TABLE 1 Structure of the PGSAS-45 Questionnaire (domains/items/subscales)

Domains		Items		Subscales
SF-8	1	Physical functioning*	5- or 6-point Likert scale	Physical component summary (PCS)*
	2	Role physical*		Mental component summary (MCS)*
	3	Bodily pain*		
	4	General health*		
	5	Vitality*		
	6	Social functioning*		
	7	Role emotional*		
	8	Mental health*		
GSRS	9	Abdominal pain	7-point Likert scale, except items 29 and 32	Esophageal reflux subscale (items 10, 11, 13, 24)
	10	Heartburn		Abdominal pain subscale (items 9, 12, 28)
	11	Acid regurgitation		Meal-related distress subscale (items 25–27)
	12	Sucking sensations in the epigastrium		Indigestion subscale (items 14–17)
	13	Nausea and vomiting		Diarrhea subscale (items 19, 20, 22)
	14	Borborygmus		Constipation subscale (items 18, 21, 23)
	15	Abdominal distension		Dumping subscale (items 30, 31, 33)
	16	Eructation		
	17	Increased flatus		Total symptom scale (above 7 subscales)
	18	Decreased passage of stool		
	19	Increased passage of stool		
	20	Loose stool		
	21	Hard stool		
	22	Urgent need for defecation		
	23	Feeling of incomplete evacuation		
Symptoms	24	Bile regurgitation		
	25	Sense of food sticking		
	26	Postprandial fullness		
	27	Early satiation		
	28	Lower abdominal pain		
	29	Number and type of early dumping symptoms		
	30	Early dumping general symptoms		
	31	Early dumping abdominal symptoms		
	32	Number and type of late dumping symptoms		
	33	Late dumping symptoms		
Meals (amount) 1	34	Ingested amount of food per meal*		–
	35	Ingested amount of food per day*		
	36	Frequency of main meals		
	37	Frequency of additional meals		
Meals (quality)	38	Appetite*	5-point Likert scale	Quality of ingestion subscale* (items 38–40)
	39	Hunger feeling*		
	40	Satiety feeling*		
Meals (amount) 2	41	Necessity for additional meals		–
Social activity	42	Ability for working		–

TABLE 1 continued

Domains	Items	Subscales
Dissatisfaction	43 Dissatisfaction with symptoms	Dissatisfaction for daily life subscale (items 43–45)
	44 Dissatisfaction at the meals	
	45 Dissatisfaction at working	

In items or subscales with *, higher scores indicate better conditions
In items or subscales without *, higher scores indicate worse conditions
Each subscale is calculated as the mean of composed items or subscales, except PCS or MCS of SF-8
Items 29 and 32 do not have scores; these items were analyzed separately

(UMIN-CTR; registration No. 000002116). This study was approved by local ethics committees at each institution. Written informed consent was obtained from all enrolled patients.

Statistics

The comparison of patient QOL following BI and RY procedures included the *t* test and Chi squared test statistical methods. All items that exhibited significant variations in univariate analysis were further analyzed using multiple regression analysis; $p < .05$ was considered statistically significant. StatView software for Windows Ver. 5.0 (SAS Institute Inc.) was used for all statistical analyses.

RESULTS

Retrieving the Questionnaire

The PGSAS-45 questionnaire was distributed to 2,922 patients between July 2009 and December 2010. Of those distributed, 2520 (86 %) were retrieved. Among the 2520 retrieved documents, 152 were determined to be ineligible because of: age >75 years ($n = 90$), postoperative period <1 year ($n = 29$), resection of other organs ($n = 8$), and other factors ($n = 25$). As a result, 2,368 patients were determined to be eligible for inclusion in the analysis. Of the eligible 2,368 patients, 393 had undergone total gastrectomy, 909 had undergone DGBI, 475 had undergone DGRY, 313 had undergone pylorus-preserving gastrectomy, 193 had undergone proximal gastrectomy, and 85 had undergone local resection. In this study, 909 patients underwent DGBI and 475 patients underwent DGRY were selected for inclusion.

Patient Characteristics

Demographic information for all study participants is listed in Table 2. In patients who underwent BI procedures,

TABLE 2 Patient characteristics

	BI	RY	*P* value
Number of patients	909	475	
Postoperative period (months)	40.7 ± 30.7[a]	31.7 ± 18.0[a]	<.0001
Age	61.6 ± 9.1[a]	62.0 ± 9.1[a]	.529
Gender			
Male	594	318	.518
Female	311	154	
Preoperative BMI[b]	22.7 ± 3.0[a]	22.9 ± 3.0[a]	.190
Postoperative BMI[b]	20.9 ± 2.8[a]	20.8 ± 2.7[a]	.680
Approach			
Open	489	320	<.0001
Laparoscopic	415	152	
Extent of lymph node dissection[c]			
D0	4	0	.568
D1	8	3	
D1a	119	60	
D1b	444	246	
D2	319	163	
Preservation of celiac branch			
Preserved	133	28	<.0001
Divided	754	442	
Combined resection			
None	743	402	.698
Gallbladder	80	51	
Miscellaneous	4	2	
Size of gastric remnant			
More than half	29	10	<.0001
One-third	799	299	
One-fourth	61	139	
Less than one-fifth	0	22	

[a] Mean ± SD
[b] Body mass index
[c] According to Japanese gastric cancer treatment guidelines

TABLE 3 Outcome measures included in the PGSAS-45 Questionnaire

Item No.	
Main outcome measures	
–	Change in body weight (%)
10, 11, 13, 24	Esophageal reflux subscale[a]
9, 12, 28	Abdominal pain subscale[a]
25–27	Meal-related distress subscale[a]
14–17	Indigestion subscale[a]
19, 20, 22	Diarrhea subscale[a]
18, 21, 23	Constipation subscale[a]
30, 31, 33	Dumping subscale[a]
9–28, 30, 31, 33	Total symptom score[a]
34	Ingested amount of food per meal*
41	Necessity of additional meals
38–40	Quality of ingestion subscale*[a]
42	Ability for working
43	Dissatisfaction with symptoms
44	Dissatisfaction at the meals
45	Dissatisfaction at working
43–45	Dissatisfaction for daily life subscale[a]
1–5	Physical component summary*[a]
4–8	Mental component summary*[a]
Other outcome measures (symptoms)	
9	Abdominal pain
10	Heartburn
11	Acid regurgitation
12	Sucking sensations in the epigastrium
13	Nausea and vomiting
14	Borborygmus
15	Abdominal distension
16	Eructation
17	Increased flatus
18	Decreased passage of stool
19	Increased passage of stool
20	Loose stool
21	Hard stool
22	Urgent need for defecation
23	Feeling of incomplete evacuation
24	Bile regurgitation
25	Sense of food sticking
26	Postprandial fullness
27	Early satiation
28	Lower abdominal pain
30	Early dumping general symptoms
31	Early dumping abdominal symptoms
33	Late dumping symptoms
Other outcome measures (dumping)	
29	Existence of early dumping general symptoms (yes/no)
29	Existence of early dumping abdominal symptoms (yes/no)
29	Existence of any early dumping symptoms (yes/no)
32	Existence of late dumping symptoms (yes/no)
29	Number of early dumping general symptoms
29	Number of early dumping abdominal symptoms
29	Number of any early dumping symptoms
32	Number of late dumping symptoms
Other outcome measures (meals)	
35	Ingested amount of food per day*
36, 37	Frequency of daily meals
38	Appetite*
39	Hunger feeling*
40	Satiety feeling*

In items or subscales with *, higher scores indicates better conditions
In items or subscales without *, higher scores indicates worse conditions
[a] Integrated subscales

the mean postoperative period was significantly longer, frequencies of laparoscopic approaches and celiac branch preservation were significantly higher, and the size of gastric remnants was significantly greater than in patients who underwent RY procedures. All patients underwent R0 resection in both groups.

Refinement of QOL Measure

Based on data from the retrieved PGSAS-45 questionnaires, outcome measures were refined through consolidation and selection. A total of 23 symptom items were consolidated into 7 symptom subscales as listed in Tables 1 and 3. Assessment data included: total symptom score, quality of ingestion, level of satisfaction with daily life, physical component summary (PCS) of SF-8, and mental component summary (MCS) of SF-8 as main outcome measures (Table 3). In addition, the following results were selected as main outcome measures: changes in body weight, amount of food ingested per meal, necessity for additional meals, ability for working, dissatisfaction with symptoms, dissatisfaction at the meals, and dissatisfaction at working. Each subscale score was calculated as the mean of composed items, and total symptom score was calculated as the mean of 7 symptom subscales (Table 3). Although change in body weight was not included in the questionnaire, we included loss of body weight as 1 of the main outcome measures in this study because body weight loss significantly influences patient's QOL after gastrectomy.

TABLE 4 Univariate analysis of main outcome measures following Billroth-I (BI) and Roux-en-Y (RY) procedures

Main outcome measures	BI		RY		Cohen's *d*	*P* value
	Mean	SD	Mean	SD		
Change in body weight	−7.9 %	0.08	−8.9 %	0.07	0.14	.022
Esophageal reflux subscale[a]	1.70	0.82	1.49	0.65	0.29	<.0001
Abdominal pain subscale[a]	1.69	0.75	1.66	0.80		.519
Meal-related distress subscale[a]	2.05	0.88	2.09	0.88		.502
Indigestion subscale[a]	1.99	0.84	2.04	0.84		.230
Diarrhea subscale[a]	2.12	1.10	2.06	1.14		.335
Constipation subscale[a]	2.23	1.03	2.12	1.02	0.11	.063
Dumping subscale[a]	1.96	1.00	1.97	1.01		.957
Total symptom score[a]	1.96	0.68	1.92	0.67		.324
Ingested amount of food per meal	7.12	1.96	7.23	1.99		.323
Necessity of additional meals	1.86	0.78	1.90	0.81		.394
Quality of ingestion subscale*[a]	3.80	0.91	3.76	0.91		.497
Ability for working	1.75	0.87	1.83	0.88		.119
Dissatisfaction with symptoms	1.81	0.92	1.81	0.92		.903
Dissatisfaction at the meals	2.19	1.08	2.18	1.11		.886
Dissatisfaction at working	1.67	0.89	1.72	0.98		.389
Dissatisfaction for daily life subscale[a]	1.89	0.83	1.90	0.86		.842
Physical component summary*[a]	50.52	5.52	50.77	5.62		.446
Mental component summary*[a]	49.86	5.74	49.84	5.68		.955

Outcome measures with * indicate higher scores and therefore better conditions

Outcome measures without * indicate higher scores and therefore worse conditions

[a] Integrated subscales

TABLE 5 Multivariate analysis of main outcome measures

Items	Change in body weight		Esophageal reflux subscale	
	β[a]	*P* value	β[a]	*P* value
Type of gastrectomy [DGBI]	0.052	.069	0.142	<.001
Postoperative period (months)	–	.290	–	.739
Age (years)	−0.064	.022	0.054	.047
Gender [male]	–	.154	−0.060	.028
Approach [laparoscopic]	–	.219	–	.421
Celiac branch of vagus [preserved]	0.079	.006	−0.053	.057
R^2	0.02	<.001	0.028	<.001

DGBI distal gastrectomy Billroth-I

Multiple regression analysis was performed if the *P* value of the item/subscale in the univariate analysis was <.05

[a] If β is positive, the score of the outcome measure of the patient belonging to the category in brackets is higher in cases when the factor is a nominal scale, and the score of the outcome measure of the patient with larger values is higher in cases when the factor is a numeral scale

QOL Assessments

Calculated QOL measurements of patients following BI and RY procedures were compared according to the aforementioned criteria (Table 4). Among the main outcome measures, patients who underwent BI procedures showed significantly lower weight loss and significantly higher esophageal reflux than patients who underwent RY procedures. There were no other significant differences in QOL.

To eliminate confounding factors, multiple regression analysis was performed by adding postoperative period, age, gender, surgical approach, and celiac branch preservation as explanatory variables (Table 5). Weight loss was shown to be influenced by age and celiac branch preservation, and esophageal reflux subscale was shown to be influenced by age and gender. Reconstruction method was a borderline significant independent predictive factor for weight loss and the most significant independent predictive factor for esophageal reflux subscale.

Each symptom item within the esophageal reflux subscale, such as heartburn ($p = .002$), acid reflux ($p < .0001$), nausea and vomiting ($p = .023$), and bile regurgitation ($p < .0001$), was significantly worse with BI procedures than with RY procedures. Symptoms of flatus were significantly worse with RY procedures ($p = .001$). Defecation symptom, such as passage of stool ($p = .004$), was significantly worse with BI procedures. There was no significant difference in QOL scores between the two groups of patients for other symptoms, meals, work, or dissatisfaction for daily life.

DISCUSSION

This study assessed QOL among postoperative DG patients, comparing two methods of surgical reconstruction.

This comparison was conducted through the use of the PGSAS-45 questionnaire, which was developed for the measurement of QOL in gastrectomized patients. This was the first nationwide survey of its type and involved 52 medical institutions throughout Japan. QOL data were successfully collected from 2,520 patients, and the final sample size, following exclusion and participant selection, was sufficient for this type of study.

Patient demographic analysis indicated that patients who underwent BI procedures had longer postoperative periods and higher frequencies of both laparoscopic gastrectomy and celiac branch preservation. In Japan, laparoscopic operations are mainly used to treat early gastric cancer.[15,16] The celiac branch is frequently preserved in limited surgical interventions for early gastric cancer. There is a possibility that these differences may affect patient QOL following gastrectomy. However, the extent of lymph node dissection, which was anticipated to have a significant effect on postoperative symptoms, did not differ between the two study groups. Therefore, there seems to be no problems with comparing the QOL scores between these two groups. The size of gastric remnants was larger in patients who underwent BI procedures, possibly due to the preference of Japanese surgeons. Many Japanese surgeons prefer BI for larger gastric remnant to avoid roux stasis by RY reconstruction, while they prefer RY for smaller gastric remnants to prevent esophageal reflux. Thus, this discrepancy may reflect the preferences of Japanese surgeons.[3,4,6]

Among the main outcome measures, significant differences were only observed for loss of body weight and esophageal reflux symptoms. It is speculated that weight loss may be affected by dietary intake, but there were no significant differences in amount of food per meal or necessity of additional meals. Although weight loss was influenced by age and celiac branch preservation, multiple regression analysis showed reconstruction methods to be a predictive factor with borderline significance. As the size of gastric remnant was significantly different between BI and RY, we also performed ANOVA followed by multiple comparisons according to the size of the remnant stomach. There was no significant influence of size of gastric remnant on the degree of weight loss (data not shown). These results suggest the possibility that physiological reconstruction methods have an effect on digestion and absorption of ingested food. However, significant differences in weight loss between BI and RY procedures have not been reported in any previously performed RCTs.[7–9] In the present study, the actual difference in weight loss and the effect size Cohen's *d* value was relatively small. It is postulated that even a slight difference was significantly detected because of large sample size. We did not include body weight in the questionnaire, because the body weight declared by patients is sometimes unreliable. All of the patients included in this study were informed about the study at the time of visit. So, in order to obtain a reliable body weight data, we measured the patients' body weight at the clinic and compared it with the preoperative body weight in medical records. We thought accurate data collection was more important than obtaining uncertain data from patient's memory with respect to the body weight changes. Therefore, we did not include body weight in the questionnaire.

In contrast to weight changes, BI procedures have shown to be disadvantageous for esophageal reflux. All symptom items related to esophageal reflux showed unfavorable results. Although these symptoms were affected by age and gender (as shown through multiple regression analysis), reconstruction methods were shown to be significant independent predictive factors. It was previously shown, via endoscopic observation or hepatobiliary scans, that bile reflux and gastritis were more frequently observed following BI procedures than RY procedures.[7–9] However, the incidence of reflux esophagitis is still controversial. Hirao et al.[8] reported a higher incidence of reflux esophagitis with BI procedures than with RY procedures. However, other investigators found no significant difference in the incidence of reflux esophagitis following each of these reconstruction methods.[7,9] This discrepancy remains the same in retrospective analysis. Most investigators have reported that bile reflux and gastritis are more frequently observed following BI procedures than RY procedures. However, the incidence of reflux esophagitis is still controversial. One study reported a significantly higher incidence of reflux esophagitis with BI procedures, while others reported no difference between BI and RY procedures.[3,17,18] Based on these reports, it is speculated that bile reflux may have occurred frequently following BI reconstruction, and that this reflux may have caused gastritis (observable via endoscopy). The incidence of reflux esophagitis may be lower based on several mechanisms that prevent bile from traveling from the stomach to the esophagus. These mechanisms contribute to a longer onset period and low incidence for development of esophagitis from transient bile reflux. Shinoto et al.[18] performed a questionnaire assessment of reflux symptoms, indicating that 63 % of patients who underwent BI procedures reported symptoms, while none of the patients who underwent RY procedures reported symptoms of esophageal reflux. In this series, the incidences of reflux esophagitis by endoscopic observation were 57 % for BI procedures and 21 % for RY procedures, respectively. Similarly, Nunobe et al.[3] reported that reflux esophagitis by endoscopic observation was found in 5 of 203 patients who underwent BI procedures and none of the 182 patients who underwent RY procedures. However, questionnaire data documented reflux symptoms in 13 of 203 patients who

underwent BI procedures and in none of the 182 patients who underwent RY procedures. That study reported that "Although there was a large difference between the groups in the proportions of patients who complained of heartburn, the difference in the incidence of endoscopically recognizable esophagitis was much smaller, with borderline significance." These results suggest that questionnaires may be more sensitive than endoscopic observation in detecting esophageal reflux. The newly developed PGSAS-45 also shows sensitivity to differentiation of reflux symptoms between BI and RY procedures.

In other outcomes measured, symptoms of flatus were significantly better following BI procedures. However, multiple regression analysis indicated that flatus was influenced by postoperative period and celiac branch preservation (data not shown), indicating that results may be affected by these factors. Constipation was shown to be more frequent in patients who underwent BI procedures. Nunobe et al.[3] reported that altered bowel habits were significantly worse in patients who underwent BI procedures than in those who underwent RY procedures. The PGSAS-45 questionnaire used in this study addressed bowel habits: "Tell us about your present bowel habits (diarrhea and constipation)." Hence, the precise incidences of diarrhea and constipation in study participants are unknown. In the present study, the incidence of diarrhea was not significantly different between BI and RY procedures, but there is a possibility that the incidence of constipation may increase after BI reconstruction.

This study has a limitation worth noting. Specifically, the study was not a prospective study and the investigation was conducted at a single time point. In particular, chronological changes are thought to be the most important issue in evaluating a patient's QOL after gastrectomy. However, we mainly focused on the long-term QOL, and we collected data more than 1 year after gastrectomy, because Kobayashi et al.[11] had reported that the conditions of the patients with more than 1 year after gastrectomy were generally stable. In addition, we performed multiple regression analysis with postoperative period as an item in order to eliminate the influence of postoperative period on patient's QOL. Further validation by prospective clinical trials with assessment of early to long-term QOL is required.

Several investigators have assessed QOL following total gastrectomy, but no large-scale QOL assessment following DG has been published to date.[10] This is the first study to use the PGSAS-45 questionnaire for investigating patient QOL following gastrectomy. The results of this study are well aligned with previously reported findings, including those of past RCTs. Based on the minimal difference in QOL between the two reconstructive methods, either BI or RY procedures may be recommended based on the individual patient's condition. At least, BI reconstruction should be avoided in order to prevent reflux esophagitis in patients having risk for gastroesophageal reflux such as small gastric remnant, hiatal hernia, or loss of His angle. In addition, results show the newly developed PGSAS-45 questionnaire to be a useful tool, as well as changes in the body weight, for evaluating patient QOL following gastrectomy.

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REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin.* 2011;61:69–90.
2. Nashimoto A, Akazawa K, Isobe Y, Miyashiro I, Katai H, Kodera Y, et al. Gastric cancer treated in 2002 in Japan: 2009 annual report of the JGCA nationwide registry. *Gastric Cancer.* 2013;16:1–27.
3. Nunobe S, Okaro A, Sasako M, Saka M, Fukagawa T, Katai H, et al. Billroth 1 versus Roux-en-Y reconstructions: a quality-of-life survey at 5 years. *Int J Clin Oncol.* 2007;12:433–9.
4. Kumagai K, Shimizu K, Yokoyama N, Aida S, Arima S, Aikou T. Questionnaire survey regarding the current status and controversial issues concerning reconstruction after gastrectomy in Japan. *Surg Today.* 2012;42:411–8.
5. Rieu PN, Jansen JB, Biemond I, Offerhaus GJ, Joosten HJ, Lamers CB. Short-term results of gastrectomy with Roux-en-Y or Billroth II anastomosis for peptic ulcer. A prospective comparative study. *Hepatogastroenterology.* 1992;39:22–6.
6. Hoya Y, Mitsumori N, Yanaga K. The advantages and disadvantages of a Roux-en-Y reconstruction after a distal gastrectomy for gastric cancer. *Surg Today.* 2009;39:647–51.
7. Ishikawa M, Kitayama J, Kaizaki S, Nakayama H, Ishigami H, Fujii S, et al. Prospective randomized trial comparing Billroth I and Roux-en-Y procedures after distal gastrectomy for gastric carcinoma. *World J Surg.* 2005;29:1415–20; discussion 1421.
8. Hirao M, Takiguchi S, Imamura H, Yamamoto K, Kurokawa Y, Fujita J, et al. Comparison of Billroth I and Roux-en-Y reconstruction after distal gastrectomy for gastric cancer: one-year postoperative effects assessed by a multi-institutional RCT. *Ann Surg Oncol.* 2013;20:1591–7.
9. Lee MS, Ahn SH, Lee JH, Park do J, Lee HJ, Kim HH, et al. What is the best reconstruction method after distal gastrectomy for gastric cancer?. *Surg Endosc.* 2012;26:1539–47.
10. Karanicolas PJ, Bickenbach K, Jayaraman S, Pusic AL, Coit DG, Guyatt GH, et al. Measurement and interpretation of patient-reported outcomes in surgery: an opportunity for improvement. *J Gastrointest Surg.* 2011;15:682–9.
11. 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.
12. Nakada K, Ikeda M, Takahsahi M, Kinami S, Yoshida M, Uenosono Y, et al. Characteristics and clinical relevance of postgastrectomy syndrome assessment scale (PGSAS)-45: newly developed integrated questionnaires for assessment of living

status and quality of life in postgastrectomy patients. *Gastric Cancer*. 2014. doi:10.1007/s10120-014-0344-4.
13. Turner-Bowker DM, Bayliss MS, Ware JE, Jr., Kosinski M. Usefulness of the SF-8 Health Survey for comparing the impact of migraine and other conditions. *Qual Life Res*. 2003;12: 1003–12.
14. Svedlund J, Sjodin I, Dotevall G. GSRS—a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. *Dig Dis Sci*. 1988;33:129–34.
15. Sasada S, Ninomiya M, Nishizaki M, Harano M, Ojima Y, Matsukawa H, et al. Survival of patients treated by an autonomic nerve-preserving gastrectomy for early gastric cancer. *Surg Today*. 2010;40:444–50.
16. Yamada H, Kojima K, Inokuchi M, Kawano T, Sugihara K. Efficacy of celiac branch preservation in Roux-en-y reconstruction after laparoscopy-assisted distal gastrectomy. *Surgery*. 2011;149:22–8.
17. Kojima K, Yamada H, Inokuchi M, Kawano T, Sugihara K. A comparison of Roux-en-Y and Billroth-I reconstruction after laparoscopy-assisted distal gastrectomy. *Ann Surg*. 2008;247:962–7.
18. Shinoto K, Ochiai T, Suzuki T, Okazumi S, Ozaki M. Effectiveness of Roux-en-Y reconstruction after distal gastrectomy based on an assessment of biliary kinetics. *Surg Today*. 2003;33:169–77.

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ORIGINAL ARTICLE

Early phase II study of robot-assisted distal gastrectomy with nodal dissection for clinical stage IA gastric cancer

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Abstract
Background Robot-assisted distal gastrectomy (RADG) is increasingly performed in Japan and Korea and is thought to have many advantages over laparoscopic gastrectomy. However, a prospective study investigating the safety of RADG has never been reported. The present study evaluated the safety of RADG with nodal dissection for clinical stage IA gastric cancer.
Methods This single-center, prospective phase II study included patients with clinical stage IA gastric cancer located within the lower two-thirds of the stomach. The primary endpoint was the incidence of postoperative intraabdominal infectious complications including anastomotic leakage, pancreas-related infection, and intraabdominal abscess. The secondary endpoints included all in-hospital adverse events, RADG completion rate, and survival outcome.
Results From May 2012 to November 2012, 18 eligible patients were enrolled for this study. The incidence of intraabdominal infectious complication was 0 % (90 % CI, 0–12.0 %). The overall incidence of in-hospital adverse events was 22.2 % (90 % CI, 8.0–43.9 %). No patient required conversion to laparoscopic or open gastrectomy; thus, the RADG completion rate was 100 %.
Conclusions This early phase II study suggested that RADG might be a safe and feasible procedure for stage IA gastric cancer, providing experienced surgeons perform the surgery. This conclusion should be clarified in subsequent late phase II studies with a larger sample size.

Keywords da Vinci · Gastric cancer · Gastrectomy · Clinical trial · Safety

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Introduction

Laparoscopy-assisted distal gastrectomy (LADG) is performed increasingly often, particularly in East Asian countries where the incidence of early gastric cancer is higher than in Western countries. The safety of LADG was clarified by prospective studies [1, 2], and survival outcome of LADG compared with open gastrectomy was under investigation in two large, nationwide, randomized controlled trials in Japan and Korea [1, 3]. However, current laparoscopic procedures have several drawbacks, including a limitation in range of forceps movement and the two-dimensional surgical view available to the operating surgeons.

Robot-assisted distal gastrectomy (RADG) may enable us to overcome these drawbacks. Using the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA, USA), surgeons were able to attain a three-dimensional surgical view, instrument flexibility, tremor suppression, and improved ergonomics, although RADG still has disadvantages such as high cost and lack of tactile sensation [4–8]. In addition, a shorter learning curve has been reported for robotic surgery compared to laparoscopic surgery [9–11].

Reported studies rate RADG as a feasible procedure, although most such studies involved a retrospective or prospective study cohort [4, 5, 8–10, 12–22]. So far, no prospective clinical trials have focused on the feasibility of RADG, a step that is necessary before RADG could be

explored further with greater number of patients. To this end, the current prospective study evaluated the safety of RADG with nodal dissection for clinical stage IA gastric cancer.

Methods

The present study was designed as a single-center, prospective phase II trial. The institutional review board of Shizuoka Cancer Center approved the study protocol, which had the following inclusion criteria: histologically confirmed adenocarcinoma of the stomach, clinical stage IA early gastric cancer according to the International Union Against Cancer classification system (UICC) [23], no indication for endoscopic submucosal dissection (ESD), a tumor located in the lower two-thirds of the stomach, no involvement of the duodenum, patient age of 20–80 years, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, a body mass index (BMI) less than 30 kg/m^2, no prior upper abdominal surgery or intestinal resection other than appendectomy, no prior chemotherapy or radiotherapy for any malignancy, adequate organ function, and written informed consent. The study was registered with clinical trials.gov (clinical trials.gov identifier: NCT 1504997).

In this study period, medical cost for hospital admission, including surgical fee, was funded by the Shizuoka Cancer Center because the national insurance system in Japan did not reimburse patients for RADG.

Surgical procedure

All RADG operations were performed using the da Vinci Surgical System with four robotic arms; a central arm for a dual-channel endoscope, and the other three for a Cadiere forceps, fenestrated bipolar forceps, and bipolar Maryland forceps or monopolar electrocautery, respectively. One assistant port was placed in the right umbilical level. The surgical procedures were similar to that used in LADG, with a standardized surgical field to achieve omentum preservation, D1+ lymph node dissection according to the Japanese gastric cancer treatment guidelines [24–27], and vagal nerve preservation [28, 29]. Removal of resected specimens and reconstruction were performed by a 4- to 5-cm upper midline incision. In the case of distal gastrectomy, a Billroth I reconstruction with circular stapler was selected in general. In the case of pylorus-preserving gastrectomy, reconstruction was performed by hand-sewn sutures.

In this study, the operations were separated into three parts. The docking time was defined as the time from skin incision to completion of docking. The console time was the time that the da Vinci system was used by the surgeon at the console. The anastomosis time was the time spent from the creation of the mini-laparotomy to the completion of the surgery.

Training for RADG

A team of two gastric surgeons who were board certified by the Japanese Society of Endoscopic Surgery (JSES) as experts in laparoscopic surgery performed RADG in all cases. To be board certified by the JSES as an expert laparoscopic surgeon, an applicant is required to perform more than 20 laparoscopic gastrectomies or alternative advanced laparoscopic surgeries within 3 years and to submit a non-edited video of one of the surgeries for a review by at least two board-qualified referees. The strict review process, which takes place once a year, allows only one-third of the applicants to be certified. Before introducing RADG at Shizuoka Cancer Center, the two surgeons completed a fixed training program for RADG as recommended by the JSES. The program consisted of e-learning, training sessions at an animal laboratory, and site visits to a specified high-volume center to observe actual RADG. In addition, surgeons with sufficient experience in RADG were invited as instructors in the initial two cases of RADG at our institution.

Endpoints

The primary endpoint in this study was the incidence of postoperative intraabdominal infectious complications, which included anastomotic leakage, pancreas-related infection, and intraabdominal abscess. Patients who developed Clavien–Dindo classification grade II or more complications by discharge were regarded as having complications [30, 31]. The secondary endpoints were overall survival (OS), relapse-free survival (RFS), RADG completion rate, and the incidence of all surgical morbidities.

Anastomotic leakage was diagnosed by radiologic examination using orally administered contrast media. Pancreas-related infection was defined as amylase-rich purulent discharge. Intraabdominal abscess was defined as an abscess not associated with anastomotic leakage or pancreas-related infection. The completion of RADG was defined as the proportion of patients without conversion from RADG to LADG or open distal gastrectomy (ODG).

Study design and statistical methods

In this phase II trial, the sample size was 18 cases, providing 70 % power under the hypothesis of a primary endpoint with an expected value of 4 % and a threshold

value of 15 %, using one-sided testing at a 10 % significance level. The expected value was decided according to the postoperative outcome of 265 patients who had undergone an ODG or LADG for early gastric cancer in the lower two-thirds of the stomach at the Shizuoka Cancer Center; the incidence of intraabdominal infectious complication among these patients was 4.5 % [32]. All statistical analyses were conducted using R Statistics version 2.13.1.

Results

A total of 18 patients were recruited in this phase II study from May 2012 to November 2012. Table 1 summarizes the patient characteristics. The male-to-female ratio was 1.57, median body mass index was 21.1 kg/m^2, and all patients had stage IA gastric cancer located within the lower two-thirds of the stomach. Undifferentiated histology was more frequently observed than differentiated histology.

Table 2 shows details of the surgical procedure. The median duration of the surgery was 311.5 min; median docking, console, and anastomosis times were 22, 212.5, and 63 min, respectively. Distal gastrectomy and pylorus-preserving gastrectomy were performed in nine patients each, and all patients underwent D1 + lymph node dissection. No patient required conversion to laparoscopic or open surgery; thus, the RADG completion rate was 100 %. Median blood loss was 32.5 ml; blood transfusion was not required in any of the patients.

Postoperative clinical course is shown in Table 3. The median duration of postoperative hospital stay was 8 days. Incidence of intraabdominal infectious complication was 0 % [0/18; 90 % confidence interval (CI), 0–12.0 %]. The overall proportion of in-hospital adverse events was 22.2 % (90 % CI, 8.0–43.9 %), with all rated as grade II, from which all patients recovered well with medical treatment only and no surgical interventions.

Table 1 Patient characteristics

Number of patients	18
Sex (cases)	
Male	11
Female	7
Age (years)	
Median	65.5
Range	53–80
Body mass index (kg/m^2)	
Median	21.1
Range	16.2–25.8
Tumor location (cases)	
Upper third	0
Middle third	11
Lower third	7
Histological type (cases)	
Differentiated	6
Undifferentiated	12
Tumor size (cm)	
Median	
Range	
Clinical stage (cases)	
IA	18
IB	0

Table 2 Details of surgical procedures

Operation time (min)	
Median	311.5
Range	225–375
Docking time (min)	
Median	22
Range	11–41
Console time (min)	
Median	212.5
Range	161–291
Anastomosis time (min)	
Median	63
Range	41–111
Blood loss (ml)	
Median	32.5
Range	0–160
Perioperative blood transfusion (cases)	
Yes	0
No	18
Type of gastrectomy (cases)	
PPG	9
DG	9
Reconstruction method	
Roux-en-Y	1
Billroth I	8
Gastro-gastrostomy	9
Extent of lymph node dissection (cases)	
D1+	18
D2	0
Number of retrieved lymph nodes (cases)	
Median	40
Range	26–89
Completion of RADG (cases)	
Yes	0
No	18

PPG pylorus-preserving gastrectomy
DG distal gastrectomy

Table 3 Postoperative clinical course

Postoperative hospital stay (days)	
Median	8
Range	7–10
Postoperative morbidities (cases)	
Intraabdominal infectious complications	0
Anastomotic leakage	0
Pancreas-related infection	0
Intraabdominal abscess	0
Other complications	
Wound infection	2
Delayed gastric emptying	1
Liver dysfunction	1

Discussion

The present study showed RADG is feasible in terms of safety if experienced laparoscopic surgeons perform the surgery, with a zero incidence of intraabdominal infectious complications recorded (90 % CI, 0–12.0 %).

Before May 2012, we had performed five RADGs as an institute, and based on this experience, we assessed RADG as technically feasible. In addition, none of these five patients developed any postoperative complications. We therefore decided to more thoroughly assess the safety of RADG in the present prospective study.

Previous retrospective studies demonstrated that RADG was a feasible treatment for gastric cancer [4, 5, 10, 12, 14, 18, 19]. Surgeons generally believed that much more meticulous surgery could be performed with the da Vinci Surgical System because of the three-dimensional surgical view provided and the flexibility of instrumentation. However, RADG required longer operation times [5, 14, 17–19, 21] and was more expensive than laparoscopic or open gastrectomy [14, 16, 21, 33]. In addition, the advantages of RADG compared to conventional procedures were not clear from these previous studies, and no prospective study investigating the safety of RADG was reported.

The incidence of postoperative intraabdominal infectious complication in the present study was 0 % (90 % CI, 0–12.2 %) with a 22.2 % overall proportion of in-hospital adverse events (90 % CI, 8.0–43.9 %) in this study. A similar complication rate (0–47.3 %) has been reported in previous retrospective studies, although none had focused on the incidence of intraabdominal infectious complication [4, 5, 8–10, 12, 17, 18, 22, 33]. With the three-dimensional magnified view available with RADG, surgeons were able to recognize anatomical structures much more precisely than with the standard two-dimensional view. In addition, the flexibility of instruments used helped surgeons perform meticulous surgery. We propose that these advantages of RADG resulted in the low complication rate.

Other possible reasons for the low complication rate recorded in this study were involving only experienced laparoscopic surgeons to perform the procedures and the relatively lower BMI of the patients compared with that reported in Western series. High BMI is a possible risk factor for postoperative complications after open and laparoscopic gastrectomy, although this association remains controversial [34–38]. The present study included only one overweight patient (BMI, 25.8). The feasibility of RADG in overweight or obese patients is still unclear and must be clarified in a future trial.

RADG procedures required longer surgical times than LADG. Indeed, there was a difference of 86.5 min in our institute between RADG and LADG [31]. We considered that the meticulousness of the procedure was inversely proportional to operation time to some degree. With the magnified and three-dimensional magnified view and instrument flexibility, surgeons were able to perform much more meticulous surgery at the expense of increased operation time.

There were other possible reasons for the longer operation times. First, RADG was performed during our learning curve period whereas LADG was not. Second, we did not use ultrasonic shears provided for RADG because such usage is not allowed in Japan with the da Vinci Surgical System. Thus, if we achieve our learning curve with RADG and the usage of ultrasonic devices is permitted in the future, we will be able to reduce the operation time.

We believe that the advantages of the da Vinci Surgical System would be enhanced when we use it for more complicated surgery such as gastrectomy with extended (D2) lymph node dissection or mediastinal lymph node dissection. During extended lymph node dissection, we were able to recognized layers precisely as well as small vessels because of the three-dimensional magnified view. In addition, the flexibility of instruments and tremor suppression enabled us to do each procedure meticulously, resulting in high-quality lymph node dissection. Similar advantages would be obtained when we perform lower mediastinal lymph node dissection for adenocarcinoma of esophagogastric junction in which the surgical field is narrow and linear instruments used in laparoscopic surgery frequently interfere. Thus, our next step is to indicate the da Vinci Surgical System for these complicated surgeries.

In the present study, early surgical outcomes of RADG were not compared with conventional open or laparoscopic surgery; thus, it is still unclear if RADG is superior to conventional surgeries in this regard. Although previous retrospective studies compared surgical outcomes of RADG with LADG or ODG, there is no prospective randomized trial comparing RADG and other procedures [5, 17, 18, 20, 22]. In addition, survival outcomes of RADG

remain unclear. Future trials are needed to clarify the superiority of RADG over other procedures, including both short- and long-term outcomes, before it can be accepted as a standard treatment for gastric cancer.

The present study had limitations including the relatively small sample size. The Japanese national insurance system does not reimburse patients for RADG; thus, either the patient or the hospital has to pay the entire admission fee in addition to the surgical fee (around USD $20,000). It was therefore challenging to recruit sufficient patient numbers even for a small phase II trial, and so long as this situation persists, the cost of such surgeries will be an issue and the forthcoming surgeries will be paid by the hospital or the patient in our hospital. We consider that the future practical use of RADG in Japan as an advanced medical technology will require a well-planned prospective trial involving sufficient patient numbers to provide important information about issues such as reimbursement. However, we also believe that accumulated evidence from smaller prospective studies such as ours will help future, larger-scale trials for RADG.

In conclusion, this early phase II study suggested that RADG might be a safe and feasible procedure for stage IA gastric cancer, providing experienced surgeons perform the surgery. This conclusion should be clarified in subsequent late phase II studies with a larger sample size.

References

1. Kim HH, Hyung WJ, Cho GS, Kim MC, Han SU, Kim W, Ryu SW, et al. Morbidity and mortality of laparoscopic gastrectomy versus open gastrectomy for gastric cancer: an interim report. A phase III multicenter, prospective, randomized trial (KLASS Trial). Ann Surg. 2010;251(3):417–20.
2. Katai H, Sasako M, Fukuda H, Nakamura K, Hiki N, Saka M, et al. Safety and feasibility of laparoscopy-assisted distal gastrectomy with supra-pancreatic nodal dissection for clinical stage I gastric cancer: a multicenter phase II trial (JCOG 0703). Gastric Cancer. 2010;13(4):238–44.
3. Nakamura K, Katai H, Mizusawa J, Yoshikawa T, Ando M, Terashima M, et al. A phase III study of laparoscopy-assisted versus open distal gastrectomy with nodal dissection for clinical stage IA/IB gastric cancer (JCOG0912). Jpn J Clin Oncol. 2013;43(3):324–7.
4. Song J, Oh SJ, Kang WH, Hyung WJ, Choi SH, Noh SH. Robot-assisted gastrectomy with lymph node dissection for gastric cancer: lessons learned from an initial 100 consecutive procedures. Ann Surg. 2009;249(6):927–32.
5. Song J, Kang WH, Oh SJ, Hyung WJ, Choi SH, Noh SH. Role of robotic gastrectomy using da Vinci system compared with laparoscopic gastrectomy: initial experience of 20 consecutive cases. Surg Endosc. 2009;23(6):1204–11.
6. Hashizume M, Sugimachi K. Robot-assisted gastric surgery. Surg Clin N Am. 2003;83(6):1429–44.
7. Kakeji Y, Konishi K, Ieiri S, Yasunaga T, Nakamoto M, Tanoue K, et al. Robotic laparoscopic distal gastrectomy: a comparison of the da Vinci and Zeus systems. Int J Med Robot. 2006;2(4):299–304.
8. Isogaki J, Haruta S, Man IM, Suda K, Kawamura Y, Yoshimura F, et al. Robot-assisted surgery for gastric cancer: experience at our institute. Pathobiol J Immunopathol Mol Cell Biol. 2011;78(6):328–33.
9. Park SS, Kim MC, Park MS, Hyung WJ Rapid adaptation of robotic gastrectomy for gastric cancer by experienced laparoscopic surgeons. Surg Endosc. 2012;26(1):60–7.
10. Lee HH, Hur H, Jung H, Jeon HM, Park CH, Song KY. Robot-assisted distal gastrectomy for gastric cancer: initial experience. Am J Surg. 2011;201(6):841–5.
11. Heemskerk J, van Gemert WG, de Vries J, Greve J, Bouvy ND. Learning curves of robot-assisted laparoscopic surgery compared with conventional laparoscopic surgery: an experimental study evaluating skill acquisition of robot-assisted laparoscopic tasks compared with conventional laparoscopic tasks in inexperienced users. Surg Laparosc Endosc Percutan Tech. 2007;17:171–4.
12. D'Annibale A, Pende V, Pernazza G, Monsellato I, Mazzocchi P, Lucandri G, et al. Full robotic gastrectomy with extended (D2) lymphadenectomy for gastric cancer: surgical technique and preliminary results. J Surg Res. 2011;166(2):e113–20.
13. Pugliese R, Maggioni D, Sansonna F, Costanzi A, Ferrari GC, Di Lernia S, et al. Subtotal gastrectomy with D2 dissection by minimally invasive surgery for distal adenocarcinoma of the stomach: results and 5-year survival. Surg Endosc. 2010;24(10):2594–602.
14. Patriti A, Ceccarelli G, Bellochi R, Bartoli A, Spaziani A, Di Zitti L, et al. Robot-assisted laparoscopic total and partial gastric resection with D2 lymph node dissection for adenocarcinoma. Surg Endosc. 2008;22(12):2753–60.
15. Pugliese R, Maggioni D, Sansonna F, Ferrari GC, Forgione A, Costanzi A, et al. Outcomes and survival after laparoscopic gastrectomy for adenocarcinoma. Analysis on 65 patients operated on by conventional or robot-assisted minimal access procedures. Eur J Surg Oncol. 2009;35(3):281–8.
16. Anderson C, Ellenhorn J, Hellan M, Pigazzi A. Pilot series of robot-assisted laparoscopic subtotal gastrectomy with extended lymphadenectomy for gastric cancer. Surg Endosc. 2007;21(9):1662–6.
17. Kim MC, Heo GU, Jung GJ. Robotic gastrectomy for gastric cancer: surgical techniques and clinical merits. Surg Endosc. 2010;24(3):610–5.
18. Woo Y, Hyung WJ, Pak KH, Inaba K, Obama K, Choi SH et al. Robotic gastrectomy as an oncologically sound alternative to laparoscopic resections for the treatment of early-stage gastric cancers. Arch Surg. 2011;146(9):1086–92.
19. Caruso S, Patriti A, Marrelli D, Ceccarelli G, Ceribelli C, Roviello F, et al. Open vs. robot-assisted laparoscopic gastric resection with D2 lymph node dissection for adenocarcinoma: a case-control study. Int J Med Robot. 2011;7(4):452–8.
20. Yoon HM, Kim YW, Lee JH, Ryu KW, Eom BW, Park JY, et al. Robot-assisted total gastrectomy is comparable with laparoscopically assisted total gastrectomy for early gastric cancer. Surg Endosc. 2012;26(5):1377–81.
21. Park JY, Jo MJ, Nam BH, Kim Y, Eom BW, Yoon HM, et al. Surgical stress after robot-assisted distal gastrectomy and its economic implications. Br J Surg. 2012;99(11):1554–61.
22. Hyun MH, Lee CH, Kwon YJ, Cho SI, Jang YJ, Kim DH et al. Robot versus laparoscopic gastrectomy for cancer by an experienced surgeon: comparisons of surgery, complications, and surgical stress. Ann Surg Oncol. 2013;20(4):1258–65.
23. Sobin L, Gospodarowicz M, Wittekind C. TNM classification of malignant tumors. 7th ed. New York: Wiley-Blackwell; 2009.
24. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer. 2011;14(2):113–23.

25. Sano T, Aiko T. New Japanese classifications and treatment guidelines for gastric cancer: revision concepts and major revised points. Gastric Cancer. 2011;14(2):97–100.
26. Hiki N, Fukunaga T, Yamaguchi T, Nunobe S, Tokunaga M, Ohyama S, et al. The benefits of standardizing the operative procedure for the assistant in laparoscopy-assisted gastrectomy for gastric cancer. Langenbecks Arch Surg. 2008;393(6):963–71.
27. Fukunaga T, Hiki N, Tokunaga M, Nohara K, Akashi Y, Katayama H, et al. Left-sided approach for supra-pancreatic lymph node dissection in laparoscopy-assisted distal gastrectomy without duodenal transection. Gastric Cancer. 2009;12(2):106–12.
28. Nunobe S, Hiki N, Fukunaga T, Tokunaga M, Ohyama S, Seto Y, et al. Laparoscopy-assisted pylorus-preserving gastrectomy: preservation of vagus nerve and infrapyloric blood flow induces less stasis. World J Surg. 2007;31(12):2335–40.
29. Tokunaga M, Hiki N, Fukunaga T, Ohyama S, Nunobe S, Yamada K, et al. Is preservation of the celiac branch of the vagal nerve effective in preventing stasis following pylorus-preserving gastrectomy? Hepatogastroenterology. 2011;58(107-108):1046–50.
30. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205–13.
31. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien–Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250(2):187–96.
32. Tokunaga M, Kondo J, Tanizawa Y, Bando E, Kawamura T, Terashima M. Postoperative intra-abdominal complications assessed by the Clavien-Dindo classification following open and laparoscopy-assisted distal gastrectomy for early gastric cancer. J Gastrointest Surg. 2012.
33. Clark J, Sodergren MH, Purkayastha S, Mayer EK, James D, Athanasiou T, et al. The role of robotic assisted laparoscopy for esophagogastric oncological resection; an appraisal of the literature. Dis Esophagus. 2011;24(4):240–50.
34. Tokunaga M, Hiki N, Fukunaga T, Ogura T, Miyata S, Yamaguchi T. Effect of individual fat areas on early surgical outcomes after open gastrectomy for gastric cancer. Br J Surg. 2009;96(5):496–500.
35. Noshiro H, Shimizu S, Nagai E, Ohuchida K, Tanaka M. Laparoscopy-assisted distal gastrectomy for early gastric cancer: is it beneficial for patients of heavier weight? Ann Surg. 2003;238(5):680–5.
36. Yamada H, Kojima K, Inokuchi M, Kawano T, Sugihara K. Effect of obesity on technical feasibility and postoperative outcomes of laparoscopy-assisted distal gastrectomy: comparison with open distal gastrectomy. J Gastrointest Surg. 2008;12(6):997–1004.
37. Makino H, Kunisaki C, Izumisawa Y, Tokuhisa M, Oshima T, Nagano Y, et al. Effect of obesity on laparoscopy-assisted distal gastrectomy compared with open distal gastrectomy for gastric cancer. J Surg Oncol. 2010;102(2):141–7.
38. Hiki N, Fukunaga T, Yamaguchi T, Ogura T, Miyata S, Tokunaga M, et al. Increased fat content and body shape have little effect on the accuracy of lymph node retrieval and blood loss in laparoscopic distal gastrectomy for gastric cancer. J Gastrointest Surg. 2009;13(4):626–33.

ロボット支援手術の安全性を評価する臨床第Ⅱ相試験

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特集

····· 特集2　食道癌・胃癌におけるロボット支援手術の有用性 ·····

ロボット支援手術の安全性を評価する臨床第Ⅱ相試験

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Early Phase Ⅱ study to Evaluate the Feasibility of Robot-Assisted Distal Gastrectomy: Terashima M[*1], Tokunaga M[*1], Tanisawa Y[*1], Bandoh E[*1], Kawamura Y[*1], Makuuchi R[*1], Miki Y[*1], Kinugasa Y[*1] and Uesaka K[*1] ([*1] Division of Gastric Surgery, [*2] Division of Gastrointestinal Surgery, Shizuoka Cancer Center)

Safety of Robot-assisted gastrectomy (RAG) with nodal dissection for clinical stage IA gastric cancer was evaluated in a single-center, prospective phaseⅡ study. Patients with clinical stage IA gastric cancer located within the lower two-thirds of the stomach were included in this study. The primary endpoint was the incidence of postoperative intraabdominal infectious complications including anastomotic leakage, pancreas-related infection, and intraabdominal abscess. A total of 18 patients were enrolled. The incidence of intraabdominal infectious complication was 0% (90% CI, 0～12.0%). No patient required conversion to laparoscopic or open gastrectomy; thus, the RAG completion rate was 100%. RAG might be a safe and feasible procedure for stage IA gastric cancer.

Key words: Robot assisted gastrectomy, da Vinci surgical system, Minimum invasive surgery, Gastric cancer, PhaseⅡ study

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はじめに

胃癌に対する腹腔鏡下胃切除（LAG）はわが国および韓国を中心として急速に普及している．その安全性に関してはいくつかの報告がなされているが，生存の成績に関しては無作為化比較試験の結果が待たれるところである．低侵襲手術として普及しているLAGではあるが，開腹手術と比較し高度な技術が必要とされ，とりわけ，二次元の視野下に自由度の少ない鉗子を使用することが特に習熟を要する手技とされている．近年，前立腺全摘に対して保険収載されたロボット支援手術は腹腔鏡手術の欠点を克服可能な方法として注目されている．即ち，三次元の視野の基に，自由度の高い鉗子を使用して，手指の震えのない繊細な手術を実施することが可能である．胃癌に対するロボット手術の報告は2003年以来いくつかなされているものの[1,2]，そのほとんどが後ろ向きの症例集積報告であり，前向きの臨床試験の報告はなされていない．ロボット支援手術が今後先進医療や保険収載を目指すには，臨床試験によるエビデンスの確立は不可欠と考えられる．

われわれは，胃癌手術に対するロボット支援手術（RAG）の前向き臨床試験を実施し，早期第Ⅱ相試験に関してはすでに論文報告しているので[3]，その結果を紹介する．

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1 対象と方法

本試験は単一施設の前向き臨床第Ⅱ相試験として立案された．症例選択基準は以下の通りである．1）組織学的に胃癌と確認されている，2）臨床的Stage ⅠA，3）ESDの適応とならない，4）腫瘍の占居部位がMもしくはL，5）十二指腸浸潤がない，6）年齢が20歳から80歳，7）PSが0もしくは1，8）BMIが30 kg/㎡未満，9）上腹部の手術や虫垂切除を除く腸管切除の既往がない，10）悪性腫瘍に対する化学療法や放射線療法の既往がない，11）主要臓器機能が保たれている，12）文書で同意が得られている．

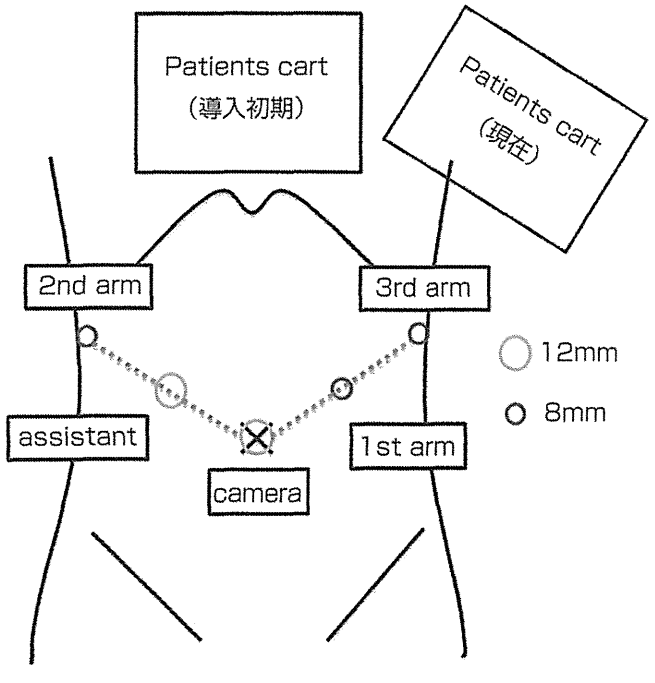
本試験は院内の倫理委員会の承認を得たうえで，NCIのclinical trials.govに登録し（NCT 1504997）実施された．

実際の手術手技に関してはda Vinci Sを使用し，当初はpatient cartを患者の頭側正中に配置していたが，最近ではやや左側で左肩越しに配置し，3rd armを患者左側におき，5ポート法にて行っている（図）．臍部（もしくは臍下部）にカメラポートを挿入，左側腹部にダビンチ用カニューラを挿入し3rd armを接続，カメラポートと3rd armの中間にダビンチカニューラを挿入し1st armを接続している．患者右側腹部にダビンチカニューラを挿入し，2nd armを接続，2nd armとカメラポートの間に助手用のアシスタントポート（12mm）を挿入した．肝臓を圧排する目的で心窩部からネイサンソン鉤を挿入した．1st armにはモノポラー剪刀もしくはバイポラーMaryland鉗子を，2nd armには有窓バイポラー鉗子を，3rd armにはCadiere鉗子を使用した．

リンパ節郭清を含めた手術手技は基本的に腹腔鏡下幽門側胃切除もしくは腹腔鏡下幽門保存胃切除術に準じており，全例で胃癌治療ガイドラインで推奨されているD1＋郭清を施行した．

早期臨床第Ⅱ相試験の対象症例はすべて上腹部に4～5cmの小切開をおいて，環状吻合器を用いた後壁打ち抜き法によるビルロートⅠ法もしくは，Gambee法による手縫いの胃胃吻合で再建していたが，最近の症例はすべて体腔内吻合としている．

手術はすべて日本内視鏡外科学会の技術認定医



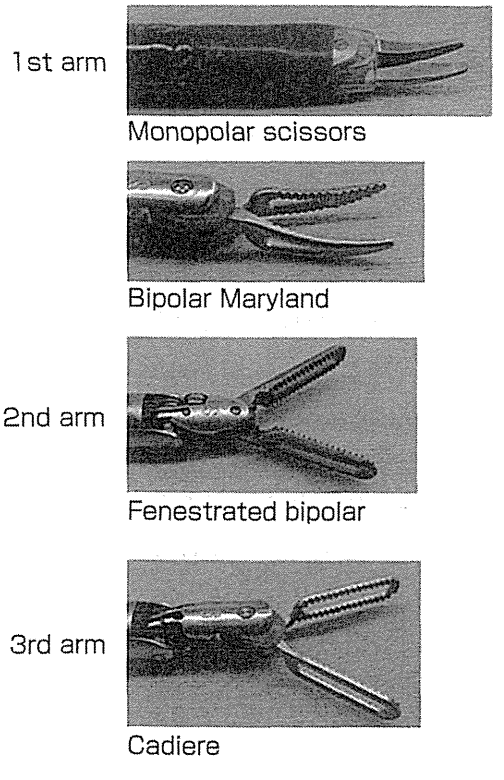


図　ポート部位とPatients cartの配置

表1　患者背景

症例数	18
性別	
男性	11
女性	7
年齢	
中央値	65.5
範囲	53～80
Body mass index (kg/㎡)	
中央値	21.1
範囲	16.2～25.8
腫瘍占居部位	
U領域	0
M領域	11
L領域	7
Clinical stage	
IA	18
IB	0

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である二人の術者によって行われ，da Vinci手術に必要とされるすべてのトレーニングプログラムを終了後，試験を開始した．尚，初期の2例はda Vinci手術の十分な経験を有する外科医を招請して手術を施行した．

早期臨床第Ⅱ相試験の主要評価項目はClavien-Dindo分類でGradeⅡ以上の縫合不全，膵液瘻，腹腔内膿瘍など腹腔内感染性合併症の発生割合とし，二次的評価項目は生存期間，無再発生存期間，ロボット手術完遂割合，すべての術後合併症発生割合とした．

過去の当施設における腹腔鏡下胃切除術（LAG）の腹腔内感染性合併症の発生割合が4.5％であったことから，期待値を4％，閾値を15％と設定し，感度を片側10％，検出力を70％と設定したところ，必要症例数は18例と算出された．導入初期に5例の習熟期間をおいた後に試験が開始された．

2 結　果

2012年5月から2012年11月までに18例の症例を集積した．表1に患者背景を示したが，男女比は1.57で一般的な手術症例と比較してやや女性が多く，BMIが低値である傾向を認めた．

手術成績を表2に示したが，手術時間の中央値は311.5分とLAGと比較しても明らかに長い傾向が認められた，その内訳はドッキング時間が22分，コンソール時間が212.5分，再建時間が63分であった．幽門側胃切除と幽門保存胃切除の症例数は同数であり，すべての症例でD1+のリンパ節郭清が行われ，開腹手術への移行症例は1例もなかった．出血量の中央値は32.5mlときわめて少なく，当然のことながら輸血を施行した症例もなかった．

術後短期成績を表3に示した．主要評価項目である腹腔内感染性合併症の発生は一例も認められなかった．全合併症の発生割合は22.2％であったが，すべてGradeⅡであり，全症例において速やかに回復し退院が可能であった．術後在院期間の中央値は8日であった．ちなみに導入初期の5例においても術後合併症の発生は認めなかった．

3 考　察

今回の検討から，腹腔鏡下手術に習熟した外科医が施行すれば，RAGは安全に施行できることが示された．本試験の結果を受けて，現在後期臨床第Ⅱ相試験を実施中である．対象症例をStage IBまで拡大し，胃全摘も含めて実施しているが，前期後期合わせて63例経過した時点での解析では依然として腹腔内感染性合併症の発生症例を認めておらず，全合併症の発生割合も9.7％ときわめて低率である．集積症例数は100例を予定している．ロボット支援手術は腹腔鏡下手術に対して三次元の術野が得られること，鉗子の自由度がきわめて高いことが大きな利点としてあげられる．これを実際の胃癌手術の場にあてはめてみると，RAGでは縫合手技が容易であり，とりわけ体腔内吻合を行う際には有利に働く．さらに，リンパ節郭清に際しては，腹腔鏡手術よりも近接した術野が取りやすいため，LAGにも増してより微細な解剖学的構築を理解しやすい．膵臓周囲のリンパ節郭清において膵被膜を剥離する際には，膵実質と被膜との境界が容易に識別可能である．さら

表2　手術成績

切除術式		手術時間（分）	
PPG	9	中央値	315
DG	9	範囲	225～375
再建方法		ドッキング時間（分）	
Roux-en-Y	1	中央値	22
Billroth I	8	範囲	11～41
胃胃吻合	9	コンソール時間（分）	
リンパ節郭清範囲		中央値	218
D1+	18	範囲	168～291
D2	0	再建時間	
郭清リンパ節個数		中央値	63
中央値	40	範囲	41～111
範囲	26～89	出血量（ml）	
RADG完遂		中央値	40
可能	18	範囲	0～160
不可能	0	輸血	
		あり	0
		なし	18

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表3　術後短期成績

術後在院日数（日）	
中央値	8
範囲	7～10
術後合併症	
腹腔内感染性合併症	0
縫合不全	0
膵液漏	0
腹腔内膿瘍	0
その他の合併症	
創感染	2
胃内容排泄遅延	1
肝機能障害	1

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に，自由度の高い鉗子の使用と相まって，膵上縁の郭清においてはほとんど膵臓を圧迫することなしに深部のリンパ節郭清が可能である．このことは膵臓に対する愛護的な操作に繋がり，ひいては膵液漏，腹腔内膿瘍の予防に繋がっているものと考えられる．現在，わが国のロボット支援手術では超音波凝固切開装置が使用できないため，電気メスだけで手術を進める必要がある．電気メスだけの手術では一旦出血させると止血が困難となるため，極力出血させないような丁寧な剥離操作が必要とされる．このことは手術時間に関してはマイナスに働くものの，ミストの発生が少ないためより近接した術野が得られること，出血量が少ないことに繋がり，先述した微細解剖の理解を深めることに大いに役立っている．現時点で，ロボット支援手術で大きな問題点とされている触覚の欠如に関しても，高精細カメラを通じて得られる，組織の緊張度の情報や，マスターコントローラと鉗子の動きの僅かな差など視覚から得られる情報により，かなりの範囲で補正が可能である．現時点で，ロボット支援手術における手技上の最大の問題点は鉗子や，アームの干渉による稼働制限であり，とりわけ身体の小さな患者が多いわが国の胃癌手術ではしばしば問題となる．体位やpatient cartの方向，微妙なポート位置などにコツが必要とされる．

これまでRAGに関しては後向きの報告しかな

されておらず，LAGとRAGを比較するメタ解析も多数報告されているものの[4]，前向きの比較試験が存在しない以上，あまり意味のある結果は得られていない．RAGが今後正当な評価を得るためには前向きの臨床試験は必須であり，われわれのような前向きの第Ⅱ相試験の積み重ねはきわめて重要であると考えている．今後はこういった第Ⅱ相試験の成績を基に，第Ⅲ相試験で有用性を評価すべきであると考えている．

まとめ

早期胃癌に対するロボット支援下の幽門側胃切除術は安全に施行可能であった．ここ四半世紀における腹腔鏡の進歩発展には目覚ましいものがある．医療機器の技術革新によって医療そのものが進化していくことが実証されてきた．確かに現在の手術支援ロボットはまだまだ解決すべき問題を多数抱えている．しかし，工業技術はわれわれ外科医の想像を遙かに超えるスピードで進歩している．恐らく今後10年で腹腔鏡手術のかなりの部分はいわゆるロボット支援下の手術にとってかわるものと考えられる．

文　献

1) Hashizume M, Sugimachi K：Robot-assisted gastric surgery. *Surg Clin North Am* **83**：1429-1444, 2003
2) Woo Y, Hyung WJ, Pak KH, et al：Robotic gastrectomy as an oncologically sound alternative to laparoscopic resections for the treatment of early-stage gastric cancers. *Arch Surg* **146**：1086-1092, 2011
3) Tokunaga M, Sugisawa N, Kondo J, et al：Early phaseⅡ study of robot-assisted distal gastrectomy with nodal dissection for clinical stage ⅠA gastric cancer. *Gastric Cancer*, 2013
4) Hyun MH, Lee CH, Kim HJ, et al：Systematic review and meta-analysis of robotic surgery compared with conventional laparoscopic and open resections for gastric carcinoma. *Br J Surg* **100**：1566-1578, 2013

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Perioperative Risk Assessment for Gastrectomy by Surgical Apgar Score

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ABSTRACT

Background. Recently, a simple and easy complication prediction system, the surgical apgar score (SAS) calculated by three intraoperative parameters (estimated blood loss, lowest mean arterial pressure, and lowest heart rate), has been proposed for general surgery. In this study, we evaluated the predictability of the original SAS (oSAS) for severe complications after gastrectomy. In addition, the predictability of a modified SAS (mSAS) was evaluated, in which the cutoff value for blood loss was slightly modified.

Methods. We investigated 328 patients who underwent gastrectomy at the Shizuoka Cancer Center in 2010. Clinical data, including intraoperative parameters, were collected retrospectively. Patients with postoperative morbidities classified as Clavien–Dindo grade IIIa or more were defined as having severe complications. Univariate and multivariate analyses were performed to elucidate factors that affected the development of severe complications.

Results. Thirty-six patients (11.0 %) had severe complications postoperatively. Univariate analyses showed that the oSAS ($p = 0.007$) and mSAS ($p < 0.001$), as well as sex, preoperative chemotherapy, cStage, type of operation, thoracotomy, surgical approach, operation time, and extent of lymph node dissection, were associated with severe complications. Multivariate analysis showed that an mSAS ≤ 6 was found to be an independent risk factor for severe complication, while an oSAS ≤ 6 was not.

Conclusions. The oSAS was not found to be a predictive factor for severe complications following gastrectomy in Japanese patients. A slightly modified SAS (i.e. the mSAS) is considered to be a useful predictor for the development of severe complications in elective surgery.

Gastrectomy with lymph node dissection is the mainstay of treatment for patients with gastric cancer to achieve a cure,[1] even though several chemotherapy regimens have been shown to be effective.[2,3] The morbidity after gastrectomy with lymph node dissection has been reported to range from 14.3 to 34.0 %.[4–6] The most frequently observed complications are pancreatic fistula, anastomotic leakage, and abdominal abscess, and these complications are sometimes fatal. This is why it is important to predict the occurrence of these complications soon after surgery, and determine the appropriate postoperative care.

Previously, several scoring models have been reported to be useful for predicting complications. However, previously reported scoring models such as the Physiologic and Operative Severity Score for the Enumeration of Mortality (POSSUM),[7] the National Surgical Quality Improvement Programme (NSQIP),[8,9] and the Estimation of Physiologic Ability and Surgical Stress (E-PASS),[10] require complex calculations using numerous perioperative variables not readily available at the bedside.

Recently, a simple and easy complication prediction system, the so-called Surgical Apgar Score (SAS), was proposed for general surgery.[11] It consists of three intraoperative parameters: estimated blood loss (EBL), lowest intraoperative mean arterial pressure (L-MAP), and lowest intraoperative heart rate (L-HR), and has been validated in

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