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

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

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

Operative Procedure

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

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

Recruitment

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

Endoscopic Examination at 1 Year after Surgery

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

RESULTS

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

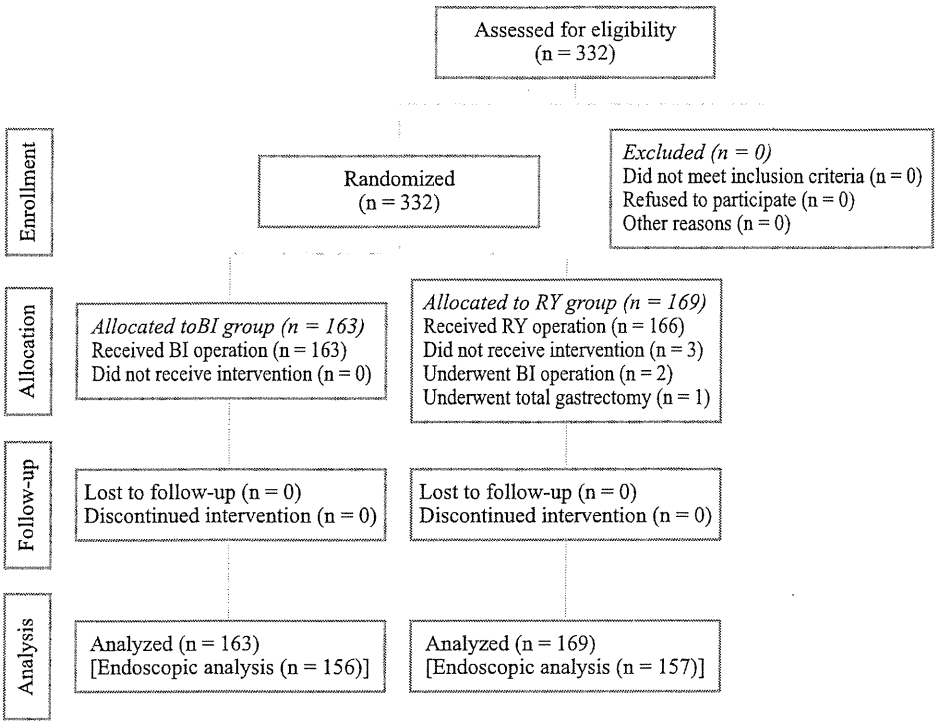

FIG. 1 Study flow chart

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

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

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

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

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

DISCUSSION

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

TABLE 1 Patient demographics, tumor characteristics, and operative details

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

PNI prognostic nutritional index, *BMI* body mass index

[a] χ2test

[b] Wilcoxon rank sum test

[c] Mann–Whitney U test

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

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

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

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

TABLE 2 Postoperative nutritional status 1 year after surgery

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

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

[a] Wilcoxon rank sum test

TABLE 3 Postoperative endoscopic examination results 1 year after surgery

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

LA Los Angeles classification

[a] χ2test

[b] Mann–Whitney *U* test

reconstruction was effective at preventing the bile reflux into the gastric remnant that causes remnant gastritis and general malaise after distal gastrectomy.[5,7] This approach was also demonstrated to improve quality of life and reduce the risk of carcinogenesis in the gastric remnant.[2] In our multi-institutional study, endoscopic examinations at 1 year after surgery demonstrated that remnant gastritis was significantly less severe in the RY group compared to the BI group. Moreover, the number of esophagitis cases categorized as grades B–D, according to the LA classification, was

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

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

Logistic regression model

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

also lower in the RY group. The RY method may have an advantage in reducing the development of oesophageal cancer and Barrett esophagus, because reflux of duodenal contents into the esophagus has been reported to be associated with the genesis of these diseases.[3,4] Moreover, although a choice of reconstruction method may need to be based on the size of remnant stomach to prevent reflux esophagitis, a remnant proportion was strictly regulated in our protocol. Multivariate analysis also revealed that only the reconstructive method was independently associated with the risk of postoperative reflux esophagitis.

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

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

ACKNOWLEDGMENTS The authors thank Dr. Tomoyuki Sugimoto at Osaka University for help with the statistical analysis. Participating institutions and chief participants: Sakai Municipal Hospital (H. Furukawa, H. Imamura), Osaka University (Y. Doki,

S. Takiguchi), Osaka National Hospital (T. Tsujinaka, K. Fujitani), Toyonaka Municipal Hospital (J. Fujita, K. Kawanishi), Osaka Medical Center for Cancer and Cardiovascular Diseases (M. Yano, I. Miyashiro), Kinki Central Hospital of the Mutual Aid Association of Public School Teachers (K. Kobayashi), NTT West Osaka Hospital (Y. Kimura), Yao Municipal Hospital (Y. Fukushima, J. Matsuyama), Hyogo Prefectural Nishinomiya Hospital (H. Yano, H. Taniguchi), Kansai Rosai Hospital (S. Tamura, H. Miki), Ikeda Municipal Hospital (K. Shibata, T. Hirao), Belland General Hospital (K. Demura), SEMPOS Seamen's Insurance hospital (Y. Tsukahara), Saiseikai Senri Hospital (H. Fukunaga), Nishinomiya Municipal Hospital (H. Oka), Suita Municipal Hospital (C. Ebisui, K. Okada), Itami Municipal Hospital (M. Hiratsuka), and Mino Municipal Hospital (S. Iijima, Y. Makari).

REFERENCES

1. Yoshino K. History of gastric cancer surgery. *J Jpn Surg Soc.* 2000;101:855–60.
2. Taylor PR, Mason RC, Filipe MI, et al. Gastric carcinogenesis in the rat induced by duodenogastric reflux without carcinogens: morphology, mucin histochemistry, polyamine metabolism, and labeling index. *Gut.* 1991;32:1447–54.
3. Fein M, Peters JH, Chandrasoma P, et al. Duodenoesophageal refluxinduces esophageal adenocarcinoma without exogenous carcinogen. *J Gastrointest Surg.* 1998;2:260–8.
4. Goldstein SR, Yang GY, Curtis SK, et al. Development of esophageal metaplasia and adenocarcinoma in a rat surgical model without the use of a carcinogen. *Carcinogenesis.* 1997;18: 2265–70.
5. Fukuhara K, Osugi H, Takeda N, et al. Reconstructive procedure after distal gastrectomy for gastric cancer that best prevents duodenenoesophageal reflux. *World J Surg.* 2002;26:1452–7.
6. Mathias JR, Fernandez A, Sninsky CA, et al. Nausea, vomiting, and abdominal pain after Roux-en-Y anastomosis: motility of the jejunal limb. *Gastroenterology.* 1985;88:101–7.
7. Kojima K, Yamada H, Inokuchi M, et al. A comparison of Roux-en-Y and Billroth-I reconstruction after laparoscopy-assisted distal gastrectomy. *Ann Surg.* 2008;247:962–7.
8. Ishikawa M, Kitayama J, Kaizaki S, et al. Prospective randomized trial comparing Billroth-I and Roux-en-Y procedures after distal gastrectomy for gastric cancer. *World J Surg.* 2005;29: 1415–20.
9. Montesani C, D'Amato A, Santella S, et al. Billroth-I versus Billroth-II versus Roux-en-Y after subtotal gastrectomy. Prospective randomized study. *Hepatogastroenterology.* 2002;49: 1469–73.
10. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma. 13th edition. Tokyo: Kanehara; 1999.
11. Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut.* 1999;45:172–80.
12. Demas GE, Drazen DL, Nelson RJ, et al. Reductions in total body fat decrease humoral immunity. *Proc R Soc B Biol Sci.* 2003;270: 905–11.
13. Marinho LA, Rettori O, Vieira-Matos AN, et al. Body weight loss as an indicator of breast cancer recurrence. *Acta Oncol.* 2001;40: 832–7.
14. Tsugane S, Sasaki S, Tsubono Y. Under- and overweight impact on mortality among middle-aged Japanese men and women: a 10-y follow-up of JPHC study cohort I. *Int J Obes Relat Metab Disord.* 2002;6:529–37.
15. Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. *Nippon Geka Gakkai Zashi.* 1984;85:1001–5.
16. Imamura H, Takiguchi S, Yamamoto K, et al. Morbidity and mortality results from a prospective randomized controlled trial comparing billroth I and Roux-en-Y reconstructive procedures after distal gastrectomy for gastric cancer. *World J Surg.* 2012;36: 632–7.
17. Takiguchi S, Yamamoto K, Hirao M, et al. A comparison of postoperative quality of life and dysfunction after Billroth I and Roux-en-Y reconstruction following distalgastrectomy for gastric cancer: results from a multi-institutional RCT. *Gastric Cancer.* 2012;15:198–205.
18. Fujita J, Imamura H, Takiguchi K, et al. Randomized controlled trial comparing Billroth-I and Roux-en-Y reconstruction in distal gastrectomy for gastric cancer. *ASCO GI.* In press.
19. Shinoto K, Ochiai T, Suzuki T, et al. Effectiveness of Roux-en-Y reconstruction after distal gastrectomy based on an assessment of biliary kinetics. *Surg Today.* 2003;33:169–77.
20. Fukuhara K, Osugi H, Takeda N, et al. Quantitative determinations of duodenogastric reflux, prevalence of *Helicobacter pyroli* infection, and concentrations of interleukin-8. *World J Surg.* 2003;27:567–70.

Gastric Cancer (2012) 15:42–48
DOI 10.1007/s10120-011-0058-9

ORIGINAL ARTICLE

Survival benefit of bursectomy in patients with resectable gastric cancer: interim analysis results of a randomized controlled trial

Junya Fujita · Yukinori Kurokawa · Tomoyuki Sugimoto · Isao Miyashiro · Shohei Iijima · Yutaka Kimura · Shuji Takiguchi · Yoshiyuki Fujiwara · Masaki Mori · Yuichiro Doki

Received: 7 February 2011 / Accepted: 18 April 2011 / Published online: 15 May 2011

Abstract
Background Bursectomy is regarded as a standard surgical procedure during gastrectomy for serosa-positive gastric cancer in Japan. There is little evidence, however, that bursectomy has clinical benefit. We conducted a randomized controlled trial to demonstrate non-inferiority of treatment with the omission of bursectomy.
Methods Between July 2002 and January 2007, 210 patients with cT2–T3 gastric adenocarcinoma were intraoperatively randomized to radical gastrectomy and D2 lymphadenectomy with or without bursectomy. The primary endpoint was overall survival (OS). Secondary endpoints were recurrence-free survival, operative morbidity, and levels of amylase in drainage fluid on postoperative day 1. Two interim analyses were performed, in September 2008 and August 2010.
Results Overall morbidity (14.3%) and mortality (0.95%) rates were the same in the two groups. The median levels of amylase in drainage fluid on postoperative day 1 were similar in the two groups ($P = 0.543$). In the second interim analysis, the 3-year OS rates were 85.6% in the bursectomy group and 79.6% in the non-bursectomy group. The hazard ratio for death without bursectomy was 1.44 (95% confidence interval [CI] 0.79–2.61; $P = 0.443$ for non-inferiority). Among 48 serosa-positive (pT3–T4) patients, the 3-year OS was 69.8% for the bursectomy group and 50.2% for the non-bursectomy group, conferring a hazard ratio for death of 2.16 (95% CI 0.89–5.22; $P = 0.791$ for non-inferiority). More patients in the non-bursectomy group had peritoneal recurrences than in the bursectomy group (13.2 vs. 8.7%).
Conclusions The interim analyses suggest that bursectomy may improve survival and should not be abandoned as a futile procedure until more definitive data can be obtained.

Keywords Omental bursectomy · Bursa omentalis · Interim analysis · Gastric cancer

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

Y. Kurokawa (✉) · S. Takiguchi · Y. Fujiwara · M. Mori · Y. Doki
Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, Osaka, Japan
e-mail: ykurokawa@gesurg.med.osaka-u.ac.jp

T. Sugimoto
Department of Biomedical Statistics, Osaka University Graduate School of Medicine, Osaka, Japan

I. Miyashiro
Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka, Japan

S. Iijima
Department of Surgery, Minoh City Hospital, Minoh, Japan

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

Introduction

To accomplish the cure of gastric cancer by surgical treatment it is of prime importance to eliminate all cancer cells from the patient. Total resection of the bursa omentalis has developed as an essential part of radical gastrectomy with extended lymphadenectomy as treatment for advanced gastric cancer in Japan [1, 2]. The operative procedure of bursectomy includes removal of the anterior

membrane of the transverse mesocolon as well as the pancreatic capsule after total omentectomy. The rationale for this procedure is that en-bloc resection of the post-gastric cavity lining, which includes free cancer cells or micrometastases, may reduce the incidence of cancer recurrence [3–5]. According to the Japanese Gastric Cancer Association *Gastric cancer treatment guidelines*, bursectomy is recommended for tumors with invasion of the serosa [6]. In the past few decades, most Japanese surgeons have continued to perform D2 lymphadenectomy with bursectomy as the conventional operation for advanced gastric cancer.

It is apparent, however, that removing the mesocolon and pancreatic capsule is physically detrimental to patients and increases the risk of intraoperative and/or postoperative complications. Some researchers have remained skeptical about prophylactic bursectomy [7–9], as no prospective clinical trial has clarified the benefits or effectiveness of this surgical procedure.

We have conducted a prospective randomized controlled trial with a non-inferiority design to evaluate prophylactic bursectomy for gastric cancer patients. Previously we reported short-term results for the study, which detailed that experienced surgeons could safely perform bursectomy without increasing major surgical complications [10]. Here, we provide a preliminary report on the results of the first and second interim analyses.

Methods

Patients

Eligibility criteria for the study included: (1) histologically proven primary adenocarcinoma of the stomach, (2) a preoperative and intraoperative classification of T2N0, T3N0, T2N1, or T3N1 according to the *Japanese classification of gastric carcinoma, second English edition* [11], (3) a lack of non-curative surgical factors except for positive lavage cytology, (4) no Borrmann type 4 (linitis plastica) cases, (5) no prior chemotherapy or radiation therapy, (6) age 20–80 years with a performance status of 0–2 according to the Eastern Cooperative Oncology Group (ECOG) scale, (7) no history of gastrectomy or other malignancy during the previous 5 years. All patients gave written informed consent before undergoing randomization. The surgeon confirmed the eligibility criteria during surgery and phoned the data center to receive a randomly generated assignment. Patients were then randomized to either the bursectomy group (a D2 gastrectomy with bursectomy) or the non-bursectomy group (a D2 gastrectomy without bursectomy), using the minimization method, according to gender, clinical T stage (cT2 vs. cT3), and gastrectomy (total vs. distal subtotal gastrectomy). The study protocol was approved by the institutional review board at each of the participating hospitals.

Surgery

The surgeons performed a total or distal subtotal gastrectomy and a D2 lymph node dissection as standard treatment for advanced gastric cancers in both groups. In total gastrectomy for T2 or deeper tumor in the proximal third of the stomach, the spleen was removed, in principle, for splenic hilar lymphadenectomy. Pancreatectomy was confined to those patients whose pancreas was involved by tumor. The type of reconstruction and the indication for prophylactic cholecystectomy were not specified in the protocol.

The details of the surgical procedure for bursectomy were described previously [10]. In brief, in the bursectomy group, the peritoneal lining of the bursa omentalis was removed en bloc as much as possible from the anterior plane of the transverse mesocolon and the pancreas. As complete removal of the left side of the bursa omentalis did not allow for a distal subtotal gastrectomy, the pancreatic serosa was removed up to the proximal half of the splenic artery. For the transverse colon mesentery, the peritoneum was removed up to the left gastroepiploic artery. In the non-bursectomy group, only a minimal amount of peritoneum could be removed for lymph node dissection. An omentectomy was performed for both groups in this study.

Patients were enrolled from 11 hospitals belonging to the Osaka University Clinical Research Group for Gastroenterological Surgery. More than 50 gastrectomies were performed every year in these 11 hospitals. All operations were performed or supervised by senior surgeons who were members of the Japanese Gastric Cancer Association. During the planning of the study, all participating surgeons reached an agreement concerning the technical details of bursectomy.

Endpoint evaluations

The primary endpoint was overall survival (OS), defined as the time from randomization to death. Secondary endpoints were recurrence-free survival (RFS), operative morbidity, and levels of amylase in drainage fluid on postoperative day 1. RFS was defined as the time from randomization to either the first event of recurrence or death from any cause. Operative methods and pathology results were recorded according to the *Japanese classification of gastric carcinoma, second English edition* [11]. Hospital mortality was defined as postoperative death of any cause within 30 days, or death within the same hospitalization period as that for the operation. Patients were followed every 3 months until

five years postoperatively. Adjuvant therapy was not permitted before the recurrence of cancer.

Statistical considerations

For the non-inferiority design, one-sided log-rank test with a non-inferiority margin was used in order to show statistically that the hazard rate of the non-bursectomy group was no less than that of the bursectomy group. We planned initially to recruit 200 patients, with an α error of 0.1 and statistical power of 80%. This allowed for detecting a hazard ratio with a non-inferiority margin of 1.56 in the non-bursectomy group with the estimation of a 60% 5-year OS in the bursectomy group. The projected accrual period and follow-up period were 3 and 5 years, respectively. The required sample size was calculated by a simulated-based approach with 100,000 replications to obtain a reasonable size, because a more conventional approach (for example, Freedman's formula) tends to overestimate the sample size as the hazard ratio margin is more greatly separated from one when there is a high censoring rate. After the registration of 204 patients, we amended the sample size and analysis to correct the estimation of 5-year OS in the bursectomy group as 75% and to reduce the α error. The amended sample size was 464, with an α error of 0.05, statistical power of 80%, and a hazard ratio non-inferiority margin of 1.50, with a 8-year accrual period (in total) and 5-year follow-up. The hazard ratio margin was designed as corresponding to a non-inferiority margin of 10% in 5-year OS.

Differences in proportions between the two groups were evaluated using Fisher's exact test or the χ^2 test. Differences in continuous variables, including age and tumor size, between the two groups were tested with the Mann–Whitney *U*-test. Data from all eligible patients were analyzed for OS and RFS on an intention-to-treat basis. Survival curves were estimated by the Kaplan–Meier method and compared using the log-rank test. Hazard ratios were calculated by Cox regression analysis without adjustment for stratification factors. Two-sided *P* values were used for testing superiority, because our interest in superiority was whether the two groups were different regardless of the direction of the difference, and hence two-sided tests were used as usual. However, one-sided *P* values were used for testing non-inferiority, because one-sided tests were performed following the study design for non-inferiority. All non-inferiority tests were conducted using the handicap log-rank test setting the hazard ratio non-inferiority margin of 1.50. All *P* values were reported as statistically significant if $P < 0.05$, to provide conventional interpretation of results. Statistical analysis was performed using SPSS Statistics software, version 17.0 (SPSS, Chicago, IL, USA) and the R programming language.

Interim analysis

In January 2007, a large-scale randomized controlled trial evaluating the efficacy of adjuvant S-1 chemotherapy for stage II/III gastric cancer patients reported positive results [12]. Since then, adjuvant S-1 chemotherapy has been the new standard treatment for stage II/III gastric cancer in Japan. As our study did not permit adjuvant treatment, including S-1 chemotherapy, we decided to close accrual of our study in January 2007.

Although the interim analysis was not initially planned, the steering committee of this study proposed interim analyses to examine survival and to provide early release of the results, because the time to definitive analysis (5 years) was very long. The data and safety monitoring committee of the Osaka University Clinical Research Group for Gastroenterological Surgery approved the interim analyses with the conditions of Korn's criteria for preliminary data release in randomized clinical trials of non-inferiority [13]. After confirmation of all conditions in Korn's criteria, interim analyses were performed in September 2008 and August 2010. The final analysis of survival data is scheduled for 2012.

Results

Between July 2002 and January 2007, 210 patients were randomized to either bursectomy (104 patients) or non-bursectomy (106 patients) (Fig. 1). Patient characteristics were well balanced between the two groups (Table 1). Total gastrectomy was performed for 22 patients (21.2%) in the bursectomy group and 27 patients (25.5%) in the non-bursectomy group, while 12 bursectomy (11.5%) and 14 non-bursectomy (13.2%) patients underwent splenectomy. Only one (0.9%) non-bursectomy patient underwent distal pancreatectomy. The reasons for R1 resection were positive lavage cytology, except in one non-bursectomy patient with a positive proximal margin.

As reported previously [10], bursectomy required a longer operative time, with a median added time of 27 min in patients with combined resection and 26 min in patients without combined resection. Intraoperative blood loss was also greater in the bursectomy group (median 475 mL) than in the non-bursectomy group (median 350 mL) ($P = 0.047$), while other surgical factors did not vary significantly. The overall morbidity rate was 14.3% for both groups. The median amylase levels in drainage fluid on postoperative day 1 were similar in the two groups ($P = 0.543$). The hospital mortality rate was 0.95%, with one patient death in each group.

At the time of the first interim analysis in September 2008, 3-year OS was 86.4% for the bursectomy group and

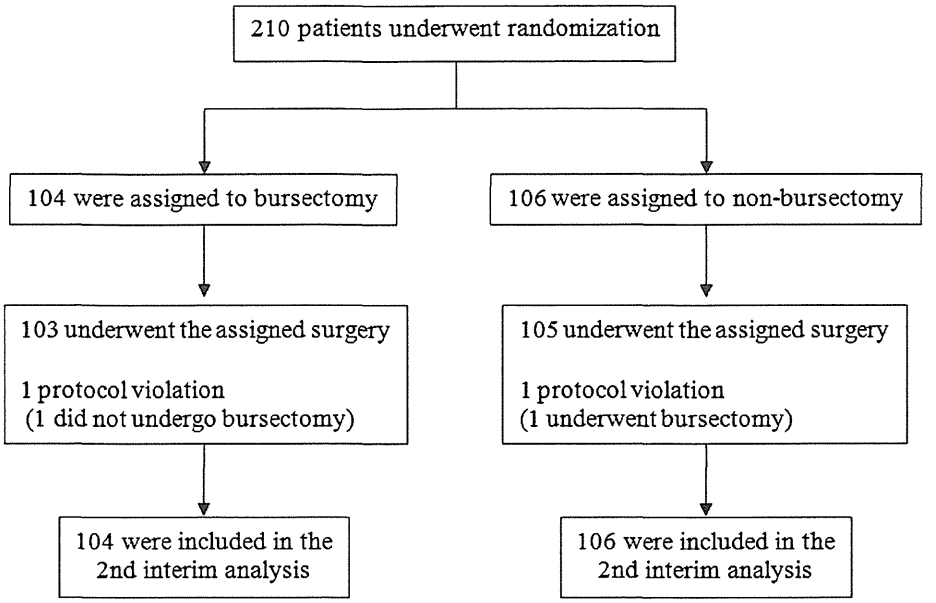

Fig. 1 Distribution of the patients

79.1% for the non-bursectomy group [14]. The hazard ratio for death in the non-bursectomy group was 1.55 (95% CI 0.84–2.84; $P = 0.155$ for superiority; $P = 0.540$ for non-inferiority). By the time of the second interim analysis in August 2010, the median patient follow-up was 46 months; there had been 19 deaths in the bursectomy group and 25 deaths in the non-bursectomy group. The 3-year OS remained better in the bursectomy group (85.6%) than in the non-bursectomy group (79.6%) (Fig. 2). The hazard ratio for death in the non-bursectomy group was 1.44 (95% CI 0.79–2.61; $P = 0.232$ for superiority; $P = 0.443$ for non-inferiority).

At the second interim analysis, 24 and 27 recurrences had been recorded in the bursectomy and non-bursectomy groups, respectively. The 3-year RFSs were 77.5 and 75.6% in the bursectomy and non-bursectomy groups, respectively (Fig. 3). The hazard ratio for recurrence in the non-bursectomy group was 1.18 (95% CI 0.68–2.04; $P = 0.563$ for superiority; $P = 0.192$ for non-inferiority). The most frequent site of first tumor recurrence was the peritoneum, as seen in nine patients in the bursectomy group and 14 patients in the non-bursectomy group (Table 2).

We performed a subgroup analysis examining pathological T stage. Among the 162 serosa-negative (pT1–T2) patients, 3-year OS was 90.5 and 88.1% for the bursectomy and non-bursectomy groups, respectively (Fig. 4a). In contrast, among the 48 serosa-positive (pT3–T4) patients, 3-year OS was 69.8% for the bursectomy patients, in contrast to 50.2% for the non-bursectomy group (Fig. 4b). The hazard ratios for death in the non-bursectomy group by pathological stage were 1.15 (95% CI 0.51–2.61; $P = 0.734$ for superiority; $P = 0.263$ for non-inferiority) for serosa-negative patients and 2.16 (95% CI 0.89–5.22; $P = 0.081$ for superiority; $P = 0.791$ for non-inferiority) for serosa-positive patients. Regarding RFS, serosa-negative patients showed similar results in the two groups ($P = 0.673$ for superiority) (Fig. 5a), while serosa-positive patients showed distinct differences in survival between the two groups ($P = 0.086$ for superiority) (Fig. 5b).

Discussion

It has been proposed that prophylactic bursectomy prevents peritoneal recurrences by eliminating cancer cells scattered on the lining of the post-gastric cavity; however, the clinical value of bursectomy has not been demonstrated previously. In our randomized controlled trial, experienced surgeons safely performed D2 gastrectomy with bursectomy without increasing major surgical complications, despite longer operative times and increased intraoperative blood loss [10]. The first and second interim analyses revealed that the bursectomy group had better OS than the non-bursectomy group, although these differences were not statistically significant.

The cavity of the bursa omentalis is not a closed chamber, but opens to the abdominal space through the foramen of Winslow. Yamamura et al. [8] reported that carcinoembryonic antigen or cytokeratin 20 mRNA was detected in peritoneal washes from the bursa omentalis, as well as from the Douglas pouch and the left subphrenic cavity. Resection of the bursa omentalis, the most frequent site of peritoneal seeding from the stomach, may eliminate the majority of cancer cells seeded within the peritoneum [15]. In our study, serosa-positive patients, who have the

Table 1 Patient characteristics

	Bursectomy ($n = 104$)	Non-bursectomy ($n = 106$)	P value
Age (years)			
Median	65	63	0.099
Range	31–79	34–78	
Gender			
Male	73	77	0.761
Female	31	29	
Tumor size (cm)			
Median	4.3	4.5	0.311
Range	0.9–11.0	1.5–12.0	
Clinical T stage			
cT2	61	67	0.572
cT3	43	39	
Clinical N stage			
cN0	59	61	1.000
cN1	45	45	
Pathological T stage			
pT1	17	19	0.902
pT2	62	64	
pT3–4	25	23	
Pathological N stage			
pN0	49	60	0.119
pN1	37	24	
pN2–3	18	22	
Residual tumor			
R0	101	102	1.000
R1	3	4	

The P values for gender, clinical T stage, clinical N stage, and residual tumor were calculated by Fisher's exact test; those for pathological T stage and pathological N stage were calculated by the χ^2 test; and those for age and tumor size were calculated by the Mann–Whitney U-test

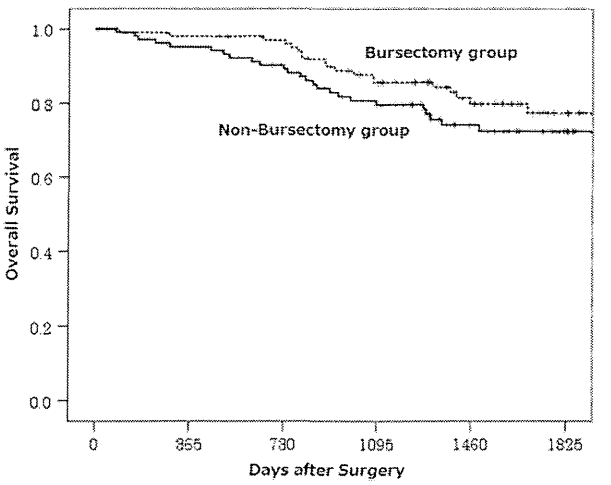

Fig. 2 Overall survival in all patients by treatment group

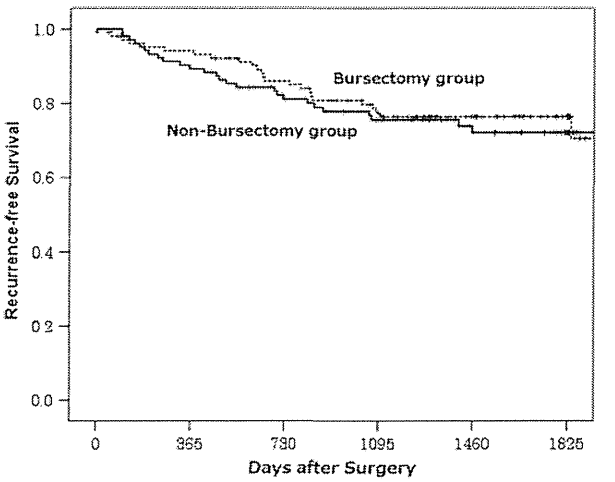

Fig. 3 Recurrence-free survival in all patients by treatment group

highest probability of peritoneal recurrence, displayed differences in 3-year OS of approximately 20% between the two groups. The bursectomy group showed a decreased frequency of peritoneal recurrence, while nodal recurrence occurred at similar rates in the two groups. The total numbers of dissected lymph nodes were similar in the two groups, with a median of 38 (range 11–98) in the bursectomy group and 37 (range 7–97) in the non-bursectomy group [10]. Even those lymph nodes dissected in the operative field of bursectomy, such as No. 6 (infrapyloric), No.14v (along the superior mesenteric vein), and No.8a (along the common hepatic artery), were similar in the two groups (data not shown). These results suggested that the survival benefit of bursectomy was attributable not to more accurate lymphadenectomy, but to the en-bloc removal of free cancer cells or micrometastases contained in the bursa omentalis.

As randomized controlled trials preserve type I and II error rates, the interim results of the trial must be powerful for a data-monitoring committee to stop a trial. The public cannot access data from the interim analyses unless the data meet the criteria for early termination of the study. Because non-inferiority trials often require a long follow-up period for definitive analysis, the early release of the data would be potentially useful to patients who face a treatment decision. Korn et al. [13] suggested that the early release of outcome data could only be done under specific conditions without harming the future conduct of the trial and without being misleading. As the present study satisfied all Korn's conditions, the study steering committee and the data and safety monitoring committee approved the early release of the interim analysis results to the public.

The difference in RFS between the two study groups in our trial was not clear in comparison to that for OS.

Table 2 Site of first tumor recurrence

	Bursectomy (n = 104)	Non-bursectomy (n = 106)
Any site of recurrence	24	26
Peritoneum	9	14
Lymph nodes	7	5
Liver	4	6
Others	4	2

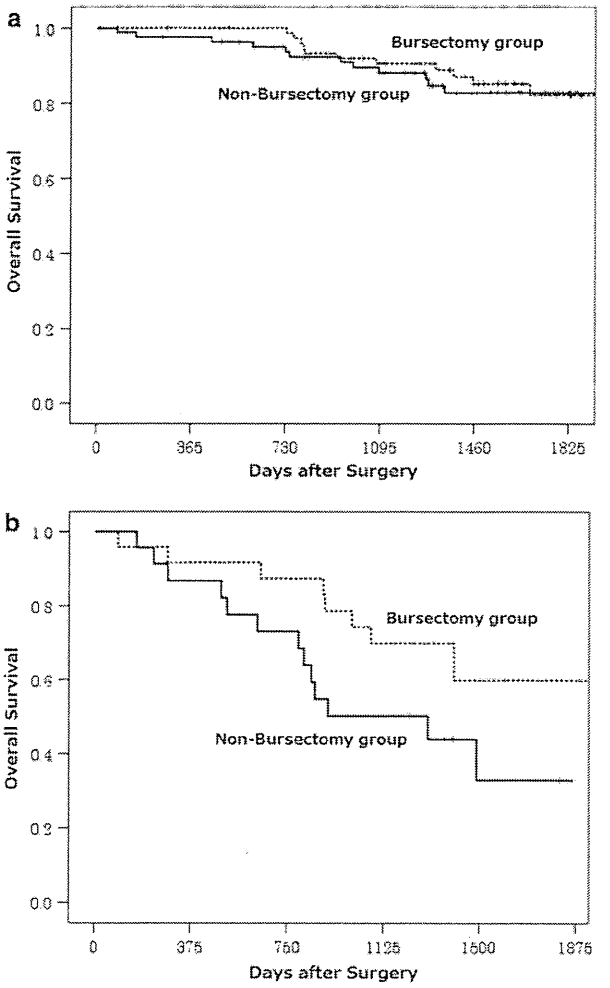

Fig. 4 Overall survival in patients with serosa-negative tumors (**a**) and those with serosa-positive tumors (**b**) by treatment group

In clinical trials of gastric cancer treatments, it is difficult to examine peritoneal recurrence, which is the most frequent pattern of relapse. We therefore focused on the endpoint of OS, not on RFS, in the interim analyses. The number of recurrence events (51 events) was smaller than expected, while the number of deaths (44 events) was similar in frequency to that reported in previous studies. The immature results on recurrence for the interim

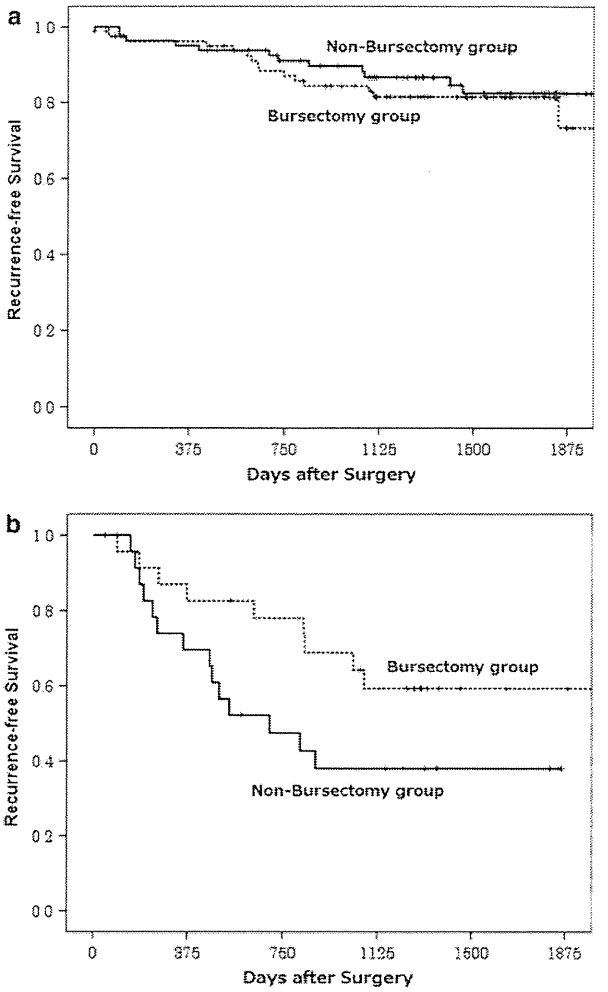

Fig. 5 Recurrence-free survival in patients with serosa-negative tumors (**a**) and those with serosa-positive tumors (**b**) by treatment group

analysis may have provided only small differences in RFS between the two groups. More accurate results concerning RFS will be provided in the final analysis.

This study is the first randomized controlled trial to evaluate omental bursectomy in gastric cancer surgery, although it may be under-powered to provide a definitive conclusion. The interim analyses suggest that bursectomy may improve survival in gastric cancer patients and should not be abandoned as a futile procedure until more definitive data can be obtained. The Japan Clinical Oncology Group (JCOG) is now conducting a large-scale randomized controlled trial (JCOG1001) with the recruitment of 1000 patients with cT3–T4 tumors to confirm the superiority of bursectomy in terms of overall survival.

Acknowledgments The authors would like to thank Professor Kunio Okajima for helpful advice; and Dr. Hiroshi Furukawa, Dr. Toshimasa Tsujinaka, Dr. Chikara Ebisui, Dr. Shigeyuki Tamura,

Dr. Masakatsu Kinuta, and Dr. Norimasa Fukushima for participating in this trial.

References

1. Jinnai D. Theory and practice of the extended radical operation for gastric cancer. Rinsho Geka. 1967;22:19–24. (in Japanese).
2. Maruyama K, Okabayashi K, Kinoshita T. Progress in gastric cancer surgery in Japan and its limits of radicality. World J Surg. 1987;11:418–25.
3. Groves EWH. On the radical operation for cancer of the pylorus, with especial reference to the advantages of the two-stage operation and to the question of the removal of the associated lymphatics. BMJ. 1910;12:366–70.
4. Oglivie WH. Cancer of the stomach. Surg Gynecol Obstet. 1939; 68:295–305.
5. Hagiwara A, Sawai K, Sakakura C, Shirasu M, Ohgaki M, Yamasaki J, et al. Complete omentectomy and extensive lymphadenectomy with gastrectomy improves the survival of gastric cancer patients with metastases in the adjacent peritoneum. Hepatogastroenterology. 1998;45:1922–9.
6. Japanese Gastric Cancer Association. Gastric cancer treatment guidelines. Tokyo: Kanehara; 2004. (in Japanese).
7. Yoshikawa T, Tsuburaya A, Kobayashi O, Sairenji M, Motohashi H, Hasegawa S, et al. Is bursectomy necessary for patients with gastric cancer invading the serosa? Hepatogastroenterology. 2004;51:1524–6.
8. Yamamura Y, Ito S, Mochizuki Y, Nakanishi H, Tatematsu H, Kodera Y, et al. Distribution of free cancer cells in the abdominal cavity suggests limitation of bursectomy as an essential component of radical surgery for gastric carcinoma. Gastric Cancer. 2007;10:24–8.
9. Fujita J, Tsukahara Y, Ikeda K, Akagi K, Kan K, Hata S, et al. Evaluation of omentum preserving gastrectomy for advanced gastric cancer. Jpn Gastroenterol Surg. 2003;36:1151–8. (in Japanese).
10. Imamura H, Kurokawa Y, Kawada J, Tsujinaka T, Takiguchi S, Fujiwara Y, et al. Influence of bursectomy on operative morbidity and mortality after radical gastrectomy for gastric cancer: results of a randomized controlled trial. World J Surg. 2011;35:625–30.
11. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma—2nd English edition. Gastric Cancer. 1998;1:10–24.
12. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med. 2007;357: 1810–20.
13. Korn EL, Hunsberger S, Freidlin B, Smith MA, Abrams JS. Preliminary data release for randomized clinical trials of noninferiority: a new proposal. J Clin Oncol. 2005;23:5831–6.
14. Kurokawa Y, Fujiwara Y, Takiguchi S, Fujita J, Imamura H, Tsujinaka T, et al. Randomized controlled trial of omental bursectomy for resectable cT2–3 gastric cancer. Proc Am Soc Clin Oncol (Gastrointest Cancers Symposium). 2011: #72 (abstr).
15. Hagiwara A, Takahashi T, Sawaki A, Taniguchi H, Shimotsuma M, Okano S, et al. Milky spots as the implantation site for malignant cells in peritoneal dissemination in mice. Cancer Res. 1993;53:687–92.

Gastric Cancer (2012) 15:198–205
DOI 10.1007/s10120-011-0098-1

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

Received: 10 May 2011 / Accepted: 11 September 2011 / Published online: 13 October 2011

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

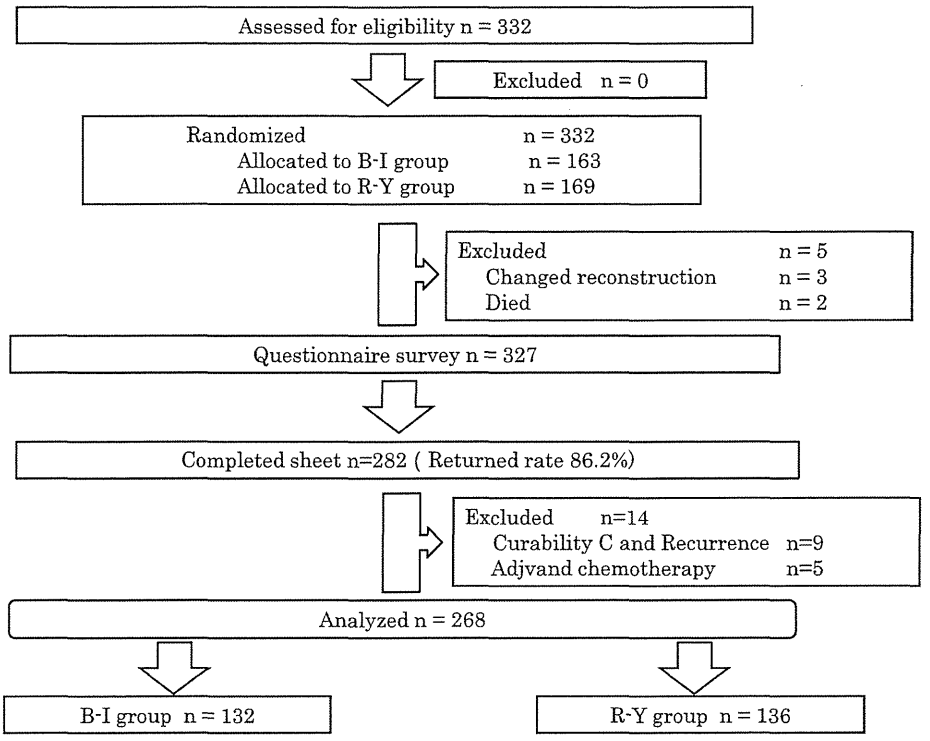

Table 1 Characteristics and operative results of patients who underwent distal gastrectomy and answered the questionnaire survey

	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,

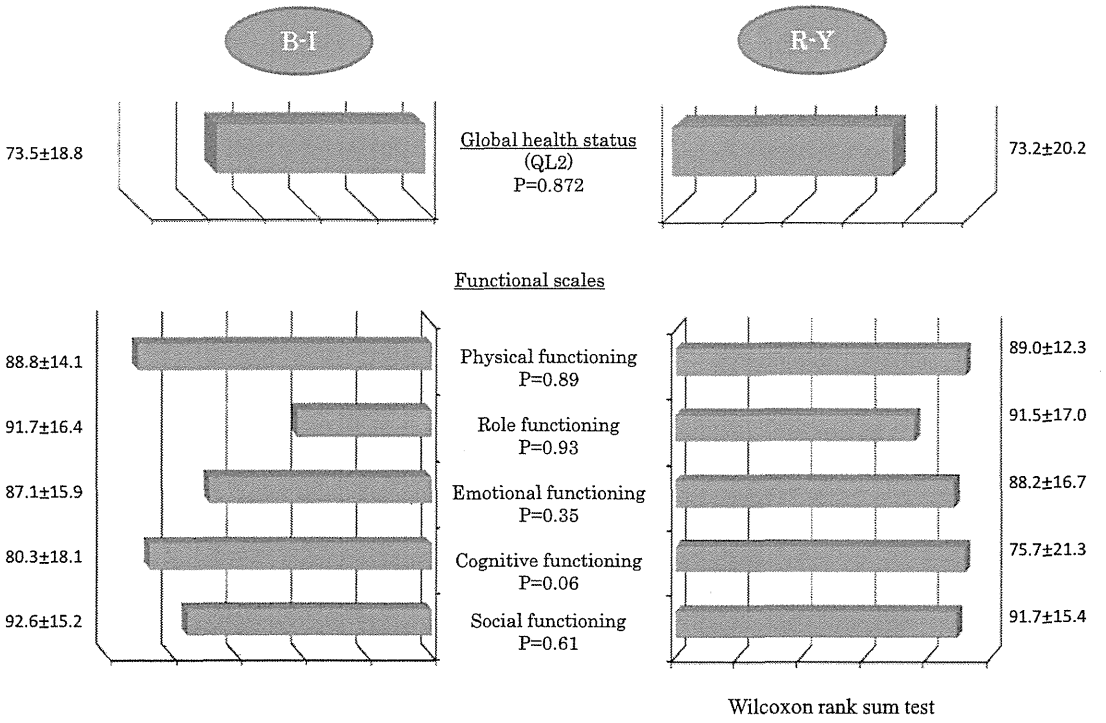

Fig. 2 The mean scores for global health status were very similar in both groups (B-I 73.5 ± 21.3, R-Y 73.2 ± 20.2, $p = 0.87$). As for the functional scales, B-I was nonsignificantly superior to R-Y on only the cognitive scale (B-I 80.3 ± 18.1, R-Y 75.7 ± 21.3, $p = 0.06$)

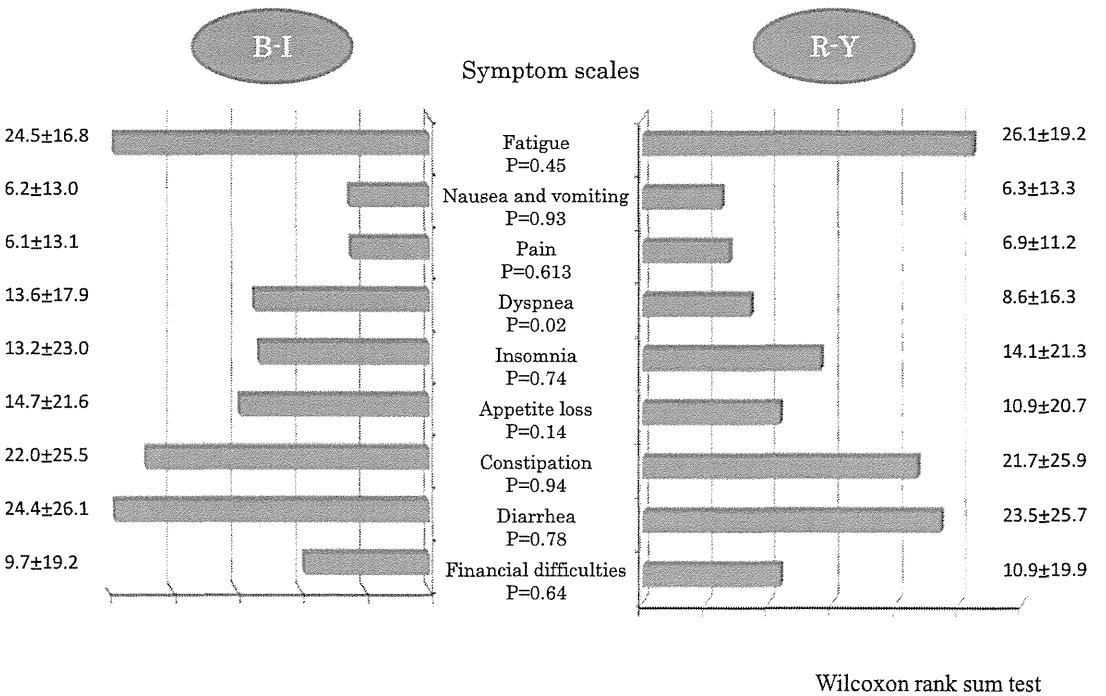

Fig. 3 B-I was significantly inferior to R-Y on the dyspnea scale (B-I 13.6 ± 17.9, R-Y 8.6 ± 16.3, $p = 0.02$). There were no significant differences on the other eight symptom scales (fatigue, nausea and vomiting, pain, insomnia, appetite loss, constipation, diarrhea, financial difficulties)

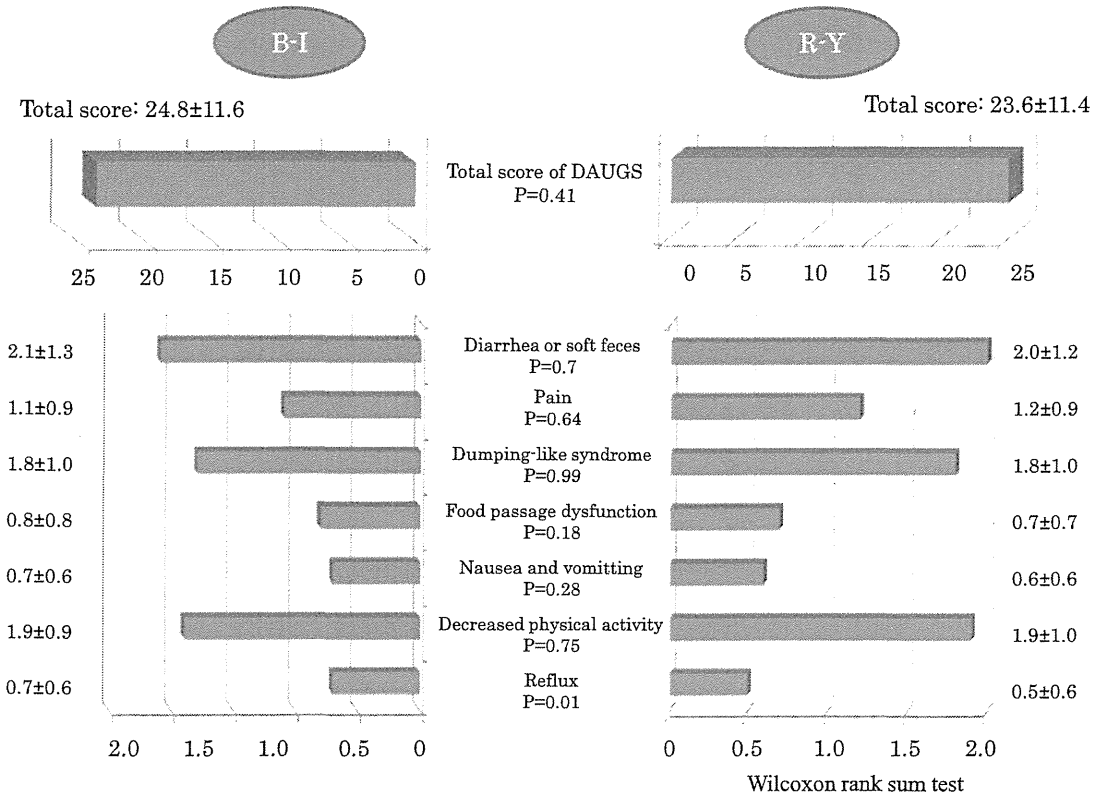

Fig. 4 The total score of the DAUGS 20 was very similar in both groups (B-I 24.8 ± 11.6, R-Y 23.6 ± 11.4, $p = 0.41$). Subclass analysis showed that B-I was significantly worse in terms of reflux symptoms (B-I 0.7 ± 0.6, R-Y 0.5 ± 0.6, $p = 0.01$)

$p = 0.99$), 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

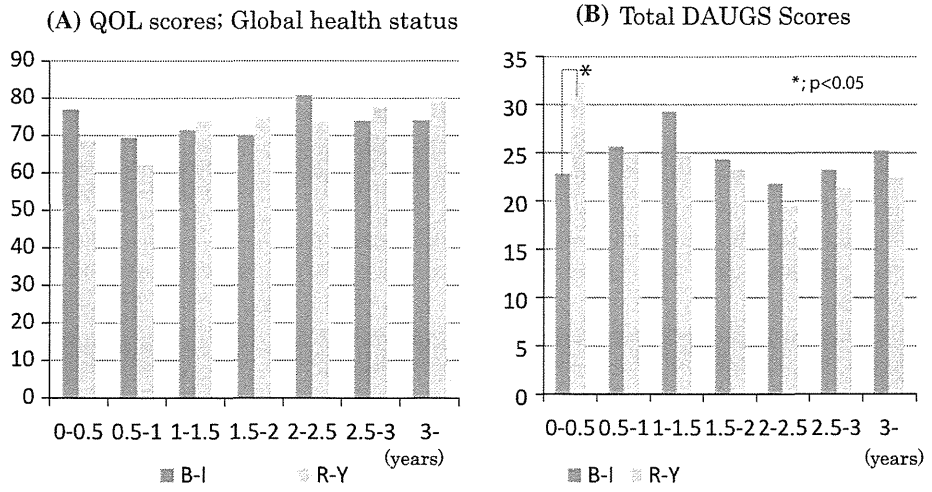

Fig. 5 There were significant differences in total DAUGS 20 scores during the first 6 months (B-I 22.8 ± 13.7, R-Y 32.4 ± 8.9, $p = 0.04$). There was no significant difference in global health status and total DAUGS 20 scores at other periods between the B-I group and the R-Y group

optimal operative approach. The Japanese version of the EORTC QLQ-C30 has been developed and validated. Kobayashi et al. [20] used this version to prospectively compare postoperative health-related QOL among gastrectomy patients and found clear difference among the operative procedures.

The DAUGS 20 scale was designed to objectively assess gastrointestinal dysfunction after surgery for upper gastrointestinal cancer. The scale has already been validated in the field of upper intestinal cancer [17, 18]. We found no significant difference between R-Y and B-I procedures in terms of overall postoperative dysfunction. However, 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, $p = 0.04$). Especially each score of food passage dysfunction and nausea and vomiting tended to be worse in the R-Y group (not significant). This may be weakened to gastrointestinal motility and delayed gastric emptying with R-Y. In this series, the frequency of nausea, vomiting, and discontinuation of food intake were significantly lower in the B-I group than in the R-Y group (3.7 vs. 12.4%, $p = 0.0027$; 3.1 vs. 8.9%, $p = 0.022$; 4.3 vs. 12.4%, $p = 0.0064$, respectively). Frequency of delayed gastric emptying in the B-I group was lower than in the R-Y group (4.3 vs. 9.5%, $p = 0.057$). In general, Roux en Y stasis occurred within the postoperative 1st month. Minor symptoms could not be detected during the hospital stay, and small amounts of nausea or vomiting might have occurred at home. Our questionnaire survey might detect this small difference between B-I and R-Y related gastrointestinal motility during the first 6 months.

The EORTC QLQ-C30 showed significant differences only in dyspnea. This symptom seemed to be physiologically unrelated to postoperative complications. Patients who received B-I gastrectomy sometimes complained of heartburn. This score seemed to be affected by esophagitis caused by bile and gastric juice reflux. In the analysis of partial items of the DAUGS, reflux symptoms also obviously appeared in the B-I group. If this limitation can be overcome, we can feel confident in continuing to perform B-I reconstructions. While Shibata reported that semifundoplication following B-I reconstruction prevented this difficulty, further surgical intervention following gastrectomy is less than ideal [21].

The questionnaire survey in the current study was performed only once for each patient and at varying time points after surgery, since co-investigators in this multi-institutional study did not agree to perform the survey several times and at regular intervals. Such a design would have delivered more convincing data, but would have been too much of a burden for the co-investigators. An alternative design would have been to perform all the surveillances at a fixed time point, such as at 1 year postoperatively. However, it was not possible to decide on the optimal time point for performing the surveillance at the time this study was designed. It has now become clear how the scores vary at different time points, and further study to confirm the differences between B-I and R-Y can now be designed and proposed.

In general, from the point of view of the surgeon, B-I reconstruction is considered to be simple and relatively easy. For the patient, nutritional and hormonal advantages might exist in this physiological route. It is easier to treat common bile duct stones using a gastrointestinal fiberscope after B-I reconstruction. In contrast, the advantage of R-Y reconstruction is thought to be less anastomotic leakage and infrequent reflux esophagitis and gastritis. However, disadvantages include a more complicated surgical procedure as well as delayed gastric emptying, so-called Roux-en-Y stasis. All surgeons recognize these issues, and their decisions on which approach to use are based on individual experience. Clinical randomized trials are very important

in providing surgeons with information to facilitate their decision-making. Ishikawa et al. [12] conducted a randomized trial and showed that B-I reconstruction was superior to R-Y in terms of shorter postoperative hospital stay. At the time it was carried out, this study was the first and most important trial comparing B-I and R-Y reconstructions, and many surgeons have referred to its results as clinical evidence. Our study should also be useful in assisting surgeons with deciding between the two procedures.

In summary, this questionnaire survey using the EORTC QLQ-C30 and DAUGS 20 scales revealed that the B-I and R-Y reconstruction approaches were nearly equal in terms of postoperative QOL and dysfunction. It is noteworthy, however, that B-1 was significantly better regarding the total DAUGS 20 score during the first 6 months after surgery. The current study revealed differences in QOL and postoperative dysfunction scores between the two modes of reconstruction at various time points. More refined prospective trials with improved designs based on these results have to be proposed.

Acknowledgments The authors thank Dr. Tomoyuki Sugimoto at Osaka University for help with the statistical analysis. Participating institutions and chief participants: Sakai Municipal Hospital (H. Furukawa, H. Imamura), Osaka University (Y. Doki, S. Takiguchi), Osaka National Hospital (T. Tsujinaka, K. Fujitani), Toyonaka Municipal Hospital (J. Fujita, Kawanishi), Osaka Medical Center for Cancer and Cardiovascular Diseases (M. Yano, I. Miyashiro), Kinki Central Hospital of the Mutual Aid Association of Public School Teachers (K. Kobayashi), NTT West Osaka Hospital (Y. Kimura), Yao Municipal Hospital (Y. Fukushima, H. Matsuyama), Hyogo Prefectural Nishinomiya Hospital (H. Yano, H. Taniguchi), Kansai Rosai Hospital (S. Tamura, H. Miki), Ikeda Municipal Hospital (K. Shibata, T. Hirao), Belland General Hospital (K. Demura), SEMPOS Seamen's Insurance hospital (Y. Tsukahara), Saiseikai Senri Hospital (H. Fukunaga), Nishinomiya Municipal Hospital (H. Oka), Suita Municipal Hospital (C. Ebisui, K. Okada), Itami Municipal Hospital (M. Hiratsuka), and Mino Municipal Hospital (S. Iijima, Y. Makari).

Conflict of interest None of the authors have financial or personal conflicts of interest to disclose.

References

1. Yoshino K. History of gastric cancer surgery. J Jpn Surg Soc. 2000;101:855–60.
2. Weil PH, Buchberger R. From Billroth to PCV: a century of gastric surgery. World J Surg. 1999;23:736–42.
3. Osugi H, Fukuhara K, Tagada N, et al. Reconstructive procedure after distal gastrectomy to prevent remnant gastritis. Hepatogastroenterology. 2004;51:1215–8.
4. Kauer WK, Peters JH, DeMeester TR, et al. Composition and concentration of bile acids reflux into the esophagus of patients with gastroesophageal reflux disease. Surgery. 1997;122:874–81.
5. Svensson JO. Duodenogastric reflux after gastric surgery. Scand J Gastroenterol. 1983;18:729–34.
6. Fein M, Peters JH, Chandrasoma P, et al. Duodenoesophageal reflux induces esophageal adenocarcinoma without exogenous carcinogen. J Gastrointest Surg. 1998;2:260–8.
7. Taylor PR, Mason RC, Filipe MI, et al. Gastric carcinogenesis in the rat induced by duodenogastric reflux without carcinogens, morphology, mucin histochemistry, polyamine metabolism, and labeling index. Gut. 1991;32:1447–54.
8. Sato T, Miwa K, Sahara H. The sequential model of Barrett's esophagus and adenocarcinoma induced by duodeno-esophageal reflux without exogenous carcinogens. Anticancer Res. 2002;22:39–44.
9. Mackman S, Lemmer KE, Morrissey JF. Postoperative reflux alkali gastritis and esophagitis. Am J Surg. 1971;121:694–7.
10. Gillison EW, Kusakari K, Bombeck CT, et al. The importance of bile in reflux oesophagitis and the success in its prevention by surgical means. Br J Surg. 1972;59:794–8.
11. Mathias JR, Fernandez A, Sninsky CA, et al. Nausea, vomiting, and abdominal pain after Roux-en-Y anastomosis: motility of the jejuna limb. Gastroenterology. 1985;88:101–7.
12. Ishikawa M, Kitayama J, Kaizaki S, et al. Prospective randomized trial comparing Billroth-I and Roux-en-Y procedures after distal gastrectomy for gastric cancer. World J Surg. 2005;29:1415–20.
13. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma—2nd English edition. Gastric Cancer. 1998;1:10–24.
14. Kobayashi K, Takeda F, Teramukai S, et al. A cross-validation of the European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30) for Japanese with lung cancer. Eur J Cancer. 1998;34:810–5.
15. Wu C, Chiou J, Ko F, et al. Quality of life after curative gastrectomy for gastric cancer in a randomized controlled trial. Br J Cancer. 2008;98:54–9.
16. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQC30: a quality of life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85:365–76.
17. Nakamura M, Kido Y, Yano M, Hosoya Y. Reliability and validity of a new scale to assess postoperative dysfunction after resection of upper gastrointestinal carcinoma. Surg Today. 2005;35:535–42.
18. Nakamura M, Hosoya Y, Yano M, Doki Y, Miyashiro I, Kurashina K, Morooka Y, Kishi K, Lefor AT. Extent of gastric resection impacts patient quality of life: the Dysfunction after Upper Gastrointestinal Surgery for Cancer (DAUGS32) Scoring System. Ann Surg Oncol. 2011;18:314–20.
19. Kim YW, Baik YH, Yun YH, et al. Improved quality of life outcomes after laparoscopy-assisted distal gastrectomy for early gastric cancer: results of a prospective randomized clinical trial. Ann Surg. 2008;248:721–7.
20. Kobayashi D, Kodera Y, Fujiwara M, Koike M, Nakayama G, Nakao A. Assessment of quality of life after gastrectomy using EORTC QLQ-C30 and STO22. World J Surg. 2011;35:357–64.
21. Shibata Y. Effect of semifundoplication with subtotal gastrectomy for prevention of postoperative gastroesophageal reflux. J Am Coll Surg. 2004;198:212–7.