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ORIGINAL SCIENTIFIC REPORT

A Multi-institutional, Prospective, Phase II Feasibility Study of Laparoscopy-Assisted Distal Gastrectomy with D2 Lymph Node Dissection for Locally Advanced Gastric Cancer (JLSSG0901)

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Abstract

Background The efficacy and safety outcomes of laparoscopy-assisted distal gastrectomy (LADG) with D2 lymph node dissection for locally advanced gastric cancer remain unclear. Therefore, we conducted a randomized, controlled phase II trial to confirm the feasibility of LADG in terms of technical safety, and short-term surgical outcomes were investigated.

Methods Eligibility criteria included pre-operatively diagnosed advanced gastric cancer that could be treated by distal gastrectomy with D2 lymph node dissection; MP, SS, and SE without involvement of other organs; and N0–2 and M0. Patients aged 20–80 years were pre-operatively randomized.

Results In total, 180 patients were registered and randomized to the open (89 patients) and laparoscopic arms (91 patients). Among 91 patients in the laparoscopic arm, 86 underwent laparoscopic gastrectomy according to the study protocol. Regarding the primary endpoint of the phase II trial, the proportion of patients with either anastomotic leakage or pancreatic fistula was 4.7 % (4/86). The grade 3 or higher morbidity rate, including systemic and local complications, was 5.8 %. Conversion to open surgery was required for 1 patient (1.2 %), without any intra-operative complication. The post-operative mortality rate was 0, and no patient required readmission for surgical complications within 6 months after initial discharge.

Conclusions The technical safety of LADG with D2 lymph node dissection for locally advanced gastric cancer was demonstrated. A phase III trial to confirm the non-inferiority of this procedure to open gastrectomy in terms of long-term outcomes is ongoing. Registered Number: UMIN 000003420 (www.umin.ac.jp/ctr/).

On behalf of the Japanese Laparoscopic Surgery Study Group.

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Introduction

Since laparoscopy-assisted distal gastrectomy (LADG) for gastric cancer was developed in 1991 [1], the number of patients undergoing the procedure has increased each year [2]. Many randomized controlled studies with small patient numbers have found that LADG is associated with better short-term outcomes [3–6]. In multi-institutional prospective studies in Japan and Korea, the safety of LADG with nodal dissection for clinical stage I gastric cancer has been evaluated and proven [7, 8].

As outlined in many treatment guidelines, gastrectomy with D2 lymph node dissection is considered to be essential in the surgical management of advanced gastric cancer [9–11]. Because of improved techniques and the development of instruments for laparoscopy-assisted gastrectomy (LAG) with lymph node dissection, the indication for the lymph node dissection range has also been expanded from D1 to D1+ and D2. However, whether adequate laparoscopic D2 lymph node dissection can be performed remains controversial in terms of technical and oncological safety. Although recent retrospective studies have supported the technical and oncological safety of D2 lymph node dissection in LAG [12–15], the results of these studies may have been influenced by selection bias.

This Japanese multi-institutional, randomized phase II study was conducted to investigate the safety of LADG with D2 lymph node dissection for locally advanced gastric cancer for extension to a phase III study. Herein, we report the short-term outcome of this technique obtained from our phase II study.

Methods

Patients

This open-label, multi-institutional, randomized, 2-arm (open and laparoscopic), phase II was conducted within the framework of the Japanese Laparoscopic Surgery Study Group (JLSSG). Patients were enrolled at 28 institutions in Japan. All study patients had been pre-operatively diagnosed with advanced gastric cancer that was treatable by distal gastrectomy. Inclusion criteria included invasion of MP, SS, or SE without involvement of other organs; and stage N0–2 and M0 based on gastroscopy and abdominopelvic computed tomography (CT) according to the Japanese Classification of Gastric Carcinoma (13th edition) [16]. Inclusion/exclusion criteria for this study are shown in Table 1.

Table 1 Inclusion/exclusion criteria

Inclusion criteria
(1) Histologically proven gastric carcinoma
(2) MP, SS, or SE without involvement of other organs, N0–2, excluding bulky N2, and M0 according to the Japanese classification system
(3) Tumor located in the body and the antrum of the stomach and the indication for distal gastrectomy
(4) No invasion to the duodenum
(5) No invasion to the esophagus
(6) PS (ECOG) 0 or 1
(7) Body mass index <30 kg/m^2
(8) No history of gastrointestinal surgery
(9) No history of chemotherapy or radiotherapy
(10) Sufficient organ functions
(11) Provided written informed consent
Exclusion criteria
(1) Synchronous or metachronous (within 5 years) malignancies other than carcinoma in situ
(2) Women who are pregnant or breastfeeding
(3) Severe mental disease
(4) Continuous systemic steroid therapy
(5) History of myocardial infarction or unstable angina pectoris within 6 months
(6) Uncontrollable hypertension
(7) Uncontrollable diabetes mellitus or administration of insulin
(8) Severe respiratory disease requiring continuous oxygen therapy

Randomization and masking

Randomization and data management were performed by the Data Center, Clinical Trial Support Division, General Clinical Research Center, Oita University Hospital. After confirmation of inclusion/exclusion criteria and after obtaining written informed consent, patients were randomly assigned to the open surgery arm or laparoscopic surgery arm by a minimization method with the following adjustment factors: depth of tumor invasion (MP/SS/SE), status of lymph node metastasis (N0/N1/N2), and the institution. The allocation procedure was not masked from investigators or patients.

Quality control of surgery

Participating surgeons

Surgeons operating on patients in the laparoscopic arm had to be certified by the Japan Society for Endoscopic Surgery

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(JSES) according to the Endoscopic Surgical Skill Qualification System [17]. In addition, surgeons with experience of more than 50 open gastrectomies and institutions with experience of at least 20 laparoscopic gastrectomies with D2 lymph node dissection were accredited by the study chair.

Central review of the surgical procedure by photo documentation

We performed a central review of the surgical procedure for all patients by evaluating photographs taken during the procedure. The committee for quality control and surgical assessment evaluated these photographs, and the surgical procedure was discussed at meetings held twice a year.

Procedures

If intra-operative staging met inclusion criteria, distal gastrectomy with D2 lymph node dissection was performed. During LADG, a pneumoperitoneum was created by insufflation of carbon dioxide. The type and placement of trocars, number of ports, and location of the mini-laparotomy incision for extracting the resected specimen were discretionary. As the tumor is generally large and has frequent lymph node metastasis in advanced cancer, the skin incision was defined as having a length of at least 7 cm or less in our protocol, which was sufficient to remove the surgical specimen from abdominal cavity.

The method for reconstruction after resection was not specified. Requests for analgesia from post-operative day 5 to the day of discharge were recorded. If histological examination of the resected specimen revealed a pathological stage of II or higher, patients underwent adjuvant chemotherapy with oral 5-fluorouracil agents.

Operative methods and pathological results were recorded according to the 13th and 14th editions of the Japanese Classification of Gastric Carcinoma [16, 18] and were translated according to the 7th edition of the International Union Against Cancer (UICC) TNM classification [19]. Intra-operative and post-operative morbidities were described according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v 4.0. Hospital mortality was defined as post-operative death from any cause within 30 days of initial surgery. The rate of readmission for any surgery-related complication within 6 months after initial discharge was evaluated.

Endpoints

The primary endpoint of this phase II trial was the incidence of anastomotic leakage with a severity of grade 1 or higher or pancreatic fistula with a severity of grade 2 or higher according to CTCAE v 4.0 assessment. The reason is that both complications are considered to be critical complications caused by LADG with D2 lymph node dissection, and are needed medication, interventional, or surgical treatments. Secondary endpoints were the proportion of cases of successfully completed LADG, the proportion of conversion to open surgery, adverse events, short-term clinical outcomes, and the number of retrieved lymph nodes.

Study design and statistical analysis

This study is a randomized phase II/III trial to investigate safety and efficacy of LADG, and the first 180 patients were enrolled in the phase II part. In order to proceed to a phase III trial to show non-inferiority of LADG to open distal gastrectomy (ODG) in terms of short- and long-term outcomes, the safety of the LADG with D2 lymph node dissection should be established through a preliminary step that determines occurrence of anastomotic leakage and pancreatic fistula as primary endpoints in a phase II trial. When we compared LDG with ODG directly and judged which was better at the phase II stage with small sample size, the result may have influenced the progress of the phase III part. Therefore, the analysis of phase II was conducted in one arm to ensure minimum safety. Additionally, we considered that owing to the nature of the randomization design in a phase II trial, the phase II data could also be used in the phase III trial.

Sample size calculation assumed a 1-sided 10 % significance level and 80 % power under the hypothesis of a primary endpoint with an expected value of 8 % and a threshold value of 18 %. The expected value was decided according to the post-operative outcome based on a national survey conducted by the Japan Society of Endoscopic Surgery (JSES). To ensure power greater than 80 % even if 20 % of patients discontinued protocol treatment, 90 patients were required.

Analyses of primary and secondary endpoints were performed for patients who received LADG and completed the protocol treatment. The primary endpoint was analyzed using the binomial test with a 1-sided significance level of 10 %. The comparison of short-term outcome of LADG with ODG was not conducted in this phase II part, but will be conducted in the phase III part. Sample size calculation and all statistical analyses were performed using S-PLUS 8.0 for Windows.

This clinical trial was registered at the University Hospital Medical Information Network (UMIN)-CTR (www.umin.ac.jp/ctr/); the identification number is UMIN 000003420.

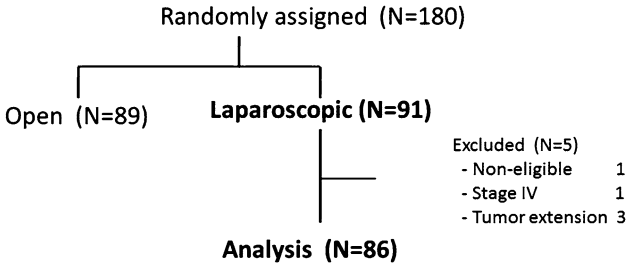

Fig. 1 Consort diagram for this study

Results

Between November 26, 2009, and June 24, 2013, a total of 180 patients were registered and randomized to the open (89 patients) or laparoscopic arms (91 patients) of the study. Of 91 patients in the laparoscopic arm, 5 were excluded: 1 patient had peritoneal metastasis, 3 patients were judged intra-operatively to require total gastrectomy or combined resection of other organs because of tumor extension, and 1 patient failed to meet inclusion criteria because of previous upper abdominal surgery. Therefore, 86 patients underwent LADG according to the study protocol (Fig. 1). Patient demographics are summarized in Table 2. The median age of patients was 63 years (range 39–80); 52 were male, and 34 were female. The median body mass index (BMI) was 21.9 kg/m^2.

Operative findings and surgical outcomes are summarized in Table 3. D2 lymph node dissection was performed for all 86 patients (100 %) who underwent LADG. Complete resection (R0) was achieved for all 86 cases. On photographic review of the laparoscopic procedures, the central committee determined that D2 lymph node resection was appropriate for each case. Billroth-I (B-I) reconstruction was performed for 45 patients, Billroth-II (B-II) for 8, and Roux-en-Y for 33. The median duration of surgeries was 296 min [interquartile range (IQR) 235–350]. The median blood loss was 30 ml (IQR 20–94), and blood transfusion was required for 1 patient because of bleeding from the primary tumor. The median length of the skin incision was 4.5 cm (IQR 3.5–5). A skin incision of more than 7 cm, defined as conversion to open surgery, was required for 1 patient (1.2 %) to enable the removal of a bulky tumor.

Pathological data are also summarized in Table 3. The median tumor size was 4.1 cm (IQR 3.0–6.0). Fifty-four patients (62.8 %) had tumors of stage T2 or higher, and lymph node metastases were present in 45 patients (52.3 %). Peritoneal lavage cytology was negative for all 76 patients who underwent this investigation. Pathological stages according to the UICC classification were as follows: stage IA, 23 (26.7 %); stage IB, 18 (20.9 %); stage II, 18 (20.9 %); and stage III, 27 (31.5 %). The median number of removed lymph nodes was 47. Both proximal and distal resection margins were negative for all patients.

Table 2 Baseline characteristics

	$N = 86$
Age	
Median	63
Range	39–80
Sex, no. (%)	
Male	52 (60.5 %)
Female	34 (39.5 %)
Performance status	
0	85 (98.8 %)
1	1 (1.2 %)
The number of co-morbidity	32
Cardiac	7
Hypertension	19
DM	8
Pulmonary	3
Hepatic	3
Renal	1
Others	1
Body mass index (BMI)	
Median	21.9
<20	20 (23.2 %)
20–25	48 (55.8 %)
≥25	18 (20.9 %)
Tumor location	
Middle third of the stomach	29 (33.7 %)
Lower third of the stomach	57 (66.3 %)
Clinical stage (13th edition, Japanese)	
IB	39 (45.3 %)
II	36 (41.9 %)
IIIA	8 (9.3 %)
IIIB	3 (3.5 %)

DM diabetes mellitus

Post-operatively, the median time from the end of surgery to the first episode of flatus was 2 days (IQR 2–3). Regarding requests for analgesia, there are cases in which epidural anesthesia is used in combination approximately 3 days post-operatively. To eliminate this bias, we decided to evaluate pain that continued for more than 5 days post-operatively, as in the previous trial. As a result, twenty-nine of 86 patients (33.7 %; 95 % confidence interval, 23.9–44.7) required analgesic medication on post-operative days 5–10. The median body temperature during the first 3 days was 37.8 °C (IQR 37.5–38.0). The median post-operative hospital stay was 11 days (IQR 10–15).

There were no cases of grade 2 or higher intra-operative complications, such as organ injury or unexpected bleeding

Table 3 Operative and pathological results

	$N = 86$
Operative results	
Procedure	
Distal gastrectomy	86 (100 %)
Lymphadenectomy	
D2	86 (100 %)
Reconstruction	
Billroth-I	45
Billroth-II	8
Roux-en-Y	33
Operative time, min	
Median	296
Range	159–465
Interquartile range	235–350
Estimated blood loss, ml	
Median	30
Range	0–500
Interquartile range	20–94
Blood transfusion	
Intra-operatively, case	1
Within 3 post-operative days, case	0
Length of wound, cm	
Median	4.5
Range	2.0–8.0
Interquartile range	3.5–5
Conversion	1 (1.2 %)
Technical conversion	1 (1.2 %)
Complicated conversion	0
Re-surgery	1
Pathological results	
Size of tumor, cm	
Median	4.1
Range	1.8–23.0
Interquartile range	3.0–6.0
Lymph node harvested	
Median	47
Range	10–104
Interquartile range	34–56
pT classification (UICC)	
pT1	32 (37.2 %)
pT2	18 (20.9 %)
pT3	19 (22.1 %)
pT4	17 (19.8 %)
pN classification (UICC)	
pN0	41 (47.7 %)
pN1	22 (25.6 %)
pN2	8 (9.3 %)
pN3a	9 (10.4 %)
pN3b	6 (7.0 %)
Peritoneal cytology	
Positive	0
Negative	76
Not examined	10
Proximal resected margin	
Negative	86 (100 %)
Distal resected margin	
Negative	86 (100 %)
Pathological stage (UICC)	
Stage IA	23 (26.7 %)
Stage IB	18 (20.9 %)
Stage II	18 (20.9 %)
Stage III	27 (31.5 %)
Radicality	
R0	86 (100 %)

UICC International Union Against Cancer

that required transfusion. Table 4 summarizes the post-operative adverse events. Grade 1 or higher anastomotic leakage was observed in 1 patient and grade 2 or higher pancreatic fistula in 3 patients. The proportion of patients with either anastomotic leakage or pancreatic fistula was 4.7 % (4/86; 95 % confidence interval, 1.3–11.5; 1-sided $P = 0.00024$; binomial test of the null hypothesis that the proportion is ≥ 18 %).

According to CTCAE v 4.0 assessment, 13 patients (13/86; 15 %) presented post-operative complications of any grade, excluding fever, and the number of adverse events was 25 (25/86; 29 %). Grades 3 and 4 post-operative complications occurred in 5 patients (5/86; 5.8 %). Local complications of grades 3 or 4 occurred in 2 patients (2/86; 2.3 %), and systemic complications of grades 3 or 4 occurred in 3 patients (3/86; 3.5 %). One patient required re-surgery for leakage at the gastroduodenostomy. Among patients who suffered from grade 2 complications, 2 patients had anastomotic stricture after B-I anastomosis. One of these patients required balloon dilatation. The post-operative mortality rate was 0, and no patient required readmission for surgical complications within 6 months after initial discharge.

Discussion

At the beginning of this study, we considered that before proceeding with a phase III trial, the safety of LADG with D2 lymph node dissection should be established through a preliminary step that determines occurrence of anastomotic

Table 4 Adverse events

	Laparoscopic surgery ($N = 86$)	
	The number of adverse events in all grades[a]	The proportion of grades 3 and 4
Anastomotic leakage	1	1 (1.2 %)
Pancreatic fistula	3	0
Intra-abdominal abscess	1	1 (1.2 %)
Bleeding	0	0
Wound complication, non-infection	0	0
Bowel obstruction	0	0
Anastomotic stenosis	2	0
Infection with normal ANC-lung	4	1 (1.2 %)
Infection with normal ANC-intestine	1	1 (1.2 %)
Infection with normal ANC-catheter	1	0
Infection with normal ANC-wound	1	0
Pulmonary effusion	3	0
Ascites	2	0
Others	3	0
Aminotransferase increased	1	1 (1.2 %)
Subcutaneous emphysema	2	0

ANC absolute neutrophil count

[a] The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v 4.0

leakage and pancreatic fistula as primary endpoints in a phase II trial. Actually, we have referred to not only the data from laparoscopic gastrectomy but also that from open gastrectomy with D2 lymph node dissection including both distal and total gastrectomy against advanced gastric cancer. It was demonstrated that rates of 5.3 and 2.3 % for anastomotic leakage and pancreatic fistula, respectively (total 7.6 %) [20]. In some cases, there is a potential risk of increased rates of anastomotic leakage and pancreatic fistula after LADG with D2 lymph node dissection for advanced gastric cancer. Thus, expected values for this surgical technique were set at most 8 % in our phase II study. This study is the first multi-institutional, prospective, randomized controlled phase II study conducted in Japan that explored the safety of LADG with D2 lymph node dissection for patients with locally advanced gastric cancer in terms of short-term outcome.

Previous studies of LADG have reported rates of 2.2–6.3 % for conversion to open surgery [13, 14, 21]. In the present study, conversion to open surgery was required for only 1 patient (1.2 %); an 8-cm skin incision was required to remove the tumor from the peritoneal cavity. Readmission for complications related to LADG reflects the quality of life post-operatively. In a study by Kim et al. [22], 21 of 223 patients (9.4 %) required readmission within 1 year of discharge following LADG. In our study, no patient required readmission for surgery-related complications within 6 months after initial discharge. These results demonstrate that LADG with D2 lymph node dissection can be safely performed for patients with locally advanced gastric cancer.

For quality control in this study, we established a number of requirements to optimize the surgical procedure. First, surgeons operating on patients in the laparoscopic arm had to be certified by the Endoscopic Surgical Skill Qualification System. This accreditation system for gastrointestinal surgery was established in 2004, and the surgical skill assessment system has contributed to the standardization of the laparoscopic technique and has enhanced the surgical skills of laparoscopic surgeons in Japan [17, 23]. In a Korean randomized trial, surgeons were assessed using the study group's own quality control system [24]. Surgical standardization is considered to be an important factor influencing the outcome of a trial. Second, only surgeons considered to have sufficient experience with the relevant procedures were accredited by the study chair. Third, we performed a central review of the surgical procedure on the basis of photographs taken after lymph node dissection for all patients and video for arbitrarily selected patients. [25] We believe this review system enabled surgical standardization in terms of D2 lymph node dissection.

Previous reports identified several risk factors for post-operative complications following LAG, including pre-operative comorbidities, obesity, and previous surgical outcomes [13, 14, 26–29]. In addition, Lee et al. recently identified B-I reconstruction as a risk factor for post-operative complications in their phase II study [21]. In the present study, anastomotic failure requiring a second surgery occurred in 1 patient who underwent B-I reconstruction. To avoid anastomotic complications, intracorporeal anastomosis techniques, such as delta-shaped anastomosis, have been developed [30]. The association between reconstruction methods and post-operative complications will be addressed in the phase III trial.

It should be considered that there are several limitations to the present study.

Patients with BMI > 30 were excluded. Obesity is considered to be a risk factor for the successful completion of LADG [31, 32]. In obese patients, suprapancreatic lymph node dissection during LADG is often challenging because it is difficult to distinguish between the upper edge of the pancreas and the fat tissue contained in the lymph node [33, 34]. Therefore, it is necessary to determine

whether the techniques for D2 lymph node dissection used in this study can be safely adapted for use in obese patients. Another potential limitation is related to the accuracy of pre-operative diagnosis. The range of lymph node dissection is determined by the degree of tumor progression; therefore, accurate pre-operative diagnosis is essential. In our results, invasion to stage T2 or beyond the stomach wall in final pathological findings was present in 62.8 % of patients pre-operatively diagnosed with advanced gastric cancer. As the results of phase III trial may strongly be affected by contamination of early diseases in terms of short- and long-term outcomes, we wish to point out that during the registration for a phase III trial and should make an effort to make a correct pre-operative diagnosis.

In conclusion, the results of this multi-institutional, randomized phase II trial demonstrated the technical safety of LADG with D2 lymph node dissection for patients with locally advanced gastric cancer. Regarding oncological feasibility, the median number of removed lymph nodes was 47 in this phase II trial, indicating that the quality of lymph node dissection can be maintained in comparison with that in previous reports [12, 13, 21]. A phase III extension of this study that compared LADG with open gastrectomy in terms of short- and long-term outcomes is ongoing.

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