



Comparison of total versus subtotal gastrectomy for remnant gastric cancer

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A concise and informative title: Comparison of total versus subtotal gastrectomy for remnant gastric cancer

Abstract

Purpose: Completion gastrectomy (CG) is a common procedure for remnant gastric cancer (RGC).

However, partial gastrectomy for gastric cancer has several benefits compared to total gastrectomy in terms of the quality of life. In this study, we evaluated the feasibility and advantage of subtotal resection of the remnant stomach (SR) for clinical stage IA RGC.

Methods: A total of 43 patients who underwent gastrectomy for clinical stage IA RGC were included. CG and SR were performed on 27 (62.8%) and 16 patients (37.2%), respectively. The short- and long-term outcomes, including the nutritional status, after CG and SR for clinical stage IA RGC were compared between the two groups.

Results: There were no significant differences in pathological stage or incidence of postoperative complications between the two groups. The decrease in body weight, body mass index and serum albumin level was significantly lower in the SR group than in the CG group ($P<0.001$, $P=0.025$ and 0.008). In the SR group, there was no recurrence at the remaining lymph nodes or gastric stump. The 5-year overall survival rate was 87.8% in the CG group and 86.1% in the SR group, without a significant difference between the two groups ($P=0.959$).

Conclusions: The present study showed the noninferiority of SR to CG based on surgical and oncological outcomes for clinical stage IA RGC. Furthermore, SR has an advantage over CG in terms of the postoperative nutritional status. Therefore, SR could be an alternative elective treatment option for early RGC located around the anastomotic site.

Key words: Remnant gastric cancer; Subtotal resection of the remnant stomach; Clinical stage; Nutritional status

Authors' contributions: HG and SK participated in the study conception and design. HG, DO, YF and MT

participated in the acquisition of data. HG participated in the analysis and interpretation of data. HG participated in the drafting of the manuscript. SK, TO, MY, TN, SS and YK participated in the critical revision of the manuscript.

Introduction

The incidence of remnant gastric cancer (RGC) after distal gastrectomy has been reported to be between 1 and 5% [1-3]. RGC refers to all carcinomas arising in the remnant stomach following gastrectomy, irrespective of the histology of the primary lesion or its risk of recurrence, the extent of resection, or the method of reconstruction [4]. The treatment of RGC is considered difficult because the anatomy around the stomach and celiac axis is changed by the initial surgery. Completion gastrectomy (CG) with lymph node dissection has been performed in most cases, although the standard surgical procedure for RGC has remained undefined in all guidelines [5].

Total gastrectomy has many disadvantages arising from changes in the nutritional status, such as postoperative body weight loss [6]. However, compared to total gastrectomy, partial gastrectomy has several benefits in terms of the quality of life for postgastrectomy patients [7]. As less invasive surgeries, pylorus- preserving gastrectomy and proximal gastrectomy have been performed in patients with early gastric cancer in recent years [8]. Therefore, less invasive surgeries could also be performed for early RGC. We performed subtotal resection of the remnant stomach (SR) for some patients with clinical stage IA RGC for whom the lesion was located at the distal side or the anastomotic side of the remnant stomach. Previously, Irino et al. reported that SR could be a feasible treatment option for patients with early RGC [9]. However, they did not evaluate changes in the nutritional status or analyze the long-term outcomes for early RGC based on pathological stage.

In the present study, we evaluated the short- and long-term outcomes, including the nutritional status after SR, to clarify whether this procedure has benefits compared to CG for clinical stage IA RGC.

Materials and Methods

Patients

From May 1998 to June 2017, 93 patients with RGC underwent gastrectomy at the Hyogo Cancer Center, Japan. Of these patients, 47 patients underwent gastrectomy for clinical stage IA RGC. Among the 47 patients, CG with lymph node dissection and SR with limited lymph node dissection were performed in 31 patients and 16 patients, respectively. In the CG group, 4 patients were excluded because the tumor location was too close to the esophagogastric junction, and they were not considered candidates for SR. Finally, 43 patients were included in this retrospective study (CG group, 27 patients; SR group, 16 patients).

In this study, the Japanese Classification of Gastric Carcinoma was used for cancer staging [4]. We performed cancer staging prior to surgery using esophagogastroduodenoscopy and computed tomography. We did not perform endoscopic ultrasound for routine cancer staging. The lymph node stations were defined using the Japanese Gastric Cancer Association (JGCA) classification [4]. Tumor histology was also evaluated according to the JGCA classification, with well and moderately differentiated tubular adenocarcinoma and papillary adenocarcinoma classified as differentiated-type carcinomas, and poorly differentiated adenocarcinoma, signet ring cell carcinoma, and mucinous carcinoma classified as undifferentiated-type carcinomas [4]. Clinical, surgical, and pathological records of the patients were obtained from our database and individual patient medical records. Data collection and analysis were approved by the institutional review board of the Hyogo Cancer Center.

Indication of subtotal resection of the remnant stomach for remnant gastric cancer

The indications of SR for RGC were clinical stage IA RGC with no obvious lymph node swelling on computed tomography and the location of tumor at the anastomotic site or adjacent to anastomosis.

When a proximal margin of at least 2cm was acquired for T1 tumors, SR was performed. However, different patients had different capacities and anatomy of the remnant stomach because the remnant stomach was affected by previous disease and range of resection. Therefore, the surgical procedure was finally decided on a case-by-case basis.

Surgical procedure

We defined SR as a segmental resection of the remnant stomach including the anastomosis, with limited lymph node dissection. The remaining lymph nodes were different among each patient due to previous disease, and the reconstruction was thus different. When the previous disease was benign, the perigastric lymph nodes along the lesser curvature (stations 1 and 3) and the lower greater curvature of the remnant stomach, stations 7 (along the trunk of the left gastric artery), 8a (along the common hepatic artery) and 9 (along the celiac artery) were removed. According to the lymphadenectomy for stations 4sa (along the short gastric artery) and 4sb (along the left gastroepiploic artery), we removed only the lymph nodes around the greater curvature of the remnant stomach with high ligation of the short gastric and left gastroepiploic vessels in the initial surgery. However, when the previous disease was malignant, only the lymph nodes around the anastomosis were removed. In CG cases, stations 1, 2 (along the esophagocardiac branch of the left subphrenic artery), 3, 4sa and the lower greater curvature of the remnant stomach, 7, 8a, 9 and 11p were removed when the previous disease was benign. When the previous disease was malignant, we removed stations 2 and 4sa. The lymph nodes in the jejunal mesentery were removed if the previous reconstruction was Billroth II. We obtained frozen sections prior to reconstruction as part of the surgical routine. For the anastomosis technique, Roux-en-Y reconstruction was performed in all cases. The surgical technique used for gastrojejunal anastomosis was performed using a liner stapler, and esophagojejunal anastomosis was performed using a circular stapler.

Outcomes

The short-term outcomes were operation time, blood loss, postoperative hospital stay, surgical complications and intra-abdominal infectious complications. Surgical complications were assessed using the Clavien-Dindo classification [10]. Intra-abdominal infectious complications included pancreas-related infection, anastomotic leakage, and intra-abdominal abscess. Complications categorized as grade II or higher were considered postoperative complications. Pancreatic fistula was defined as the presence of amylase-rich purulent discharge (>3000 IU/L), and anastomotic leakage was diagnosed as the presence of discharge of contrast agent from the anastomosis site upon radiological examination. Intra-abdominal abscess was defined as an abscess that was not associated with pancreas-related infection or anastomotic leakage. Nutritional parameters after gastrectomy were assessed based on the changes in body weight, body mass index, serum albumin level and hemoglobin level at 12 months after surgery. The 5-year overall survival rates were compared between the two groups. We performed esophagogastroduodenoscopy and computed tomography as routine follow-up after surgery for RGC. Esophagogastroduodenoscopy was performed every year, and computed tomography was performed every 6 months.

Statistics

All statistical analyses were carried out using JMP version 13.0 software (SAS Institute Inc., Cary, NC, USA). The two groups were compared using the Chi-squared or Fisher's exact test. All continuous variables are presented as medians (range). The medians were compared using the Mann-Whitney test. Postoperative changes in body weight and serum albumin level were compared between the two groups by Student's *t* test. *P*-values less than 0.05 were considered significant. The Kaplan-Meier method was used to estimate survival curves, and survival curves were compared using the log-rank test.

Results

Patient characteristics

The clinicopathological characteristics of the 43 patients included in this study are summarized in Table 1. In total, 27 patients underwent CG, and 16 patients underwent SR. All patients underwent R0 resection in this study. There were no significant differences in age, sex, body mass index, histological type, tumor size, tumor depth, nodal status or pathological stage between the two groups. According to previous disease, the diagnosis of benign disease included gastric or duodenal ulcer. The patients for whom the previous disease was malignant comprised 31.3% of the SR group, and this proportion was significantly lower than that in the CG group (81.5%, $P=0.003$). For previous surgery, the proportion of Billroth II reconstruction was higher in the SR group than in the CG group ($P=0.009$). The median interval between the initial and second surgeries was significantly longer in the SR group than in the CG group ($P=0.002$). The median distance from the anastomotic site in the initial surgery to the proximal site of the lesion was 20 mm in the SR group.

Surgical outcomes and postoperative complications

The details of the surgical procedures and postoperative complications are shown in Table 2. There were no significant differences in blood loss, number of retrieved lymph nodes or postoperative hospital stay between the two groups. The median operation time was 289 min for the CG group and 241 min for the SR group ($P=0.016$). Splenectomy was performed for 5 patients with invasion of the greater curvature in the CG group. No conversion to CG due to intraoperative diagnosis (frozen section diagnosis) occurred. With regard to postoperative complications, grade II or higher in the Clavien-Dindo classification occurred in 5 patients (18.5%) in the CG group, including 1 patient (3.7%) with intra-abdominal infectious complications (pancreas-related infection: 1 case). On the other hand, in the SR group, grade II or higher postoperative complications occurred in 4 patients (25.0%), and no intra-abdominal infectious

complications occurred. No anastomotic leakage occurred in either group. There were no significant differences in the incidence of postoperative complications or intra-abdominal infectious complications between the two groups ($P=0.706$ and 0.436 , respectively). The patients did not have an intensive care unit stay or undergo-reoperation or readmission for surgical complications. Only one patient required treatment for pancreas-related infection, and radiological intervention for drainage tube management was performed. No deaths related to surgical complications or within 30 days and no in-hospital mortality occurred in either group.

Postoperative nutritional status

We evaluated postoperative changes in body weight and serum albumin levels in 43 patients who were followed up for 1 year after gastrectomy (Figs. 1 and 2). The decrease in body weight rate and body mass index was significantly smaller in the SR group than in the CG group ($P<0.001$, $P=0.025$). Additionally, compared to that in the CG group, the decrease in serum albumin levels in the SR group was smaller ($P=0.008$). No significant difference was observed in the hemoglobin level at 1 year after gastrectomy between the two groups ($P=0.839$).

Oncological outcomes

No incidence of lymph node metastasis was observed in the CG group. In contrast, in the SR group, 2 patients (12.5%) had lymph node metastasis at station 3a (along the branches of the left gastric artery). The median follow-up periods in both groups were 60 months. The 5-year overall survival rate was 87.8% in the CG group and 86.1% in the SR group, without any significant difference between the two groups ($P=0.959$; Fig. 3). In the SR group, 1 patient developed recurrence and died of bone metastasis 39 months after surgery.

Discussion

In the present study, we assessed the short- and long-term outcomes, including the nutritional status, of patients who underwent SR for clinical stage IA RGC and compared these results with those in patients who underwent CG. The short- and long-term outcomes were similar between the two groups. Although one patient who underwent SR died because of bone metastasis, there was no recurrence at the gastric stump or regional lymph nodes. Furthermore, regarding postoperative body weight loss and decrease in serum albumin level, SR demonstrated an advantage over CG. Therefore, SR is a feasible elective procedure for patients with clinical stage IA RGC.

The incidence of lymph node metastasis is the most important factor for performing SR because lymph node dissection in SR is limited compared to that in CG. The present study showed that lymph node metastasis at station 3a was observed in only 2 patients (12.5%) in the SR group, where these lymph nodes could be removed even by SR. Irino et al. reported that lymph node metastasis in RGC occurs in only 2.6% of mucosal cancer and 10.3% of submucosal cancer cases, whereas it is observed in more than a quarter of patients with advanced RGC [9]. Additionally, given the survival rates of the CG and SR groups in the present study, we conclude that SR could be an acceptable surgical procedure for patients with clinical stage IA RGC.

The lymphatic flow in RGC is different from that in gastric cancer due to the dissection of lymph vessels and anastomosis during the initial surgery [11, 12]. According to a previous report, the lymphatic flow to the splenic hilum was predominant, particularly if the initial surgery was for malignant disease [13]. There is concern regarding the possibility of lymph node metastasis in the splenic hilum, even in early RGC. However, for early RGC, it has been shown that the previous disease and surgery do not affect the pattern of lymph node metastasis [9]. In our study, there was no lymph node metastasis in the splenic hilum for patients with clinical stage IA RGC. Therefore, we conclude that lymph node metastasis in early RGC rarely occurs in the remaining lymph nodes after SR.

Our present study showed that the postoperative decrease in body weight, body mass index and serum albumin levels was significantly lower in the SR group than in the CG group. Previous studies have demonstrated that distal gastrectomy for gastric cancer has advantages over total gastrectomy in terms of the postoperative nutritional status and quality of life [7, 14-16]. For patients with RGC who have a low body mass index and are undernourished, the preservation of the stomach could be more advantageous in terms of the nutritional status than for gastric cancer patients. Body weight loss after gastrectomy is caused not only by a reduction in the volume of the stomach following surgery but also by a decrease in ghrelin, the only gastrointestinal hormone known to increase appetite [17-19]. The small extent of body weight loss after SR might result from preservation of the gastric fundus, which is the primary location of ghrelin secretion [20].

The proportions of mucosal lesions in the CG and SR groups in the present study were 63.0% and 50.0%, respectively. The presence of mucosal lesions could be an indication for endoscopic resection in the present gastric cancer treatment guidelines [8]. Recently, there have been several reports of endoscopic submucosal dissection (ESD) for RGC, despite some technical difficulties [21, 22]. ESD is the first choice, especially for RGC with mucosal lesions, if the technical level of ESD is feasible. However, tumors located around the anastomotic site are expected to be much more difficult to remove because of severe fibrosis and staples from the initial surgery. In our hospital, RGC with a mucosal lesion located other than at the anastomotic site is an indication for ESD. Therefore, we consider SR as a good treatment option for early RGC located around the anastomotic site. In our hospital, 33 patients underwent ESD for RGC. Regarding complications, perforation occurred 3 patients (9.1%), and bleeding occurred 2 patients (6.1%). No significant difference in the incidence of complications was observed between the ESD and SR groups ($P=0.449$, data not shown). However, the treatment for perforation caused by ESD required a longer hospital stay. The 5-year overall survival rate was 86.3% in the ESD group, resulting in no significant difference between the two groups ($P=0.819$, data not shown).

Laparoscopic gastrectomy has become one of the standard treatments for gastric cancer [23, 24]. In our institution, laparoscopic surgery for RGC has not been performed for the technical difficulties due to adhesions and anatomical alterations caused by the initial surgery. Recently, laparoscopic gastrectomy for RGC has been reported sporadically, and the incidence of laparoscopic esophagojejunostomy leakage was 1.7% [25, 26]. As more evidence emerges, such as the technical and oncological safety, the laparoscopic SR is expected to become a good treatment option because of the extent of resection is small.

The present study has several limitations. First, it was a retrospective study performed at a single institution, and only 43 patients were included. Although the sample size was small, the incidence of RGC is generally low, and these data were collected for the past two decades. There was no significant difference in the selection of surgical procedures between early and late periods of the study ($P=0.755$, data not shown). Additionally, there were no significant differences in age, sex, body mass index, previous disease, type of reconstruction, operation time and blood loss between the two groups. It was possible that the patients with prior benign disease tended to have a large capacity of the remnant stomach because lymphadenectomy was not performed in the initial surgery. Therefore, SR might be selected in many cases. Second, we could not evaluate the other nutritional assessments and supplements, and long-term nutritional status for demonstrating the advantage of SR [27, 28]. Finally, the incidence of lymph node metastasis was low, and this result should be carefully interpreted because mucosal lesions accounted for the majority of cases.

Conclusion

The present study showed the noninferiority of SR to CG based on surgical and oncological outcomes for patients with clinical stage IA RGC. Furthermore, SR has an advantage over CG in terms of the postoperative nutritional status. Therefore, SR could be an alternative elective treatment option for patients with clinical stage IA RGC.

Compliance with Ethical Standards

This study received no funding contributions. The authors declare that they have no conflict of interest.

This retrospective study does not contain any experiments with animals or human participants.

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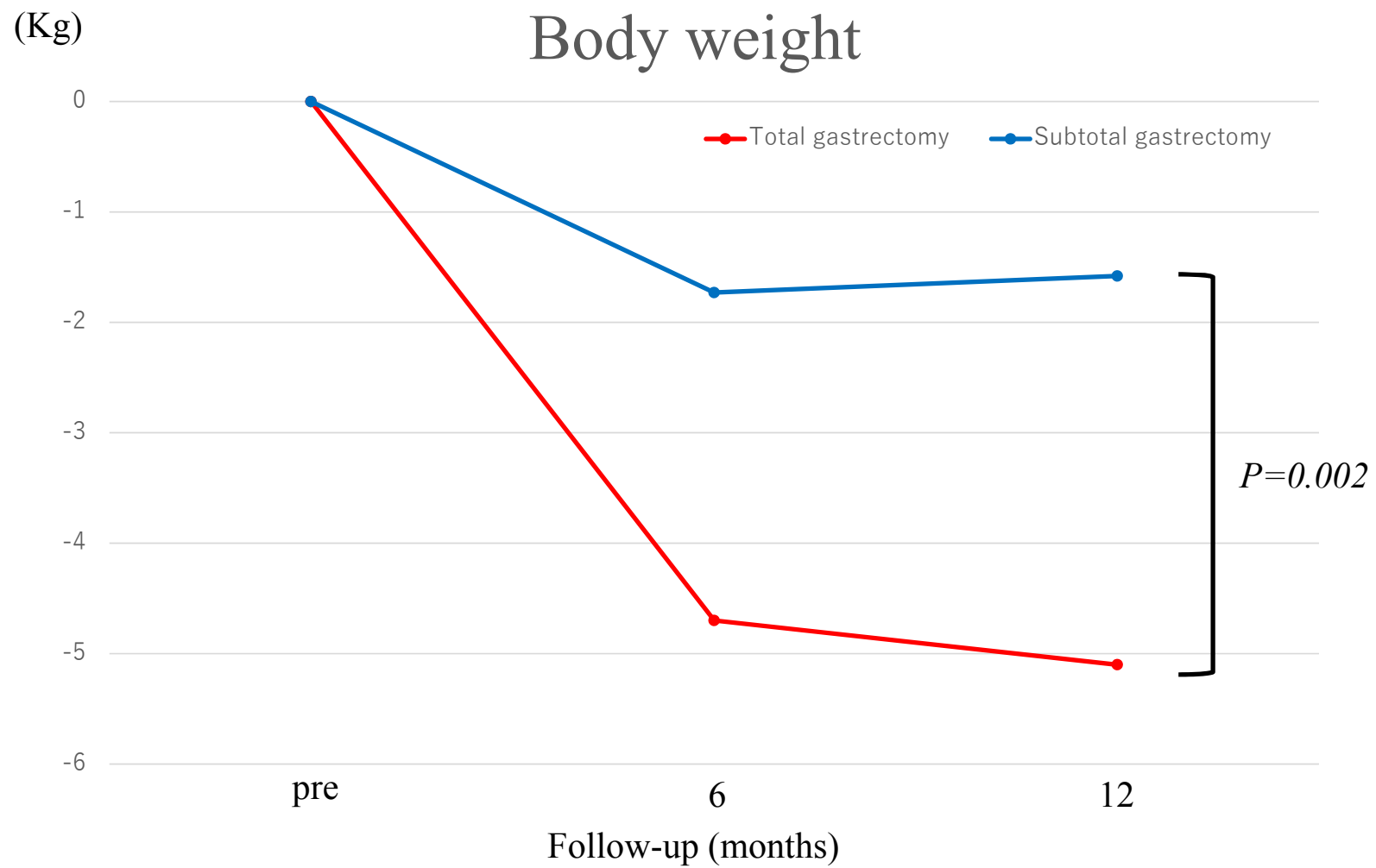
Figure Legends

Fig. 1a: Postoperative changes in body weight in the completion gastrectomy and subtotal resection of the remnant stomach groups.

Fig. 1b: Postoperative changes in body mass index in the completion gastrectomy and subtotal resection of the remnant stomach groups.

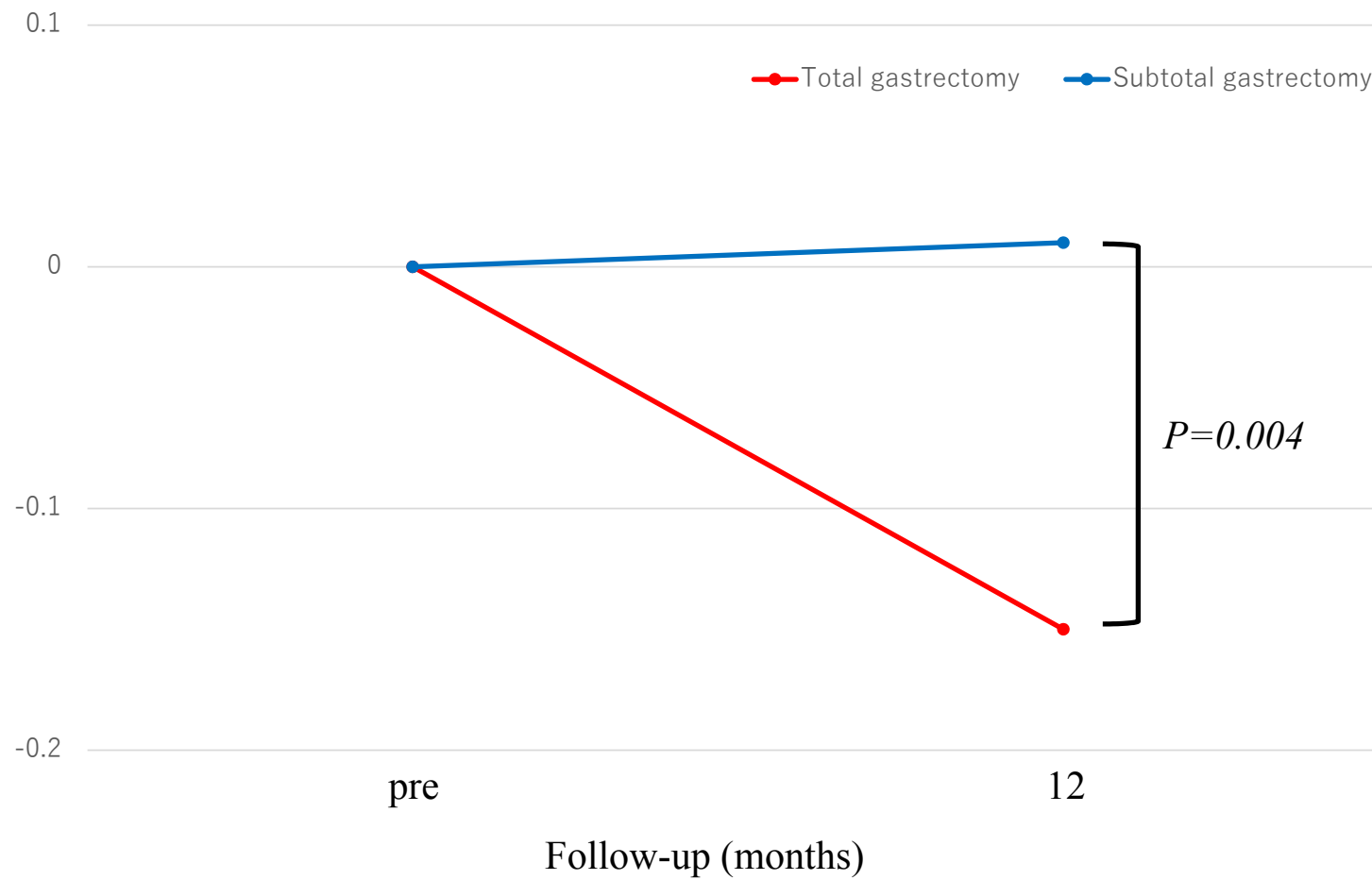
Fig. 2: Postoperative changes in serum albumin level in the completion gastrectomy and subtotal resection of the remnant stomach groups.

Fig. 3: The 5-year overall survival rates in the completion gastrectomy and subtotal resection of the remnant stomach groups. The 5-year survival rate was 87.8% in the completion gastrectomy group and 86.1% in the subtotal resection of the remnant stomach group. The difference was not significant ($P=0.959$).



(g/dl)

Albumin



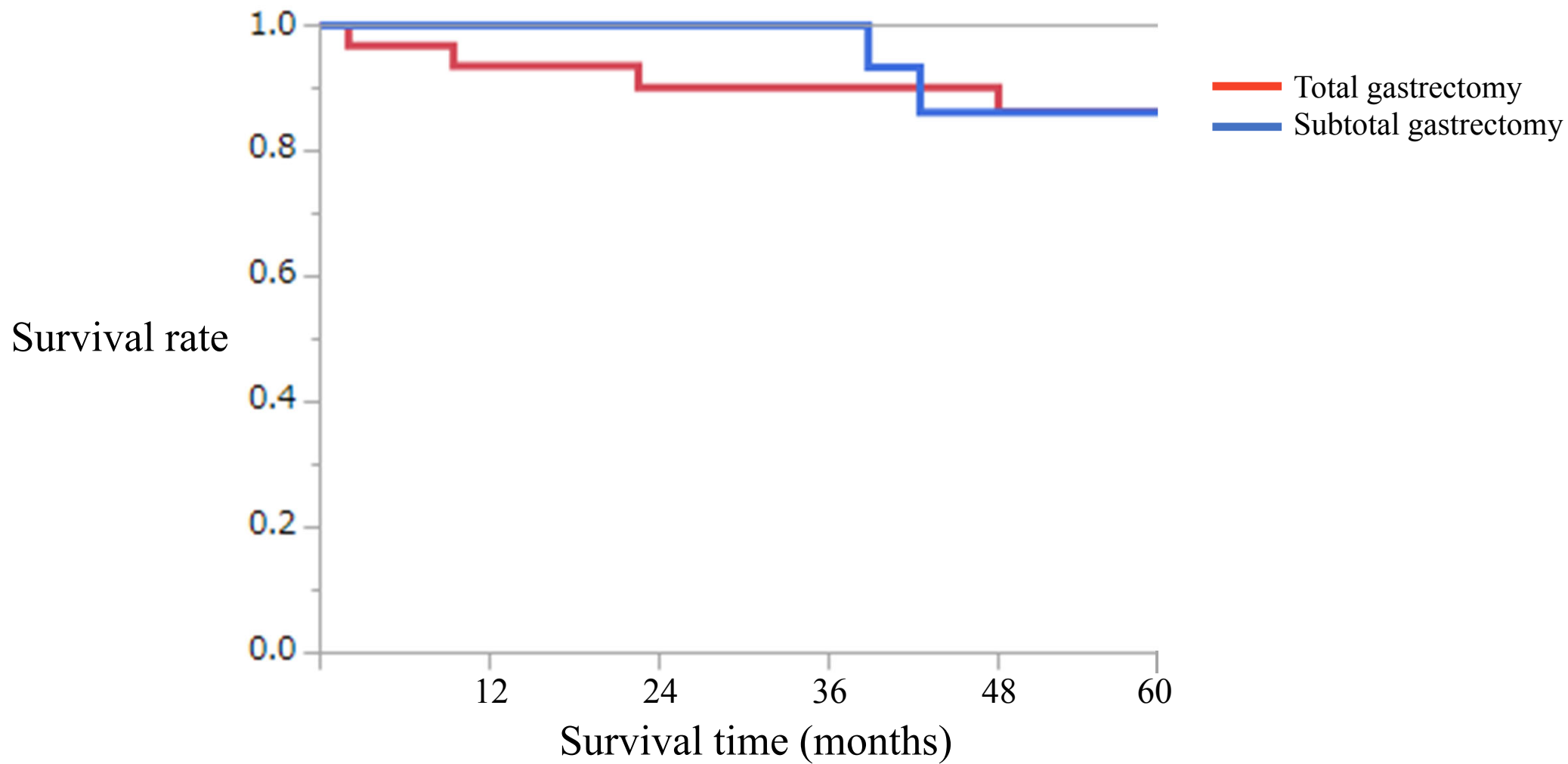


Table 1 : Characteristics of the 47 patients with clinical Stage IA remnant gastric cancer

Parameters		Completion gastrectomy (n=27)	Subtotal resection of the remnant stomach (n=16)	P value
Age	Median / range, years	70 / 52–85	70 / 52–86	0.841
Sex	Male	21 (77.8 %)	13 (81.3 %)	0.787
	Female	6 (22.2 %)	3 (18.7%)	
Body mass index	Median / range, kg/m2	20.2 / 17.1–26.2	19.6 / 14.3–23.2	0.366
Previous disease	Benign	5 (18.5 %)	11 (68.8 %)	0.003
	Malignant	22 (81.5 %)	5 (31.2 %)	
Prevoius reconstruction	Billroth I	15 (55.6 %)	2 (12.5 %)	0.009
	Billroth II	12 (44.4 %)	14 (87.5 %)	
Years since previous surgery	Median / range, years	8 / 1–47	30 / 10–48	0.002
Histological type	Differentiated	19 (70.4 %)	10 (62.5 %)	0.739
	Undifferentiated	8 (29.6 %)	6 (37.5 %)	
Tumor size	Median / range, mm	25 / 2–65	27 / 8–55	0.554
Tumor depth (pathological)	Mucosa	17 (63.0 %)	8 (50.0 %)	0.697
	Submucosa	9 (33.3 %)	7 (43.8 %)	
	Muscularis propria	1 (3.7 %)	1 (6.2 %)	
Nodal status (pathological)	Positive	0 (0 %)	2 (12.5 %)	0.133
	Negative	27 (100 %)	14 (87.5 %)	
Stage (pathological)	IA	26 (96.3 %)	14 (87.5 %)	0.545
	IB	1 (3.7 %)	2 (12.5 %)	
Follow up	Median / range, months	60 / 2–60	60 / 12–60	0.601

Table 2 :Details of the surgical procedures

Parameters		Completion gastrectomy (n=27)	Subtotal resection of remnant stomach (n=16)	P value
Operation time	Median \angle range, min	289 \angle 181–515	241 \angle 151–370	0.016
Blood loss	Median \angle range, ml	500 \angle 100–1360	330 \angle 120–1100	0.269
Splenectomy		5 (18.5 %)	0 (0 %)	0.025
Retrieved lymph nodes	Median \angle range	8 \angle 1–46	8 \angle 1–43	0.687
Postoperative hospital stay	Median \angle range, days	17 \angle 9–32	17 \angle 10–39	0.705
Complications, grade II or higher ^a		5 (18.5 %)	4 (25.0 %)	0.706
	<u>Pneumonia</u>	<u>1 (3.7 %), grade II</u>	<u>2 (12.5 %), grade II</u>	
	<u>Biliary infection</u>	<u>1 (3.7 %), grade II</u>	<u>1 (6.2 %), grade II</u>	
	<u>Superficial incisional surgical site infection</u>	<u>1 (3.7 %), grade II</u>	<u>1 (6.2 %), grade II</u>	
	<u>Enterocolitis</u>	<u>1 (3.7 %), grade II</u>	—	
	Intra-abdominal infectious complication ^b	1 (3.7 %)	0 (0 %)	0.436
	<u>Anastomatic leakage</u>	<u>0 (0 %)</u>	<u>0 (0 %)</u>	
	<u>Pancreas-related infection</u>	<u>1 (3.7 %), grade IIIa</u>	<u>0 (0 %)</u>	
	<u>Intra-abdominal abscess</u>	<u>0 (0 %)</u>	<u>0 (0 %)</u>	

^aBased on the Clavien–Dindo classification [10]^bAnastomotic leakage, pancreas-related infection and intra-abdominal abscess