

## ORIGINAL

# Short-term outcomes of laparoscopic/robotic gastrectomy compared with open gastrectomy for advanced gastric cancer following chemotherapy

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**Abstract : Purpose :** This study aimed to investigate the short-term outcomes of laparoscopic gastrectomy/robotic gastrectomy after chemotherapy in patients with advanced gastric cancer and compare these outcomes with those of open gastrectomy. **Methods :** Fifty patients who underwent radical gastrectomy for advanced gastric cancer after chemotherapy between 2007 and 2021 were retrospectively analyzed. The patients were divided into two groups : the laparoscopic gastrectomy/robotic gastrectomy (n = 11) and open gastrectomy (n = 39) groups. The short-term outcomes of these procedures were subsequently examined. **Results :** The laparoscopic gastrectomy/robotic gastrectomy group had significantly shorter hospital stays and lower intraoperative blood loss than the open gastrectomy group. The overall complication rates were 12.8% (5 of 39 patients) and 0% (0 of 11 patients) in the open gastrectomy and laparoscopic gastrectomy/robotic gastrectomy groups, respectively (P = 0.1). **Conclusions :** Laparoscopic gastrectomy/robotic gastrectomy may be a surgical option after chemotherapy for patients with advanced gastric cancer. *J. Med. Invest.* 69: 261-265, August, 2022

**Keywords :** Chemotherapy, Laparoscopic/robotic gastrectomy, Short-term outcome

## BACKGROUND

Globally, gastric cancer is the third leading cause of cancer death, with >70% of the cases reported in Asian populations, and it remains a major health problem (1-3). Furthermore, long-term outcomes in advanced cases remain unsatisfactory. Neoadjuvant chemotherapy (NAC) has been increasingly used in the treatment of locally advanced gastric cancer (4) and is generally accepted in Western countries based on the results of the FLOT4 and MAGIC trials (5, 6). Stage IV gastric cancer is categorized into four groups, category 1 and 2 patients have a chance to be performed curative surgery (7) and owing to advances in chemotherapy, resection of localized unresected gastric cancer has become possible, and the conversion rate is gradually increasing (8).

Regarding the surgical approach, laparoscopic gastrectomy (LG), a minimally invasive surgery, is recommended for early stages of gastric cancer. Recently, the usefulness of LG for advanced gastric cancer has been reported and have confirmed the efficacy and safety of LG for advanced gastric cancer (3). Furthermore, the CLASS-01 trial, which was a phase II study (9), suggested that, oncologically, LG was safe and comparable to open gastrectomy (OG). Recently, robotic gastrectomy (RG), which can be used to perform more sensitive surgeries compared with LG, has become more prevalent (10). The feasibility of RG for advanced gastric cancer has become gradually accepted and the complications of this type of surgery have been reported to be similar to those of LG.

Chemotherapy-induced tissue fibrotic changes and edema lead to technical difficulties in laparoscopic procedures. Few studies

have compared the safety and efficacy of OG and LG/RG following NAC and conversion surgery in patients with advanced gastric cancer. Therefore, the indication of LG/RG in such patients remains controversial.

The aim of this study was to investigate the short-term outcomes of LG/RG in patients with advanced gastric cancer who underwent chemotherapy and evaluate its feasibility as a treatment for advanced gastric cancer compared with OG.

## METHODS

### Patients

We performed a retrospective analysis of the gastric cancer database at the Department of Surgery, Tokushima University, Japan. Between October 2007 and February 2021, 64 patients were diagnosed with advanced gastric cancer and underwent preoperative chemotherapy followed by gastrectomy. The indications for NAC were large type 3 (>80 mm) or type 4 advanced gastric cancer or bulky lymph node metastasis. Patients with unresectable gastric cancer had undergone chemotherapy. The indication of the conversion surgery is that the CT and gastric fiber reveals that R0 surgery can be performed. NAC regimens and regimens for unresectable gastric cancer mainly consisted of docetaxel+cisplatin+TS-1 (DCS), TS-1+cisplatin, or TS-1+oxaliplatin. Patients with human epidermal growth factor 2 (HER2)-positive gastric cancer also received trastuzumab. Patients who underwent palliative gastrectomy (n = 14) were excluded from the present study. Fifty patients were finally selected and subsequently divided into two groups : the LG/RG group

### Abbreviations :

NAC : Neoadjuvant chemotherapy, LG : laparoscopic gastrectomy, OG : open gastrectomy, RG : robotic gastrectomy, DCS : docetaxel+cisplatin+TS-1, HER2 : human epidermal growth factor 2, JGCA : Japanese Gastric Cancer Association, ESSQS : Endoscopic Surgical Skill Qualification System, JSES : Japan Society for Endoscopic Surgery

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(n = 11) and the OG group (n = 39). All patients had undergone radical gastrectomy according to the treatment guidelines of the Japanese Gastric Cancer Association (JGCA) (11). All LG/RG procedures were performed by qualified surgeons certified by the Endoscopic Surgical Skill Qualification System (ESSQS) of the Japan Society for Endoscopic Surgery (JSSES). This study was approved by the Tokushima University Review Board.

#### Operative technique

All surgical procedures were performed in accordance with the guidelines of JGCA (11). Total or distal gastrectomy was performed in accordance with the location of the primary tumor. During total gastrectomy, splenectomy was performed in patients for whom the tumor invaded the upper one-third of the greater curvature of the stomach. The reconstruction method used in both groups comprised either the Billroth I or Roux-en-Y(R-Y) procedure depending on the remnant volume of the stomach and the extent of tumor invasion in the duodenum. The selection of LG/RG or OG was based on the decision made during departmental conference. In the LG/RG group, reconstruction was performed via intracorporeal anastomosis. During intracorporeal reconstruction, R-Y gastrojejunostomy and delta-shaped Billroth I anastomosis were performed in patients undergoing distal gastrectomy. Esophagojejunostomy was performed using the circular method. In the OG group, Billroth I anastomosis was performed via hand suturing. R-Y gastrojejunostomy was performed via functional side-to-side anastomosis. In total gastrectomy, R-Y esophagojejunostomy was performed using the circular method.

#### Data collection

Clinicopathological parameters and perioperative data (age, body mass index, American Society of Anesthesiologists (ASA) score (12), intraoperative blood loss, operative time, postoperative complications, length of postoperative hospital stay, clinicopathological TNM stage, and tumor regression grade) were evaluated according to the JGCA classification of gastric carcinoma (13). Postoperative complications were defined according to the Clavien–Dindo classification system, and only those of grade 3 or higher were recorded (14). Hospital mortality was defined as death from any cause within the postoperative 30 days.

#### Statistical analyses

Data were analyzed using the JMP statistical software program (SAS Institute Inc., Cary, NC). Patient characteristics were compared using the  $\chi^2$  test. Quantitative variables are presented as means  $\pm$  standard deviation. A P-value of  $<0.05$  was considered statistically significant.

## RESULTS

The median ages of the patients in the OG and LG/RG groups were 65.8 and 70.4 years, respectively. ASA score of 1 was more frequent in the OG group. The tumor diameter was larger in the OG group than in the LG/RG group (53.5 vs. 27.6 mm,  $P < 0.01$ ). The most frequent regimen was DCS in both groups. The pathological stage was higher in the OG group, whereas the pathological response was higher in the LG/RG group. The indication of preoperative chemotherapy was similar between the two groups (Table 1).

The surgical data of the two groups are summarized in Table 2. There were significant differences in the procedure of gastrectomy between the two groups: in the OG group, total gastrectomy was more frequently performed; therefore, R-Y reconstruction was more frequently implemented. The operative time tended to

be longer in the LG/RG group compared with the OG group (304 vs. 273 min,  $P = 0.29$ ). There was a significant difference in the intraoperative blood loss between the two groups: blood loss was lower in the LG/RG group than in the OG group (60 vs. 153 ml,  $P = 0.04$ ). Further, in the LG/RG group, D2 lymph node dissection was performed in all patients. D1+ lymph node dissection was performed in open group for shrunken tumor. No patients in the LG/RG group required switching to open surgery. There was no significant difference in the number of dissected lymph nodes between the two groups (30 vs. 28,  $P = 0.69$ ).

The postoperative factors are presented in Table 3. The overall

Table 1. Patient's characteristics

	OG group (n = 39)	LG/RG group (n = 11)	P value
Age (years)	65.8 $\pm$ 1.5	70.4 $\pm$ 2.8	0.15
Sex			0.95
Male	28	8	
Female	11	3	
BMI	21.2 $\pm$ 0.5	21.9 $\pm$ 0.9	0.49
ASA			0.03
1	24	2	
2	14	8	
3	1	1	
Tumor size (mm)	53.5 $\pm$ 4.9	27.6 $\pm$ 9.3	0.01
Histologic type			0.28
Differentiated	11	5	
Undifferentiated	28	6	
Regimen			0.12
DCS/DCS-Tmab	28	6	
S1+ipPTX	4	1	
SP/SOX/SOX-Tmab	7	4	
Total cycle of chemotherapy	4.1 $\pm$ 0.4	6.6 $\pm$ 0.8	$<0.01$
Pathological stage			0.01
No tumor	4	2	
I	4	3	
II	15	6	
III	16	0	
Pathological response*			0.01
Grade 0	3	2	
Grade 1	20	0	
Grade 2	7	6	
Grade 3	5	3	
Operation			0.1
NAC	8	5	
Conversion	31	6	

OG : Open gastrectomy

LG : Laparoscopic gastrectomy

RG : Robotic gastrectomy

BMI : Body mass index

ASA : American social of Anesthesiologists

DCS : Docetaxel + Cisplatin + S-1

ipPTX : Intraperitoneal Paclitaxel

SP : S-1 + Cisplatin

SOX : S-1 + Oxaliplatin

NAC : Neoadjuvant chemotherapy

\* : According to the Japanese Classification of Gastric Cancer

complication rates were 12.8% (5 of 39 patients) and 0% (0 of 11 patients) in the OG and LG/RG groups, respectively ( $P = 0.1$ ). The surgical complications included anastomotic leakage ( $n = 2$ ), pancreatic fistula ( $n = 1$ ), ascites ( $n = 1$ ), and chylothorax ( $n = 1$ ). In the OG group, one patient required reoperation owing to hemothorax and hemorrhage. The LG/RG group had a significantly shorter length of postoperative hospital stay than the OG group (10.1 vs. 16.7 days,  $P = 0.04$ ). Hospital mortalities were not observed in either group.

Table 2. Intraoperative outcomes

	OG group (n = 39)	LG/RG group (n = 11)	P value
Type of gastrectomy			0.05
Distal gastrectomy	9	6	
Total gastrectomy	30	5	
Lymph node dissection			0.21
D1+	3	0	
D2	36	11	
Splenectomy	1	0	0.47
Liver metastatic resection	5	1	0.72
Reconstruction			<0.01
Billtorh-I	2	6	
Roux-en-Y	37	5	
Operation time	273 ± 13	304 ± 25	0.29
Intraoperative blood loss	153 ± 21	60 ± 41	0.04
The number of dissected lymph nodes	30 ± 1.9	28 ± 3.6	0.69

OG : Open gastrectomy

LG : Laparoscopic gastrectomy

RG : Robotic gastrectomy

Table 3. Postoperative outcomes

	OG group (n = 39)	LG/RG group (n = 11)	P value
Complication CD grade ≥ 3			0.1
Overall	5	0	
Pancreatic fistula	1	0	
Anastomotic leakage	2	0	
Ascites	1	0	
Chylothorax	1	0	
Requiring re-operation	1	0	
Post operative hospital stay	16.7 ± 1.5	10.1 ± 2.8	0.04
Hospital mortality	0	0	

CD : Clavien-Dindo

## DISCUSSION

This study retrospectively investigated the surgical outcomes of LG/RG following chemotherapy and compared them with those of OG. The results showed that LG/RG following chemotherapy is safe and feasible owing to its good short-term outcomes.

The development of new anticancer drugs and highly effective

regimens has enabled remarkable tumor shrinkage with chemotherapy, whereby some patients with stage IV gastric cancer demonstrating a good response to chemotherapy have been able to undergo curative resection followed by long-term survival (15). The current literature demonstrates that the so-called conversion surgery for unresectable stage III or stage IV gastric cancer is associated with longer survival than chemotherapy alone. On the other hand, NAC has been proven to increase the R0 resection rate and reduce lymph node metastases compared with surgery alone (16). The European Organization for Research and Treatment of Cancer randomized trial illustrated that the R0 dissection rate in the NAC group was significantly higher than that in the surgery-alone group and that the NAC group had fewer lymph node metastases (17).

LG is accepted as being more effective than conventional open surgery and is commonly used to treat clinical stage I gastric cancer in accordance with the recent technical and instrumental improvements. Even for locally advanced gastric cancer, the technical safety of LG has been demonstrated in a randomized phase II study. A large phase III trial, KLASS-02(18), reported that LG with D2 lymphadenectomy was associated with lower postoperative complication rates, faster recovery, and less pain compared with OG. Moreover, laparoscopic surgery also offers benefits in gastrectomy for locally advanced gastric cancer after neoadjuvant chemotherapy, such as better postoperative safety and adjuvant chemotherapy tolerance, compared with conventional open surgery. A randomized controlled study conducted in east Asia confirmed that the technical feasibility of gastrectomy with D2 lymphadenectomy performed by laparoscopy was comparable to that of OG (19). For patients with advanced gastric cancer who have not undergone preoperative chemotherapy, RG with D2 lymphadenectomy is feasible and safe for the treatment of advanced gastric cancer in terms of the lower incidence and severity of its complications (10). Robot-assisted D2 gastrectomy is also technically reasonable, although its long-term outcomes are yet to be evaluated in prospective studies in Japan.

In the current study, patients in the LG/RG group had significantly lower intraoperative blood loss and better postoperative recovery compared with the OG group, with previous studies reporting similar findings for patients with advanced gastric cancer who had not undergone NAC and conversion surgery (3, 20). The findings of the current study show that the advantages of LG/RG remain the same for patients with advanced gastric cancer who undergo preoperative chemotherapy. The precise operative techniques involved in LG/RG help to minimize intraoperative blood loss. Because intraoperative blood loss is associated with the prognosis of gastric cancer (21-23), LG/RG may help improve the prognosis for some patients.

No significant differences were observed between the postoperative complication rates in the LG/RG (0 patients, 0%) and OG groups (5 patients, 13%) ( $P = 0.1$ ) in this study, a finding which was consistent with the morbidity rates about 10% reported in previous studies on patients who underwent open D2 gastrectomy following NAC and conversion (3, 8). The incidence of surgical complications in the LG/RG group can be considered low.

Chemotherapy causes tissue fibrosis, tissue edema and necrosis and destroy the anatomical dissection plane. As the result, these reactions may interfere with the surgical procedure and makes surgery more difficult, therefore, increase postoperative complication rates. Therefore, more operative blood loss has been observed in patients who have previously undergone neoadjuvant therapy, in whom it was harder and more tedious to stop the bleeding. D2 lymphadenectomy after neoadjuvant chemotherapy is more risky than D2 lymphadenectomy without preoperative treatment. Such issues may be resolved by LG/RG because this procedure allows for visual magnification, better exposure, and

more delicate maneuvers of organs, vessels, and nerves (24, 25). Operative hemorrhage can be easily induced by fibrosis and tissue edema, although an ultrasonic knife plays an important role in hemostasis. No postoperative complications and mild intraoperative bleeding were observed in this study. Although the operative time tends to be longer, LG/RG should be considered for patients who have undergone preoperative chemotherapy.

Previously, patients who received preoperative chemotherapy underwent open surgery. However, as laparoscopic and robotic surgery became increasingly adopted, the indication for LG/RG was expanded to pretreatment cases. All procedures were performed by qualified surgeons certified by the ESSQS of the JSES who had adequate experience. It is therefore difficult to state that RG/LG itself is effective in all cases of preoperative chemotherapy. LG performed by credentialed surgeons was surgically safe and feasible for patients with advanced gastric cancer compared with conventional OG (26).

This study had several limitations. First, the indications of the preoperative chemotherapy were different for patients undergoing NAC and conversion surgery. Hence, these two should be investigated individually in the future. This study focused on short-term results based on the surgical method; therefore, both patients undergoing NAC and conversion surgery were included. Other limitations of this study were the limited sample size, the retrospective nature, and the lack of randomization in the two treatment arms and concerning the selection of surgical procedure, there is a selection bias and operator bias. Finally, only the short-term outcomes were examined, and the long-term outcomes remain to be investigated.

## CONCLUSIONS

In conclusion, the findings of this study revealed that LG/RG following chemotherapy for advanced gastric cancer has good short-term outcomes, which suggests that LG/RG is a good option for patients with gastric cancer who have undergone chemotherapy.

## CONFLICT OF INTERESTS-DISCLOSURE

All authors have no conflict of interest.

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