study evaluated the significance of splenectomy and splenic hilar LN dissection in patients who underwent radical total gastrectomy with splenectomy for type 4 GC by investigating short- and long-term outcomes. The postoperative morbidity of patients in the

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present study was as high as that reported in the splenectomy group of the JCOG0110 study. Most patients developed postoperative recurrence, predominantly peritoneal dissemination. Patients with #10 metastasis displayed significantly worse survival outcomes than those without #10 metastasis, and the TVI of #10 was low. Similar results were obtained in the analysis, excluding patients in stage IV, who had the option of omitting splenectomy based on intraoperative rapid histopathological diagnosis and cytological findings. The clinical significance of splenectomy for #10 dissection is limited.

Previous studies have reported that gastrectomy with splenectomy is associated with higher rates of postoperative complications than gastrectomy without splenectomy [5,10]. In the JCOG0110 study, overall postoperative morbidity in the splenectomy group was 30.3% and the pancreatic fistula rate was 12.6%, which were higher than that in the spleen-preserving group (overall postoperative morbidity, 16.7%; pancreatic fistula rate, 2.4%) [11]. In our study, postoperative complications were evaluated using CTCAE v3.0, as used in the JCOG0110 study. The complication rate was 28.6% and pancreatic fistula rate was 10.7%, which were very similar to those in the splenectomy group in the JCOG0110 study. Although there was no comparison with the spleen-preserving group in our study, it was not definitively concluded that splenectomy for type 4 GC may also be associated with a higher postoperative complication rate.

We evaluated the significance of splenectomy and #10 dissection for type 4 GC using TVI. TVI signified the efficacy of dissection based on the proportion of patients who had nodal metastasis and survived for more than 5 years due to nodal dissection. Since this concept was presented by Sasako et al. [18], it has been used in many studies to evaluate the significance of nodal dissection. Although some reports have evaluated the significance of splenectomy for proximal advanced GC using TVI [20-24], only a few studies have mentioned type 4 GC.

Sasako et al. [18] divided 1,281 patients with advanced GC into 4 subgroups (upper, middle, and lower third of the stomach, and whole stomach) according to tumor location and evaluated the TVI of each LN station in each group. Whole stomach cancer was defined as involving more than two-thirds of the stomach, in which it was assumed that most type 4 GCs were included. The incidence of #10 metastasis in patients with whole stomach cancer was more than 20%, the 5-year OS rate of patients with #10 metastasis was <10% (from the figure in Sasako et al. [18] study), and the TVI of #10 was 1.6. The survival benefit of the #10 dissection for whole stomach cancer was low. The results of our study showed that the incidence of #10 metastasis was 28.6%, the 5-year OS rate of the patients with #10 metastasis was 6.7%, and the TVI of #10 was 1.92, which are very similar to those of whole stomach cancer in the study by Sasako et al. [18].

On the other hand, Hayashi et al. [25] investigated the survival benefit of splenectomy using TVI in scirrhous GC and reported that the TVI of #10 was 5.09, which was relatively high, and stated that splenectomy for #10 dissection would be justified in scirrhous GC. The incidence of #10 metastasis was 15.3%, which is lower than our result, whereas the 5-year OS rate of patients with #10 metastasis was 33.3%, much better than the present rate. Most of the patients in their study had undifferentiated adenocarcinoma, pathological depth of invasion of T4, and large tumors sized ≥10 cm in diameter, which are similar to that of the patients in our study. However, in our study, more than two-thirds of the patients were female, which was very different from not only the study by Hayashi et al. [25] but also the general trend for GC [26], which includes more male patients. This trend is more common in females, and

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encircling tumors, large tumors, and serosal exposure are characteristic features of LP, which is a type of GC with an extremely poor prognosis.

LP-type GC is a large, advanced cancer that develops from the fundic glands in the proximal stomach and involves diffuse spread below the submucosal layer of the entire stomach. As the tumor progresses, it invades all layers of the gastric wall. These pathological features are characterized by a leather bottle-shaped deformity and giant fundic folds due to thickening and lack of dilatation (fibrous contraction) of the stomach wall associated with fibrous sclerosis [27-30]. LP-type GC is more frequent among women than other types of advanced GCs [27,30], and the non-curative resection rate is high because of the difficulty of early diagnosis [14,28,31]. Even if R0 resection can be achieved, the peritoneal recurrence rate is high. LP-type GC is a rapidly progressing GC with a more dismal prognosis than non-LP GC [14,28,32,33]. Because of the lack of a standardized definition, LP-type GC, scirrhous GC, and Borrmann type 4 GC are often confused. However, these cancers are not the same [27,28].

According to a retrospective view of the cases in the present study, 42 of the 56 patients showed LP-type GC with leather bottle-shaped deformity and a giant fundic fold. The low survival rate of patients with #10 metastasis and the low TVI of #10 in the present study might be attributable to the fact that many of our patients had LP-type GC. These findings suggest that the clinical significance of total gastrectomy with splenectomy is low for LP-type GC with poor prognosis. In other words, the results suggested that there is a population with a poorer prognosis in type 4 GC, and the significance of splenectomy for them might be very limited.

Our study has several limitations. First, this was a retrospective study conducted at a single institution. Second, theoretical limitations exist in TVI. In the TVI concept, the evaluation of survival is based only on whether the OS exceeds 5 years. In addition, the method of retrieving LNs from the specimen and pathological evaluation of LNs may affect the metastatic rate, thereby affecting TVI [18,34,35]. Third, we did not compare splenectomy and non-splenectomy groups. At our institution, splenectomy is performed for all cases of type 4 GC. Patients who underwent spleen-preserving total gastrectomy were pre- or intraoperatively judged to avoid splenectomy due to reasons such as R2 resection, old age, multiple comorbidities, and other poor general conditions, and the background characteristics of these patients were quite different from those of patients who underwent splenectomy. Therefore, comparing survival outcomes and treatment effects between splenectomy and non-splenectomy was difficult.

In conclusion, we considered splenectomy to achieve R0 resection is acceptable when spleen preservation is impossible due to direct invasion or when #10 metastasis is suspected in preoperative imaging. However, in the present study, the TVI of #10 was low, suggesting the limited clinical significance of splenectomy to dissect #10 for type 4 GC, and splenectomy for splenic hilar dissection alone should be omitted. The study population was predominantly females and possibly included more patients with LP-type GC with poor prognoses. Although LP-type GC should be distinguished from non-LP-type GC, randomized controlled trials or multi-institutional retrospective studies would be needed to prove the survival benefits of splenectomy for patients with type 4 GC.

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