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Short- and long-term outcomes of laparoscopic versus open gastrectomy for locally advanced gastric cancer following neoadjuvant chemotherapy

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Abstract

Background This study aimed to investigate the short- and long-term outcomes of laparoscopic gastrectomy (LG) in patients with advanced gastric cancer following neoadjuvant chemotherapy (NAC) to determine its safety and feasibility.

Methods We retrospectively investigated 51 patients who underwent gastrectomy for locally advanced gastric cancer [cT3-4/N1-3 or macroscopic type 3 (> 80 mm) or type 4] following NAC between November 2009 and January 2018. After excluding two patients who underwent palliative surgery due to peritoneal dissemination, 49 patients were ultimately selected for this cohort study. The patients were then divided into the LG group and open gastrectomy (OG) group, after which the clinicopathological characteristics as well as short- and long-term outcomes were examined.

Results Compared with the OG group, the LG group demonstrated a significantly lower amount of intraoperative blood loss and a shorter hospital stay. The overall complication rates were 10% (2 of 20 patients) and 24% (7 of 29 patients) in the LG and OG groups ($P = 0.277$), respectively. No significant differences in 5-year disease-free (LG 44.4% vs. OG 53.3%; $P = 0.382$) or overall survival rates (LG 46.9% vs. OG 54.0%; $P = 0.422$) were observed between the groups. Multivariate analysis revealed that the surgical procedure (LG vs. OG) was not an independent risk factor for disease-free ($P = 0.645$) or overall survival ($P = 0.489$).

Conclusions LG may be a potential therapeutic option for patients with gastric cancer following NAC considering its high success rates and acceptable short- and long-term outcomes.

Keywords Gastric cancer · Laparoscopic surgery · Neoadjuvant chemotherapy · Short-term outcome · Long-term outcome

Gastric cancer, the third leading cause of cancer death worldwide, remains a major health problem [1]. Although surgical treatment has been considered the primary therapy, long-term outcomes in advanced cases have still been unsatisfactory. Neoadjuvant chemotherapy (NAC) for advanced gastric cancer has been widely accepted in Western countries based on the results of the MAGIC and FLOT4 trials [2, 3]. In East Asia, however, adjuvant chemotherapy following gastrectomy with D2 lymph node dissection has been the standard treatment for advanced gastric cancer with NAC only being recommended for limited locally advanced cases with specific metastasis.

Surgical approaches for gastric cancer have drastically changed over the past two decades. Since first reported by Kitano et al. [4], laparoscopic gastrectomy (LG), a minimally invasive procedure, has progressed to the point of becoming the established procedure for early gastric cancer and has continued to rapidly spread among developed countries. Despite the limited evidence supporting the use of LG for advanced gastric cancer several years ago, a number of retrospective studies [5–8] and small-scale randomized controlled trials (RCTs) [9, 10] have confirmed the efficacy and safety of LG for advanced gastric cancer. Moreover, the most recent phase III study, namely, the CLASS-01 trial from China [10], suggested that LG was safe and oncologically comparable to open gastrectomy (OG). In addition,

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other large-scale RCTs from Japan (JLSSG0901) and Korea (KLASS-02) have been ongoing [11, 12]. However, most of the studies on LG for advanced gastric cancer were from East Asia and excluded patients receiving NAC. Chemotherapy-induced tissue fibrotic changes and edema provide new technical challenges for laparoscopic procedures, while only a few studies have compared the safety and efficacy of OG and LG for patients with advanced gastric cancer following NAC. Therefore, the applicability of LG in such patients remains controversial. This study aimed to investigate the short- and long-term outcomes of LG for patients with locally advanced gastric cancer following NAC to determine its safety and feasibility.

Materials and methods

Patients

This was a retrospective analysis of a prospectively maintained gastric cancer database in the Department of Surgery at four affiliated hospitals from the Jikei University School of Medicine, Tokyo, Japan and the Department of Surgery at Machida Municipal Hospital, a regional referral hospital in Tokyo, Japan. Between November 2009 and January 2018, 51 patients had been diagnosed with advanced gastric cancer and underwent NAC followed by gastrectomy. The eligibility criteria for NAC were cT3-4/N1-3 or macroscopic type 3 (> 80 mm) or type 4 advanced gastric cancer. Routine NAC regimens consisted of TS-1 + cisplatin (SP) or TS-1 + oxaliplatin (SOX). Patients with human epidermal growth factor 2 (HER2)-positive gastric cancer received trastuzumab + TS-1 + oxaliplatin (tmab + SOX) or trastuzumab + capecitabine + oxaliplatin (tmab + CAPOX). Surgery was performed 4 to 6 weeks after the completion of chemotherapy. Patients who underwent palliative gastrectomy ($n = 1$) and staging laparoscopy ($n = 1$) for macroscopic peritoneal dissemination were excluded from the present study. Ultimately, 49 patients were selected and subsequently divided into two cohorts: the LG group and the OG group. All patients underwent gastrectomy according to the treatment guidelines of the Japanese Gastric Cancer Association [13].

All surgeries were performed by board-certified surgeons from the Japanese Society of Gastroenterological Surgery. In addition, all LG procedures were performed by qualified surgeons certified by the Endoscopic Surgical Skill Qualification System of the Japan Society for Endoscopic Surgery. This study was approved by our Institutional Review Board and included prospective data collection and retrospective analysis of data obtained from patients undergoing gastrectomy. All patients and their families were informed about the innovative nature of the study, and written informed consent was obtained before surgery.

Operative technique

All patients underwent radical gastrectomy with D2 lymph node dissection according to the Japanese classification of gastric carcinoma by the Japanese Gastric Cancer Association [14]. Total or distal gastrectomy was performed depending on the location of the primary tumor. During total gastrectomy, the spleen was removed when the tumor invaded the upper one-third of the greater curvature. The reconstruction method used in both groups comprised either Billroth I/II or Roux-en-Y procedures depending on the surgeon's preference. The selection of either a laparoscopic or an open surgical approach was based on the attending surgeon's discretion or on the patient's preference.

In the LG group, reconstruction was achieved through intracorporeal anastomosis. During intracorporeal reconstruction, Roux-en-Y gastrojejunostomy, Billroth II anastomosis with a functional side-to-side anastomosis, or delta-shaped Billroth I anastomosis was performed for patients with distal gastrectomy [15]. Esophagojejunostomy was performed using a functional end-to-end anastomosis or overlap anastomosis among patients with total gastrectomy [16].

In the OG group, Billroth I anastomosis was performed using a circular stapler or hand suturing. Billroth II or Rouen-Y gastrojejunostomy was conducted using a functional side-to-side anastomosis. In cases that required total gastrectomy, Rou-en-Y esophagojejunostomy was performed using a circular stapler.

Data collection and perioperative management

Adverse events from NAC were evaluated using the Common Terminology Criteria for Adverse Events version 4.0, and only those with grade 3 or higher were recorded. The radiological responses in all patients were assessed using the Response Evaluation Criteria In Solid Tumors (RECIST, version 1.1) based on enhanced computed tomography conducted before and after NAC [17]. All patients were managed using a standardized clinical pathway protocol during the perioperative period. Oral feeding was started after the passage of flatus. Patients were discharged once they were free from complications. Clinicopathological parameters, such as age, body mass index, American Society of Anesthesiologists score, and Carlson comorbidity index [18], as well as perioperative data, such as operative time, intraoperative blood loss, presence or absence of postoperative complications, length of postoperative hospital stay, clinicopathological TNM stage, and tumor regression grade, were evaluated according to the Japanese classification of gastric carcinoma by the Japanese Gastric Cancer Association

[14]. Anastomotic stricture was defined as a condition that required endoscopic dilation. Anastomotic leakage was radiologically evaluated using water-soluble contrast material on the third postoperative day. Postoperative complications were defined according to the Clavien–Dindo classification system, and only those with grade 2 or higher were recorded [19]. Hospital mortality was defined as death during hospitalization or postoperative death of any cause within 30 days. Some patients underwent adjuvant chemotherapy with TS-1 alone or TS-1 plus cisplatin for 1 year based on the pathological stage and patients' preference. Patients were followed via outpatient clinic visitations every 3 months for the first 2 years after surgery, every 6 months for the next 3 years, and annually thereafter. All patients were followed from the date of surgery until death or until the end of the follow-up period (September 2019).

Statistical analysis

The chi-square test was used to compare percentages of events between dichotomous groups, while Fisher's exact test was used when cells had an expected frequency of less than 5. The Mann–Whitney U test was used to compare continuous variables between the groups. Survival rates were calculated using the Kaplan–Meier method, and statistical analysis was performed using the log-rank test. Uni- and multivariate analyses using Cox proportional hazards regression were performed to determine the risk factors for survival. A cutoff point for each continuous variable associated with survival was identified using the sample median. Thereafter, all variables with P values less than 0.2 on univariate analysis, including pathological stage and surgical procedure (LG vs. OG), were entered into multivariate analysis. A P value of less than 0.05 was considered statistically significant. All statistical analyses were performed using Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA).

Results

The patient characteristics are summarized in Table 1. The median ages of the patients in the LG and OG groups were 71.5 and 67.0 years, respectively. Most of the variables were comparable between the two groups. Although the tumor diameter tended to be larger in the LG group than in the OG group (75 vs. 50 mm), the difference was not statistically significant ($P = 0.106$). The most frequent NAC regimen was SP in both groups. The clinical response rates were 60% (12 of 20 patients) and 62% (18 of 29 patients) in the LG and OG groups ($P = 0.935$), respectively. Among all included patients, only one in the OG group achieved a pathological complete response.

The adverse events that occurred during NAC are presented in Table 2. Grade 3 or 4 toxic events occurred in 20% (4 of 20 patients) and 17% (5 of 29 patients) of the patients in the LG and OG groups ($P = 1.000$), respectively. The most frequent event was neutropenia, followed by leukopenia and anemia. No chemotherapy-related deaths were noted.

Table 3 presents the surgical data of the two groups. No significant differences in the type of gastrectomy, presence or absence of splenectomy, or number of dissected lymph nodes were observed between the groups. Despite having a longer operative time (362 vs. 314 min; $P = 0.082$), the LG group exhibited a significantly lower amount of intraoperative blood loss than the OG group (56.5 vs. 501 mL; $P < 0.001$). One patient in the LG group underwent R1 resection due to positive peritoneal lavage cytology. No patients in the LG group required conversion to open surgery.

The postoperative variables are presented in Table 4. The overall rates of complications were 10% (2 of 20 patients) and 24% (7 of 29 patients) in the LG and OG groups ($P = 0.277$), respectively. The most common surgical complications were pancreatic fistula and abdominal abscess ($n = 2$ for each, 4%). Among all included patients, three required reoperation due to abdominal bleeding ($n = 2$) and anastomotic leakage ($n = 1$). The LG group demonstrated a significantly shorter time to postoperative oral feeding and duration of postoperative hospital stay compared to the OG group ($P = 0.001$ and 0.005, respectively). No hospital deaths were observed in either group.

Disease-free survival (DFS) and overall survival (OS) were then analyzed in the two groups. The median follow-up period was 38 (range 3–115) months, and no patients were lost to follow-up. A total of 23 patients died during the follow-up period, of them 20 died because of cancer and 3 because of other diseases. The calculated 5-year DFS rates were 44.4% and 53.2% in the LG and OG groups ($P = 0.382$; Fig. 1a), respectively. Nine patients in the LG group developed disease recurrence, with 6 (30%), 2 (10%), and 2 (10%) occurring in the peritoneum, liver, and lymph nodes, respectively. On the other hand, 12 patients in the OG group developed disease recurrence, with 6 (21%), 4 (14%), and 3 (10%) occurring in the peritoneum, liver, and lymph nodes, respectively. Recurrence patterns were similar between the groups. The calculated 5-year OS rates were 46.9% and 56.0% in the LG and OG groups, respectively, with no significant difference between the groups ($P = 0.422$; Fig. 1b).

The univariate analysis results of the risk factors for long-term outcomes are summarized in Table 5. An age of 70 years or older was significantly associated with OS ($P = 0.009$) and tended to be associated with DFS albeit not significantly ($P = 0.063$). Multivariate analysis incorporating the type of surgical procedure (LG vs. OG) revealed that an age of 70 years or older ($P = 0.009$) and postoperative

Table 1 Patient characteristics

	LG group ($n=20$)	OG group ($n=29$)	*P* value
Age (years)[a]	71.5 (44–79)	67.0 (46–80)	0.218
Sex *n* (%)			0.408
Male	13 (65)	22 (76)	
Female	7 (35)	7 (24)	
BMI (kg/m^2)[a]	21.9 (17.0–26.5)	21.9 (14.8–29.5)	0.873
ASA score *n* (%)			0.329
1	3 (15)	9 (31)	
2	15 (75)	19 (66)	
3	2 (10)	1 (3)	
CCI *n* (%)			0.769
0	9 (45)	16 (55)	
1	9 (45)	11 (38)	
> 2	2 (10)	2 (7)	
Tumor size (mm)[a]	75 (30–150)	50 (20–100)	0.106
Histological type *n* (%)			0.356
Differentiated	7 (35)	14 (48)	
Undifferentiated	13 (65)	15 (52)	
Clinical stage *n* (%)[b]			1.000
II	4 (20)	6 (21)	
III	16 (80)	23 (79)	
NAC regimen *n* (%)			0.655
SP	17 (85)	26 (90)	
SOX	2 (10)	1 (3)	
tmab + SOX	1 (5)	1 (3)	
tmab + CAPOX	0	1 (3)	
Total cycle of NAC *n* (%)			0.730
1	1 (5)	2 (7)	
2	17 (85)	22 (76)	
> 3	2 (10)	5 (17)	
Radiological response *n* (%)[c]			0.935
PR	12 (60)	18 (62)	
SD	7 (35)	9 (31)	
PD	1 (5)	2 (7)	
Pathological stage *n* (%)[b]			0.374
pCR-I	1 (5)	3 (10)	
II	8 (40)	16 (55)	
III	10 (50)	10 (35)	
IV	1 (5)	0	
Pathological response *n* (%)[b]			0.711
Grade 0	2 (10)	2 (7)	
Grade 1a	8 (40)	14 (48)	
Grade 1b	7 (35)	6 (21)	
Grade 2	3 (15)	6 (21)	
Grade 3	0	1 (4)	
Adjuvant chemotherapy *n* (%)			
Yes	15 (75)	23 (79)	0.722
No	5 (25)	6 (21)	

LG laparoscopic gastrectomy; *OG* open gastrectomy; *BMI* body mass index; *ASA* American Society of Anesthesiologists, *CCI* Carlson Comorbidity Index, *NAC* neoadjuvant chemotherapy; *SP* TS-1 + cisplatin; *SOX* TS-1 + oxaliplatin; tmab, trastuzumab; *CAPOX* capecitabine + oxaliplatin; *PR* partial response; *SD* stable disease, *PD* progressive disease; *pCR* pathological complete response

[a]Values are shown as median (range)

[b]According to the Japanese Classification of Gastric Cancer [14]

[c]According to the Response Evaluation Criteria In Solid Tumors guideline (RECIST, version 1.1) [17]

Table 2 Adverse event associated with neoadjuvant chemotherapy

	LG group ($n=20$)	OG group ($n=29$)	*P* value
Adverse event, *n* (%)[a]			
Overall	4 (20)	5 (17)	1.000
Neutropenia	2 (10)	3 (10)	1.000
Leukopenia	2 (10)	2 (7)	1.000
Anemia	2 (10)	1 (3)	0.559
Thrombocytopenia	0	1 (3)	1.000
Anorexia	1 (5)	1 (3)	1.000
Nausea	1 (5)	0	0.408
Diarrhea	0	1 (3)	1.000

LG laparoscopic gastrectomy, *OG* open gastrectomy

[a]According to the National Cancer Institute Common Terminology Criteria for Adverse Event version 4.0

complications ($P=0.027$) were independently associated with OS, whereas no factors were associated with DFS (Table 6).

Discussion

To date, only a few studies have compared short-term outcomes between laparoscopic distal gastrectomy and open surgery in patients with gastric cancer following NAC [20, 21]. Moreover, the long-term safety and feasibility of LG, including total gastrectomy, for patients with advanced gastric cancer following NAC have remained unclear. This study was designed to investigate the surgical outcomes and survival rates of LG following NAC and to compare them to those of OG. To the best of our knowledge, this is the first cohort study investigating the long-term outcomes of LG in patients with gastric cancer following NAC. The present study showed that laparoscopic gastrectomy following NAC was safe and feasible given its good short- and long-term outcomes.

While the main NAC regimen used was SP in the current study, several useful NAC regimens have been reported for advanced gastric cancer including epirubicin + cisplatin + fluorouracil [2], docetaxel + oxaliplatin + fluorouracil + leucovorin (FLOT) [3], oxaliplatin + fluorouracil + leucovorin (FOLFOX) [22], SP [23], SOX [24], and CAPOX [25]. Among the aforementioned regimens, SP has been one of the most utilized regimens in Japan, with previous reports showing a clinical response rate of 65.0–69.7% and grade 3 or 4 adverse event rates of 15.4–19.0% [23, 26]. Although our study included a few other regimens, their efficacy and toxicity appeared to be acceptable. On the other hand, the most effective NAC regimen for advanced gastric cancer remains unknown. According to the treatment guidelines of the Japanese Gastric Cancer Association [13], SP is the standard first-line regimen for unresectable/recurrent gastric cancer and was mostly adopted in this study. However, there is less evidence of SP use for NAC regimen [27]. The efficacy of several NAC regimens (i.e., FLOT, FOLFOX, or CAPOX) have recently been demonstrated [3, 22, 25], and this issue requires to be further evaluated.

The LG group demonstrated a significantly lower amount of intraoperative blood loss and better postoperative recovery (i.e., a shorter time to first oral intake and a shorter hospital stay) compared with the OG group, with previous

Table 3 Intraoperative outcomes

	LG group ($n=20$)	OG group ($n=29$)	*P* value
Type of gastrectomy, *n* (%)			0.990
Distal	11 (55)	16 (55)	
Total	9 (45)	13 (45)	
Operative time (min)[a]	362 (191–603)	314 (209–452)	0.082
Intraoperative blood loss (mL)[a]	56.5 (6–450)	501 (65–1580)	< 0.001
Splenectomy, *n* (%)[a]			1.000
Yes	4 (20)	5 (17.2)	
No	16 (80)	24 (82.8)	
The number of dissected lymph nodes[a]	34.5 (21–104)	39 (17–72)	0.222
Residual tumor, *n* (%)[b]			0.408
R0	19 (95)	29 (100)	
R1	1 (5)	0	
Conversion to open surgery, *n*	0	N/A	

LG laparoscopic gastrectomy; *OG* open gastrectomy

[a]Values are shown as median (range)

[b]According to the treatment guidelines issued by the Japanese Cancer Association [13]

Table 4 Postoperative outcomes

	LG group ($n=20$)	OG group ($n=29$)	*P* value
Complications, *n* (%)[a]			
Overall	2 (10)	7 (24)	0.277
Pancreatic fistula	0	2 (7)	0.507
Abdominal abscess	0	2 (7)	0.507
Abdominal bleeding	1 (5)	1 (3)	1.000
Anastomotic stricture	0	1 (3)	1.000
Anastomotic leakage	0	1 (3)	1.000
Pneumonia	0	1 (3)	1.000
Pulmonary embolism	0	1 (3)	1.000
Heart failure	1 (5)	0	0.408
Requiring reoperation, *n* (%)	1 (5)	2 (7)	1.000
Time of first oral intake (days)[b]	3.5 (3–21)	5 (3–32)	0.001
Postoperative hospital stay (days)[b]	10 (7–31)	14 (7–46)	0.005
Hospital death, *n*	0	0	1.000

LG laparoscopic gastrectomy; *OG* open gastrectomy

[a]According to a modification of the Clavien–Dindo grade [19]

[b]Values are shown as median (range)

studies reporting similar findings for advanced gastric cancer patients without NAC [7, 28]. Thus, the current study suggests that the benefits of laparoscopic procedures remain the same for patients with advanced gastric cancer who undergo NAC. In particular, intraoperative blood loss has been reported to be associated with the prognosis of many malignant tumors, including gastric cancer [29–31]. Therefore, careful operative techniques should be utilized to minimize intraoperative blood loss.

No significant differences in postoperative complication rates were observed between the LG (2 patients, 10%) and OG groups (7 patients, 24%) ($P=0.277$), a finding consistent with the morbidity rates (10.5–30.7%) reported in previous studies on patients who underwent open D2 gastrectomy following NAC [32–35]. Moreover, among the two cases of postoperative complications that developed in the LG group, one was due to heart failure, a nonsurgical complication classified as a patient-related factor. Hence, the incidence of surgical complications in the LG group can be considered quite low (1 of 20, 5%). A previous study on patients with NAC showed that LG reduced postoperative complication rates by half [21]. Moreover, the study suggested that the advantages of LG over OG for postoperative complications might be more substantial among those receiving NAC for the following reasons. Although chemotherapy-induced tissue fibrotic changes can make surgery more difficult and perhaps increase postoperative complication rates, such issues may be mitigated by laparoscopy given that it allows for visual magnification, better exposure, and more delicate maneuvers of organs, vessels, and nerves. While we agree with the aforementioned reasons, our study may have a certain bias. As previously mentioned, all laparoscopic procedures in the current study were performed by qualified surgeons certified by the Endoscopic Surgical Skill Qualification System of the Japan Society for Endoscopic Surgery. These surgeons performed more than 50 laparoscopic surgeries for gastric cancer annually and had more surgical experience than some of the surgeons performing OG in the current study. With several studies indicating an association between surgical experience and postoperative complications [36, 37], generalizing our findings among surgeons with various levels of expertise is rather difficult.

The results of long-term outcomes showed that the LG and OG groups had 5-year OS rates of 46.9% and 56.0%, respectively. Previous clinical trials on NAC for locally advanced gastric cancer, such as large type 3, type 4, cT3-4, or N+, showed 5-year OS rates of 47.0%–57.7% [22, 35, 38]. Directly comparing such results with those of the current study is difficult because of the differences in patient

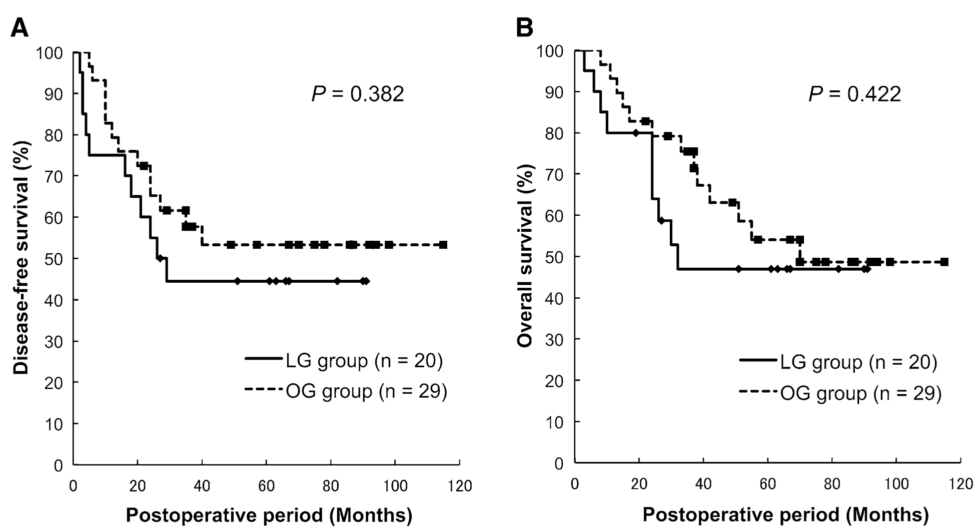

Fig. 1 Kaplan–Meier analyses of disease-free survival (**A**) and overall survival (**B**) for the laparoscopic gastrectomy and open gastrectomy groups

Table 5 Univariate analysis of risk factors for disease-free survival and overall survival

	DFS			OS		
	P value	HR	95% CI	*P* value	HR	95% CI
Age (< 70 vs. ≥ 70 years)	0.063	2.25	0.96–5.27	0.021	2.87	1.17–7.04
Sex (male vs. female)	0.442	0.70	0.28–1.76	0.450	0.70	0.27–1.78
BMI (< 21.9 vs. ≥ 21.9)	0.856	1.08	0.48–2.41	0.984	1.01	0.44–2.29
ASA (1 or 2 vs. 3)	0.574	1.52	0.36–6.45	0.536	1.58	0.37–6.79
CCI (0 or 1 vs. ≥ 2)	0.818	1.19	0.28–5.05	0.766	1.25	0.29–5.33
Tumor size (< 60 vs. ≥ 60 mm)	0.799	1.11	0.50–2.47	0.874	1.07	0.47–2.43
Histological type (differentiated vs. undifferentiated)	0.580	1.26	0.55–2.89	0.287	1.59	0.68–3.77
Clinical stage (II vs. III)	0.689	1.22	0.46–3.28	0.740	1.18	0.44–3.20
Radiological response (PR vs. SD/PD)	0.149	1.86	0.80–4.30	0.122	1.94	0.84–4.94
Adverse event associated with NAC (yes vs. no)	0.545	1.39	0.47–4.08	0.625	1.31	0.44–3.86
Surgical procedure (laparoscopy vs. open)	0.389	0.70	0.31–1.57	0.428	0.72	0.31–1.64
Type of gastrectomy (distal vs. total)	0.391	1.42	0.64–3.17	0.468	1.35	0.60–3.08
Operative time (< 331 vs. ≥ 331 min)	0.336	1.49	0.66–3.35	0.455	1.37	0.60–3.13
Intraoperative blood loss (< 320 vs. ≥ 320 mL)	0.750	1.14	0.51–2.55	0.816	1.10	0.48–2.52
Splenectomy (yes vs. no)	0.660	0.80	0.30–2.15	0.780	0.87	0.32–2.35
Postoperative complication (yes vs. no)	0.275	0.60	0.24–1.51	0.190	0.54	0.21–1.36
Pathological Stage (pCR-I or II vs. III or IV)	0.227	1.66	0.73–3.77	0.217	1.68	0.74–3.82
Pathological response (0 or 1a vs. 1b-3)	0.139	0.53	0.23–1.23	0.148	0.54	0.23–1.25
Adjuvant chemotherapy (yes vs. no)	0.339	0.59	0.20–1.73	0.338	0.59	0.20–1.74

DFS disease-free survival; *OS* overall survival; *HR* hazard ratio; *CI* confidence interval; *BMI* body mass index; *ASA* American Society of Anesthesiologists; *CCI* Carlson Comorbidity Index; *PR* partial response; *SD* stable disease; *PD* progressive disease; *NAC* neoadjuvant therapy; *pCR* pathological complete response

Table 6 Multivariate analysis of risk factors for disease-free survival and overall survival

	DFS			OS		
	P value	HR	95% CI	*P* value	HR	95% CI
Age (< 70 vs. ≥ 70 years)	0.124	1.99	0.83–4.81	0.009	3.75	1.39–10.10
Radiological response (PR vs. SD/PD)	0.175	1.79	0.77–4.16	0.364	1.53	0.61–3.83
Surgical procedure (laparoscopy vs. open)	0.645	0.81	0.33–2.00	0.489	0.71	0.27–1.88
Postoperative complication (yes vs. no)				0.027	0.29	0.09–0.87
Pathological Stage (pCR-I or II vs. III or IV)	0.385	1.50	0.60–3.76	0.329	1.61	0.62–4.19
Pathological response (0 or 1a vs. 1b-3)	0.543	0.73	0.27–1.99	0.287	0.58	0.21–1.59

DFS disease-free survival; *OS* overall survival; *HR* hazard ratio; *CI* confidence interval; *PR* partial response; *SD* stable disease; *PD* progressive disease; *pCR* pathological complete response

background and study design. However, the patient population included in the current study does overlap with those in previous studies, suggesting that long-term outcomes may not be disappointing. In addition, multivariate analysis was performed to determine the risk factors for long-term outcomes in gastric cancer patients with NAC. The current study indicated that the surgical procedure was not an independent risk factor for OS and DFS. One of the major concerns of using laparoscopic procedures for advanced cancer is the possibility of intraoperative peritoneal seeding of malignant cells. However, the study by Shoup et al. indicated that port-site recurrence for advanced disease was relatively rare [39]. Furthermore, the LOC-A study, one of the largest studies in Japan that focused on long-term outcomes for advanced gastric cancer, showed that laparoscopic procedures did not cause any specific recurrence [8]. In the present study, the pattern of recurrence was similar between both groups, while no incidence of port-site recurrence was noted in the LG group. Although we believe that LG following NAC does not affect recurrence patterns, larger-scale studies are required to establish oncological safety.

Previous reports have shown that the incidence of postoperative complications is a negative prognostic factor that affects not only OS but also RFS in patients with gastric cancer [40, 41]. One possible reason for this association is that patients with postoperative complications may have some factors that promote decreased host immunity against cancer cells [42]. Our findings also indicated that postoperative complications were independently associated with OS. However, this factor was not included in the multivariate analysis for DFS given that it had a P value > 0.2 in univariate analysis. Accordingly, after entering this variable into multivariate analysis and repeating our analysis, we found that postoperative complications were not independently associated with DFS ($P = 0.066$, data not shown). Other reasons for the correlation between postoperative complications and long-term outcome must therefore be considered. If frail patients with potentially poor prognosis easily developed postoperative complications, the incidence of these complications might not be an independent negative prognostic factor [43]. Accordingly, given that the current study included many elderly patients, our results might have been affected by the frailty of some patients.

One clear limitation of the present study was the lack of randomization in the two treatment arms. Another limitation was the retrospective design and limited sample size. Moreover, type II error probably existed in our study due to the small sample size. Further large-scale randomized prospective studies are thus required to clearly establish the safety and efficacy of LG for gastric cancer following NAC.

In conclusion, this preliminary retrospective study showed that LG and OG for advanced gastric cancer following NAC had comparable short- and long-term outcomes. Moreover, the present study suggests that LG may be a therapeutic option for patients with gastric cancer following NAC.

Compliance with ethical standards

Conflict of interest Muneharu Fujisaki, Norio Mitsumori, Toshihiko Shinohara, Naoto Takahashi, Hiroaki Aoki, Yuya Nyumura, Seizo Kitazawa, and Katsuhiko Yanaga have no conflicts of interest or financial ties to disclose.

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