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ORIGINAL

Short-Term Outcomes of Laparoscopic Distal Gastrectomy for Advanced Gastric Cancer

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Abstract : The purpose of this study was to investigate the oncologic outcomes of laparoscopic distal gastrectomy (LDG) for advanced gastric cancer (AGC). Between April 2003 and March 2014, LDG was performed for 392 patients, 91 patients (23.2%) had histopathologically diagnosed AGC beyond T2 depth. The clinicopathological features, postoperative outcomes, mortality, morbidity, recurrence rate, and survivals of those patients were reviewed. The TNM stages of the tumor were IB in 26 patients (28.5%), IIA in 20 (21.9%), IIB in 18 (19.7%), IIIA in 13 (14.2%), IIIB in 6 (6.5%), IIIC in 6 (6.5%), and IV in 2 (2.1%). Major morbidity occurred in 14 patients (15.3%), with no postoperative mortality. Median follow-up was 24.5 months ; 10 patients developed recurrence during the follow-up period, and 10 patients died, including 6 cancer deaths. The 5-year overall and disease-free survival rates were 76.8% and 72.6%, respectively. By stage, OS/DFS was 92.3%/91.8% in stage IB, 85.4%/85.4% in stage II, and 49.3%/26.9% in stage III. Oncologic outcomes were good in patients with AGC, especially with stage IB-IIB, who underwent LDG. LDG appears to be an effective approach for treating stage IB and II gastric cancer. J. Med. Invest. 63 : 68-73, February, 2016

Keywords **:** *Advanced gastric cancer, Gastrectomy, Laparoscopic surgery*

INTRODUCTION

Gastric cancer is the fourth most common cancer and the second leading cause of cancer-related deaths worldwide (1). Surgical resection for gastric cancer is the only therapeutic modality for cure (2), and regional lymphadenectomy is recommended as part of radical gastrectomy (3). Laparoscopic gastrectomy is an emerging surgical approach that offers significant advantages with respect to short-term outcomes, such as less postoperative pain, earlier postoperative recovery of gastrointestinal function and ability to move, and shorter postoperative hospital stay, when compared with open gastrectomy. Recently, laparoscopic surgery has come to be regarded as the treatment of choice for early gastric cancer (EGC), but the indications and outcomes of laparoscopic gastrectomy for advanced gastric cancer (AGC) are still controversial due to its technical difficulties and the lack of long-term results. The purpose of this study was to evaluate the oncologic outcomes of laparoscopic distal gastrectomy (LDG) for AGC.

METHODS

Patients

Between April 2003 and March 2014, laparoscopic distal gastrectomy (LDG) was performed for 392 patients with gastric cancer, 91 (23.2%) of those were histopathologically diagnosed as AGC beyond T2 depth. The clinicopathological features, postoperative outcomes, mortality, morbidity, recurrence, and survival of the patients who underwent LDG for AGC were reviewed retrospectively.

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The eligibility criteria for LDG in our hospital are cT1-3N0-1 (Union Internationale Contre le Cancer 7th edition (4)) gastric cancer in the lower or middle body of the stomach. In the case of cT2-3N1 gastric cancer, D2 lymphadenectomy was performed. All patients were informed that LDG is regarded as experimental treatment by the Japanese gastric cancer treatment guideline (5), and a written, informed consent was obtained from all patients. Patient anonymity should be preserved.

In our hospital, laparoscopic surgery for gastric cancer was introduced in April, 2003, and the indication for LDG for gastric cancer was cT1N0 according to the 6th edition of the UICC staging criteria (6). Laparoscopy-assisted distal gastrectomy (LADG), which means reconstruction under minilaparotomy, was performed. We extended the indication to cT3N1 based on development of the operative procedures with D2 lymphadenectomy, and performed totally laparoscopic gastrectomy, which included intracorporeal anastomosis, from April, 2012. If the tumor depth was obviously beyond T4, LDG was converted to open surgery. In the case of suspicious T4 depth, washing cytology was performed twice (just after laparotomy and before closure the wound) during the surgery and evaluated postoperatively.

Gastrointestinal fiberscopy, barium fluoroscopy, and contrast-enhanced computed tomography were performed for preoperative staging. All patients provided their written, informed consent. Data obtained for each patient included the followings : age, sex, body mass index (BMI), histological type, tumor invasion (T stage), nodal status (N stage), gastric cancer stage classified according to the 7th edition of the UICC staging criteria, postoperative outcomes, postoperative morbidity, recurrences, adjuvant therapy, and survival. The classification of lymph node dissection was done according to the 2014 Japanese gastric cancer treatment guidelines (ver.4) (5). All values are expressed as means±standard deviations.

Surgery

All patients were placed in the lithotomy position under general anesthesia. The surgeon stood on the patient's left, with the first assistant on the patient's right and the camera assistant between the patient's legs. Routinely, an umbilical trocar (12 mm) was inserted using the open method. Carbon dioxide pneumoperitoneum was created through the umbilical port, and the pressure was maintained around 10 mmHg. A 10-mm flexible laparoscope was then introduced through the umbilical port. Under laparoscopic guidance, five trocars were introduced, consisting of bilateral subcostal (5 mm), bilateral mid-abdominal (12 mm), and epigastric (5 mm) ports.

First, the gastrocolic ligament was divided at the mid position of the transverse colon about 5 cm from the gastroepiploic arcade toward the lower pole of the spleen using laparosonic coagulating shears (LCS).

Next, the right gastrocolic ligament and lymph nodes were dissected along the right gastroepiploic vessels (No.4d). The infrapyloric nodes (No.6) and the nodes along the superior mesenteric vein (No.14v) were dissected. A gauze was placed on the common hepatic artery, and the hepatogastric ligament was cut using LCS toward the esophagogastric junction on this gauze, and the right crus was revealed. After the suprapyloric nodes along the right gastric vessels (No.5) and the nodes along the proper hepatic artery (No.12a) were dissected, the duodenum just distal to the pyloric ring was transected by a linear stapler. Then, the nodes along the common hepatic artery (No.8a) and the proximal splenic artery (No.11p) were dissected. The left gastric vein and artery were cut. After dissecting the nodes along the left gastric artery (No.7) and the nodes around the celiac artery (No.9), dissection of the right cardial nodes (No.1) and the nodes along the lesser curvature (No.3a) was performed. Billroth I gastroduodenostomy or Billroth II gastrojejunostomy reconstruction was performed totally under laparoscopy, using flexible laparoscopic stapling devices. Finally, the resected specimen in the collection bag was removed from the umbilical port, which was extended 3 cm.

Postoperative treatment and follow up

In AGC cases with stages beyond stage II, adjuvant chemotherapy with S-1 alone for 33 cases (7) and S-1 and cisplatin for 4 cases (8-9) was performed.

Adjuvant chemotherapy was to be started within 4 to 8 weeks after surgery, following sufficient recovery from the intervention. All patients were followed according to an established protocol in our hospital, which includes medical history, physical examination, and laboratory studies, such as tumor markers. Multi-Detector CT examinations was performed every 3-6 months, and gastrointestinal fiberscopy was performed annually.

Complications

Morbidity was classified according to the revised version of the Clavien-Dindo classification suggested by Dindo *et al.* (10).

Statistical analyses

All results were presented as near±SD and analyzed with the log-rank test. P-value of 0.05 or less was considered significant. All statistical analyses were performed using Stat View version 5.0 for Windows (SAS Institute Inc., Cary, NC)

RESULTS

Clinicopathological characteristics

The clinicopathological characteristics of the patients are presented in Table 1. The mean age was 69.2±11.2 years (range, 38-88 years). Of the 91 patients who underwent LDG, 66 were men (72.5%), and 25 were women (27.4%). The mean body mass index was 23.3±3.4 kg/m^2 (range, 14.0-33.2 kg/m^2). The most common histologic type was poorly differentiated adenocarcinoma (50.5%). The TNM stages (UICC, 7th edition) were : stage IB in 26 (28.5%) patients ; IIA in 20 (21.9%) ; IIB in 18 (19.7%) ; IIIA in 13 (14.2%) ; IIIB in 6 (6.5%) ; IIIC in 6 (6.5%) ; and IV in 2 (2.1%). Two patients were in stage IV due to liver metastases and peritoneal dissemination. Liver metastasis, which was very small, was first found intraoperatively and gastrectomy was performed to control tumor bleeding. Peritoneal dissemination, which existed only around the tumor, was not detected with intraoperative rapid histological examination and was found postoperatively.

Table 1. Clinicopathological features of patients undergoing LDG

No. patient	91
Age, years, mean±SD	69.2±11.2
Sex, M : F	66 : 25
Body mass index, kg/m^2, mean±SD	23.3±3.4
Histologic type	
Papillary	2 (2.1%)
Well differentiated	18 (19.7%)
Moderately differentiated	20 (21.9%)
Poorly differentiated	46 (50.5%)
Signet ring cell	2 (2.1%)
Mucinous	2 (2.1%)
Others	1 (1.0%)
Tumor invasion*	
T2 (MP)	36 (39.5%)
T3 (SS)	34 (37.3%)
T4a (SE)	21 (23.0%)
Nodal status*	
pN0	47 (51.6%)
pN1	17 (18.6%)
pN2	15 (16.4%)
pN3	12 (13.1%)
Tumor staging*	
IB	26 (28.5%)
IIA	20 (21.9%)
IIB	18 (19.7%)
IIIA	13 (14.2%)
IIIB	6 (6.5%)
IIIC	6 (6.5%)
IV	2 (2.1%)

Where appropriate, data are given as means±SD or as numbers of patients with percentages given in parentheses.
*According to the 7th edition of the TNM classification.

Postoperative Outcomes

For all 91 patients, the mean operation time was 177.2±26.4 min (range, 119-258 min), and the mean estimated blood loss was 15.2±45.8 ml. A total of 59 patients (64.8%) received over D2 dissection according to the 2014 Japanese gastric cancer treatment guidelines (ver.4) (5). The mean number of retrieved lymph nodes during LDG was 31.4±14.7. The most frequent type of reconstruction was Billroth I (64.8%). Conversion to open surgery was done in one patient (1.0%), as a result of suspected T4 wall invasion.

Radicality of the operation was R0 in 97.8%, R1 in 1.0%, and R2 in 1.0%. The R1 operation was decided because of peritoneal dissemination revealed by pathological examination postoperatively, and the R2 case was due to liver metastases (patient in stage Ⅳ). The mean postoperative hospital stay was 12.0±20.2 days (range, 6-177) (Table 2). There were 14 postoperative complications (15.3%), and no surgery-related deaths occurred (Table 3). Most complications could be treated conservatively, but complications beyond Clavien-Dindo classification grade Ⅲ occurred in three cases. Grade Ⅲa was duodenal stump leakage, which was successfully treated by single drainage. Grade Ⅳa complications were anastomotic leakage and pancreatic fistula, which required reoperation and intensive care for 34 days and 39 days respectively.

Table 2. Postoperative outcomes

Operation time (min)	177.2±26.4
Estimated blood loss (mL)	15.2±45.8
Lymph node retrieved (n)	31.4±14.7
Degree of lymph node dissection* (n)	
D1	12 (13.1%)
D1+	20 (21.9%)
D2	59 (64.8%)
Conversion to open surgery (n)	1 (1.0%)
Combined with other organ resection	0
Type of reconstruction	
Billroth I	59 (64.8%)
Billroth Ⅱ	20 (21.9%)
Roux-en-Y	12 (13.1%)
LADG : LDG	53 : 38
Radicality	
R0	89 (97.8%)
R1	1 (1.0%)
R2	1 (1.0%)
Postoperative complications, n	14 (15.3%)
Postoperative hospital stay, days	12.0±20.2

Where appropriate, data are given as mean±SD or numbers of patients with percentages given in parentheses.
LADG Laparoscopy-assisted distal gastrectomy *LDG* Laparoscopic distal gastrectomy.
*According to the 2014 Japanese gastric cancer treatment guidelines (ver.4).

Follow-up Results

The median follow-up period was 24.5 months (range, 0.3-114 months). Tumor recurrence was detected in 10 patients (10.9%) during follow-up. The sites of recurrences are shown in Fig 1. Liver metastasis occurred in five patients (stage IB, two patients ; stage ⅢA, one patient ; stage ⅢC, two patients), peritoneal dissemination in four patients (stage ⅢA, one patient ; stage ⅢB, one patient ; stage ⅢC, two patients), paraaortic lymph node metastasis in three patients (stage ⅢA, two patients ; stage ⅢC, one patient), lung metastasis in one patient (stage ⅢC), and ovarian metastasis in one patient (stage ⅢB) (there is some overlap). There were no recurrences in regional lymph nodes around the stomach.

In AGC cases with stages beyond stage Ⅱ, adjuvant chemotherapy based on S-1 or other drugs was given (Table 4). The most common regimen was S-1 alone (76.7%). S-1/cisplatin was given for the patients with stage Ⅳ and stage Ⅲ with extensive lymph node metastasis, S-1/docetaxel was given for the patients with stage Ⅲ as clinical trial. Other patients didn't received adjuvant chemotherapy for advanced age, postoperative complications (Clavien-Dindo classification grade Ⅳa), renal dysfunction and

Table 3. Posto perative morbidity

Complications	n	%
Grade I*		
Delirium	3	3.3
Dumping syndrome	1	1.1
Grade Ⅱ*		
Surgical Site Infection	1	1.1
Urinary tract infection	1	1.1
Drug rash	1	1.1
Aspiration pneumonia	2	2.2
Anastomotic stricture	2	2.2
Grade Ⅲa*		
Duodenal stump leakage	1	1.1
Grade Ⅳa*		
Anastomotic leakage	1	1.1
Pancreatic fistula	1	1.1
Total	14	15.4

Where appropriate, data show the numbers of patients, with percentages.
*According to the Clavien-Dindo classification.

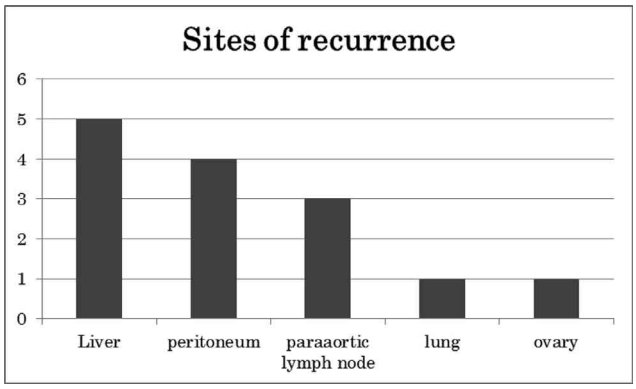

Fig 1. Sites of recurrence
There is some overlapping.

Table 4. Adjuvant therapy

Initial chemotherapy regimen	n	%
S-1	33	76.7
S-1+cisplatin	4	9.3
S-1+docetaxel	2	4.6
Others	4	9.3
CPT-11/CDDP	1	2.3
UFT	1	2.3
5-FU (oral)	1	2.3
Docetaxel	1	2.3
Total	43	

Where appropriate, data show the number of patients, with percentages.

patients' hope.

During this observation period, ten patients died, including six cancer deaths (stage IB, one patient ; stage ⅢA, two patients ; stage ⅢB, one patient ; stage ⅢC, two patients).

According to TNM stage, the overall 5-year OS and DFS rates were 92.3% and 91.8% with stage IB, 85.4% and 85.4% with stage Ⅱ, and 49.3% and 26.9% with stage Ⅲ, respectively (Fig. 2). Since the two patients with stage Ⅳ had not yet been followed for over one year, OS or DFS could not be calculated for these patients.

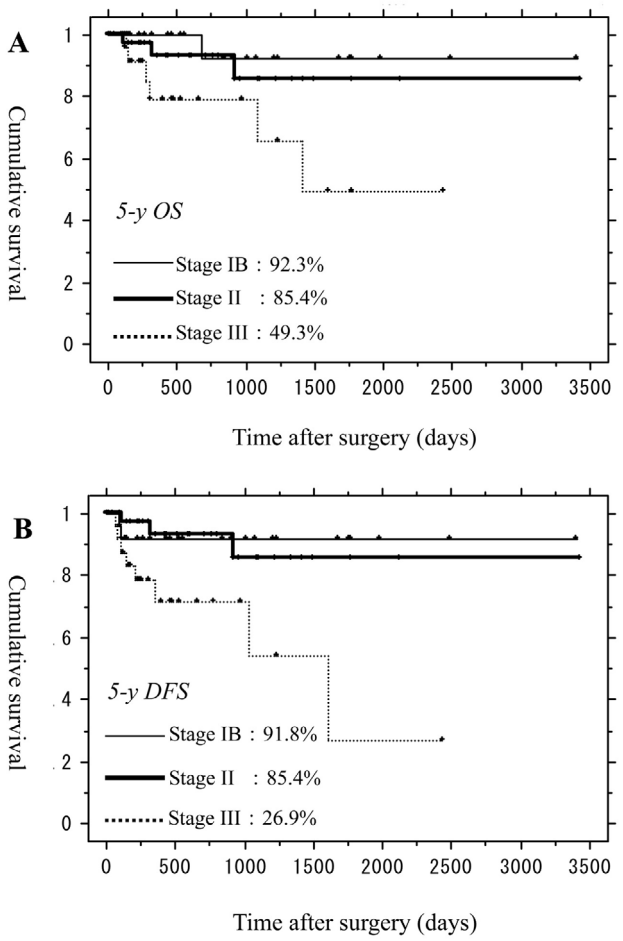

Fig 2. Overall survival and disease-free survival
Kaplan-Meier overall survival (A) and disease-free survival (B) curves according to tumor stage, based on the 7th edition of the TNM classification. Stage Ⅳ disease was omitted because of the small sample size.

DISCUSSION

Since LADG for EGC was first performed in 1991 and first reported in 1994 (11), improvements in instruments and laparoscopic technique have allowed for widespread acceptance (12-13). The laparoscopic approach is used in approximately 39% of gastric cancer surgeries in Japan (14). This approach offers important advantages when compared with open surgery, such as a better cosmetic effect, improved quality of life, less intense pain, shortened hospital stay, early rehabilitation, and early return to social activity (15-17). The safety of LADG for clinical stage I cancers (including patients with T3(SS)N0) was demonstrated in a multicenter, controlled trial (JCOG 0703) (18), and a randomized, controlled trial to compare long-term survival after LADG and open distal gastrectomy for clinical stage I cancers is ongoing in Japan (JCOG 0912) (19), and the results are awaited. Recently, some surgeons have been concerned about laparoscopic surgery for AGC (20). Since Uyama *et al.* (21) reported laparoscopy-assisted total gastrectomy with D2 lymph node dissection and distal pancreaticosplenectomy for advanced upper-third gastric cancer, there have been several studies to determine the technical feasibility of D2 lymph node dissection in AGC. Gordon *et al.* (22) demonstrated that LDG with D2 dissection for AGC was feasible and could match the survival rate of open distal gastrectomy using a cohort in which 67.2% had a tumor of stage ⅡB or higher with an average follow-up period of 49.2 months. Fukunaga *et al.* (23) reported that oncologic outcomes were good in patients with T1N0-1 and T2N0 gastric cancer who underwent LADG with extended lymph node dissection. Extended lymph node dissection has been reported in Japan and Europe to improve outcomes of gastric cancer (24). However, the use of laparoscopic surgery with extended lymph node dissection for AGC still continues to be controversial because of the technical difficulty of lymphadenectomy and the lack of data on the procedure's oncologic adequacy. Laparoscopic extended lymph node dissection should be performed by an expert. In our hospital, the operators are limited to experts who have passed an endoscopic surgical skill qualification system (25). We have established the procedure of D2 lymphadenectomy in LDG, which is needed for standard surgery with AGC, so the eligibility criteria for LDG were extended to cT3N1 gastric cancer.

With regard to accuracy, analysis of many cases of advanced cancer in which open surgery was performed have found that retrieval of a sufficient number of lymph nodes is important to improve the diagnostic accuracy and prognosis, and retrieval of 25 lymph nodes is recommended in T2 (26). In the present study, 31.4 lymph nodes were retrieved, which does not seem to be a problem in terms of accuracy compared with open surgery.

With regard to safety, conversion to open surgery was done in 1 patient (1.0%) because of advanced stage disease, T4 depth, in the present study. There were no specific complications attributable to laparoscopic surgery.

Several studies presented mortality and morbidity data associated with laparoscopy-assisted gastrectomy. In the KLASS-I trial (27), the authors reported mortality of 1.1% and morbidity of 10.5%. In the present study, there were 14 cases (15.3%) of postoperative morbidity and no mortality. Complications that required reoperation and intensive care, Clavien-Dindo classification grade Ⅳa, occurred in two cases. In one case, anastomotic leakage occurred seven days after operation, and drainage was performed under laparotomy. In another case, a pancreatic fistula occurred that caused secondary anastomotic leakage. There two cases finally recovered and were discharged.

Several authors have shown no difference in recurrence or survival following laparoscopic surgery and open surgery for EGC. However, in the case of AGC, the difference has remained controversial. Recently, Song *et al.* (28) reported on their multicenter, retrospective analysis of recurrence following laparoscopy-assisted gastrectomy. They stated that the incidence of recurrence was 3.5% in all patients, 1.6% in EGC, and 13.4% in AGC. During the present follow-up period, ten patients (10.9%) were found to have tumor recurrence. They reported that the peritoneum and liver were the most common recurrence sites. In the present study, liver metastasis occurred in five patients (50.0%), which was the most common recurrence site. There were no recurrences in regional lymph nodes. Peritoneal dissemination occurred in four patients (T3, one patient ; T4a, three patients), but there were no cases with port site recurrences. Effects of pneumoperitoneum manipulations on progression of the cancer and effects of the manipulation on tumor dissemination have been reported (29), so

continued follow-up and are needed.

Kitano *et al.* (15) reported on the long-term outcomes of laparoscopic gastrectomy in a retrospective, multicenter study of laparoscopic gastrectomy for EGC that analyzed 1294 patients from 16 institutions. They reported that the 5-year DFS rates were 99.8%, 98.7%, and 85.7% for stages IA, IB, and II, respectively. In the case of laparoscopic surgery for AGC, some authors reported their short-term and long-term outcomes. Lee and Kim (30) presented the long-term outcomes of AGC, with OS of 81.4% and DFS of 72.4%. In all of the present cases, the 5-year OS and DFS rates were 76.8% and 72.6%, respectively.

This study has the drawbacks that there was no comparative analysis with open gastrectomy, and the follow-up period was short. For the elucidation of oncologic safety and clinical feasibility of laparoscopic distal gastrectomy for AGC, a comparative study of short-term and long-term results with the open method will be necessary. Although further study comparing laparoscopic distal gastrectomy to open gastrectomy for AGC is needed, laparoscopic distal gastrectomy with adequate lymph node dissection for AGC appears to be an oncologically safe, feasible, and curative procedure. A large-scale, randomized trial is needed to confirm the oncological safety and feasibility of laparoscopic distal gastrectomy for patients with advanced gastric cancer.

CONFLICT OF INTERESTS-DISCLOSURE

The authors declare that they have no conflict of interest.

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