Clinical advantages of robotic gastrectomy for clinical stage I/II gastric cancer: a multi-institutional prospective single-arm study

Ichiro Uyama¹ · Koichi Suda¹ · Masaya Nakauchi¹ · Takahiro Kinoshita² · Hirokazu Noshiro³ · Shuji Takiguchi^{4,5} · Kazuhisa Ehara⁶ · Kazutaka Obama^{7,8} · Shiro Kuwabara⁹ · Hiroshi Okabe¹⁰ · Masanori Terashima¹¹

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Abstract

Background Robotic gastrectomy (RG) for gastric cancer (GC) has been increasingly performed for a decade; however, evidence for its use as a standard treatment has not yet been established. The present study aimed to determine the safety, feasibility, and effectiveness of RG for GC.

Methods This multi-institutional, single-arm prospective study, which included 330 patients from 15 institutions, was designed to compare morbidity rate of RG with that of a historical control (conventional laparoscopic gastrectomy, LG). This trial was approved for Advanced Medical Technology (“Senshiniryo”) B. The included patients were operable patients with cStage I/II GC. The primary endpoint was morbidity (Clavien–Dindo Grade $\geq$ IIIa). The specific hypothesis was that RG could reduce the morbidity rate to less than half of that with LG (6.4%). A sample size of 330 was considered sufficient (one-sided alpha 0.05, power 80%).

Results Among the 330 study patients, the protocol treatment was suspended in 4 patients. Thus, 326 patients fully enrolled and completed the study. The median patient age and BMI were 66 years and 22.4 kg/m², respectively. Distal gastrectomy was performed in 253 (77.6%) patients. The median operative time and estimated blood loss were 313 min and 20 mL, respectively. No 30-day mortality was seen, and morbidity showed a significant reduction to 2.45% with RG ($p=0.0018$).

Conclusions RG for cStage I/II GC is safe and feasible. It may be effective in reducing morbidity with LG.

Keywords Stomach neoplasms · Gastrectomy · Robotic surgical procedure · Minimally invasive surgical procedures · Postoperative complications

Abbreviations

RG	Robotic gastrectomy
GC	Gastric cancer
LG	Laparoscopic gastrectomy
DVSS	Da Vinci surgical system

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✉ Ichiro Uyama
iuyama@mac.com

¹ Department of Surgery, Fujita Health University, 1-98 Dengakugakubo, Kutsukake, Toyoake, Aichi 470-1192, Japan

² Gastric Surgery Division, National Cancer Center Hospital East, Kashiwa, Japan

³ Department of Surgery, Saga University Faculty of Medicine, Saga, Japan

⁴ Department of Surgery, Graduate School of Medicine, Osaka University, Osaka, Japan

⁵ Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Nagoya City University, Nagoya, Japan

⁶ Department of Gastroenterological Surgery, Saitama Cancer Center, Saitama, Japan

⁷ Department of Surgery, Kyoto City Hospital, Kyoto, Japan

⁸ Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan

⁹ Digestive Surgery, Niigata City General Hospital, Niigata, Japan

¹⁰ Department of Surgery, Otsu City Hospital, Otsu, Japan

¹¹ Division of Gastric Surgery, Shizuoka Cancer Center, Shizuoka, Japan

POPF	Postoperative pancreatic fistula
C-D	Clavien–Dindo classification
EQ-5D	EuroQol 5 dimension
CECT	Contrast-enhanced computed tomography
MHLW	Ministry of Health, Labour, and Welfare
CRF	Case report form

Introduction

Gastric cancer (GC) has been shown to be the fifth most common cancer and the third leading cause of cancer-related death worldwide [1]. Surgical resection is the only curative treatment approach, and regional lymphadenectomy is recommended as a part of radical gastrectomy [2, 3]. Laparoscopic gastrectomy (LG) is being increasingly used because of its beneficial short-term effects when compared with open gastrectomy [4].

The da Vinci surgical system (DVSS) was developed to overcome several disadvantages that were identified in standard minimally invasive surgery using a laparoscope [2]. In the field of gastric surgery, most laparoscopic surgeons expect that the use of the DVSS will help to overcome the technical difficulties of LG, improving its safety, reproducibility, and long-term outcomes [2, 5, 6]. However, the only large nonrandomized prospective study (NCT01309256) comparing the DVSS with LG demonstrated that the use of the DVSS increased operative time and cost and that no difference in morbidity was observed, suggesting that the use of the DVSS might reduce cost-effectiveness [7]. In the meantime, at Fujita Health University, robotic gastrectomy (RG) was introduced in 2009 and actively used this approach in operable patients with resectable GC at the patient's own expense [2, 8]. The double-bipolar method, the da Vinci's plane theory, and the monitor quadrisection theory, which are universally available for gastrointestinal and hepatopancreato-biliary surgeries, were established by I.U. and K.S., and the technique was standardized [9]. Consequently, it was demonstrated that the morbidity (overall complications) rate with RG was about one-fifth the rate with LG and that reduced morbidity, including postoperative pancreatic fistula (POPF), with RG led to an improvement in the short-term postoperative course [2]. The safety, feasibility, and economical efficiency of RG for GC remain unclear.

Therefore, the aim of the present study (UMIN000015388) was to determine if the advantageous short-term outcomes achieved at Fujita Health University could be well reproduced in a prospective multicenter setting, so that insured use of RG for GC may be approved by the Ministry of Health, Labour, and Welfare (MHLW). We hereby present the data on the short-term outcomes. Survival analysis is scheduled to take place in January 2020.

Materials and methods

Study design and endpoints

This was a multi-institutional, single-arm prospective phase II study. RG was performed prospectively in consecutive patients with cStage I or II GC. The primary endpoint was morbidity determined by Clavien–Dindo classification (C-D) Grade IIIa or higher [10]. We selected this endpoint, because postoperative complications requiring surgical, endoscopic, or radiological intervention, which correspond to C-D Grade IIIa, remarkably extend the admission period, threaten the patient's life, and increase medical cost [2, 10–12]. The secondary endpoints were morbidity rate (C-D Grade $\geq$ II); health outcomes measured with EuroQol 5 Dimension (EQ-5D) [13] and total medical cost; RG completion rate; open surgery conversion rate; intraoperative adverse events; surgical outcomes, including operative time, console time, estimated blood loss, and number of dissected lymph nodes; short-term outcomes, including time to oral intake, postoperative hospital stay, and mortality; and long-term outcomes, including 3-year overall and relapse-free survival rates.

For sample size calculation, we used data from historical controls in three leading institutions (Fujita Health University, Saga University, and Kyoto University). In these institutions, 998 LG procedures were performed between 2009 and 2012. Of these 998 LG procedures, 801 were performed on patients preoperatively diagnosed with cStage I or II. Morbidity (C-D Grade $\geq$ IIIa) occurred in 51 of these 801 patients (6.4%). We hypothesized that RG could reduce the morbidity rate to less than half of that with LG, as RG has many advantages to reduce postoperative complications. Therefore, the threshold level was set as 6.4% and the expected level was set as 3.2%. The required sample size was calculated to be 330 (one-sided alpha of 0.05 and power of 80%). In addition, in these three hospitals, morbidity (C-D Grade $\geq$ IIIa) in patients with cStage IA diseases who underwent laparoscopic distal gastrectomy was only 4.7%. The planned patient enrollment period was 2 years and the follow-up period was 3 years. Interim analysis was scheduled at registration of the initial 220 cases to evaluate the efficacy of RG using Bayesian inference.

Clinicopathological findings and tumor stages were recorded according to the 14th edition of the Japanese Classification of Gastric Carcinoma (JCGC) [14]. Cancer staging was performed according to the findings of contrast-enhanced computed tomography (CECT), gastrography, endoscopic study, and endosonography. Lymph nodes > 8 mm in the short-axis diameter in < 5 -mm-thickness CECT images were considered to indicate positive

lymph-node metastasis. The extent of lymph-node dissection, as well as gastric resection, was determined according to the Japanese Gastric Cancer Treatment Guidelines ver. 3 [15]. The reconstruction approach was selected according to surgeon preference. Intra- or extra-corporeal anastomosis was allowed in this study.

Patient eligibility

Patients who met the following criteria were included: operable under general anesthesia; histologically proven gastric adenocarcinoma; cStage I or II disease not indicated for endoscopic resection according to the Japanese Gastric Cancer Treatment Guidelines ver. 3 [15]; curably treated with total, distal, or proximal gastrectomy involving D1+ or D2 lymph-node dissection; age ≥ 18 years. Patients who met the following criteria were excluded: preoperative use of chemotherapy and presence of mental disorders. Informed consent was obtained from all patients. This study was conducted in accordance with the amended Declaration of Helsinki under approval by the institutional review board of each participating institution. In addition, this clinical trial was approved for Advanced Medical Technology (“Senshiniryo”) B, which is managed by the MHLW. “Senshiniryo” is a special interim system for newly developed uninsured medical technologies approved by the MHLW, in which patients are requested to pay for the designated technology [16]. Using this system, the MHLW determines whether it is feasible to cover the designated technology under the universal medical insurance program from the standpoint of technical and social validity including a cost-effectiveness point of view [17].

Criteria for participating institutions and quality control of surgery

To control for the safety and quality of robotic operations, the institutions and operating surgeons were required to meet certain criteria. The criteria for the institutions were as follows: (1) introduced RG ≥ 1 year previously; (2) managed ≥ 20 RG procedures (including ≥ 5 total gastrectomies); (3) managed ≥ 50 LG procedures over the past 4 years; (4) achieved a morbidity rate (C-D Grade $\geq$ IIIa) for LG procedures of $\leq 12\%$ over the past 4 years. The criteria for operating surgeons were as follows: (1) considered a qualified surgeon (Japan Society for Endoscopic Surgery) according to the endoscopic surgical skill qualification system; (2) achieved board certification in gastroenterology (The Japanese Society of Gastroenterological Surgery); (3) received a certificate for da Vinci Surgical System Off-site Training as a Console Surgeon; (4) performed ≥ 10 RG procedures (including ≥ 1 total gastrectomies).

Initially, three institutions participated in this trial. However, during the enrollment period, the study group gradually

expanded, and finally, 15 institutions registered patients. Before the inclusion of an operating surgeon in this study, the principle investigator (PI; I.Uyama) shared the generalized technique of RG, including the double-bipolar method, the da Vinci’s plane theory, and the monitor quadrisection theory [2, 9], with each surgeon via a proctorship program provided by Intuitive Surgical, Inc. (Sunnyvale, CA, USA), and reviewed the surgeon’s adherence to technical details using a non-edited video of an entire robotic total gastrectomy procedure. Any critical adverse effect (C-D Grade IV or V) was required to be reported to the PI within a week after its occurrence. If the total number of patients who experienced any critical adverse effect related to the robotic operation reached ≥ 10 , it was decided that this study would be suspended according to the decision of the data and safety monitoring board. All intracorporeal manipulations during the robotic operation were required to be recorded on a Digital Versatile Disc (DVD) and provided to the data center.

Protocol treatment

Patients who met the aforementioned inclusion criteria were registered after obtaining informed consent. RG was performed according to the Japanese Gastric Cancer Treatment Guidelines ver. 3 [15]. If distant metastasis, including peritoneal dissemination, was found during the operation, the treatment deviated from this protocol. Patients who underwent curative operation completed this protocol regardless of conversion to the laparoscopic or open method.

Data management

The data center (Center for Research Promotion and Support, Fujita Health University) performed data management and site-visit monitoring. The center provided monitoring reports twice during the study and the reports were submitted to and reviewed by the PI. The center collected all data from the participating patients in case report forms (CRFs) in a linkable anonymized fashion and stored the data for 5 years after the completion of the study. In detail, a case registry form was faxed a day before the operation. A perioperative CRF, the DVDs onto which the operation was recorded, a discharge reporting form, and a medical expense reporting form were sent within 28 days after patient discharge. Quality-of-life (QOL) data (EQ-5D) were sent within 120 days after the operation. Prognosis reporting forms were sent within 1 month after 1, 2, and 3 postoperative years.

Follow-up and postoperative management

Patients with pathological stage II or III cancer received adjuvant chemotherapy using S-1 for 1 year, while those

with pathological stage IV cancer received S-1-based palliative chemotherapy according to the Japanese Gastric Cancer Treatment Guidelines ver. 3 [15]. Data on QOL and prognosis were investigated after 1 and 3 months and after 12, 24, and 36 months, respectively.

Statistical analysis

The primary endpoint (morbidity C-D Grade $\geq$ IIIa) was analyzed using the one-tailed binomial test. Independent continuous variables were compared using the Mann–Whitney *U* test or Kruskal–Wallis test. Categorical variables were compared using the Chi-square test. Data are expressed as median (range), unless otherwise stated. All statistical analyses related to the study design and endpoints were conducted by Sogo Rinsho Medefi Co., Ltd. Within-group analyses and subanalyses were performed by K.S. using IBM SPSS Statistics 22 (IBM Corporation, Armonk, NY, USA). A *p* value < 0.05 (two-tailed) was considered statistically significant.

Results

Patient background

Between October 2014 and December 2016, 330 patients from 15 institutions were registered into this study (Supplementary Table 1). The flow diagram of the study process is shown in Fig. 1. All registered patients met the criteria of this study. Among the 330 patients, peritoneal dissemination was noted during the operation in 2 patients, and they underwent non-curative operation. No patient had CY1P0 status. In 2 patients, after these patients were registered, the credential surgeon for RG (K.E.) sustained such severe finger injuries before the scheduled date of RG that he could not manipulate the robot. Thus, protocol treatment was discontinued and LG was performed instead. Therefore, 326 patients completed the protocol treatment (full analysis set; FAS) and their data were analyzed. Patient background data are summarized in Table 1. Age and BMI were 66 (26–85) years and 22.4 (15.0–31.5) kg/m², respectively. Among the 326 patients, 216 (66.3%) had preoperative comorbidity with ≥ 2 in the ASA performance status classification. Most of the patients had cStage I disease located at the middle or lower third of the stomach.

Operative findings

The operative findings are summarized in Table 2. All patients underwent R0 resection. With regard to the extent of gastric resection, distal gastrectomy, total gastrectomy, and proximal gastrectomy were performed in 253 (77.6%),

Table 1 Patient background

	<i>N</i> = 326
Sex (M:F)	201:125
Age (years)	66 (26–85)
BMI (kg/m ²)	22.4 (15.0–31.5)
Performance status (0/1/2/3)	316/10/0/0
ASA (1/2/3/4)	110/214/2/0
History of laparotomy, <i>n</i> (%)	141 (43.3)
Tumor size (mm)	30 (0–102)
Location, <i>n</i> (%)	
U	60 (18.4)
M	181 (55.5)
L	85 (26.1)
Histology, <i>n</i> (%)	
Pap	5 (1.5)
Tub1	77 (23.6)
Tub2	72 (22.1)
Por1	58 (17.8)
Por2	42 (12.9)
Sig	72 (22.1)
Type, <i>n</i> (%)	
0–I	4 (1.2)
0–II	265 (81.3)
0–III	6 (1.8)
1	9 (2.8)
2	23 (7.1)
3	13 (4.0)
4	4 (1.2)
5	1 (0.3)
Other	1 (0.3)
Clinical JCGC stage	
IA	242 (74.2)
IB	47 (14.4)
IIA	22 (6.8)
IIB	15 (4.6)
Clinical T factor	
1a	65 (19.9)
1b	189 (58.0)
2	43 (13.2)
3	21 (6.4)
4a	8 (2.5)
4b	0 (0)
Clinical N factor	
0	301 (92.3)
1	23 (7.1)
2	2 (0.6)
3	0 (0)

ASA American Society of Anesthesiologists Physical Status Classification System, JCGC Japanese Classification of Gastric Carcinoma

Fig. 1 Flow diagram of the study process

47 (14.4%), and 26 (8%) patients, respectively. D2 lymph-node dissection was performed in 118 (36.2%) patients. The operative time and estimated blood loss were 313 (167–587) min and 20 (0–612) mL, respectively. Intraoperative adverse events were noted in 5 patients (redo of reconstruction: 2, injury to surrounding organs: 2, and others: 1). No severe intraoperative adverse event extended the duration of hospital stay or resulted in irreversible deterioration of QOL. Conversion to the open method was noted in 1 patient (0.3%) because of extended resection combined with splenectomy for tumor invasion. Pathological JGCG stage IA, IB, IIA, IIB, IIIA, IIIB, IIIC, and IV cancers were noted in 201 (61.7%), 46 (14.1%), 25 (7.7%), 35 (10.7%), 10 (3.1%), 4 (1.2%), 5 (1.5%), and 0 (0%) patients, respectively.

Postoperative findings

Postoperative findings are shown in Table 3. During the 30 days following the operation, the morbidity rate (C-D grade $\geq$ IIIa) with RG was 2.45% (8/326). As the morbidity rate was significantly lower than that of the historical control (6.4%), the null hypothesis was rejected [95% confidence interval 0.9755 (0.9522–0.9893) and $p=0.0018$]. Intra-abdominal bleeding was noted in 3 (0.9%) patients. A pancreatic fistula with intra-abdominal bleeding and an internal hernia with small bowel obstruction were each noted in 1 (0.3%) patient. The reoperation rate was 1.2% ($n=4$).

Complication of C-D grade IVa was seen in 1 (0.3%) patient (intra-abdominal bleeding). No C-D grade IVb complication or 30-day mortality was noted. One of the ten patients, who were preoperatively scheduled to undergo distal gastrectomy but actually underwent total gastrectomy, developed C-D grade I complication (constipation, classified as Local-Others in Table 3). The total medical cost, including the operative fee and admission expense, was 1,799,628 (1,530,170–5,173,706) JPY. The surgical cost per procedure was 1,063,800 (950,000–1,158,970) JPY. The changes in the QOL score measured using EQ-5D were 1.0 (0.5920–1.0) (preoperative), 0.8040 (0.3940–1.0) (postoperative day 7), and 1.0 (0.3940–1.0) (postoperative day 30).

Impact of postoperative complications on outcomes

Postoperative hospital stay was longer, total medical cost was higher, and the QOL score at postoperative day 30 was lower in patients with morbidity (C-D grade $\geq$ IIIa, $n=8$) than in those without morbidity ($n=318$) [morbidity + vs. – : postoperative hospital stay, 25 (12–62) vs. 9 (6–56) days, $p=0.014$; total medical cost, 2,936,159 (2,522,180–5,173,706) vs. 1,795,506 (1,530,170–3,268,218) JPY, $p=0.004$; QOL score at postoperative day 30, 0.786 (0.444–1.000) vs. 1.000 (0.394–1.000), $p=0.015$]. In addition, operative time was longer and the reoperation rate was higher in patients with morbidity than in those

Table 2 Operative and pathological findings

	<i>N</i> = 326
Model of da Vinci, <i>n</i> (%)	
S	8 (2.5)
Si	287 (88.0)
Xi	31 (9.5)
Type of resection, <i>n</i> (%)	
DG	253 (77.6)
PG	26 (8.0)
TG	47 (14.4)
Extent of lymphadenectomy, <i>n</i> (%)	
D1+	208 (63.8)
D2	118 (36.2)
Type of reconstruction, <i>n</i> (%)	
B-I	120 (36.8)
B-II	49 (15.0)
R-Y	131 (40.2)
Esophagogastric	13 (4.0)
DT	12 (3.7)
DF	1 (0.3)
Operation time (min)	313.0 (167–587)
Console time (min)	251.5 (68–551)
Blood loss (mL)	20 (0–612)
Conversion, <i>n</i> (%)	1 (0.31)
No. of dissected nodes	38.5 (10–103)
Intraoperative adverse events, <i>n</i> (%)	5 (1.5)
Time to diet resumption (days)	3 (1–41)
Postoperative stay (days)	9 (6–62)
Medical cost (JPY)	1,799,628 (1,530,170– 5,173,706)
Pathological JCGC stage	
IA	201 (61.7)
IB	46 (14.1)
IIA	25 (7.7)
IIB	35 (10.7)
IIIA	10 (3.1)
IIIB	4 (1.2)
IIIC	5 (1.5)
IV	0 (0)
Pathological T factor	
1a	115 (35.3)
1b	116 (35.6)
2	42 (12.9)
3	30 (9.2)
4a	23 (7.1)
4b	0 (0)
Pathological N factor	
0	249 (76.4)
1	47 (14.4)
2	17 (5.2)
3	13 (4.0)

DG distal gastrectomy, PG proximal gastrectomy, TG total gastrectomy, B-I Billroth I reconstruction, B-II Billroth II reconstruction, R-Y Roux-en Y reconstruction, DT double tract, DF esophagogastrostomy using the double-flap technique, JCGC Japanese Classification of

Table 2 (continued)

Gastric Carcinoma			
Table 3 Postoperative complications			
C-D grade	I	II	≥ IIIa
Morbidity (overall complications)	65 (19.9)	61 (18.7)	8 (2.5)
Local	16 (4.9)	46 (14.1)	8 (2.5)
Pancreatic fistula	7 (2.2)	11 (3.4)	1 (0.3)
Delayed gastric emptying	2 (0.6)	13 (4.0)	0 (0)
Wound infection	3 (0.9)	6 (1.8)	0 (0)
Intra-abdominal abscess	0 (0)	8 (2.5)	0 (0)
Intra-abdominal bleeding	1 (0.3)	1 (0.3)	3 (0.9)
Bowel obstruction	2 (0.6)	4 (1.2)	2 (0.6)
Anastomotic bleeding	1 (0.3)	1 (0.3)	0 (0)
Anastomotic leakage	0 (0)	2 (0.6)	1 (0.3)
Internal hernia	0 (0)	0 (0)	1 (0.3)
Seroma	0 (0)	0 (0)	1 (0.3)
Bowel fistula	0 (0)	0 (0)	1 (0.3)
Others	1 (0.3)	5 (1.5)	0 (0)
Systemic	50 (15.3)	18 (5.5)	0 (0)
Gastrointestinal	22 (6.7)	3 (0.9)	0 (0)
Hepatic	22 (6.7)	2 (0.6)	0 (0)
Pulmonary	4 (1.2)	5 (1.5)	0 (0)
Renal	2 (0.6)	1 (0.3)	0 (0)
Cardiac	0 (0)	2 (0.6)	0 (0)
Others	5 (1.5)	7 (2.1)	0 (0)

C-D Clavien–Dindo

without morbidity [morbidity + vs. – : operative time, 374.5 (299–587) vs. 312 (167–580) min, $p=0.010$; reoperation rate, 50% vs. 0%, $p=0.033$]. However, there were no differences in age, sex, BMI, blood loss, comorbidities, history of laparotomy, institution, type of reconstruction, extent of resection, extent of lymph-node dissection, number of dissected lymph nodes, number of metastatic lymph nodes, tumor size, cStage, pStage, and conversion rate.

Subanalyses of patient characteristics and surgical outcomes in the historical control

The results of the subanalyses of patient characteristics and surgical outcomes in the historical control are presented in the supplementary text and Tables 2 and 3.

Discussion

The present “Senshiniryo” B clinical trial clearly demonstrated not only the feasibility and safety but also the clinical advantage (reduction in morbidity) and disadvantage (higher

cost) of RG. To our knowledge, this is the first study to demonstrate the benefit of RG for postoperative complications, with a multi-institutional prospective approach.

In this study, our hypothesis that RG reduces the morbidity rate to less than half of that with LG was confirmed and the primary endpoint was met. The reduction in morbidity reduced the total medical cost, reduced the duration of postoperative hospital stay, and improved the QOL of the patient. These data suggested that RG would likely show improved cost-effectiveness if the surgical cost per procedure for RG was reduced to about the same amount as that for LG. Thus, the MHLW finally decided to recognize RG as a part of LG from the standpoint of medical insurance coverage as of April 2018. Thus, an operable patient with resectable GC could undergo RG, similar to LG, for 80,000–100,000 JPY/month using the High-cost Medical Expense Benefit system. However, no additional fee is reimbursed to the hospital, although RG is performed instead of the conventional LG. Currently, in the Japanese universal medical insurance system, amounts of 796,200, 787,300, and 960,900 JPY are reimbursed for laparoscopic distal gastrectomy, proximal gastrectomy, and total gastrectomy, respectively. On the other hand, the median surgical cost for RG was 1,063,800 JPY in this study, suggesting that not only competition among rival robots developed by Medtronic, Inc. [18], Medtronic, Inc. [19], Verb Surgical, Inc. [20], TransEnterix, Inc. [21], and Meere Company, Inc. [22], but also efforts by Intuitive Surgical Inc. to lower prices are desirable to reduce cost from an administrative point of view.

For GC, robotic procedures have been developed according to procedures in the conventional LG, which has been more commonly performed. Thus, the impact of the use of the DVSS for GC treatment has been assessed mostly in comparison with LG [2, 8, 23–39]. Most previous reports have failed to demonstrate clear clinical advantages of RG over LG [7, 40]. However, the benefits of RG for reducing morbidity, including POPF, were identified in the present multi-institution prospective study, as well as in a previous single-institution retrospective study performed in Japan [2, 41]. This may be at least partly because common technical principles for robotic set-up and dissection [2, 9] were used across the institutions. In fact, following the death of a patient soon after RG, the Japan Society for Endoscopic Surgery took the initiative to safely introduce robotic surgery nationwide according to the “proposal on the introduction of robotic surgery” issued in July 2011 [9]. In accordance with this proposal, I.U., as a proctor, made the best efforts to mentor the potential collaborating surgeons in this study for their initial few cases. Another possible reason may be the strict requirements for participating institutions and operating surgeons. In particular, operating surgeons were included if they had performed ≥ 10 RG procedures, including ≥ 1 total gastrectomies, and institutions were included if

they had managed ≥ 20 RG procedures, including ≥ 5 total gastrectomies, considering the learning curve of RG for experienced laparoscopic gastric surgeons [9]. Thus, since April 2018, RG with health insurance coverage has been performed by the qualified surgeons (Japan Society for Endoscopic Surgery) according to the endoscopic surgical skill qualification system who had previously performed ≥ 10 RG procedures in institutions that managed ≥ 50 gastrectomies, including ≥ 20 LG or RG procedures annually.

The present study had several limitations. First, this study was conducted as a single-arm study. A historical control was used to assess the statistical hypothesis. In this study, blood loss and duration of stay improved when compared to the findings in the historical control; however, some parts of the patient background significantly differed. Therefore, there might have been data bias, and the overall results should be interpreted with caution. We decided to use such a study design instead of a randomized-controlled trial mainly because of our limited budget. Randomization was technically difficult, as each patient who underwent RG needed to pay approximately 700,000 JPY, even when using the “Senshiniryo” B system in combination with the reimbursement of 500,000 JPY from Intuitive Surgical, Inc., whereas the use of LG involved a cost of only approximately 100,000 JPY per patient. In fact, according to the results of the subanalyses, considerable differences in the patient background were observed. We plan to perform propensity score-matched analyses once the long-term outcomes are obtained in the prospective cohort of this study. Second, the quality of the historical control may be a concern. While the design of this study was considered, MHLW requested a historical control with higher level of evidence. However, no multi-institutional large randomized-controlled trial on LG for advanced GC has been completed worldwide [42]. The Nationwide Survey of Endoscopic Surgery in Japan biennially conducted by the Japan Society of Endoscopic Surgery [43] could not be used, because all types of postoperative complications were not registered and severity of those was not graded. National Clinical Database [44] was also lined up as a candidate, but it had been just a little, while since registration had started. Thus, after a long discussion, MHLW finally allowed us to use short- and long-term (3-year) outcomes from historical controls in the three leading institutions (Fujita Health University, Saga University, and Kyoto University) between 2009 and 2012, although the data were unpublished. As a matter of fact, the morbidity rate (C-D Grade $\geq$ IIIa) in patients with cStage I disease who underwent laparoscopic distal gastrectomy with D1+ lymph-node dissection was only 4.7% in the historical control, which was less than the rate of 5.1% noted in the Japan Clinical Oncology Group 0703 trial [4], suggesting excellent quality with regard to LG. Third, as GC is commonly found in Korea and Japan, where population-based screening

is being undertaken [45], more reports, predominantly on the early GC, are being published in these countries than in Western countries. Most of the patients in this study had cStage I disease. It may be challenging to extend the present findings to the Western population. As our previous study suggested that larger extents of gastric resection and lymph-node dissection are associated with more effective use of the robot [2], a multi-institutional prospective study with a considerable number of patients with advanced GC is warranted.

In conclusion, RG reduced the morbidity rate when compared to the findings with LG. RG might be safe, feasible, and effective for GC. Medical insurance coverage in combination with a reduction in the cost of the robotic system would accelerate the spread of robotic surgery in Japan.

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Author contributions All the authors have fully met the ICMJE authorship criteria as follows: (1) study design—IU and KS; data collection—MN, MT, TK, HN, ST, KE, KO, SK, and HO; statistical analysis and interpretation of results—MN, KS, and IU. (2) Drafting of the manuscript—KS and MN; critical revision of the manuscript for important intellectual content—KS, IU, MN, MT, TK, HN, ST, KE, KO, SK, and HO. All authors read and approved the final manuscript. All authors are accountable for all the aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with ethical standards

Conflict of interest In this study, Intuitive Surgical, Inc. reimbursed 500,000 JPY to each patient. Koichi Suda received a grant of Intuitive Surgical Operations, Inc. 2015 Clinical Robotic Research Grant for this study. The other authors have no conflicts of interest or financial ties to disclose.

References

- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018 <https://doi.org/10.3322/caac.21492>.
- Suda K, Man IM, Ishida Y, Kawamura Y, Satoh S, Uyama I. Potential advantages of robotic radical gastrectomy for gastric adenocarcinoma in comparison with conventional laparoscopic approach: a single institutional retrospective comparative cohort study. *Surg Endosc*. 2015;29:673–85.
- Uyama I, Suda K, Satoh S. Laparoscopic surgery for advanced gastric cancer: current status and future perspectives. *J Gastric Cancer*. 2013;13:19–25.
- Katai H, Sasako M, Fukuda H, Nakamura K, Hiki N, Saka M, et al. Safety and feasibility of laparoscopy-assisted distal gastrectomy with suprapancreatic nodal dissection for clinical stage I gastric cancer: a multicenter phase II trial (JCOG 0703). *Gastric Cancer*. 2010;13:238–44.
- Shinohara T, Satoh S, Kanaya S, Ishida Y, Taniguchi K, Isogaki J, et al. Laparoscopic versus open D2 gastrectomy for advanced gastric cancer: a retrospective cohort study. *Surg Endosc*. 2013;27:286–94.
- Isogaki J, Haruta S, Man IM, Suda K, Kawamura Y, Yoshimura F, et al. Robot-assisted surgery for gastric cancer: experience at our institute. *Pathobiology*. 2011;78:328–33.
- Kim HI, Han SU, Yang HK, Kim YW, Lee HJ, Ryu KW, et al. Multicenter prospective comparative study of robotic versus laparoscopic gastrectomy for gastric adenocarcinoma. *Ann Surg*. 2016;263:103–9.
- Uyama I, Kanaya S, Ishida Y, Inaba K, Suda K, Satoh S. Novel integrated robotic approach for suprapancreatic D2 nodal dissection for treating gastric cancer: technique and initial experience. *World J Surg*. 2012;36:331–7.
- Suda K, Nakauchi M, Inaba K, Ishida Y, Uyama I. Robotic surgery for upper gastrointestinal cancer: current status and future perspectives. *Dig Endosc*. 2016;28:701–13.
- 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;240:205–13.
- 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;250:187–96.
- Lee JH, Park DJ, Kim HH, Lee HJ, Yang HK. Comparison of complications after laparoscopy-assisted distal gastrectomy and open distal gastrectomy for gastric cancer using the Clavien–Dindo classification. *Surg Endosc*. 2012;26:1287–95.
- EuroQol G. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16:199–208.
- Japanese Gastric Cancer A. Japanese classification of gastric carcinoma: 3rd english edition. *Gastric Cancer*. 2011;14:101–12.
- Japanese Gastric Cancer A. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer*. 2011;14:113–23.
- Sakurai H. Advanced medical technology and health insurance in Japan. *JMAJ*. 2006;49:41–3.
- The flow from application to advanced medical technology to approval for national health insurance coverage. <https://www.mhlw.go.jp/file/05-Shingikai-12404000-Hokenkyoku-Iryouka/0000021162.pdf>. Accessed 8 Nov 2018. (in Japanese).
- Medicaroid, Inc. <https://www.medicaroid.com/en/>. Accessed 8 Nov 2018.
- Medtronic, Inc. <https://www.medtronic.com/us-en/index.html>. Accessed 8 Nov 2018.
- Verb Surgical, Inc. <https://www.verbsurgical.com/>. Accessed 8 Nov 2018.
- TransEnterix, Inc. <https://transenterix.com/>. Accessed 8 Nov 2018.
- Abdel Raheem A, Troya IS, Kim DK, Kim SH, Won PD, Joon PS, et al. Robot-assisted fallopian tube transection and anastomosis using the new REVO-I robotic surgical system: feasibility in a chronic porcine model. *BJU Int*. 2016;118:604–9.
- 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;24:2594–602.

24. Kim MC, Heo GU, Jung GJ. Robotic gastrectomy for gastric cancer: surgical techniques and clinical merits. *Surg Endosc*. 2010;24:610–5.
25. 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;146:1086–92.
26. Eom BW, Yoon HM, Ryu KW, Lee JH, Cho SJ, Lee JY, et al. Comparison of surgical performance and short-term clinical outcomes between laparoscopic and robotic surgery in distal gastric cancer. *Eur J Surg Oncol*. 2012;38:57–63.
27. Kang BH, Xuan Y, Hur H, Ahn CW, Cho YK, Han SU. Comparison of surgical outcomes between robotic and laparoscopic gastrectomy for gastric cancer: the learning curve of robotic surgery. *J Gastric Cancer*. 2012;12:156–63.
28. 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;26:1377–81.
29. Huang KH, Lan YT, Fang WL, Chen JH, Lo SS, Hsieh MC, et al. Initial experience of robotic gastrectomy and comparison with open and laparoscopic gastrectomy for gastric cancer. *J Gastrointest Surg*. 2012;16:1303–10.
30. Kim KM, An JY, Kim HI, Cheong JH, Hyung WJ, Noh SH. Major early complications following open, laparoscopic and robotic gastrectomy. *Br J Surg*. 2012;99:1681–7.
31. 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;99:1554–61.
32. 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;20:1258–65.
33. Kim HI, Park MS, Song KJ, Woo Y, Hyung WJ. Rapid and safe learning of robotic gastrectomy for gastric cancer: multidimensional analysis in a comparison with laparoscopic gastrectomy. *Eur J Surg Oncol*. 2014;40:1346–54.
34. Huang KH, Lan YT, Fang WL, Chen JH, Lo SS, Li AF, et al. Comparison of the operative outcomes and learning curves between laparoscopic and robotic gastrectomy for gastric cancer. *PLoS One*. 2014;9:e111499.
35. Junfeng Z, Yan S, Bo T, Yingxue H, Dongzhu Z, Yongliang Z, et al. Robotic gastrectomy versus laparoscopic gastrectomy for gastric cancer: comparison of surgical performance and short-term outcomes. *Surg Endosc*. 2014;28:1779–87.
36. Noshiro H, Ikeda O, Urata M. Robotically-enhanced surgical anatomy enables surgeons to perform distal gastrectomy for gastric cancer using electric cautery devices alone. *Surg Endosc*. 2014;28:1180–7.
37. Son T, Lee JH, Kim YM, Kim HI, Noh SH, Hyung WJ. Robotic spleen-preserving total gastrectomy for gastric cancer: comparison with conventional laparoscopic procedure. *Surg Endosc*. 2014;28:2606–15.
38. Seo HS, Shim JH, Jeon HM, Park CH, Song KY. Postoperative pancreatic fistula after robot distal gastrectomy. *J Surg Res*. 2015;194:361–6.
39. Lee J, Kim YM, Woo Y, Obama K, Noh SH, Hyung WJ. Robotic distal subtotal gastrectomy with D2 lymphadenectomy for gastric cancer patients with high body mass index: comparison with conventional laparoscopic distal subtotal gastrectomy with D2 lymphadenectomy. *Surg Endosc*. 2015;29:3251–60.
40. Hyun MH, Lee CH, Kim HJ, Tong Y, Park SS. Systematic review and meta-analysis of robotic surgery compared with conventional laparoscopic and open resections for gastric carcinoma. *Br J Surg*. 2013;100:1566–78.
41. Nakauchi M, Suda K, Shibasaki S, Kadoya S, Inaba K, Ishida Y, Uyama I. Comparison of the long-term outcomes of robotic radical gastrectomy for gastric cancer and conventional laparoscopic approach: a single institutional retrospective cohort study. *Surg Endosc*. 2016;30:5444–52.
42. Suda K, Nakauchi M, Inaba K, Ishida Y, Uyama I. Minimally invasive surgery for upper gastrointestinal cancer: our experience and review of the literature. *World J Gastroenterol*. 2016;22:4626–37.
43. Bandoh T, Shiraishi N, Yamashita Y, Terachi T, Hashizume M, Akira S, Morikawa T, Kitagawa Y, Yanaga K, Endo S, Onishi K, Takiguchi S, Tamaki Y, Hasegawa T, Mimata H, Tabata M, Yozu R, Inomata M, Matsumoto S, Kitano S, Watanabe M. Endoscopic surgery in Japan: the 12th national survey (2012–2013) by the Japan Society for Endoscopic Surgery. *Asian J Endosc Surg*. 2017;10:345–53.
44. Gotoh M, Miyata H, Hashimoto H, Wakabayashi G, Konno H, Miyakawa S, Sugihara K, Mori M, Satomi S, Kokudo N, Iwanaka T. National clinical database feedback implementation for quality improvement of cancer treatment in Japan: from good to great through transparency. *Surg Today*. 2016;46:38–47.
45. Choi JJ. Endoscopic gastric cancer screening and surveillance in high-risk groups. *Clin Endosc*. 2014;47:497–503.