and a reduction in human resources would lead to reduced global cost. Because the ultrasonic scalpel also reduces practice opportunities for assistant surgeons, we will need to develop and implement efficient learning strategies to maximize the experience of young surgeons in the clinical setting.

Conflict of interest The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Overweight is a risk factor for surgical site infection following distal gastrectomy for gastric cancer

Motohiro Hirao · Toshimasa Tsujinaka · Hiroshi Imamura · Yukinori Kurokawa · Kentaro Inoue · Yutaka Kimura · Toshio Shimokawa · Hiroshi Furukawa · Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG)

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Abstract
Background Our objective was to assess the risk factors for surgical site infections (SSIs) in gastric surgery using the results of the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) 0501 phase 3 trial.
Methods The OGSG 0501 trial was conducted to compare standard prophylactic antibiotic administration versus extended prophylactic antibiotic administration in 355 patients who underwent open distal gastrectomy for gastric cancer. Various risk factors associated with the incidence of SSI following gastrectomy were analyzed from the results of this multi-institutional randomized controlled trial.
Results Among the 355 patients, there were 24 SSIs, for an overall SSI rate of 7 %. Multivariate analysis using eight baseline factors (administration of antibiotics, age, sex, body mass index [BMI], prognostic nutritional index, tumor stage, lymph node dissection, reconstructive method) identified that BMI $\geq$25 kg/m^2 was an independent risk factor for the occurrence of SSI (odds ratio 2.82; 95 % confidence interval [CI] 1.05–7.52; $P = 0.049$). BMI also showed significant relationships with the volume of blood loss and the operation time ($P = 0.001$ and $P < 0.001$, respectively).
Conclusion Compared with patients of normal weight, overweight patients had a significantly higher risk of SSI after distal gastrectomy for cancer.

Keywords Overweight · SSI · Gastric cancer · Gastrectomy · Obesity

Introduction

Surgical site infection (SSI) is one of the most common nosocomial infections, accounting for 14–16 % of nosocomial infections overall, and 38 % of nosocomial infections among surgical patients [1]. Previous studies on SSIs have provided feedback to surgeons and healthcare workers, and are important contributors to strategies for reducing the risk of SSI. Several studies concerning SSIs following gastric surgery have been conducted and reported. Prospective trials involving patients undergoing gastrointestinal surgery have reported some factors, such as overweight and hypo-albuminemia, which increase the risk of deep or organ SSI [2, 3].

Previously, we conducted a phase 3 randomized controlled trial (RCT), the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) 0501, to compare standard antimicrobial prophylaxis administration versus extended antimicrobial prophylaxis administration in patients receiving open distal gastrectomy for gastric

M. Hirao (✉) · T. Tsujinaka
Department of Surgery, National Hospital Organization, Osaka National Hospital, 2-1-14 Hoenzaka, Chuou-ku, Osaka 540-0006, Japan
e-mail: hiraom@onh.go.jp

H. Imamura · H. Furukawa
Department of Surgery, Sakai Municipal Hospital, Osaka, Japan

Y. Kurokawa
Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, Osaka, Japan

K. Inoue
Department of Surgery, Kansai Medical College, Osaka, Japan

Y. Kimura
Department of Surgery, NTT West Osaka Hospital, Osaka, Japan

T. Shimokawa
Graduate School of Medicine and Engineering, University of Yamanashi, Yamanashi, Japan

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cancer, and the results concerning the primary and secondary endpoints have been reported [4]. Because the OGSG 0501 trial was based on a single elective surgical procedure performed under uniform conditions, it is worthwhile to analyze the risk factors associated with SSIs following gastrectomy, using the data of the OGSG 0501.

Patients and methods

From June 2005 to December 2007, 355 gastric cancer patients underwent open distal gastrectomy under general anesthesia at multiple institutions. All 355 patients, 174 with Billroth-I reconstruction, 165 with Roux-en-Y reconstruction, and 16 with other methods of reconstruction following gastrectomy were included in the statistical analysis.

We defined SSI according to the surgical patient component of the 1999 Centers for Disease Control and Prevention (CDC) National Nosocomial Infection Surveillance (NNIS) System manual [1, 5, 6]; this definition includes superficial, deep, and organ/space SSIs. The patients were monitored for SSI according to the NNIS criteria until 30 days after the operation at each institution. The definitions of SSI are listed below [4, 5].

Superficial incisional SSI

Infection involves only skin or subcutaneous tissue of the incision and at least one of the following: purulent drainage, with or without laboratory confirmation, from the superficial incision; organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision; and at least one of the following signs of infection: pain or tenderness, localized swelling, redness or heat, and superficial incision that has been deliberately opened by the surgeon, unless the incision is culture-negative.

Deep incisional SSI

Infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision and at least one of the following: purulent drainage from the deep incision but not from the organ or space component of the surgical site; a deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38 °C localized pain, or tenderness, unless the site is culture-negative; or an abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathological or radiological examination.

Organ or space SSI

Infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation and at least one of the following: purulent drainage from a drain that is placed through a stab wound into the organ or space; organisms isolated from an aseptically obtained culture of fluid or tissue in the organ or space; or an abscess or other evidence of infection involving the organ or space that is found on direct examination, during reoperation, or by histopathological or radiological examination.

Risk factors considered in the present study included age, sex, body mass index (BMI), preoperative laboratory data (white blood cell number, lymphocyte number, albumin, and prognostic nutritional index [PNI]), gastric carcinoma stage, and operative characteristics (duration of surgery, operative blood loss, extent of lymph node dissection, operative curability, and method of reconstruction following gastrectomy). According to the World Health Organization classification, BMI $\geq$25 is considered as overweight and BMI <25 as non-overweight [7]. The operation and disease staging were performed according to the guidelines for clinical and pathologic studies in the 13th edition of the *Japanese classification of gastric carcinoma* [8]. PNI was calculated as follows: PNI = 10 $\times$ albumin (mg/dl) + 0.005 $\times$ lymphocyte number (cells/mm^3) [9]. There were no patients who underwent neoadjuvant chemotherapy.

Outline of OGSG 0501, as the original trial

The protocol for the prospective study OGSG 0501 was reviewed and approved by the ethics review board of each participating institution. Eligible patients at each institution participating in the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) provided written consent to participate in the trial, clinical follow up, and data collection. The OGSG 0501 was a multi-institutional RCT to evaluate the optimal duration of prophylactic antibiotic administration in patients initially planned to have distal gastrectomy with D2 lymphadenectomy for gastric cancer. Patients were randomly assigned to either the standard antibiotic prophylaxis group (standard group) or the extended prophylactic antibiotic group (extended group). The standard group received 1 g of cefazolin less than 30 min before the incision and every 3 h intraoperatively. The extended group received 2 g/day of cefazolin on postoperative days 1 and 2 in addition to receiving the same dose as that given to the standard group. The primary endpoint of OGSG 0501 was the incidence of SSIs. Analysis was based on the intention-to-treat principle. The

results concerning the endpoints and other details of the study design have been reported [4].

The OGSG 0501 trial was registered with the University Hospital Information Network (UMIN-CTR) (http://www.umin.ac.jp/ctr/) under identification number UMIN000000631.

Statistical analysis

All enrolled patients were divided into two groups according to whether or not they developed SSI postoperatively. All factors were compared between the two groups by univariate analysis, i.e., the χ^2 test or Fisher's exact test for categorical variables, or a two-sided Mann–Whitney *U*-test for continuous variables.

Multivariate analysis was also performed using a logistic regression model to assess the effects of the factors on SSI. A P value of <0.05 was considered to be statistically significant. Statistical analyses were performed with SPSS version 17.0 (SPSS Japan, Tokyo, Japan).

Results

There were 355 distal gastrectomies (176 patients in the standard group, 179 patients in the extended group) performed as inpatient procedures for gastric cancer (Fig. 1). The baseline patient and operative characteristics are shown in Table 1. The results concerning the detailed patient characteristics can be referred to in the previously reported data [4]

The overall SSI rate for open distal gastrectomy was 7 % (24/355), 5 % (8/176) for the standard group, and 9 % (16/179) for the extended group. Six patients had superficial type SSIs and 18 had organ/space type SSIs. There were no deep SSIs.

Univariate analysis of risk factors for SSI demonstrated that extended administration of antibiotics, male sex, BMI ≥ 25 kg/m^2, and duration of operation >200 min were associated with a higher, but non-significant, incidence of SSIs ($P = 0.105$, $P = 0.098$, $P = 0.158$, and $P = 0.076$, respectively). However, multivariate analysis revealed that only BMI ≥ 25 kg/m^2 was independently associated with an increase in the incidence of SSIs (odds ratio 2.82; 95 % confidence interval [CI] 1.05–7.52; $P = 0.049$) (Table 2). For the risk factors in the multivariate analysis, we included only the baseline factors, because if operative data, such as duration of operation and blood loss, had been added for the analysis, the results would have been confusing.

Subgroup analysis showed that surgery for the patients with BMI ≥ 25 resulted in a larger volume of blood loss and a longer duration of operation when compared with finding in patients with BMI <25 ($P = 0.001$ and $P < 0.001$, respectively) (Table 3).

The relationship between BMI and the type of SSI (superficial or organ/space) was not significant (Table 4).

Discussion

The present study focused on the risk factors for SSI. The risk of SSI after gastric surgery for gastric cancer was

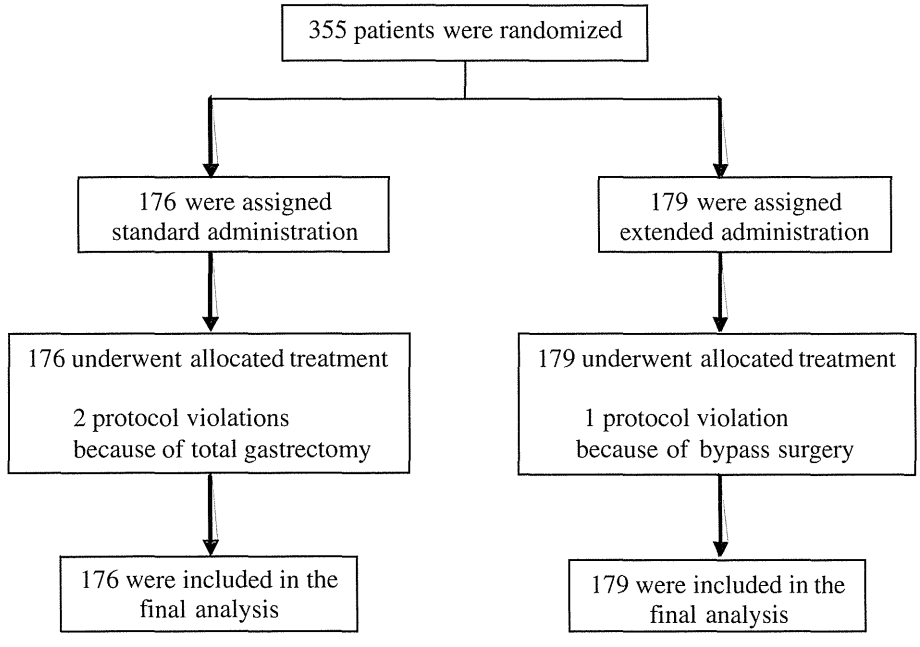

Fig. 1 CONSORT flowchart of Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) 0501 trial. *Administration* administration of antibiotics

statistically evaluated using a logistic regression model. Our data suggest that the risk of SSI depends on whether the patient's BMI is less than 25 or 25 or greater.

Investigators have reported the overall SSI incidence for open distal gastrectomy to be in the range of 10–16 % [3, 10]. The incidence was 7 % in the present study. Watanabe et al. [10] reported a higher incidence of organ/space SSIs than superficial and deep incisional SSIs in gastric surgery.

Table 1 Baseline and operative characteristics of study patients ($n = 355$)

Age (years)[a]	65 (35–84)
Sex, male/female	240/115
BMI (kg/m^2)[a]	22.4 (12.4–33.0)
Stage IA/IB/II/IIIA/IIIB/IV	189/58/47/24/17/20
Antimicrobial prophylaxis administration	
Extended/standard	179/176
White blood cell number (cells/mm^3)[a]	5700 (2890–10800)
Lymphocyte number (cells/mm^3)[a]	1814 (510–4679)
Hemoglobin (mg/dl)[a]	13.4 (7.0–18.4)
Albumin (mg/dl)[a]	4.2 (2.0–5.3)
PNI[a,b]	51.42 (25.1–68.9)
Duration of surgery (min)[a]	204 (58–428)
Operative blood loss (ml)[a]	200 (0–1700)
Lymph node dissection D0/1/2/3	16/96/240/3
Curability R0–1/2	332/23
Reconstruction method BI/BII/RY/other	174/4/165/12

BMI body mass index, *BI* Billroth-I reconstruction, *BII* Billroth-II reconstruction, *RY* Roux-en-Y reconstruction

[a] Values are expressed as medians (ranges)

[b] PNI (prognostic nutritional index) was calculated as follows: PNI = 10 × albumin (mg/dl) + 0.005 × lymphocyte number (cells/mm^3)

However, many investigators have reported that colorectal surgery is more frequently associated with superficial incisional SSIs than with deep incisional or organ/space SSIs [10–12]. Complications specific to gastric surgery with lymphadenectomy, such as pancreatic fistula, may affect the incidence of organ/space SSIs. The difference in thickness between upper and lower abdominal subcutaneous tissues may also affect the incidence of various types of SSIs. In our study, the relationship between BMI and the type of SSI (superficial, deep, and organ/space) was not significant.

The impact of BMI on specific complications after elective abdominal or general surgery, especially colorectal surgery for cancer, has been assessed. SSI is the most common complication after colectomy, and obesity or overweight is thought to increase this risk by 2.5- to 5-fold as compared with patients of normal weight [13–16]. This risk may be related to the decreased oxygen tension in relatively avascular adipose tissue, differences in wound healing, greater wound size, or technical difficulties [13, 17]. However, another report suggests that obesity or overweight is not a risk factor for SSI after colectomy [18].

Recently, risk factors associated with SSI in upper gastrointestinal surgery have been reported. Watanabe et al. [10] reported that in upper alimentary tract surgery, significant relationships were observed between the incidence of SSI and both intraoperative blood loss and combined resection procedures, but BMI was not associated with the incidence of SSI. Imai et al. [19] found, in a retrospective study, that diabetic gastric surgery patients had a 2.7-fold higher risk of SSI as compared with the patients without diabetes, open surgery had a 1.9-fold higher risk of SSI as compared with laparoscopic surgery, and operations lasting for 6 h or longer had a 2.8-fold

Table 2 Univariate and multivariate analysis for the risk of SSI ($n = 355$)

	SSI present ($n = 24$)	SSI absent ($n = 331$)	Univariate logistic	Multivariate logistic	
			P value	Odds ratio (95 % CI)	*P* value
Extended administration of antibiotics	16	163	0.105	1.89 (0.72–4.93)	0.167
Age >65 years	14	173	0.566	1.15 (0.46–2.89)	0.535
Male sex	20	220	0.098	2.22 (0.69–7.09)	0.179
BMI ≥25 kg/m^2	8	69	0.158	2.82 (1.05–7.52)	0.049*
PNI >50	14	169	0.531	3.70 (0.61–22.7)	0.412
Stage >III	4	57	0.945	1.06 (0.29–3.88)	0.516
Lymph node dissection D2 or 3	16	227	0.846	1.08 (0.41–2.85)	0.885
Reconstruction BII or RY	13	156	0.506	1.33 (0.52–3.41)	0.528
Duration of surgery >200 min	17	171	0.076	–	
Operative bleeding >200 ml	15	174	0.349	–	

All factors in the two groups were compared by univariate analysis. Multivariate analysis was performed using a logistic regression model

CI confidence interval, *BII* Billroth-II reconstruction, *RY* Roux-en-Y reconstruction

* *P* value of <0.05 was considered to be statistically significant

Table 3 Relationship between overweight and surgical outcome ($n = 355$)

	BMI <25 ($n = 278$)	BMI ≥25 ($n = 77$)	*P* value
Operative blood loss (ml)			0.001*
<200	143 (51)	23 (30)	
≥200	135 (49)	54 (70)	
Operation time (min)			<0.001*
<200	147 (53)	20 (26)	
≥200	131 (47)	57 (74)	

Compared by χ^2 test. Values in parentheses are percentages

* *P* value of <0.05 was considered to be statistically significant

Table 4 Relationship between BMI and type of SSI ($n = 24$)

	BMI <25 ($n = 16$)	BMI ≥25 ($n = 8$)	*P* value
Type of SSI			0.317*
Superficial	3 (19)	3 (38)	
Organ/space	13 (81)	5 (62)	

Compared by χ^2 test. Values in parentheses are percentages

* *P* value of <0.05 was considered to be statistically significant

higher risk of SSI compared with shorter operations, but high BMI was not associated with the risk of SSI. On the other hand, a prospective trial found that among overweight and hypo-albuminemic patients undergoing gastrointestinal surgery, there was an increased risk of deep/organ SSI [2, 3]. The data from our present multivariate analysis suggested that BMI ≥25 kg/m^2 was independently associated with an increased incidence of SSI after distal gastrectomy for gastric cancer. However, other clinical baseline characteristics (such as PNI), operative characteristics (such as duration of surgery, operative blood loss, lymph node dissection, the method of reconstruction following gastrectomy), and the extended administration of antibiotics had no significant association with the incidence of SSI. Moreover, in our study, because surgery for overweight patients required more time and incurred a larger volume of blood loss, it appeared that the incidence of SSI for overweight patients was higher than that in patients of normal weight. Our data are comparatively reliable and noteworthy, because this study was derived from the data of a phase 3 prospective randomized trial that was based on a single elective surgical procedure performed under uniform conditions

In conclusion, the present study has revealed that, compared with patients of normal weight, overweight patients have a significantly higher risk of SSI after distal gastrectomy for cancer, and the SSIs in overweight patients may not be prevented by the extended administration of antibiotics. Quality improvement initiatives for overweight patients undergoing gastric surgery should focus on the complication of SSI.

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Conflict of interest We declare that we have no conflicts of interest.

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Intraoperative versus extended antimicrobial prophylaxis after gastric cancer surgery: a phase 3, open-label, randomised controlled, non-inferiority trial

Hiroshi Imamura, Yukinori Kurokawa*, Toshimasa Tsujinaka, Kentaro Inoue, Yutaka Kimura, Shohei Iijima, Toshio Shimokawa, Hiroshi Furukawa*

Summary

Background **Although evidence for the efficacy of postoperative antimicrobial prophylaxis is scarce, many patients routinely receive such treatment after major surgeries. We aimed to compare the incidence of surgical-site infections with intraoperative antimicrobial prophylaxis alone versus intraoperative plus postoperative administration.**

Methods **We did a prospective, open-label, phase 3, randomised study at seven hospitals in Japan. Patients with gastric cancer that was potentially curable with a distal gastrectomy were randomly assigned (1:1) to receive either intraoperative antimicrobial prophylaxis alone (cefazolin 1 g before the surgical incision and every 3 h as intraoperative supplements) or extended antimicrobial prophylaxis (intraoperative administration plus cefazolin 1 g once after closure and twice daily for 2 postoperative days). Randomisation was stratified using Pocock and Simon's minimisation method for institution and American Society of Anesthesiologists scores, and Mersenne twister was used for random number generation. The primary endpoint was the incidence of surgical-site infections. We assessed non-inferiority of intraoperative therapy with a margin of 5%. Analysis was by intention-to-treat. During hospital stay, infection-control personnel assessed patients for infection, and the principal surgeons were required to check for surgical-site infections at outpatient clinics until 30 days after surgery. This study is registered with UMIN-CTR, UMIN000000631.**

Findings **Between June 2, 2005, and Dec 6, 2007, 355 patients were randomly assigned to receive either intraoperative antimicrobial prophylaxis alone (n=176) or extended antimicrobial prophylaxis (n=179). Eight patients (5%, 95% CI 2–9%) had surgical-site infections in the intraoperative group compared with 16 (9%, 5–14) in the extended group. The relative risk of surgical-site infections with intraoperative antimicrobial prophylaxis was 0·51 (0·22–1·16), which revealed statistically significant non-inferiority (p<0·0001).**

Interpretation **Elimination of postoperative antimicrobial prophylaxis did not increase the incidence of surgical-site infections after a gastrectomy. Therefore, this treatment is not recommended after gastric cancer surgery.**

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*These authors contributed equally to this work

Department of Surgery, Sakai Municipal Hospital, Osaka, Japan (H Imamura MD, H Furukawa MD); **Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, Osaka, Japan** (Y Kurokawa MD); **Department of Surgery, Osaka National Hospital, Osaka, Japan** (T Tsujinaka MD); **Department of Surgery, Kansai Medical College, Osaka, Japan** (K Inoue MD); **Department of Surgery, NTT West Hospital, Osaka, Japan** (Y Kimura MD); **Department of Surgery, Minoh City Hospital, Osaka, Japan** (S Iijima MD); **Graduate School of Medicine and Engineering, University of Yamanashi, Yamanashi, Japan** (T Shimokawa PhD)

Correspondence to: Dr Yukinori Kurokawa, Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, 2-2-E2, Yamadaoka, Suita, Osaka, Japan **ykurokawa@gesurg.med.osaka-u.ac.jp**

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Introduction

The Centers for Disease Control and Prevention in the USA has issued guidelines that recommend administration of a first-generation cephalosporin for intraoperative antimicrobial prophylaxis to prevent surgical site infections in clean or clean-contaminated operations.[1] This treatment is usually given within 30 min of the first surgical incision, with supplementary treatments every 3 h or 4 h throughout the operation.[2] Results of a large-scale national cohort study in the USA showed that only 14·5% of 32 603 patients who had major surgery had discontinued antimicrobial prophylaxis within 12 h after the surgery ended and that 26·7% of patients were still receiving this treatment at 48 h after surgery.[3] Furthermore, a questionnaire administered to 3823 Japanese surgeons showed that 56·4% of them gave antimicrobial prophylaxis in clean-contaminated operations until 3–4 days after surgery, whereas only 2·4% of surgeons gave the treatment for 24 h or less after surgery ended.[4] Because of a high prevalence of drain use in gastrointestinal surgery in Japan and the potential risk of surgical-site infections, the Japanese Association for Infectious Diseases and the Japanese Society of Chemotherapy developed guidelines that recommend postoperative antimicrobial prophylaxis for 1–3 days after gastrointestinal surgery.[5] However, postoperative antimicrobial prophylaxis is controversial because evidence for its efficacy is scarce.

Gastric cancer is the third leading cause of cancer deaths worldwide and the most common in eastern Asia. Surgery for gastric cancer is usually accompanied by extended lymph node dissection, known as a D2 lymphadenectomy.[6] The Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) did a preliminary multicentre phase 2 trial (OGSG0202)[7] to examine the clinical outcomes when postoperative antimicrobial prophylaxis is not given to patients with gastric cancer. 56 patients who were scheduled to have a distal gastrectomy were registered in this study. Cefazolin was given 30 min before the skin incision and every 3 h during the operation without postoperative antimicrobial prophylaxis. Surgical-site infections were recorded in three patients (5·4%), which was similar to the prevalence in historical controls who had received postoperative antimicrobial prophylaxis (6·7%).[7] After the

phase 2 trial, we designed this multicentre, randomised, phase 3 trial (OGSG0501) to assess non-inferiority of the omission of postoperative antimicrobial prophylaxis in patients with gastric cancer.

Methods

Patients

We enrolled patients who had histologically proven gastric adenocarcinoma that was deemed curable with a distal gastrectomy. Patients were also required to have an American Society of Anesthesiologists (ASA) score of 1 or 2. Patients were excluded from the study if they had an active or uncontrolled infection, received neoadjuvant chemotherapy, or had been given steroids. Seven institutions of the OGSG in Japan participated in the trial. The study protocol was approved by the OGSG Steering Committee and the institutional review boards of all of the participating hospitals. All patients provided written informed consent before randomisation. This study was registered with UMIN-CTR,UMIN000000631.

For the **UMIN-CTR database** see http://www.umin.ac.jp/ctr/

Panel 1: **Definitions of surgical-site infections**[1]

Superficial incisional

Infection occurs within 30 days after the operation and involves only skin or subcutaneous tissue of the incision and at least one of the following:

- purulent drainage, with or without laboratory confirmation, from the superficial incision;
- organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision;
- at least one of the following signs or symptoms of infection: pain or tenderness, localised swelling, redness or heat, and superficial incision is deliberately opened by surgeon, unless incision is culture-negative.

Deep incisional

Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection seems to be related to the operation. The infection involves deep soft tissues (eg, fascial and muscle layers) of the incision and at least one of the following:

- purulent drainage from the deep incision but not from the organ or space component of the surgical site;
- a deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localised pain, or tenderness, unless site is culture-negative;
- an abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathological or radiological examination.

Organ or space

Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection seems to be related to the operation. The infection involves any part of the anatomy (eg, organs or spaces), other than the incision, which was opened or manipulated during an operation and at least one of the following:

- purulent drainage from a drain that is placed through a stab wound into the organ or space;
- organisms isolated from an aseptically obtained culture of fluid or tissue in the organ or space;
- an abscess or other evidence of infection involving the organ or space that is found on direct examination, during reoperation, or by histopathological or radiological examination.

Randomisation and masking

After confirming the eligibility of patients during surgery, surgeons contacted the OGSG data centre by telephone to receive a randomly generated assignment (1:1) placing the patients in one of the treatment groups. We used Pocock and Simon's minimisation method to stratify treatment groups according to institution and ASA scores, and Mersenne twister for random number generation.[8] The surgeon gave the assigned treatment. Interventions were not masked. The OGSG data centre was responsible for assigning the intervention, data management, central monitoring, and statistical analyses.

Procedures

For both groups, the surgeon did distal gastrectomies and lymphadenectomies according to Japanese Gastric Cancer Treatment Guidelines.[9] In short, D1 lymphadenectomy plus suprapancreatic node dissection (D1+β dissection) was done for patients with cT1 tumours, whereas D2 lymphadenectomy was done for patients with cT2–4 tumours. The reconstruction method and the surgical approach (open or laparoscopic) were not prespecified.

1 g of cefazolin was given 30 min after anaesthesia, and an additional dose was given every 3 h during surgery. For the extended antimicrobial prophylaxis group, 1 g of cefazolin was given on postoperative day 0 (at night) and every 12 h until postoperative day 2 (2 g per day for 2 postoperative days). Care before and after surgery and wound management were done according to respective institutional standards.

Operative methods and pathology results were recorded according to the 13th edition of the Japanese Classification of Gastric Carcinoma.[10] The prognostic nutritional index was calculated as: 0·005×lymphocyte count (cells per μL)+10×serum albumin (g/dL).[11] Infection control personnel monitored and detected surgical-site infections during the patient's hospital stay. Principal surgeons were required to check for the presence or absence of surgical-site infections at outpatient clinics until 30 days after surgery. The Centers for Disease Control and Prevention's National Nosocomial Infection Surveillance system was used to diagnose surgical-site infections (panel 1),[1] which were classified as superficial incisional, deep incisional, and organ or space.

Statistical analysis

The primary endpoint was the incidence of surgical-site infections. Secondary endpoints were the incidence of infection at remote sites, the incidence of fever higher than 38°C, body temperature on postoperative day 3, duration of hospital stay after surgery, and severe adverse reactions to antimicrobial prophylaxis.

We intended to recruit 342 patients with a power of 80% for the Dunnet–Gent test at a one-sided α of 0·05 to show non-inferiority of incidence of surgical-site infections. This allowed us to detect a non-inferiority margin of 5% for incidence of surgical-site infections in the intraoperative antimicrobial prophylaxis group with an estimation of a 6·7% incidence of these infections in the extended treatment group. The projected accrual period was 3 years, and no interim analysis was planned.

For secondary endpoints, we compared binary variables with Fisher's exact test, and continuous variables with the Mann-Whitney *U* test. Logistic regression analysis was done to adjust for potential confounding factors, including age, sex, lymphadenectomy, reconstruction method, postoperative cancer stage, body-mass index, prognostic nutritional index, and transfusions. Nine subgroups were also analysed with logistic regression to assess statistical interactions between the treatment and various subgroups. Because of the exploratory nature of subgroup comparisons, test results are reported without multiplicity adjustment of type I error.

Because the study was designed to use a one-sided test, we present one-sided p values for the primary analysis results of the non-inferiority test of surgical-site infections. Two-sided p values were calculated for all other tests. All p values less than 0·05 were judged to be statistically significant. Analysis was by intention-to-treat. Statistical analyses were done with SPSS version 17.0 and R version 2.12.2.

Role of the funding source

This study was funded by OGSG, which is a non-profit organisation established to develop cancer treatment. The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between June 2, 2005, and Dec 6, 2007, 355 patients from seven hospitals were randomly assigned: 176 to receive intraoperative antimicrobial prophylaxis, and 179 to the extended antimicrobial prophylaxis group (figure 1). Two patients underwent a total gastrectomy because they had a positive resection margin, and one had palliative bypass surgery with gastrointestinal anastomosis. All patients received all planned antimicrobial doses and were monitored during their hospital stay and until 30 days after surgery. No severe adverse reactions to antimicrobial prophylaxis occurred in either group.

The patients' characteristics in the two groups were well balanced (table 1). Median body-mass index and median prognostic nutritional index were much the same between the two groups. About 60% of patients in both groups had early (T1) gastric cancer. A D2 or more extended lymphadenectomy was done in 123 patients assigned to the intraoperative antimicrobial prophylaxis group (70%) and in 120 patients assigned to the extended antimicrobial prophylaxis group (67%). The between-group differences in median operation time was 9 min and in median blood loss was 10 mL. 14 patients had laparoscopy-assisted distal gastrectomy.

24 patients had surgical-site infections (table 2), all of whom had undergone distal gastrectomy without protocol violation. The incidence of surgical-site infections was 5% (95% CI 2–9%) in the intraoperative antimicrobial prophylaxis group compared with 9% (5–14%) in the extended antimicrobial prophylaxis group. Intraoperative administration was non-inferior to postoperative treatment (one-sided p<0·0001). On the basis of a multiple logistic regression analysis, the odds ratios (ORs) for surgical-site infections with intraoperative antimicrobial prophylaxis was 0·49 (95% CI 0·20–1·16) before and 0·55 (0·21–1·45) after adjusting for eight variables (age, sex, lymphadenectomy, reconstruction method, postoperative cancer stage, body-mass index, prognostic nutritional index, and transfusions).

Most surgical-site infections involved organ or space, and no deep incisional infections arose (table 2).

We assessed statistical interactions between the treatment effects and patient characteristics, including body-mass index, prognostic nutritional index, and operation time (figure 2). No subgroups showed a decrease in the incidence of surgical-site infections with extended antimicrobial prophylaxis. The OR for surgical site infections with intraoperative antimicrobial prophylaxis was 0·31 (95% CI 0·099–0·998; p=0·050) for patients who were not overweight (body-mass index <25)

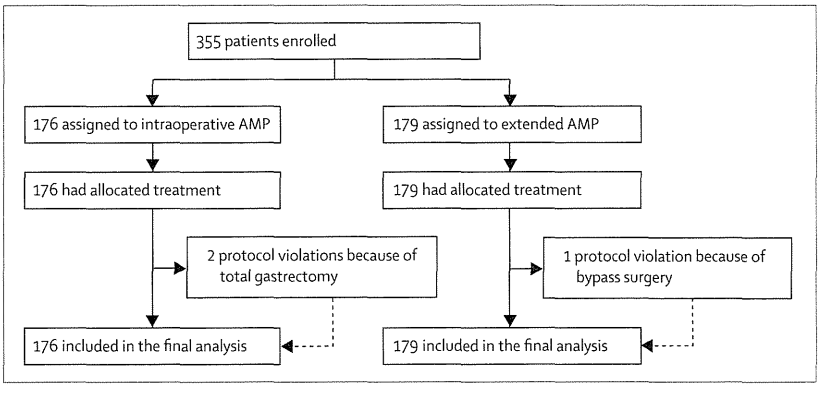

Figure 1: **Trial profile**
AMP=antimicrobial prophylaxis.

	Intraoperative AMP (n=176)	Extended AMP (n=179)
Age (years)	66 (36–84)	65 (35–84)
Sex		
Male	115	125
Female	61	54
Lymphadenectomy		
D1*	53	59
D2–3	123	120
Reconstruction method		
Billroth-I	83	103
Billroth-II	3	1
Roux-Y	90	75
pT stage		
T1	104	111
T2	46	42
T3–4	26	26
pN stage		
N0	114	122
N1	38	36
N2–3	24	21
Body-mass index	22·3 (16·3–33·0)	22·5 (12·4–32·9)
Prognostic nutrition index†	51·1 (25·1–68·9)	51·7 (26·6–66·0)
Approach		
Open	169	172
Laparoscopic	7	7
Anastomotic method		
Hand-sewn	21	34
Autosuture	119	119
Mixed	36	26
Drainage tube		
Yes	157	153
No	19	26
Operation time (min)	209 (58–428)	200 (64–415)
Blood loss (mL)	200 (1–880)	210 (1–1700)
Transfusion		
Yes	0	4
No	176	175

Data are number or median (range). AMP=antimicrobial prophylaxis. pT=primary tumour. pN=lymph node status. *One patient in the extended AMP group who underwent palliative bypass surgery was included in D1. †Data from 28 patients in the intraoperative AMP group and 23 patients in the extended AMP group are missing.

Table 1: **Characteristics of patients**

	Intraoperative AMP (n=176)	Extended AMP (n=179)	Relative risk (95% CI)	p value*
Surgical-site infections	8 (5%)	16 (9%)	0·51 (0·22–1·16)	0·138
Superficial incisional	1 (<1%)	5 (3%)	..	0·215
Deep incisional	0	0	..	..
Organ or space	7 (4%)	11 (6%)	..	0·469
With anastomotic leakage	1	4	..	..
Without anastomotic leakage	6	7	..	..

AMP=antimicrobial prophylaxis. *Two-sided p value for superiority test.

Table 2: **Incidence of surgical-site infections**

and 1·09 (0·25–4·72; 0·91) for patients who were overweight (body-mass index ≥25).

All secondary endpoints were compared between the intraoperative antimicrobial prophylaxis group and extended administration group (table 3). The incidence of remote site infections was 5% (95% CI 2–10) with intraoperative antimicrobial prophylaxis and 3% (1–7) with extended treatment. For remote site infections, two patients had pneumonia or bronchitis and one patient had a urinary tract infection in each group. The incidence of fever higher than 38°C was 34% (27·1–41·6) and 29% (22·5–36·3) in the intraoperative and extended groups, respectively. Median body temperature on postoperative day 3 was about 37°C in both groups and median duration of hospital stay was 12 days with both treatments.

Discussion

Omitting postoperative antimicrobial prophylaxis does not increase the incidence of surgical-site infections in patients with gastric cancer. Extended antimicrobial prophylaxis is associated with greater costs than intraoperative treatment alone because of the use of unnecessary drugs and might increase the risk of adverse drug reactions. Additionally, shortening of the antimicrobial prophylaxis period could help prevent the emergence of resistant strains.[12,13] For these reasons, we do not recommend antimicrobial prophylaxis after gastric cancer surgery.

In a US study, about 60% of patients who had had major surgery were still receiving antimicrobial prophylaxis at 24 h after surgery.[3] Results of a survey of 14 high-volume hospitals in South Korea and Japan showed that at 11 institutions antimicrobial prophylaxis was routinely given for longer than 24 h.[14] Although the national surgical infection prevention guidelines in the USA recommend that this treatment should be discontinued within 24 h of surgery,[15] this approach has not yet been adopted worldwide, because the recommendation is not based on clear evidence. Previously, the standard surgical treatment for gastric cancer was extended D2 lymphadenectomy in eastern Asia,[6,16] but was limited to D0 or D1 lymphadenectomy in the USA and Europe.[17,18] However, in 2010, the European Society for Medical Oncology guidelines for gastric cancer[19] were revised and they now recommend an extended D2 lymphadenectomy as the standard procedure, as in Japanese guidelines. Furthermore, in the latest version (2.2011) of the National Comprehensive Cancer Network Guidelines for gastric cancer, an extended D2 lymphadenectomy was recommended in the USA.[20] Therefore, the question of the appropriate length of antimicrobial prophylaxis after an extended D2 gastrectomy is relevant worldwide.

Mohri and colleagues[21] reported that the incidence of surgical-site infection in gastric cancer surgery was much the same (9·5% *vs* 8·6%) for single-dose and multiple-dose antimicrobial prophylaxis, although their study did not fix the type of surgery and the antibiotics to a single

drug (panel 2). Other retrospective studies have reported incidences of surgical-site infections of 8–12% after a gastrectomy.[23,24] In our phase 3 study, the overall incidence of these infections was 5% in the intraoperative antimicrobial prophylaxis group, which was much the same as the incidence in our previous phase 2 trial (5·4%). The Japanese health system is a suitable setting in which to assess the frequency of surgical-site infections because Japanese institutions allow a long hospital stay after surgery. The median length hospital stay after surgery was 12 days in each group, which enabled infection control personnel to accurately assess the incidence of surgical-site infections for almost half of the follow-up period. Our study required the principal surgeons to check for the presence or absence of surgical-site infections at outpatient clinics until 30 days after surgery. Systematic measurement instruments, which are independent of principal investigators, often result in an underestimation of the incidence of surgical-site infections.[25] Therefore, our results are likely to be an accurate assessment of the frequency of surgical-site infections after a distal gastrectomy.

Several factors such as obesity, malnutrition, transfusions, and operation time increase the incidence of surgical-site infections.[23,26–29] In this study, body-mass index, prognostic nutritional index, and operation time were much the same between the two groups. However, the number of patients who required a transfusion differed between the two groups (none in the intraoperative group and four in the extended group). Of the four patients who received a transfusion, one had an organ or space surgical-site infection after the gastrectomy, which might have led to the unexpected result that the incidence of surgical-site infections was higher in the extended antimicrobial prophylaxis group than in the intraoperative administration group. However, after adjusting for all the potential confounding factors including transfusions by a multivariate analysis, the OR for surgical-site infection with intraoperative antimicrobial prophylaxis was essentially unchanged (0·49 before adjustment *vs* 0·55 after adjustment). An Italian small-scale randomised study[22] that included patients with gastric cancer and colorectal cancer reported that the incidence of surgical-site infections was 16·1% in the intraoperative antimicrobial prophylaxis group and 44·0% in the extended administration group (panel 2). These results and ours suggest that elimination of postoperative antimicrobial prophylaxis might in fact reduce the risk of such infections, although our study was not planned to assess superiority.

The incidence of surgical-site infections in patients who were not overweight (body-mass index <25) was significantly higher in the extended group than in the intraoperative group (p=0·05), whereas the incidence of these infections in patients who were overweight (body-mass index ≥25) was almost same between the two groups (p=0·91). Why postoperative antimicrobial prophylaxis significantly increased the incidence of surgical-site infections in patients who were not overweight is unclear. In the additional analysis in this

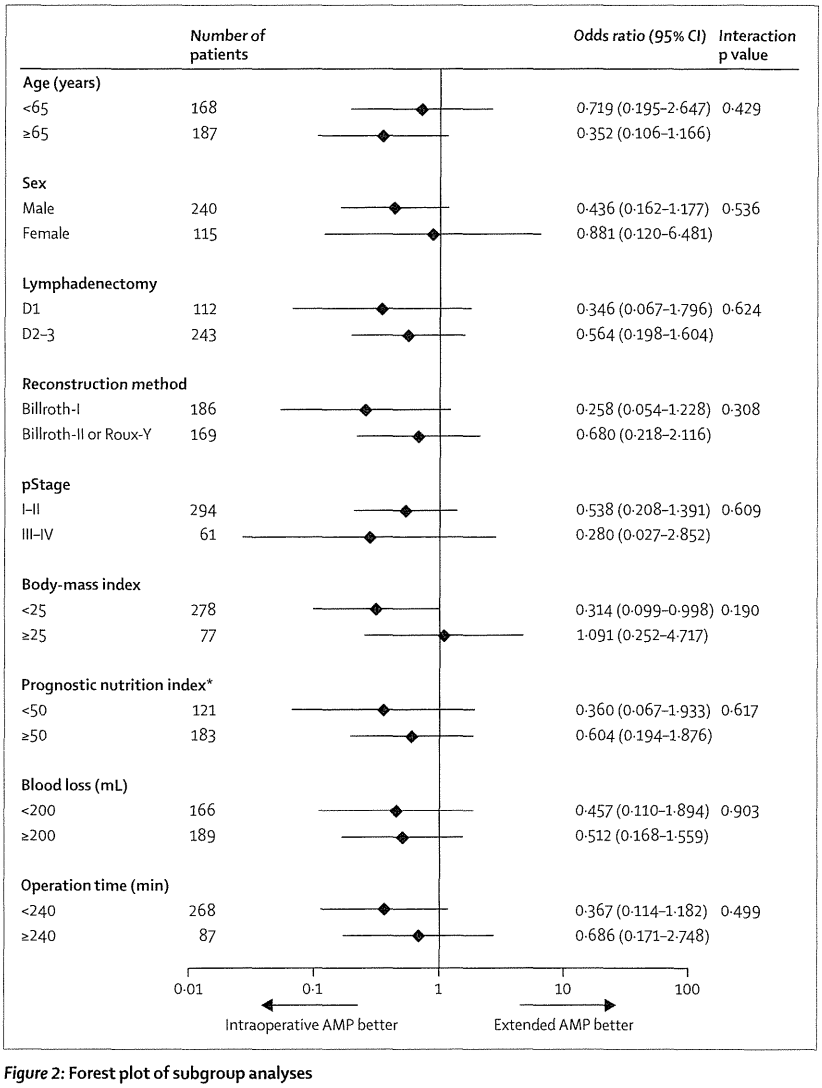

Figure 2: **Forest plot of subgroup analyses**
p values for interactions and odds ratios for surgical-site infections with intraoperative antimicrobial prophylaxis (AMP).*Data for prognostic nutrition index from 51 patients are missing.

	Intraoperative AMP (n=176)	Extended AMP (n=179)	Relative risk (95% CI)	p value
Remote site infections	..	..	1·53 (0·56–4·20)	0·441
Yes	9	6	..	
No	167	173	..	
Fever higher than 38°C	60	52	1·17 (0·86–1·60)	0·361
Body temperature on POD 3 (°C)	37·0 (35·7–40·0)	36·9 (35·3–39·1)	..	0·145
Duration of hospital stay after surgery (days)	12 (7–114)	12 (7–87)	..	0·742

Data are number or median (range) unless otherwise specified. AMP=antimicrobial prophylaxis. POD=postoperative day.

Table 3: **Secondary endpoints**

Panel 2: Research in context

Systematic review

We searched PubMed with the terms "gastric cancer", "surgery", and "antibiotics". Two randomised controlled studies[21,22] including patients with gastric cancer have been reported. A small-scale study in Italy[22] included both patients with gastric cancer and those with colorectal cancer and compared 1-day antimicrobial prophylaxis with clindamycin plus gentamicin to 7-day antimicrobial prophylaxis with ampicillin. A Japanese study compared intraoperative antimicrobial prophylaxis to intraoperative plus postoperative (until 3 postoperative days) treatment with cefazolin or ampicillin-sulbactam.[21] Neither study fixed the type of surgery or the antibiotics to a single agent.

Interpretation

Most of the previous studies used as the basis for the US Centers for Disease Control and Prevention guidelines did not include patients with gastric cancer. Because of absence of strong evidence to show that intraoperative administration of antimicrobial prophylaxis is sufficient to prevent surgical-site infections after D2 gastrectomy, antimicrobial prophylaxis is commonly prescribed for more than 24 h to prevent postoperative complications. Our multicentre study group did a phase 2 study to assess the feasibility of intraoperative antimicrobial prophylaxis alone and to confirm the prevalence of surgical-site infections after distal gastrectomy.[7] This is the first phase 3 study to assess the effectiveness of a fixed regimen for postoperative antimicrobial prophylaxis after distal gastrectomy. Our results show that postoperative antimicrobial prophylaxis is not recommended for patients with gastric cancer even after extended lymphadenectomy.

subgroup, patients who were underweight (body-mass index <18·5) and those of normal weight (body-mass index ≥18·5 and <25) had much the same OR for surgical-site infections (underweight 0·36, 95% CI 0·03–4·50; normal weight 0·29, 0·078–1·08). This result could be a false positive resulting from multiple testing. However, this does not affect the most important findings, which are that extended antimicrobial prophylaxis did not decrease the incidence, even in high-risk subgroups, such as patients with a high body-mass index, low prognostic nutritional index, or long operation time.

Our study included only patients with gastric cancer undergoing a distal gastrectomy. A total gastrectomy is usually associated with greater blood loss and a longer operation time than a distal gastrectomy. Because extended antimicrobial prophylaxis was not beneficial in this study, even in subgroups with a long operation time or much blood loss, we believe that our conclusion can be applied to patients with gastric cancer who are undergoing a total gastrectomy and therefore have a similar microflora in the operative field. However, our findings might not apply to patients who require surgery for other organs such as the colon or hepatobiliary tract because of differences in the microflora in the operative field and the baseline incidence of surgical-site infections.[24,30] Further studies are needed to assess postoperative antimicrobial prophylaxis with surgeries that typically have an increased incidence of surgical-site infections.

In three patients who had protocol violations, no surgical-site infections were recorded. Therefore, per-protocol analysis excluding these three patients gave much the same results as the intention-to-treat analysis. One of the limitations of our study was the absence of blinding. We did not use a placebo in this study, and surgeons and care providers were not masked to treatment allocation. The protocol did not specify that patients should be told about their allocation, so that whether they were masked to their treatment group is uncertain. However, during hospital stay, the assessment of surgical-site infections was done by infection control personnel who were not involved in this study. Therefore, we feel the possibility of a bias in assessment of endpoints is negligible.

Contributors

HI and HF conceived and designed the trial. Data collection and statistical analyses were done by TS. YKu and TT drafted the paper. KI, YKi, and SI revised the paper. All authors approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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ORIGINAL ARTICLE

A comparison of postoperative quality of life and dysfunction after Billroth I and Roux-en-Y reconstruction following distal gastrectomy for gastric cancer: results from a multi-institutional RCT

Shuji Takiguchi · Kazuyoshi Yamamoto · Motohiro Hirao · Hiroshi Imamura · Junya Fujita · Masahiko Yano · Kenji Kobayashi · Yutaka Kimura · Yukinori Kurokawa · Masaki Mori · Yuichiro Doki · Osaka University Clinical Research Group for Gastroenterological Study

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Abstract
Background Both Billroth I (B-I) and Roux-en-Y (R-Y) reconstructions are commonly performed as standard procedures, but it has yet to be determined which reconstruction is better for patients. A randomized prospective phase II trial with body weight loss at 1 year after surgery as a primary endpoint was performed to address this issue. The current report delivers data on the quality of life and degree of postoperative dysfunction, which were the secondary endpoints of this study.

Methods Gastric cancer patients who underwent distal gastrectomy were intraoperatively randomized to B-I or R-Y. Postsurgical QOL was evaluated using the EORTC QLQ-C30 and DAUGS 20.

Results Between August 2005 and December 2008, 332 patients were enrolled in a randomized trial comparing B-I versus R-Y. A mail survey questionnaire sent to 327 patients was completed by 268 (86.2%) of them. EORTC QLQ-C30 scores were as follows: global health status was similar in each group (B-I 73.5 ± 18.8, R-Y 73.2 ± 20.2, $p = 0.87$). Scores of five functional scales were also similar. Only the dyspnea symptom scale showed superior results for R-Y than for B-I (B-I 13.6 ± 17.9, R-Y 8.6 ± 16.3, $p = 0.02$). With respect to DAUGS 20, the total score did not differ significantly between the R-Y and B-I groups (24.8 vs. 23.6, $p = 0.41$). Only reflux symptoms were significantly worse for B-I than for R-Y (0.7 ± 0.6 vs. 0.5 ± 0.6, $p = 0.01$).

Conclusions The B-I and R-Y techniques were generally equivalent in terms of postoperative QOL and dysfunction. Both procedures seem acceptable as standard reconstructions after distal gastrectomy with regard to postoperative QOL and dysfunction.

Keywords Distal gastrectomy · Roux-en-Y · Billroth I · QOL · Randomized trial

S. Takiguchi (✉) · K. Yamamoto · Y. Kurokawa · M. Mori · Y. Doki
Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0876, Japan
e-mail: stakigichi@gesurg.med.osaka-u.ac.jp

M. Hirao
Department of Surgery, Osaka National Hospital, Osaka, Japan

H. Imamura
Department of Surgery, Sakai Municipal Hospital, Osaka, Japan

J. Fujita
Department of Surgery, Toyonaka Municipal Hospital, Osaka, Japan

M. Yano
Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan

K. Kobayashi
Department of Surgery, Kinki Chuou Hospital, Itami, Japan

Y. Kimura
Department of Surgery, NTT West Japan Hospital, Osaka, Japan

Introduction

Both Billroth I (B-I) and Roux-en-Y (R-Y) anastomoses have been performed as standard procedures after distal gastrectomy [1]. B-I was once commonly performed because this procedure was simple and the foods passed physiologically [2]. R-Y reconstruction was chosen to

prevent postoperative alkaline reflux gastritis and esophagitis of the remnant stomach after distal gastrectomy [3–5]. In addition to these problems, some surgeons reported postoperative carcinogenesis of the remnant stomach [6–8]. In contrast, R-Y stasis syndrome, which occurs occasionally during the early postoperative period, is one of the major complications of R-Y reconstruction [9–11]. Most surgeons choose a reconstruction procedure according to personal preferences or degree of experience. It is difficult to select the reconstruction procedure scientifically because few studies have directly compared the B-I and R-Y techniques.

We performed a randomized prospective multicenter trial comparing B-I and R-Y reconstruction. The primary endpoint was a comparison of body weight loss 1 year after surgery. Postoperative quality of life (QOL) was one of the secondary endpoints of the study.

QOL evaluation using questionnaire surveys was once considered to be unreliable because of their subjective nature. However, questionnaires have since been developed and validated as important tools for comprehensively assessing physical conditions. They are now considered to be reliable measurements for evaluating surgical outcomes, especially in randomized clinical trials.

This study is the first to use a questionnaire survey to evaluate QOL and dysfunction following B-I and R-Y reconstructions after distal gastrectomy.

Methods

Study design

This prospective trial was initiated in August 2005. We conducted a multicenter randomized phase II study that was approved by the institutional review boards of all participating hospitals and was conducted in accordance with the Declaration of Helsinki. Our hypothesis was that R-Y reconstruction would result in lower postoperative body weight loss than the B-I technique while maintaining similar surgical results. The primary endpoint was postoperative body weight loss, and secondary endpoints were surgical morbidity and postoperative QOL.

Patients

After completion of the informed consent process, patients were included in the study if they met the following eligibility criteria: histologically proven gastric cancer, a lack of non-curative surgical factors except for positive lavage cytology, age between 20 and 90 years, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, no prior chemotherapy or radiation therapy, and no history of gastrectomy or other malignancy (except carcinoma in situ of uterus cervical cancer and focal cancer in adenoma of colorectal cancer) during the past 5 years. All patients gave written informed consent before undergoing randomization. Exclusion criteria included: 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%), and severe reflux esophagitis. After the surgeon confirmed the above eligibility and exclusion criteria immediately following the initial laparotomy, patients were intraoperatively randomized to either the B-I group or the R-Y group. Randomization was performed by the minimization method according to BMI and institutional preferences.

In our surgical study group, the Osaka University Clinical Research Group for Gastroenterological Study, the standard reconstructive method following 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% following BI operations [12]. In this study we hypothesized that relative to the BI operation, the RY operation may decrease body weight loss at 1 year after surgery by 5%.

The sample size was determined to provide 80% power to detect an effect size of 5% using a one-sided alpha error of 5% under the normal distribution with a standard deviation of 0.1 in both groups. The primary endpoint was evaluated by t test. The planned sample size was 320 patients (160 for each arm), allowing for a 10% dropout rate at the postoperative 1-year point.

Surgical treatment

In both groups, the surgeon performed standard treatment for gastric cancer according to the Japan classification of gastric carcinoma [13]. As a result of this study's design as a multicenter trial, a variety of procedures were employed during reconstructions, including use of mechanical suture devices or hand-sewn techniques, choice of antecolic or retrocolic routes during the R-Y approach, and laparoscopic or open procedures. There were no detailed regulations concerning each reconstruction procedure so as to provide patients with the highest quality of care based on the specific institution in which they were hospitalized. The only requirement was an R-Y limb length of 30 cm, because this length could affect postoperative nutrition and R-Y stasis.

Patients were enrolled from 18 hospitals belonging to the Osaka University Clinical Research Group for Gastroenterological Surgery. All operations were performed or

supervised by senior surgeons who were members of the Japaneses Gastric Cancer Association. Patients were followed up every 3 or 6 months until 5 postoperative years. Adjuvant therapy was not specified in the protocol.

Assessment of QOL

The European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30) (Japanese version) is a 30-item cancer-specific integrated system for assessing the health-related QOL of cancer patients [14–16]. The questionnaire comprises five scales related to function (physical role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health and QOL scale, and single items for the assessment of additional symptoms commonly reported by cancer patients (e.g., dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea), and perceived financial impact of the disease and treatment. All items are scored using 4-point Likert scales. All scales were linearly transformed to a 0 to 100 score, with 100 representing the best global health status or functional status or the worst symptom status.

Assessment of postoperative dysfunction

The Dysfunction After Upper Gastrointestinal Surgery for Cancer (DAUGS 20) scoring system was to assess postoperative dysfunction. The DAUGS 20 has previously undergone extensive development and testing [17, 18], and was originally developed for simultaneous use with the EORTC QLQ-C30. The patients rated 20 items related to postoperative gastrointestinal dysfunction according to a scale of 1 (not at all) to 5 (very severe). High scores indicated more severe dysfunction. The 20 items were divided into the following 7 categories: (1) diarrhea or soft feces, (2) pain, (3) dumping-like symptoms, (4) food passage dysfunction, (5) nausea and vomiting, (6) decreased physical activity, and (7) reflux symptoms.

Questionnaire survey

A self-administered questionnaire that included the EORTC QLQ-C30 and DAUGS 20 was dispatched by mail 3 months after the last case had been registered. The patients completed the questionnaire and returned it by mail to the clinical study register center. Because this questionnaire survey was not administered by a primary care doctor, bias was minimized.

Statistical analysis

Stastical analysis was performed with the JMP stastical package, version 8 (SAS, Cary, NC, USA). Data are expressed as means ± SD. Total scores for the EORTC QLQ-C30 and DAUGS 20 were compared between the two groups using the Mann–Whitney test. p values of less than 0.05 were considered significant.

Results

Questionnaire, compliance, and missing data

A CONSORT flowchart of the trial design is shown in Fig. 1. A total of 332 adult patients (220 men and 112 women) with gastric cancer were enrolled: 163 in the B-I group and 169 in the R-Y group. Five cases were excluded because of errors in which the reconstruction procedure was performed ($n = 3$) or death ($n = 2$). Of the 327 participants, 282 (86.2%) returned the questionnaire sheets. Fourteen cases were excluded from the analysis because of curability C (definite residual tumor) and recurrence ($n = 9$) and ongoing adjuvant chemotherapy ($n = 5$), which would strongly affect postoperative QOL and dysfuntion. Finally, 268 cases (132 B-I, 136 R-Y) were analyzed for the evaluation of postoperative QOL. The median observation period was 21 months (range 3–34). The clinicopathological characteristics of the 268 patients are summarized in Table 1. No significant differences were observed in age, sex, depth of tumor invasion, or stage of gastric cancer. The rates of distant and lymphatic metastasis were also similar. The laparoscopic approach was selected in 29 of 163 patients who underwent B-I reconstruction and 33 of 169 patients who were treated by R-Y. Blood loss did not differ between the two groups. The operative time in the R-Y group was significantly longer than in the B-I group (214 vs. 180 min, respectively, $p < 0.0001$).

EORTC QLQ-C30

The results of global health status and functional scales of EORTC QLQ-C30 are shown in Fig. 2. The mean scores for global health status were very similar in both groups (B-I 73.5 ± 21.3, R-Y 73.2 ± 20.2, $p = 0.87$). As for the functional scales, B-I was not significantly superior to R-Y on only the cognitive scale (B-I 80.3 ± 18.1, R-Y 75.7 ± 21.3, $p = 0.06$). There were no significant differences between the two groups on the other four functional scales (physical, role, emotional, and social functioning). The results of symptom scales of EORTC QLQ-C30 are shown in Fig. 3. Regarding symptom scales, B-I was significantly inferior to R-Y on the dyspnea scale (B-I 13.6 ± 17.9, R-Y 8.6 ± 16.3, $p = 0.02$). There were no significant differences on the other eight symptom scales (fatigue, nausea and vomiting, pain, insomnia, appetite loss, constipation, diarrhea, financial difficulties).

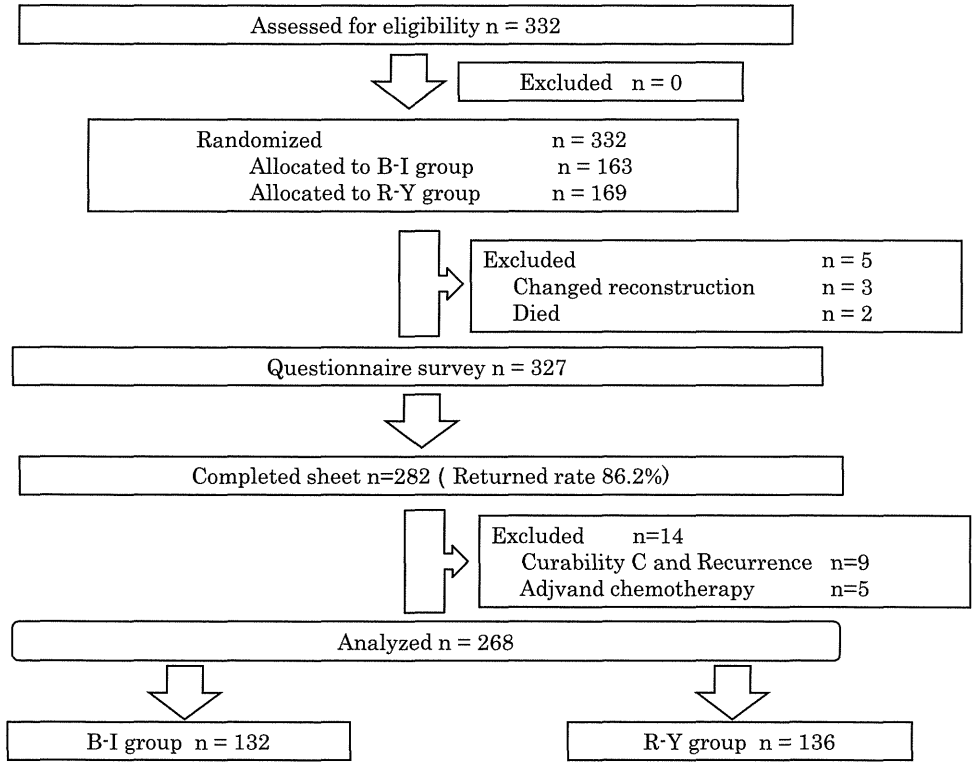


Fig. 1 Consort flow chart

Table 1 Characteristics and operative results of patients who underwent distal gastrectomy and answered the questionnaire survey

	B-I group (n = 132)	R-Y group (n = 136)	p
Sex (male/female)	105/58	113/53	0.48*
Age	64.5 ± 9.8	64.1 ± 10.5	0.68†
Height (cm)	161.3 ± 8.3	161.1 ± 9.7	0.89†
Weight (kg)	58.3 ± 9.7	59.5 ± 11.3	0.29†
Macroscopic appearance (0/1/2/3/5)	98/5/17/9/3	100/8/13/14/1	0.50**
Location (L/M)	92/40	91/45	0.62*
Tumor size (cm)	2.9 ± 1.7	2.9 ± 1.5	0.93*
Approach (open/laparoscopic)	134/29	136/33	0.68*
Dissection level (D1+/D2/D3)	58/105/0	59/106/1	0.61*
Operation time (min)	180 ± 48	214 ± 44	<0.0001†
Blood loss (ml)	210 ± 230	203 ± 153	0.78†
m/sm/mp/ss/se	48/54/15/11/4	45/57/17/13/4	0.98**
pN (−/+)	107/25	104/32	0.35*
pStage (IA/IB/II/IIIA/IIIB/IV)	91/24/15/2/0/0	90/24/14/6/1/1	0.43**

Clinical findings and staging classifications are described according to the Japanese Classification of Gastric Carcinoma

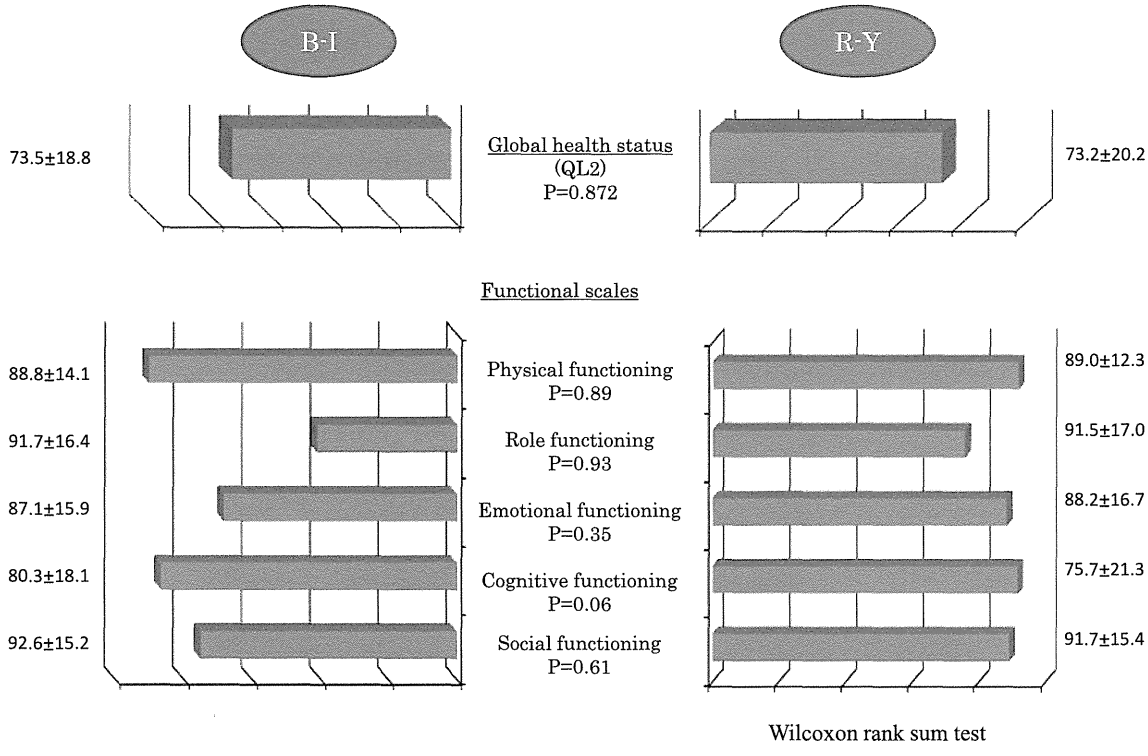
* χ^2 test

** Mann-Whitney U test

† Wilcoxon rank sum test

DAUGS 20 scoring system

The results of the DAUGS 20 score are shown in Fig. 4. The total score of the DAUGS 20 was very similar in both groups (B-I 24.8 ± 11.6, R-Y 23.6 ± 11.4, $p = 0.41$). Subclass analysis showed that B-I was significantly worse in terms of reflux symptoms (B-I 0.7 ± 0.6, R-Y 0.5 ± 0.6, $p = 0.01$). There were no significant differences between the two groups in terms of the other six subclasses: diarrhea or soft feces (B-I 2.1 ± 1.3, R-Y 2.0 ± 1.2, $p = 0.7$), pain (B-I 1.1 ± 0.9, R-Y 1.2 ± 0.9, $p = 0.64$), dumping-like syndrome (B-I 1.8 ± 1.0, R-Y 1.8 ± 1.0,



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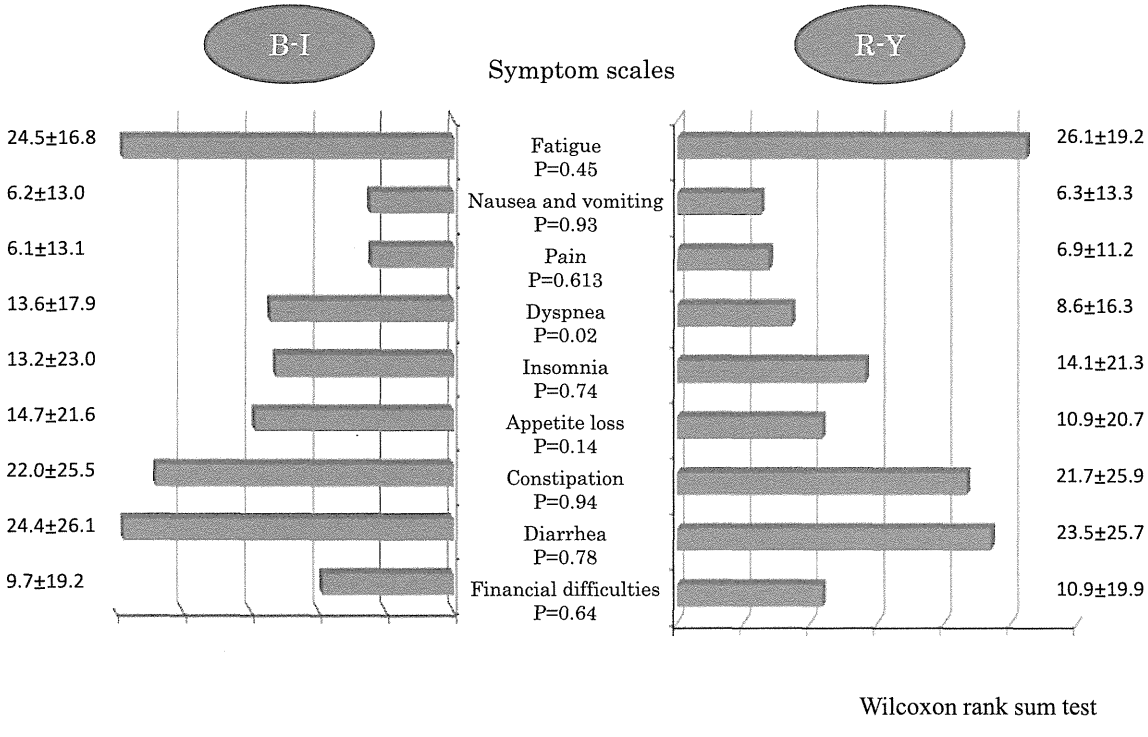

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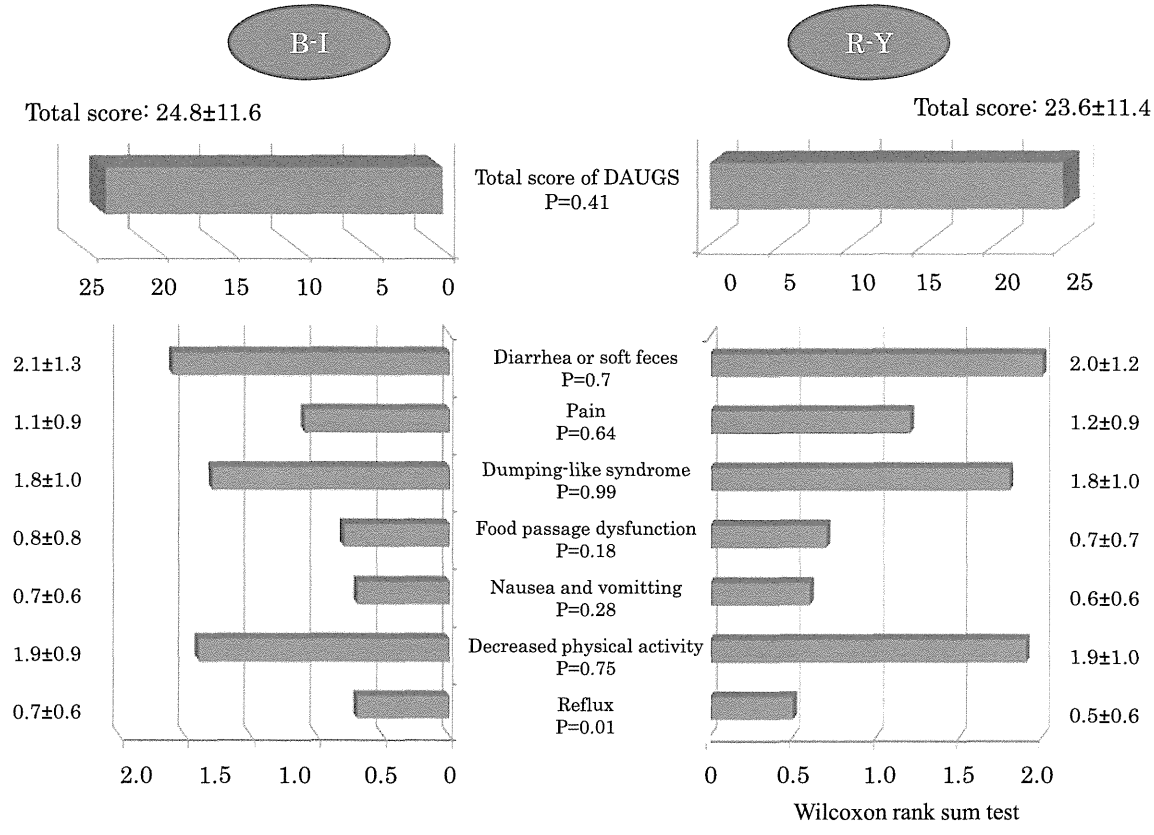

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$p = 0.99$), food passage dysfunction (B-I 0.8 ± 0.8, R-Y 0.7 ± 0.7, $p = 0.18$), nausea and vomiting (B-I 0.7 ± 0.6, R-Y 0.6 ± 0.6, P = 0.28), and decreased physical activity (B-I 1.9 ± 0.9, R-Y 1.9 ± 1.0, $p = 0.75$).

Comparison of survey scores every 6 months

The global health status scores and total DAUGS 20 scores were summarized every 6 months (Fig. 5). There were significant differences in total DAUGS 20 scores during the first 6 months (B-I 22.8 ± 13.7, R-Y 32.4 ± 8.9, $p = 0.04$). There was no significant difference in global health status and total DAUGS 20 scores at other periods between the B-I group and the R-Y group.

Discussion

This prospective randomized trial showed no significant differences between the B-I and R-Y groups in terms of postoperative QOL and dysfunction, as evaluated by a questionnaire using the EORTC QLQ-C30 and DAUGS 20 scales. In this study, body weight loss at 1 year after surgery, which was the primary endpoint in this study, was 9.1% for the B-I group and 9.7% for the R-Y group ($p = 0.39$). Body weight change would be related to the QOL and dysfunction. The results of the questionnaire survey did not contradict the results of body weight loss. This study included a larger number of cases than other randomized clinical trials evaluating postoperative QOL and dysfunction after distal gastrectomy. It was particularly interesting that patients in the two groups evaluated their QOL and dysfunction almost equally despite the significant anatomic differences between the reconstruction procedures.

Prognosis or overall survival has been the most important factor when evaluating cancer treatments. Since cancer is now detected more frequently in its early stages and postoperative prognosis has improved, postoperative QOL and dysfunction have come to be acknowledged as important endpoints in addition to oncologic outcomes and safety issues. For example, Kim et al. [19] reported that laparoscopy-assisted distal gastrectomy was superior to conventional open distal gastrectomy in terms of QOL outcomes 3 months after surgery. Precise evaluation of the effectiveness of minimally invasive surgery is difficult; however, if the oncologic outcome is equal between procedures, QOL findings will be useful in deciding on the