Japanese Laparoscopic Gastric Surgery Study Group

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JLSSG0901

A randomized Phase II/III Study of Laparoscopy-assisted Versus Open Distal Gastrectomy with D2 Nodal Dissection for Locally Advanced Gastric Cancer

Abbreviated title: JLSSG0901

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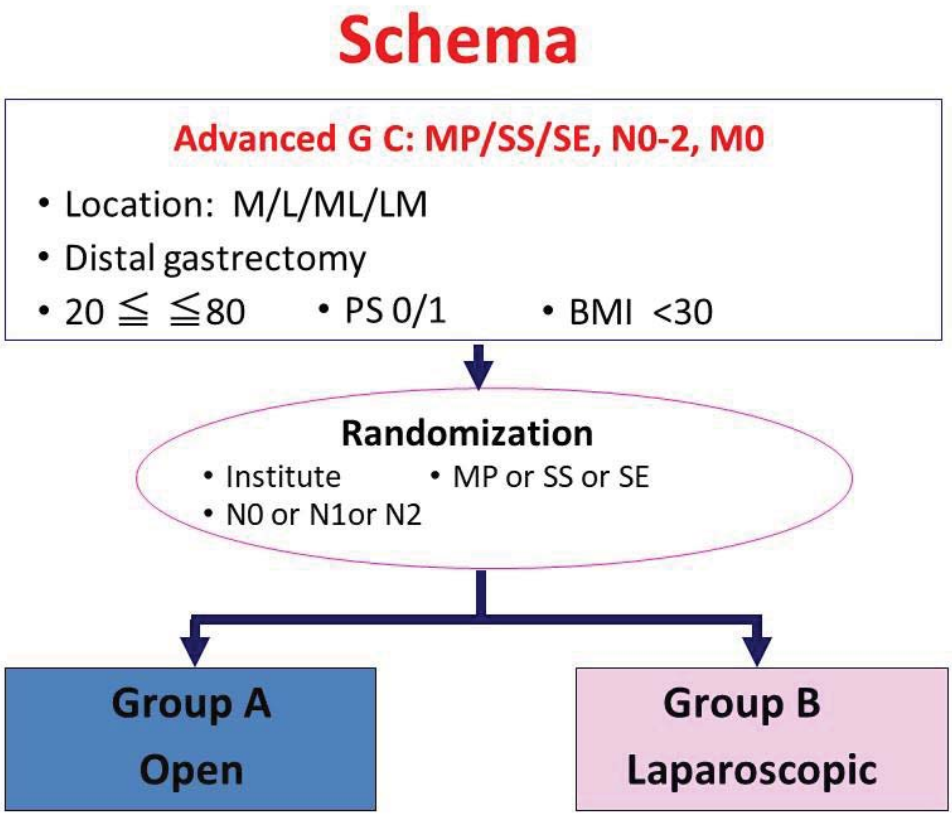
0. Summary

0.1. Outline



0.2. Objectives

The aim of this study is to confirm the non-inferiority of LADG to ODG in terms of relapse-free survival (RFS) for locally advanced gastric cancer.

Primary endpoint: 5-year relapse free survival

Secondary endpoint: 5-year overall survival, rate of morbidity and mortality, Rate of laparoscopic surgery completion, Rate of conversion to open surgery, Number of retrieved lymph nodes, Early postoperative course (days until flatus, proportion of analgesic use, highest body temperature during the first three days after surgery and while hospitalized) and Form of recurrence were set as the secondary endpoints.

Subjects

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 13th 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
12) Aged 20–80 years old

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.

0.3. Treatment

Group A: Open gastrectomy

- Perform open distal gastrectomy with D2 lymph node dissection as stipulated in the Gastric Cancer Treatment Guidelines in Japan (3rd edition for physicians).

Group B: LADG

- Perform LADG with D2 lymph node dissection as stipulated in the Gastric Cancer Treatment Guidelines in Japan (3rd edition for physicians).

0.4. Planned sample size and study duration

Planned sample size: 500 patients

Enrollment period: 7 years

Follow up period: 5 years after completion of enrollment, Overall study duration: 12 years

However, extension of an enrollment period for less than 6 months does not require protocol revision.

0.5. Contacts

For queries regarding:

Eligibility criteria, treatment change criteria, and clinical diagnoses: Study Coordinator (refer to 16.5)

Enrollment procedure and case report form (CRF) input: Data Center (16.11.)

Adverse event reports: Data and Safety Monitoring Committee (16.9.)

Contents

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2. Background and Rationale for the Study Plan

2.1 Subjects

1.1.1. 2.1.1Epidemiology

The mortality rate for gastric cancer has continued to decline in Japan for both men and women since the 1970s. For men, the mortality rate for gastric cancer was surpassed by that of lung cancer in 1993, and gastric cancer dropped to second place[1]. Worldwide, the mortality rates for gastric cancer in East Asia and Eastern Europe are approximately the same as those in Japan, whereas they are lower in other regions. When data from all countries is totaled, lung cancer has the highest mortality rate, followed by gastric cancer[2]. Meanwhile, in Japan, the prevalence (total for men and women, per 100,000 of the population, adjusted for age) is highest for gastric cancer (47.7)[3], and that of lung cancer is second (37.8). However, the mortality rate (per 100,000 population) for gastric cancer is on a downward trend. The decrease in mortality rate is considered to be due to an increase in the overall 5-year survival rate for gastric cancer to nearly 70%. This increase is due to the relative increase in early-stage gastric cancer and improved treatment outcomes for advanced gastric cancer.

The standard treatment for gastric cancer is surgical treatment. According to the Gastric Cancer Treatment Guidelines for Physicians, second edition) of the Japanese Gastric Cancer Association, the 5-year survival rate following standard surgery (D2 dissection) for gastric cancer was 93.4% for stage IA, 87.0% for stage IB, 68.3% for stage II, 50.1% for stage IIIA, 30.8% for stage IIIB and 16.6% for stage IV[4]. The prognosis is extremely good for stages IA and IB, which include early-stage gastric cancer, and the frequency of gastric regional lymph node metastasis is low. Even in advanced gastric cancer, the 5-year survival rate for depth of invasion T2 (limited to the subserosa tissue [SS]) and lymph node metastasis N2 (up to group 2 lymph nodes) is almost 80% if curative resection is performed[4]. However, depth of invasion of T3 or T4 results in a poor prognosis even if there is no distant metastasis (M0), and 5-year survival rates of T3M0 and T4M0 are approximately 45% and 25%, respectively[5].

2.1.2 Rationale for Selection of Study Population

1) Reason for targeting cT2-3, cN0-2 and cM0

Following the development of laparoscopic-assisted surgery for gastric cancer in Japan during 1991, the number of surgeries has been increasing every year. According to the 9th National Questionnaire Survey (2008) of the Japan Society for Endoscopic Surgery, the number of laparoscopic-assisted surgeries for gastric cancer was 4765 in 2007, of which distal gastrectomy accounted for 78%[6].

The research group of the “Research for expanding indications for endoscopic surgery in cancer” as part of a grant-in-aid for cancer research from the Ministry of Health, Labour and Welfare conducted a multi-center retrospective study of laparoscopic-assisted surgery in 1294 patients with early-stage gastric cancer. The long-term results showed no difference in survival compared to open surgery, and even for safety, the frequency of intraoperative and postoperative complications was 1.7% and 12.7% lower,

respectively[7]. However, in facilities where laparoscopic-assisted gastrectomy is performed as a first-line treatment, the indication for even advanced T2 and T3 gastric cancer has been expanded. According to the 9th National Questionnaire Survey (2008) of the Japan Society for Endoscopic Surgery, 10% of the facilities had performed laparoscopic-assisted gastrectomy for advanced gastric cancer. The research group of the "Research for expanding indications for endoscopic surgery in cancer" as part of the same grant-in-aid for cancer research from the Ministry of Health, Labour and Welfare conducted a multi-center retrospective study of laparoscopic-assisted surgery in 272 patients with advanced gastric cancer. The long-term results showed no difference in survival compared to open surgery. For safety, the frequency of intraoperative and postoperative complications was 3% and 12%, respectively, with no difference compared to those for early-stage gastric cancer[8].

As well, with the improvement of lymph node dissection techniques for laparoscopic-assisted gastrectomy, the range of lymph node dissection has also been expanded from D1+alpha to D1+beta and D2. According to the 9th National Questionnaire Survey (2008) of the Japan Society for Endoscopic Surgery, the frequencies of D1+alpha, D1+beta, and D2 were 29%, 59% and 18%, respectively, for the gastric cancer patients who underwent laparoscopic-assisted gastrectomy. The percentages of pN2 in cT2 and cT3 lesions covered by this study are 25% and 40%, respectively. The frequency of lymph node metastasis in two or more groups is high (National Cancer Center Central Hospital, 1972-91)[9]. Although it is technically possible to perform D2 dissection by laparoscopic-assisted surgery, randomized controlled trials have not been conducted to verify that the efficacy and safety of this surgery for T2 and T3 gastric cancer are not inferior to open surgery. Therefore, T2 and T3 gastric cancers according to the 13th Japanese classification system are included in this study. Patients with peritoneal metastasis or hematogenous metastasis (liver, lung and bone) are not included in this study because they are not targeted for radical resection.

2) Reasons for excluding subjects requiring total gastrectomy

A survey of nine facilities promoting laparoscopic-assisted surgery by the research group of the "Research for expanding indications for endoscopic surgery in cancer" as part of the grant-in-aid for cancer research from the Ministry of Health, Labour and Welfare[8] found that laparoscopic-assisted surgery was performed on approximately 1,600 cases of early-stage gastric cancer. However, total gastrectomy accounted for only 4% of these, indicating that the use of this procedure is not yet widespread. In particular, as an anastomosis technique has yet to be established, including such cases in a multi-institutional cooperative clinical trial at the current stage is not appropriate.

3) Reasons for excluding obese patients (Body Mass Index [BMI] ≧30)

It has also been reported that the frequency of complications for standard open surgery increases for obese patients[10] and that the reliability of lymph node dissection drops[11]. Although it has been reported that obese patients have the same frequency of onset of complications as do non-obese patients for

laparoscopic-assisted gastrectomy, there is an apparent increase in operation time, and the difficulty of the technique also increases[12, 13].

As it can be considered appropriate to exclude obese patients, who involve a high degree of difficulty and are infrequent in Japan, from the general indications, patients with BMI ≧30 who are classified as obese according to the WHO classification[14] were excluded (approximately 3% of Japanese people) from this study to ensure safety.

2.1.3 Tumor-related Complications

Approximately 10% of the patients with advanced gastric cancer covered by this study have chronic bleeding from the primary tumor and associated anemia. Oral intake may become difficult due to pyloric stenosis, and retention of ascites may occur as the disease stage progresses.

2.1.4 Recurrence/Growth Pattern

The percentage of recurrence types in advanced gastric cancer were as follows: peritoneal seeding 44.2%, local including lymph nodes 23.0%, liver 13.8% and distant metastases 10.6%[9]. About 25% of T3 lesions show peritoneal seeding, followed by about 10% for lymph node recurrence.

Basic research indicates that the dispersion of cancer cells exposed by laparoscopic-assisted surgery may increase postoperative wound metastasis, a form of recurrence unique to laparoscopic-assisted surgery[15]. In addition, an animal experiment investigating the effects of CO_2 pneumoperitoneum on cancer cells found that metastasis to the liver was promoted more than with open surgery[16]. At the same time, another study found that pneumoperitoneum inhibited lung metastasis[17].There is no consensus regarding the effects on metastasis.

The research group of the “Research for expanding indications for endoscopic surgery in cancer” funded by the grant-in-aid for cancer research from the Ministry of Health, Labour and Welfare conducted a multi-center retrospective study of laparoscopic-assisted surgery in 272 patients with advanced gastric cancer, in which the long-term results showed that the types of recurrence were comparable to those of open surgery[8]. However, the subjects considered to receive the most significant benefit from laparoscopic-assisted surgery and have the lowest risk are as follows: N0-1, for which differences in dissection technique are least likely to affect prognosis; T1-2, for which the effects of tumor cells on pneumoperitoneum can be ignored; and T1-2 gastric cancer, which does not require careful handling of lesions on the peritoneal side so as not to cause peritoneal metastasis. In this study, which also includes T3 according to the 13th Japanese classification system, verification from the oncological point of view is necessary.

2.1.5 Prognostic Factors/Predictive Factors

Maruyama et al. conducted a retrospective study using multivariate analysis to investigate factors

affecting prognosis for gastric cancer and found that the most important prognostic factors were distant metastasis, depth and lymph node metastasis[18]. Okajima et al. performed multivariate analysis and reported that important prognostic factors included depth of invasion into the stomach wall, lymph node metastasis, age and liver/peritoneal metastasis[5, 19].

2.2 Standard Treatment for Subjects

2.2.1 Surgical Resection

The Japanese Gastric Cancer Association prepared the Gastric Cancer Treatment Guidelines in 2001 and specified the standard treatment for each stage of progression, as shown in Table 2.2.1. The surgical treatment for advanced gastric cancer involves a 2/3rds or greater gastrectomy and routine gastrectomy with D2 dissection and has showed promising outcomes in terms of safety and curability in Japan[20]. As multi-institutional randomized controlled trials conducted in the Netherlands and the UK did not prove a superior survival period for D2 dissection over D1 dissection, D1 dissection is the standard surgical treatment for gastric cancer in Western countries[21, 22]. However, some are of the opinion that this result was due to the extremely high number of surgery-related mortalities for D2 dissection, and some facilities in Western countries do perform D2 dissection.

Table 2.2.1. Treatment indications per stage classification in routine clinical practice (Gastric Cancer Treatment Guidelines in Japan 2nd edition)

	N0	N1	N2	N3
T1(M)	IA EMR (differentiated, 2.0 cm or less, for concave type UL (-) only D1+alpha (except above)	IB D1+beta (2.0 cm or less) Standard D2 (2.1 cm or less)	II Standard D2	IV
T1(SM)	IA D1+alpha (differentiated, 1.5 cm or less) D1+beta (except above)		IIIA Standard D2	IV
T2	IB Standard D2	II standard D2	IIIB Standard D2	IV
T3	II Standard D2	IIA Standard D2	IIIB Standard D2	IV
T4	IIIA Extensive surgery	IIIB Extensive surgery	IV	IV

▪- EMR (differentiated, 2.0 cm or less, for concave type UL (-) only)

- D1+alpha (except above)

- D1+alpha (differentiated, 1.5 cm or less)

- D1+beta (except above)

Standard D2

Extensive surgery

- D1+beta (2.0 cm or less)

- Standard D2 (2.1 cm or more)

Lymph node dissection alpha and beta sites

Alpha: dissect #7 regardless of site, also dissect #8a if the lesion is in the lower area.

Beta: dissect #7, #8a and #9.

2.3 Basis for Treatment Planning

2.3.1 Laparoscopic-assisted Surgery for Subjects in this Study

Laparoscopic-assisted surgery was mainly introduced initially for benign diseases due to its minimal invasiveness. However, with advances in equipment and techniques, it has now being applied to cancer treatment. Large-scale comparative clinical trials have been conducted with open surgery for colorectal cancer in Europe and the U.S. Reports of large-scale comparative trials conducted in the late 1990s by research groups in the U.S. (NCI trial[23]), the U.K. (Classic trial[24]), Australia, Germany, Spain[25] and Europe (COLOR Trial[26]) indicated that there is no difference in the length of survival between laparoscopic-assisted surgery and open surgery. According to a randomized controlled trial conducted by a Surgical Therapy Study Group to compare laparoscopic-assisted surgery and open surgery in 872 stage 0–IV colorectal cancer patients[27], non-inferiority for overall survival period was proven (3-year survival rate: Laparoscopic-assisted surgery group: 86% vs. open surgery group: 85%). The JCOG Colorectal Cancer Surgery Group is also currently conducting a non-inferiority study (JCOG0404) for laparoscopic-assisted surgery and open surgery for cT3-4 colorectal cancer.

Although laparoscopic-assisted surgery for gastric cancer has not yet become as widespread as that for colorectal cancer, it has gradually increased in popularity since first being reported by Kitano et al. in 1991[28]. Approximately 4,700 patients per year throughout Japan had undergone gastrectomy with lymph node dissection, according to the 9th National Questionnaire Survey (2008) of the Japan Society for Endoscopic Surgery. The short-term results of laparoscopic-assisted distal gastrectomy have shown a year-by-year decrease in intraoperative and postoperative complications, which were 1.7% and 8.2%, respectively, according to the results of the 2008 survey[29]. The short-term results of laparoscopic-assisted gastrectomy with D2 lymph node dissection were also good, with postoperative complications in 3–7% of the cases[30-33]. Thus, distal gastrectomy and lymph node dissection techniques have already been established at a limited number of facilities. In contrast, with regard to long-term outcome, laparoscopic-

assisted surgery does not yet have a long history; however, Kitano et al. reported no cases of recurrence or death in 116 analyzed cases, but these do not constitute long-term follow-up results as the median observation period was 53 months[34]. Other retrospective analyses of survival are rare, but Mochiki et al. reported 5-year survival rates for early-stage gastric cancer of 98% for laparoscopic-assisted surgery and 95% for open surgery[35]. In a randomized controlled trial with a limited sample of 59 cases that included both advanced and early-stage gastric cancer, Huscher et al. reported postoperative 5-year survival rates of 58.9% for the laparoscopic-assisted surgery group and 55.7% for the open surgery group. Thus, no reports have indicated a clear difference in survival rates between laparoscopic-assisted surgery and open surgery[36].

2.3.2 Advantages and Disadvantages of Laparoscopic-assisted Surgery

The advantages of laparoscopic-assisted surgery include reduced postoperative pain compared to open surgery, fast recovery of intestinal peristalsis, reduced hospitalization, quicker return to society and a smaller surgical wound[37-40]. Although large-scale clinical studies of gastric cancer have not been reported, the results of the abovementioned randomized controlled trial between the laparoscopic-assisted surgery group and open surgery group conducted by the Surgical Therapy Study Group for 872 colorectal cancer patients indicated that the median hospitalization period was five days for the laparoscopic-assisted surgery group and six days for the open surgery group, and the median number of days during which non-orally administered painkillers were required was three days for the laparoscopic-assisted group and four days for the open surgery group. Both periods were reported to be statistically significantly shorter in the laparoscopic surgery group. In a small-scale randomized comparative study of 30 gastric cancer patients, Kitano et al. reported that significantly superior results were shown for the laparoscopic-assisted group versus open surgery group for bleeding volume (117 vs. 258 mL), days until flatus (2.9 vs. 3.9 days), days until leaving bed (1.8 vs. 2.6 days), pain according to pain visual analog scale (hospital day 1: 35 vs. 79; hospital day 3: 15 vs. 55) and lung capacity (hospital day 3: 2,144 vs. 1,444 mL).

In contrast, the disadvantages of laparoscopic-assisted surgery include an increase in the number of complications due to operation angles of the surgical instruments and the restricted field of vision. However, the randomized controlled trial of colorectal cancer treatment by the Surgical Therapy Study Group reported no statistically significant difference between the laparoscopic-assisted surgery group versus open surgery group for intraoperative complications (8% vs. 16%) or early postoperative complications (19% vs. 19%). However, due to the anatomical complexity of gastric cancer surgery, the difficulty of lymph node dissection and inadequate reconstructive techniques after gastrectomy in laparoscopic-assisted surgery, the frequency of occurrence of suture failure and pancreatic fistula associated with lymph node dissection is expected to increase. The possibility of increased complications leading to prolonged hospitalization and even death during hospitalization has also been pointed out[41].

Recently, to verify the safety of laparoscopic-assisted distal gastrectomy, the JCOG (Japan Clinical Oncology Group) Gastric Cancer Surgery Group conducted JCOG0703 (a phase II trial on the safety of

laparoscopic-assisted distal gastrectomy for clinical stage I gastric cancer) for 177 patients with cStage IA (cT1N0) and IB (cT1N1, cT2N0), with the frequency of occurrence of anastomotic leakage and pancreatic fistula as the primary endpoints. In addition, the results of the main analysis conducted after excluding one case that breached the enrollment rules indicated that the incidence of anastomotic leakage and pancreatic fistula as the primary endpoints was in three in 176 enrolled patients (1.7%); therefore, the upper limit of the 80% confidence interval at 3.6% (p=0.0003) was lower than the threshold of 8% that was initially set up. According to the First Period Monitoring Report of 2008, no treatment-related deaths or other severe (grade 3 or greater) complications occurred, and there were no cases requiring blood transfusions or repeat surgery. Moreover, only one case was converted to open surgery, and the incision for this case was over 6 cm.

2.3.3 Post Treatment

In this study, when only postoperative pathological findings were investigated in cases diagnosed as pStage II, IIIA, IIIB and curability of A or B, the recommended post-treatment was postoperative adjuvant chemotherapy with S-1 (see "6.5. Post-treatment"). S-1 has been established as the standard treatment in Japan because a randomized controlled trial (ACTS-GC) conducted in Japan targeting pStage II (excluding T1N2) in IIIA and IIIB cases that underwent curability surgery proved statistically superior survival in the postoperative S-1 group (n=529) compared to the surgery only group (n=530) (overall survival hazard ratio: 0.68, p=0.002)[42]. In this study, however, we decided to include T1N2 cases in the target of TS-1, considering that N2 cases with poor prognosis should be treated with chemotherapy. Although there is no evidence on the significance of postoperative adjuvant chemotherapy with S-1 for patients between 76 and 80 years old, oral administration is recommended in principle if the medication criteria are met.

2.4 Study Design

2.4.1 Rationale for Setting Endpoints

1) Primary endpoints

Phase II trial:

The safety of laparoscopic-assisted surgery, including D2 dissection of cT1N0, cT1N1 and cT2N0 gastric cancer, has been shown by the results of the JCOG study (JCOG0703) mentioned above, and screening for safety in a single-arm phase II trial at an advanced center for laparoscopic-assisted surgery was considered not to be necessary. However, if advanced gastric cancer is targeted as in this study, the tumor is larger than that in the early-stage gastric cancer, and dissection of lymph nodes is expected to be more difficult, and the possibility of increased intraoperative incidents and postoperative complications cannot be ruled out. Therefore, a randomized phase II/III trial was planned to ensure safety.

The randomized phase II/III trial will be conducted as a preliminary step to conduct a phase III trial for evaluating whether laparoscopic-assisted surgery is significantly inferior to open surgery in terms of the

incidence of anastomotic leakage and pancreatic fistula, which are the primary endpoints. The incidences of anastomotic leakage and pancreatic fistula were selected as the primary endpoints because these complications are considered to be characteristically more common in laparoscopic-assisted surgery than in open surgery and have a significant impact on the patient's life and duration of hospitalization.

In other words, as the range of motion of instruments such as forceps and suturing devices are limited in laparoscopic-assisted surgery, performing anastomosis and suturing is difficult, and an increase in suture failure is a concern. Similarly, the limited range of motion of instruments for dissection, thermal coagulation and ultrasonic coagulation, etc., increases the possibility of damaging the pancreas during surgical operations around the pancreas, which may lead to an increase in pancreatic fistulas. Although anastomotic stenosis is also considered to be more common in laparoscopic-assisted surgery, its occurrence is less likely to impact life. Therefore only the more important complications, anastomotic leakage and pancreatic fistula, were selected as the primary endpoints.

Phase III trial:

If it becomes apparent in the phase II trial of the study that laparoscopic-assisted surgery is a treatment that can be performed safely, then a phase III trial will be conducted to prove the non-inferiority of laparoscopic-assisted surgery compared to open surgery. Relapse free survival time will be the primary endpoint as a surrogate for the incidence and timing of hepatic, peritoneal and lymph node metastases.

Secondary endpoints

(1) Overall survival, (2) Rate of morbidity and mortality, (3) Rate of laparoscopic surgery completion, (4) Rate of conversion to open surgery, (5) Number of retrieved lymph nodes, (6) Early postoperative course (days until flatus, proportion of analgesic use, highest body temperature during the first three days after surgery and while hospitalized) and (7) Form of recurrence were set as the secondary endpoints. (1) is selected as the true endpoint. (2) and (6) are items for evaluating the minimal invasiveness of laparoscopic-assisted surgery. As the same items were set as secondary endpoints in the non-inferiority study (JCOG0404) of laparoscopic-assisted surgery versus open surgery for colorectal cancer, we decided to use these items in this study as well.

Items (3) and (4) are set as the secondary endpoints with a view that if the proportion of conversions of laparoscopic-assisted surgery to open surgery is high, then data obtained in this study cannot be said to be the outcome only of laparoscopic-assisted surgery. Item (5) is set as one of the evaluations of curability, and (7) is set to evaluate the impact of recurrence, which is a concern in laparoscopic-assisted surgery.

2.4.2 Clinical Hypothesis and Rationale for Sample Size Determination

In the phase II trial in this study, the incidence of at least one of the two is determined as a composite endpoint for the incidence of anastomotic leakage and pancreatic fistula, which are set as the primary endpoints. If the percentage is below the rejection threshold, then laparoscopic-assisted surgery is

determined to have good prospects from the safety point of view, and the phase III trial will be conducted. However, if the percentage is not below the rejection threshold, then laparoscopic-assisted surgery is determined not to have good prospects from the safety perspective, and the phase III trial will not be conducted.

On the basis of the results of the questionnaire survey described in 2.2.1. and 2.3.2., we set the expected incidence of at least one of suture failure or pancreatic fistula as 8% and the threshold as 18%. Based on the considerations described in "12.2 Sample size, enrollment and follow-up period", the required number of patients to be enrolled was calculated assuming a one-sided α=0.10 and $\beta \leq 0.20$ (power of 80% or higher). The planned sample size for the laparoscopic-assisted surgery group was set at 90, with an enrollment period of 1.5 years. The planned number of enrollments in both groups was set at a total of 180.

In the phase III of the study, the 5-year relapse free survival rate for the open surgery group is assumed to be 65% based on previous report[43], and it was determined to be clinically unacceptable if the rate falls by 8% or more in the laparoscopic-assisted surgery group. The required number of enrollments was calculated with a one-sided α=0.05, statistical power 75%, an enrollment period of 4 years, and a follow-up period of 5 years (follow-up up to 9 years after the start of the study). Thus, planned sample size in both the open surgery and laparoscopic-assisted surgery groups was set at 500.

<Additions in the first revision>

At the plenary session of the JLSSG0901 advanced gastric cancer randomized controlled trial held on July 19, 2013, a decision was taken to extend the enrollment period by 3.5 years, leaving the planned sample size unchanged at 500 cases as the actual enrollment number was 180 cases, and the planned number of enrollments up to June 2013 was about 400 cases. The extension period was set considering that about eight cases per month can be registered as the number of participating institutions had increased. The end of the study will be five years after completing the protocol treatment of the last enrolled patient, as originally planned.

2.4.3 Patient Enrollment Expectation

According to the survey conducted of the facilities participating in this trial, approximately 300 patients will be eligible for the trial in one year. The projected annual enrollment is 150 patients assuming that the percentage of informed consent (IC) for this study is 50%. The enrollment period is planned to be 1.5 years for Phase II, considering the time required for IRB approval.

If safety is confirmed and the study moves to Phase III, 2.5 years will be scheduled for the remaining enrollment.

2.5 Summary of Expected Advantages and Disadvantages Associated with Trial Participation in the Trial

2.5.1 Expected Advantages

The laparoscopic-assisted gastrectomy performed in this study can be conducted as routine care covered by health insurance. Furthermore, because all medical fees of the participants required during the trial are paid with insurance or by the patient themselves, by participating in this trial, patients will not gain any special treatment or economic benefits compared to routine medical treatment.

2.5.2 Expected Risks and Disadvantages

The disadvantages mentioned in 2.3.2. could form the risks and disadvantages associated with participation in this study. The risk of these adverse events and disadvantages were minimized by including as participating institutions only facilities experienced in laparoscopic-assisted surgery, and procedures were only performed by physicians with sufficient experience in laparoscopic-assisted surgical procedures (see “6.1.1. Physicians in Charge of Surgery”). “4. Patient Selection Criteria” and “6. Treatment Schedule and Criteria for Change in Treatment”, etc., were carefully considered within the group. Routine monitoring twice a year from the start of the trial is required. Whether the incidence of adverse events is within the predicted range will be monitored by the Data Center and Efficacy and Safety Monitoring Committee. If severe or unforeseen adverse events occur, they will be carefully investigated and reviewed.

Regarding medical fees, no advantages or disadvantages related to hospitalization fees should arise as medical fees incurred at participating institutions in this study fall under comprehensive medical care. As the costs associated with laparoscopic-assisted surgery are higher than those for open surgery, overall medical expenses will be higher based on the total NHI points. If the high-cost medical reimbursement system is applicable, there will be no difference in cost between open surgery and laparoscopic-assisted surgery as the patients can claim expenses exceeding the maximum out-of-pocket expense.

2.6 Significance of the Present Trial

Gastric cancer has the highest prevalence of all types of cancer in Japan. With advances in equipment and techniques, minimally invasive laparoscopic-assisted surgery is becoming increasingly popular for early-stage gastric cancer cases. Laparoscopic-assisted surgery has been expanded to include advanced gastric cancer at advanced facilities with laparoscopic-assisted surgery. Because laparoscopic-assisted surgery is technically more difficult for gastric cancer than colorectal cancer, the procedure is not yet recognized as one of the standard treatments. However, considering that laparoscopic-assisted surgery is likely to be introduced gradually in daily clinical practice in the future, conducting a scientific evaluation of the efficacy and safety for laparoscopic-assisted surgery as soon as possible is imperative. Therefore, if we can confirm the safety of laparoscopic-assisted surgery for advanced gastric cancer in this phase II trial and conduct the next phase III trial to verify the procedure’s usefulness, then laparoscopic-assisted

surgery can be offered as a new minimally invasive treatment for patients with advanced gastric cancer.

In addition, if the safety of laparoscopic-assisted surgery is not proven, this treatment cannot be recommended as a routine treatment, taking into consideration the fact that laparoscopy-assisted surgery experts who have cleared certain criteria performed the procedures in this trial. Therefore, this information could be very important as it will warn against the widespread use of laparoscopic-assisted surgery, which is riskier than open surgery.

2.7 Quality Control of Surgical Technique

As this study investigates a surgical technique, quality control of the technique is important. Therefore, "15.1 Central Review of the Validity of Laparoscopic-assisted Surgery" with use of photographs of the operative field and resected specimens, and "15.2 Investigation of Surgical Technique via Video" will be used for quality control of surgical technique. Physicians responsible for surgery will be determined (See "6.1.1.1 Physicians in Charge of Surgery"), and we will strive to further improve the quality of the surgical procedures. The goal is to conduct a high-quality trial with these measures.

2.8 Ancillary Study (Ancillary studies are being planned for this study)

- Evaluation of IC acquisition rate

3. Criteria and definitions used in the present trial

Notations used in this protocol conform to the Japanese Classification of Gastric Carcinoma 13th edition (See 3.3.)[44] and Gastric Cancer Treatment Guidelines in Japan (2nd edition). The Japanese Classification of Gastric Carcinoma 14th edition[45] (see 3.4.) was also used in the items mentioned etc. for CRF and, in such instances, it is mentioned which version has been used.

3.1. Anatomical items

3.1.1. Primary lesion site of gastric cancer

The greater curvature and lesser curvature of the stomach is divided into 3 equal section, with each corresponding point connected to divide the stomach into 3 areas, i.e. the U (upper), M (middle), and L (lower) areas. E (esophageal) and D (duodenal) invasion will also be mentioned. In the event that the lesion extends over two adjacent areas, the main area will be noted first followed by the area where the invasion has spread to.

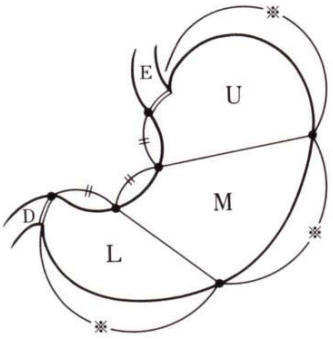


Fig. 3.1.1.Three portions of the stomach

3.2. Macroscopic classification

Basic classification

Type 0: superficial type

Type 1: mass type

Type 2: Ulcerative type

Type 3: Infiltrative ulcerative

Type 4: Diffuse infiltrative type

Type 5: Unclassable (difficult to classify in types 0-4 above)

Subclassification of type 0 (superficial type)

Type I: protruding

Type II: superficial type

IIa: superficial elevated type

IIb: superficial flat type

IIc: superficial depressed type

Type III: excavated type

3.3. Disease staging criteria (Japanese Classification of Gastric Carcinoma, 13th ed.)

3.3.1. Data recording method

Finding categories include T (invasion depth), N (lymph node), H (hepatic metastasis), P (peritoneal metastasis) and M (distal metastasis), which shall all be indicated in capital letters. The extent of each of these findings is to be shown in numerals after the finding category and if unclear place an 'X'. Four types of findings at the time of diagnosis, i.e. clinical findings, surgical findings, pathological findings, and final findings are to be indicated by the small letters c, s, p, and before the finding category. However the small letter 'f' can be omitted for final findings.

3.3.2. Depth of tumor invasion

The depth of tumor invasion is defined as follows.

T1: Tumor invasion of mucosa (M) or submucosa (SM)

T2: Tumor invasion of muscularis propria (MP) or subserosa (SS)

T3: Tumor penetration of serosa (SE)

T4: Tumor invasion of adjacent structures (SI)

TX: unknown

Regardless of the presence or absence of lymph node metastasis, T1 is called 'early stage gastric cancer', and T2-4 is called 'advanced gastric cancer'

3.3.3. Recording metastasis

1) Lymph node metastasis

N0: No evidence of lymph node metastasis

N1: Metastasis to Group 1 lymph nodes, but no metastasis to Groups 2 or 3 lymph nodes

N2: Metastasis to Group 2 lymph nodes, but no metastasis to Group 3 lymph nodes

N3: Metastasis to Group 3 lymph nodes

NX: the extent of lymph node metastasis is unknown

Regional lymph nodes

The regional lymph nodes of the stomach are classified into stations numbered below and in Fig. 3.3.3.

Lymph node number and name (the underlined section is the definition in the Japanese Classification of Gastric Carcinoma, 14th ed.)

No. 1 Right paracardial lymph node

No. 2 Left paracardial lymph node

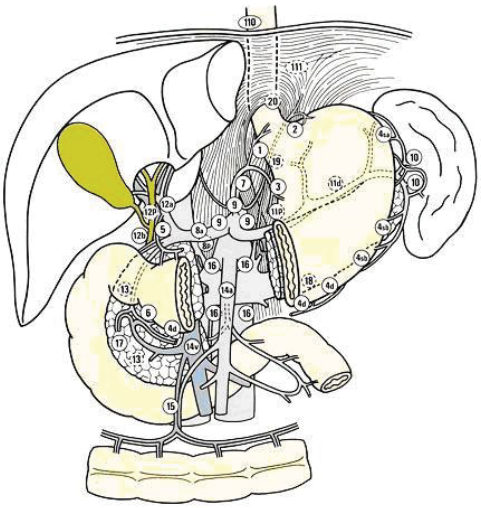
No. 3a Lesser curvature lymph node (along the left gastric artery)

No. 3b Lesser curvature lymph node (along the right gastric artery)

No. 4sa Left greater curvature lymph nodes (along the short gastric artery)

No. 4sb Left greater curvature lymph nodes (along the left gastroepiploic artery)

No. 4d	Right greater curvature lymph nodes (along the right gastroepiploic artery)
No. 5	Suprapyloric lymph nodes
No. 6	Infrapyloric lymph nodes
No. 7	Lymph nodes along the trunk of the left gastric artery
No. 8a	Anterosuperior lymph nodes along the common hepatic artery
No. 8p	Posterior lymph nodes along the common hepatic artery
No. 9	Celiac artery lymph nodes
No. 10	Splenic hilar lymph nodes
No. 11p	Proximal splenic artery lymph nodes
No. 11d	Distal splenic artery lymph nodes
No. 12a	Hepatoduodenal ligament lymph nodes (along the hepatic artery)
No. 12b	Hepatoduodenal ligament lymph nodes (along the bile duct)
No. 12p	Hepatoduodenal ligament lymph nodes (along the portal vein)
No. 13	Lymph nodes on the posterior surface of the pancreatic head
No. 14v	Lymph nodes along the superior mesenteric vein
No. 14a	Lymph nodes along the superior mesenteric artery
No. 15	Lymph nodes along the middle colic vessels
No. 16a1	Abdominal para-aortic lymph nodes, a1
No. 16a2	Abdominal para-aortic lymph nodes a2
No. 16b1	Abdominal para-aortic lymph nodes b1
No. 16b2	Abdominal para-aortic lymph nodes b2



numbers

Lymph node group classification for dissection

In this classification regional lymph nodes were classified into 3 groups based on lymph flow from the tumor location. Accordingly, some regional lymph nodes of the stomach that deviate from the specific area are not included in the group classification, and metastasis to such lymph nodes will be defined as distal metastasis (M).

Table 3.3.3.Lymph node group classification for dissection

site / Lymph node number	LMU/MUL MLU/UML	LD/L	LM/M/ML	MU/UM	U	E+
1	1	2	1	1	1	
2	1	M	3	1	1	
3	1	1	1	1	1	
4sa	1	M	3	1	1	
4sb	1	3	1	1	1	
4d	1	1	1	1	2	
5	1	1	1	1	3	
6	1	1	1	1	3	
7	2	2	2	2	2	
8a	2	2	2	2	2	
8p	3	3	3	3	3	
9	2	2	2	2	2	
10	2	M	3	2	2	
11p	2	2	2	2	2	
11d	2	M	3	2	2	
12a	2	2	2	2	3	
12b/p	3	3	3	3	3	
13	3	3	3	M	M	
14a	M	M	M	M	M	
14v	2	2	3	3	M	
15	M	M	M	M	M	
16a2/b1	3	3	3	3	3	M
16a1/b2	M	M	M	M	M	M

2) Liver metastasis

H0: No liver metastasis

H1: Liver metastasis

HX: Unknown

3) Peritoneal metastasis

P0: No peritoneal metastasis

P1: Peritoneal metastasis

PX: Unknown

4) Peritoneal cytology

CY0: Benign / indeterminate cells on peritoneal cytology

CY1: Cancer cells on peritoneal cytology

CYX: Peritoneal cytology was not performed

5) Other distant metastasis

M0: No other distant metastases, (although peritoneal, liver, or cytological metastases may be present)

M1: Distant metastases other than the peritoneal, liver, or cytological metastases

MX: Unknown

The category M1 should be specified according to the following notations.

Lymph nodes (LYM), skin (SKI), lungs (PUL), bone marrow (MAR), bone (OSS), pleura (PLE), brain (BRA), meninx (MEN), and other (OTH)

3.3.4. Stage

Table 3.3.4. Stage grouping

	N0	N1	N2	N3
T1	IA	IB	II	IV
T2	IB	II	IIIA	IV
T3	II	IIIA	IIIB	IV
T4	IIIA	IIIB	IV	IV
H1,P1,CY1,M1 (regardless of T)	IV	IV	IV	IV

3.4. Staging criteria (Japanese Classification of Gastric Carcinoma, 14th ed.)

3.4.1. Data recording method

Finding categories include T (invasion depth), N (lymph node), H (hepatic metastasis), P (peritoneal metastasis) and M (distal metastasis), which shall all be indicated in capital letters. The extent of each of these findings is to be shown in numerals after the finding category and if unclear place an 'X'. Two types of findings at the time of diagnosis, i.e. clinical classification, pathological classification are to be indicated by the small letters c and p before the finding category. Any data without a prefix indicates clinical classification.

3.4.2. Depth of tumor invasion

The depth of tumor invasion is defined as follows.

T1: Tumor confined to the confined to the mucosa (M) or submucosa (SM)

T1a-M: Tumor confined to the mucosa

T1b-SM: Tumor confined to the submucosa (SM)

T2-MP: Tumor invades the muscularis propria (MP)

T3-SS: Tumor invades the subserosa (SS)

T4: Tumor invasion is contiguous to or exposed beyond the serosa (SE) or tumor invades adjacent structures (SI)

T4a-SE: Tumor invasion is contiguous to the serosa or penetrates the serosa and is exposed to the peritoneal cavity (SE)

T4b-SI: Tumor invades adjacent structures (SI).

TX: Unknown

Regardless of the presence or absence of lymph node metastasis, T1 is called 'early stage gastric cancer', and T2-4 is called 'advanced gastric cancer'

3.4.3. Recording of metastasis

1) Lymph node metastasis

N0: No regional lymph node metastasis

N1: Metastasis in 1-2 regional lymph nodes

N2: Metastasis in 3-6 regional lymph nodes

N3: Metastasis in 7 or more regional lymph nodes

N3a: Metastasis in 7-15 regional lymph nodes

N3b: Metastasis in 16 or more regional lymph nodes

NX: Regional lymph nodes cannot be assessed

Regional lymph nodes: In the Japanese Classification of Gastric Carcinoma, 13th ed., lymph nodes No. 1-12 are defined as regional lymph nodes of the stomach. All lymph node metastasis other than in these regional lymph nodes of the stomach will be defined as M1. However in the event of esophageal invasive cancer, lymph nodes No. 19, 20, 110, and 111 will be considered regional lymph nodes.

2) Hepatic metastasis

H0: No hepatic metastasis

H1: Hepatic metastasis

HX: Hepatic metastasis is unknown

3) Peritoneal metastasis

P0: No peritoneal metastasis

P1: Peritoneal metastasis

PX: Peritoneal metastasis is unknown

4) Peritoneal cytology

CY0: Peritoneal cytology negative for carcinoma cells

CY1: Peritoneal cytology positive for carcinoma cells

CYX: Peritoneal cytology not performed

5) Distant metastasis

M0: No distant metastasis

M1: Distant metastasis

MX: Distant metastasis status unknown

Previously, distal metastasis was defined as 'hepatic metastasis, peritoneal metastasis, and metastasis excluding positive peritoneal cytology', however in the 14th ed., all metastasis other in regional lymph nodes is defined as M1.

In the event of M1 the site must be recorded. The sites are listed below.

Peritoneum (PER), liver (HEP), lymph nodes (LYM), skin (SKI), lungs (PUL), bone marrow (MAR), bone (OSS), pleura (PLE), brain(BRA), meninx (MEN), adrenal (ADR), and other (OTH).

3.4.4. Stage: Japanese Classification of Gastric Carcinoma 14th edition

Table 3.2.4. Stage grouping

	N0	N1	N2	N3
T1a-M, T1b-SM	IA	IB	IIA	IIB
T2-MP	IB	IIA	IIB	IIIA
T3-SS	IIA	IIB	IIIA	IIIB
T4a-SE	IIB	IIIA	IIIB	IIIC
T4b-SI	IIIB	IIIB	IIIC	IIIC
H1,P1,VY1,M1(unrelated to T).	IV	IV	IV	IV

3.5. Histological classification (Japanese Classification of Gastric Carcinoma. 13th ed.)

The shaded types are included in the present trial.

Common type

Papillary adenocarcinoma (pap)

Tubular adenocarcinoma (tub)

- Well differentiated type (tub1)
- Moderately differentiated type (tub2)

Poorly differentiated adenocarcinoma (por)

- Solid type (por1)
- Non-solid type (por2)

Signet-ring cell carcinoma (sig)

Mucinous adenocarcinoma (muc)

Special type

Adenosquamous carcinoma

Squamous cell carcinoma

Carcinoid tumor

Miscellaneous carcinomas

3.6. Definition of lymph node dissection (Japanese Gastric Cancer Treatment Guidelines, 3rd ed.)

The systematic extent of lymph node dissection is determined according to the type of gastrectomy.

1) Total gastrectomy

D0 : Less than D1 dissection

D1 : No. 1～7

D1+ : D1 ＋ No.8a、9、11p

D2 : D1 ＋ No.8a、9、10、11p、11d、12a

D2+ : Extended dissection exceeding D2

However in esophageal invasive cancer, No.110 will be additionally removed in D1, and nodes N0. 19, 20, 110, and 111 will be removed in D2.

2) Distal gastrectomy

D0 : Less than D1 dissection

D1 : No. 1、3、4sb、4d、 5、6、7

D1+ : D1 ＋ No.8a、9

D2 : D1 ＋ No.8a、9、11p、12a

D2+ : Extended dissection exceeding D2

3) Pylorus preserving gastrectomy

D0 : Less than D1 dissection

D1 : No. 1、3、4sb、4d、6、7

D1+ : D1 ＋ No.8a、9

4) Proximal gastrectomy

D0 : Less than D1 dissection

D1 : No. 1、2、3a、4sa、4sb、7

D1+ : D1 ＋ No.8a、9、11p

However in esophageal invasive cancer, No.110 will be additionally removed in D1.

3.7. Evaluation after resection (Japanese Classification of Gastric Carcinoma, 14th ed.)

3.7.1. Surgical specimen resection margin

1) Proximal margin (PM)

PMX: Involvement of the proximal margin cannot beassessed

PM0: No involvement of the proximal margin

PM1: Involvement of the proximal margin

2) Distal margin (DM)

DMX: Involvement of the distal margin cannot be assessed

DM0: No involvement of the distal margin

DM1: Involvement of the distal margin

3.7.2. Extent of lymph node dissection

D0: No dissection or incomplete dissection of the Group 1 nodes

D1: Dissection of all the Group 1 nodes

D2: Dissection of all the Group 1 and Group 2 nodes

D3: Dissection of all the Group 1and Group 2 and Group 3 nodes

3.7.3. Evaluation of curability

Table 3.7.3. shows evaluation of the surgical and overall curability for resection including the primary lesion.

Table 3.7.3. Curative potential of gastric resection

Surgical/overall	T	N・D	H	P	M	PM・DM
Curability A	T1 or T2	N0/D1 or greater or N1/D2 or greater	H0	P0	M0	No cancer invasion within 10 mm of the resection stump
Curability B	No residual disease but not fulfilling criteria for “Curability A”					
Curability C	Definite residual disease					

3.7.4. Residual tumor (Japanese Classification of Gastric Carcinoma, 14th ed.)

The presence or absence of residual tumor after surgery is described as the R status. R0 is a curative resection with negative resection margins; R1 andR2 are non-curative resections.

RX: Presence of residual tumor cannot be assessed

R0: No residual tumor

R1: Microscopic residual tumor (positive resection margin or positive peritoneal cytology)

R2: Macroscopic residual tumor

4. Patient selection criteria

Patients are eligible for enrollment if they meet all of the following eligibility criteria and do not meet any of the exclusion criteria. Staging and histological type classification etc. are in accordance with the Japanese Classification of Gastric Carcinoma (13th edition).

4.1. Eligibility criteria (inclusion criteria)

1) Histologically diagnosed with gastric cancer (general type: pap, tub1, tub2, por1, por2, sig or muc) via an endoscopic biopsy from a primary gastric lesion.
2) MP, SS, or SE without involvement of other organs, N0–2, excluding bulky N2, and M0 according to the Japanese Classification of Gastric Carcinoma (the 13th edition) based on endoscopic testing and contrast-enhanced CT scanning of the upper abdominal region (slice thickness <1 cm. Plain CT also possible if allergic to contrast medium).
3) Endoscopic testing shows the location of the tumor to be either M, L, ML or LM and curative resection with distal gastrectomy is expected to be achievable. Simultaneous multiple carcinomas is allowed if within the resection range.
4) No invasion of the duodenum.
5) Aged 20–80 years on the enrollment day.
8) PS (ECOG) of 0 or 1.
9) BMI of below 30. (BMI = weight (kg) / height $(m)^2$)
10) No history of upper abdominal surgery or surgery accompanied by intestinal resection (including the stomach). However, appendectomy for appendicitis is not included within the scope of intestinal resection.
11) No history of chemotherapy (including endocrine therapy) or radiation therapy including treatment for other cancers.
12) Most recent test values within 56 days prior to registration (same day of the week 8 weeks before registration day allowed) meet all of the following conditions.
    (1) White blood cell count≧3,000/mm3
    (2) Platelet count≧100,000/mm3
    (3) AST≦100 IU/L
    (4) ALT≦100 IU/L
    (5) Total bilirubin≦2.0 mg/dL
    (6) Creatinine≦1.5 mg/dL
13) Written consent from the patient to participate in the study.

4.2. Exclusion criteria

1) Active multiple cancer (synchronous multiple cancers and metachronous multiple cancers with a disease-free interval of less than 5 years. However carcinoma in situ (intraepithelial carcinoma) cured by local therapy and

lesions equivalent to intramucosal carcinoma will not be included in active multiple cancer).

2) Infection that requires systemic treatment.
3) Fever of 38℃ or greater.
4) Pregnant, possibly pregnant, or breast feeding women.
5) Patients for whom participation in this trial was deemed difficult because of complications of mental illness or psychiatric symptoms.
6) Continuous systemic steroid therapy (oral or intravenous).
7) Presence of unstable angina (recent onset or exacerbation of attacks of less than 3 weeks), and a history of myocardial infarction of less than 6 months.
8) Poorly controlled hypertension.
9) Poorly controlled diabetes, or undergoing treatment of continues insulin use.
10) Presence of respiratory disease that requires continuous oxygen therapy.

5. Enrollment/ randomization

5.1. Procedure for enrollment

Once it has been confirmed that the target patient satisfies all the inclusion criteria and does not fall under any of the exclusion criteria, fill out all the necessary items on the enrollment confirmation form and either fax the form to the Data Center or contact them by telephone.

Contact and reception hours for primary enrollment

Data Center

For queries regarding the patient selection criteria

Tsuyoshi Etoh of Department of Gastroenterological and Pediatric Surgery
Oita University Faculty of Medicine
Hasama-machi, idaigaoka 1-1, Yufu city, Oita 879-5593, Japan
Fax: 81-97-549-6039, Tel: 81-97-586-5843,
E-mail: teto@oita-u.ac.jp

5.1.1. Important notes regarding enrollment

1) Precautions for telephone, fax

i) Without exception, enrollments will not be permitted after the start of the protocol treatment.

ii) Excluding the withdrawal of consent, patients who have been enrolled, including those who refuse the use of their data in this trial, will not be removed from the trial (erased from the database). In the event of double registration, enrollment data (registration number) from the first enrollment will be used.

iii) In the event that misregistration or double enrollment is discovered, the Data Center should be contacted as soon as possible.

2) In the event of telephone and fax enrollments

i) When enrolling by telephone, an enrollment eligibility confirmation form should be sent to the Data Center within 2 days of enrollment (by mail, fax, or in person).

ii) If the enrollment eligibility confirmation form is incomplete, the enrollment will not be accepted until it is completed.

iii) After the Data Center confirms eligibility, a registration number will be issued. Enrollment will be completed on notification of the registration number by telephone, or confirmation by fax for fax enrollments.

iv) After completion of enrollment, the Data Center will fax an 'enrollment confirmation notification' to the institutional coordinator to be kept on file.

i) Web enrollments are made by accessing the URL noted in 5.1 'contact and reception hours for primary enrollment (preoperative)'.

ii) Web enrollments do not require an enrollment eligibility confirmation form to be sent to the Data Center.

iii) If the input data is incomplete, the enrollment will not be accepted until it is completed.

iv) After confirming eligibility on the enrollment screen, enrollment will be completed on issue of a registration number.

v) After completion of enrollment, an 'enrollment confirmation notification' and CRF will be sent by post to the institutional coordinator to be kept on file.

5.2. Randomization and balancing factors

Treatment groups will be randomly assigned by the data center at registration.

A minimization method will be used with balancing factors for (1) institution, (2) depth of tumor invasion (MP, SS or SE according to the 13th Japanese classification system) and degree of lymph node metastasis (N0 or N1 or N2) so that large biases do not emerge in these factors during randomization. Researchers at the participating institutions will not be informed of the details of the methods for randomization.

6. Treatment schedule and criteria for change in treatment

Treatment and changes in treatment will proceed as outlined in this section while doing the utmost to preserve the safety of patients.

Treatment may be changed as per the medical judgement of the attending physician when he/she determines that there is medical risk to following the protocol. This results in “deviation of protocol.” Cases will be treated as “clinically appropriate deviation” when this deviation is deemed medically appropriate (refer to ‘14.1.3 Deviation from and violation of protocol’). Deviation to attempt to increase efficacy will not be treated as “clinically appropriate deviation.”

6.1. Protocol treatment

Protocol treatment in this study is laparoscopy-assisted or open distal gastrectomy with lymph node dissection (D2) in accordance with the Gastric Cancer Treatment Guidelines in Japan (3rd edition for physicians).

If, for some reason, the date of surgery is 29 days or more after enrollment, this reason must be stated on the pre-treatment report sheet. If exacerbation of clinical test results etc. is observed after enrolment before the date of surgery, the physician in charge determines whether or not to perform surgery. If surgery is performed, the physician records the details in the “pre-treatment report sheet” and if surgery is canceled, the physician states the details behind the decision in the “treatment conclusion report sheet.”

6.1.1. credentialed surgeon

The principal investigator designates the physicians in charge of open surgery and laparoscopy-assisted surgery at each participating facility in accordance with the following rules.

1)credentialed surgeon of open surgery

Has performed at least 50 open gastrectomies.

Those applying for practitioner certification have received practitioner certification from the principal investigator (study coordinator) before sending the IRB approval certificate to the data center. Those applying for practitioner certification should contact the principal investigator rather than the data center.

2) credentialed surgeon of laparoscopy-assisted surgery

Surgeons with experience performing at least 20 procedures each of laparoscopy-assisted and holding certification by Endoscopic Surgical Skill Qualification System of the Japan Society for Endoscopic Surgery.

Group A: Open gastrectomy

Perform open gastrectomy in accordance with the Gastric Cancer Treatment Guidelines in Japan (3rd edition for physicians).

1) Surgeon

The credentialed surgeon of open surgery performs the procedure as either the surgeon or teaching assistant.

2) Surgery rules

(1) Intraperitoneal investigation and intraoperative pathological diagnosis

- Conduct intraperitoneal investigation directly after starting surgery (presence or absence of liver

metastasis, peritoneal metastasis etc.).

- Perform intraoperative biopsy or intraperitoneal lavage cytology if necessary.
- If diagnosed as sStage IV intraoperatively, protocol treatment is discontinued. The decision regarding whether or not to perform resection of the primary gastric lesion or metastatic lesion is left up to the physician in charge.

(2) Gastrectomy

- Perform gastrectomy when distant metastasis or invasion to other organs is not observed.

(3) Lymph node dissection and major artery treatment

- Perform distal gastrectomy with D2 lymph node dissection in accordance with the Gastric Cancer Treatment Guidelines in Japan (3rd edition for physicians).

(4) There are no stipulations regarding preservation of the greater omentum or the omental bursa

(5) The method of reconstruction is not prescribed.

(6) Combined surgery

In addition to the protocol treatment of gastrectomy, the following surgical procedures may be performed in combination. For all of these procedures, surgery time, blood loss and complications will be included with those for gastric cancer surgery.

- Cholecystectomy for benign diseases of the gallbladder that are not suspected to be cancer (gallstones, gallbladder polyps etc.)
- Surgery for inguinal hernia with an intraperitoneal approach (hernia orifice reefing, mesh method)
- Minor surgery for benign disease of the body surface (hernioplasty, lipoma resection etc.)

3) Photography

Pictures are taken for open surgery.

6.1.2. Group B: Laparoscopy-assisted gastrectomy

1) Surgeon

The credentialed surgeon of laparoscopic surgery performs the procedure as either the surgeon or teaching assistant.

2) Laparoscopy-assisted operation

(1) Pneumoperitoneum

Gastrectomy is performed using a laparoscope with carbon dioxide pneumoperitoneum. Surgery is not performed with the lifting method[*1].

*1: Method of surgery in which specialized tools are used to lift up the small abdominal incision and the operation is performed in the created intraperitoneal space.

(2) Skin incision

- Port location, number of ports, type of ports and small abdominal incision are not prescribed.
- There is only one small abdominal incision and the skin incision should be ≤7 cm.
- If the small abdominal incision is larger than 7 cm, a judgment should always be made by the credentialed surgeon and the reason should be recorded in the medical records and CRF.

(3) Site of surgical operation

- “Intraperitoneal examination” should always be performed with laparoscopic assistance.
- “Lymph node dissection and major artery treatment” and “combined surgery” should, as a general rule, always be performed with laparoscopic assistance. Parts of these surgical operations may be performed from a small abdominal incision of ≤7 cm. “Gastrectomy and treatment of bordering vessels” and “reconstruction” may be performed either with “laparoscopic assistance” or “from a small abdominal incision of ≤7 cm.”
- Surgical operations refer to operations included in “3) Surgery rules.”

(4) Other

- If the credentialed surgeon determines that intraoperative complications or similar have made hand-assisted laparoscopic surgery (HALS; method of surgical operation in which the hand is inserted from the small abdominal incision) necessary, HALS may be performed. However, HALS may not be planned to be performed as part of the surgical procedure preoperatively. If HALS is performed, the details must be recorded in the medical records (or surgery notes) and CRF. If the HALS small abdominal incision is 6 cm or larger, the procedure is considered conversion to open surgery.
- Procedures such as so-called “sliding window method”[*2] and “moving window method”[*2] shall not be performed.
- *2 Using specialized tools to pull and move the small abdominal incision before performing surgery.

6.1.3. Consultations regarding protocol treatment

If there are any questions regarding protocol treatment, contact the study coordinator.

Study coordinator contact: Tsuyoshi Etoh

Department of Gastroenterological and Pediatric Surgery
Oita University Faculty of Medicine
Hasama-machi, idaigaoka 1-1, Yufu city, Oita 879-5593, Japan
Fax: 81-97-549-6039, Tel: 81-97-586-5843,
E-mail: teto@oita-u.ac.jp

6.1.4. Perioperative management

There are no particular rules regarding the use of postoperative analgesics until four days postoperatively. However, from postoperative day five onward, they should not be used regularly; only if the use of analgesics is clinically determined to be in the patient’s best interests. Timing, methods and type of antibiotics to prevent infection, perioperative fluid transfusions and nutritional management, methods of wound and drain management and timing and methods for restarting eating meals postoperatively are not subject to any particular rules. However, at the same facility, the same perioperative management should be given to both groups in accordance with the rules of that particular facility.

6.2. Photography for central review regarding investigation of the validity of distal gastrectomy with D2 lymph node dissection

To confirm whether laparoscopy-assisted distal gastrectomy or open distal gastrectomy with D2 lymph node

dissection is being accurately performed by central review, the surgical field, small abdominal incision and resected gastric samples will be photographed.

1) Photography timing and site

Photography will be performed with a digital camera or digital video camera. Examples of actual photographs of surgical field, small abdominal incision and resected specimens will be exhibited (Fig. 6.5.a.–g.).

(1) Pre-reconstruction: Surgical field

- Infrapyloric lymph node dissection site (at least one photograph)

  Photograph the right gastroepiploic blood vessel base (resected site) to portray the extent of infrapyloric lymph node dissection. If the infrapyloric vessels have been preserved, photographs are taken so as to portray the operated sites of each vessel.

- Pancreatic superior border lymph node dissection site (at least two photographs)

  Photographs of the left gastric artery stump area after performing lymph node dissection around the left gastric artery (#7). One photograph of the common hepatic artery side of the stump and one photograph of the splenic artery side of the stump so as to portray the extent of lymph node dissection around the celiac artery.

- Superior mesenteric vein area (at least one photograph): Only if the lesion occupies L and D2 dissection is performed

  Only photograph if superior mesenteric vein lymph node (#14v) dissection is performed.

- Hepatoduodenal ligament (at least one photograph):

  Only photograph when lymph node (#12a) dissection performed along the hepatic artery of the hepatoduodenal ligament. Take photograph so as to portray operated site of the right hepatic artery.

(2) During laparotomy closure: Small abdominal incision (at least one photograph)

Photograph small abdominal incision with a ruler. A metal ruler is not recommended as it reflects the flash of the camera.

(3) Upon conclusion of surgery: Resected gastric specimen (at least one photograph)

Photograph the entire resected specimen from the intragastric cavity side so as to portray the distance from the margin of the tumor to the proximal and distal sides of the gastric resection stump.

2) Settings for image file names

File identification information will be set as each image file name in the following manner. All images will be stored in JPG format.

3) Sending image files

Image files will be sent via electronic mail to the Study Coordinator from the Site Coordinator within four weeks after surgery.

(Addressee) Study Coordinator:

Tsuyoshi Etoh E-mail: teto@oita-u.ac.jp

Figure. 6.5.a.Infrapyloric lymph node dissection site

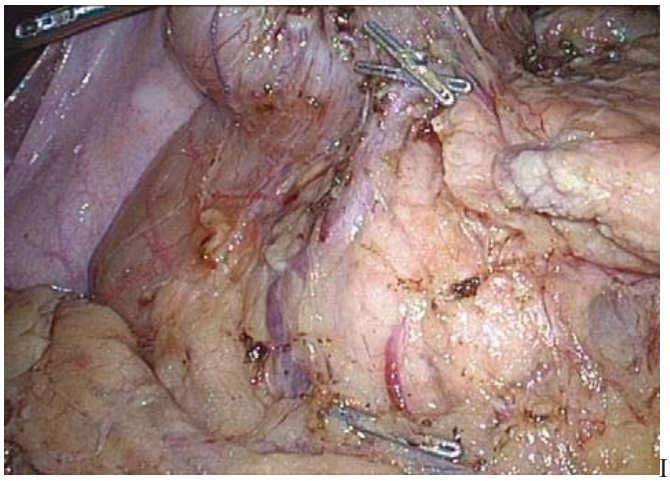

I

Figure 6.5.b. Pancreatic superior border lymph node dissection site (common hepatic artery side)

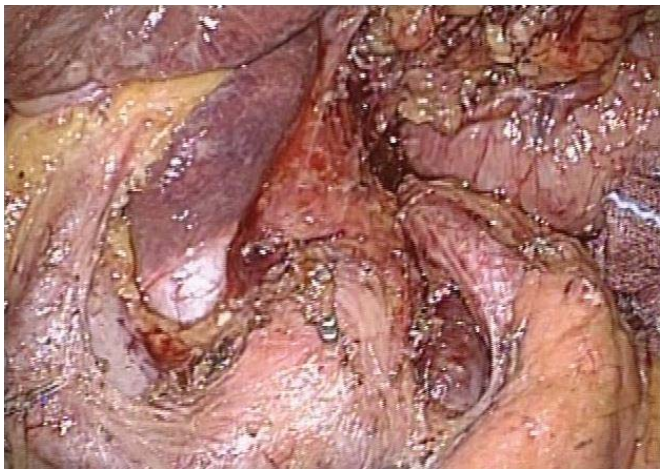


Figure 6.5.c. Pancreatic superior border lymph node dissection site (splenic artery side)

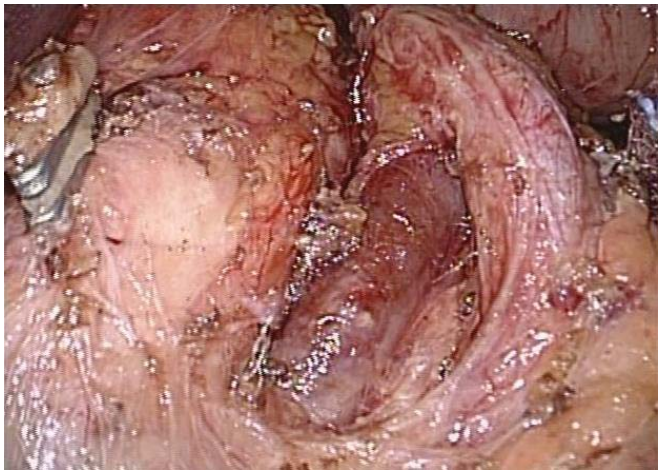


Figure 6.5.d. Superior mesenteric vein area lymph node dissection site

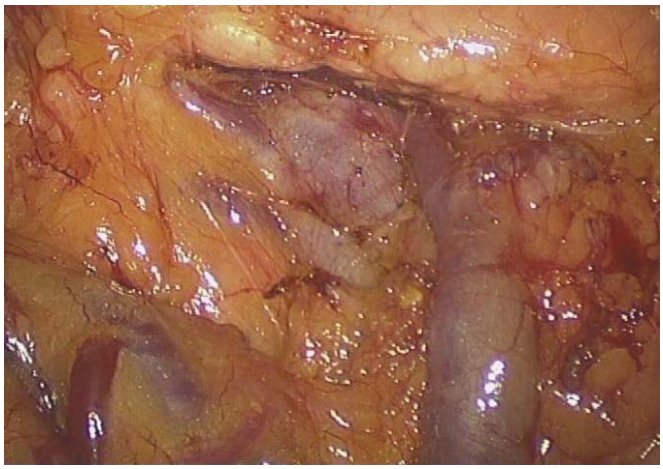


Figure 6.5.e. Hepatoduodenal ligament lymph node dissection site

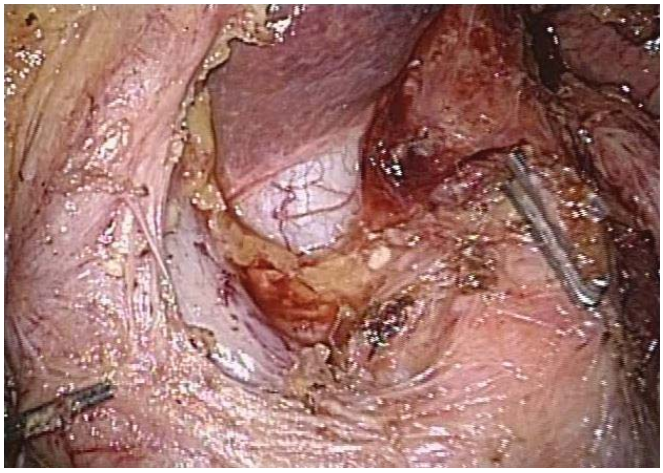


Figure 6.5.f. Small abdominal incisions

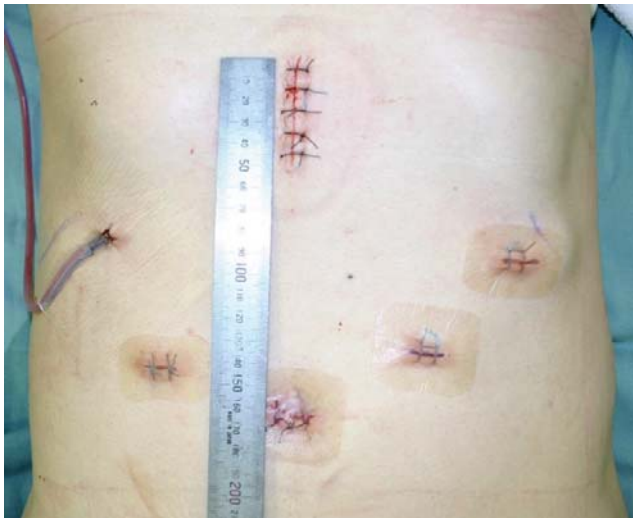
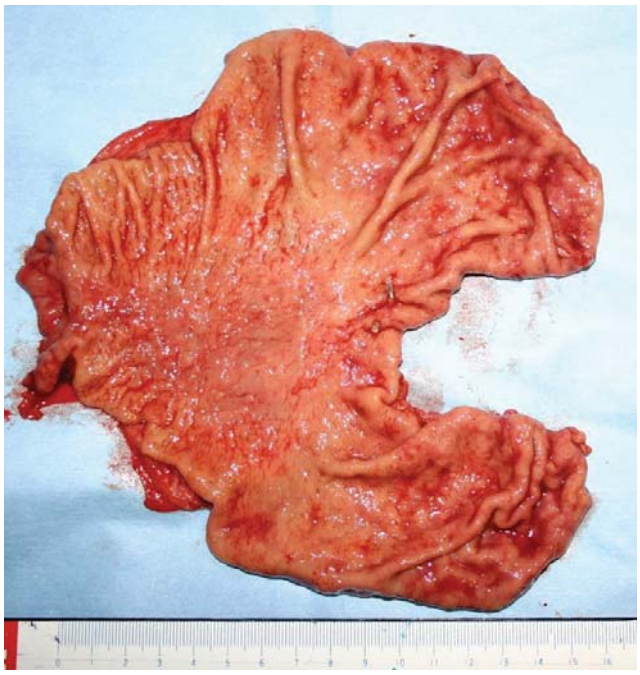


Figure 6.5.g. Resected gastric specimen



6.3. Completion and termination criteria of protocol treatment

6.3.1. Definition of protocol treatment completion

Protocol treatment is considered completed when the surgery designated as the protocol treatment (including both open gastrectomy and laparoscopy-assisted gastrectomy) is concluded. Conclusion of surgery is considered to be when the abdominal incision has been closed.

6.3.2. Termination criteria of protocol treatment

Protocol is terminated if any of the following situations occur.

1) Protocol treatment is determined as ineffective due to one of the following.
   - Diagnosed as sStage IV based on intraoperative findings
   - Conversion to total gastrectomy
   - Direct in invasion to other organs
2) Protocol treatment unable to be continued due to an adverse event
   - Continuation of surgery in accordance with protocol made difficult by intraoperative complications
3) The patient asks to terminate protocol treatment due to a reason that could be related to an adverse event
4) The patient asks to terminate protocol treatment due to a reason that is not related to an adverse event
   - This classification only includes cases that are clearly unrelated to adverse events such as

relocation of the patient or their family.

5) Death during protocol treatment
   - Death due to another reason before protocol treatment termination

6) Reasons such as other exacerbation after enrollment before starting treatment (protocol treatment could not be started due to sudden exacerbation), protocol violation ascertained, ineligibility ascertained and treatment changed due to new diagnostic imaging findings or a change in pathological diagnosis after enrollment

The day of termination of protocol treatment is the day of surgery for 1) and 2), the date of death for 5) and the day that protocol discontinuation was determined in the case of other reasons.

6.4. Combination therapy and supportive therapy

6.4.1. Surgical combination therapy and supportive therapy

Rules regarding combination and supportive therapy are not prescribed. Rather, these are to be performed in accordance with the policies of each individual facility. However, intraoperative and directly postoperative administration of heparin and preventive treatments such as leg massage are recommended for patients at a high risk for pulmonary infarction such as elderly and obese patients and smokers. At the same facility, the same combination and supportive therapy should be given to both groups in accordance with the rules of that particular facility.

6.5. Posttreatment

Treatment after completion of the protocol treatment will be performed in accordance with postoperative pathological findings and will conform to the following rules. There are no particular rules regarding recurrence following completion of the protocol treatment or posttreatment after discontinuation of the protocol treatment.

1) If pStage IA, IB, II (T1N2) and curability of A, B

   Regular follow-up observations with no treatment.

2) If pStage II (excluding T1N2), IIIA or IIIB and curability of A or B

   It is recommended to start postoperative S-1 chemotherapy with a dosage regiment within six weeks after gastrectomy and continue this for one year postoperatively. Use of agents other than S-1 is not allowed. Even if postoperative adjuvant chemotherapy is not performed, this is not considered a deviation from protocol.

3) If pStage IV or curability C

   Posttreatment may be freely determined.

<u>S-1 dosage and method of administration</u>

One course involves 28 days of continuous administration of S-1, followed by a 14-day washout period. This is conducted for one year following surgery (eight courses: 48 weeks).

S-1 dosage	Method of administration	Dosage days	Washout days
80-120 mg/body	Oral administration twice per day	Day 1-28	Day 29-42

S-1 dosage is determined as follows.

Body surface	S-1 dosage
<1.25 m^2	80 mg/day (20 mg x 4 cap)
≥1.25 m^2, <1.50 m^2	100 mg/day (25 mg x 4 cap)
≥1.50 m^2	120 mg/day (20 mg x 6 cap)

S-1 administration is divided throughout the day in the following manner.

S-1 dosage	After breakfast	After dinner

Usage and dosage may be changed or administration discontinued using the following as a reference if an adverse event occurs.

Level	Usage	One course	Dosage days	Washout days
Level 0	120 100 80	42 days	Day 1-28	Day 29-42
Level -1	100 80 50	42 days	Day 1-28	Day 29-42
Level -2	100 80 50	42 days	Day 1-14 Day 22-35	Day 15-21 Day 36-42

If one of the treatment groups is determined to be better in either the main or interim analysis, the trial results will be explained and what appears to be the best treatment method will be provided based on a consideration of the patient's individual treatment history.

If a case meets the criteria for protocol treatment discontinuation but is clinically determined as eligible for "protocol treatment continuation," as a rule (as time permits), the decision will not be made by the physician in charge; rather a consultation will be held with the study coordinator through the facility staff member responsible for research or facility coordinator. An agreement will be reached between the study coordinator and facility staff member responsible for research or facility coordinator regarding whether to implement "protocol treatment discontinuation → treatment as posttreatment" or "dropout from study and continue protocol treatment." Consultations and the decision-making process with the study coordinator will involve writing a treatment conclusion report for the said patient or recording in detail a progress record sheet. Moreover, if there are many cases of "dropout from study and continue protocol treatment," suggesting that the criteria for protocol treatment discontinuation may be clinically inappropriate, the study coordinator will use a group meeting or the group mailing list to review the criteria for protocol treatment discontinuation.

7. Expected adverse reactions

Assessments in the present trial will be performed using CTCAE v4.0.

7.1. Expected adverse reactions

The following adverse reactions are expected in the present trial.

7.1.1. Expected adverse reactions to surgical resection and surgical complications

CTCAE v4.0 Term

Underlined terms are adverse reactions or surgical complications that are foreseeable for Group B (laparoscopy-assisted gastrectomy group) only

1) Expected adverse reactions during surgery

Intraoperative bleeding, thromboembolism, myocardial infarction, supraventricular tachycardia, atrial fibrillation, atrial flutter, ventricular arrhythmia, cerebral ischemia, fever, hypothermia, esophageal hemorrhage, gastric hemorrhage, duodenal hemorrhage, hepatobiliary injury, spleen injury, endocrine system impairment, gastrointestinal disorders, arterial injury, venous injury, nervous system injury, other injuries/toxicities and procedural complications (peritoneum, and lymph ducts), peripheral neuropathy, and allergic reactions.

2) Expected adverse events early after surgery (until first hospital discharge)

(1) Expected adverse events cause by postoperative hemorrhage

(2) Esophageal hemorrhage, gastric hemorrhage, duodenal hemorrhage, hypotension, hyperkalemia, dehydration, and hemoglobin

- Expected adverse events caused by postoperative pancreatitis/pancreatic fistula

(3) Pancreatitis, pancreatic fistula, peritoneal abscess, disseminated intravascular coagulation. Pancreatic hemorrhage, intraperitoneal hemorrhage

- Expected adverse events caused by general anesthesia

(4) Allergic reaction, and voice abnormality

- General expected adverse events early after surgery

  Fatigue, fever, chills, excess sweating, hypothermia, lethargy, nausea, vomiting, loss of appetite, diarrhea, stomach pains, colitis, cholecystitis, biliary infection, salivary gland infection, inflammatory phlebitis, catheter-related infection, bladder infection, kidney infection, urinary tract infection, ileus, jejunal obstruction, ileal obstruction, large bowel obstruction, small bowel obstruction, suture failure, gastric anastomotic leakage, gastrointestinal anastomotic leakage (leakage in the region of esophageal anastomosis, esophageal stenosis, gastric stenosis, duodenal stenosis, jejunal stenosis, ileal stenosis, colonic stenosis, other gastrointestinal disorder (dumping syndrome), <u>cutaneous and subcutaneous disorder (subcutaneous emphysema)</u>, biliary fistula, gastric fistula, duodenal fistula, jejunal fistula, ileal fistula, colonic fistula, pancreatic fistula, esophageal necrosis, gastric necrosis, ileal ulcer, jejunal ulcer, colonic ulcer, esophageal perforation, gastric perforation, duodenal perforation, jejunal perforation, ileal perforation, colonic perforation, pleural infection (empyema), abdominal infection, wound infection, wound complications, ascites, lymphorrhea (chylous ascites), pleural effusion, other nervous system

disorders (phrenic nerve injury), urinary retention, pulmonary infection, atelectasis, pneumothorax, hypoxemia, hiccups, increased aspartate aminotransferase, increased alanine aminotransferase, increased serum amylase, increased alkaline phosphatase, increased creatinine, hypernatremia, hyponatremia, hyperglycemia, hypoalbuminemia, delirium, thromboembolism, myocardial infarction, supraventricular tachycardia, atrial fibrillation, atrial flutter, ventricular arrhythmia, cerebral ischemia, other gastrointestinal disorders (delayed gastric emptying), wound dehiscence, infection-related enterocolitis, abdominal infection, septicemia, depression, spleen infection, liver infection, other injuries/poisoning and procedural complications (hepatic infarction, liver abscess, splenic infarction, and splenic abscess)

3) Expected complications late after surgery (after the first hospital discharge)

(1) Expected complications with the surgical wound

- Skin induration, wound dehiscence, wound complications, and wound infection.

(2) Expected complications in gastrectomy

- Dysgeusia, constipation, diarrhea, abdominal pain, weight loss, anemia, esophagitis, esophageal stenosis, small intestinal stenosis, and colonic stenosis.

(3) General expected complications late after surgery

Pulmonary infection, other gastrointestinal disorders (dumping syndrome), other gastrointestinal injuries (delayed gastric emptying), gastric anastomotic leak, upper gastrointestinal hemorrhage,jejunal obstruction, ileal obstruction, colonic obstruction, esophageal stenosis, gastric stenosis, duodenal stenosis, jejunal stenosis, ileal stenosis, colonic stenosis, ileus, swelling of the limbs, swelling of the trunk, cholecystitis, gall bladder infection, biliary infection, anemia, osteoporosis, infection-related enterocolitis, abdominal infection, septicemia, loss of appetite, depression, splenic infection, liver infection, other injuries/poisoning and procedural complications (hepatic infarction, liver abscess, splenic infarction, splenic abscess).

Underlined terms are adverse reactions or surgical complications that are foreseeable for Group B (laparoscopy-assisted gastrectomy group) only

7.1.2. Expected adverse reactions to deterioration of the underlying disease

Adverse events expected in form of exacerbation of the underlying disease shall be described using the terminology in the CTCAE v4.0. Note that such adverse events are ‘expected’ only when an applicable form of exacerbation is observed.

1) Expected adverse events caused by the primary lesion or lesions from peritoneal dissemination

Loss of appetite, constipation, bloating, indigestion, nausea, gastric obstruction, gastric stenosis, gastric perforation, gastric hemorrhage, duodenal obstruction, duodenal stenosis, duodenal perforation, duodenal hemorrhage, jejunal obstruction, jejunal stenosis, jejunal perforation, jejunal hemorrhage, ileal obstruction, ileal stenosis, ileal perforation, ileal hemorrhage, colonic obstruction, colonic stenosis, colonic perforation, colonic hemorrhage, vomiting, hyponatremia, genitourinary obstruction (bladder and ureter), and kidney

failure.

2) Expected adverse events caused by exacerbation of liver metastasis

   Increased aspartate aminotransferase, increased alanine aminotransferase, increased serum bilirubin, increased alkaline phosphatase and liver dysfunction

3) Expected adverse events caused by exacerbation of pulmonary metastasis

   Atelectasis, respiratory failure, hypoxia, bronchial obstruction, pulmonary infection, and bronchial infection

4) Expected adverse events caused by exacerbation of other metastatic lesions

   Sharp pain, and hypercalcemia.

5) Expected adverse events associated with the worsening of the patient's general condition

   Fatigue, weight loss, anemia, thrombopenia, hypotension, edema (face, limbs, trunk, and genitals), hypoalbuminemia, increased aspartate aminotransferase, increased alanine aminotransferase, acidosis, increased creatinine, hyperglycemia, hypoglycemia, hypernatremia, hyponatremia, hyperkalemia, hypocalelmia, disseminated intravascular coagulation, pleural effusion, respiratory failure, hypoxia, bladder infection, acute renal failure, urinary retention, ascites, and constipation.

7.2. Evaluation of adverse events/ adverse reactions

Adverse events should be graded according to the definitions of grade 0-4, whichever is closest.

Moreover, when specific treatments are listed for a particular grade, the adverse event should be graded according to those clinical requirements. For example, if pleural effusion increases the patient may refuse oxygen inhalation or thoracic cavity drainage despite being a candidate for those treatments. In such instances, grading should be based on the medical judgment of what should be done rather than what was actually done.

In the event of a treatment related death, the adverse event that caused the original NCI-CTAE is grade 5, however in the present trial, 'grade 4' and not 'grade 5' will be recorded on the CRF. Considerations on the causal relationship observed between the adverse event and the TRD should be noted in the section 'condition at the time of death' on the treatment discontinuation report and the follow-up survey. Thereafter an urgent report will be dispatched (classification of grade 5 will be determined via post-hoc investigation, including the urgent report).

For adverse events defined in '8.2. Test and evaluation items during the treatment period', the grade and the day that the grade first appeared should be noted on the appropriate CRF. For any other adverse events, only those greater than grade 3 should be noted in the free comment section on the progress report form, with the adverse event, grade, and day of grade appearance.

The grade recorded on the CRF should also be recorded on the medical chart for verification in the event of a site-visit audit.

8. Evaluation items, laboratory testing and schedule for evaluations

8.1. Evaluation items prior to enrollment

Tests conducted within 56 days prior to primary enrollment

1) Performance status: PS (ECOG), height, weight
2) Peripheral blood count: leukocytes, neutrophils, lymphocytes, hemoglobin, platelets
3) Blood biochemistry: albumin, total bilirubin, AST, ALT, creatinine, sodium, potassium, CRP, fasting blood sugar
4) Tumor markers: CEA, CA19-9
5) Upper abdomen/pelvic CT (slice thickness under 10 mm, simple CT permitted when patient is allergic to contrast agent)
6) Upper gastrointestinal endoscopy (histopathologic examination)
7) Chest X-P: lung window
8) Resting 12-lead electrocardiogram
9) Respiratory function test: FEV 1.0%, %VC

8.2. Evaluation items and tests during the treatment period

8.2.1. Surgical evaluation items

1) Name of specialist performing the procedure
2) Duration of procedure
3) Surgical method, presence or absence of combined resection, degree of lymph node dissection; whether or not combined resection was performed (excluding cholecystectomy)
4) Maximum diameter of skin incision
5) Group B only: Number of ports, whether or not special assistive techniques were used, conversion to open surgery, reason for open surgery
6) Blood lost (from incision to closing), blood transfusion volume (intraoperative and until initial discharge)
7) Tumor location
8) Tumor diameter
9) Surgical findings: invasion depth, lymph node metastases, surgical progress, liver metastasis, peritoneal dissemination, peritoneal lavage cytology, distal metastasis
10) Presence or absence of dissection of each lymph node.
11) Proximal margin, distal margin, evaluation of post-resection curability
12) Intraoperative complications (CTCAE v4.0 Term) of Grade 3 or higher: from incision to closing. The causal relationship with treatment as determined by the attending physician will also be reported.
    - Thromboembolism, intraoperative damage to the hepatobiliary system (pancreas, common bile duct, portal vein), intraoperative arterial injury, intraoperative venous injury, intraoperative gastrointestinal disorders (esophagus, duodenum, jejunum, ileum, colon), intraoperative splenic

injury

- Grade 3 or greater intraoperative complications aside from those listed above

8.2.2. Evaluation items for the postoperative period of hospitalization

1) Histopathological findings

Histological type, depth of invasion, lymph node metastases, liver metastasis, peritoneal dissemination, distant metastasis, peritoneal lavage cytology, lymphatic invasion, vascular invasion, proximal stump, distal stump, degree of residual tumor, progression, presence or absence of metastasis to each lymph node

2) Early stage, postoperative complications

Early stage, postoperative complications: from completion of procedure to postoperative, initial discharge of patient. The causal relationship with treatment as determined by the attending physician will also be reported. Grading will be done by both CTCAE v4.0.

3) Blood tests

- Peripheral blood counts: White blood cell count, hemoglobin, platelets
- Blood biochemistry: Albumin, sodium, potassium, total bilirubin, AST, ALT, creatinine

4) Evaluation items for short-term clinical outcomes

- Days until passed gas: number of days from the first postoperative day until passed gas or defecation was confirmed for the first time
- Whether or not painkillers were used from postoperative day five to postoperative day 10
- Maximum body temperature within 3 days after surgery: Maximum body temperature (°C) from postoperative day one until postoperative day three
- Maximum body temperature during the hospitalization: Maximum body temperature (°C) from postoperative day one until initial discharge following surgery

Each of the “days” referred to above is calculated as one day starting from 0:00 until 24:00. Therefore, the day of surgery lasts until 24:00 and is considered postoperative day 0. The following day until 24:00 is then considered “postoperative day one.”

8.2.3. Evaluation items for the post-discharge period

1) Early stage, postoperative complications

Late postoperative complications: checked every 6 months from postoperative, initial discharge of the patient to five years after the procedure. The causal relationship with treatment as determined by the attending physician will also be reported. Grading should be performed with both the CTCAE v4.0.

2) Blood tests: Once per year for five years postoperatively

- Peripheral blood counts: White blood cell count, hemoglobin, platelets
- Blood biochemistry: Albumin, sodium, potassium, total bilirubin, AST, ALT, creatinine
- Tumor markers: CEA, CA19-9

3) Imaging tests: Once per year for five years postoperatively

- Contrast-enhanced CT of the upper abdominal and pelvic regions (slice thickness: ≤ 10 mm, if

contrast-enhanced CT impossible due to allergy to contrast medium, plain CT may be performed)

- Upper gastrointestinal endoscopy
- Chest X-P (one or two directions): Lung window

8.3. Study Calendar (same for both groups)

	Pre-enrollment	For both groups		Follow-up period
		Post-enrollment, prior to surgery	After surgery, during hospitalization period	Every 6 months for five years
General condition				
Physical findings, PS	○		○	○
Weight	○			
Height	○			
Blood tests				
Peripheral blood counts	○		○	○
Blood biochemistry	○		○	○
CEA, CA19-9	○			○
Radiological examination				
Contrast-enhanced CT of upper abdominal and pelvic regions	○			○
Chest X-P	○			○
Upper gastrointestinal endoscopy	○			○*1
12-lead electrocardiogram during rest	○			
Respiratory function test	○			
Toxicity evaluation				
Subjective symptom check			○	○
Objective symptom check			○	○
Submission of forms for records				
Enrollment eligibility confirmation slip	○			
Pre-treatment report		○		
Surgical findings record			○	
Pathological findings record			○	
Postoperative record			○	
Treatment conclusion report			○	
Follow-up test form*2				○

*1 Once per year for five years.

*2 Follow-up test forms will be sent until five years after the enrollment of the final enrolled patient. These forms should be submitted in accordance with the deadline even after over five years have passed since enrollment for each individual patient.

9. Data collection

9.1. Data sheets (Case Report Form: CRF)

9.1.1. Types of CRF and submission dead lines

CRFs and deadlines used in the present trial are as follows:

1) Primary enrollment eligibility checklist (white) － Submit the form to the Data Center within 2 days of enrollment. (via mail, fax, or in person. However not necessary with Web enrollment)
2) Pretreatment report (blue) － Submit within 2 weeks of enrollment
3) Report of operative findings(green) － Submit within 2 weeks of surgery
4) Postoperative report(green) － Submit within 2 weeks after patient discharge
5) Report of pathological findings(green) －Submit within 2 weeks after determination of pathological diagnosis
6) Treatment termination report (red) －Submit within 2 weeks after discontinuation/ completion of protocol-based treatment
7) Follow-up survey (white) － Submit by the deadline noted on the follow-up survey

- The enrollment eligibility checklist (1. above) will be distributed to each facility by the Study Coordinator prior to the start of the trial along with the protocol. They can also be obtained by downloading from the JCOG homepage (http://www.jcog.jp).
- The pretreatment report (2. above) and treatment termination report (6. Above) will be mailed by the Data Center preprinted with the patient's basic information (registration number, facility name, etc.) after enrollment. If the forms are not received after 1 week of enrollment, or if the CRF is lost or destroyed, telephone the Data Center to request for new forms to be sent.
- The 'follow-up survey' (7 above) will be mailed the Data Center during the monitoring period, or in conjunction with the interim/final analyses.

9.1.2. CRF storage

- All filled in CRFs will be stored as copies or in electronic format at the facility.
- CRF copies will be stored until the issue of final analysis report so that they can be used as a reference when filling out other CRFs, or for responding to queries from the data center.

9.1.3. CRF submission

- Excluding the enrollment eligibility checklist, all CRFs should be mailed to the Data Center or delivered in person. If enrollment is completed by telephone, the enrollment eligibility checklist may exceptionally faxed for rapid delivery. Furthermore, when enrolling by fax, the enrollment eligibility notification will be faxed to the facility by the Data Center.
- To avoid potential identity theft, when contacting the Data Center for CRF submission etc., the patient registration number should be used, not the facility's medical chart number.

9.1.4. CRF corrections

Once the trial is initiated, if the CRF is incomplete (i.e., missing required data or incorrect category classification, it may be corrected with the approval of the Data Center Director and the Study Coordinator, so long as the correction does not exceed the range of collected data stipulated in section 8 above, 'Evaluation items, laboratory tests and evaluation schedule', and if the correction will cause no further medical or financial burden to the patient. For CRF corrections that do not require protocol revision. The regulations of the facility will be referenced to determine whether a report or revision application concerning CRF corrections should be sent to the director of the medical facility.

10. Adverse event reporting

In the event of a “severe adverse event”, or “unexpected adverse event”, the principal investigator of the facility should report to the Study Coordinator/research chair.

Furthermore, side effects etc. are reported to the Minister of Health, Labour and Welfare in accordance with the Pharmaceutical and Medical Device Act (PMD Act) (Addressee: Safety Information Section of Office of SafetyI, Pharmaceuticals and Medical Devices Agency. FAX: 0120-395-390,E-mail: anzensei-hokoku@pmda.go.jp, format: http://www.info.pmda.go.jp/info/houkoku.html). In accordance with the ethical guidelines on clinical research (public notice 415; the Ministry of Health, Labour and Welfare, 2008, http://www.mhlw.go.jp/general/seido/kousei/i-kenkyu/index.html) reports regarding severe adverse events must be submitted to the director of each facility, and reports regarding unexpected severe adverse events are to be submitted by the director of the medical facility to the Ministry of Health Labour and Welfare. Industry will be contacted by the medical institution by the principal investigator of each facility as required in accordance with the regulations of each medical facility.

10.1. Adverse events that require reporting

Myelodysplastic syndrome (MDS) and secondary cancer do not require adverse event reporting because the information will be collected in the follow-up survey. The incidence should be reported in the monitoring report.

10.1.1. Adverse events that require expedited reporting

An adverse event falling under any of the criteria below requires expedited reporting.

1) Death during the protocol-based treatment or less than 30 days from the last day of protocol treatment

Regardless of the causal relationship with the protocol treatment, in patients who have completed the protocol treatment and started on after-treatment, if adverse events occur or within 30 days from the last day of protocol treatment expedited reporting is required.

(‘30 days’ refers to 30 days from the day following the last day of treatment, when that day is 0.)

※If death occurs after enrollment when the protocol treatment is not being administered, expedited reporting is not required. However necessary evaluations, including eligibility tests at the time of enrollment, should be adequately performed during the monitoring period.

2)Unexpected grade 4 adverse events

Grade 4 adverse events are not noted as “severe adverse reactions” in ‘section 7’ above.

Events determined as having a causal relationship with the protocol treatment (either definite, probable, or possible) require expedited reporting.

10.1.2. Adverse events that require routine reporting

Of 1-4 below, events determined to have a causal relationship with the protocol treatment (either definite, probable, or possible) require routine reporting.

1)Death after 31 days from the last day of protocol treatment

Deaths suspected to be TRDs, and are not clearly caused by the cancer.

2)Anticipated grade 4 non-hematotocixities※

Grade 4 non-hematotoxicities noted as “severe adverse reactions” in section 7, ‘anticipated adverse reactions’.

Note that even if anticipated, severe adverse events require routine reporting.

* ‘non-hematotoxocities’ are adverse events listed in the CTCAE v4.0, other than the following:

Anemia, hypocellular marrow, lymphopenia, neutropenia, leukopenia, thrombopenia, bone marrow failure and CD4 lymphopenia.

3)Unexpected grade 3 adverse events

Adverse events equivalent of grade 3 that are not noted in section 7, ‘anticipated adverse events’.

4)Other serious medical events

Important information that does not fall under 10.1.1.1),2), or 10.1.2. 1),2),3), but should be shared with the research group, such as persistent or marked disturbances (excluding MDS and secondary cancer), or disturbances that may impact offspring, such as congenital abnormalities.

10.2. Mandatory reporting and report procedures of the facility’s principal investigator

10.2.1. Expedited reporting

In the event of an adverse event that requires expedited reporting, the attending physician should immediately notify the facility’s principal investigator. If the facility’s primary investigator is unavailable, then the facility coordinator or attending physician must assume the duties of the facility’s principal investigator.

Primary report:

The facility’s principal investigator must record the prescribed items on the ‘adverse event report’ to the best of their ability within 72 hours of discovering the adverse event and either email, fax or telephone in the information to the Study Coordinator.

Secondary report:

The facility’s principal investigator must complete all prescribed items on the ‘adverse events report’ to create a ‘adverse event detailed report’, which contains more detailed information, and submit both reports by email, fax, mail or in person to the Study Coordinator office within 15 days of discovering the adverse event. If an autopsy has been performed, as a general rule, the autopsy report should also be sent immediately. When submitting the reports care should be taken so as not to include the patient’s personal information, including the patient’s name and medical chart number (same below).

10.2.2. Routine reporting

The facility’s principal investigator must complete the prescribed items on the ‘adverse events report’ to create a ‘adverse event detailed report’, and email, fax, mail or submit in person to the Study Coordinator within 15 days of discovering the adverse event. If an autopsy has been performed, as a general rule, the autopsy report should also be sent immediately.

10.2.3. Reporting to the medical facility director

In the event of adverse events (excluding 'unexpected grade 3 adverse events') requiring expedited routine reporting, the facility's principal investigator is to report it as a 'severe adverse event related to the clinical trial' to the director of the medical facility in accordance with the regulations of the medical facility concerned. Furthermore, when reporting the adverse event, they must notify the Data and Safety Monitoring Committee via the research representative/research coordinator of the planned examinations.

10.2.4. Reports for other destinations

The following reports required by the regulations applied in the present trial must be completed as required by the supervisor of each facility in accordance with the regulations of each medical facility.

Reports on pharmaceutical product, medical equipment and reproductive medicine device safety information:

In accordance with Article 68, paragraph 10, clause 2 of the Pharmaceutical and Medical Device Act (PMD Act), information deemed necessary to report is to be reported to the Minister of Health, Labour and Welfare.

10.3. Duties of the research chair and Study Coordinator

10.3.1. Guidelines for urgent notification to the facilities and termination of enrollment

On receiving reports from the facility's principal investigator, the Study Coordinator will report to and consult with the research chair and the group representative to determine the urgency, importance, and degree of influence of the report content, and when necessary, they will take measures to temporarily suspend enrollment and immediately communicate the findings to the participating facilities. The Data Center or facility may be contacted by telephone in an emergency; however written communication (fax, mail, email, or in person) should follow as soon as possible.

10.3.2. Reporting to the Data and Safety Monitoring Committee

If the Study Coordinator determines that an adverse event reported by a facility via expedited or routine reporting falls under 'section 10.1. Adverse events that require reporting', after consulting with the research chair and the group representative, a written report must be submitted to the Data and Safety Monitoring Committee within 15 days of discovering the adverse event. Simultaneously, they are asked to examine the research chair's opinion of the adverse event concerned and the appropriateness of the responses to the adverse event.

At this time, the 'adverse event report' and the 'adverse event detailed report' sent from the facility should include a written opinion noting the results of the investigations and measures by the Study Coordinator and research chair taken (including determination of trial continuation/termination). Moreover, death within 30 days of 10.1.1 (1) or after 31 days of 10.1.2 (1) is considered a TRD. For a 10.1.2 (2) anticipated grade 4 non-hematotoxicity, regardless of the individual patient's progress, reporting should include details on whether the incidence was within the expected range.

10.3.3. Notification facility researchers

In the event of the Study Coordinator/research chair having reported to the Data and Safety Monitoring Committee, the must communicate the content of the investigations and advice of the Data and Safety Monitoring Committee (email is acceptable) to the principal investigators of all facilities participating in the trial.

In the event of not having reported to the Data and Safety Monitoring Committee, the Study Coordinator/research chair must communicate their decision in writing (email is acceptable) to the principal investigator of the facility that submitted the report.

10.3.4. Examination of adverse events in routine monitoring

In the event of routine monitoring, the research chair/Study Coordinator should carefully examine the adverse event report in the monitoring report created by the Data Center, and verify that there are no omissions in the report from the facility. In addition, they must verify that all reported adverse events have been listed in the routine monitoring report. Any report omissions will be specified in the space for group examination reporting on the routine monitoring report.

10.4. Measures taken by the principal investigator of participating facilities (including the facility concerned)

The principal investigators of the facilities participating in the present trial will take measures as instructed by the Study Coordinator/research chair, Moreover in the event of an adverse event requiring expedited or routine reporting (excluding ‘anticipated grade 3 adverse events’), the facility’s principal investigator will report the event as a ‘clinical trial related serious adverse event’ to the director of the medical facility concerned in accordance with the regulations of that particular medical facility.

10.5. Examinations by the Data and Safety Monitoring Committee

The Data and Safety Monitoring Committee will examine/investigate the report content according to the procedures described in the ‘guidelines for clinical safety data management’, and those approved by the operations committee. Then, they will communicate the measures to be implemented, including whether the enrollment should be continued or if the protocol should be revised, to the research chair, Study Coordinator, group representative, group coordinator, director of the Data Center in writing.

11. Definitions of response and endpoints

11.1. Definition of analyzed patients

Groups for analysis in routine monitoring, interim analysis, and final analysis will be defined as follows.

11.1.1. All registered patients

Populations excluding duplicate registration and false registration from patients registered according to 5.1. 'Procedure of registration' are defined as "all registered patients".

11.1.2. All eligible patients

Populations excluding "ineligible patients" determined by the Study Group from all registered patients are defined as "all eligible patients". The "ineligible patients" judged only by institutional physicians are not regarded as ineligible formally. Approval by the Group Chair is necessary for the final decision of the "ineligible patients"; however, for interim analysis, regular interim monitoring, or analysis for a presentation at a scientific meeting before the final analysis report is fixed, the Data Center and the Study Coordinator can determine tentative "ineligible patients".

11.1.3. All treated patients

Patients who receive any part of the protocol treatments among all registered patients are defined as "all treated patients". The Data Center and the Study Coordinator can determine whether patients who never receive any part of the protocol treatment are included in the safety analyses or not.

11.2. Definitions of endpoints

11.2.1. Overall survival

Overall survival is measured from the date of registration (randomization) to the date of death from any cause (confirmation of survival by telephone is allowed).

-Overall survival is censored at the latest day of survival confirmation for surviving patients.

-For patients lost to follow-up, overall survival is censored at the latest day of survival confirmation before loss to follow-up

11.2.2. Relapse free survival (RFS)

Relapse free survival is the period from the date of registration until diagnosis of recurrence or death from any cause, whichever is earlier.

- "Relapse" includes that which can be confirmed by image diagnosis and exacerbation of symptoms (clinical exacerbation) which cannot be confirmed by image diagnosis. In the former case, the day of imaging examination will be regarded as the day of relapse, whereas in the latter case the day of diagnosis of symptomatic deterioration will be regarded as the day of relapse. An increase in tumor marker values only will not be regarded as an event of RFS; rather, the day of relapse is defined as the day of confirmation by imaging examination or the day of diagnosis of symptomatic deterioration.

- RFS will be censored on the last day of survival confirmation for surviving patients with no relapse (final confirmed date of RFS: the most recent date among the survey dates during hospitalization, the latest outpatient visit during outpatient care and the most recent date the patient has been seen for testing). Confirmation by telephone only is not allowed.
- When recurrence is diagnosed with imaging modalities, "the day of examination with suggestive findings" will not be used as the event day; rather, "the day with definitive findings" will be used as the event day. When relapse is diagnosed not by imaging but by clinical observation, the day of clinical judgment will be regarded as the event day.
- Onset of secondary cancer (metachronous multiple cancers) will not be considered as an event or a censoring of RFS, RFS will be continued until detection of other events.
- Carcinoma in situ and intramucosal carcinoma declared cured by local treatment is not considered relapse.
- The day of surgery will be considered as an event of RFS if R2 residual carcinoma, which is synonymous with curability C according to the 13th edition of the Japanese Classification of Gastric Carcinoma, is evident.

11.2.3. Proportion of LADG completion (Group B)

The proportion of LADG completion is defined as that of patients with whom LADG is completed without conversion to open surgery among all operated patients in Group B. In this study, cases will be considered as a conversion to open surgery if a skin incision of 6 cm or greater is made or if the case is diagnosed as sStage IV and protocol treatment is discontinued.

11.2.4. Proportion of conversion to open surgery (Group B)

Of all treated cases in Group B, the proportion of conversion to open surgery will be calculated. In this study, performing a skin incision of 7 cm or greater will be considered as a conversion to open surgery.

11.2.5. Proportion of adverse event (adverse reaction)

Among all treated patients, frequencies of the worst grade of the following adverse events are calculated in both arms according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

1) Intraoperative complications (CTCAE v4.0): Until surgery completion (abdominal incision closure) with open surgery

The worst Grade frequency for each of the following adverse events (toxicity) with CTCAE v4.0 will be calculated with all treated patients as the denominator.

Thromboembolism, intraoperative hepatobiliary injury, intraoperative splenic injury, intraoperative arterial injury, intraoperative venous injury, intraoperative gastrointestinal injury

2) Early postoperative complications (CTCAE v4.0): From completion of surgery until initial postoperative discharge

With all treated patients as the denominator, the worst Grade frequency will be calculated for each of the following adverse events (toxicity) using CTCAE v4.0.

Pancreatic fistula, postoperative hemorrhage, peritoneal infection (intraabdominal abscess), esophageal anastomotic leak/gastric anastomotic leak /gastrointestinal anastomotic leak/small intestinal anastomotic leak (anastomotic leak), other injury/poisoning and procedural complication- anastomotic stenosis, cholecystitis, other gastrointestinal disorders-dumping syndrome and delayed gastric emptying, gastroesophageal reflux disease, ileus, thromboembolism, lung infection (pneumonia), ascites, wound infection, wound dehiscence (abdominal incisional hernia)

3) Late postoperative complications (CTCAE v4.0): From initial postoperative discharge until five years postoperatively

With all treated patients as the denominator, the worst Grade frequency will be calculated for each of the following adverse events (toxicity) using CTCAE v4.0.

Cholecystitis, gastroesophageal reflux disease, ileus, peritoneal infection (intraabdominal abscess),other injury/poisoning and procedural complication- anastomotic stenosis, other gastrointestinal injury-dumping syndrome- anastomotic stenosis, other gastrointestinal disorders-dumping syndrome, lung infection (pneumonia), wound infection, abdominal incisional hernia

For adverse events other than those above, only if a Grade 3 or higher adverse event other than CTCAE v4.0 blood toxicity (“anemia,” “hypocellular marrow,” “decreased lymphocyte count,” “decreased neutrophil count,” “decreased white blood cell count,” “decreased platelet count,” “bone marrow failure,” “decreased CD4 lymphocytes”) is observed, 1) is recorded in the surgical findings record, 2) is recorded in the postoperative record and 3) is recorded in the follow-up test form. Therefore, the onset ratio is not totaled as a general rule, except if many specific adverse events are observed.

11.2.6. Proportion of surgery-related mortality

The proportion calculated with the number of patients (all treated cases) that underwent at least part of the protocol treatment as the denominator and the number of mortality cases out of all mortality cases determined to have been in a causal relationship with protocol treatment (either definite, probable or possible) as the numerator.

11.2.7. Proportion of early mortality

The proportion calculated with all treated cases as the denominator and the number of mortality cases that occurred either during the protocol treatment period or within 30 days from the final protocol treatment day as the numerator. The presence or absence of a causal relationship between mortality and protocol treatment is irrelevant.

11.2.8. Proportion of Grade 4 non-hematological toxicity

The proportion calculated with all treated cases as the denominator and the number of patients in who at least one of the adverse events recorded in the 11.3.8. regular items and CRF free comment column were Grade 4 non-hematological toxicity diagnosed either during the protocol treatment period or within 30 days from the final protocol treatment day as the numerator. The presence or absence of a causal relationship between mortality and protocol treatment is irrelevant. Non-hematological toxicity refers to adverse events other than “anemia,” “hypocellular marrow,” “decreased lymphocyte count,” “decreased neutrophil count,” “decreased white blood cell count,” “decreased platelet count,” “bone marrow failure” or “decreased CD4 lymphocytes.”

*[Non-hematological toxicity] is an adverse event according to CTCAE v4.0 other than “anemia,” “hypocellular marrow,” “decreased lymphocyte count,” “decreased neutrophil count,” “decreased white blood cell count,” “decreased platelet count,” “bone marrow failure” or “decreased CD4 lymphocytes.”

11.2.9. Short-term clinical outcomes after surgery

1) Time to pass first flatus (days)

The period at which patients pass first flatus is recorded by POD 21. If patients don’t pass first flatus or stool, they are censored at POD 21. The patient can simply report whether or not flatus occurred.

2) Proportion of analgesic use

The proportion of analgesic use is calculated with all treated cases as the denominator and the number of patients who used painkillers at least once from postoperative day five to postoperative day 10 as the numerator. Painkillers include the following

- Non-narcotic analgesics including non-steroidal anti-inflammatory drugs (NSAIDs)
- Narcotic analgesics
- If epidural anesthesia inserted postoperatively is continued from postoperative day five onward

3) Maximum body temperature within 3 days after surgery

Maximum body temperature from the day following surgery (postoperative day one) until postoperative day three. Temperature will be measured at least three times per day during this period.

4) Maximum body temperature during the hospitalization

Maximum body temperature from the day following surgery (postoperative day one) until initial postoperative discharge. Temperature will be measured at least once per day during this period.

12. Statistical consideration

12.1. Primary analysis and decision criteria

The aim of primary analysis of the randomized phase II part is to evaluate the safety of LADG in the target population. The primary endpoint in this part is the incidence of pancreatic fistula or anastomotic leakage, and the null hypothesis that the true incidence proportion in LADG group is greater than or equal to 18% is to be tested. This test is conducted by the binomial test with one-sided significance level of 10%.

The aim of primary analysis of randomized phase III part is to confirm that the RFS in LADG group is non-inferior to that of ODG. In this analysis Cox proportional hazard model is fitted with the adjustment of the randomization factors, the institution, clinical depth of invasion, and clinical N category. However the institution wouldn't be included in the Cox model if there are some institutions in which the numbers of enrolled patients are not enough. The non-inferiority (NI) in RFS is assessed by testing the null hypothesis that the hazard ratio (HR) of LADG relative to ODG is larger than or equal to 1.31, with the one-sided significance level of 5%. If this test shows the NI in RFS, we conclude that LADG is an effective approach, in case secondary endpoints do not differ largely from the expected results even if they do not show the superiority of LADG to ODG.

12.2. Sample size, enrollment and follow-up periods

In the phase II part, the required sample size is calculated to be more than 80, assuming the threshold proportion of 18%, a one-sided alpha level of 10%, and 80% statistical power. To keep the statistical power more than 80% even if some ineligible or untreated patients occurred, we decided to enroll 90 patients in the LADG group (180 patients in both groups). The enrollment period is 1.5 years since the annual number of enrollments is expected to be about 150. The patient enrollments will not be suspended between phases II and III.

The primary analysis of the Phase II part will be performed at the appropriate time of regular monitoring after the protocol treatments of all enrolled patients are completed and the patients will be discharged from the hospitals. The result of the primary analysis is summarized by the data center, and submitted to the study coordinator, the study chair, and the data and safety monitoring committee. Follow up of the patients enrolled in the phase II part are continued to interpret RFS and OS appropriately. The follow-up period is for five years after the end of the enrollment of the phase III part.

In the phase III part, the expected 5-year RFS rate for the ODG group was assumed to be 65% based on previous report[43]. The efficacy of LADG was expected to be equivalent to ODG, and we set the enrollment period of 4 years, the follow-up period of 5 years, one-sided alpha of 5%, and statistical power of 75%. The follow-up period is from the beginning of the enrollment to the end of the study, which is after 5 years from the time that the finally enrolled patient completes the protocol treatment. It was determined to be clinically unacceptable if the 5-year RFS rate decreased by 8% or more in the LADG group relative to the ODG group. The corresponding NI margin for the HR is 1.31. We need to enroll a total of 500 patients in two groups to achieve the aim of this study under the above setting.

<Additional notes at the 1st revision>

We decided to extend the enrollment period to 7.5 years based on the consideration that about eight patients

could be enrolled in a month due to the increase of the institutions, while the total sample size remained unchanged at 500.

12.3. Interim analyses

If this study moves to the phase III part, two interim analyses will be performed in the middle of the study to evaluate whether the main purpose of this study is achieved. The first interim analysis is performed after half of the planned sample size of the phase III part is obtained, and it is determined whether it is appropriate to continue enrollment. The second interim analysis is performed early after the completion of the enrollment, and it is determined whether to follow up for the scheduled period. If the main purpose of this study has been achieved, the study will be discontinued, and the results will be published promptly in academic societies and papers.

Interim analysis is performed in the Data Center, and patient enrollment is continued during the interim analysis.

To keep the study-wise significance level at a one-sided 5%, multiplicity is adjusted using the Lan-DeMets method with the O'Brien-Fleming alpha spending function.

The decision criteria based on the interim analyses is as follows:

- If the RFS of the LADG is shown to be non-inferior to the ODG, this study is terminated. Comprehensive judgement will be made considering the results of secondary endpoints.
- If the RFS of the LADG is shown to be non-inferior to the ODG and also superior, the study is terminated.
- If the point estimate of the hazard ratio of the LADG to the ODG exceeds 1.31, this study will be discontinued.

12.4. Analyses of secondary endpoints

12.4.1. Secondary endpoints for safety

Secondary endpoints for safety are proportion of LADG completion, proportion of the conversion to the ODG, proportion of adverse events, early postoperative course, number of harvested lymph nodes, and recurrence sites. Confidence intervals for proportions are estimated by the exact method based on the binomial distribution.

12.4.2. Secondary endpoint for efficacy

Secondary endpoint for efficacy is the OS, and it is analyzed only at the final analysis. The OS curves are estimated by the Kaplan-Meier method. Confidence intervals for OS proportions for each year are calculated using the Greenwood's formula.

12.5. Final analysis

All endpoints are analyzed after the follow-up period is over and the data is finalized. The final analysis is performed by the Data Center and the report is submitted to the study coordinator, study chair, and the data and safety monitoring committee.

13. Ethical items

13.1. Patient protection

All participating researchers are required to conduct this trial in accordance with the Helsinki Declaration (http://dl.med.or.jp/dl-med/wma/helsinki2013j.pdf) and the "Ethical Guidelines on Clinical Research" (public notice 415 of the Ministry of Health Labour and Welfare,http://www.mhlw.go.jp/general/seido/kousei/i-kenkyu/index.html).

In the protocol guidelines 'medical facility' corresponds to 'clinical research facility' in the guidelines above.

13.2. Informed consent

13.2.1. Explanation given to patients

Prior to enrollment, the attending physicians will provide patients with a written explanation of the trial (written explanation in the appendix and written explanation with modifications by the medical facilities) with the approval of the medical facility and a verbal explanation as outlined below:

Furthermore, in this protocol, "approval of the medical facility" refers to either of the following:

1. When the director of the medical facility provides written approval to the researcher on the basis of the results of an investigation by the ethical review board in consultation with the director of the medical facility (institutional review board: IRB).
2. When the committee provides written approval to the researcher on the basis of the results of an investigation by the ethical review board in consultation with the director of the medical facility.

1) Explanation of disease classification, staging, and anticipated prognosis.
2) Confirmation that the present trial is a clinical trial conducted by the JLSSG.
3) Trial design and rationale (significance, enrollment number, prerequisites, purpose, allocation tc.)
4) Details of the protocol treatment
   Drug name, administration method, dosage, treatment period, and total duration of protocol treatment, etc.
5) Anticipated response to treatment
   Anticipated life prolongation, tumor shrinkage, symptom alleviation, etc.
6) Anticipated adverse events, complications, sequelae, and related treatment methods
   Explanation of the incidence and extent of anticipated adverse events, including complications, sequelae, TRD rate, and related treatment methods.
7) Financial burden and compensation
   Costs incurred because of treatment will be covered by the national health insurance scheme, and any compensation in the event of injury will be treated as part of general medical care.
8) Alternative treatment
   Details of current common treatments (including palliative medicine), and standard treatments, effects, and toxicities, etc.Advantages and disadvantages of choosing an alternative treatment

9) Anticipated advantages and potential disadvantages

Explanation of potential benefits and disadvantages incurred from trial participation.

10) Verification of medical history documents

Explanation of auditing methods, such as 'obtaining medical professionals from other facilities and obtaining permission from the director of the medical facility to verify source documents related to medical history for quality control'.

11) Consent withdrawal and refusal

Trial participants are free to refuse consent before the trial or withdraw consent once given, and if they do so, there will be no disadvantages in terms of unfair treatment.

* Consent withdrawal is divided into withdrawal of participation consent (in accordance with 2) and 3) below), and refusal to continue the protocol treatment (as in 1) below). If a participant declares that they wish to withdraw consent, either 2) or 3) below needs to be specified and the JCOG Data Center needs to be contacted immediately.

1) Patient refusal: refusal to continue protocol treatment (follow-up will be continued)
2) Consent withdrawal: withdrawal of consent to participate in the trial. Thereafter , all treatment and follow-up in accordance with the protocol will not be permitted
3) Consent withdrawal (including all data used in the trial): withdrawal of consent to participate in the trial. All data from the start of participation will not be permitted for use in the present trial.

12) Protection of patient confidentiality

All efforts will be made to maintain the confidentiality of patient identity and personal information.

13) Secondary utilization of data

Only with the approval of the JLSSG committee, may date be used for secondary purposes (meta-analysis, etc.) independent of information related to personal identity.

14) Open questioning

Contact details of the attending physician, the medical facility's principal investigator, and the research chairperson (or Study Coordinator) of the present trial will be provided in writing to enable open questioning pertaining to the trial or treatment.

13.2.2. Consent

Participation in the present trial will be requested after explaining the trial to potential participants, and allowing sufficient time for reflection, so that they fully understand the trial details. If the patient consents to participate in the present trial, the following should be verified in the consent forms in the appendix and those for the trial in a template determined by the medical facility: the name of the physician who gave the explanation, the name of the patient who received the explanation and gave consent, and the date that consent was given.

Two copies of the consent form are required; one is to be given to the patient, and the second copy is to be filed by the facility coordinator. The original document will be kept with the patient's medical records.

13.3. Protection of personal information and patient identification

JLSSG recognizes privacy-related information such as personal and medical information as part of the concept of having deep respect for the individual and strictly and carefully protects such information.

13.3.1. Policies, laws and standards

As a rule, all research complies with the following laws and standards. If any other laws, standards or policies are applicable, they are also complied with.

- Act on the Protection of Personal Information (Act No. 57 of May 30, 2003, final revision: Act No. 119 of July 16, 2003)
- Declaration of Helsinki (Japan Medical Association translation)
- Ethical guidelines for clinical studies (enacted: July 30, 2003, full revision: December 28, 2004, full revision: July 31, 2008, Ministry of Health, Labour and Welfare notice No. 415)

13.3.2. Personal information objectives for use, items for use and methods of use

1) Objectives for use

JLSSG complies with the basic principle of "providing the best method of treatment to more patients." The personal information is used with the objective of "identifying individual patients and surveying them not only during treatment but after concluding treatment in the long-term to achieve accurate clinical research results and appropriately manage the acquired data."

2) Items for use

JLSSG uses the following items as they are considered the minimum necessary for patient identification and inquiry.

Patient ID (medical record number), date of birth, initials, pathological specimen number (when necessary)

Thus, personal information other than the above such as patient names is not sent to the data center from the participating medical institutions. If such information is communicated by mistake, it will be destroyed without using recording media or stored after correct processing such as making it ineligible with masking.

3) Utilization method

The patient's personal and medical information will be recorded on various CRFs by researchers of the medical facility, and, as a general rule, it will be submitted to the Data Center by mail or in person for collection. However, submission of information be telephone and fax may only be used for patient enrollments that require rapid communication.

In addition, to ensure the accuracy of the collected data, when exchanging copies of various CRFs between the Data Center and researchers of medical facilities, data submission will be limited to mail or in person.

Furthermore, personal information will not be communicated by e-mail.

13.3.3. Secondary utilization of date

Only with the approval of relevant JLSSG committees may data obtained in this trial be used for secondary purposes (meta-analyses, etc.) independent of personal identity.

13.3.4. Safety management responsibility

A privacy protection supervisory manager and privacy protection officer will be appointed to take various safety control measures to minimize the risk of personal information being revealed.

13.3.5. Managing disclosure of patient information

As a general rule, a researcher of the facility of the patient concerned (facility principal investigator, institutional coordinator, or attending physician) will handle requests by the patient for the disclosure of privacy-related patient information collected by the JLSSG

13.4. Protocol compliance

Researchers participating in this trial will abide by this protocol as long as it does not affect patient safety or patient rights.

13.5. Approval of the ethics review board at medical facilities

13.5.1. Approval at the start of trial participation

Approval of each medical facility will be required to participate in this trial, and a written explanation of the trial must be provided to each patient with a copy of the present protocol.

After obtaining approval, the coordinator of each medical facility must send a copy of the written approval to the Data Center. The original written approval form will be kept by the facility coordinator, while a copy will be kept by the Data Center.

Furthermore, all medical facilities may make additions to the written explanation for use with the approval of the medical facility concerned and given to the patient as long as the changes do not deviate from the scope of the clinical trial, however each medical facility are not permitted to make changes to the protocol. The same protocol will be used by all facilities. If content changes are required, amendments or revisions will be made to the protocol used by all medical facilities. Therefore, when there is a revision request made by a medical facility, the institutional coordinator must consult the Study Coordinator. If the written explanation is modified as instructed by the medical facility, the modified form must be submitted to the Study Coordinator. If the Study Chair or Coordinator deems the modifications (deletions or content change) to be inappropriate, then the medical facility may request the primary investigator/institutional coordinator to reconsider the modifications.

13.5.2. Annual renewal of the approval of each medical facility

Each medical facility will determine whether annual renewal of the approval for the protocol and written explanation for the patient is necessary in accordance with the regulations of each medical facility. If the approval is renewed annually, the JLSSG does not require each medical facility to submit written approval for annual renewal.

13.6. Change in details of protocol

13.6.1. Classification of protocol content changes

If changes are made to the protocol content, prior to implementation (activation) of the changes a 'protocol amendment application' must be submitted to the Data and Safety Monitoring Committee and approval obtained. However extension of the enrollment period of less than 6 months does not require protocol amendment.

While the JLSSG will process changes to the protocol as either amendments or revisions after approval by the Protocol Review Committee, the director of the Data and Safety Monitoring Committee will differentiate amendments from revisions, and therefore all committee applications should be submitted by researchers as 'revision applications'. Furthermore, additional explanations that do not fall under the criteria of protocol content changes will be classified as a memorandum. Definitions and processing are as follows:

1) Amendment

Partial changes to the protocol may increase the risk to patients participating in the trial, or may substantially impact the primary endpoint of the trial; therefore, amendments require approval from the Data and Safety Monitoring Committee and each medical facility.

Furthermore, approval from the group representative concerned and the Data Center director is also required prior to submission of the application to the Data and Safety Monitoring Committee. The Data and Safety Monitoring Committee will add the dates of the approval and validation to the protocol cover page.

If patient enrollment continued at a point in time deemed to correspond to an 'amendment' by the Data and Safety Monitoring Committee, patient enrollment will be temporarily suspended until approval is obtained from each medical facility for the amendment content. In the event that approval is obtained, the institutional coordinator of each medical facility must send a copy of the written approval from each medical facility to the Data Center. Enrollments will be recommenced from facilities that confirmed the written approval.

2) Revision

A revision is considered a change to the protocol that will not increase patient risk, or substantially impact the primary endpoint of the trial. Revisions require approval from the Data and Safety Monitoring Committee director, and each medical facility. Each medical facility will determine at their own discretion whether they will conduct a normal or rapid examination of the revision. As a general rule, patient enrollments will not be temporarily suspended for revisions.

Before the application is submitted to the Data and Safety Monitoring Committee chairperson, approval must be obtained from the representative of the group concerned, and the Data Center director.

The dates that the Data and Safety Monitoring Committee approved and validated the revision will be noted on the cover page of the protocol.

After validation of the revision, as a rule, the trial will be conducted in accordance with the approved revision content even before approval from medical institutions. If circumstances prevent the institution from implementing the revision content before approval from the medical facility, the Study Coordinator and Data Center should be consulted. When approval is obtained from each facility, a copy of the written approval from each medical facility does not need to be sent to the Data Canter, however the original document is to be kept by the institution coordinator

for verification in the event of an audit.

3) Memorandum

A supplementary explanation of the protocol in any format must be distributed by the Study Chair/Coordinator to all involved in the trial. This is not a change in protocol content but to decrease inconsistencies in interpretation of the text content, or to draw particular attention to the content.

Approval is required from the group representative and the Data Center director prior to distribution. Memorandums should be reported to the Data and Safety Monitoring Committee prior to, or immediately after distribution.

Memorandums do not need to be noted on the protocol's cover page.

13.6.2. Medical facility approval at the time of protocol amendment/revision

During the trial, if any revision is made to the protocol or written explanation given to the patient with the approval of the Data and Safety Monitoring Committee, the revised protocol or written explanation must be approved by each medical facility. If during patient enrollment, enrollments will be temporarily suspended until approval is obtained from each medical facility, and the institution will subsequently reopen enrollments after approval is obtained. Following approval for the revision, the institutional coordinator of each medical facility must send a copy of the written approval from each medical facility to the Data Canter. The original written approval will be kept by the institutional coordinator, while the copy will be kept by the Data Center.

Revisions (not amendments) made to the content also require approval from each medical facility. Each medical facility will determine whether to perform normal or rapid examination of the revision at their own discretion. When approval is obtained from each medical facility, a copy of the written approval from each medical facility does not need to be sent to the Data Center; however the original written approval must be kept by the institutional coordinator for verification in the event of an audit.

13.6.3. CRF correction

Once the trial is initiated, if the CRF is incomplete (i.e., missing required data or incorrect category classification, it may be corrected with the approval of the Data Center Director and the Study Coordinator, so long as the correction does not exceed the range of collected data stipulated in section 8 above, 'Evaluation items, laboratory tests and evaluation schedule', and if the correction will cause no further medical or financial burden to the patient. For CRF corrections that do not require protocol revision. The regulations of the facility will be referenced to determine whether a report or revision application concerning CRF corrections should be sent to the director of the medical facility.

13.7. Management of conflicts of interest for members involved in research

Conflicts of interest (COI) of researchers involved in JLSSG trials or individuals supporting the JLSSG trial will be managed as described below:

1) COI of individuals involved in JLSSG trials to investigate medical treatments in participating facilities, such as the facility's primary investigator or coordinator, will be managed in accordance with the regulations of the participating facility.

2) COI of individuals who play a key role in JLSSG trials, such as the Study Chair, Coordinator, or Group Chair/Coordinator, will be managed by the JLSSG committee.

13.8. Compensation

Health injury incurred by participating in the present clinical trial will be treated appropriately according to the symptoms in the way as normal medical care and will be covered by the national health insurance scheme. Any medical expenses not covered by the national health insurance scheme will be incurred by the patient. Furthermore, patients will not receive any financial compensation such as consolations or various bonus medical treatment.

13.9. Regarding intellectual property

Results, data and intellectual property obtained in this clinical trial will be returned to the four parties of the principal investigator, study coordinator, group representative. Specific methods of handling and distribution will be determined by the four parties in consultation. The question as to whether to return intellectual property regarding the principal investigator, study coordinator or group representative to the individual or to the medical institution that they belong to will be decided in accordance with the rules of the medical institution that they belong to.

14. Monitoring and auditing

14.1. Routine monitoring

As a general rule, biannual routine monitoring will be conducted to verify trial safety, protocol adherence, and accurate data collection.

Central monitoring will be performed based on data recorded on the CRFs collected from the Data Center, and there will be no site-visit monitoring including comparison with the original documents.

A routine monitoring report prepared by the Data Center will be submitted to the Study Coordinator, Study Chair, Group Chair, Data and Safety Monitoring Committee.

Routine monitoring is designed to provide feedback on problem areas and improve science-related ethics, but not to expose problem areas of the trial or facility. The group representative will distribute the routine monitoring report at each group meeting for examination, so that the Study Coordinator, Study Chair, and principal investigator can improve the problem areas indicated in the report.

14.1.1. Monitoring items

1) Cumulative achievement status: enrollment number-accumulation/period, group/facility
2) Eligibility: ineligible cases/patients who may be ineligible: group/facility
3) Background factors prior to treatment: group
4) During treatment/ following treatment, reason for termination/completion: group/facility
5) Protocol deviation: group/facility
6) Severe adverse events: group/facility
7) Adverse reaction/adverse event: group
8) Overall survival, progression0free survival: all enrolled cases
9) Other problems related to trial progress and safety

14.1.2. Acceptable range for adverse events

It is unlikely that surgery will cause treatment-related deaths or life-threatening complications at participating facilities. Therefore, the onset rates for these are not allowed to exceed 3%. If a treatment-related death or Grade 4 non-blood toxicity* caused by surgery is suspected, each case will be reported in an adverse events report to the efficacy and safety evaluation committee. If 14 or more cases of treatment-related death or Grade 4 non-blood toxicity* caused by surgery occur in either group, enrollment will immediately be paused as the final onset rate point estimation will clearly exceed 3%. The efficacy and safety evaluation committee will then be asked to determine whether or not the trial should be continued.

*Non-blood toxicity: CTCAE v4.0 term referring to adverse events other than “anemia,” “hypocellular marrow,” “decreased lymphocyte count,” “decreased neutrophil count,” “decreased white blood cell count,” “decreased platelet count,” “bone marrow failure” and “decreased CD4 lymphocytes.”

15. Special instructions

15.1. Central review of the validity of distal gastrectomy with D2 lymph node dissection

- Timing: Every six months
- Subjects: Of all enrolled patients, those for whom operative field photographs have been collected at the time of central review.
- Method: Photographs of the operative field taken intraoperatively at enrolled facilities (at least five photographs: see "6.5. Photography for central review regarding investigation of the validity of distal gastrectomy with D2 lymph node dissection are collected and results are determined by at least two surgical procedure central review members designated by the group representative.
- Photograph management: Study coordinator
- Report of central review to each facility: After the central review member results have been determined, the study coordinator will report the results to the facilities of each of the patients. This will be accompanied by a written report of the grounds for the decision.

15.2. Investigation of surgical procedure via video (Group B)

The surgical procedure will be investigated via video for quality control of laparoscopy-assisted surgery techniques.

- Timing: Each group meeting
- Subjects: Of all enrolled patients, one patient each at two to three facilities designated by the group representative
- Methods: At the designated facilities, surgery videos of approximately 15 to 20 minutes taken intraoperatively of enrolled patients will be edited and shown at each group meeting. By discussing surgical techniques at the group meeting, it is hoped that the details of these techniques can be coordinated.

16. Research organizations

Changes to the content of this chapter will be considered a revision; not an amendment.

Although revisions of the Data and Safety Monitoring Committee do not require inspection, they do require the approval from the research Group Chair. If a change is made, the Study Chair/ Coordinator must notify, in writing, each participating facility and the Data Center as soon as possible.

16.1. Research group and Group Chair

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Oita University

Study Chair: Seigo Kitano

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16.2. Participating institutions

Aichi Cancer Center Hospital,

Izumiotsu Municipal Hospital,

Ehime University,

Osaka City General Hospital,

Osaka University,

Komagome Hospital,

Kyushu University,

Gifu University,

Kobe University,

Saitama Medical University

International Medical Center,

Fukuoka University,

Nihon University Hospital,

Tokyo Medical and Dental University,

Oita University,

Fukui Saiseikai Hospital,

Nagano Municipal Hospital,

Nigata Municipal Hospital,

Hyogo Cancer Center,

Ishikawa Prefectural Central Hospital,

Iwate Medical University,

Osaka Medical and Pharmaceutical University,

Osaka City University,

Okayama University,

Kitasato University,

Kinki University,

Keio University,

Saga University,

Shizuoka Cancer Center,

St. Marianna University School of Medicine,

Saiseikai Toyama Hospital,

Nagoya University,

Hakodate Goryoukaku Hospital,

Yokohama City University Medical Center,

Saga-ken Medical Center Koseikan,

National Cancer Center East Hospital,

Cancer Institute Hospital,

Saitama Cancer Center

16.3. Data and Safety Monitoring Committee

During the trial period, the Data and Safety Monitoring Committee will oversee the adverse event reports, interim analysis reports, monitoring report reviews, and protocol revision reviews.

Chair: Yasuyuki Seto, Department of Gastrointestinal Surgery, Tokyo University
Members: Yasunori Emi, Department of Surgery, Saiseikai Fukuoka Hospital
Kenichi Yoshimura, Future Medical Center, Hiroshima University
Kuniaki Shirao, Keiwa International Clinic

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16.4. Statistical section / Data Center

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16.5. Protocol development

Protocol preparation

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Oita University Faculty of Medicine	Norio Shiraishi
Tokyo Medical and Dental University	Kazuyuki Kojima

Protocol preparation support

Statistical section (design supervisor) Tsutomu Kotegawa, Nobuyoshi Ejima

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17. Publication of trial results

The main article for publication will be submitted to an English-language journal.

When presenting the final analyses, other than the principal analysis stipulated in the protocol, approval must be obtained beforehand from the Data and Safety Monitoring Committee.

However, the Study Chair or Coordinator may announce publications introducing the trial at scientific meetings or articles (general remarks), but it may not include analytical results of the trial endpoints. After enrollment completion, scientific meetings/articles on safety data and distribution of patient background may be presented with the approval of the research group chairman and the Data Center director; however, approval from the Data and Safety Monitoring Committee is not required.

As a general rule, the hierarchy for the authors of the main publication of the trial results will include the Study Coordinator at the top, followed by the Study Chair, the statistical officer of the Data Center (one officer at the time of conducting analyses for publication), and the group chairman. Following the names of these individuals, depending on the limitations stipulated by the author contribution guidelines, co-authors will be selected by each institutional coordinator or principal investigator and will be listed in order of the highest enrollment number.

All co-authors will review the article content prior to submission, and only those who agree to present the content will be included. If agreement to the content is not obtained even after having discussed it, with the approval of the Study Chair or group chairman, that researcher may not be included as a co-author.

Because there may be several conference presentations, the Study Coordinator, Study Chair, principal investigator, and coordinators of facilities with high enrollments will take turns making the presentations. The presenter will be determined by the Study Chair with the approval of the group chairman. However, in the event of conference presentations, the preparation and content of the presentation will be the responsibility of the Study Chair, and, as a general rule, the Study Chair will contact the Data Center. Presenters other than the Study Coordinator may receive the aggregated/analysis results directly from the Data Center, without approval of the Study Coordinator or the Data Center director.

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