Yonago Acta Medica 2020;63(2):99–106 doi: 10.33160/yam.2020.05.005

The Advantages of Robotic Gastrectomy over Laparoscopic Surgery for Gastric Cancer

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ABSTRACT

Background We compared short- and long-term clinical outcomes including inflammatory marker levels between robotic gastrectomy (RG) and laparoscopic gastrectomy (LG) to define the advantages of RG over LG.

Methods We enrolled 209 patients with gastric cancer who underwent curative distal gastrectomy. We compared short- and long-term clinical outcomes including inflammatory marker levels between RG and LG to define the advantages of RG over LG. C-reactive protein (CRP) levels; the CRP-to-albumin, neutrophil-to-lymphocyte, and platelet-to-lymphocyte ratios; and the prognostic nutritional index were compared as systemic inflammatory markers.

Results RG was associated with a longer operative time. The incidence of postoperative infectious complications of grade II or higher according to the Clavien–Dindo classification was not significantly different between the two groups. Amylase levels in drainage fluid on postoperative days 1 and 3 were significantly lower in the RG group than in the LG group. The incidence of pancreatic fistula in the RG group (4.3%) was lower than that in the LG group (7.5%), albeit without significance. There were no significant differences in inflammatory marker levels either before or after surgery between the two groups. The 3-year overall survival rate did not significantly differ between the RG and LG groups (91.1% vs. 91.1%). Similar results were observed regarding the 3-year disease-specific survival rate (100% vs. 97.1%).

Conclusion RG might be feasible and safe for treating gastric cancer from both surgical and oncological perspectives. The use of robotic assistance is associated with decreased amylase levels in drainage fluid, which may reduce the risk of pancreatic fistula and prevent pancreatic injury.

Key words gastric cancer; robotic gastrectomy

Gastric cancer remains the fourth most common cancer and the second leading cause of cancer-related death worldwide, and the mainstays of curative treatment are surgical resection and lymphadenectomy based on the stage of the disease and co-morbidities of the patient.[1] Laparoscopic gastrectomy (LG) has been reported as a valid alternative to open surgery for the treatment of gastric cancer, particularly in Eastern countries and for patients with early-stage cancer.[2, 3] In patients with early gastric cancer of the lower two-thirds of the stomach, LG is accepted as a standard treatment option based on the results of randomized controlled trials conducted in Eastern countries.[4, 5] In 2003, Hashizume and Sugimachi were the first researchers ever to report robotic gastrectomy (RG) in the world.[6] As a minimally invasive surgery, the use of RG is increasing with advances in robot technology. Three-dimensional vision, high magnification, increased degrees of freedom including endo-wristed instrumentation, a stable optical platform, and tremor reduction technology can be provided using the da Vinci Surgical System (Intuitive Surgical Inc., Sunnyvale, CA).

Surgical tissue damage and the accompanying inflammatory response lead to proteasome activation, the initiation of damaged protein degradation, and the induction of the acute-phase inflammatory response, which might affect the clinical outcomes of various cancer surgeries.[7] Several systemic inflammatory markers are derived from peripheral blood tests, such as C-reactive protein (CRP), the CRP-to-albumin (CAR),

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Received 2020 April 14
Accepted 2020 April 28
Online published 2020 May 18

Abbreviations: BMI, body mass index; CAR, C-reactive protein-to-albumin ratio; CRP, C-reactive protein; DSS, disease-specific survival; LG, laparoscopic gastrectomy; NLR, neutrophil to lymphocyte ratio; OS, overall survival; PLR, platelet-to-lymphocyte ratio; pN, pathological lymph node metastasis; PNI, prognostic nutritional index; POD, postoperative day; POPF, postoperative pancreatic fistula; pStage, pathological stage; RFS, relapse-free survival rate; RG, robotic gastrectomy

neutrophil-to-lymphocyte (NLR), and platelet-to-lymphocyte ratios (PLR), and the prognostic nutritional index (PNI).[8–11] Several studies demonstrated significant differences in inflammatory responses between laparoscopic and open surgery for endometrial and colorectal cancers.[7, 8] However, no reports have described the differences of inflammatory responses between RG and LG. Therefore, clarifying differences in inflammatory responses between laparoscopic and robotic surgery for gastric cancer is important to demonstrate the benefits of RG over LG.

Several studies reported the short-term comparative results of LG and RG for gastric cancer; however, few studies reported the long-term outcomes.[9–11] This study compared short- and long-term clinical outcomes including inflammatory marker levels between RG and LG to define the advantages of RG over LG.

SUBJECTS AND METHODS

Patients

This study conducted retrospective analyses of 209 patients with gastric cancer who underwent robotic-assisted or laparoscopic distal gastrectomy at our institution between January 2011 and December 2017. All enrolled patients had undergone curative gastrectomy with lymphadenectomy. The extent of lymph node dissection (D1+ or D2) was determined according to the Japanese gastric cancer treatment guidelines.[12] Patients with multiple primary cancers were excluded from this study. All RG procedures were performed by one of the two experienced surgeons who were board-certified by the Japanese Society for Endoscopic Surgery and completed a training program for da Vinci surgery. LG was either performed or supervised by one of these two surgeons. The da Vinci Surgical System Si was used for all patients who underwent RG. The clinicopathological findings were determined according to the Japanese Classification of Gastric Carcinoma.[13] All patients underwent placing of an abdominal drain tube, and if there was no problem with the clinical course, patients started eating postoperatively on day (POD) 3. The drain tube was removed on POD 4 if the condition of the drainage fluid was normal.

Patients were periodically checked for recurrence via physical examination and blood tests every 3 months after discharge from the hospital. Abdominal ultrasonography and/or computed tomography were performed at least every 6 months. Causes of death and patterns of recurrence were determined by reviewing medical records, including the results of laboratory examinations, ultrasonography, computed tomography, and scintigraphy, or via the direct inquiry of family members.

The Institutional Review Board of our institution approved the study (18A154). The informed consent requirement was waived.

Serum markers

The results of peripheral blood tests including white blood cell, total platelet, neutrophil, and lymphocyte counts and serum albumin and CRP levels were obtained from patients' records. Postoperative data were obtained on postoperative days 1 and 3. CAR was obtained by dividing the peripheral CRP level by the albumin level.[14] NLR[15] and PLR[16] were obtained by dividing the peripheral neutrophil and platelet counts, respectively, by the peripheral lymphocyte count. PNI was calculated as follows: 10 × Alb concentration + 0.005 × total lymphocyte count.[17]

Statistical analysis

Continuous variables were expressed as the mean ± SD and compared using the Mann–Whitney *U* test. The χ^2 test or Fisher's exact test was used to compare categorical variables. Survival curves were calculated using the Kaplan–Meier method, and differences between survival curves were examined using the log-rank test. All statistical analyses were performed using JMP v9.0.1 software (SAS Institute, Inc., Cary, NC).

RESULTS

Patient characteristics are shown in Table 1. Age, gender, and body mass index were comparable between the two groups, as were tumor size, histology, depth of tumor invasion, lymph node metastasis, and pathological stage.

The operative characteristics of the groups are shown in Table 2. The operative time was significantly longer for RG than for LG (541 ± 144 min vs. 329 ± 77 min, $P < 0.001$). Billroth I reconstruction was performed significantly more frequently in the RG group than in the LG group ($P = 0.037$). The RG group tended to have greater intraoperative blood loss than the LG group, albeit without significance (86.4 ± 105.9 mL vs. 40.8 ± 55.6 mL, $P = 0.063$). The extent of lymph node dissection was comparable between the two groups.

When the patients of the RG group were divided into 14 cases in the early period of 2011-2012 and 9 cases in the later period of 2013-2017, the operative time of the later period was significantly shorter than that of the early period (604 ±152 min vs. 443±70 min, $P = 0.011$). The patients with early period tended to have greater intraoperative blood loss than those with later period, albeit without significance (116.8±121.6 mL vs.

Table 1. Clinicopathologic features of patients in the LG and RG groups

	LG (n = 186)	RG (n = 23)	P value
Age (years)	68.9 ± 11.4	66.6 ± 11.0	0.189
Gender			0.814
Male	127 (69.4)	15 (65.2)	
Female	59 (30.6)	8 (34.8)	
BMI	22.5 ± 3.0	22.7 ± 1.9	0.515
Tumor size (mm)	33.5 ± 20.4	30.4 ± 13.0	0.875
Histology			0.825
Differentiated	106 (57.0)	14 (60.9)	
Poorly differentiated	80 (43.0)	9 (39.1)	
Depth of tumor invasion			0.424
T1	146 (78.5)	20 (86.9)	
≥ T2	40 (21.5)	3 (13.1)	
Lymph node metastasis			0.540
Absent	157 (84.4)	21 (91.3)	
Present	29 (15.6)	2 (8.7)	
Lymphatic invasion			0.370
Absent	107 (57.5)	16 (69.6)	
Present	79 (42.5)	7 (30.4)	
Venous invasion			0.083
Absent	120 (64.5)	19 (82.6)	
Present	66 (35.5)	4 (17.4)	
pStage			0.487
IA	135 (72.6)	19 (82.6)	
IB	17 (9.1)	0	
IIA	19 (10.2)	2 (8.7)	
IIB	15 (8.1)	2 (8.7)	

Data are presented as the mean ± SD or n (%). BMI, body mass index; LG, laparoscopic gastrectomy; pStage, pathological stage; RG, robotic gastrectomy.

53.9 ± 74.9 mL, P = 0.241).

The incidence of postoperative infectious complications of grade II or higher according to the Clavien–Dindo classification[18] was not significantly different between the two groups (P = 0.887). As shown in Table 2, four complications (17.3%) were reported in the RG group, and 35 complications (18.8%) were reported in the LG group. In addition, the length of postoperative hospital stay did not differ between the two groups (15.6 ± 13.8 days vs. 14.3 ± 7.4 days, P = 0.261). The incidence of pancreatic fistula was lower in the RG group than in the LG group, but the difference was not significant (4.3% vs. 7.5%, P = 0.519). Figure 1 presents amylase levels in drainage fluid on PODs 1 and 3 in both groups. Amylase levels in drainage fluid on POD 1 were significantly lower in the RG group (374 ± 203 IU/L) than in the LG group (877 ± 1519 IU/L, P = 0.029), and similar results were obtained on POD 3 (108 ± 59 IU/L vs. 246 ± 357 IU/L, P = 0.003). No postoperative mortality occurred in either group.

The levels of systemic inflammatory markers in the LG and RG groups are shown in Table 3. There were no significant differences in any inflammatory marker level between the groups either before or after surgery.

The median follow-up time of the 190 surviving patients was 50.3 months (range, 2.8–105.4 months). Of the 19 deaths, five were related to gastric cancer recurrence (bone metastasis, n = 2; liver metastasis, n = 1; peritoneal metastasis, n = 1; lymph node metastasis, n = 1). The 3-year overall survival (OS) rate did not

Table 2. Operative characteristics of the LG and RG groups

	LG (n = 186)	RG (n = 23)	P value
Operative time	329 ± 77	541 ± 144	<0.001
Bleeding	40.8 ± 55.6	86.4 ± 105.9	0.063
Lymph node dissection extent			0.975
D1+	145 (78.0)	18 (78.3)	
D2	41 (22.0)	5 (21.7)	
Reconstruction			0.037
B-1	121 (65.1)	21 (91.3)	
B-2	9 (4.8)	0	
Roux-en-Y	56 (30.1)	2 (8.7)	
Postoperative hospital stay	15.6 ± 13.8	14.3 ± 7.4	0.261
Infectious complication			0.887
Absent	151 (81.2)	19 (82.7)	
Present	35 (18.8)	4 (17.3)	
Pancreatic fistula			0.519
Absent	172 (92.5)	22 (95.7)	
Present	14 (7.5)	1 (4.3)	
Anastomosis leakage			0.261
Absent	177 (95.2)	23	
Present	9 (4.8)	0	

Data are presented as the mean ± SD or n (%). B-1, Bilroth-1; B-2, Bilroth-2; LG, laparoscopic gastrectomy; RG, robotic gastrectomy.

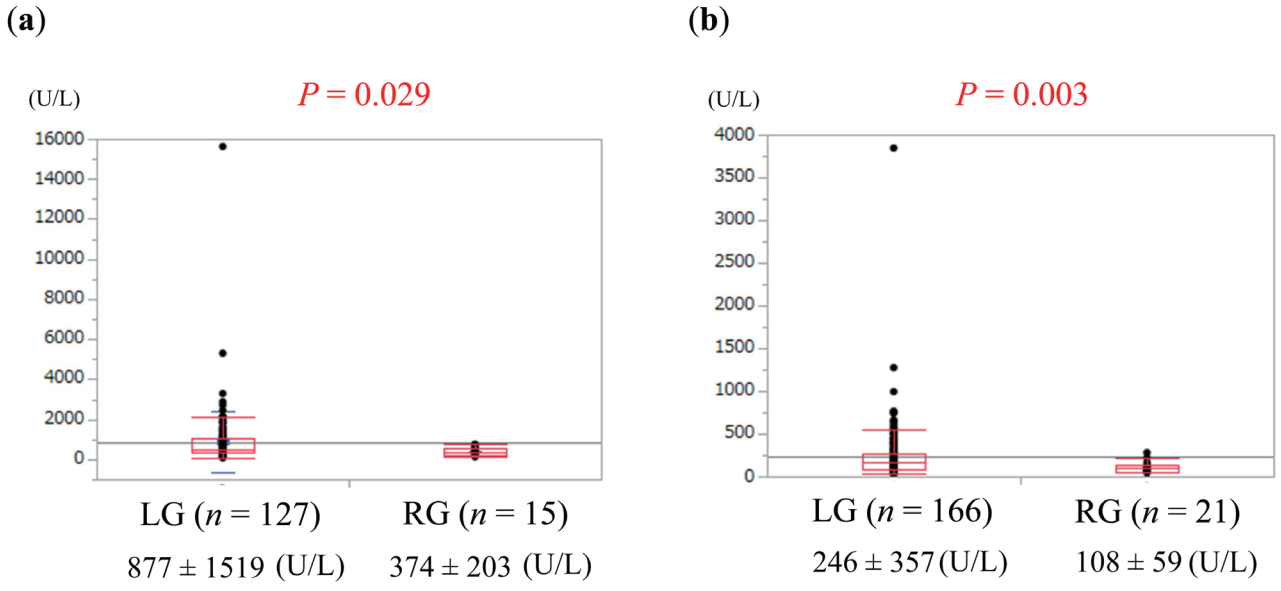

Fig 1. Postoperative amylase levels in drainage fluid. (**a**) Amylase levels in drainage fluid on POD 1. (**b**) Amylase levels in drainage fluid on POD 3.
POD, postoperative day.

Table 3. Inflammatory marker levels in the LG and RG groups

Variables	Preoperative			Postoperative day 1			Postoperative day 3		
	LG (n = 186)	RG (n = 23)	P value	LG (n = 186)	RG (n = 23)	P value	LG (n = 186)	RG (n = 23)	P value
WBC	5796 ± 1660	5972 ± 1907	0.850	9833 ± 2547	10,213 ± 2943	0.722	7729 ± 2563	7017 ± 1652	0.286
CRP	0.16 ± 0.36	0.18 ± 0.22	0.582	4.08 ± 2.11	3.64 ± 1.68	0.605	11.27 ± 6.82	10.25 ± 6.14	0.543
Platelet	22.44 ± 5.72	22.66 ± 7.35	0.567	18.23 ± 4.82	17.18 ± 5.62	0.110	18.40 ± 5.09	18.22 ± 5.38	0.758
Albumin	4.22 ± 0.39	4.32 ± 0.38	0.308	3.05 ± 0.30	2.93 ± 0.45	0.252	3.04 ± 0.89	3.08 ± 0.46	0.276
CAR	0.041 ± 0.095	0.045 ± 0.059	0.689	1.357 ± 0.723	1.303 ± 0.691	0.921	3.850 ± 2.648	3.330 ± 2.236	0.355
NLR	2.52 ± 1.67	2.21 ± 0.79	0.775	9.28 ± 4.99	9.37 ± 4.79	0.917	6.53 ± 4.42	5.30 ± 1.90	0.426
PNI	50.36 ± 5.11	51.86 ± 4.60	0.161	35.57 ± 3.95	34.59 ± 5.45	0.501	35.54 ± 4.94	35.94 ± 4.95	0.380
PLR	152.14 ± 64.01	135.86 ± 41.42	0.422	200.98 ± 91.47	174.66 ± 49.08	0.438	194.69 ± 104.26	183.18 ± 59.68	0.962

Data are presented as the mean ± SD. CAR, C-reactive protein-to-albumin ratio; CRP, C-reactive protein; LG, laparoscopic gastrectomy; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutrition index; RG, robotic gastrectomy; WBC, white blood cell.

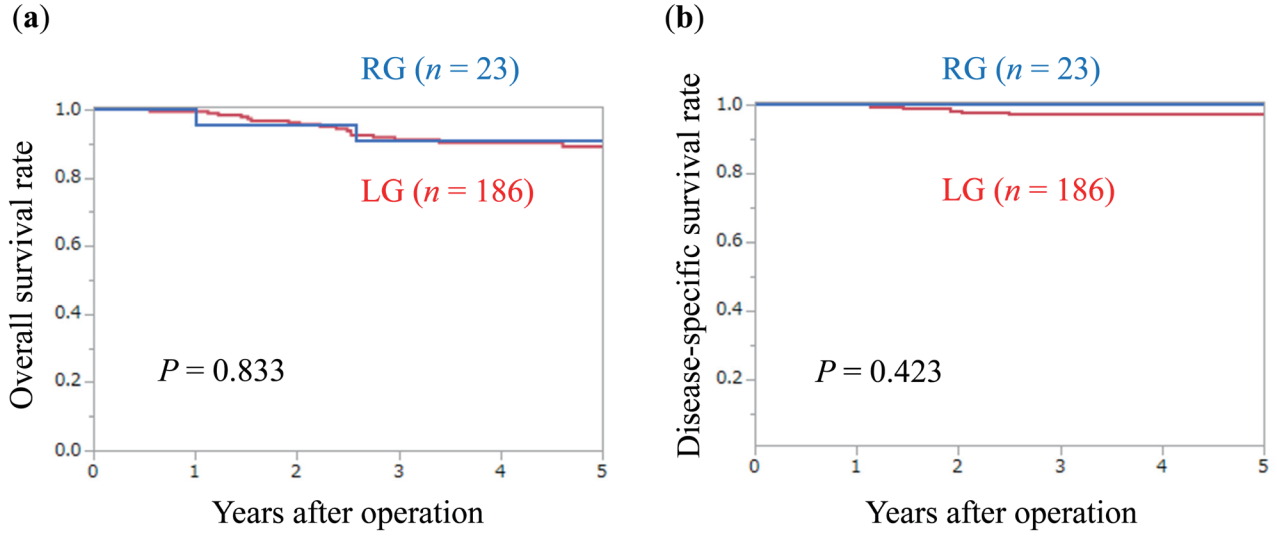

Fig. 2. Overall (**a**) and disease-specific survival curves (**b**) in the LG and RG groups. LG, laparoscopic gastrectomy; RG, robotic gastrectomy.

significantly differ between the RG and LG groups (91.1% vs. 91.1%, P = 0.833, Fig. 2a). Similar results were observed for the 3-year disease-specific survival (DSS) rate (100% vs. 97.1%, P = 0.423, Fig. 2b).

DISCUSSION

According to this study, the operative time was longer for RG than for LG. Amylase levels in drainage fluid on PODs 1 and 3 were significantly lower in the RG group than in the LG group, and the incidence of pancreatic fistula in the RG group was approximately half that in the LG group. There were no differences in any inflammatory marker level between the groups, and OS and DSS rates were similar.

Postoperative pancreatic fistula (POPF) is a complication encountered at a relatively high frequency after surgery for gastric cancer. The incidence of POPF after LG is reportedly 4.3–7.0%.[19, 20] Because POPF sometimes becomes a life-threatening complication, it should be given close attention when performing LG. In this study, amylase levels in drainage fluid on PODs 1 and 3 were significantly lower in the RG group than in the LG group. These results are consistent with those of a recent study by Ojima et al., who compared the surgical results of RG and LG for gastric cancer in 659 patients.[21] They reported that POPF occurred in 4.7% of patients in the LG group, compared with no patients in the RG group. In addition, amylase levels in drainage fluid on POD 1

were significantly lower in the RG group than in the LG group. Retraction of the pancreas is indispensable for obtaining a clear view of the supra-pancreatic region and precisely performing lymph node dissection in this field. However, retraction of the pancreas can cause parenchymal injury, which may result in pancreatic juice leakage. As a countermeasure against pancreas injury, surgical assistants should retract the pancreas gently and carefully with gauze. Conversely, the articulated forceps of the robot make it easier to access the supra-pancreatic region without strong retraction of the pancreas.[21] Therefore, robotic surgery may reduce the incidence of POPF by avoiding unnecessary pancreatic injury.

The 3-year OS and DSS rates were comparable between the RG and LG groups in this study. These results are similar to those of a recent study by Nakauchi et al., who compared the surgical results of RG and LG for gastric cancer in 521 patients.[22] They reported no differences in OS and relapse-free survival (RFS) rates between the RG and LG groups. Several prognostic factors related with OS and RFS have been reported for gastric cancer surgery, and the presence of postoperative complications and the amount of blood loss were important clinical markers for the prognosis of patients with gastric cancer.[23, 24] Whether RG results in less bleeding than LG remains controversial, and meta-analyses reported that the RG approach is associated with a lower bleeding tendency.[9, 25, 26] In our study, intraoperative blood loss tended to be higher in the RG group, albeit without significance. The finding may be attributable to the bipolar devices used in RG to fully utilize the robotic dexterity with articulating function. The bipolar cautery has relatively lower hemostability than ultrasonic laparoscopic coagulation shears and vessel sealing systems, which we usually use in LG.[22, 25] Furthermore, the incidence of postoperative infectious complications was not significantly different between the two groups. These results indicate that RG for gastric cancer was at least as feasible and safe as LG from both surgical and oncological perspectives.

In this study, the operative time was longer for RG than for LG. This result is similar to that of a recent study by Bobo et al., who retrospectively evaluated short outcomes of RG and LG in 4576 patients with gastric cancer.[26] These results indicate that RG requires a longer operative time, because RG requires "setting and docking" time for the robotic arm, which can be time-consuming. The learning curve is also an influence on operative time. In this study, the operative time of the later period was significantly shorter than that of the early period. It is reported that 11 to 25 cases of surgical experiences are required to overcome the learning curve of RG.[27] Therefore, with the development of the da Vinci robotic surgery system and more experience, the operative time may be shortened.

To date, no reports have compared inflammatory responses after surgery between RG and LG. It has been reported that the increase in CRP levels was proportional to the severity of surgical trauma, indicating the magnitude of tissue destruction.[28] Shishido et al. found that postoperative infectious complications significantly increased inflammatory marker levels during gastric cancer surgery.[29] In this study, there were no differences in inflammatory marker levels between the RG and LG groups, and the incidence of postoperative infectious complications was not significantly different between the two groups. Because changes in postoperative inflammatory markers are related to surgical stress, the study results suggest that surgical stress does not differ between RG and LG.

There were several limitations to the present study. First, this study was conducted at a single institution in a retrospective manner. The sample size, particularly in the RG group, was small, and the observation period was relatively short. Second, the statistical power of our study was insufficient for drawing firm conclusions because the number of events such as deaths and recurrences were small. Because the prognosis of patients with early gastric cancer is extremely good, larger numbers of patients, including patients with advanced-stage disease, are needed to obtain a conclusive result for the survival comparison.

In conclusion, RG might be a feasible and safe alternative to LG for treating gastric cancer from both surgical and oncological perspectives. The use of robotic assistance is associated with decreased amylase levels in drainage fluid, which may reduce the risk of pancreatic fistula and avoid pancreatic injury. Further analysis is needed to clarify the advantages of LG over LG, especially in terms of long-term surgical outcomes.

Acknowledgements: We thank Joe Barber Jr., PhD from Edanz Group (www.edanzediting.com/ac), for editing a draft of this manuscript.

The authors declare no conflict of interest.

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