ORIGINAL ARTICLE

Differences of the Lymphatic Distribution and Surgical Outcomes Between Remnant Gastric Cancers and Primary Proximal Gastric Cancers

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Abstract

Background Although remnant gastric cancer (RGC) following distal gastrectomy is located in the proximal stomach, little is known about the differences of the lymphatic distribution and surgical outcomes between RGC and primary proximal gastric cancer (PGC).
Methods Between 1997 and 2008, 1,149 patients underwent gastrectomy for gastric cancer. Of these, 33 (2.9%) RGC patients and 207 (18.5%) PGC patients were treated at our department. We reviewed their hospital records retrospectively.
Results Compared with the PGC patients, those with RGC had a slightly higher age at onset ($p=0.09$), higher incidence of undifferentiated cancer ($p=0.06$), higher incidence of vascular invasion ($p=0.09$), and higher incidence of T4 ($p=0.07$). Gastrectomy for RGC involved greater blood loss ($p<0.005$), longer surgical duration ($p=0.01$), combined resection, and high incidence of complications. However, the survival rate for RGC patients was similar to that for PGC patients ($p=0.67$). 2) Patients with RGC had a different pattern of lymph node metastasis compared with that in PGC. Particularly in advanced RGC with pT2–T4 tumors, RGC frequently demonstrated jejunal mesentery lymph node metastases (RGC vs. PGC, 35% vs. 0%) and splenic hilar lymph node metastases (RGC vs. PGC, 17% vs. 10%). The jejunal mesentery lymph node metastases were detected only following Billroth II reconstruction (Billroth I vs. Billroth II, 0% vs. 67%).
Conclusion Although the clinical behaviors of the two gastric cancers were different, the survival rates were similar. The pattern of metastasis indicates that the jejunal mesentery and splenic hilar lymph nodes should be specifically targeted for en bloc resection during complete gastrectomy in RGC.

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Introduction

Gastric cancer is the second leading cause of cancer-related death in the world[1]. However, recent advances in diagnostic methods, less invasive treatment techniques, and perioperative management have increased the early detection of gastric cancer and decreased the mortality and morbidity rates.[2–4] Consequently, the number of successfully treated patients has been increasing, and some of these patients are at risk of developing second primary cancer in the remnant stomach. This implies that more cases of remnant gastric cancer (RGC) will be encountered in the future.

In previous studies, RGC was commonly found at an advanced stage, resulting in low rates of curative resection

(38–40%) and a consequent poor prognosis.[5,6] However, recently, the prognosis of RGC following distal gastrectomy has been improving due to diagnostic and technological advances. Indeed, at our institute, more than half of the RGC patients were treated for T1 or T2, node-negative, and early stage cancer and almost 80% of patients with RGC underwent curative resection. Therefore, it is necessary to characterize the clinical features of RGC to develop optimal surgical and treatment planning. However, there is limited information available to help guide the treatment of patients with RGC. RGC after distal gastrectomy is located in the same proximal stomach as a primary proximal gastric cancer (PGC). This study was designed to clarify the differences of the lymphatic distribution and surgical outcomes between RGC and PGC.

Patients and Methods

Patients

Between 1997 and 2008, 1,149 patients underwent gastrectomy for gastric cancer. Of these, 33 consecutive patients with primary RGC (2.9%) and 207 patients with PGC (18.5%) were treated in the Department of Digestive Surgery, Kyoto Prefectural University of Medicine. The follow-up program after gastrectomy consisted of regular physical examinations and laboratory blood tests, chest X-rays, an upper gastrointestinal series or endoscopy, and ultrasonography or computer tomography for the first 5 years and yearly endoscopy thereafter if possible. All patients underwent gastrectomy with lymphadenectomy for RGC. The clinicopathological findings of these patients were determined retrospectively on the basis of their hospital records. Macroscopic and microscopic classifications of gastric cancers were based on the Japanese Classification of Gastric Carcinomas.[7] Consistent with the TNM staging system,[8] patients with lymph node metastases were reclassified into three groups based on the total number of positive nodes. Histological types were classified as differentiated (papillary, moderately, or well-differentiated adenocarcinoma) and undifferentiated (poorly or undifferentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous adenocarcinoma).

Comparison of associated clinical factors between RGC and PGC patients

Comparison between RGC and PGC was performed because RGC was located in the proximal stomach. To examine treatment targets in particular, several clinicopathological factors such as age, sex, histological types, lymphatic invasion, venous invasion, tumor size, depth of tumor, area and number of lymph node metastases, pathological stage, and surgical factors such as surgical duration, bleeding amount, organs with combined resection, and complications were retrospectively evaluated from the hospital records.

Statistical Analysis

Cause-specific death was recorded when the cause of death was specified as recurrent RGC. Chi-square test and Fisher's exact probability test were performed for categorical variables, while Student's t test and Mann–Whitney U test for unpaired data of continuous variables were performed to compare the clinicopathological characteristics between two groups. The cumulative cause-specific overall survival rates were calculated using the Kaplan–Meier method, and log rank test was used for assessment of differences between clinical factors. A $p < 0.05$ was considered significant.

Results

Clinicopathological characteristics of patients with primary remnant gastric cancer

Table 1 shows the characteristics of the 33 RGC patients. The mean patient age was 68 years, and the male/female ratio was 2.7:1. Ten patients had symptoms and the remaining 23 patients were asymptomatic. Regarding the initial gastric disease, there were 19 patients with benign disease and 14 patients with gastric cancer. Reconstruction during the first surgery was mainly Billroth I or II. More than half of the RGC patients demonstrated T1 or T2, undifferentiated, node-negative, and early stage cancer. In 78.8% (26/33) of the patients, resections were performed with curative intent. En bloc resection of the tumor by total remnant gastrectomy was performed with jejunal mesentery and D2 lymphadenectomy and concomitant organ resection. In addition, splenectomy was performed in 18 patients, distal pancreatectomy in four, partial colon resection in two, and liver resection in two. Reconstruction was performed in 16 patients by Billroth I, in 16 patients by Billroth II, and in one by Roux-en Y procedure for all resected RGC tumors. Tumors were located at the anastomotic site in 16 (61%) patients, corpus and/or cardia in nine (34%), and throughout the entire remnant in one (4%). The median interval between the first and second surgery was 20 years. Of the 33 RGC patients, RGC was detected in 19 (58%) by routine screening in whom the follow-up periods were short (0.5–2 year). On the other hand, RGC was detected incidentally in 14 (42%) patients in whom the follow-up periods were more than 5 years. Patients with early stage RGC such as stages I and II tended to have been diagnosed every second year (data not shown). Therefore, surveillance endoscopic screening following distal gastrectomy should be performed every second year for at least 20 years.

Table 1 Clinicopathologic characteristics of patients with primary RGC

Age	Mean±SD (years)	68±10	
Sex	Male	24	(72.7%)
	Female	9	(27.3%)
Symptom	Yes	11	(33.3%)
	No	22	(66.7%)
Initial gastric disease	Benign	19	(57.6%)
	Cancer	14	(42.4%)
Interval between first and second surgeries	Median (year)	20 (2–51)	
Reconstruction of first surgery	Billroth I	16	(48.5%)
	Billroth II	16	(48.5%)
	Roux en Y	1	(3.0%)
Depth of invasion	T1	10	(30.3%)
	T2	10	(30.3%)
	T3	7	(21.2%)
	T4	6	(18.2%)
Histology	Well	11	(33.3%)
	Moderate	2	(6.1%)
	Poor	13	(39.4%)
	Sig	7	(21.2%)
Lymph node metastasis	N0	20	(60.6%)
	N1	7	(21.2%)
	N2≤	6	(18.2%)
Stage	I	17	51.5%)
	II	5	(15.2%)
	III	4	(12.1%)
	IV	7	(21.2%)
Surgery type	Total	33	(100.0%)
	Partial	0	(0.0%)
Extent of lymphadenectomy	D1	9	(27.3%)
	D2	22	(66.7%)
	D2<	2	(6.1%)
Combined resection	Spleen	18	(54.5%)
	Distal pancreas	4	(12.1%)
	Liver	2	(6.1%)
	Colon	2	(6.1%)

Primary Remnant Gastric Cancer and Upper One Third Gastric Cancers

Table 2 shows a comparison of clinicopathological factors between the 33 RGC and 207 primary PGC. RGC patients had a slightly higher age at onset ($p=0.09$), higher incidence of undifferentiated cancer ($p=0.06$), higher incidence of vascular invasion ($p=0.09$), and higher incidence of T4 ($p=0.07$) than those with PGC. Gastrectomy for RGC involved greater blood loss ($p<0.005$), longer surgical duration ($p=0.01$), combined resection, and high incidence of complications. As shown in Fig. 1, the survival curves for the two groups were similar. Figure 2 shows the metastatic region and extent of lymph node involvement between RGC and PGC. Particularly in advanced RGC with pT2–T4

tumors, compared with PGC, RGC more frequently demonstrated jejunal mesentery lymph node metastasis (RGC vs. PGC, 35% vs. 0%) and splenic hilar lymph node metastasis (RGC vs. PGC, 17% vs. 10%) because RGC had a different pattern of lymphatic flow after initial distal gastrectomy. The jejunal mesentery lymph node metastases were detected only following Billroth II reconstruction (Billroth I vs. Billroth II, 0% vs. 67%).

Discussion

RGC following distal gastrectomy has been reported to account for 1–2% of all gastric cancers in Japan.[9,10] Previously, RGC was reported to be caused by multiple factors, and the

Table 2 Comparison of clinico-pathological factors between 33 RGC and 207 PGC patients

Variables		RGC (n=33)		PGC (n=207)		p value
Age	Years (mean)	68		65		0.09
Sex	Male	24	(73%)	157	(76%)	
	Female	9	(27%)	50	(24%)	0.87
Histological type	Differentiated	13	(39%)	118	(57%)	
	Undifferentiated	20	(61%)	89	(43%)	0.06
Lymphatic invasion	Negative	16	(48%)	96	(46%)	
	Positive	17	(52%)	111	(54%)	0.82
Venous invasion	Negative	16	(48%)	132	(64%)	
	Positive	17	(52%)	75	(36%)	0.09
Tumor size	mm (mean)	55		51		0.53
Depth of tumor	T1	10	(30%)	69	(33%)	
	T2	10	(30%)	75	(36%)	
	T3	7	(21%)	54	(26%)	
	T4	6	(18%)	9	(4%)	0.07
Lymph node metastasis	Negative	20	(61%)	118	(57%)	
	Positive	13	(39%)	89	(43%)	0.70
Stage	I	17	(52%)	104	(50%)	
	II	5	(15%)	24	(12%)	
	III	4	(12%)	43	(21%)	
	IV	7	(21%)	36	(17%)	0.84
Surgical duration	min (mean)	381		326		**<0.05**
Bleeding	g (mean)	931		604		**<0.005**
Combined resection	Spleen	18	(55%)	81	(39%)	0.09
	Distal pancreas	4	(12%)	9	(4%)	0.16
	Liver	2	(6%)	4	(2%)	0.42
	Colon	2	(6%)	6	(3%)	0.68
Postoperativre complication	Leakage	6	(18%)	12	(6%)	**<0.05**
	Pancreatic fistula	3	(9%)	6	(3%)	0.21
	Wound infection	4	(12%)	8	(4%)	0.11
	Pneumonia	3	(9%)	6	(3%)	0.21

Significant values are shown in boldface type

P values were derived from χ^2 or Fisher's exact test and were considered significant at < 0.05

incidence, pathological features, and potential mechanisms have been extensively investigated.[11–13] RGC is commonly
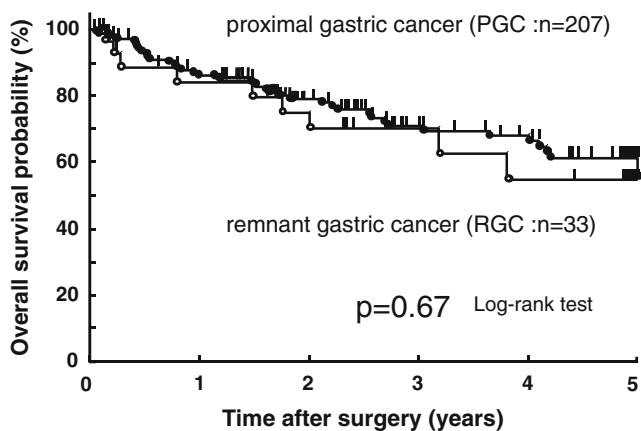

Fig. 1 Survival curves of 33 RGC and 207 PGC patients

found at an advanced stage, resulting in low rates of curative resection (38–40%) and a consequently poor prognosis.[5,6] However, recently, the incidence and etiology of RGC have been changing[14] because of the long latency periods, decreasing prevalence of gastrectomy for benign disease,[5,15] early detection, and improved outcomes in patients with gastric cancers.[16,17] Moreover, recent advances in diagnostic and treatment techniques have led to a higher detection rate of early RGC following distal gastrectomy.[18] Consequently, endoscopic therapy such as EMR or ESD is performed for treatment of early stage RGC[19,20]. Therefore, it is important to re-evaluate the clinical features of RGC in order to develop optimal surgical and treatment planning.

In comparison between RGC and primary PGC, the two survival rates were similar (Fig. 1) even though RGC showed a slightly higher involvement of jejunal mesenteric or splenic hilar nodes and a higher incidence of undifferentiated cancer, vascular invasion, and T4 cancers, and gastrectomy for RGC

Fig. 2 Comparison of the metastatic region and extent of lymph node metastasis between RGC and PGC. Compared with that in PGC, RGC frequently showed jejunal mesentery lymph node metastasis and splenic hilar lymph node metastasis because RGC has a different pattern of lymphatic flow after the initial distal gastrectomy
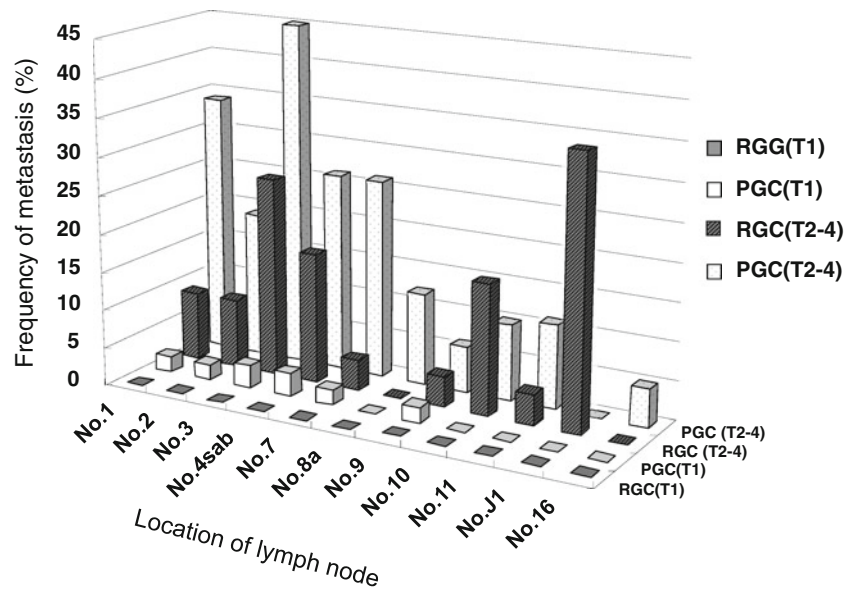
involved more blood loss, longer surgical duration, combined resection, and a higher incidence of complications than PGC (Table 2). These results are consistent with several recent reports;[6,21,22] however, the reason for this similarity remains unclear. One of reasons might be that the incidence and etiology of RGC following distal gastrectomy have been changing owing to diagnostic and technological advances, although previously RGC was commonly found at more advanced stage, resulting in low rates of curative resection (38–40%) and a consequent poor prognosis. Indeed, at our department, more than half of the RGC patients were treated for T1 or T2, node-negative, and early stage cancer, in contrast to that in previous series (Table 1) and almost 80% of patients underwent curatively resection with extensive lymphadenectomy. On the contrary, in recent years, the incidence of PGC has been increasing, whereas the prognosis of PGC has not been improved in comparison with middle and lower gastric cancers (data not shown). Therefore, the prognoses of RGC and PGC might be similar at this point in time. Indeed, RGC is not always advanced at diagnosis, and if it is, extensive surgery for RGC is not necessarily associated with poor prognosis in comparison to that for primary gastric cancer.

Concerning lymph node metastasis from RGC, the main lymphatic flow from a tumor located in the upper one third of the stomach drains into lymph nodes along the celiac artery through the lymph nodes at the lesser curvature, the right side of cardia, and the left gastric artery. In the remnant stomach, these lymphatic pathways have been transected during the initial surgery, thus altering the lymphatic flow at the greater curvature, splenic artery, and splenic hilum.[5,23] Indeed, patients with RGC have a different pattern of lymph node metastasis compared with that in PGC (Fig. 2). Regarding the ligation of the left gastric artery, of the 33 RGC patients analyzed, 14 (42%) patients underwent the initial

gastrectomy for gastric cancer and all left gastric arteries were ligated. On the other hand, there were no patients who underwent ligation of the left gastric artery for the initial benign disease. As a result, four (12%) patients exhibited splenic hilar lymph node metastasis out of the 33 RGC patients: Two patients had initial gastric cancer, and the remaining two patients had initial benign disease. Thus, the ligation of the left gastric artery was not the main reason for the metastases to the splenic hilar lymph node. Indeed, other interruption of lymphatic flows might also influence lymphatic flow from a tumor. In our hospital, the incidence of splenic hilar lymph node metastasis from RGC was higher than that from PGC [RGC vs. PCG, 12% (4/33) vs. 7% (14/207)]. Therefore, the interruption of lymphatic flow at the initial surgery might alter lymphatic flow from a tumor. However, the detailed mechanisms of lymphatic flow remain unclear.

In early RGC, no lymph node metastasis was detected although a low incidence of peri-gastric lymph node metastasis was noted in PGC. Namely, differences of the metastatic region and extent of lymph node involvement between RGC and PGC were small. On the other hand, in advanced RGC, the incidences of splenic hilar lymph node metastasis (RGC vs. PGC, 17% vs. 10%) and jejunal mesentery lymph node metastasis (RGC vs. PGC, 35% vs. 0%) were higher because RGC has a different pattern of lymphatic flow after initial distal gastrectomy. Concerning the initial surgery, the splenic hilar lymph node metastases occurred following every type of reconstruction. In contrast, the jejunal mesentery lymph node metastases occurred only following Billroth II reconstruction (Billroth I vs. Billroth II, 0% vs. 67%). This incidence of metastasis was higher than the previously reported incidences of 9–26%.[23–25] Therefore, the splenic hilar lymph node dissection is essential for curative gastrectomy in all RCG

patients. Additionally, the jejunal mesentery lymph node dissection should be performed in patients with RGC following Billroth II reconstruction.

Owing to recent advances in diagnostic and treatment techniques, RGC is not always advanced at diagnosis and, if it is, extensive surgery for RGC does not necessarily lead to poor prognosis in comparison to that for primary PGC. Patients with RGC have a different pattern of lymph node metastasis compared with that in PGC. Therefore, in decision making regarding the area of lymphadenectomy, the jejunal mesentery and splenic hilar lymph nodes should be specifically targeted for en bloc resection during complete gastrectomy in RGC.

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