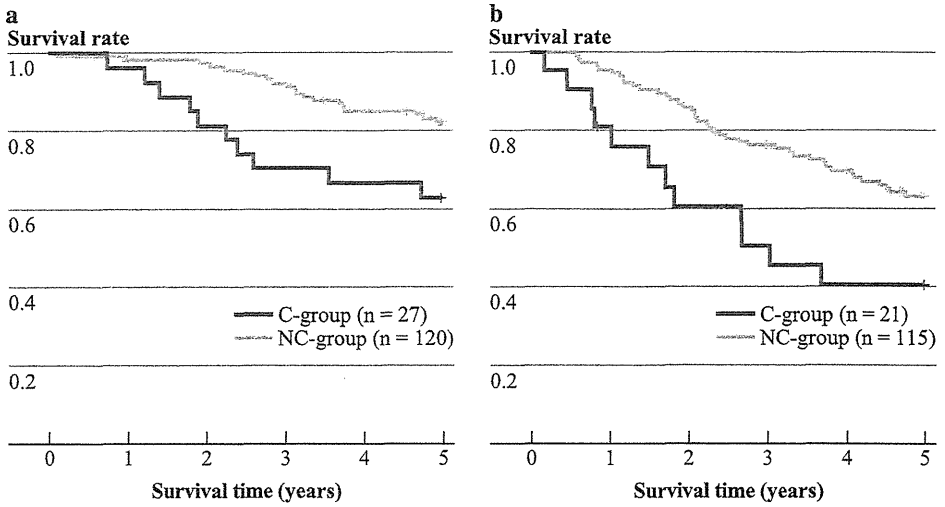

FIG. 1 **a** Overall survival curves of 147 stage II patients who underwent curative gastrectomy for gastric cancer. The 5-year overall survival rate is significantly better in the group of patients without postoperative intra-abdominal infectious complications (NC-group, 81.1 %) than in the group with complications (C-group, 63.0 %; $P = .02$). **b** Overall survival curves of 136 stage III patients who underwent curative gastrectomy for gastric cancer. The 5-year overall survival rate is significantly better in the NC-group (63.3 %) than in the C-group (40.5 %; $P = .03$)

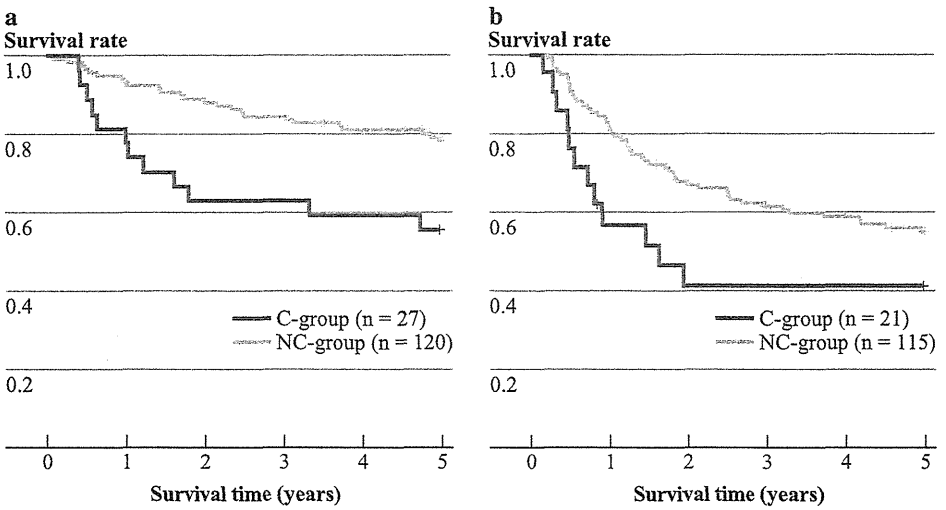

FIG. 2 **a** Relapse-free survival curves of 147 stage II patients who underwent curative gastrectomy for gastric cancer. The 5-year relapse-free survival rate is significantly better in the group of patients without postoperative intra-abdominal infectious complications (NC-group, 78.0 %) than in the group with complications (C-group, 55.6 %; $P = .02$). **b** Relapse-free survival curves of 136 stage III patients who underwent curative gastrectomy for gastric cancer. The 5-year relapse-free survival rate tends to be better in the NC-group (55.1 %) than in the C-group (41.3 %), although the difference is not significant ($P = .11$)

adopted the CD classification to evaluate postoperative problems.[31,32] In contrast, previous studies that investigated the effect of complications on long-term outcomes following surgeries generally used their own criteria to grade the severity of the complications, making it difficult to evaluate the results of the study[15–23] In the present study, to overcome this potential problem, we used the CD classification to assess the severity of complications. In the present study, patients with grade II or more severe intra-abdominal infection were regarded as having complications since we considered these complications to cause systemic inflammatory response syndrome, resulting in excess surgical trauma and tissue damage.

Administration of perioperative chemotherapies has been accepted as it increases the survival rate of patients with advanced gastric cancer.[33–36] In Japan, postoperative administration of S-1 for 1 year after curative surgery has been a standard treatment in patients with advanced gastric cancer since the results of a prospective randomized controlled trial were reported in October 2006.[33] Therefore, in the present study, we only included patients who underwent surgery before 2006 and excluded patients who received neoadjuvant chemotherapy to eliminate the effects of perioperative chemotherapies.

It is unclear why postoperative intra-abdominal infectious complications affect the long-term outcome of

TABLE 4 Results of multivariate analysis to identify independent prognostic factors for overall survival

Covariates	*P* value	Hazard ratio (HR)	95 % CI
Age (≥ 65 vs < 65 years)	.138	1.241	.933–1.651
Sex (male vs female)	.683	1.099	.700–1.725
Surgery (total gastrectomy vs partial gastrectomy)	.496	1.165	.751–1.806
Histology (differentiated vs undifferentiated)	.162	1.340	.889–2.022
pStage (III, IV vs II)	<.001	2.564	1.681–3.912
Duration of surgery (≥ 200 vs < 200 min)	.773	.949	.666–1.353
Intraoperative blood loss (≥ 300 vs < 300 mL)	.057	.726	.523–1.009
Intra-abdominal infectious complications (yes vs no)	<.001	2.448	1.475–4.060
Lymph node dissection (≥ D2 vs < D2)	.248	.761	.478–1.210

CI confidence interval

TABLE 5 Results of multivariate analysis to identify independent prognostic factors for relapse-free survival

Covariates	*P* value	Hazard ratio (HR)	95 % CI
Age (≥ 65 vs < 65 years)	.213	1.187	.906–1.555
Sex (male vs female)	.590	1.127	.729–1.743
Surgery (total gastrectomy vs partial gastrectomy)	.747	.933	.614–1.419
Histology (differentiated vs undifferentiated)	.375	1.191	.810–1.751
pStage (III, IV vs II)	<.001	2.657	1.782–3.962
Duration of surgery (≥ 200 vs < 200 min)	.492	1.123	.807–1.562
Intraoperative blood loss (≥ 300 vs < 300 mL)	.140	.795	.586–.178
Intra-abdominal infectious complications (yes vs no)	.002	2.219	1.330–3.409
Lymph node dissection (≥ D2 vs < D2)	.135	.716	.462–1.110

CI confidence interval

patients. Following colorectal surgery, it was reported that anastomotic leakage increased the rate of local recurrence presumably due to viable colorectal cancer cells being deposited extraluminally into the pelvis.[16–18] However, in the present study the incidence of local recurrence did not increase even after anastomotic leakage; thus, we consider implantation of cancer cells into the abdominal cavity not a contributing factor in the present series.

Another possible factor promoting metastatic growth and early recurrence is immune suppression.[37,38] Specifically, cell-mediated immunity, in particular natural killer cells and cytotoxic T lymphocytes, is compromised, and the degree of suppression is considered to be related to the extent of surgical trauma and tissue damage. Goldfarb et al. reported treatment aimed at perioperative enhancement of cell-mediated immunity with simultaneous inhibition of excessive catecholamine and prostaglandin responses could be successful in limiting postoperative immune suppression and metastatic progression.[38] In the C-group, postoperative intra-abdominal infectious complications increased surgical stress and caused severe tissue damage due to local and generalized inflammatory reactions, resulting in more severe immune suppression than in the NC-group. We consider, therefore, that the difference in the degree of immune suppression between the groups is a possible contributing factor to the survival difference between the groups.

The present retrospective study has limitations. Firstly, backgrounds were different between patients with and without complications. Of different backgrounds, pathological stage is assumed to be the strongest prognostic factor for gastric cancer following curative gastrectomy.[1,2,6] Therefore, we stratified patients by their pathological stage, and multivariate analysis was conducted. Even after stratification, the same trend, better survival outcomes in patients without intra-abdominal infectious complications, was still observed in stage II and III patients. Multivariate analysis also identified intra-abdominal infectious complications as an independent prognostic factor. In addition, we investigated hazard ratio for death among subgroups. In each subgroup, long-term outcome tended to be better in the NC-group than in the C-group. Secondly, the degree of immune suppression was not assessed in this study. This should be examined in a future trial to clarify whether our hypothesis, that patients with intra-abdominal infectious complications have severe immune suppression resulting in high recurrence rates and poor overall and relapse-free survival rates, is correct or not.

D2 lymph node dissection and splenectomy were frequently performed in the C-group, and these procedures were thought to increase the incidence of intra-abdominal infectious complications. We also investigated the effect of D2 lymph node dissection on long-term survival rate by

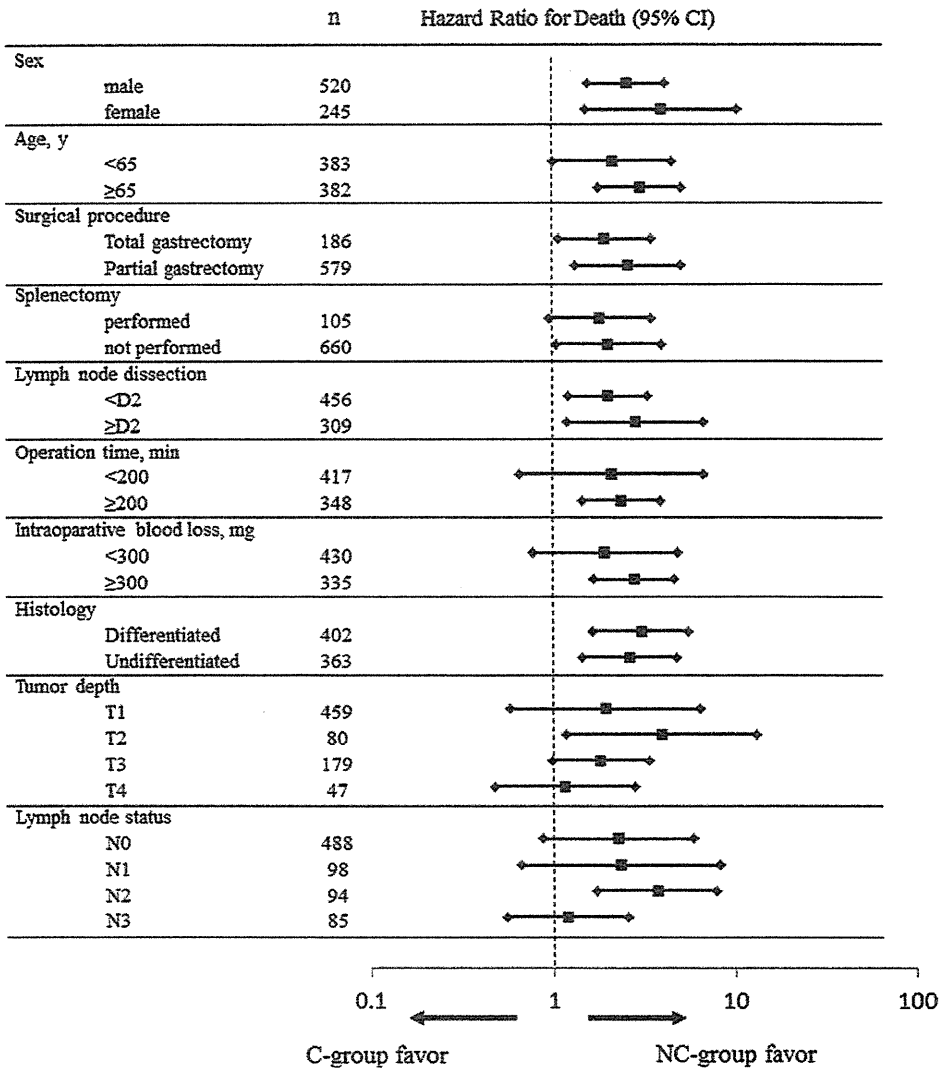

FIG. 3 Hazard ratio for death among subgroups. Long-term survival is better in NC-group than in C-group in most subgroups

multivariate analysis, and it was not identified as an independent prognostic factor. In addition, splenectomy was not identified as an independent prognostic factor even when we included it as a covariate instead of D2 lymph node dissection (data not shown). In Western countries, the most recent European Society for Medical Oncology clinical practice guidelines recommend a D2 gastrectomy as the standard procedure for curable advanced gastric cancer.[39,40] However, in their guidelines, splenectomy is only indicated if there is direct invasion, presumably due to the increased morbidity and mortality seen in 2 European randomized controlled trials.[12–14] In Japan, splenectomy is still a standard treatment for patients with upper-third advanced gastric cancer, although early results from a randomized clinical trial investigating the efficacy of splenectomy showed an increased incidence of postoperative pancreas-related infections. The effect of splenectomy on the long-term survival rate is still unclear even in Japan, and we have to wait for the final results of the randomized clinical trial.[41]

Perhaps surgeons have the urge to decrease postoperative complications in order to improve early surgical outcomes. However, the results of the present study show there are also poor long-term outcomes in patients with postoperative intra-abdominal infections. Therefore, surgeons must perform the surgery with extreme precision, not only to decrease postoperative complications, but also to improve long-term outcomes for patients.

In conclusion, postoperative intra-abdominal infectious complications adversely affect the overall and relapse-free survival of patients with stage II and III advanced gastric cancer. Surgeons have to perform the surgery with meticulous care in order to decrease the complication rate and improve the long-term outcome of patients following curative gastrectomy.

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ORIGINAL ARTICLE

Pattern of abdominal nodal spread and optimal abdominal lymphadenectomy for advanced Siewert type II adenocarcinoma of the cardia: results of a multicenter study

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Abstract
Background It remains uncertain whether radical lymphadenectomy combined with total gastrectomy actually contributes to long-term survival for Siewert type II adenocarcinoma of the cardia. We identified the pattern of abdominal nodal spread in advanced type II adenocarcinoma and defined the optimal extent of abdominal lymphadenectomy.
Methods Eighty-six patients undergoing R0 total gastrectomy for advanced type II adenocarcinoma were identified from the gastric cancer database of 4,884 patients. Prognostic factors were investigated by multivariate analysis. The therapeutic value of lymph node dissection for each station was estimated by multiplying the incidence of metastasis by the 5-year survival rate of patients with positive nodes in each station.
Results The overall 5-year survival rate was 37.1 %. Age less than 65 years [hazard ratio, 0.455 (95 % confidence interval (CI), 0.261–0.793)] and nodal involvement with pN3 as referent [hazard ratio for pN0, 0.129 (95 % CI, 0.048–0.344); for pN1, 0.209 (95 % CI, 0.097–0.448); and for pN2, 0.376 (95 % CI, 0.189–0.746)] were identified as significant prognosticators for longer survival. Perigastric nodes of the lower half of the stomach in positions 4d–6 were considered not beneficial to dissect, whereas there were substantial therapeutic benefits to dissecting the perigastric nodes of the upper half of the stomach in positions 1–3 and the second-tier nodes in positions 7 and 11.
Conclusions Limited lymphadenectomy attained by proximal gastrectomy might suffice as an alternative to extended lymphadenectomy with total gastrectomy for obtaining

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potential therapeutic benefit in abdominal lymphadenectomy for advanced Siewert type II adenocarcinoma.

Keywords Advanced adenocarcinoma of the cardia · Siewert type II · Abdominal nodal spread · Optimal lymphadenectomy · Multicenter study

Introduction

Recent studies have reported a continuing rise in the incidence of adenocarcinoma of the gastroesophageal junction (GEJ) despite a decline in the overall incidence of gastric carcinoma in Western countries [1, 2]. Adenocarcinoma of the GEJ is defined as carcinoma centered within 5 cm of the anatomic GEJ, which is further classified into three distinct entities (types I, II, and III) according to the anatomic location of the tumor center [3, 4]. Type I carcinoma, with the tumor center located 1–5 cm above the anatomic GEJ and often associated with Barrett's esophagus, was reported to be the most prevalent type in Western countries [3, 5]. In Eastern countries, type III has been reported to be the most common type, with type I tumors rarely observed [6–9]. However, an increasing trend of GEJ adenocarcinoma has recently been reported in Japan, especially in type II (true carcinoma of the cardia), which is defined as carcinoma with its center located within 1 cm above and 2 cm below the anatomic GEJ, although the incidence of type I carcinoma still remains at approximately 1 % [7].

Difficulties in surgical management and an unfavorable prognosis with 5-year survival rates of 30–50 % make this disease a malignancy of great universal concern [4, 5, 10–12]. The subclassification of GEJ carcinoma provides a useful tool for the selection of the appropriate surgical procedure [4]. Briefly, the standard procedure for type I carcinoma is a subtotal esophagectomy through a right thoracotomy with proximal gastric resection, whereas a total gastrectomy with transhiatal resection of the distal esophagus is usually performed for type III tumors [3]. With respect to the procedure of choice for type II carcinoma, there has been some debate whether a transthoracic subtotal esophagectomy, as in type I tumors, or a total gastrectomy with transhiatal resection of the distal esophagus, as in type III tumors, is optimal. However, two recent phase III trials [11, 12] demonstrated the transhiatal approach to be preferable.

Although total gastrectomy has become the procedure of choice for patients with type II adenocarcinoma because radical lymphadenectomy achieved by removing the entire stomach with all its lymphatic drainage is believed to have the best potential for long-term survival [13], there have been no prospective studies demonstrating that formal D2 nodal dissection along with total gastrectomy really contributes to long-term survival in patients with type II tumors.

In this study, we identified the pattern of abdominal nodal spread in type II adenocarcinoma of the cardia and defined the appropriate extent of abdominal lymphadenectomy for type II adenocarcinoma by evaluating the prognostic significance of each lymph node station.

Patients and methods

Study population

A review of the gastric cancer database from nine hospitals belonging to the Osaka University Clinical Research Group for Gastroenterological Surgery identified 4,884 patients who underwent gastrectomy for primary gastric adenocarcinoma between 1 January 2001 and 31 December 2005. Among these 4,884 patients, a total of 86 patients (1.76 %) who underwent microscopically curative (R0) total gastrectomy for primary cancer of the true cardia (Siewert type II) [3] were retrospectively identified on their pathological specimens and recruited into this study. Patients with early gastric cancer (pT1), tumor invading adjacent organs (pT4b), linitis plastica, systemic metastasis, positive cytology of peritoneal lavage, or concurrent malignancy within 5 years were excluded. The clinical and histopathological tumor characteristics of these 86 patients are summarized in Table 1. Patients included 67 men and 19 women with a median age of 65.5 (range, 36–85) years. All patients underwent total gastrectomy, plus distal esophagectomy through the transhiatal approach, right thoracotomy, and left thoracotomy in 71, 7, and 8 patients, respectively. Combined resection of the spleen and distal pancreas was performed in 69 and 7 patients, respectively. Histologically, 48 patients had intestinal-type adenocarcinoma and 38 patients had diffuse-type adenocarcinoma according to the Lauren classification. Median tumor size was 50 mm (range, 20–150 mm). Pathological T stage and nodal involvement were classified according to the 7th edition of the Union for International Cancer Control (UICC) pTNM staging guidelines [14]. All patients had locally advanced tumors (pT2, pT3, and pT4a), of which 80 % were node positive. Adjuvant chemotherapy with S-1 or other fluoropyrimidine agents was carried out only in 28 patients with no adjuvant radiotherapy because there had been no standard adjuvant treatment until 2007 when S-1, the current standard of care in Japan, was established.

Extent of abdominal lymphadenectomy

Lymph nodes were retrieved from the excised specimens and assigned to the appropriate station according to Japanese Gastric Cancer Association criteria [15] as follows:

Table 1 Patient and tumor characteristics

Patient numbers	86
Gender	
Male	67
Female	19
Age, years	
Median (range)	65.5 (36–85)
Type of surgery	
Transhiatal approach	71
Right thoracoabdominal approach	7
Left thoracoabdominal approach	8
Combined resection	
Spleen	69
Distal pancreas	7
Lauren type	
Intestinal	48
Diffuse	38
Tumor size (mm)	
Median (range)	50 (20–150)
Depth of invasion (pT)	
pT2 (MP)	11
pT3 (SS)	38
pT4a (SE)	37
No. of positive nodes (pN)	
pN0: 0	17
pN1: 1–2	22
pN2: 3–6	19
pN3: ≥7	28
R category	
R0	86
R1/2	0

no. 1, right paracardial; no. 2, left paracardial; no. 3, lesser curvature; no. 4sa, greater curvature along the short gastric vessels; no. 4sb, greater curvature along the left gastroepiploic artery; no. 4d, greater curvature along the right gastroepiploic artery; no. 5, suprapyloric along the right gastric artery; no. 6, infrapyloric at the base of the right gastroepiploic artery; no. 7, left gastric artery; no. 8, suprapancreatic along the common hepatic artery; no. 9, celiac trunk; no. 10, splenic hilum; and no. 11, suprapancreatic along the splenic artery. The preferred lymph node dissection was a D2 abdominal lymphadenectomy (i.e., dissection of nodes in stations 1–11) with the paraesophageal, lower posterior mediastinal, and diaphragmatic nodes. A complete D2 dissection was not achieved in 17 patients. Abdominal nodal spread was examined thoroughly for each lymph node station, and both the number and site of nodal metastasis were evaluated for nodal staging (pN). The frequency of nodal metastasis in each abdominal station was also studied in all 86 patients.

Survival analysis

All patients were followed for a minimum of 5 years or until death. None was lost to follow-up. Overall survival (OS) was defined as the time from the date of surgical resection to the date of death from any cause or last follow-up. When calculating disease-specific survival, deaths from causes other than relapsed disease were treated as censored cases at the time of death. Univariate analysis was used to assess the association between each clinicopathological factor and OS. Multivariate analysis was performed to identify variables independently associated with survival. Postoperative deaths were not excluded from the survival analyses.

Therapeutic value of lymph node dissection

The therapeutic value of lymph node dissection for each station was estimated by multiplying the incidence of metastasis by the 5-year survival rate of patients with positive nodes in that station [16]. The incidence of metastasis was calculated by dividing the number of patients with metastasis in each station by the number of patients who underwent dissection of that station. The 5-year survival rate of patients with positive nodes in each station was calculated independently for each lymph node station, without any reference to nodal metastasis to other stations.

Statistical analysis

SAS statistical software 9.1 (SAS Institute, Cary, NC, USA) was used for all statistical analyses, and a P value less than 0.05 was considered statistically significant. Survival rates were calculated according to the Kaplan–Meier method, and differences were evaluated by the log-rank test. A Cox proportional hazards regression model was used to identify prognostic factors for survival.

Results

Distribution of nodal metastases

Figure 1 shows the distribution of nodal metastases to each lymph node station. Overall, 69 of the 86 patients (80.2 %) showed some involvement of the abdominal nodes. There was a substantially higher frequency of metastatic spread to the perigastric nodes of the upper half of the stomach in positions 1–3 as well as to the second-tier nodes in positions 7 and 11, whereas the perigastric nodes of the lower half of the stomach in positions 4d–6, and the second-tier node at the splenic hilum (no. 10), were less frequently involved.

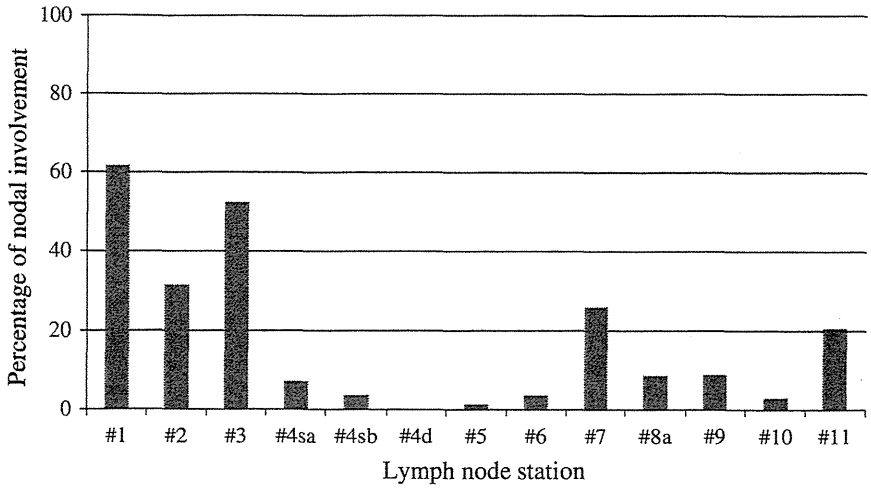

Fig. 1 Frequency of nodal involvement to each abdominal lymph node station for the 86 patients under study. Lymph node stations are classified according to Japanese criteria 17

Correlation between survival and nodal involvement

During the follow-up period, 59 of the 86 patients died, of whom 48 died of relapsed disease and 11 from other causes such as cerebral infarction in 1, abrupt cardiac arrest in 2, arrhythmia in 1, pneumonia in 2, lung cancer in 2, colon cancer in 1, postoperative complications during the hospital stay in 1 (operative mortality rate, 1.2 %), and no details specified but classified as other cause of death in 1. The overall 5-year survival rate was 37.1 %, with median survival time (MST) of 1,210 days; the disease-specific 5-year survival rate was 44.8 % with MST of 1,522 days. As shown in Table 2, multivariate analysis confirmed the independent prognostic value of age less than 65 years [hazard ratio, 0.455 (95 % confidence interval (CI), 0.261–0.793)] and nodal involvement with pN3 as referent [hazard ratio for pN0, 0.129 (95 % CI, 0.048–0.344); for pN1, 0.209 (95 % CI, 0.097–0.448); and for pN2, 0.376 (95 % CI, 0.189–0.746)]. Overall survival according to the presence of nodal metastasis for each station is depicted in Table 3.

Potential benefit from lymph node dissection

The incidence of metastasis ranged from 0 % to 61.6 %, and the overall 5-year survival rate of patients with lymph node metastasis ranged from 0 % to 50.0 % in the perigastric stations. The incidence of metastasis was between 2.9 % and 25.9 % in the second-tier nodes (no. 7 through 11), and the 5-year survival rate ranged from 14.3 % to 50.0 %. Based on these results, the therapeutic value of lymph node dissection for each station was estimated as shown in Table 3. For some perigastric lymph node stations (no. 4d, 5, 6), dissection was considered to be not beneficial. Similarly, in terms of the disease-specific 5-year survival rate of affected patients that ranged from 0 % to 50.0 % in perigastric stations and from 14.3 % to 50.0 % in the second-tier nodes, lymph node stations numbered 4d, 5, and 6 were deemed unnecessary to dissect (Table 4). In contrast, substantially higher therapeutic value were observed in the perigastric nodes of the upper half of the stomach in positions 1–3 as well as in the second-tier nodes in positions 7 and 11, as shown in Tables 3 and 4.

Discussion

There have been several reports regarding the pattern of abdominal lymph node spread of Siewert type II adenocarcinoma [17–20]. Italian investigators reported that 44 of 62 patients (71 %) with pT2–4 Siewert type II tumors had lymph node metastases, and a high frequency of nodal involvement in the perigastric nodes of the upper half of the stomach (right paracardial 50 %, left paracardial 32 %, lesser curvature 53 %) was seen, in contrast to the fairly low percentage of metastases in the lymph nodes along the right gastroepiploic artery (7 %), suprapyloric (2 %), and infrapyloric lymph nodes (2 %) [17, 18]. These results were consistent with our findings as shown in Table 1 and Fig. 1, in which metastatic nodal spread was seen in 80 % of patients with a striking contrast in the frequency between the perigastric nodes of the upper half of the stomach in positions 1–3 and those of the lower half of the stomach in positions 4d–6. With regard to the second-tier stations, lymph nodes along the left gastric artery (station 7) were affected in a substantial percentage of patients (18–65 %) with type II tumors in previous reports [5, 17–22], which was compatible with our findings shown in Fig. 1. A low percentage of metastases to the second-tier nodes at the splenic hilum was observed in this study (2.9 %), which is also in accordance with previous reports (3.9–5.0 %) [18–20]. A precise understanding of how type II adenocarcinoma spreads to abdominal lymph nodes helps guide the surgeon when choosing the appropriate type of resection and lymphadenectomy.

Table 2 Survival according to clinicopathological characteristics

Characteristics	Univariate analysis				Multivariate analysis		
	No. of patients	Median survival time (MST) (days)	5-year survival rate (%)	*P*	Hazard ratio	95 % CI	*P*
Gender							
Male	67	1,211	38.7	0.3198	0.852	0.464–1.565	0.6053
Female	19	1,073	31.6				
Age (years)							
<65	40	1,855	52.5	0.0231	0.455	0.261–0.793	0.0055
≥65	46	939	23.7				
Lauren type							
Intestinal	48	1,299	39.4	0.6111	1.209	0.678–2.160	0.5197
Diffuse	38	1,073	34.2				
Depth of invasion (pT)							
pT2 (MP)	11	1,855	54.5	0.4474	0.876	0.351–2.185	0.7758
pT3 (SS)	38	1,299	36.8		0.968	0.556–1.685	0.9075
pT4a (SE)	37	905	32.4				
No. of positive nodes (pN)							
pN0: 0	17	>3,382	64.7	<0.0001	0.129	0.048–0.344	<0.0001
pN1: 1–2	22	1,855	54.5		0.209	0.097–0.448	<0.0001
pN2: 3–6	19	1,522	31.6		0.376	0.189–0.746	0.0052
pN3: ≥7	28	526	10.7				
Level of positive nodes							
pN0	17	>3,382	64.7	0.0113			
First-tier (no. 1–6)	33	1,339	33.3				
Second-tier (no. 7–11)	36	848	27.8				

In this study, long-term survival was mostly limited to the patients with fewer than 7 metastatic nodes, and the independent prognostic value of nodal involvement was demonstrated in the multivariate analysis. Similar to these results, the involvement of second-tier lymph nodes [6, 10, 23] and the presence of more than 6 metastatic nodes [18, 19, 21] have already been reported as negative prognostic factors in GEJ adenocarcinoma. Although age less than 65 years was identified as a significant positive prognostic factor, the depth of invasion (pT) was not an independent determinant of survival, as shown in Table 2, which is supported by other report [19]. In our series, 48 patients died of relapsed disease, involving nodal recurrence in 29 patients (4 cervical, 7 mediastinal, 20 para-aortic), hematogenous (liver, lung, bone, adrenals, brain, skin) recurrence in 23 patients, peritoneal dissemination in 7 patients, and local relapse in 4 patients. Both para-aortic lymph node metastasis and hematogenous metastasis were the predominant mode of recurrence, with peritoneal dissemination being less frequent; this was consistent with previous reports [19, 24].

Although surgical treatment with sufficient lymphadenectomy aimed at complete removal of tumor is the mainstay of treatment, the optimal extent of lymph node dissection for advanced type II carcinoma of the cardia remains unclear. When deciding whether dissection of a particular lymph node station could be a part of the optimal lymphadenectomy, the frequency of metastasis to a given lymph node station and the proportion of long-term survivors among patients with metastasis to that station are both important factors to consider. A particular lymph node station is considered clinically irrelevant to dissect unless (1) metastasis to the station is commonly observed and (2) long-term survivors exist among patients with metastasis dissected at that station [16]. According to this concept, the therapeutic value of lymph node dissection for each station was estimated by multiplying the incidence of metastasis and the 5-year survival rate of patients with metastasis dissected at that station [16] (Tables 3, 4). Dissection of the paracardial and lesser curvature nodes yielded the highest potential therapeutic benefit, whereas perigastric lymph node stations numbered 4d, 5, and 6 and the second-tier nodes at the splenic hilum (no. 10) were considered nonbeneficial to dissect in terms of both overall and disease-specific survival. Similar results have been obtained in two recent reports [19, 20]. However, in marked contrast to our current study, Yamashita et al. included a significant proportion of patients with early gastric (pT1) cancer (22.7 %)

Table 3 Estimated benefit from lymph node dissection in each station, according to the incidence of lymph node metastasis and overall 5-year survival rate of each station

Lymph node station	Incidence of metastasis (%)	MST (days)	Overall 5-year survival rate (%)	Estimated therapeutic value
1 Right paracardial	61.6 (53/86)	848	26.4	16.3
2 Left paracardial	31.4 (27/86)	905	18.5	5.8
3 Lesser curvature	52.3 (45/86)	848	22.2	11.6
4sa Short gastric vessels	7.0 (6/86)	2,171	50.0	3.5
4sb Left gastroepiploic artery	3.5 (3/86)	466	33.3	1.2
4d Right gastroepiploic artery	0 (0/86)	–	–	0
5 Suprapyloric	1.2 (1/86)	329	0	0
6 Infrapyloric	3.5 (3/86)	905	33.3	1.2
7 Left gastric artery	25.9 (22/85)	850	22.7	5.9
8a Common hepatic artery	8.5 (7/82)	781	28.6	2.4
9 Celiac trunk	8.8 (7/80)	329	14.3	1.3
10 Splenic hilum	2.9 (2/69)	1,990	50.0	1.5
11 Splenic artery	20.5 (15/73)	846	40.0	8.2

Data in parentheses are number of patients with metastasis in each station/number of patients undergoing lymph node dissection. Estimated therapeutic value corresponds to the percentage of patients who will benefit from dissection of each lymph node station *MST* mean survival time

Table 4 Estimated benefit from lymph node dissection in each station, according to the incidence of lymph node metastasis and disease-specific 5-year survival rate of each station

Lymph node station	Incidence of metastasis (%)	MST (days)	Disease-specific 5-year survival rate (%)	Estimated therapeutic value
1 Right paracardial	61.6 (53/86)	848	24.5	15.1
2 Left paracardial	31.4 (27/86)	939	22.7	7.1
3 Lesser curvature	52.3 (45/86)	1,210	25.7	13.4
4sa Short gastric vessels	7.0 (6/86)	2,171	50.0	3.5
4sb Left gastroepiploic artery	3.5 (3/86)	466	33.3	1.2
4d Right gastroepiploic artery	0 (0/86)	–	–	0
5 Suprapyloric	1.2 (1/86)	329	0	0
6 Infrapyloric	3.5 (3/86)	1,925	50.0	1.8
7 Left gastric artery	25.9 (22/85)	850	27.4	7.1
8a Common hepatic artery	8.5 (7/82)	781	28.6	2.4
9 Celiac trunk	8.8 (7/80)	329	14.3	1.3
10 Splenic hilum	2.9 (2/69)	1,990	50.0	1.5
11 Splenic artery	20.5 (15/73)	1,211	35.2	7.2

and those undergoing proximal gastrectomy (24.8 %). Hosokawa et al. reported that 19.6 % of the patients in the Siewert type II cohort had pT1 disease, and the therapeutic value of lymph node dissection was calculated for the whole population of GEJ carcinoma patients without taking into account the classification of the three distinct types. Although these findings would be helpful in defining the optimal extent of nodal dissection and the most appropriate extent of gastric resection, a prospective randomized controlled trial comparing total gastrectomy plus extended lymphadenectomy with proximal gastrectomy plus limited lymphadenectomy should be conducted to establish the optimal surgical approach for advanced type II carcinoma. With respect to the role of splenectomy combined with nodal dissection at the splenic hilum, it will be clarified as the results of a Japanese prospective trial in which more than 500 patients with T2 or deeper carcinoma in the proximal third of the stomach were randomized to total gastrectomy plus either splenectomy or spleen preservation [25].

In this study, we excluded patients with early carcinoma (pT1). In early gastric cancer of the true cardia, abdominal lymph node involvement is known to be limited to the perigastric nodes of the upper half of the stomach and the lymph nodes of the celiac trunk [17]. Based on these patterns of abdominal nodal spread and the virtual absence of lymph node metastases, a limited resection of the distal esophagus, cardia, and proximal stomach is commonly performed and is considered to provide adequate disease control for early carcinoma of the true cardia [26].

On the other hand, there have been some controversies regarding the appropriate extent of gastric resection and the therapeutic value of extended lymphadenectomy for the treatment of advanced adenocarcinoma of the cardia [3, 13, 17, 19, 20]. Some investigators advocate total gastrectomy because of the possible metastasis to the distal perigastric stations numbered 4d, 5, and 6 [3, 17]. However, similar to our results, the frequency of metastasis to these distal stations was less than 7 % [6, 17–19], and few 5-year survivors existed among patients with metastasis to the nodes numbered 4d, 5, and 6 [6, 19, 20]. These findings suggest that resection of these stations is likely to have little impact on the survival of patients with type II carcinoma. If these nodes can be omitted from the routine lymphadenectomy procedure, proximal gastrectomy might suffice as an alternative to total gastrectomy [27, 28]. However, some investigators reported a survival trend in

favor of total gastrectomy [13]. Others pointed out there were no differences in the 5-year survival rate as well as in operative mortality between total gastrectomy versus proximal gastrectomy for advanced (pT2–pT4) type II and III carcinoma [6, 27–30]. Of note, it has never been clarified whether proximal gastrectomy can really provide some benefits, such as a better postoperative quality of life, when compared with total gastrectomy in patients with carcinoma of the cardia. As opposed, proximal gastrectomy would induce intractable reflux more often than in cases of total gastrectomy, depending on the distance of resected abdominal esophagus and the size of the remnant stomach. In addition, patients after proximal gastrectomy were demonstrated to fare less well than those after total gastrectomy in most function and symptom scales, such as reflux, nausea/vomiting, eating restrictions, and anxiety scales, using validated gastric cancer-specific questionnaires throughout the first 12-month period following gastrectomy [31]. The optimal extent of gastric resection and appropriate lymphadenectomy, which achieves complete histological negative margins with a reconstruction that yields optimal long-term functional outcome, still remains uncertain because of a lack of prospective randomized trials for the treatment of advanced type II adenocarcinoma.

In conclusion, we investigated the pattern of abdominal nodal spread and its prognostic significance in advanced Siewert type II adenocarcinoma. Limited lymphadenectomy with proximal gastrectomy could be an alternative to extended lymphadenectomy with total gastrectomy for obtaining the potential therapeutic benefit in abdominal lymphadenectomy for advanced Siewert type II adenocarcinoma. Although to the best of our knowledge the present study is the first multicenter study with the third largest sample size of 86 patients with advanced type II adenocarcinoma in the literature [5, 6, 8, 9, 17–22] (the first and second largest studies were conducted by Feith et al. [5] with 406 advanced cases and by Yamashita et al. [19] with 174 advanced patients, respectively), the retrospective nature of this study warrants further studies focusing on postoperative quality of life and long-term survival to discriminate whether total gastrectomy plus extended lymphadenectomy or proximal gastrectomy plus limited lymphadenectomy is the optimal surgical procedure to treat advanced Siewert type II adenocarcinoma.

Conflict of interest None.

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Comparison of Billroth I and Roux-en-Y Reconstruction after Distal Gastrectomy for Gastric Cancer: One-year Postoperative Effects Assessed by a Multi-institutional RCT

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ABSTRACT

Purpose. This randomized, controlled trial evaluated the clinical efficacy of Billroth I (BI) and Roux-en-Y (RY) reconstruction at 1 year after distal gastrectomy for gastric cancer.

Methods. The primary end point was the amount of body weight lost at 1 postoperative year, and secondary end points included other items related to nutritional status such as serum albumin and lymphocyte count, as well as endoscopic examination findings of the remnant stomach and esophagus. Of the 332 patients enrolled, 163 were assigned to the BI group and 169 were randomized to the RY group.

Results. The loss in body weight 1 year after surgery did not differ significantly between the BI and RY groups (9.1 % and 9.7 %, respectively, $p = 0.39$). There were no significant differences in other aspects of nutritional status between the 2 groups. Endoscopic examination 1 year after gastrectomy showed reflux esophagitis in 26 patients (17 %) in the BI group versus 10 patients (6 %) in the RY group ($p = 0.0037$), while remnant gastritis was observed in 71 patients (46 %) in the BI group versus 44 patients (28 %) in the RY group ($p = 0.0013$); differences were significant for both conditions. Multivariable analysis showed that the only reconstruction was the independently associated factor with the incidence of reflux esophagitis.

Conclusions. RY reconstruction was not superior to BI in terms of body weight change or other aspects of nutritional status at 1 year after surgery, although RY more effectively prevented reflux esophagitis and remnant gastritis after distal gastrectomy.

The selection of the reconstruction method after distal or subtotal gastrectomy is still controversial worldwide. Billroth I (BI) reconstruction has conventionally and commonly been performed after distal gastrectomy in Japan because of the physiological advantage of allowing food to pass directly through the stomach to the duodenum.[1] After BI operations, patients typically display a good clinical course, and it may be easy to perform the duodenoscopic examination after surgery. However, after a BI operation, many patients experience significant symptoms, including epigastralgia and dyspepsia. Gastroduodenal reflux has been recognized as a major cause of clinical symptoms after BI operations. Bile reflux has also been reported to have the potential to cause malignancies in the remnant stomach and lower esophagus.[2–4]

On the other hand, Roux-en-Y (RY) reconstruction of gastrojejunal continuity is an established means of draining the gastric remnant after distal gastrectomy. RY operations are reported to be superior to the conventional BI and Billroth II (BII) reconstructions in preventing duodenal juice

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reflux into the gastric remnant and in impeding gastritis, although the RY reconstructive method is complicated in comparison with the BI method, and gastrojejunostomy may cause delayed gastric emptying, known as the RY syndrome, with functional obstruction of the Roux limb.[5,6] RY reconstruction has been frequently performed in Japan after distal gastrectomy for gastric cancer, as well as BI reconstruction.

Some reports have evaluated BI and RY reconstruction in terms of the clinical benefits to patients who had undergone distal gastrectomy.[7–9] However, these reports were based on small-sized studies, and the assessment of clinical benefits was controversial. We conducted a large multi-institutional randomized, controlled trial (RCT) in Japan. We prospectively compared clinical efficacy at 1 year after BI and RY operations for gastric cancer. We used as the primary end point the change in body weight 1 year after surgery because this is a reliable factor that reflects the postoperative course of patients after an operation. At secondary end points, we evaluated other aspects of nutritional status as well as endoscopic examination of the remnant stomach and esophagus 1 year after surgery because these factors also may be influenced by reconstructive operations.

PATIENTS AND METHODS

Trial Objectives, End Points, and Eligibility Criteria

This trial was a multi-institutional RCT designed to compare the clinical effects of BI or RY reconstructive operation for gastric cancer resection at 1 year after surgery. Disease staging and operation were performed according to the guidelines for clinical studies in the 13th edition of the Japanese classification of gastric carcinoma.[10] Patients who required distal gastrectomy for gastric cancer with BI or RY reconstructions were eligible for this study. Tumor was located at the middle or lower third of stomach, and a proportion of residual stomach was regulated as a one third. Both reconstruction procedures could be chosen after distal gastrectomy, taking the length of the residual stomach into consideration. Other key eligibilities included the following: histologically proven adenocarcinoma of the stomach; a lack of noncurative surgical factors except for positive lavage cytology; age between 20 and 90 years; Eastern Cooperative Oncology Group performance status of 0–1; and sufficient renal, hepatic, cardiac, and bone marrow function. None of the following conditions was permitted: history of laparotomy (except appendectomy and laparoscopic cholecystectomy), interstitial pneumonia or pulmonary fibrosis, severe heart disease, liver cirrhosis or active hepatitis, chronic renal failure, severe diabetes (HbA1c $\geq$ 9.0 %), reflux esophagitis (Los Angeles [LA] classification grade A or higher), and Barrett esophagus.[11] After confirmation of the eligibility criteria, patients were randomized intraoperatively at the data center at Osaka University to either the BI reconstructive group or the RY reconstructive group after distal gastrectomy.

The primary end point was change in body weight 1 year after surgery because this was considered to be the relatively reliable factor reflecting the postoperative nutritional course of patients after gastrectomy. Body weight correlates well with decline in postoperative quality of life and is the reliable indicator of malnutrition, which impairs immune function, infection susceptibility, and survival.[12–14] Secondary end points included the following: (1) other nutritional status characteristics such as serum albumin concentration, lymphocyte count, and prognostic nutritional index (PNI) value, (2) endoscopic examination findings of the remnant stomach and esophagus 1 year after surgery, (3) perioperative morbidity and in-hospital mortality, (4) postoperative quality of life and intestinal dysfunction with the European Organisation for Research and Treatment of Cancer QLQ C30 and DAUGS20 assessment tools, and the results concerning perioperative morbidity, mortality, postoperative quality of life and intestinal dysfunction were already published.[15–18]

In our surgical study group, the Osaka University Clinical Research Group for Gastroenterological Study, the standard reconstructive method after distal gastrectomy has been the BI reconstruction because of the physiological advantage of allowing food to pass through the duodenum and the surgical simplicity of the BI reconstructive method in comparison with the RY method. It has been reported that the rate of body weight loss at 1 postoperative year was 10–15 % after BI operations.[7,8] In this study, we hypothesized that relative to the BI operation, the RY operation may result in decreased body weight loss at 1 year after surgery of 5 %. The sample size was chosen so as to provide 80 % power to detect an effect size of 5 % using a one-sided alpha error of 5 % under normal distribution with a standard deviation of 0.1 in both groups. The primary end point was evaluated by *t* test. The planned sample size was 330 patients (165 for each arm), allowing for a 10 % dropout rate under the selection design of a randomized phase II trial. Details of the study protocol have been previously reported.[17,18]

Written informed consent was obtained from all enrolled patients and the institutional review boards from all participating institutions approved the study protocol. This study was registered with clinical trial identification number UMIN000000878.

Randomization and Statistical Analyses

The surgeon examined the tumor location and confirmed the possibility of adoption of both BI and RY reconstruction

in addition to the eligibility and exclusion criteria immediately. Patients were randomly assigned intraoperatively to undergo either BI or RY reconstruction after distal gastrectomy performed with the minimization method, according to body mass index and institutional preferences.

This protocol tracked each patient's nutritional status as assessed by body weight, serum albumin concentration, lymphocyte count, and PNI value for 1 year after surgery. The PNI value was calculated as 10× serum albumin concentration (mg/dL) + 0.005 × lymphocyte count in peripheral blood (cells/mm^3).[11] The analysis of RCT results was based on the intention-to-treat principle.

The Student *t* test, Wilcoxon rank sum test, Mann–Whitney *U*-test, and Chi-square test were used where appropriate to assess differences between groups. Multivariable analysis was also performed using a logistic regression model to assess the effects of these risk factors on the reflux esophagitis at 1 postoperative year. All statistical analyses were performed with SPSS software, version 15.0 J (SPSS, Chicago, IL). Two-sided *p* values were calculated and presented. A *p* value of <0.05 was considered to indicate statistical significance.

Operative Procedure

Endotracheal general anesthesia and standard laparotomy or laparoscopic operations were used for all patients in each institution. Gastric tumors located in the lower or middle third of the stomach were treated with distal gastrectomy. After initial laparotomy, tumor was confirmed to be located at a middle or lower third of stomach, and a proportion of residual stomach was regulated as a one-third. It was also reconfirmed that both reconstruction procedures could be chosen after distal gastrectomy taking the length of the residual stomach into consideration. Lymphadenectomy approaches were categorized as D1–D3, as defined by the Japanese Classification for Standard Dissection.[10] D1 involves dissecting the paragastric nodes, while D2 adds dissection of the nodes along the left gastric artery, those along the common hepatic artery, and those around the celiac artery. D3 includes the D2 procedure and adds dissection of the hepatoduodenal nodes, retropancreatic nodes, those along the superior mesenteric vein, and the para-aortic nodes between the level of the celiac axis and the inferior mesenteric artery.

For BI reconstruction, the duodenum and remnant stomach were sutured. For RY reconstruction, the jejunum was divided 20 cm distal to the ligament of Treitz, and the portion of the jejunum closest to the patient's head was closed, followed by the remaining gastric pouch, which was isoperistaltically anastomosed to the jejunum. The oral portion of the jejunum was then anastomosed to the mid-jejunum 30 cm distal to the gastrojejunostomy. The concrete anastomotic procedures, such as hand-sewn or automatic sutures, and by standard laparotomy or laparoscopic operation, were not regulated in detail by the protocol.

Recruitment

Between May 2004 and October 2009, we enrolled 332 patients with gastric cancer assessed at 18 high-volume institutions in Osaka, Japan. All 18 institutions were participating in the surgical study group Osaka University Clinical Research Group for Gastroenterological Study. Overall, more than 50 gastrectomies were performed every year in these 18 hospitals. All operations were performed or supervised by senior surgeons who were members of the Japanese Gastric Cancer Association. During the planning of the study, all participating surgeons reached an agreement concerning the technical details of the reconstructive procedures.

Endoscopic Examination at 1 Year after Surgery

Endoscopic examination was performed 1 year after surgery to observe whether the mucosal appearance in the lower esophagus and remnant stomach had changed. Evaluation was based on the endoscopic classification of oesophageal reflux established in the LA classification in 1996.[11] Remnant gastritis and the persistence of residual food in the stomach were evaluated by endoscopic study. Remnant gastritis was evaluated in accordance with the classification established by Shinoto et al.[19] Endoscopic examination was performed with patients' informed consent. The questionnaire information about conditions 1 year after surgery were included on the case report form for prospective data collection.

RESULTS

A total of 332 adult patients (220 men and 112 women) with gastric adenocarcinoma who underwent gastrectomy at the institutions participating in the surgical study group Osaka University Clinical Research Group for Gastroenterological Study were enrolled onto the study, with 163 patients in the BI group and 169 in RY group (Fig. 1). The numbers of patients with each disease stage were as follows: stage IA, 207; stage IB, 56; stage II, 47; stage IIIA, 13; stage IIIB, 4; and stage IV, 5. D1 lymphadenectomy was performed in 119 patients, D2 in 212, and D3 in 1. Standard laparotomy was performed in 270, and laparoscopy-assisted surgery in 62. In RY group, 58 underwent an antecolic reconstruction and 109 retrocolic.

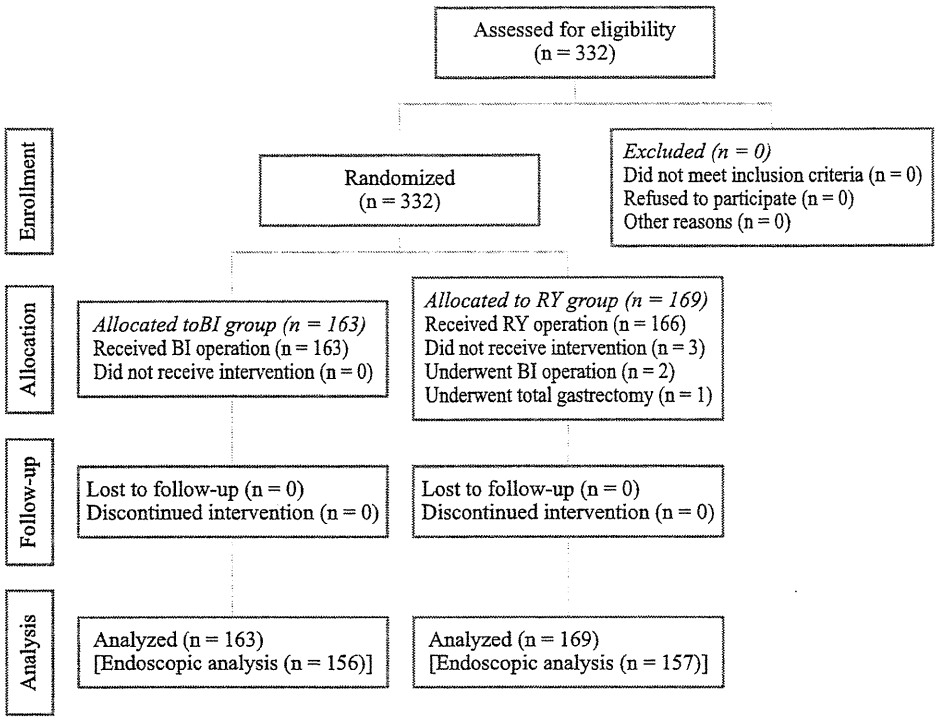

FIG. 1 Study flow chart

Postoperative adjuvant chemotherapy, such as S-1, was orally administrated for 45 patients (20 in the BI group and 25 in the RY group) during the follow-up year. Patient characteristics were well balanced between the 2 groups (Table 1).

Because 1 patient in the RY group underwent total gastrectomy with RY reconstruction and 2 patients in the RY group mistakenly underwent BI reconstructive operation intraoperatively, they were included in the RY group based on the intent-to-treat principle (Fig. 1).

Body weight loss at 1 year after surgery was 9.1 % for the BI group and 9.7 % for the RY group. Serum albumin levels, lymphocyte counts, and PNI values did not differ after 1 year. There were no statistically significant changes in relative body weight ($p = 0.39$), serum albumin ($p = 0.54$), and number of lymphocytes ($p = 0.39$) between the 2 groups (Table 2).

Table 3 shows the endoscopic study results at 1 year after surgery. Substantial inflammation in the lower esophagus was observed in 26 patients (17 %) in the BI group and in 10 patients (6 %) in the RY group. There was a statistically significant difference between the 2 groups ($p = 0.0037$). Moreover, esophagitis categorized as grades B to D, according to the LA classification, was observed in 6 patients in the BI group but in no patients in the RY group ($p = 0.0036$). Remnant gastritis was observed in 71 patients (46 %) in the BI group versus 44 patients (28 %) in the RY group ($p = 0.0013$). The persistence of residual food in the stomach was observed in 47 patients (30 %) in the BI group versus 37 patients (24 %) in the RY group ($p = 0.18$). Thus, the incidence of remnant gastritis was lower in the RY group. Table 4 indicates that in multivariate analysis that aimed to explore the influence of clinical baseline and surgical factors on the risk of postoperative reflux esophagitis, only the reconstructive method was independently associated.

Regarding the questionnaire about conditions 1 year after surgery, the incidence of patients who experienced delayed gastric emptying (DGE) symptoms was 1 and 2 in the BI and RY groups, respectively. The incidence of patients who had dumping symptoms was 2 and 3 in the BI and RY groups, respectively. The incidence of DGE and dumping symptoms at 1 year after surgery were statistically similar between both groups.

DISCUSSION

The clinically optimal reconstructive method for patients who have undergone distal gastrectomy for gastric cancer remains controversial. BI reconstruction has conventionally been used after distal gastrectomy in Japan because of the physiological advantage of allowing food to pass through the duodenum.[1] On the other hand, RY reconstruction allows for gastrojejunal continuity and is an established means of draining the gastric remnant after

TABLE 1 Patient demographics, tumor characteristics, and operative details

Characteristic	BI group (n = 163)	RY group (n = 169)	p
Sex, M/F	105/58	115/54	0.48[a]
Age (years)			
Median (range)	65 (40–84)	65 (32–84)	0.89[b]
Preoperative serum albumin, mg/dL,			
Median (range)	4.2 (2.9–5.2)	4.2 (2.4–7.0)	0.18[b]
Preoperative lymphocyte count			
Median (range)	1,790 (582–4,454)	1,897 (517–3,518)	0.25[b]
Preoperative PNI			
Median (range)	51.2 (34.6–65.1)	51.1 (33.9–67.8)	0.68[b]
Preoperative BMI,			
Median (range)	22.4 (15.4–33.0)	22.5 (14.8–31.6)	0.16[b]
Surgical stage			
IA	103	104	0.48[c]
IB	30	26	
II	23	24	
IIIA	5	8	
IIIB	2	2	
IV	0	5	
Tumor location			
Middle	108	112	0.99[a]
Lower	55	57	
Lymphadenectomy			
D1	58	61	0.50[c]
D2	105	107	
D3	0	1	
Approach			
Laparotomy	134	136	0.68[a]
Laparoscopic	29	33	
Anastomosis			
Hand sewn	62	20	<0.0001
Mechanical	101	149	
Postoperative adjuvant chemotherapy			
Yes	143	144	0.50[a]
No	20	25	

PNI prognostic nutritional index, *BMI* body mass index

[a] χ2test

[b] Wilcoxon rank sum test

[c] Mann–Whitney U test

distal gastrectomy. The RY operation is reported to be superior to the conventional BI and BII reconstructions in preventing bile reflux into the gastric remnant and in preventing impeding gastritis.[5,20] The RY surgical procedure is complicated in comparison with the BI method. Several prospective or retrospective studies have compared BI and RY reconstruction after distal gastrectomy.[7–9] However, the numbers in each group in these studies were insufficient, and the results are therefore controversial. In this study, we conducted a large multi-institutional RCT to compare the short-term effects of BI and RY reconstructions. The present study compared the clinical efficacy of these reconstructions after gastric cancer resection to determine which method provides better functional and clinical results at 1 year after surgery. The study results suggested that postoperative changes in nutritional status were similar between the 2 groups, although RY reconstruction was superior at preventing reflux esophagitis and remnant gastritis.

Concerning postoperative nutritional status, it has been reported that serum albumin levels 6 months after surgery were significantly lower in BI patients than in RY patients.[8] Kojima et al. found that food intake 1 year after surgery was significantly higher in RY patients than in BI patients.[7] This study noted that a higher rate of heartburn in the BI group due to the bile reflux into the gastric remnant or esophagus would have reduced food intake in this group as compared with the RY group. However, other nutritional parameters, such as body weight, serum albumin, and total cholesterol were similar between the 2 groups. In our study, the primary end point was defined as loss in body weight because we hypothesized that the RY operation would suppress body weight loss at 1 year after surgery compared to the BI operation. However, our study showed that postoperative changes in nutritional status (body weight and serum albumin levels) at 1 year after surgery were similar between the 2 groups. Moreover, we evaluated 2 other objective nutritional parameters, lymphocyte count and PNI value. These parameters were also similar between the 2 groups at 1 year after surgery.

However, adjuvant chemotherapy may have great influence on postoperative weight loss; postoperative adjuvant chemotherapy was administrated impartially to both groups to a small number of patients (13 % in total). Postoperative changes in nutritional status may not be influenced by adjuvant chemotherapy.

It has been reported that RY reconstruction is superior to both BI and BII at preventing bile reflux into the gastric remnant based on 24 h bilirubin monitoring.[5] Shinoto et al. showed that bile reflux into the remnant stomach, as assessed by biliary scintigraphy, was significantly lower in RY patients than in BI and BII patients.[19] Some investigators have reported that bile reflux into the gastric stump was infrequently found with RY reconstruction according to endoscopic observation.[7,8] Montesani et al.[9] reported that the rate of histologic alteration in the gastric stump was significantly lower with RY anastomosis than with BI and BII. Moreover, investigators have shown that RY

TABLE 2 Postoperative nutritional status 1 year after surgery

Characteristic	BI group ($n = 163$)	RY group ($n = 169$)	p
Body weight loss (%)			
Mean ± SD	9.1 ± 6.3	9.7 ± 7.3	.39[a]
Change in serum albumin (mg/dL)			
Mean ± SD	0.03 ± 0.45	0.06 ± 0.48	.54[a]
Change in lymphocyte count			
Mean ± SD	−12 ± 542	−66 ± 580	.39[a]
PNI			
Median (range)	50.8 (33.4–64.6)	51.4 (33.1–62.2)	.39[a]

BI Billroth I, *RY* Roux-en-Y, *SD* standard deviation, *PNI* prognostic nutritional index

[a] Wilcoxon rank sum test

TABLE 3 Postoperative endoscopic examination results 1 year after surgery

Characteristic	BI group ($n = 156$)	RY group ($n = 157$)	p
Reflux esophagitis			
No	130 (83 %)	147 (94 %)	0.0037[a]
Yes	26 (17 %)	10 (6 %)	
LA grade of esophagitis			
N	130	147	0.0036[b]
M	4	2	
A	16	8	
B	3	0	
C	2	0	
D	1	0	
Remnant gastritis			
No	85 (54 %)	113 (72 %)	0.0013[a]
Yes	71 (46 %)	44 (28 %)	
Residual food in the stomach			
No	109 (70 %)	120 (76 %)	0.18[a]
Yes	47 (30 %)	37 (24 %)	

LA Los Angeles classification

[a] χ2test

[b] Mann–Whitney *U* test

reconstruction was effective at preventing the bile reflux into the gastric remnant that causes remnant gastritis and general malaise after distal gastrectomy.[5,7] This approach was also demonstrated to improve quality of life and reduce the risk of carcinogenesis in the gastric remnant.[2] In our multi-institutional study, endoscopic examinations at 1 year after surgery demonstrated that remnant gastritis was significantly less severe in the RY group compared to the BI group. Moreover, the number of esophagitis cases categorized as grades B–D, according to the LA classification, was also lower in the RY group. The RY method may have an advantage in reducing the development of oesophageal cancer and Barrett esophagus, because reflux of duodenal contents into the esophagus has been reported to be associated with the genesis of these diseases.[3,4] Moreover, although a choice of reconstruction method may need to be based on the size of remnant stomach to prevent reflux esophagitis, a remnant proportion was strictly regulated in our protocol. Multivariate analysis also revealed that only the reconstructive method was independently associated with the risk of postoperative reflux esophagitis.

TABLE 4 Multivariate analysis for the association of reflux esophagitis at 1 postoperative year and clinical or surgical factors of BI and RY groups combined

Characteristic	Parameter	OR (95 % CI)	p
Age	≥70 y (vs. <70 y)	1.37 (0.64–2.86)	0.413
Preoperative BMI	<25 kg/m^2 (vs. ≥25 kg/m^2)	1.85 (0.68–6.51)	0.243
Tumor location	Middle (vs. lower)	1.24 (0.58–2.57)	0.566
Lymphadenectomy	≥D2 (vs. <D2)	0.90 (0.4–2.16)	0.804
Anastomosis	Hand sewn (vs. mechanical)	1.27 (0.56–2.8)	0.555
Approach	Laparotomy (vs. laparoscopic)	1.95 (0.60–7.62)	0.277
Reconstructive method	BI (vs. RY)	2.62 (1.2–6.1)	0.015

Logistic regression model

OR odds ratio, *CI* confidence interval, *BMI* body mass index, *BI* Billroth I, *RY* Roux-en-Y

The incidence of patients who experienced DGE did not differ between the BI and the RY groups at 1 year after surgery. One type of DGE after RY reconstruction is known as the RY stasis syndrome, which is reportedly due to the functional obstruction of the Roux limb.[6] In our study, only 2 cases of DGE were observed at 1 year after RY operation, which was similar to the 1 case seen after BI operation. The incidence of patients who experienced dumping symptoms was also similar in both groups.

In conclusion, our multi-institutional prospective study indicated that there is no advantages to RY reconstruction relative to BI in terms of change in nutritional status at 1 year after operation, although RY reconstruction after gastric resection was superior to BI reconstruction at preventing remnant gastritis and lower esophagitis. The results of this study should be verified by long-term follow-up to better determine the clinical efficacy of RY and BI reconstruction after distal gastrectomy for gastric cancer.

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