ORIGINAL ARTICLE



Clinical advantage of standardized robotic total gastrectomy for gastric cancer: a single-center retrospective cohort study using propensity-score matching analysis

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Received: 22 December 2021 / Accepted: 3 March 2022 / Published online: 17 March 2022 © The Author(s) under exclusive licence to The International Gastric Cancer Association and The Japanese Gastric Cancer Association 2022

Abstract

Background Although recent studies have shown that robotic gastrectomy offers clinical advantages over laparoscopic gastrectomy in decreasing gastric cancer (GC) morbidity, studies focusing on robotic total gastrectomy (RTG) remain limited. The current study aimed to clarify whether the use of a robotic system could clinically improve short-term outcomes.

Methods Between January 2009 and June 2021, 371 patients diagnosed with both clinical and pathological Stage III or lower GC and underwent RTG or laparoscopic total gastrectomy (LTG) were enrolled in this study. The primary outcome was the incidence of intra-abdominal infectious complications over Clavien–Dindo classification grade IIIa. Demographic characteristics of those who underwent the RTG and LTG were matched using propensity-score matching (PSM), after which short-term outcomes were compared retrospectively.

Results After PSM, 100 patients were included in each group. The RTG group had a significantly shorter duration of hospitalization following surgery [RTG 13 (11–16) days vs. LTG 14 (11–19) days; p = 0.032] and a greater number of dissected LNs [RTG 48 (39–59) vs. LTG 43 (35–54) mL; p = 0.025], despite having a greater total operative time [RTG 511 (450–646) min vs. LTG 448 (387–549) min; p < 0.001]. In addition, the RTG group had significantly fewer total complications (3% vs. 13%, p = 0.019) and intra-abdominal infectious complications (1% vs. 9%; p = 0.023).

Conclusions The current study showed that robotic surgery might improve short-term outcomes following minimally invasive radical total gastrectomy by reducing intra-abdominal infectious complications.

Keywords Stomach neoplasms · Gastrectomy · Robotic surgical procedure · Minimally invasive procedures · Morbidity

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Abbreviations

GC	Gastric cancer
RTG	Robotic total gastrectomy
LTG	Laparoscopic total gastrectomy
PSM	Propensity-score matching
NCD	National Clinical Database
RCT	Randomized control trial
LG	Laparoscopic gastrectomy
ESSQS	Endoscopic surgical skill qualification system
MIS	Minimally invasive surgery
RG	Robotic gastrectomy
DVSS	Da Vinci surgical system
JSES	Japan Society for Endoscopic Surgery
USAD	Ultrasonically activated device
ICG	Indocyanine green
CD	Clavien–Dindo
BMI	Body mass index
ASA	American Society of Anesthesiologists

SD	Standardized difference
SD	Standardized differenc

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OR Odds ratio
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Introduction

Gastric cancer (GC) is the fifth most common malignancy and the third leading cause of cancer-related death worldwide [1]. Accordingly, surgical resection with regional lymphadenectomy has continued to play an important role in the curative treatment of GC [2, 3]. With the recent technological advancements, laparoscopic distal gastrectomy has become a more common alternative radical procedure to open distal gastrectomy for GC [4-7]. In contrast, laparoscopic total gastrectomy (LTG) has not been regarded as a common procedure. A study based on the Japanese National Clinical Database (NCD) showed that LTG accounted for only 27.5% of all total gastrectomy procedures performed in 2019 throughout Japan [8]. Although no large-scaled randomized control trials (RCTs) have compared LTG and open total gastrectomy, two multicenter prospective studies had demonstrated the technical safety of LTG performed by experts for clinical stage I GC [9, 10]. Furthermore, esophagojejunostomy remains a technically demanding procedure considering the relatively high incidence rate of anastomotic leakage after LTG (4.4-5.7%) based on realworld data from the Japanese NCD [11-13].

In 1997, our institute launched laparoscopic gastrectomy (LG) for both early and advanced GC and had successfully established a stable and highly reproducible methodology, including outermost layer-oriented lymph node dissection and intracorporeal anastomosis [14–18]. Consequently, we demonstrated that laparoscopic D2 gastrectomy and open D2 gastrectomy had comparable short- and long-term outcomes [19] and that Endoscopic Surgical Skill Qualification System (ESSQS)-qualified and non-ESSQS-qualified surgeons had comparable morbidity rates following LG due to standard-ized procedure and established educational program [20]. Even when focusing on LTG, we demonstrated the technical and oncological feasibility of LTG [21]. Therefore, minimally invasive surgery (MIS) has been the first standard radical procedure of choice for GC at our institute.

To further improve surgical outcomes, we introduced robotic gastrectomy (RG) using the da Vinci Surgical System (DVSS; Intuitive Surgical, Sunnyvale, the USA) in 2009. The DVSS had been developed to overcome the limitations of laparoscopic surgery, including the limited range of motion with straight forceps and hand tremors. Moreover, its unique potencies facilitate safer, more precise, and more reproducible procedures by surgeons in a confined surgical field with impressive dexterity [22–25]. Given our abundant collective experience with LG, we have also successfully established standardized radical RG methodologies for

GC and demonstrated its promising short-term outcomes, focusing on the lower local complication rates [23, 26] and more favorable long-term oncological outcomes compared to those achieved with LG [27, 28].

Recently, several prospective studies and RCTs have demonstrated that RG promoted significantly lower total morbidity rates compared to LG [29–31]. However, limited reports have focused on determining whether robotic total gastrectomy (RTG) caused better reduction in morbidity over LTG. Thus, the present study aimed to clarify whether the use of a robotic system promoted improvements in short-term clinical outcomes, including a decrease in the incidence of complications and shortening of the postoperative hospitalization, using a propensity-score matching (PSM) analysis. Accordingly, we hypothesized that the robotic system would be more clinical advantageous for a technically demanding procedure such as LTG.

Materials and methods

Patients

Between January 2009 and June 2021, 2159 consecutive patients underwent gastrectomy at our division, among whom 564 underwent total gastrectomy for primary GC eligible for surgical treatment. From the prospective database in our institute, the present study ultimately enrolled 371 patients (robotic, n = 118 and laparoscopic, n = 253), with both clinical and pathological Stage III or lower GC after excluding 193 patients with open gastrectomy (n = 27), remnant GC (n = 46), clinical or pathological stage IV GC (n = 105), double cancer (n = 4), and palliative or limited lymphadenectomy (n=11) due to insufficient physical function. The E, EG, and E = G categories in adenocarcinoma of the esophagogastric junction according to the 15th edition of the Japanese Classification of Gastric Carcinoma [32] were not registered as gastric cancer into our prospective database, because the therapeutic strategy for EGJ cancer, especially category E, EG, and E = G, has been determined basically on a patient-by-patient basis, in terms of type of resection (total gastrectomy or proximal gastrectomy combined with lower esophagectomy or subtotal esophagectomy), extent of lymph node dissection, approach for the mediastinal procedures (transhiatal, transthoracic, or cervical approach), and reconstruction method (esophagogastrostomy, esophagojejunostomy, or esophagocolostomy), and thus not included in this study. Cancer staging was described according to the 15th edition of the Japanese Classification of Gastric Carcinoma [32] and performed based on the findings of contrastenhanced computed tomography, gastrography, endoscopic study, and endosonography before any treatment initiation and, when applicable, after completing chemotherapy, as

previously described [23, 26]. Indications for endoscopic treatment and radical gastrectomy, including the extent of systematic lymph node dissection, were determined based on the Japanese Gastric Cancer Treatment Guidelines [32–34]. The microscopic tumor-negative status in the cut end was routinely confirmed by intraoperative frozen section diagnosis, and margins of resection (R0 or R1 resection) was pathologically diagnosed by permanent section diagnosis, as previously reported [26]. Previous reports have detailed indications for physical function assessment, surgical procedures, perioperative radical gastrectomy management, and postoperative chemotherapy, in addition to oncologic follow-up [19, 23, 26, 35]. This study was approved by the Institutional Review Board of Fujita Health University.

Decision on procedure selection

Patients were completely involved in the decision-making process, and informed consent was obtained from all patients. During the study period, however, decisions regarding patient procedures depended on circumstances surrounding the national medical insurance coverage. Accordingly, RTG had not been included in the national medical insurance coverage in Japan between January 2009 and March 2018, during which patients needed to be charged 2,200,000 JPY upon perioperative admission to undergo RTG [23]. All patients were equally offered robotic surgery without considering their backgrounds, including physical and oncological status. Hence, 46 patients who agreed to uninsured DVSS application underwent RTG, whereas the remaining 241 patients who refused uninsured DVSS application underwent LTG with health insurance coverage. Meanwhile, between October 2014 and January 2017, we organized a multi-institutional, single-arm prospective clinical study approved for Advanced Medical Technology ("Senshiniryo") B [29]. Accordingly, 16 patients with cStage I/II GC who were enrolled in our institution's Senshiniryo B trial were also included in the present analysis. Since its approval for national medical insurance coverage based on the outcomes of the Senshiniryo B trial in April 2018, 56 patients underwent RTG, whereas 12 underwent LTG.

Operating surgeon selection

In all LTG procedures, only ESSQS-qualified surgeons were involved as either the operating surgeon or instructive assistant. In addition, all the participating LTG surgeons had previously performed \geq 30 LGs [21], and the criteria for the selection of the surgeon were determined according to our basic policy as previously described [20]. In all RTG procedures, we referred to the Japan Society for Endoscopic Surgery (JSES) guidelines when identifying surgeons for RG as previously described [36, 37]. I.U., who had performed over 1,500 LG and 500 RG procedures, selected the surgeons considering skill levels and patients conditions and supervised all LG and RG procedures.

Operative procedure

The entire process of laparoscopic or robotic total gastrectomy with nodal dissection was performed using a five-port system with Nathanson hook liver retractors (Yufu Itonaga, Tokyo, Japan), as previously described [15, 17, 21, 24, 38, 39]. As the energy device for nodal dissection, the ultrasonically activated device (USAD) was mainly employed in LTG, whereas the Maryland bipolar forceps (Intuitive Surgical) using the Macrobipolar mode at 60 W (ForceTriadTM energy platform; Medtronic, Minneapolis, MN) was mainly employed in RTG [37]. To further widen the operative field around the esophageal hiatus, the hepatic left lateral segment was mobilized and the esophageal hiatus was dissected, if necessary [39]. To prevent collision of the robotic arms during RG, the patient cart was docked in accordance with "da Vinci's plane theory," and intracorporeal positioning of the forceps was determined based on the "monitor quadrisection theory" as previously described [23]. Lymph node dissection was performed along the outermost layer using the double bipolar method in RG and using the laparoscopic coagulating shears in LG as previously described [37].

Splenectomy

When the tumor invaded the greater curvature or when the No. 10 lymph node was clinically diagnosed as N+, splenectomy was performed. Since the FireflyTM Fluorescence Imaging of DVSS with the indocyanine green (ICG) became available after introducing the DVSS-Xi, we have performed RTG with splenectomy using this imaging system. Briefly, after dividing all arteries supplying the stomach, except for the short gastric artery, the splenic artery was encircled immediately distally to the origin of the major pancreatic artery and was clamped using a detachable clamp forceps (Fig. 1a). Thereafter, 12.5 mg of ICG solution was intravenously injected, and the blood perfusion in the pancreatic tail was visually confirmed using the FireflyTM Fluorescence Imaging of DVSS within 1 min. Homogenous staining of the pancreatic tail (Fig. 1b) confirmed that blood perfusion was sufficient, and thus the splenic artery was ligated precisely at the site of clamping (Fig. 1c). In contrast, heterogeneous or barely any staining of the pancreatic tail (Fig. 1d) indicated inadequate blood, and thus the caudal pancreatic artery was preserved and ligated distally to the origin of the caudal pancreatic artery (Fig. 1e). After completing total gastrectomy with splenectomy and the extraction of the specimens, the same amount of ICG was injected to re-evaluate blood perfusion in the pancreatic tail (Fig. 1f). When blood perfusion in

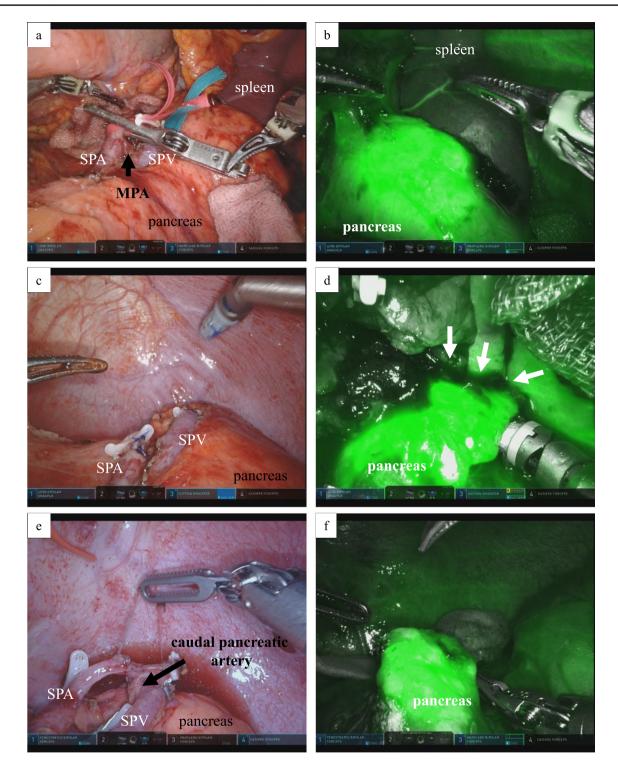


Fig. 1 a After the splenic artery (SPA) was encircled immediately distally to the origin of the major pancreatic artery (black arrow), the SPA was clamped via a detachable clamp forceps. **b** Sufficient blood perfusion in the pancreatic tail was visually confirmed using the FireflyTM Fluorescence Imaging after administration of the indocyanine green (ICG, 12.5 mg) solution. **c** The SPA was ligated precisely at

the site of clamping. **d** The tip of the pancreatic tail was partly heterogeneously stained after the ICG injection, suggesting insufficient blood perfusion. **e** Preservation of the caudal pancreatic artery (black arrow). **f** The pancreatic tail was stained homogeneously, suggesting sufficient blood perfusion after completing total gastrectomy with splenectomy

the pancreatic tail was determined to be inadequate, distal pancreatectomy was additionally performed. This procedure was not applied to LTG with splenectomy, because we did not have the laparoscopic fluorescence imaging system.

Reconstruction

Roux-en-Y reconstruction was performed via two methods based on our standardized intracorporeal anastomotic procedure using a linear stapler in laparoscopic distal gastrectomy as previously reported [16]. The first method was functional end-to-end anastomosis, in which anastomosis is performed at the entry point in the left wall of the esophagus, followed by closure of the common stab using a linear stapler [17]. The second was the overlap method, in which an entry point is made in the right or mid wall of the esophagus and anastomosis was performed on the posterior wall, followed by closure of the common stab using hand-sewn suturing [18]. As a common procedure before the first fire of the linear stapler, the esophageal mucosal and muscular layers of the entry point were fixed by suturing. After creating the jejunal entry, a cartridge fork was inserted into the entry point, after which an anvil fork was inserted into the esophageal entry point guided by the nasogastric tube. In RTG, selection of linear staplers by the assistant surgeon or robotic linear staplers (SureForm[™], Intuitive Surgical) by the operating surgeon him/herself was dependent on the surgeon's preference. In earlier period, esophagojejunostomy using a circular stapler was also performed for a small scaled patients by the surgeon's preference.

Measurements

All patients were observed for 30 days following surgery. The primary endpoint was the incidence of intra-abdominal infectious complications, including anastomotic leakage, intra-abdominal abscess, and pancreatic fistula, as well as the previous study [26]. The secondary endpoints comprised short-term surgical outcomes, including operative time, surgeon console time, estimated blood loss, number of dissected lymph nodes, complication rates, mortality rates, and length of postoperative hospitalization. All grade IIIa or higher clinically relevant postoperative complications were recorded based on the Clavien-Dindo (CD) classification [40] and classified according to the Japan Clinical Oncology Group Postoperative Complications Criteria based on the CD classification version 2.0 [41]. Total operative time was defined as the duration from the start of abdominal incision until complete wound closure, whereas the surgeon console time was defined as the duration of DVSS operation during surgery, excluding the time to extract the resected specimen from the umbilical incision and to redock for reconstruction.

Blood loss was estimated by weighing the suctioned blood and gauze pieces that had absorbed blood.

PSM analysis

PSM analysis was used to limit confounders and address possible patient selection bias. Propensity scores for all patients were calculated using a logistic regression model based on the following variables: period, age, sex, body mass index (BMI), American Society of Anesthesiologist (ASA) classification, presence of neoadjuvant chemotherapy, cT, cN, cStage, extent of lymph node dissection, and splenectomy. Consequently, rigorous adjustment for significant differences in the baseline characteristics of PSM patients was performed using nearest neighbor matching without replacement and a caliper width of 0.2 logit of the standard deviation. An absolute standardized difference (SD) was used to measure covariate balance, in which an absolute standardized mean difference above 0.1 indicated a meaningful imbalance as previously described [20, 26].

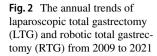
Statistical analysis

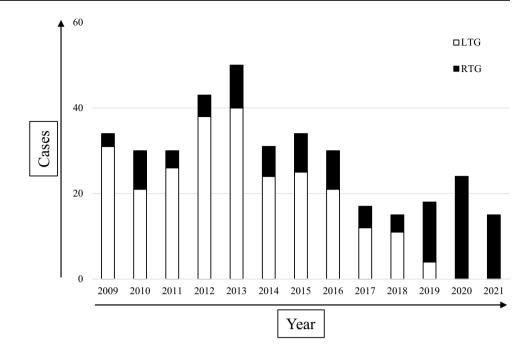
Between-group comparisons were performed using the χ^2 test or Mann–Whitney *U* test. Univariate χ^2 analysis and multivariate logistic regression analysis were performed to determine risk factors for the occurrence of postoperative complications. Data were expressed as median (interquartile range) unless otherwise specified. All analyses were conducted using IBM SPSS Statistics 27 (IBM Corporation, Armonk, NY, USA), with *p* < 0.05 indicating statistical significance.

Results

Clinicopathological features and surgical outcomes after minimally invasive total gastrectomy

The chronological changes in the annual number of patients who underwent LTG and RTG are shown in Fig. 2. Since 2019, proportion of RTG drastically increased. Patient characteristics and surgical outcomes of minimally invasive total gastrectomy for GC are summarized in Supplementary material 1. Among them, 174 (46.9%) and 163 (43.9%) patients had cStage I and pStage I disease, respectively, and 53 (14.3%) patients received preoperative chemotherapy. A total of 118 and 253 patients underwent RTG and LTG, respectively. Moreover, 154 and 217 patients underwent D1 + and D2 dissection, respectively. The rates for conversion to open procedure, reoperation within 30 days, in-hospital mortality within 30 days, and morbidity within 30 days after operation were 0%, 2.2%, 0.3%, and 10.2%, respectively





(Supplementary material 1). All patients completed successfully R0 resection. To compare the two periods by the half, we divided into two groups, period 2009-2013 (187 patients) and period 2014-2021 (184 patients) as shown in Supplementary material 2. In the LTG group, with significantly increasing the proportion of advanced GC patients and D2 nodal dissection in the later period, the operative time and intraoperative estimated blood loss were also significantly increased. In contrast, the rates of the morbidity and intra-abdominal infectious complications were comparable between two periods (Supplementary material 2). Similarly, the proportion of advanced GC patients and D2 dissection significantly increased in the later period of the RTG group. However, the operative time, intraoperative estimated blood loss, and rates of morbidity and intra-abdominal infectious complications were comparable between two periods (Supplementary material 2). Univariate analysis identified two significant risk factors for postoperative CD grade IIIa or more complications, including LTG, and estimated blood $loss \ge 100$ mL. Multivariate analysis determined that LTG [OR 6.579 (1.770–24.390); p = 0.005] was the only significant independent risk factor for morbidity (Table 1).

Patient background factors

Patient characteristics according to type of procedure are summarized in Table 2. Patients who underwent RTG were younger, with higher proportion of women, with higher BMI, and more advanced disease. Factors having an SD over 0.1 included period, age, sex, BMI, ASA classification, tumor size, use of preoperative chemotherapy, type of resection, extent of lymphadenectomy, and splenectomy (Table 2). To compensate for such differences, PSM analysis was used. The average and standard deviation of the propensity score was 0.318 and 0.191, respectively, thereby yielding a caliper width of 0.0382 for this study. After PSM, 100 patients were included in each group. After matching, the SD for period, age, sex, BMI, ASA classification, presence of neoadjuvant chemotherapy, history of laparotomy, tumor size, cT, cN, cStage, extent of lymph node dissection, and splenectomy decreased to \leq 0.10, indicating that a sufficient balance was achieved (Table 2). The SD for history of laparotomy, which did not include the covariables, was over 0.10 after PSM.

Surgical and short-term outcomes stratified according to type of procedure

Surgical outcomes and short-term postoperative courses of the entire and PSM cohorts are summarized in Table 3. In the RTG group, overlap reconstruction was more performed than the LTG group. After PSM, the RTG group had a significantly shorter duration of hospitalization following surgery [RTG 13 (11–16) days vs. LTG 14 (11–19) days; p = 0.032] and a greater number of dissected LNs [RTG 48 (39-59) vs. LTG 43 (35–54) mL; p = 0.025] compared to the LTG group, despite having a greater total operative time [RTG 511 (450–646) min vs. LTG 448 (387–549) min; p < 0.001]. No significant differences in estimated blood loss, number of dissected lymph nodes, reoperation rate, in-hospital mortality, pT, pN, pStage, and number of metastatic LNs were observed. The postoperative drain amylase levels of RTG were significantly lower than those of LTG for 3 days after surgery [1POD, RTG 478 (253-1086) IU/L vs. LTG 810 (479–1652) IU/L; p < 0.001; 2POD, RTG 293 (153–588)

Table 1 Risk factors for
morbidity after minimally
invasive gastrectomy (n=371)

	Univariate analysis OR (95% CI)	<i>p</i> value	Multivariate analysis OR (95% CI)	p value
LTG (vs. RTG)	5.000 (1.494–16.737)	0.003	6.579 (1.770–24.390)	0.005
Period (2009–2013)	1.156 (0.393–3.397)	0.793		
Male	1.647 (0.565-4.805)	0.351		
$Age \ge 70$	1.193 (0.453–3.143)	0.721		
Body mass index \geq 23 kg/m ²	1.041 (0.431–2.513)	0.929		
ASA score 2 or higher	1.292 (0.525-3.180)	0.578		
History of laparotomy	1.975 (0.598-6.519)	0.256		
cT2 ^a or higher	1.679 (0.530-5.322)	0.374		
cN ^a positive	1.910 (0.720-5.068)	0.188		
cStage II ^a or higher	3.000 (0.951-9.463)	0.051	2.508 (0.733-8.587)	0.143
Use of neoadjuvant chemotherapy	1.620 (0.431-6.087)	0.471		
Splenectomy	3.181 (0.929–10.887)	0.054	2.472 (0.616-9.925)	0.202
D2 lymph node dissection	1.038 (0.408-2.643)	0.937		
Non-qualified surgeons	1.043 (0.224-4.861)	0.957		
Operative time \geq 480 min	1.677 (0.603-4.662)	0.318		
Estimated blood loss \geq 100 mL	2.897 (1.071-7.839)	0.030	2.257 (0.784-6.499)	0.131
Tumor size $\geq 50 \text{ mm}$	1.476 (0.753–2.893)	0.254		
pT2 ^a or higher	1.193 (0.428-3.325)	0.736		
pN ^a positive	1.250 (0.472-3.311)	0.653		
pStage II ^a or higher	1.822 (0.623–5.328)	0.267		

Data are shown as odds ratio (95% confidence interval). The χ^2 test was used for univariate analysis. Multivariate logistic regression was used for multivariate analyses of factors having a *p* value of <0.10 during univariate analysis

LTG laparoscopic total gastrectomy, RTG robotic total gastrectomy, ASA American Society of Anesthesiologist, OR odds ratio

^aJapanese Classification of Gastric Carcinoma, 15th edition

Table 2 Patient characteristics and clinical features by each type of procedure

	Entire cohort $(n=371)$		SD	SD Propensity-score matched cohort $(n=200)$		SD
	RTG $(n = 118)$	LTG (n=253)		RTG $(n = 100)$	LTG (n = 100)	
Period (2009–2013:2014–2021)	31:87	156:97	0.76	31/69	30/70	0.02
Age (years)	68 (60–75)	71 (63–76)	0.28	69 (60–75)	68 (61–75)	0.03
Gender (M:F)	71:47	189:64	0.31	69:31	67:33	< 0.01
Body mass index (kg/m ²)	22.9 (20.2–25.0)	22.0 (20.1-24.3)	0.18	23.0 (20.3–25.3)	23.1 (21.1–25.3)	0.01
ASA grade (1:2:3)	43:59:16	87:136:30	0.08	33:53:14	33:56:11	0.09
cT ^a (1:2:3:4a)	33:23:37:25	99:43:66:45	0.24	30:20:28:22	33:20:24:23	0.10
$cN^{a}(-:+)$	69:49	170:83	0.18	57:43	61:39	0.08
cStage ^a (I:II:III)	46:36:36	128:57:68	0.25	41:27:32	47:20:33	0.06
Use of preoperative chemotherapy, n (%)	18 (15.3)	35 (13.8)	0.04	13 (13)	10 (10)	0.09
Extent of lymphadenectomy (D1+:D2)	34:84	120:133	0.39	31:69	34:66	0.06
Splenectomy, <i>n</i> (%)	17 (14.4)	33 (13.0)	0.04	11 (11)	8 (8)	0.10
History of laparotomy, n (%)	18 (15.3)	45 (17.8)	0.07	16 (16)	11 (11)	0.15

Data are shown as median with interquartile range unless otherwise specified. The χ^2 test was used for between-group comparison of period, gender, ASA grade, history of laparotomy, cT, cN, cStage, use of preoperative chemotherapy, extent of lymphadenectomy, and splenectomy. The Mann–Whitney U test was applied for between-group comparison of age, body mass index, and number of metastatic LNs

RTG robotic total gastrectomy, LTG laparoscopic total gastrectomy, SD standardized difference, ASA American Society of Anesthesiologist, LNs lymph nodes

^aJapanese Classification of Gastric Carcinoma, 15th edition

Tuble 9 Burgleur outcomes und short term postoperunte course	Table 3	Surgical	outcomes an	d short-term	postoperative course
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	Entire cohort (n=371) Propensity-score mate		natched cohort ($n = 200$)	p value	
	RTG (<i>n</i> =118)	LTG $(n=253)$	RTG $(n = 100)$	LTG (<i>n</i> = 100)	
No. of operators (Qualified surgeon)	9 (9)	32 (19)	9 (9)	26 (18)	N.A.
Reconstruction (FEEA:overlap:circular)	68:49:1	179:60:14	60:38:1	76:22:2	0.039
Total operative time (min)	511 (450-629)	445 (383–537)	511 (450–646)	448 (387–549)	< 0.001
Console time (min)	444 (390–543)	N.A.	445 (392–555)	N.A.	N.A.
Estimated blood loss (mL)	62 (34–141)	57 (23–135)	65 (38–146)	70 (30–161)	0.781
Number of dissected LNs	48 (40–59)	43 (32–53)	48 (39–59)	43 (35–54)	0.025
Reoperation rate, n (%)	1 (0.8)	7 (2.8)	1(1)	2 (2)	1.000
Hospitalization following surgery (days)	13 (11–16)	16 (12–21)	13 (11–16)	14 (11–19)	0.032
In-hospital mortality, n (%)	1 (0.8)	0 (0)	1(1)	0	1.000
Tumor size (mm)	55 (30-80)	45 (27–70)	60 (27–73)	50 (30-75)	0.548
pT ^a (1:2:3:4a)	44:11:17:46	105:25:40:83	41:9:13:37	33:7:17:43	0.552
pN ^a (0:1:2:3)	63:17:15:23	140:38:40:35	55:15:13:17	44:17:24:15	0.192
pStage ^a (I:II:III)	50:30:38	113:61:79	46:23:31	34:26:40	0.210
Number of metastatic LNs	0 (0-4)	0 (0–5)	0 (0-4)	0 (0–5)	0.246
Postoperative drain amylase levels (IU/L)					
1POD	437 (263–992)	733 (383–1287)	478 (253–1086)	810 (479–1652)	< 0.001
2POD	300 (150-577)	343 (196–837)	293 (153-588)	458 (227-1065)	0.001
3POD	132 (79–289)	152 (85–319)	131 (75–284)	203 (113-436)	0.005

Data are presented as median with interquartile range unless otherwise stated. The χ^2 test was used for between-group comparison of comparison of proportion of qualified and non-qualified surgeons, conversion to open procedure, reoperation rate, in-hospital mortality, pT, pN, and pStage. The Mann–Whitney U test was applied for between-group comparison of total operative time, estimated blood loss, number of dissected LNs, hospital stay following surgery, tumor size, and No. of metastatic LNs

RTG robotic total gastrectomy, LTG laparoscopic total gastrectomy, N.A. not applicable, LNs lymph nodes, POD postoperative day

IU/L vs. LTG 458 (227–1065) IU/L; p = 0.001; 3POD, RTG 131 (75–284) IU/L vs. LTG 203 (113–436) IU/L; p = 0.005]. Regarding the entire cohort, results similar to those for the post-PSM cohort were obtained (Table 3).

Postoperative complications

Postoperative complications are summarized in Table 4. After PSM analysis, the RTG group had a significantly better morbidity rate than the LTG group (RTG 3% vs. LTG 13%; p = 0.019). Robotic surgery promoted better attenuation of intra-abdominal infectious complications compared to nonrobotic surgery (RTG 1% vs. LTG 9%; p = 0.023), whereas no significant differences in other local (RTG 1% vs. LTG 3%; p = 0.614) or systemic (RTG 1% vs. LTG 1%; p = 1.000) complication rates were observed. Regarding the entire cohort, results remained almost same (Table 4). Univariate analysis using covariables using PSM identified LTG as the only significant risk factor for intra-abdominal infectious complications (Table 5). Also, multivariate analysis clearly identified LTG [odds ratio (OR) 10.989 (1.350-90.909); p = 0.025] as the only independent risk factor for intraabdominal infectious complications (Table 5).

Discussion

Through PSM analysis, the current study demonstrated that the RTG group had a significantly lower incidence of total and intra-abdominal infectious complications compared to LTG group. Additionally, multivariate analysis of the PSM cohort showed that non-robotic MIS was a significant independent risk factor for intra-abdominal infectious complications. Compared to our previous study, which showed an odds ratio of 2.591 (1.418-4.717) for complication risk after comparing RG and LG using PSM analysis including distal, proximal, and total gastrectomy [26], the current study, which was limited total gastrectomy, showed an odds ratio of 10.989 (1.350-90.909), which is approximately four times greater. In addition, the rates of both morbidity and intra-abdominal infectious complications in RTG still remains low, although technically demanding procedures including D2 dissection and for advanced GC patients were significantly increased in the later period. Further, multivariate analysis indicated that D2 dissection, cT2 or higher, cN+status, and cStage-II/III GC were not identified as significant risk factors for morbidity. Therefore, we consider that the use of the DVSS may reduce the negative impact of potential high-risk factors on morbidity, including D2

Table 4 Postoperative complications with a Clavien-Dindo grade of IIIa or higher, n (%)

	Entire cohort (n	cohort $(n=371)$ Propensity-score matched cohort $(n=200)$		p value	
	RTG (<i>n</i> =118)	LTG (<i>n</i> =253)	RTG ($n = 100$)	LTG $(n = 100)$	
Morbidity	4 (3.4)	34 (13.4)	3 (3)	13 (13)	0.019
Intra-abdominal infection	1 (0.8)	22 (8.7)	1(1)	9 (9)	0.023
Anastomotic leakage	0	9 (3.6)	0	1(1)	1.000
Intraperitoneal abscess	1 (0.8)	4 (1.6)	1(1)	3 (3)	0.614
Pancreatic fistula	0	9 (3.6)	0	5 (5)	0.070
Other local complications	2 (1.7)	7 (2.8)	1(1)	3 (3)	0.614
Intra-abdominal bleeding	2 (1.7)	2 (0.8)	1(1)	1(1)	1.000
Bowel obstruction	0	5 (2.0)	0	2 (2)	0.477
Systemic complications	1 (0.8)	6 (2.4)	1(1)	1(1)	1.000
Pneumonia	0	4 (1.6)	0	1(1)	1.000
Pulmonary embolism	1 (0.8)	0	1(1)	0	1.000
Cardiovascular disease	0	2 (0.8)	0	0	1.000

Data are presented as n (%)

The χ^2 test was used for between-group comparison

RTG robotic total gastrectomy, LTG laparoscopic total gastrectomy

Table 5 Risk factors for intra-abdominal infectious complications (propensity-score matched cohort, n = 200)

Factors	Univariate analysis OR (95% CI)	p value	Multivariate analysis OR (95% CI)	p value
LTG (vs RTG)	9.000 (1.162–69.723)	0.023	10.989 (1.350–90.909)	0.025
Period	1.802 (0.371-8.743)	0.459		
$Age \ge 70$	1.159 (0.325-4.135)	0.820		
Male	1.882 (0.411-8.613)	0.404		
Body mass index \geq 23 kg/m ²	1.083 (0.324-3.626)	0.897		
ASA score 2 or higher	1.103 (0.276-4.414)	0.889		
cT2 ^a or more	1.891 (0.390–9.175)	0.422		
cN+ ^a	3.658 (0.917-14.591)	0.051	2.852 (0.332-24.521)	0.340
cStage II ^a or more	3.379 (0.699–16.330)	0.110	1.727 (0.151–19.796)	0.660
D2 dissection	1.354 (0.395-4.632)	0.629		
Splenectomy	2.719 (0.532-13.902)	0.212		
Use of neoadjuvant chemotherapy	1.112 (0.148-8.368)	0.917		

Data are presented as odds ratio (95% confidence interval). The χ^2 test was used for univariate analysis. Multivariate logistic regression was used for multivariate analyses of factors having a p value of <0.15 during univariate analysis

ASA American Society of Anesthesiologist

^aJapanese Classification of Gastric Carcinoma, 15th edition

dissection, cN+status, and cStage-II/III GC. These findings and speculations partly support our hypothesis, which stated that using the robotic system would promote greater clinical advantage for technically demanding procedures, such as LTG.

Based on the three major studies regarding LTG using the Japanese NCD [11–13], the rate of intra-abdominal infectious complications after LTG have hardly improved throughout this decade. Kodera et al. reported that the rates of anastomotic leakage, intra-abdominal abscess, and

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pancreatic fistula using the NCD from 2012 to 2013 was 5.4%, 4.7%, and 1.7% in cStage I GC and 5.7%, 5.9%, and 2.5% in cStage-II–IV GC, respectively [11]. Moreover, the rates of the same complications were 5.3%, 3.9%, and 2.7% in cStage I-IV GC, respectively, according to the study by Etoh et al. using the NCD from 2014 to 2015 [12] and 4.4%, 5.4%, and 1.5% in cStage I-III GC, respectively, according to the study by Suda et al. using the NCD from 2018 to 2019 [13]. Similarly, the current study found that the rates of the aforementioned complications in the entire cohort

were 3.6%, 3.6%, and 1.6% in cStage I-III GC, respectively. Therefore, our results regarding the rates of intra-abdominal infectious complications after LTG seem to be nearly comparable to those studies. In contrast, the rates of intraabdominal complications, particularly anastomotic leakage, intraperitoneal abscess, and pancreatic fistula, in the entire cohort of the RTG group were 0%, 0.8%, and 0%, respectively, and were significantly lower compared to those in the LTG group. These findings seem to be better than those published in the recent study by Suda et al. based on the NCD from 2018 to 2019 (i.e., 4.6%, 7.2%, and 1.3%, respectively) [13]. The most remarkable difference between our study and the aforementioned one was that the current NCD study included numerous operating surgeons who have yet to reach the plateau in their learning curve for RG or have not been fully standardized in each institution where RG was launched within 1 year after RG was covered by the national insurance.

Previously, only a couple of studies have recently focused on comparing RTG and LTG [42-44]. Notably, the prospective study by Chen et al. showed no significant difference in postoperative morbidity (CD-IIIa or more) between both groups (RTG 4.2% vs. LTG 5.1%, p = 0.748) [42]. Moreover, Roh et al. reported no significant differences in CD grade IIIa or higher complications between RTG and LTG (10.8% vs. 14.9%, no significant difference) [43], same as with Kumamoto et al. (RTG 0% vs. LTG 6.9%, p = 0.492) [44]. However, the aforementioned studies could not determine whether RTG promoted clinical advantages over LTG, particularly in improving morbidity. In contrast, the current study clearly demonstrated that RTG offered better clinical advantages over LTG in reducing complications as evidenced by its low incidence rates of total morbidity (3.4%)and intra-abdominal infectious complications (0.8%). The great difference from those previous studies was the energy device to use for nodal dissection. In the current study, bipolar dissection was employed in RTG as the main dissecting energy device, in contrast to those three previous studies, in which the USAD was mainly employed [42–44]. As a result, we could achieve the very low incidence of intra-abdominal infectious complications and lower postoperative drain amylase levels in the RTG group. However, it still remains unknown whether only the robotic bipolar dissection procedure could account for the difference. Further investigation is warranted to clarify whether the bipolar dissection procedure truly contribute to the organ-protective effects even in the other institute.

The major reason of these favorable outcomes could likely be the success in standardizing RG procedures, including RTG, at our institute through sharing of surgical concepts, technical principles, and robotic methodologies to fully utilize the robotic characteristics as previously described [25, 36, 37]. In particular, the outermost layer-oriented nodal dissection using the "double bipolar" method has played a key role, which enables operating surgeons to conduct radical lymph node dissection with little contact with the pancreas. This is the definite different point from LTG procedure in which the USAD was mainly employed for nodal dissection. Actually, the postoperative drain amylase levels of RTG were significantly lower than those of LTG in this study. These findings suggest that nodal dissection using the "double bipolar" method has the potential advantage to protect the pancreas from the surgical injury. In addition, most operating surgeons performed RTG after reaching a plateau in their learning curve based on our education system [36]. Hence, the RTG group achieved drastically lower postoperative intra-abdominal infectious complications compared to the LTG group. Notably, none of the patients developed anastomotic leakage or pancreatic fistulas, despite our inclusion of nine operating surgeons for RTG. These findings suggest that systematic education reaching levels comparable to those of experts and standardization of the procedure highlighted by sharing common surgical concepts and technical principles could increase the safety and repeatability of RTG, leading to further improvements in short-term outcomes. On the other hand, the impact of robotic staplers on reducing anastomotic leakage remains unknown given that the selection of linear staplers depended on the surgeon's preference. Moreover, details regarding linear staplers, including assistant-manipulating linear staplers, linear staplers with reinforcement content, and robotic staplers, were not investigated. This seems to be a considerable limitation of the current study. However, we believe that RTG still remains feasible for anastomotic-related procedures, including suturing, adjusting the anastomotic line alignment, and manipulating the esophagus and alimentary jejunum, even when robotic staplers are not used. To establish robust evidence for RTG, further studies including multicenter prospective trials are required.

Apart from the reduction in morbidity rate, the current study also demonstrated that the RTG group had a significantly greater number of dissected LNs compared to the LTG group. This seems to suggest that outermost layer-oriented nodal dissection using the "double bipolar" method, which allows the full utilization of the intuitive characteristics of the DVSS, greatly increased precision and meticulousness at which operating surgeon performed dissection, thereby contributing to this favorable outcome. Unfortunately, long-term outcome surveillance was outside the endpoints of this study and thus requires further studies. Therefore, the advantages of RTG on oncological outcomes remains inconclusive. However, as previously reported, RG promoted superior long-term oncological outcomes compared to LG, especially for pathological stage II/ III GC patients [28]. Moreover, some reports had demonstrated that intra-abdominal infectious complications after gastrectomy had a negative impact on long-term oncological outcomes [45]. Accordingly, further investigations are warranted to determine whether the effects of RTG in reducing intra-abdominal infectious complications and increasing the number of dissected LNs actually translates to improvements in oncological outcomes after RG in the present cohort. In addition, this study could not clarify which area of the LN's station were more dissected by RTG. Further investigations should be conducted to clarify the LN station areas that the advantages of RTG can be maximally exerted.

The present study has several limitations that need consideration. First, this study employed a single-center, retrospective, and non-randomized design. In particular, financial resources necessary for RTG had been changed from each patient's own expense, Senshiniryo B, to the national insurance coverage. Together with this modification in financial circumstance, the indication for RTG also drastically changed such that almost all minimally invasive total gastrectomy procedures were performed using the robotic system after national medical insurance coverage. Therefore, several sources of patient bias, especially patient selection bias, could not be excluded, despite compensating for differences in preoperative patient's characteristics by PSM. In addition, the LTG group tended to include more patients with advanced pathological findings, although not significantly different. Moreover, the study period was so long as about 13 years. Therefore, this can also lead to considerable chronological bias, although there were little differences in surgical outcomes between the former and later study-periods. Further studies, including prospective trials, are warranted to provide sufficient evidence needed to support our hypothesis. Second, this study has concerns regarding operator bias given that all RTG procedures were performed by the ESSQS-qualified surgeons who had rich experienced of LTG, while all LTG procedures were performed by not only the ESSQS-qualified surgeons but also the non-ESSQS-qualified surgeons. We consider that the influence of differences in the skills of operating surgeons was not so much in this study for the following two reasons. First, the multivariate analyses indicated that the non-ESSQS-qualified surgeons were not identified as the risk factor for morbidity. Second, we have previously reported that there were no significant differences in the morbidity rate between ESSQS-qualified surgeons and non-ESSQS-qualified surgeons [20]. However, the protective effects of RTG on morbidity could be potentially attributed from the learning effects of the operating surgeons based on the rich experiences of LTG. To address this issue, well-designed comparative studies focusing on the influence of the differences of operator's experiences on surgical outcomes would be necessary. Third, the SD for history of laparotomy was 0.15 after PSM, indicating that a well balance was not achieved on this parameter. However, history of laparotomy affects the extent of intra-abdominal adhesion, particularly, adhesion to the abdominal wall, most of which is removed in a laparoscopic manner even in RG before the patient cart is docked to the patient; therefore, we consider that the impact of this parameter on the primary outcome measure is negligible. Fourth, the cost-effectiveness of RTG could not be assessed. We had previously estimated that the total cost associated with use of the robotic system was only 123.5 USD per patient more than that for LG [23]. Further studies are nonetheless needed to clarify the cost-effectiveness of RTG.

In conclusion, the present study showed that robotic surgery might improve short-term outcomes following minimally invasive radical total gastrectomy by reducing intraabdominal infectious complications.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10120-022-01288-8.

Acknowledgements The authors would like to thank MARUZEN-YUSHODO Co., Ltd. (https://kw.maruzen.co.jp/kousei-honyaku/) for the English language editing.

Author contributions All authors have fully satisfied the ICMJE authorship criteria as detailed in the following: study design: SS, IU, KS; data collection: SS, MN, AS, KN, TT; statistical analysis and interpretation of results: SS, MN, SA, KI, KS; drafting of the manuscript: SS, KS; critical revision of the manuscript for important intellectual content: IU, KS. All authors have read and approved the final manuscript and are accountable for all aspects of the work, particularly in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding This work was not supported by any grants or funding.

Declarations

Conflict of interest Susumu Shibasaki, Masaya Nakauchi, Akiko Serizawa, Kenichi Nakamura, Shingo Akimoto, Tsuyoshi Tanaka, Kazuki Inaba, Ichiro Uyama, and Koichi Suda have no commercial association with or financial involvement that might be construed as a conflict of interest in connection with the submitted article. Ichiro Uyama has received lecture fees from Intuitive Surgical, Inc., outside of the submitted work. Tsuyoshi Tanaka and Ichiro Uyama have been funded by Medicaroid, Inc. in relation to the Collaborative Laboratory for Research and Development in Advanced Surgical Technology, Fujita Health University. Koichi Suda has been funded by Medicaroid, Inc. in relation to the Collaborative Laboratory for Research and Development in Advanced Surgical Intelligence, Fujita Health University, and has also received advisory fees from Medicaroid, Inc., outside of the submitted work.

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