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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

The Therapeutic Survival Benefit of Splenic Hilar Nodal Dissection for Advanced Proximal Gastric Cancer Invading the Greater Curvature

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ABSTRACT

Background. The Japan Clinical Oncology Group phase 3 study confirmed the survival non-inferiority of spleen-preserving surgery against splenectomy for advanced proximal gastric cancer not invading the greater curvature. However, the efficacy of #10 lymph node (LN) dissection for tumors that involve the greater curvature remains unclear.

Methods. Data from patients who underwent D2-total gastrectomy with splenectomy between January 2000 and December 2012 were retrospectively reviewed. The study included 593 patients. The patients were split into two groups, with 212 patients in the tumor invasion of the greater curvature (Gre) group and 381 patients in the non-Gre group. Survival curves and the state of LN metastasis and the index of estimated benefit from LN dissection of each station were evaluated.

Results. The incidence of #10 LN metastasis was 8.1% (48/593): 15.1% in the Gre group and 4.2% in the non-Gre group. The 5-year overall survival rates for the patients with and without #10 metastasis were respectively 46.9 and 50.2% ($P = 0.829$) in the Gre group and 49.6 and 62.3% ($P = 0.074$) in the non-Gre group. The indices for #10 LN dissection were 7.1 in the Gre group and 2.3 in the non-Gre group. In the Gre group, the node station with the highest index was #3, followed by #4d, #1, #4sb, #4sa, #7, #2, #10 (index > 7).

Conclusion. The splenic hilar nodes should be prioritized as a component of D2 lymphadenectomy for advanced gastric cancer invading the greater curvature based on its high metastatic rate and index.

For locally advanced gastric cancer, D2 gastrectomy is a globally accepted surgical procedure. In Japan, total gastrectomy with splenectomy is performed for complete removal of the splenic hilar lymph nodes (LNs), defined as the #10 station according to the classification used by the Japanese Gastric Cancer Association (JGCA).[1] Conversely, splenectomy is not commonly performed in Western countries due to its high rates of morbidity and mortality.[2]

Recently, the Japan Clinical Oncology Group conducted a phase 3 study (JCOG0110) that compared splenectomy with spleen-preserving surgery and confirmed the survival non-inferiority of spleen-preserving surgery against splenectomy for advanced proximal gastric cancers not invading the greater curvature.[3] As such, spleen-preserving D2 gastrectomy is a standard procedure for this population. However, the optimal surgery for tumors involving the greater curvature remains unclear.

The therapeutic efficacy of splenic hilar nodal dissection has not been fully evaluated, and the Japanese guideline states that the effect of splenectomy on advanced proximal gastric cancer invading the greater curvature is unknown. If the therapeutic effect achieved is less than the effects achieved at other regional LN stations, splenic hilar dissection by splenectomy may be reconsidered as a treatment option for these tumors.

Some retrospective studies have insisted on the survival benefit of splenic hilar nodal dissection for gastric cancer invading the greater curvature. Recently, Maezawa et al.[4] reported that the metastatic rate and therapeutic index of #10 were relatively high for patients with advanced proximal gastric cancer invading the greater curvature. However, the sample comprised only 82 patients, and the

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indications for splenectomy were unclear. These factors reduced the reliability of that study. Moreover, these authors did not perform analyses of patients with gastric cancer not invading the greater curvature.

More recently, Watanabe et al.[5] also examined the metastatic rate and therapeutic index of #10 for tumors invading and those not invading the greater curvature in 421 patients and reported similar results. In their study, however, many patients were lost to follow-up evaluation based on the key survival curve and number at risk, suggesting that the reliability of the key survival rate was low. Moreover, the patients in that study underwent surgery from 1992 to 2009. Recent advances in surgical devices and perioperative care may decrease the surgical morbidity and mortality rates, which would increase the therapeutic index.

Therefore, the current study analyzed a large cohort of patients who recently underwent surgery, most of whom were followed up for 5 years or until death, whichever was earlier. This study aimed to evaluate the therapeutic efficacy of #10 LN dissection compared with that for other regional nodes in patients who underwent total gastrectomy with splenectomy for locally advanced gastric cancer invading the upper third of the stomach.

MATERIALS AND METHODS

Patients

We retrospectively reviewed the clinical records of 593 patients with gastric cancer diagnosed as stage T2–T4 invading the upper third of the stomach who underwent R0 total gastrectomy with simultaneous splenectomy (D2) between January 2000 and December 2012 at the National Cancer Center Hospital of Japan. During that period, splenectomy was the standard therapeutic procedure for these tumors. The vast majority of the patients were followed up until death or for 5 years, whichever was earlier. Patients with remnant gastric cancer and those with postoperative confirmation of stage 4 disease (#16 LN metastasis, positive cytology) were excluded from the study. Resected specimens were examined and evaluated according to the *Japanese Classification of Gastric Carcinoma,* 15th edition.[1]

Surgical Methods

Total gastrectomy with splenectomy using laparotomy with full mobilization of the pancreatic body and spleen and D2 lymph node dissection was performed according to the Japanese gastric cancer treatment guidelines.[6] Surgery was performed by experienced surgeons.

Postoperative Therapy and Follow-up Evaluation

Based on the results from the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) in Japan,[7] S-1 has been the standard postoperative chemotherapy regimen since 2007. Thus, for the patients in this study, postoperative adjuvant chemotherapy with S-1 was principally administered when the final tumor stage was consistent with the ACTS-GC criteria. Outpatient follow-up evaluation involved physical examination and blood tests, including tumor marker evaluation every 3 months for the first 2 years postoperatively. Chest and abdominal computed tomography were performed every 6 months for the first 3 years and then annually until 5 years postoperatively.

Clinical and Pathologic Factors

The 8th edition of the Union for International Cancer Control (UICC) tumor-node-metastasis classification of gastric carcinoma was used for tumor staging.[8] We reviewed the following clinical and pathologic factors: sex, age, maximum tumor size, macroscopic type according to the Borrmann classification, tumor location, histologic type, pathologic T and N factors, and stage.

The cross-sectional, circumferential location of each tumor was defined according to the Japanese Gastric Cancer Association (JGCA) classification,[1] in which the stomach wall is divided into four equal parts. Macroscopic and pathologic images were reviewed to determine whether the tumors invaded the greater curvature or not. The JGCA classification of gastric cancer was used to evaluate tumor progression and histologic grade. The histopathologic diagnosis was determined by experienced pathologists. The JGCA classification of gastric carcinoma was used to number the LN stations.[1]

Therapeutic Value of Lymph Node Dissection

To evaluate the therapeutic value of dissection at each LN station, we used the therapeutic value index presented by Sasako et al.[9] The therapeutic value of nodal dissection (as a percentage) was obtained by multiplying the LN metastasis rate by the 5-year survival rate. The rate of LN metastasis was calculated by multiplying the number of patients with LN metastasis at each station by the number of those in whom that station was retrieved. The 5-year overall survival (OS) rates for the patients with LN metastasis were calculated for each nodal station regardless of LN metastasis at other stations. We defined OS as the period from the date of surgery to the date of death due to any cause. Data for the patients who did not experience an event were censored on the date of the final observation.

Survival data were obtained from hospital records. The Institutional Review Board of the National Cancer Center approved this study (no. 2017-077).

Statistical Analysis

All statistical analyses were performed using the SPSS statistical software (ver. 24; SPSS Inc., Chicago, IL, USA). The chi-square test and Student's *t* test were used for statistical analysis. Kaplan–Meier survival curves were constructed. The log-rank test was used to assess survival differences, and Cox regression analysis was performed to calculate hazard ratios. All *P* values of 0.05 or lower were considered to be indicative of statistical significance.

RESULTS

Background Characteristics and Pathologic Findings of the Patients

A flow diagram of the patients is shown in Fig. 1. The 593 patients were divided into two groups: the Gre group ($n = 212$; those with gastric cancer involving at least one fourth of the cross-section of the greater curvature) and the non-Gre group ($n = 381$; those with gastric cancer not involving the greater curvature).

The clinicopathologic characteristics of the patients are summarized in Table 1. The Gre group had more advanced-stage cases due to larger tumors, deeper invasion to the wall, and higher rates of LN metastasis. The Gre group also had significantly higher incidences of type 4 tumors and undifferentiated tumors than the non-Gre group. The incidence of adjuvant chemotherapy did not differ significantly between the two groups.

Lymph Node Metastasis and the Therapeutic Value Index for Lymph Node Dissection

The metastatic rates, 5-year survival rates, and therapeutic indices are shown in Table 2. The overall incidence of #10 LN metastasis was 8.1% (48/593), with the Gre group showing an incidence of 15.1% (32/212, 95% confidence interval [CI], 10.2–19.9%), and the non-Gre group showing an incidence of 4.2% (16/381, 95% CI, 2.1–6.3%).

The incidence of metastasis to regional LN stations in both groups is shown in Table 2. In the Gre group, the most frequent metastatic station was #3, followed by #4d, #1, #4 sb, #4sa, #7, #2, and #10 (all metastatic rates > 15%). In the non-Gre group, the most frequent metastatic station was #3, followed by #1, #7, and #4d (all metastatic rates > 15%). In the Gre group, the node station with the highest index was #3, followed by #4d, #1, #4sb, #4sa, #7, #2, and #10 (index > 7). The index for the #10 station was 7.1, exceeding the indices for #6, #8a, #9, #11p, and #11d. Conversely, the therapeutic value index for the #10 station in the non-Gre group was 2.3, lower than those for other LN stations. Figure 2a and b show the incidence of metastasis and the therapeutic index for each LN station.

DISCUSSION

The JCOG0110 outcomes enabled clear conclusions to be reached,[3] but questions remain concerning tumors that involve the greater curvature. Although two previous studies of this issue reported that #10 nodal dissection by splenectomy had a survival benefit for tumors invading the greater curvature, concerns exist regarding the sample size, the follow-up evaluation, and the period that the patients received surgery.

Because the current study was large, with few patients lost to follow-up evaluation, the results are likely reliable. As expected, the current study found a higher incidence of #10 LN metastasis in the Gre group. These results are consistent with the previous two reports.[4,5] We also found

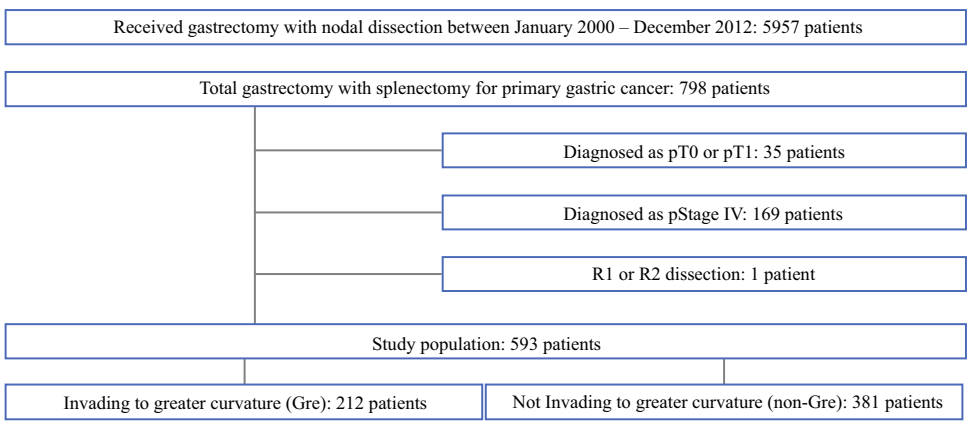

FIG. 1 Study flow diagram for the 5957 patients who underwent gastrectomy for gastric cancer between January 2000 and December 2012

TABLE 1 Background clinicopathological factors in patients with (Gre) and without (non-Gre) tumors involving the greater curvature

	Gre (n = 212)	non-Gre (n = 381)	p value
Age (years), mean (± SD)	59.4 (± 12.1)	63.3 (± 10.5)	< 0.001
Sex			< 0.001
Male	125 (59.0%)	293 (76.9%)	
Female	87 (41.0%)	88 (23.1%)	
Main tumor location			< 0.001
Upper third	87 (41.0%)	260 (68.3%)	
Middle–lower third	112 (52.9%)	119 (31.2%)	
Whole body	13 (6.1%)	2 (0.5%)	
Macroscopic type			< 0.001
Type IV	99 (46.7%)	32 (8.4%)	
Others	113 (53.3%)	349 (91.6%)	
Histological type			< 0.001
Differentiated	46 (21.7%)	176 (46.2%)	
Undifferentiated	164 (77.4%)	190 (49.9%)	
Others	2 (0.9%)	15 (3.9%)	
Tumour size (mm), mean (± SD)	117.1 (± 69.3)	69.3 (± 33.4)	< 0.001
UICC 8th/JCGC 15th			
Pathological T factor			< 0.001
T2 (MP)	15 (7.1%)	48 (12.6%)	
T3 (SS)	40 (18.9%)	194 (50.9%)	
T4a (SE)	145 (68.4%)	124 (32.5%)	
bT4b (SI)	12 (5.6%)	12 (4.0%)	
Pathological N factor			0.029
N0	56 (26.3%)	95 (24.9%)	
N1	29 (13.7%)	88 (23.1%)	
N2	44 (20.8%)	98 (25.7%)	
N3a	57 (26.9%)	75 (19.7%)	
N3b	26 (12.3%)	25 (6.6%)	
Pathological stage			< 0.001
IB	8 (3.8%)	20 (5.2%)	
IIA	11 (5.2%)	65 (17.1%)	
IIB	48 (22.7%)	74 (19.4%)	
IIIA	59 (27.8%)	120 (31.5%)	
IIIB	59 (27.8%)	73 (19.2%)	
IIIC	27 (12.7%)	29 (7.6%)	
Preoperative chemotherapy			0.002
Yes	45 (21.2%)	45 (11.8%)	
No	167 (78.8%)	336 (88.2%)	
Adjuvant chemotherapy			0.082
Yes	80 (37.7%)	117 (30.7%)	
No	132 (62.3%)	264 (69.3%)	

Gre greater curvature, *UICC* Union for International Cancer Control, *JCGC* Japanese classification of gastric carcinoma

that the metastatic rate of the splenic hilar node in the Gre group was higher than 15%, comparable with those for the #6 and #7 perigastric nodes. The priority of splenic hilar node dissection also was greater than for LNs along the common hepatic artery and the splenic artery. Thus, the results of the current study confirm those of the two previous reports. These findings suggested that the splenic hilar node was pivotally involved in D2.

TABLE 2 Details of metastatic rate, overall survival (OS), and therapeutic value index with regional lymph nodes; Gre group versus non-Gre group

Station No.	Gre group (n = 212)			Non-Gre group (n = 381)		
	Metastatic rate (%)	5-year OS (%)	Therapeutic value index	Metastatic rate (%)	5-year OS (%)	Therapeutic value index
1	31.6	44.9	14.2	31.2	53.6	16.7
2	16.1	48.5	7.8	13.4	52.3	7.0
3	46.2	45.1	20.8	52.2	60.8	31.8
4sa	19.8	43.9	8.7	7.6	35.5	2.7
4sb	21.2	43.5	9.2	6.8	52.0	3.5
4d	37.0	42.3	15.6	15.0	44.8	6.7
5	5.2	9.1	0.5	2.1	12.5	0.3
6	14.7	29.0	4.3	5.5	28.6	1.6
7	18.9	43.6	8.2	22.8	49.0	11.2
8a	8.0	41.2	3.3	7.9	33.3	2.6
9	11.3	39.2	4.4	8.7	37.3	3.2
10	15.1	46.9	7.1	4.2	55.6	2.3
11p	11.3	42.1	4.8	14.2	49.7	7.0
11d	9.0	42.1	3.8	6.3	40.6	2.6
12a	1.5	0.0	0.0	1.1	25.0	0.3

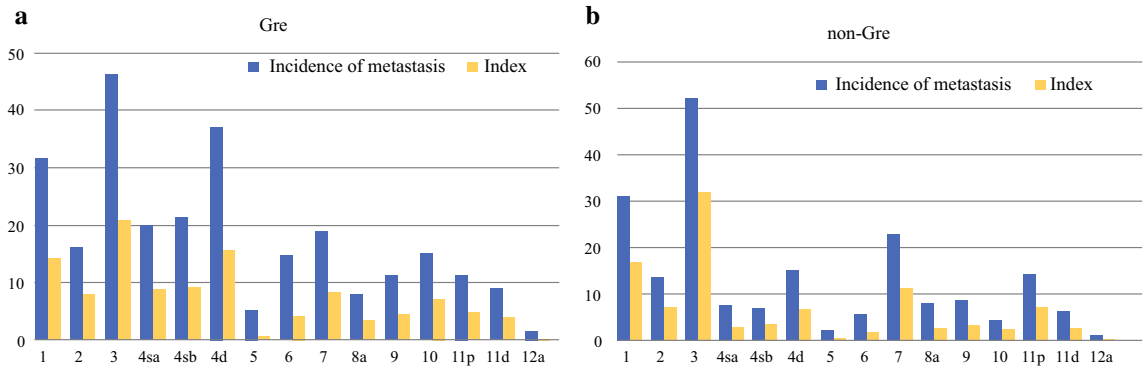

FIG. 2 **a** Incidence of lymph node (LN) metastasis and index in the Gre group. The incidence and index for the #10 station were similar to those for #2, #4s, #6, and #7. **b** Incidence of LN metastasis and index in the non-Gre group. The incidence and index for the #10 station were lower than for other LN stations: #1 right paracardial LNs, #2 left paracardial LNs, #3 LNs along the lesser curvature, #4sa LNs along the short gastric vessels, #4sb LNs along the left gastroepiploic vessels, #4d LNs along the 2nd branch and distal part of the right gastroepiploic artery, #5 suprapyloric LNs, #6 Infrapyloric LNs, #7 LNs along the trunk of left gastric artery, #8a anterosuperior LNs along the common hepatic artery, #9 celiac artery LNs, #10 splenic hilar LNs, #11p proximal splenic artery LNs, #11d distal splenic artery LNs, #12a hepatoduodenal ligament LNs along the proper hepatic artery

Sasako et al.[9] reported an 18% metastatic rate at the #10 station for tumors located along the upper third of the stomach. Their study included all proximal tumors regardless of greater curvature invasion. In previous retrospective studies from two high-volume cancer centers, the metastatic rates for #10 LNs in cases of advanced proximal gastric cancer invading the greater curvature were 13.4% and 15.9%, respectively,[4,5] compared with 15.1% in the current study.

On the other hand, the metastatic rate for #10 LNs was only 2.4% in the JCOG0110 trial,[3] which excluded tumors invading the greater curvature, and the metastatic rate for #10 LNs in the non-Gre group in the current study was only 4.2%. Thus, metastasis to the #10 station is frequently observed in gastric cancers located at the greater curvature, which is strikingly different from those of the non-greater curvature.

To confirm whether dissection of #10 LNs has therapeutic value, we calculated the therapeutic index by multiplying the metastatic rate by the 5-year survival rate. The index for the #10 station in the Gre group was 7.1. The nodal station with the highest index was #3, followed by #4d, #1, #4sb, #4sa, #7, #2, and #10. The therapeutic value index for the #10 station was substantially higher than those for #6, #8a, #9, #11p, and #11d, all of which are usually removed during D2 dissection. This finding suggests that the priority of #10 LNs for patients with advanced tumor invading the greater curvature is comparable with that for the perigastric nodes and greater than those for the common hepatic artery and splenic artery LNs.

For the #10 station with tumor invasion of the greater curvature, Maezawa et al.[4] and Watanabe et al.[5] reported indices of 4.02 and 5.6, respectively. Maezawa et al.[4] identified the highest-priority LN stations as the perigastric nodes of #3, #7, #4d, #1, #4sb, #4sa, #2, and #9, followed by #10. The index for the #10 station was higher than for the #8 and #11 stations. Watanabe et al.[5] reported that the index for the #10 station was lower than for #1, #3, and #4d, similar to those for #2, #4s, #7, and #11, and higher than those for #8a and #9. The results of these studies are very similar to our own. Given these data, we recommend prioritization of #10 LNs in D2 dissection. Conversely, the therapeutic value index for the #10 station in the non-Gre group was 2.3, lower than for other LN stations.

The survival rates for the patients in the Gre group with and without #10 LN metastasis differed only slightly. This result was consistent with those reported by Ikeguchi et al.,[10] Aoyagi et al.,[11] and Watanabe et al.[5] Likewise, the survival curves for LNs with therapeutic value were similar between the metastasis and non-metastasis groups. Thus, #10 LN dissection may contribute to overall patient survival (Fig. 3).

For complete dissection of #10 LN, splenectomy is necessary. However, splenectomy is not recommended in Western countries because it is a risk factor for morbidity and mortality.[12,13] Besides splenectomy, elderly status, male sex, high BMI, and severe comorbidities are reported to be risk factors for morbidity. When selecting splenectomy, surgeons must consider whether benefit by splenectomy can exceed the surgical risk.

Several limitations were associated with this study. The first limitation was related to potential selection bias in the cohort due to the retrospective nature of the study. Second, chemotherapy administration varied somewhat in that some patients did not receive chemotherapy. The results could have been altered in the cohorts that received chemotherapy. Third, therapeutic index is a theoretical index that ignores patient characteristics, tumor factors, and adjuvant treatment completion, and assumes that

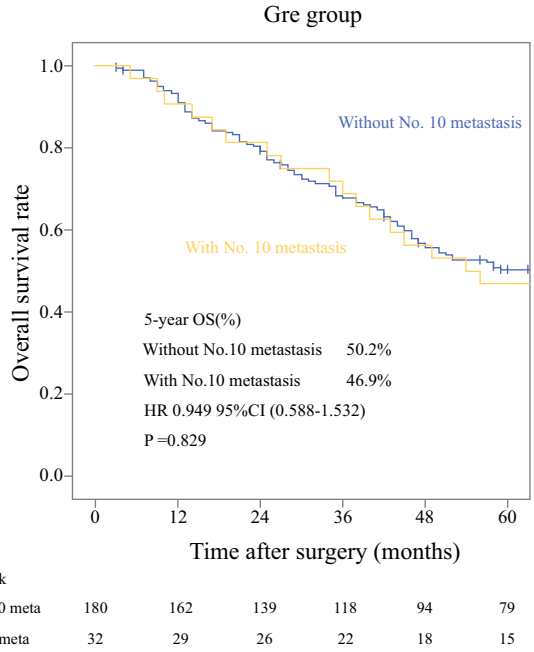

FIG. 3 Survival curve for the patients in the Gre group with and without #10 LN metastasis. No significant difference was observed between the two groups (P = 0.829, hazard ratio, 0.949)

overall survival is proportional to the individual LN metastatic rate. Direct comparison between the two groups with different backgrounds has been criticized. Finally, this study was retrospective and undertaken at a single institution, and no comparison of splenectomy and non-splenectomy groups was performed. Ultimately, a randomized controlled trial would be the most definitive and probably the only way to prove that splenectomy truly has an impact on survival for patients with cancer involving the greater curvature.

In conclusion, the current study showed that gastric cancer invading the upper third of the greater curvature had high rates of metastasis to the splenic hilar LNs and a high therapeutic index. The splenic hilar nodes should be prioritized as a component of D2 lymphadenectomy for tumors invading the greater curvature of the stomach.

DISCLOSURE The authors declares that they have no conflict of interest.

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