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Non-Randomized Confirmatory Trial of Laparoscopy-Assisted Total Gastrectomy and Proximal Gastrectomy with Nodal Dissection for Clinical Stage I Gastric Cancer: Japan Clinical Oncology Group Study JCOG1401

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Several prospective studies on laparoscopy-assisted distal gastrectomy for early gastric cancer have been initiated, but no prospective study evaluating laparoscopy-assisted total gastrectomy or laparoscopy-assisted proximal gastrectomy has been completed to date. A non-randomized confirmatory trial was commenced in April 2015 to evaluate the safety of laparoscopy-assisted total gastrectomy and laparoscopy-assisted proximal gastrectomy for clinical stage I gastric cancer. A total of 245 patients will be accrued from 42 Japanese institutions over 3 years. The primary endpoint is the proportion of patients with anastomotic leakage. The secondary endpoints are overall survival, relapse-free survival, proportion of patients with completed laparoscopy-assisted total gastrectomy or laparoscopy-assisted proximal gastrectomy, proportion of patients with conversion to open surgery, adverse events, and short-term clinical outcomes. The UMIN Clinical Trials Registry number is UMIN000017155.

Key Words: Laparoscopy; Gastrectomy; Nonrandomized clinical trial

Introduction

The proportion of patients with early gastric cancer is more than 50% of the total incidences in Japan.[1] Since the first laparoscopy-assisted distal gastrectomy (LADG) for early gastric cancer was reported in 1994,[2] the number of LADGs has rapidly increased because of better cosmetic outcomes, more rapid recovery of bowel function, less pain, and a shorter hospital stay than that for open distal gastrectomy (ODG). The Stomach Cancer Study Group of the Japan Clinical Oncology Group (JCOG) has been engaged in establishing evidence for laparoscopic gastrectomy. We conducted a multicenter phase II trial (JCOG0703) and confirmed the safety of LADG for early gastric cancer.[3] We are now conducting a randomized phase III trial to confirm the non-inferiority of LADG to ODG in terms of overall survival (JCOG0912).[4] Patient accrual has already been completed, and primary analysis results will be released in 2018. Current Japanese guidelines indicate that the evidence is still too weak for LADG to be considered a standard treatment for gastric cancer because long-term efficacy has not been demonstrated in a confirmatory trial. Thus, the efficacy results of JCOG0912 are awaited.

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However, laparoscopy-assisted total gastrectomy (LATG) and laparoscopy-assisted proximal gastrectomy (LAPG) have not been widely used compared with LADG because of the difficult reconstruction method. When we first planned JCOG0703, the proportion of LATG or LAPG cases among laparoscopy-assisted gastrectomies was only 11.9%, according to a questionnaire-based survey of the Japan Society for Endoscopic Surgery, and the surgical technique of LATG or LAPG was not yet standardized. Thus, LATG or LAPG was not applied in the treatment protocol of JCOG0703 or JCOG0912. However, a standard procedure for LATG and LAPG has since been established, and the proportion of LATG and LAPG cases among laparoscopy-assisted gastrectomies has increased to 20.0%, according to a survey in 2011. Thus, a clinical trial to evaluate the safety and efficacy of LATG and LAPG for early gastric cancer is needed.

Technical aspects of LATG and LAPG are similar to those of LADG with regard to lymph node dissection in early gastric cancer. Therefore, we assumed that the evidence for efficacy of LADG would be applicable to LATG and LAPG if LADG becomes a treatment option based on the results of JCOG0912. However, because the reconstruction method of LATG and LAPG is more difficult than that of LADG, the safety of the method, particularly of esophagojejunal anastomosis, must be evaluated. Accordingly, we planned a multicenter non-randomized confirmatory trial to evaluate the safety of LATG and LAPG for early gastric cancer.

The JCOG Protocol Review Committee approved this study in February 2015 and patient enrollment began in April 2015. Approval from the Institutional Review Board was obtained prior to activation at each institution. The UMIN Clinical Trials Registry number is UMIN000017155 (http://www.umin.ac.jp/ctr/).

Protocol digest of JCOG1401

1. Objectives

The aim of this trial is to demonstrate the safety of LATG and LAPG with nodal dissection for patients with clinical stage I gastric cancer.

2. Study setting

This is a multi-institutional non-randomized confirmatory trial.

3. Endpoints

The primary endpoint is the proportion of patients with anastomotic leakage. This is defined as the proportion of patients with a grade 2 Common Terminology Criteria for Adverse Events (CTCAE) v 4.0[5] or greater esophageal anastomotic leak among all operated patients. A grade 2 esophageal anastomotic leak in CTCAE v 4.0 is defined as "symptomatic; medical intervention indicated," and corresponds to a grade II or greater gastrointestinal anastomotic leak in JCOG Postoperative Complication Criteria according to the Clavien-Dindo Classification.[6] A grade II gastrointestinal anastomotic leak is defined as "medical management (e.g., antibiotics) or enteral/intravenous nutrition (including total parenteral nutrition) indicated." An anastomotic leak caused by other postoperative complications (e.g., pancreatic fistula) is also included as an event.

The secondary endpoints are overall survival, relapse-free survival, proportion of LATGs or LAPGs completed, proportion of patients converted to open surgery, adverse events, and short-term clinical outcomes. The proportion of LATGs or LAPGs completed is defined as the proportion of patients in whom LATG or LAPG is completed without conversion to open surgery among all surgically-treated patients. The proportion of patients converted to open surgery is defined as the proportion of those converted among patients diagnosed with clinical stage IA or IB before gastrectomy. The short-term clinical outcomes include: (i) the time from the end of surgery until the first episode of flatus, (ii) the proportion of patients requesting an analgesic on postoperative days 5 to 10, (iii) the highest body temperature during the first 3 days after surgery, and (iv) the highest body temperature during hospitalization.

4. Eligibility criteria

Gastric cancer is staged according to the Japanese Classification of Gastric Carcinoma — 14th Japanese version, which corresponds to the 3rd English edition.[6]

1) Histologically proven gastric papillary adenocarcinoma (pap), tubular adenocarcinoma (tub1, tub2), poorly-differentiated adenocarcinoma (por1, por2), signet-ring cell carcinoma (sig), or mucinous adenocarcinoma (muc).
2) Clinical T1N0, T1N(+)*, or T2N0 according to the 14th edition of the Japanese Classification of Gastric Carcinoma (3rd English edition).

*T1N(+) corresponds to T1N1 according to the 13th edition of the Japanese Classification of Gastric Carcinoma (2nd English edition[7]).

3) In cases of T2N0, the tumor does not involve the greater curvature.

4) In cases without preceding endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), either cN(+) or cN0 with no indication for EMR or ESD is eligible.
5) In cases with preceding EMR or ESD, the following conditions are all fulfilled:
   i) pathological findings require additional gastrectomy
   ii) within 91 days of EMR or ESD
   iii) no perforation from EMR or ESD
6) R0 resection is expected by total gastrectomy or proximal gastrectomy.
7) No invasion to the duodenum or esophagus.
8) Aged 20 to 80 years.
9) Performance Status (Eastern Cooperative Oncology Group) of 0 or 1.
10) Body mass index less than 30.
11) No history of upper abdominal surgery or intestinal resection, except for appendectomy.
12) No prior treatment with chemotherapy or radiation therapy for any other malignancies. Cases with a history of hormone therapy after at least 1 year since the last administration are eligible.
13) Sufficient organ functions.
   i) White bold cells $\geq$3,000/mm^3
   ii) Platelets $\geq$100,000/mm^3
   iii) Total bilirubin level $\leq$2.0 mg/dl
   iv) Aspartate transaminase level $\leq$100 IU/L
   v) Alanine transaminase level $\leq$100 IU/L
   vi) Creatinine level $\leq$1.5 mg/dl
14) Written informed consent provided.

5. Exclusion criteria

1) Synchronous or metachronous (within 5 years) malignancies except for carcinoma in situ or mucosal tumors curatively treated with local therapy.
2) Infectious disease with systemic therapy indicated.
3) Body temperature of $\geq$38 degrees Celsius.
4) Pregnancy, possible pregnancy, or within 28 days after delivery or breast-feeding.
5) Severe psychiatric disease.
6) Continuous systemic steroid or immunosuppressive drug therapy.
7) Unstable angina pectoris, or history of myocardial infarction within 6 months.
8) Poorly controlled hypertension.
9) Poorly controlled diabetes mellitus in spite of continuous use of insulin.
10) Severe respiratory disease requiring continuous oxygen therapy.

6. Registration

After confirming fulfillment of the eligibility criteria, registration is performed using the web-based system of the JCOG Data Center.

7. Treatment methods

LATG or LAPG will be performed. The extent of nodal dissection will be decided according to the surgical T and N stage, which is based on the 4th version of the Japanese Gastric Cancer Treatment Guidelines.[8] D1 or greater dissection will be applied for clinical stage IA tumor, and D2 dissection for clinical stage IB tumor. Splenectomy or bursectomy is not allowed, but preservation of the omentum and/or celiac branch of the vagus nerve is discretionary. When total gastrectomy is performed, only Roux-en-Y reconstruction is allowed. When proximal gastrectomy is performed, only double-tract or jejunal interposition reconstruction is allowed. Mini-laparotomy should be limited to 1 site, and the length of the skin incision should be 6 cm or less. When the skin incision requires extension by more than 6 cm, the case will be considered a conversion to open surgery. If the intraoperative findings reveal a tumor stage of II or greater, LATG or LAPG will be converted to open surgery.

8. Quality control of surgery

1) Certified surgeon for laparoscopic gastrectomy

All of the following criteria (1)~(3) of a certified surgeon must be fulfilled.

(1) Experience of performing 30 or more laparoscopic gastrectomies.

(2) Certification in the area of gastric cancer by either a surgical quality assurance (QA) committee or the Japan Society for Endoscopic Surgery.

(3) Either i) or ii) must be fulfilled.
   i) Experience of performing 15 or more esophagojejunal anastomoses by using a linear stapler.
   ii) Experience of performing 15 or more esophagojejunal anastomoses by using a circular stapler.

A surgical QA committee, which is credentialed by the study chair, judges the video of laparoscopic gastrectomy. Certified surgeons should perform LATG or LAPG as an operator or

teaching assistant.

9. Intraoperative photographs and video recording

A surgical QA committee performs central peer review of the surgical procedure by photographing all patients. Central peer review is performed every 6 to 12 months. Intraoperative video of arbitrarily selected patients is also shown in a group conference that is held 3 times a year to share the operation procedure.

10. Follow-up

All registered patients will be followed up for at least 5 years without any adjuvant chemotherapy, except for the patients who are finally diagnosed with pathological stage II, IIIA, or IIIB. Adjuvant chemotherapy with S-1 for 1 year is recommended for these patients. Tumor markers, chest radiography, upper gastrointestinal endoscopy, and enhanced abdominal computed tomography will be evaluated at least every year and for at least 5 years.

11. Study design and statistical analysis

This is a trial to demonstrate the safety of LATG or LAPG in terms of the proportion of patients with anastomotic leakage among all patients. When the proportion of this postoperative complication is low, as expected, we will consider LATG or LAPG to be as safe as open total or proximal gastrectomy. When the safety of LATG or LAPG is demonstrated, and LADG becomes a treatment option based on the results of JCOG0912, we will consider LATG or LAPG as one of the standard treatment options for clinical stage IA/IB gastric cancer.

Previous large-scale studies reported that the proportion of patients with esophagojejunal anastomotic leakage was 2% to 3% when open total or proximal gastrectomy was performed.[9,10] Similarly, when LATG or LAPG was performed, the proportion of patients with esophagojejunal anastomotic leakage was reported to be 0% to 4% according to available retrospective data.[11-14] Taking these reports into account, the sample size was calculated as 242 patients in order to provide 90% power, with the hypothesis that the primary endpoint would have an expected value of 3% and threshold value of 8%, using one-sided testing at a 2.5% significance level. The total sample size was set at 245 patients by assuming that a few patients will not undergo gastrectomy. The Kaplan-Meier method will be used for analysis of overall survival or relapse-free survival. All statistical analyses will be conducted at the JCOG Data Center.

12. Interim analysis and monitoring

Interim analysis is not planned. When treatment-related death or severe (grade 4) surgical morbidity is observed in 8 or more patients, the registration will be suspended and the JCOG Data and Safety Monitoring Committee will determine whether the trial can restart.

In-house interim monitoring will be performed every 6 months by the JCOG Data Center to evaluate and improve study progress, data integrity, and patient safety.

13. Participating institutions

Hakodate Goryoukaku Hospital, Keiyukai Sapporo Hospital, Iwate Medical University, Miyagi Cancer Center, Yamagata Prefectural Central Hospital, Tochigi Cancer Center, Saitama Cancer Center, Saitama International Medical Center, National Cancer Center Hospital East, Chiba Cancer Center, National Cancer Center Hospital, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo Medical and Dental University Hospital, Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Toranomon Hospital, Kanagawa Cancer Center, Yokohama City University Medical Center, Niigata Cancer Center Hospital, Nagaoka Chuo General Hospital, Toyama Prefectural Central Hospital, Ishikawa Prefectural Central Hospital, Gifu University Hospital, Shizuoka General Hospital, Shizuoka Cancer Center, Aichi Cancer Center Hospital, National Hospital Organization Kyoto Medical Center, Osaka University Graduate School of Medicine, Kinki University School of Medicine, Osaka Prefectural Hospital Organization Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka National Hospital, Osaka General Medical Center, Osaka Medical College, Toyonaka Municipal Hospital, Sakai Municipal Hospital, Kansai Medical University Hirakata Hospital, Osaka Rosai Hospital, Kobe University Graduate School of Medicine, Kansai Rosai Hospital, Itami City Hospital, Tenri Hospital, Wakayama Medical University School of Medicine, Shimane University Faculty of Medicine, Okayama University Hospital, Hiroshima University Hospital, Fukuyama City Hospital, Tokushima Red Cross Hospital, and Oita University Faculty of Medicine.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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