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ORIGINAL ARTICLE

Postoperative Intra-abdominal Complications Assessed by the Clavien–Dindo Classification Following Open and Laparoscopy-Assisted Distal Gastrectomy for Early Gastric Cancer

Masanori Tokunaga · Junya Kondo · Yutaka Tanizawa · Etsuro Bando · Taiichi Kawamura · Masanori Terashima

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Abstract
Background Laparoscopy-assisted gastrectomy (LAG) has been increasingly used for the treatment of early gastric cancer, and many advantages over open gastrectomy (OG) have been reported. However, only a few reports have assessed postoperative complications following LAG using the Clavien–Dindo classification.
Methods A total of 265 patients who underwent distal gastrectomy or pylorus-preserving gastrectomy with D1+ lymph node dissection for clinical stage IA early gastric cancer at the Shizuoka Cancer Center between June 2009 and December 2011 were included in this study. Clinicopathological characteristics and early surgical outcomes were compared between patients who underwent LAG (LAG group, $n=129$) and those who underwent OG (OG group, $n=136$). The severity of postoperative morbidities was assessed according to the Clavien–Dindo classification.
Results There were no differences in sex or age between the two groups. Body mass index (21.97 vs 23.19, $P<0.001$) was lower in the LAG group than the OG group. The duration of the postoperative hospital stay was similar between the two groups (9 days each, $P=0.511$). There was no difference in the overall morbidity rate (grade II or higher) between the two groups (LAG group, 7.0 %; OG group, 8.1 %; $P=0.818$). The incidence of grade IIIa or more severe morbidities was also not significantly different between the LAG group (4.7 %) and OG group (2.9 %, $P=0.532$).
Conclusions There was no significant difference in postoperative complication rates between the LAG and the OG groups. The more severe Clavien–Dindo grade III complications, which required surgical interventions, were observed at similar rates between the two groups. Laparoscopic gastrectomy for early gastric cancer is therefore feasible in terms of the incidence and severity of intra-abdominal complications.

Keywords Clavien–Dindo · Morbidity · LAG · Gastric cancer

Introduction

Laparoscopy-assisted gastrectomy (LAG) has been performed increasingly, particularly in Japan and Korea, where the incidence of early gastric cancer is higher than in Western countries. Several advantages of LAG compared to open gastrectomy (OG) have been reported, including less intraoperative bleeding, preserved postoperative respiratory function, early recovery of bowel movements, and better cosmetic results.[1–5]

However, several disadvantages are also associated with LAG, and these include prolonged operation times, technical difficulties, and high costs.[1,2,4] In addition, the safety of LAG is a contentious issue due to the absence of solid evidence from randomized controlled trials. To date, a number of retrospective studies and a few prospective studies have investigated and compared the incidence of postoperative complications following LAG

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with those following OG.[6–11] However, most of these studies adopted their own subjective criteria to assess the postoperative complications, making it difficult to compare the complication rates between the studies.[6,7] The Clavien–Dindo classification uses objective criteria to assess the severity and incidence of postoperative complications. This classification system was first reported in 2004 and validated thereafter.[12,13]

The aim of the present study was to clarify the incidence and the severity of postoperative intra-abdominal complications following LAG using the Clavien–Dindo classification and to compare these with postoperative complications following OG.

Materials and Methods

A total of 287 patients underwent distal gastrectomy or pylorus-preserving gastrectomy with D1+ lymph node dissection for clinical stage IA early gastric cancer at the Shizuoka Cancer Center between June 2009 and December 2011. Fifteen of these patients underwent simultaneous surgery for other malignant diseases and were therefore excluded. Seven patients whose preoperative body mass index (BMI) were 30 or higher were also excluded. The remaining 265 patients were included in the present study.

The patients' characteristics, pathological findings, and surgical findings were collected from our database records and individual patient electronic medical records. The postoperative clinical course of each patient, including the incidence and severity of intra-abdominal infection complications, was collected from individual electronic medical records. Data collection and analysis were approved by the institutional review board of the Shizuoka Cancer Center.

Pathological tumor depth, nodal status, and curability of surgery were assessed according to the International Union Against Cancer (UICC) TNM Classification of Malignant Tumours, seventh edition.[14]

Japanese gastric cancer treatment guidelines 2010 was used to designate the degree of lymph node dissection.[15,16]

Indications for LAG and OG

A distal or pylorus-preserving gastrectomy with D1+ lymph node dissection was performed if patients had clinical stage IA early gastric cancer located lower two-thirds of the stomach, which did not fulfill the criteria for endoscopic submucosal dissection.[15,16] LAG was not indicated for patients with a BMI over 30.0 throughout the study period; thus, all patients with a BMI over 30.0 underwent OG irrespective of their preferred approach.

Surgical Approaches for Patients with Early Gastric Cancer

Between June 2009 and March 2010, the surgical approach (open or laparoscopy) used to treat early gastric cancer was determined by the patient's preference. After preoperative examinations, surgeons explained the advantages and disadvantages of both LAG and OG, leaving the patients to decide on the surgical approach. During this period, 88 patients underwent distal or pylorus-preserving gastrectomy for early gastric cancer. A total of 41 patients chose open surgery and 47 patients chose laparoscopic surgery.

After April 2010, a randomized controlled trial comparing LAG and OG was undertaken in Japan (JCOG 0912 trial); thus, patients who fulfilled the inclusion criteria and agreed to participate in the study were randomly assigned to undergo LAG or OG (62 patients). Otherwise, patients chose the surgical approach they preferred (115 patients). During this period, 95 patients underwent open surgery and 82 patients underwent laparoscopic surgery.

All open surgeries were performed or supervised by one of five experienced surgeons in our institute, each of whom had performed more than 200 cases of open gastrectomy before the study period. Of these five surgeons, two also had much experience of laparoscopic surgery (more than 100 cases of LAG before the study) and had board certification by Japanese Society of Endoscopic Surgery. In this study, all laparoscopic surgeries were performed or supervised by one of these two board-certified surgeons.

Definition of Postoperative Intra-abdominal Complications

The postoperative intra-abdominal complications assessed in this study included pancreas-related infections, postoperative bleeding, anastomotic leakage, anastomotic stenosis, bowel obstruction, and wound infections observed within 30 days after the surgery.

The Clavien–Dindo classification was adopted to grade the severity of the postoperative intra-abdominal complication for each patient. According to the Clavien–Dindo classification, patients were classified as having grade II complications if medical treatment, such as antibiotic administration, was used. Patients were classified as grade IIIa if surgical intervention without general anesthesia was indicated, and classified as grade IIIb if surgical intervention under general anesthesia was indicated. If patients required admission to the intensive care unit, they were regarded as having grade IVa (with single organ dysfunction) or IVb (with multiorgan dysfunction) complications. Postoperative mortality was defined as a grade V complication.

In this study, patients with intra-abdominal complications classified as Clavien–Dindo grade II or higher were regarded as having complications. The incidence and grade of each complication was recorded prospectively in medical records.

Comparison of Short-Term Outcomes Between LAG and OG

Of the 265 patients included in the present study, early surgical outcomes were compared between patients who underwent LAG (LAG group, n=129) and those who underwent OG (OG group, n=136).

Statistics

All continuous variables are presented as the median (range). Statistical analyses were performed using Fisher's exact test, the Student's t test, and the Mann–Whitney test. A P value less than 0.05 was considered significant. All statistical analyses were conducted using R Statistics version 2.13.1.

Results

Patient characteristics are shown in Table 1. There were no differences in sex or age between the two groups. The BMI was higher in the OG group than in the LAG group. All patients included in this study had preoperative clinical stage IA early gastric cancer. Surgical findings are indicated in Table 2. Pylorus-preserving gastrectomy was frequently performed in the LAG group although the difference was not statistically significant. Operation times were longer, and there was less intraoperative bleeding in the LAG group compared to the OG group. One patient in the both groups each required perioperative transfusions. The patient in the LAG group required a transfusion for intra-abdominal bleeding, and a re-operation was also required (grade IIIb). The reason for the transfusion in the OG group was intra-abdominal bleeding. The patients recovered well without additional treatment (grade II).

Pathological findings are shown in Table 3 and were not different between the two groups. All surgeries were designated as R0 resections according to the seventh edition of the UICC TNM Classification of Malignant Tumours.

Patient postoperative outcomes are described in Table 4. There was no difference in the duration of the postoperative hospital stay between the two groups. Overall morbidity rates (grade II or higher) were not different between the two groups (LAG group, 7.0 %; OG group, 8.1 %; P= 0.818). The incidence of grade IIIa or more severe morbidities was also not significantly different between the LAG group (4.7 %) and OG group (2.9 %, P=0.532).

Table 1 Patient characteristics

	LAG group	OG group	*P* value
Number of patients	129	136	
Sex (*n*)			
Male	85	91	0.897
Female	44	45	
Age (years)			
Median	64	66	0.692
Range	19-88	33-84	
Body mass index (kg/m^2)			
Median	21.97	23.19	<0.001
Range	6.94–29.81	15.35–29.74	
Preoperative morbidities (*n*)			
Yes	50	62	0.266
No	79	74	
Previous laparotomy (*n*)			
Yes	43	48	0.796
No	86	88	

Discussion

The present study revealed no difference in the postoperative intra-abdominal complication rates between the LAG group and the OG group. In addition, there was no difference in the severity of complications as assessed by the Clavien–Dindo classification between the two groups.

The incidence of postoperative morbidity following laparoscopic gastrectomy has been reported as 4.7–25.3 %.[7,11,17–22] The heterogeneity between studies may be attributed to the differences in patient backgrounds, degree of lymph node

Table 2 Surgical findings of patients

	LAG group	OG group	*P* value
Operative procedure (*n*)			
DG	57	73	0.141
PPG	72	63	
Operation time (min)			
Median	225	202	<0.001
Range	146–400	102–318	
Bleeding (ml)			
Median	30.5	208	<0.001
Range	0–372	16–1,695	
Number of retrieved lymph nodes			
Median	42	45	0.257
Range	26–94	19–108	
Transfusion (*n*)	1	1	0.948

DG distal gastrectomy, *PPG* pylurus-preserving gastrectomy, *TG* total gastrectomy

Table 3 Pathological results of patients

	LAG group	OG group	*P* value
Tumor depth (*n*)			
T1 (m/sm)	118	129	0.470
T2 (mp)	8	4	
T3 (ss)	3	3	
T4 (se/si)	0	0	
Nodal status (*n*)			
N0	114	120	0.472
N1	10	14	
N2	4	1	
N3a	1	1	
N3b	0	0	
Pathological stage (*n*)			
Ia	107	119	0.063
Ib	13	11	
IIa	8	2	
IIb	0	3	
IIIa	0	1	
IIIb	1	0	
IIIc	0	0	
IV	0	0	

dissection, and criteria used to assess the severity of the complications.[7,11,17–22] The same heterogeneity is also observed following open gastrectomy, presumably due to the absence of widely accepted specific criteria to assess postoperative complications.

Table 4 Postoperative clinical course of patients

	LAG group	OG group	*P* value
Postoperative intra-abdominal complications (*n* (%))			
Pancreas-related infection	2 (1.6)	3 (2.2)	1.000
Bleeding	1 (0.8)	1 (0.7)	1.000
Intra-abdominal abscess	3 (2.3)	1 (0.7)	0.359
Anastomotic leakage	2 (1.6)	1 (0.7)	0.614
Anastomotic stenosis	2 (1.6)	1 (0.7)	0.614
Bowel obstruction	1 (0.8)	1 (0.7)	1.000
Wound infection	0 (0)	3 (2.2)	0.248
Severity of complications (*n*)			
Grade II	3 (2.3)	7 (5.1)	–
Grade IIIa	3 (2.3)	3 (2.2)	–
Grade IIIb	1 (0.8)	0 (0)	–
Grade IVa	2 (1.6)	1 (0.7)	–
Grade IVb	0 (0)	0 (0)	–
Grade V	0 (0)	0 (0)	–
Grade II or more severe (*n* (%))	9 (7.0)	11 (8.1)	0.818
Grade IIIa or more severe (*n* (%))	6 (4.7)	4 (2.9)	0.532
Postoperative hospital stay (days)			
Median	9	9	0.511
Range	6–71	6–49	

The Clavien–Dindo classification of surgical complications was first reported in 2004, and its utility has been validated by many reports.[12,13] Recently, the incidence of postoperative complications assessed by the Clavien–Dindo classification following LAG was reported.[20,21,23,24] Jiang et al. reported a 13.3 % overall incidence rate of Clavien–Dindo grade II or higher postoperative complications following LAG. However, the complication rate following OG was unclear in their series.[23] Lee et al. reported no difference in the incidence of postoperative complications assessed by the Clavien–Dindo classification following LAG compared to those following OG. In their series, 72.8 % of patients who underwent LAG had stage IA early gastric cancer and underwent a limited lymphadenectomy, while most patients who underwent OG had advanced disease and received D2 lymphadenectomy.[20] It is possible that the differences in tumor stages and degree of lymph node dissection affected the results. In the present study, therefore, we included patients who underwent distal or pylorus-preserving gastrectomy with D1+ lymph node dissection.

Most studies comparing early surgical outcomes between LAG and OG reported longer operation times and less intraoperative blood loss in the LAG group than in the OG group, and the same results were obtained in the present study.[1,2,4] The quality of lymph node dissection was assessed by comparing the number of harvested lymph nodes, and it is under debate whether the quality of lymph node dissection is identical between both approaches.[1,2,4] In this study, the number of harvested lymph nodes was not different between the groups; thus, we consider laparoscopic approach as feasible in terms of quality of D1+ lymph node dissection.

A surgeon's experience has been reported as being associated with postoperative morbidity and mortality following LAG. Surgeons require 30 to 50 cases to complete their learning curve.[17,25–27] In this study, all laparoscopic surgeries were performed or supervised by board-certified, experienced surgeons; thus, we consider that the surgeons' skill did not affect the results.

Currently, there are two ongoing multicenter randomized trials comparing LAG and OG in Japan and Korea. In the KLASS trial conducted in Korea, no difference in early surgical outcomes including morbidity rate has been reported, although the final results are not yet available.[7] In the KLASS trial, the definition and grade of each complication was not mentioned. A phase II trial in Japan, JCOG 0703, revealed the safety of LAG, and a subsequent randomized controlled trial, JCOG 0912, has already started.[6] In the JCOG 0912 trial, the Clavien–Dindo classification system is being used to assess each complication. The final results of these randomized trials are required to conclude which procedure is best for patients with early gastric cancer in terms of postoperative complications.

The present retrospective study has some limitations. Firstly, patient characteristics were different between the groups, such as BMI. In our institute, laparoscopic surgery had not been indicated in patients with high BMI (>30), and all patients with high BMI (>30) were treated with open gastrectomy; thus, we excluded these patients to minimize the heterogeneity between the groups. However, the median BMI was still higher in the OG group than in the LAG group. It is unclear whether difference in BMI really affected the incidence of intra-abdominal complications.[28–30] Recently, Hiki et al. reported that a high BMI was not necessarily associated with a higher incidence of postoperative complications following LAG.[31] However, possible biases must be taken into account when interpreting the results of the present study. When the final results of the randomized controlled trials become available, the clinical relevance of LAG in the treatment of gastric cancer will become more apparent.

In conclusion, the present retrospective study revealed no significant difference in the postoperative complication rates between the LAG and the OG groups. The more severe Clavien–Dindo grade III complications, which required surgical interventions, were observed at a similar rate between the two groups. Therefore, the use of laparoscopic gastrectomy for the treatment of early gastric cancer is feasible from the viewpoint of the incidence and severity of intra-abdominal complications.

Disclosures We have no conflict of interest to be declared.

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Clinical Trial Note

A Phase II Study of Systemic Chemotherapy with Docetaxel, Cisplatin, and S-1 (DCS) Followed by Surgery in Gastric Cancer Patients with Extensive Lymph Node Metastasis: Japan Clinical Oncology Group Study JCOG1002

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A Phase II trial was initiated in Japan to evaluate the efficacy and safety of preoperative chemotherapy with docetaxel, cisplatin and S-1 for gastric cancer with extensive lymph node metastasis. Patients are eligible to participate in the study if they have para-aortic lymph node metastases (stations no. 16a2/16b1) and/or a bulky lymph node ($\geq$3 cm $\times$ 1 or $\geq$1.5 cm $\times$ 2) along the celiac, splenic, common or proper hepatic arteries or the superior mesenteric vein, while patients with other distant metastases are ineligible. A total of 50 patients will be enrolled over 2.5 years. The primary endpoint is the response rate of the preoperative chemotherapy, which will be assessed based on the Response Evaluation Criteria in Solid Tumors ver. 1.0. The secondary endpoints are %3-year survival, %5-year survival, proportion of patients with R0 resection, proportion of patients who complete the preoperative chemotherapy and surgery, proportion of patients who complete the protocol treatment, pathological response rate and adverse events. This trial was registered at the UMIN Clinical Trials Registry (www.umin.ac.jp/ctr/) as UMIN000006069.

Key words: gastric cancer – extensive lymph node metastasis – preoperative chemotherapy – Phase II

INTRODUCTION

Gastric cancer with extensive lymph node metastasis (ELM) is often unresectable. Furthermore, patients with gastric cancer and ELM often have a poor prognosis, even after an R0 resection. The Stomach Cancer Study Group of the Japan Clinical Oncology Group (SCSG/JCOG) has addressed this problem.

Since 2000, we have performed two Phase II trials (JCOG0001 and JCOG0405) to evaluate the preoperative chemotherapy followed by gastrectomy with D2 plus para-aortic lymph node dissection (PAND) for gastric cancer with ELM. In JCOG0001, the patients received two or three courses of irinotecan (70 mg/m^2 on days 1 and 15) and cisplatin (80 mg/m^2 on day 1), and then underwent surgery.

This study showed a good %3-year survival of 27.0%, but was terminated because of three treatment-related deaths (TRDs) among 55 enrolled patients (1). To develop a safer and more effective treatment, we conducted JCOG0405, in which patients received two or three courses of cisplatin (60 mg/m^2 on day 8) and S-1 (80 mg/m^2 from days 1–21) (CS) as preoperative chemotherapy and then underwent surgery. This study also showed an excellent %3-year survival of 58.8% with no TRD and low toxicity (2). Preoperative chemotherapy with CS is highly promising and is considered the current standard treatment for gastric cancer patients with ELM in SCSG/JCOG.

JCOG9501 demonstrated that prophylactic PAND did not improve survival (3). However, an integrated analysis of JCOG0001 and JCOG0405 showed a greater therapeutic index (multiplication of frequency of lymph nodes metastasis by a 3-year survival rate) (4) of para-aortic lymph node than JCOG9501 even in patients with bulky lymph node without para-aortic lymph node preoperatively (JCOG0001: 4.3, JCOG0405: 12, JCOG9501: 2.7). Therefore, we adopted the same surgical procedure as in previous studies, D2 plus PAND, for all this population.

Recently, the addition of docetaxel to cisplatin and 5-FU was shown to improve the outcome of unresectable or recurrent gastric cancer patients in the USA and Europe (5). In Japan, several Phase I and Phase II trials have been conducted to evaluate a combination of docetaxel, cisplatin and S-1 (DCS) in patients with unresectable or recurrent gastric cancer (6–9). Although neutropenia and febrile neutropenia frequently occurred, the response rate was extremely high in each trial. Among several DCS regimens, we adopted the one used in the Phase II trial at Kitasato University (the Kitasato regimen) because this regimen was shown to have less toxicity and a higher response rate than other regimens. Here, we are conducting a multi-institutional Phase II trial (JCOG1002) to evaluate the efficacy and safety of DCS (the Kitasato regimen) as a preoperative chemotherapy for gastric cancer with ELM. If the efficacy and safety prove to be sufficient, we will conduct a Phase III trial to compare preoperative DCS with the current standard CS.

The JCOG Protocol Review Committee approved this study protocol in June 2011, and this study was activated in July 2011. This trial was registered at the UMIN Clinical Trials Registry (www.umin.ac.jp/ctr/) as UMIN000006069.

PROTOCOL DIGEST OF THE JCOG1002

Purpose

The aim of this study is to evaluate the efficacy and safety of DCS as a preoperative chemotherapy for gastric cancer with ELM.

Study Setting

A multi-institutional (50 specialized centers), single-arm Phase II trial.

Endpoints

The primary endpoint is the response rate to preoperative chemotherapy as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.0. RECIST ver. 1.0 is used instead of ver. 1.1 because we will compare the results with previous studies using the same criteria. The secondary endpoints are %3-year survival, %5-year survival, proportion of patients with R0 resection, proportion of patients who complete the preoperative chemotherapy and surgery, proportion of patients who complete the protocol treatment, pathological response rate and adverse events.

Inclusion Criteria

(i) Histologically proven primary gastric adenocarcinoma
(ii) Contrast-enhanced abdominal computed tomography (CT; 10 mm or less of slice thickness) revealed one or both of the following:
  (a) Para-aortic lymph node metastasis ≥1.0 cm between the upper margin of the celiac artery and the upper border of the inferior mesenteric artery (stations no. 16a2/16b1)
  (b) Bulky lymph nodes (≥3 cm × 1 or ≥1.5 cm × 2) along the celiac, splenic, common or proper hepatic arteries, or the superior mesenteric vein
(iii) Contrast-enhanced thoracic/abdominal/pelvic CT revealed none of the following:
  (a) Mediastinal lymph node metastasis
  (b) Lung metastasis
  (c) Peritoneal metastasis
  (d) Liver metastasis
  (e) Pleural effusion, ascites
  (f) Para-aortic lymph node metastasis other than stations no. 16a2/16b1
  (g) Other distant metastases
(iv) The macroscopic tumor type is neither the Borrmann type 4 nor large (8 cm or more) type 3
(v) No esophageal invasion or an invasion of 3 cm or less
(vi) No gastric stump cancer
(vii) No clinical signs of cervical lymph node or distant metastases
(viii) A staging laparoscopy or laparotomy performed within 28 days revealed negative washing cytology and no peritoneal metastasis
(ix) Aged between 20 and 75 years
(x) An Eastern Cooperative Oncology Group performance status of 0 or 1
(xi) No prior chemotherapy, radiotherapy or endocrine therapy for any malignancies
(xii) No prior surgery for gastric carcinoma except bypass surgery and endoscopic resection
(xiii) Fair oral intake with or without bypass surgery
(xiv) Adequate organ function
(xv) Written informed consent

Exclusion Criteria

(i) Synchronous or metachronous (within 5 years) malignancies other than carcinoma *in situ* or mucosal carcinoma
(ii) Pregnant or breast-feeding women
(iii) Severe mental disease
(iv) Currently treated with systemic steroids
(v) HBs antigen positive
(vi) Currently treated with flucytosine, phenytoin or warfarin
(vii) Iodine allergy
(viii) History of hypersensitivity to docetaxel, cisplatin or polysorbate 80
(ix) Peripheral motor neuropathy or peripheral sensory neuropathy for any reason
(x) Edema of the limbs and trunk for any reason
(xi) Interstitial pneumonia, pulmonary fibrosis or severe emphysema
(xii) Active bacterial or fungal infections
(xiii) History of myocardial infarction or unstable angina pectoris within 6 months
(xiv) Uncontrolled hypertension
(xv) Uncontrolled diabetes mellitus or routine administration of insulin.

TREATMENT METHODS

Preoperative Chemotherapy

Patients receive an infusion of docetaxel (40 mg/m^2/day) and cisplatin (60 mg/m^2/day) on day 1, and take oral S-1 (80 mg/m^2/day) for 2 weeks from days 1–14 followed by a 2-week rest period. Two courses of preoperative chemotherapy are administered unless unequivocal progression or unacceptable toxicities are observed. After the second course, the tumor response and feasibility of R0 resection are evaluated. When possible, the patient undergoes surgery within 56 days (preferably 28 days) after the last S-1 treatment. When R0 resection is considered difficult despite tumor shrinkage after the second course, the patient receives the third course of DCS before surgery.

Preoperative Examinations

Before enrollment, contrast enhanced thoracic/abdominal/pelvic CT (<10 mm slice thickness) and staging laparoscopy (or intra-abdominal exploration during bypass surgery) are mandatory to check the eligibility criteria. After the second or third course of preoperative chemotherapy, patients are evaluated by the following examinations to check the feasibility of the surgery:

(i) Contrast-enhanced thoracic CT
(ii) Contrast-enhanced abdominal/pelvic CT (the same slice width as baseline evaluation)
(iii) Staging laparoscopy is not mandatory
(iv) Tumor marker (CEA, CA19-9)
(v) Adequate organ function.

Surgery

A total or distal gastrectomy with D2 plus PAND is performed. In the total gastrectomy for an upper gastric tumor, the spleen is also removed. Involved adjacent organ(s), if any, is also removed to achieve R0 resection. A laparoscopic gastrectomy is not allowed. If resectable M1 disease (hepatic, peritoneal and/or lymphatic metastases) is found during surgery, it is removed to achieve R0 resection. If R0 resection is impossible, the protocol treatment is terminated. When total gastrectomy with thoracotomy, left upper abdominal exenteration, pancreaticoduodenectomy or Appleby's operation is required to achieve the R0 resection, the protocol treatment is terminated after the operation is completed.

Postoperative Chemotherapy

After the R0 resection, adjuvant chemotherapy with S-1 is initiated within 42 days from surgery. A 6-week course consisting of 4 weeks of daily oral S-1 administration at a dose of 80 mg/m^2/day followed by 2 weeks of rest is repeated during the first year after surgery. If S-1 treatment is not initiated within 12 weeks after surgery for any reason, the protocol treatment is terminated. Even after the R0 resection, if the tumor progressed during the preoperative chemotherapy and histological examination of the resected specimen showed no chemotherapeutic effect, the protocol treatment is terminated and S-1 is not administered.

Follow-up

All enrolled patients are followed for 5 years. Physical and blood examinations are conducted every 3 months for the first 3 years and every 6 months for the last 2 years. An abdominal CT is performed every 6 months for the first 3 years and every year for the last 2 years. Chest X-ray and upper gastrointestinal endoscopy are conducted every year.

Study Design and Statistical Analysis

This trial investigates the efficacy and safety of preoperative DCS followed by gastrectomy with D2 plus PAND and postoperative S-1. The primary endpoint is analyzed after the tumor response of all enrolled patients is evaluated. If this regimen proves promising, a Phase III trial will be designed to evaluate the superiority of preoperative DCS to preoperative S-1 plus cisplatin in terms of overall survival. In this Phase II trial, the sample size is 50 cases, which provides 80% power based on the hypothesis as the expected value of 80% and a threshold value of 65% in the primary endpoint using one-sided testing at a 10% significance level.

INTERIM ANALYSIS AND MONITORING

Interim analysis is not planned. The JCOG Data Center conducts data management, central monitoring and statistical analysis. If the number of TRDs reaches 3 or the number of cases with R1/R2 resection reaches 13, the registration will be suspended unless the JCOG Data and Safety Monitoring Committee approves the continuation of this trial.

PARTICIPATING INSTITUTIONS

Hakodate Goryoukaku Hospital, Iwate Medical University, National Hospital Organization, Sendai Medical Center, Miyagi Cancer Center, Yamagata Prefectural Central Hospital, Tochigi Cancer Center, National Defense Medical College, Saitama Cancer Center, National Cancer Center Hospital East, National Cancer Center Hospital, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, Tokyo Medical and Dental University Hospital, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo Metropolitan Bokutoh Hospital, Kanagawa Cancer Center, Kitasato University School of Medicine, Yokohama City University Medical Center, Niigata Cancer Center Hospital, Nagaoka Chuo General Hospital, Tsubame Rosai Hospital, Toyama Prefectural Central Hospital, Ishikawa Prefectual Central Hospital, Gifu University Hospital, Gifu Municipal Hospital, Shizuoka General Hospital, Shizuoka Cancer Center, Aichi Cancer Center Hospital, Nagoya University School of Medicine, National Hospital Organization Kyoto Medical Center, Osaka University Graduate School of Medicine, Kinki University School of Medicine, Osaka Prefectural Hospital Organization Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka National Hospital, Osaka Medical College, Toyonaka Municipal Hospital, Sakai Municipal Hospital, Kansai Medical University Hirakata Hospital, Kobe University Graduate School of Medicine, Kansai Rosai Hospital, Hyogo College of Medicine, Hyogo Cancer Center, Itami City Hospital, Wakayama Medical University School of Medicine, Shimane University School of Medicine, Hiroshima City Hospital, Hiroshima City Asa Hospital, Fukuyama City Hospital, National Hospital Organization Shikoku Cancer Center, Kochi Health Science Center and Oita University Faculty of Medicine.

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Conflict of interest statement

Mitsuru Sasako and Takeshi Sano state that they have received honoraria from Taiho Pharmaceutical Company for promotion of education and research in 2011.

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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.

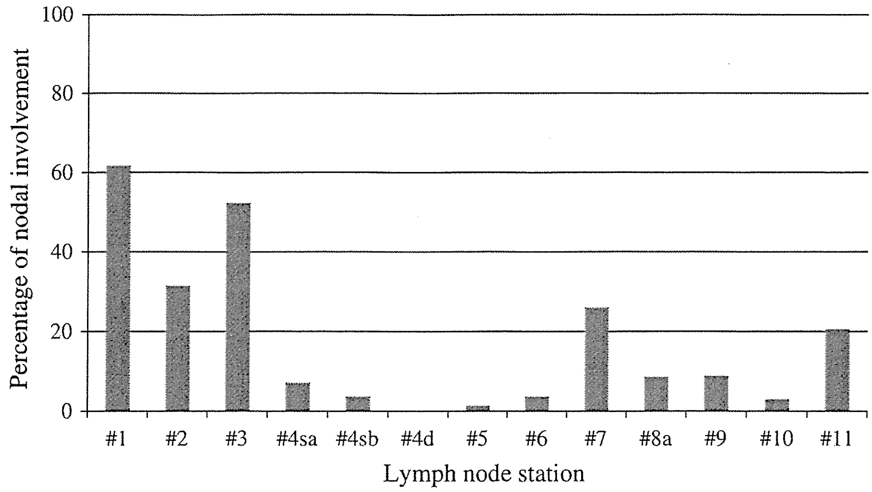

Fig. 1 Frequency of nodal involvement to each abdominal lymph node station for the 86 patients under study. Lymph node stations are classified according to Japanese criteria 17

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 non-beneficial 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.

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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 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