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Laparoscopic gastrectomy for gastric carcinoma with neoadjuvant chemotherapy

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Abstract

Objectives: Neoadjuvant chemotherapy is a widely-accepted potential treatment for locally-advanced gastric carcinoma. Laparoscopic gastrectomy is performed for advanced gastric carcinoma because it is minimally invasive, which could lead to accessibility to combined chemotherapies. We evaluated the feasibility of performing laparoscopic gastrectomy in patients with or without neoadjuvant chemotherapy.

Methods: We performed a retrospective cohort study that was conducted from 2005–2013. We assessed 49 and 35 patients with clinical stage III disease who underwent laparoscopic gastrectomy with and without neoadjuvant chemotherapy, respectively, using a two-cycle regimen of S-1 plus cisplatin. We evaluated patients' background data, efficacy and adverse events of chemotherapy, and perioperative factors, including the postoperative complication rate, reoperation rate, and length of hospital stay.

Results: Adverse events of grade 3 or higher during neoadjuvant chemotherapy were observed in five (10.2%) patients. The response and disease control rates were 61.2% and 93.9%, respectively. There were no significant differences in the postoperative complication rate, reoperation rate, and length of hospital stay between the groups. There were no conversions to laparotomy and no in-hospital deaths. Multivariate analyses showed that total gastrectomy was the only significant independent risk factor for determining postoperative complications, and neoadjuvant chemotherapy was not a risk factor.

Conclusions: Our protocol of laparoscopic gastrectomy for locally-advanced gastric carcinoma following neoadjuvant chemotherapy resulted in a considerable response to the chemotherapy and sufficient feasibility in the selected patients. Our strategy is a promising therapeutic option for patients with locally-advanced gastric carcinoma.

Keywords: Gastric cancer, Gastrectomy, Laparoscope, Drug therapy, Morbidity

Introduction

Gastric carcinoma (GC) is one of the most frequent cancers,[1] and surgical resection is performed in the early stage. However, resection only has limited success in locally-advanced disease. Therefore, attempts of multimodal approaches to GC have been made to improve patients' survival. In the last 20 years, large-scale, randomized trials have demonstrated the efficacy of adjuvant chemoradiation (INT-0116 trial),[2] adjuvant single-drug chemotherapy (ACTS-GC trial),[3] and perioperative three-drug combination chemotherapy (MAGIC trial).[4] After publication of those results, standard treatment for locally-advanced GC is no longer based on surgery alone.

Adjuvant chemotherapy after D2 lymphadenectomy is currently considered the standard treatment for GC.[3,5] However, the prognosis for locally-advanced GC remains poor compared with early-stage GC with 5-year survival rates greater than 90%,[6] and there is no established method to increase survival.[7,8]

Neoadjuvant chemotherapy (NAC) is a potential treatment for locally-advanced GC. NAC can reduce tumor size, decrease clinical stage, and increase the curative resection rate.[9,10] S-1 (Taiho Pharmaceutical Company, Tokyo, Japan), which is a promising oral anticancer drug for GC,[11] plus cisplatin therapy (SP) had a 54% response rate for advanced GC in a phase III trial.[12] Although there were no treatment-related deaths in this trial, a considerable number of grade 3 or 4 adverse events were reported. Severe adverse events that occur in the NAC setting could lead to incomplete treatment or delayed surgery, and the ideal timing of surgery may be missed.

Although laparoscopic gastrectomy (LG) is currently often performed for advanced GC and potentially improves accessibility to combined chemotherapies, there are no feasibility studies of LG following NAC. Therefore, in this study, we evaluated the feasibility of undergoing LG for patients with locally-advanced GC with or without SP-NAC. To the best of our knowledge, this is the first report on the short-term outcome of LG following NAC for patients with GC.

Methods

Study design

Between 2005 and 2013, 1182 consecutive patients underwent gastrectomy for GC in our institute. Among these patients, we enrolled 100 with clinical stage III disease according to the Japanese Classification of Gastric Carcinoma (JCGC) guidelines[13] in the first step (Figure 1). The remaining 1082 patients were

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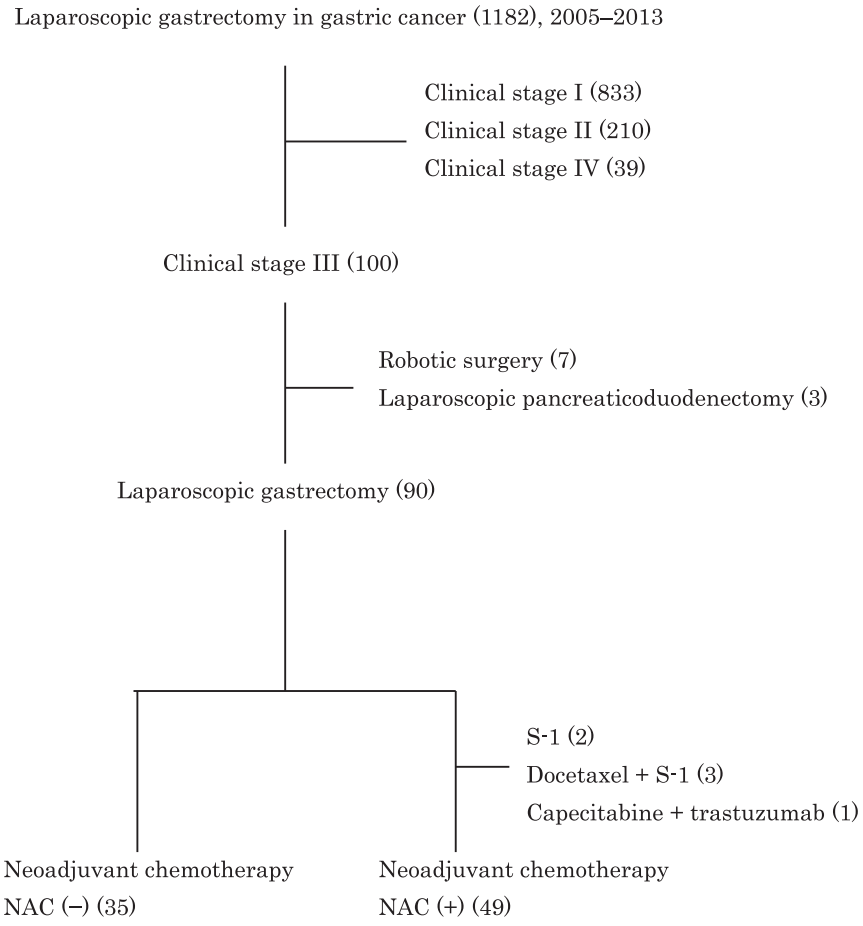

Figure 1 Study design.
We enrolled 84 patients with clinical stage III gastric carcinoma who underwent conventional (distal or total) laparoscopic gastrectomy with lymph node dissection in our institute between 2005 and 2013. We assigned patients to the without neoadjuvant chemotherapy (NAC (–)) group (n=35) or to the with neoadjuvant chemotherapy using S-1 plus cisplatin (NAC (+)) group (n=49). NAC: neoadjuvant chemotherapy.
Third block.

excluded because they had early-stage (clinical stage I, n=833) and clinical stage II (n=210) GC with a good prognosis with surgery alone, or had advanced-stage (clinical stage IV, n=39) GC and surgery was potentially palliative. Sixteen patients with clinical stage III were excluded because of the type of surgery (robotic surgery, n=7; and laparoscopic pancreaticoduodenectomy, n=3) or the type of NAC regimen (S-1, n=2; capecitabine +cisplatin+trastuzumab, n=1; and docetaxel+cisplatin+S-1, n=3). Finally, 49 and 35 patients with clinical stage III disease who underwent conventional (distal or total) LG with SP-NAC (NAC (+) group) or without NAC (NAC (–) group) were selected for the final analysis (Figure 1).

We collected data on the patients' background, including sex, age, body mass index, comorbidity, history of laparotomy, JCGC clinical stage (IIIA, IIIB, IIIC), and histology (differentiated or undifferentiated adenocarcinoma).

Patients were fully involved in the decision-making process for the treatment, and informed consent was obtained from all of the patients. The data obtained through review of the medical records were managed according to the privacy policy and ethical code of our institute.

Neoadjuvant chemotherapy (NAC)

The selected treatment strategy was based on the patient's and surgeon's preferences following informed consent and discussion of the disease and treatment. Table 1 shows the patients' background. Generally, patients in the NAC (+) group tended to be younger and underwent more extensive lymphadenectomy than those in the NAC (–) group.

The regimen of SP as NAC (SP-NAC) was administered for two cycles preoperatively consisting of S-1 (patients with a body-surface area <1.25 m^2 received 80 mg; those with a body-surface area ≥ 1.25 m^2 and <1.5 m^2 received 100 mg; and those with a body-surface area ≥ 1.5 m^2 received 120 mg, daily, for days 1–21) and cisplatin (60 mg/m^2 on day 8). Adverse events were evaluated in accordance with Common Terminology Criteria for Adverse Events version 4.02.[14] Responses to chemotherapy were evaluated in accordance with Response Evaluation Criteria in Solid Tumors criteria 1.1.[15]

Surgical procedure

Most of the details of our technical and perioperative management in LG were reported previously.[16–19] The Japanese Gastric Cancer Association (JGCA) has defined standard (with curative intent) gastrectomy for potentially curable gastric carcinomas as resection of not less than two-thirds of the stomach with D2 lymphadenectomy[20]. The extent of lymph nodes to be dissected in D1 plus or D2 lymphadenectomy was clearly

Table 1 Characteristics of all patients who underwent laparoscopic gastrectomy

Patients' characteristics	NAC (–) (n=35)	NAC (+) (n=49)	p value
Sex (male/female)	26/9	36/13	0.933
Age (y)	73 [54–87]	65 [36–79]	<0.001
Body mass index (kg/m^2)	20.9 [15.0–32.1]	21.5 [14.5–32.4]	0.334
Comorbidity	21 (60)	23 (47)	0.273
History of laparotomy	9 (25.7)	12 (24.5)	0.898
Clinical JCGC Stage (IIIA/IIIB/IIIC)	21/11/3	34/12/3	0.373
Histological malignant grade (differentiated/undifferentiated)	20/15	39/20	0.852

Data are shown as range [median] or n (%). The χ^2 test was used for between-group comparisons of sex, comorbidity, history of laparotomy, and histological malignancy grade. We used the Mann–Whitney U test for between-group comparisons of age, body mass index, and clinical JCGC stage.
JCGC: Japanese Classification of Gastric Carcinoma.
NAC (–) group: patients without neoadjuvant chemotherapy using S-1 plus cisplatin with laparoscopic gastrectomy.
NAC (+) group: patients with neoadjuvant chemotherapy using S-1 plus cisplatin followed by laparoscopic gastrectomy.

defined in the third edition of the JGCA Guidelines.[20] Therefore, in our study, distal gastrectomy was used for tumors that were localized to M and/or L areas, whereas total gastrectomy was used for tumors that infiltrated the U area, both with lymphadenectomy.

Evaluation of perioperative indicators and postoperative complications

Patients in each group were assessed regarding the type of resection (distal or total), extent of lymphadenectomy (D1 plus or less, or D2 or more), operation time, blood loss during surgery, and number of dissected lymph nodes as operative indicators. Short-term postoperative indicators included postoperative complications and the reoperation rate during a 30-day postoperative period, length of postoperative hospital stay, and in-hospital mortality. Postoperative complications were defined as those that required surgical, endoscopic, or radiological intervention, and that corresponded to Clavien–Dindo classification grade III or higher.[21–23]

Terminology and cancer staging

Carcinoma stage was described according to the JCGC guidelines[13]. Staging was performed based on contrast-enhanced computed tomography, gastrography, endoscopic studies, and endosonography before beginning any treatments.

Statistical analysis

All analyses were conducted using IBM SPSS Statistics 23 (IBM, NY, USA). Between-group comparisons were evaluated by the chi-square test or Mann–Whitney U test. The univariate chi-square test and multivariate logistic regression analysis were used to determine the factors contributing to postoperative complications. Data are expressed as median and range or odds ratio and 95% confidence interval, unless otherwise noted. A p value <0.05 (two-tailed) was considered statistically significant.

Results

Patients' background

The patients' characteristics are shown in Table 1. The only significant difference between the groups was age. The NAC (–) group was significantly older (73 years, 54–87 years) than the NAC (+) group (65 years, 36–79 years p<0.001).

Dose intensity, adverse events, and effects of NAC

The relative dose intensities were 87.4% and 80% for S-1 and cisplatin, respectively, for the 49 patients in the NAC (+) group. Forty (81.6%) patients completed two cycles of NAC. Five patients received only one cycle of NAC because of adverse events (n=4) and worsening coexisting disease (n=1). In two patients, the second NAC cycle was discontinued because of adverse events (n=1) and tumor growth (n=1). Two patients received more than two cycles of NAC. These patients extended their cycle based on the patient's and surgeon's preferences (good response for advanced disease). A reduction in dose was required in 14 patients who underwent two cycles because of adverse events. Adverse events that were observed during NAC are shown in Table 2. Grade 3 or higher adverse events were observed in five (10.2%) patients. All of the patients who received NAC underwent surgery thereafter. The responses were a complete response in three (6.1%) patients and partial response in 27 (55.1%) patients. The response rate was 61.2% (30/49) and the disease control rate was 93.9% (46/49).

Table 2 Adverse events of S-1 plus cisplatin in the NAC (+) group (n=49)

Adverse events (grade 3 or 4)	Number of patients	Incidence (%)
Leukopenia	1	2
Anemia	4	8.2
Thombocytopenia	0	0
Hypoalbuminemia	1	2.6
Increase in serum creatinine levels	0	0
Hypokalemia	1	2.6
Weight loss	0	0
Mortality	0	0
Total adverse events	5	10.2

NAC (+) group: patients with neoadjuvant chemotherapy using S-1 plus cisplatin followed by laparoscopic gastrectomy.

Surgical outcomes and short-term postoperative course

Surgical outcomes and the short-term postoperative course are shown in Table 3. A significant difference was found only for the extent of lymphadenectomy (p=0.007) between the groups. With regard to postoperative short-term outcomes, there was no significant difference in the complication rate, reoperation rate, or hospital stay between the groups. There were also no conversions to laparotomy or in-hospital deaths in either group.

Factors determining postoperative complications

The factors determining postoperative complications are

Table 3 Surgical outcomes and short-term postoperative course in patients who underwent laparoscopic gastrectomy (n=84)

Patients' characteristics	NAC (–) (n=35)	NAC therapy (+) (n=49)	p value
Total operation time (min)	376 [210–663]	421 [196–722]	0.302
Estimated blood loss (mL)	57 [0–2267]	87 [5–1233]	0.377
Type of resection (LDG/LTG)	24/11	26/23	0.181
Extent of lymphadenectomy (D1 plus or less/D2 or more)	9/26	2/47	0.007
Number of dissected lymph nodes	44 [19–79]	45 [15–78]	0.541
Reoperation	1 (2.8)	0 (0)	0.417
Hospital stay following surgery (days)	15 [7–59]	17 [8–77]	0.468
Complication rate	5 (14.2)	11 (22.4)	0.409
In-hospital mortality	0	0	—

Data are shown as range [median] or n (%). The χ^2 test was used for between-group comparisons of type of resection, extent of lymphadenectomy, reoperation rate, and complication rate. The Mann–Whitney U test was used for between-group comparisons of total operation time, estimated blood loss, number of dissected lymph nodes, and hospital stay following surgery.
Complications=Clavien–Dindo grade III or higher.
LTG: laparoscopic total gastrectomy, LDG: laparoscopic distal gastrectomy.
D1 plus and D2 lymph node dissections were defined according to the JCGC guidelines.
NAC (–) group: patients without neoadjuvant chemotherapy using S-1 plus cisplatin with laparoscopic gastrectomy.
NAC (+) group: patients with neoadjuvant chemotherapy of S-1 plus cisplatin followed by laparoscopic gastrectomy.

Table 4 Factors determining postoperative complications in patients who underwent laparoscopic gastrectomy (n=84)

	Univariate analysis OR (95 % CI)	p value	Multivariate analysis OR (95 % CI)	p value
NAC	1.737 (0.544–5.543)	0.351	1.317 (0.365–4.755)	0.674
Total gastrectomy (vs distal)	9.698 (2.497–37.663)	0.001	6.102 (1.117–33.347)	0.037
D2 or more lymphadenectomy (vs under D1 plus or less)	1.068 (0.207–5.500)	0.937		
Male	1.080 (0.308–3.782)	0.904		
Age	0.981 (0.931–1.035)	0.486		
Body mass index	0.982 (0.831–1.161)	0.831		
Comorbidity	0.889 (0.299–2.643)	0.832		
History of laparotomy	1.000 (0.284–3.517)	1.000		
Estimated blood loss	1.001 (0.999–1.002)	0.477		
Total operation time	1.007 (1.002–1.012)	0.004	1.002 (0.996–1.008)	0.567
Number of dissected lymph nodes	1.036 (0.997–1.076)	0.070	1.018 (0.974–1.064)	0.432

Data are shown as the OR (95% CI). The χ^2 test and multivariate logistic regression analysis were used for univariate and multivariate analyses, respectively.
NAC: neoadjuvant chemotherapy, OR: odds ratio, CI: confidence interval.

shown in Table 4. Univariate analyses showed two significant determinants: total gastrectomy and operation time. Multivariate analyses showed that total gastrectomy (odds ratio: 6.102 [95% confidence interval 1.117–33.347], p=0.037) was the only significant independent risk factor. NAC was not a significant determining risk factor.

Discussion

This single-institutional, retrospective cohort study showed that using NAC with the SP regimen achieved a considerable dose intensity and efficacy without increasing postoperative complications after LG with lymphadenectomy for GC.

NAC for GC is widely accepted following the results of the MAGIC trial.[4] Several NAC regimens are used for GC, including epirubicin, cisplatin, and fluorouracil (ECF) epirubicin,[4] fluorouracil, folic acid, and oxaliplatin (FOLFOX7),[24] SP of one cycle,[25] docetaxel, cisplatin, and S-1 (DCS),[26] S-1 and oxaliplatin (SOX),[27] and fluorouracil and cisplatin (FP).[28] However, concern about NAC regimens remains regarding preoperative adverse events with loss of appropriate surgical timing, and a possible increase in postoperative complications.

The incidence of adverse events in NAC has been reported as 10%, 25%, and 38% for SP of one cycle,[25] DCS,[26] and FP.[28] The rate in our series is comparable with these previous reports. A total of 81.6% of our patients completed two cycles of NAC with dose intensities of 87.4% and 80% for S-1 and cisplatin, respectively. All of the patients underwent surgery thereafter. Similar completion rates of 86% (83.6% underwent surgery) and 89% were shown for ECF[4] and FP,[28] respectively. Reported response rates were >50%, 38.25% 68.8%, and 68.8% for FOLFOX7,[24] SP of one cycle,[25] DCS,[26] and SOX,[27] respectively, and 61.2% for the regimen in the present study. Our regimen had comparable feasibility and efficacy to other regimens and is a promising candidate for NAC in GC.

The incidence of postoperative complications after NAC has been reported as 10%–46% and varies with the experience of surgeons, multi-visceral resections, extended lymphadenectomy, regimens, and older patients with comorbidities.[4,24–27] The incidence of postoperative complications in this study for patients in the NAC (+) group was 22.4%, which is comparable with other studies,[4,24–27] and not significantly different from that for NAC (–). Additionally, NAC was not a significant determining factor for postoperative complications. LG is generally thought to be less invasive than open procedure, which benefits patients who have NAC and already have preoperative damage, even if LG is performed with lymphadenectomy for locally-advanced GC. Therefore, our strategy was to perform LG following SP-NAC in

our patients with stage III disease. We found that the complication rate after surgery in the NAC (+) group was acceptably low and similar to that in the NAC (–) group. Our study showed that LG following SP-NAC was a promising strategy for locally-advanced GC.

One of the limitations of our study is its retrospective design involving surgeons' and patients' preferences to select the treatments. The NAC (+) group consisted of younger patients with higher lymphadenectomy. During the decision-making process, younger patients tended to choose aggressive surgery with NAC, whereas older patients tended to avoid this type of surgery. Aggressive surgery with more lymphadenectomy in the NAC (+) group was expected to lead to an increased complication rate. However, a younger population may have a lower rate of complications, and this has the potential to distort the results. Therefore, we analyzed the postoperative complication rate in a 65 years or older subgroup. We found no significant difference between the older subgroups for NAC (–) and NAC (+) (data not shown), although the number of patients in each group (27 and 29, respectively) was small. We also analyzed total gastrectomy subgroups because total gastrectomy was the only significant factor that determined postoperative complications. Although there was a possibility of a higher complication rate after NAC with more invasive total gastrectomy, we found no difference between the NAC (–) and NAC (+) subgroups, even in total gastrectomy patients (n=11 and n=24, respectively; data not shown).

The long-term oncological efficacy of NAC followed by gastrectomy for GC is still controversial. Ychou et al. reported that the NAC of cisplatin and 5-fluorouracil (FU) significantly improved overall and disease-free survival in patients with gastroesophageal adenocarcinoma compared with surgery alone in their randomized trial.[28] However, a randomized trial for locally advanced cancer of the stomach and cardia showed that NAC with cisplatin and 5-FU led to a significantly increased R0 resection rate, but failed to demonstrate a survival benefit.[29] Further investigations are required for oncological efficacy of NAC for GC, especially in the recent situation with application of laparoscopic surgery to locally advanced diseases, such as in the present study.

In conclusion, our protocol of LG for locally-advanced GC following SP-NAC resulted in a considerable response to the chemotherapy and sufficient feasibility for the whole treatment process in the selected patients. Our strategy is a promising therapeutic option for patients with locally-advanced GC. Further studies are required to investigate the long-term oncological efficacy of our strategy.

Conflict of Interest

The authors have no conflicts of interest directly relevant to the content of this article.

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