ANTICANCER RESEARCH *38*: 1677-1683 (2018)
doi:10.21873/anticanres.12401

Evaluation of Optimal Lymph Node Dissection in Remnant Gastric Cancer Based on Initial Distal Gastrectomy

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Abstract. *Background/Aim: The purpose of this study was to reveal the optimal lymph node (LN) dissection in remnant gastric cancer (RGC) patients. Patients and Methods: We retrospectively analyzed 46 RGC patients divided into two groups: patients who underwent initial gastrectomy for benign (group B) and malignant (group M) diseases. Results: Metastasis was more frequently observed at the left (nos. 2, 4sa, 4sb, 10, and 11p/d) and right (nos. 1, 3, 4d, 7, 8a, and 12a) side LNs of RGC in groups M and B. Modified IEBLD scores (frequency of LN metastasis by median survival time of patients with metastatic LNs) were high at station nos. 10 (4.7), 11p/d (4.3/9.9), and 16 (4.3) in group M and nos. 1 (2.1), 7 (1.9) and mesojejunal (3.0) in group B. Conclusion: After lymphadenectomy for initial gastric cancer, lymphatic flow toward the splenic artery was predominant. Therefore, splenectomy with para-aortic LN dissection is an option.*

Remnant gastric cancer (RGC) is defined as a cancer in the remnant stomach after initial gastrectomy, and its incidence is low (1-3). Some studies have reported the incidence of RGC in approximately 5% of gastric cancers (1, 2). The lymphatic distribution of proximal gastric cancer has been well studied, and several studies have compared the clinicopathological characteristics of RGC with those of proximal gastric cancer (4-7). Despite diagnostic advancements and progress in medical technology, RGC has a poor prognosis. Moreover, optimal surgical treatments have not been established, a major reason of which is a clinicopathological diversity of RGC, including surgical procedures for initial diseases and gastrectomies. Some studies have shown that vascular ligation and lymph node (LN) dissection promote lymphangiogenesis *via* anastomosis at the initial gastrectomy. Furthermore, lymphangiogenesis affects the distribution of LN metastasis in RGC (3, 8). However, no optimal method and field of LN dissection for RGC have been established because of its diversity. The optimal LN dissection for RGC is not described in the Japanese Gastric Cancer Treatment Guidelines (English edition, ver. 4) (9).

Thus, the diversity of the lymphatic flow of RGC principally depends on the degree of LN dissection and the reconstruction method of the initial gastrectomy. Recently, gastrectomy for benign gastric disease has remarkably decreased because of developments in medical treatments. Therefore, establishing a surgical strategy for patients undergoing initial gastrectomy with LN dissection for gastric cancer is important. The aim of this study was to evaluate the optimal LN dissection for RGC on the basis of type of gastrectomy, particularly after initial gastrectomy for gastric cancer.

Materials and Methods

Study subjects. According to the Japanese Classification of Gastric Carcinoma (English edition, ver. 3) (10), RGC is defined as a cancer in the remnant stomach after distal gastrectomy, irrespective of the histology of the primary lesion (benign/malignant) or its risk of recurrence, extent of resection, or method of reconstruction in this study. A total of 48 patients, who underwent total remnant gastrectomy for RGC at the Department of Surgery Gastroenterological Center, Yokohama City University, between May 1993 and December 2015, were enrolled, of which two were excluded because one underwent pancreaticoduodenectomy with partial gastrectomy for pancreatic cancer and the other underwent proximal gastrectomy with jejunal interposition reconstruction for gastric cancer. Finally, 46 patients were included and divided into two groups: primary surgery for benign disease (group B, 22 patients

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Key Words: Gastric stump, lymphatic metastasis, lymphadenectomy.

Table I. *Comparison of clinicopathological factors according to the initial gastrectomy.*

	Group M (n=24)	Group B (n=22)	*p*-Value
Gender (%)			
Male	20 (83.3)	20 (90.1)	0.667
Female	4 (16.7)	2 (9.1)	
Age (years)			
Median (range)	70 (55-87)	66 (57-82)	0.392
Body mass index			
Median (range)	19.9 (14.3-25.8)	21.9 (16.1-26.8)	0.021
Interval (years)			
Median (range)	8 (1-31)	42 (17-59)	<0.001
Reconstruction Method (%)			
Billroth-I	21 (87.5)	6 (27.3)	<0.001
Billroth-II	3 (12.5)	16 (72.7)	
Region of tumor (%)			
Anastomotic site	5 (20.8)	12 (54.5)	0.036
Suture site	4 (16.7)	4 (18.2)	
Other	15 (62.5)	6 (27.3)	
Histology (%)			
Differentiated	15 (62.5)	12 (54.5)	0.584
Undifferentiated	9 (37.5)	10 (45.5)	
Tumor diameter (mm)			
Median (range)	38 (14-94)	42 (15-160)	0.231

(47.8%)) and for malignant disease (group M, 24 patients (52.2%)). Clinicopathological characteristics were retrospectively determined based on their medical records. Tumors and LNs of the stomach were defined according to the Japanese Classification of Gastric Carcinoma (English edition, ver. 3) (10). LNs were classified according to the Japanese Gastric Cancer Treatment Guidelines (English edition, ver. 4) (9). Histological types were classified into two groups: differentiated (papillary, moderately, or well-differentiated carcinoma) and undifferentiated (poorly or undifferentiated adenocarcinoma, signet ring cell carcinoma, and mucinous adenocarcinoma). Tumor locations were divided into three groups depending on the method of initial surgery: anastomosis, suture, and non-anastomosis or non-suture. All postoperative complications were defined according to the Clavien–Dindo Classification, and grade II or higher was marked as major complications (11).

Evaluation of LN dissection efficacy. To assess the efficacy of LN dissection, the index of estimated benefit from LN dissection (IEBLD) has been used (12). In this study, modified IEBLD score was calculated by multiplying the frequency of LN metastasis to each station by the median survival time of patients with metastatic LNs at each station.

Statistical analysis. Statistical analysis was performed using the Student's *t*-test for continuous variables with parametric distribution and Mann–Whitney *U*-test for variables with non-parametric distribution. The chi-square and Fisher's exact probability tests were used for the analysis of proportion. Survival curves were plotted using the Kaplan–Meier method and compared using the log rank test. *p*-Value <0.05 was considered statistically significant.

Table II. *Operative, postoperative and pathological findings according to the initial gastrectomy.*

	Group M (n=24)	Group B (n=22)	*p*-Value
Operative findings			
Operation time (min)			
Median (range)	300 (166-640)	242 (133-618)	0.06
Bleeding (ml)			
Median (range)	497 (182-3983)	430 (35-2600)	0.316
Number of dissected lymph nodes			
Median (range)	10 (0-39)	22 (0-47)	0.02
Lymphadenectomy (%)			0.09
D1	11	4	
D2	10	16	
D2+para-aortic lymph node dissection	3	2	
Splenectomy (%)			0.361
Yes	17 (70.8)	12 (54.5)	
No	7 (29.2)	10 (45.5)	
Pancreatectomy (%)			0.268
Yes	5 (20.8)	2 (9.1)	
No	19 (79.2)	20 (90.9)	
Curability (%)			0.775
R0	20 (83.3)	19 (86.4)	
R1/R2	4 (16.7)	3 (13.6)	
Postoperative course			
Major complications (%)			0.734
Pancreatic fistula	5 (20.8)/	6 (27.3)/	
Yes/No	19 (79.2)	16 (72.7)	
Anastomotic leakage	2 (8.3)/	1 (4.5)/	
Yes/No	22 (91.7)	21 (95.5)	
Ileus	1 (4.2)/	0 (0)/	
Yes/No	23 (95.8)	22 (100)	
Abdominal abscess	1 (4.2)/	0 (0)/	
Yes/No	23 (95.8)	22 (100)	
Hospital stay			
Median (range)	21 (11-105)	15 (10-213)	0.751
Adjuvant chemotherapy (%)			0.268
Yes	5 (20.8)	2 (9.1)	
No	19 (79.2)	20 (90.9)	
Pathological findings			
pT (%)			0.616
T1	9 (37.5)	8 (36.4)	
T2	4 (16.7)	2 (9.1)	
T3	4 (16.7)	7 (31.8)	
T4	7 (29.2)	5 (22.7)	
pN (%)			0.930
N0	18 (75.0)	18 (81.8)	
N1	2 (8.3)	1 (4.5)	
N2	3 (12.5)	2 (9.1)	
N3	1 (4.2)	1 (4.5)	
pStage (%)			0.278
I	13 (54.2)	10 (45.5)	
II	4 (16.7)	9 (40.9)	
III	5 (20.8)	2 (9.1)	
IV	2 (8.3)	1 (4.5)	

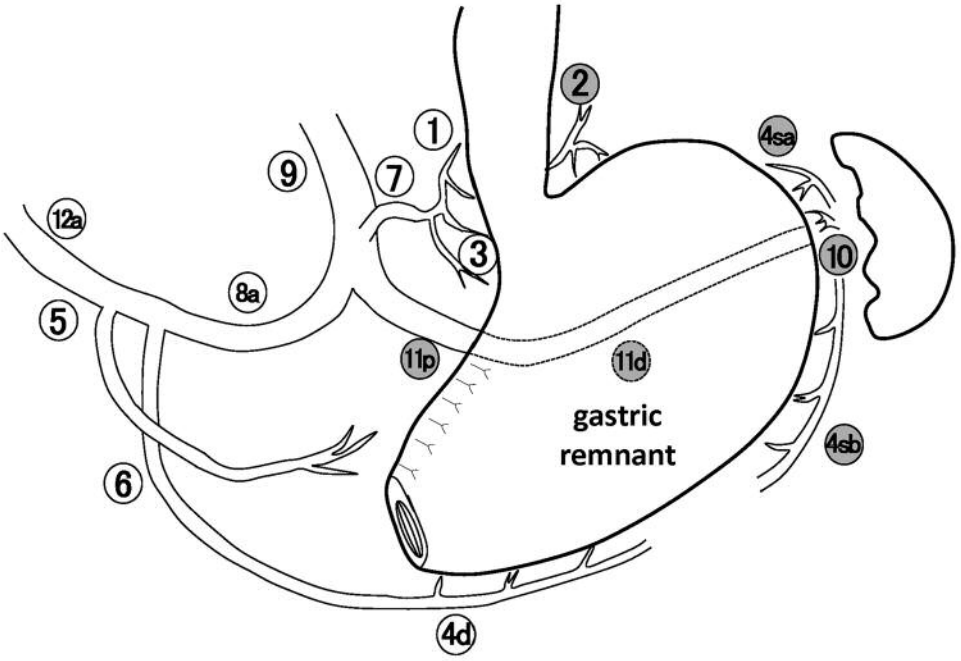

Figure 1. *The schema of LN station of RGC. Left side LNs of RGC are shaded.*

Results

Patient characteristics. Clinicopathological characteristics of patients are summarized in Table I. Body mass index was significantly lower and interval from the initial gastrectomy was shorter in group M than in group B. The Billroth-I reconstruction method and tumors in non-anastomotic and non-suture sites were frequent in group M. Other factors did not differ between the two groups.

Surgical outcomes. Surgical outcomes and pathological results of RGCs are summarized in Table II. All patients underwent total gastrectomy with the Roux-en-Y (RY) reconstruction method. D2 lymphadenectomy was performed in 31 (67.4%) patients, of which five, who were preoperatively suspected of metastasis of para-aortic LNs, underwent para-aortic LN dissection, and remaining 15 (32.6%) underwent D1 lymphadenectomy. In patients receiving the Billroth-II reconstruction method, mesojejunal LNs were routinely resected to dissect LNs along the first jejunal artery. Splenectomy was employed for patients with advanced gastric cancer irrespective of initial gastrectomy. Combined splenectomy was performed in 29 (63.0%) patients, and distal pancreatosplenectomy was performed in seven (15.2%). There was no significant difference in the incidence of combined splenectomy and pancreatosplenectomy between the groups. Of the 46 patients included, R0 resection was performed in 39 (84.8%). Operation time was longer and the number of dissected LNs was significantly lower in group M than in group B. Adjuvant chemotherapy was performed in seven (15.2%) patients.

Pathological findings. LN metastasis was observed in six (25.0%) patients in group M and in four (18.2%) patients in group B. LN metastasis with pT3 or pT4 tumors was detected in 10 (21.7%) patients, whereas that with pT1 or pT2 tumors was not detected in any patient. Pathological staging did not differ between the groups.

Site of metastatic LNs. Figure 1 shows the schema of LN station of RGC, and Table III shows the incidence of metastatic LNs. Metastatic LN sites were divided into the right (nos. 1, 3, 4d, 7, 8a, 12a) and left (nos. 2, 4sa, 4sb, 10, 11p/d) side groups. The celiac artery (no. 9) and para-aortic (no. 16) LNs were separately examined. In group M, metastatic LNs were more frequently observed at the left side stations. However, LN metastases in nos. 1 and 3 were also observed in one patient. In contrast, in group B, LN metastasis was frequent at the right side stations. All metastatic LNs were observed in patients with advanced RGC.

Comparison of efficacy of LN dissection between the groups. Modified IEBLD scores of each LN station between the groups are summarized in Table IV. We examined the number of patients with LN metastasis and the incidence of metastatic LNs at each LN station. The number of patients

Table III. *Lymph node metastasis according to the initial gastrectomy.*

Station No.	Number of patients with metastatic lymph node (%)		*p*-Value
	Group M (n=24)	Group B (n=22)	
Right side (1,3,4d,7,8a,12a)	1/11 (9.1)	4/22 (18.2)	0.492
Left side (2,4sa,4sb,10,11p/d)	5/24 (20.8)	2/22 (9.1)	0.268
9	1/4 (25.0)	0/14 (0)	0.222
16	1/3 (33.3)	0/2 (0)	0.361
Mesojejunum	1/3 (33.3)	2/16 (12.5)	0.364

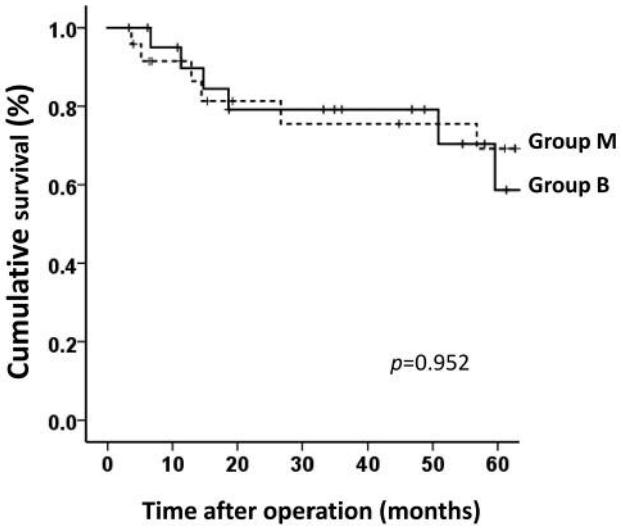

Figure 2. *Survival times between groups M and B. There was no significant difference between the two groups (p=0.952).*

with plural metastatic LN stations was calculated redundantly in this study. In group M, modified IEBLD scores of nos. 10, 11p/d, and 16 were high and those of nos. 1 and 3 were low. In contrast, in group B, the scores of nos. 1 and 7 were high. The metastatic rate of mesojejunal LN was 15.8% in patients receiving Billroth II reconstruction method for primary gastrectomy, which did not differ between the groups.

Survival time. The 5-year OS did not differ between the groups (group M, 69.2% *vs*. group B, 58.6%; p=0.952) (Figure 2).

Patient characteristics with/without splenectomy. In the splenectomy group, younger patients, longer operation time, greater number of dissected LNs, and higher incidence of pancreatic fistula were significantly frequent (Table V).

Discussion

This study revealed that the lymphatic flow of RGC depends on initial surgery including LN dissection and reconstruction methods. The lymphatic flow along the splenic artery may be predominant in RGC after gastric cancer surgery. RGC has clinicopathological diversity, and the prognosis remains poor (4, 13), which may be because RGC patients have poor subjective symptoms. As a result, most patients get diagnosed at an advanced stage (14). Furthermore, the treatment strategy depends on the type of initial gastrectomy, including LN dissection, and the reconstruction method (13, 15, 16). Thus, because of the clinicopathological diversity of RGC, an efficacious treatment strategy is necessary. Evaluating the lymphatic flow of RGC to establish an optimal LN dissection area is also important.

In the present study, operation interval from initial gastrectomy to surgery for RGC was significantly shorter in group M than in group B, which is consistent with that observed in previous studies (17, 18). Although operation time was longer, the number of dissected LNs was significantly lower in group M, which was considered to be related to LN dissection of primary gastrectomy. Several studies have shown duodenogastric reflux as the most important factor for the pathogenesis of RGC. However, precancerous lesions such as those in *Helicobacter pylori* infection (that existed before the initial surgery) have been reported for cases of RGC after gastric cancer surgery (13, 19, 20).

For years now, surgical treatments for benign disease have dramatically decreased because of advances in medical technology and appearance of new drugs, such as proton pomp inhibitors (13, 21). We considered that the ratio of RGC patients after gastrectomy for malignant tumor to all RGC patients would yearly increase. Thus, the treatment strategy for RGC after initial gastrectomy with LN dissection would be more important. According to our results, LN metastasis was only shown in advanced RGC with pT3/pT4 tumors. Therefore, regular checkup for RGC and early detection may improve the prognosis of RGC.

The lymphatic distribution of RGC has several pathways, including celiac artery and abdominal aorta pathway through the blood stream from left gastric artery of lesser curvature and splenic artery pathway from short gastric artery, posterior gastric artery, and left gastroepiploic artery of greater curvature. Furthermore, anastomosis, suture, and adhesion due to primary surgery make extraordinary lymphatic pathway (3, 17, 22, 23). One of these pathways is a mesenteric LN pathway that is formed by gastrojejunal anastomosis (3, 22, 24). In our study, mesenteric LN metastasis was observed in three patients, with a high incidence (Table III). Further, these patients received Billroth II reconstruction method for primary

Table IV. *Comparison of efficacy for lymph node dissection to each station.*

Station No.	Group M (n=24)			Group B (n=22)		
	Patients with metastatic lymph node (%)	Mean survival time (month)	Modified IEBLD score	Patients with metastatic lymph node (%)	Mean survival time (month)	Modified IEBLD score
1	1/9 (11.1)	3.7	0.41	3/21 (14.3)	14.8	2.1
2	0/24 (0)	0	0	2/22 (9.1)	13	1.2
3	1/6 (16.7)	3.7	0.62	1/21 (4.8)	11.3	0.5
4sa	2/18 (11.1)	4.4	0.49	1/17 (5.9)	11.3	0.67
4sb	1/11 (9.1)	5.2	0	1/17 (5.9)	11.3	0.67
4d	0/1 (0)	0	0	0/6 (0)	0	0
7	0/0 (0)	0	0	1/19 (5.3)	36	1.9
8a	0/0 (0)	0	0	0/16 (0)	0	0
9	1/4 (25.0)	3.7	0.93	0/14 (0)	0	0
10	3/17 (17.6)	26.7	4.7	0/12 (0)	0	0
11p	2/14 (14.3)	30.2	4.3	1/14 (7.1)	14.8	1.1
11d	2/12 (16.7)	59.3	9.9	0/11 (0)	0	0
12a	0/2 (0)	0	0	0/4 (0)	0	0
Mesojejunum	1/3 (33.3)	5.1	1.7	2/16 (12.5)	23.6	3.0
16	1/3 (33.3)	12.9	4.3	0/2 (0)	0	0

gastrectomy. Thus, considering such an abnormal lymphatic pathway and metastasis to mesenteric LN, patients undergoing remnant gastrojejunostomy with the Billroth II or RY method should be considered for performing lymphadenectomy of jejunum mesenteric LNs.

The incidence of metastases to left-side LNs was higher in group M than in group B. The difference is related to the presence or absence of LN dissection of the initial surgery. Lymphatic flow from lesser curvature is blocked particularly in patients who underwent LN dissection around the left and right gastric artery for primary gastrectomy (5, 22, 25). As a result, the lymphatic distribution of greater curvature becomes predominant in such patients, which should be taken into account when determining the range of lymphadenectomy in RGC patients who underwent initial gastrectomy for gastric cancer. Hence, splenic hilum and splenic artery LN (station nos. 10 and 11) should be considered, particularly in patients undergoing initial gastrectomy for gastric cancer. Earlier studies have reported that metastasis to splenic hilar and splenic artery LN is more frequent in RGC than in primary cancer at the upper third of stomach (5, 26). Our study showed that the ratio of LN metastases of the splenic hilum and along the splenic artery was higher in group M than in group B. Further, there was no patient with LN metastasis along the common hepatic arteries in group M. Our results also showed a high efficacy of LN dissection along the splenic artery and abdominal aorta in group M. Thus, lymphatic flow toward the splenic artery becomes dominant in patients who undergo initial gastrectomy for gastric cancer. Therefore, splenectomy and para-aortic LN dissection may be an important option in these patients.

Table V. *Comparison of clinical factors in patients with and without splenectomy.*

	Splenectomy (n=29)	Non-Splenectomy (n=17)	p-Value
Gender (%)			
Male	26 (89.7)	14 (82.4)	0.655
Female	3 (10.3)	3 (17.6)	
Age (years)			
Median (range)	68 (55-80)	76 (61-87)	0.010
Initial gastrectomy			0.361
Group M	17	7	
Group B	12	10	
Operation time (min)			
Median (range)	300 (182-640)	223 (133-481)	0.011
Bleeding volume (ml)			
Median (range)	650 (35-3983)	350 (90-1918)	0.054
Number of dissected lymph nodes			
Median (range)	16 (0-47)	12 (0-34)	0.041
Pancreatic fistula			
Yes	10 (34.5)	1 (5.9)	0.036
No	19 (65.5)	16 (9.4)	
Hospital stay (day)			
Median (range)	21 (12-213)	17 (13-108)	0.621

Whether splenectomy is required during surgery for the treatment of RGC is a key issue. JCOG0110 trial, which

examined the importance of splenectomy in patients with advanced gastric cancer, showed that splenectomy is an option if tumor is located at a greater curvature (27). In contrast, several reports have reported the complications of splenectomy, one of which is the risk of compromised immune function, which sometimes causes serious or life-threatening infections. Furthermore, splenectomy carries the potential risk of bleeding and injury to nearby organs (2, 28, 29). In this study, patients with splenectomy had large blood loss and the surgery time was significantly longer than those without splenectomy. Thus, combined organ resection is more invasive for patients. Similarly, the indications for para-aortic LN dissection should be carefully considered (30). Therefore, gastric surgeons should determine the extent of LN dissection according to the background of patients and select patients tolerant to splenectomy and para-aortic lymph node dissection (30, 31). In the present study, metastatic LNs were shown only in patients with pT3/4 advanced RGC, and several studies have reported that LN metastasis is not frequently observed in early RGC (5, 21, 25). Moreover, our study revealed that lymphatic flow along the splenic artery is predominant in group M. These results indicated that splenectomy is an option for patients with advanced RGC who underwent initial gastrectomy for gastric cancer. Further, the impact of splenectomy was quite low in patients with early RGC who received initial gastrectomy for gastric cancer.

The limitations of this study included the small sample size and retrospective and single-institution design. Therefore, it is necessary to conduct future studies with large sample sizes in multiple institutions.

In conclusion, this study showed alterations in the lymphatic flow and lymphangiogenesis according to LN dissection and the reconstruction method of initial gastrectomy. Therefore, it is necessary to employ optimal LN dissection for RGC surgery according to the type of initial distal gastrectomy. Particularly, LN dissection along the splenic artery, including splenectomy with/without para-aortic LN dissection, is appropriate in patients receiving initial distal gastrectomy for gastric cancer. However, future studies with large sample sizes are required.

Acknowledgements

The Authors would like to thank Dr. Yoshiaki Inayama from the Department of Diagnostic Pathology at Yokohama City University Medical Center, who provided carefully considered feedback and valuable comments.

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Received December 11, 2017
Revised December 23, 2017
Accepted December 29, 2017