A Phase III study was started in Japan to evaluate the non-inferiority of overall survival of laparoscopy-assisted distal gastrectomy with open distal gastrectomy in patients with clinical IA (T1N0) or IB [T1N1 or T2(MP)N0] gastric cancer. This study followed the previous Phase II study to confirm the safety of laparoscopy-assisted distal gastrectomy (JCOG0703) and began in March 2010. A total of 920 patients will be accrued from 33 institutions within 5 years. The primary endpoint is overall survival. The secondary endpoints are relapse-free survival, proportion of laparoscopy-assisted distal gastrectomy completion, proportion of conversion to open surgery, adverse events, short-term clinical outcomes, postoperative quality of life. Only a credentialed surgeon can be responsible for both open distal gastrectomy and laparoscopy-assisted distal gastrectomy.

**Key words:** gastric cancer – laparoscopic surgery – gastrectomy – clinical trial – Phase III
In our previous multi-institutional Phase II trial, we evaluated the safety of LADG with nodal dissection for clinical stage IA and IB gastric cancer (JCOG0703) (6). In this Phase II study, the proportion of patients with either anastomotic leakage or pancreatic fistula, the primary endpoint, was only 1.7% (3/173), which was much less than the pre-specified threshold (8%). In addition, the overall proportion of in-hospital grade 3 or 4 adverse events was as low as 5.1%. We concluded that the safety of LADG was confirmed in this Phase II study, and now have launched a randomized controlled trial to compare the efficacy of LADG and ODG for clinical IA/IB gastric cancer.

The Protocol Review Committee of the Japan Clinical Oncology Group (JCOG) approved this protocol in February 2010 and the patient enrollment was started in March 2010. The approval by the institutional review board was obtained before starting patient recruitment in each institution. This trial was registered at the UMIN Clinical Trials Registry as UMIN000003319 (http://www.umin.ac.jp/ctr/index.htm).

PROTOCOL DIGEST OF THE JCOG0912

OBJECTIVES

The aim of this study is to confirm the non-inferiority of overall survival of LADG with nodal dissection with ODG for clinical stage IA (T1N0) or IB [T1N1 or T2(MP)N0] gastric cancer.

STUDY SETTING

A multi-institutional randomized Phase III study.

ENDPOINTS

The primary endpoint is overall survival in all eligible patients. Overall survival is defined as days from randomization to death from any cause, and it is censored at the last day when the patient was alive. The secondary endpoints are relapse-free survival, proportion of LADG completion, proportion of conversion to open surgery, adverse events, short-term clinical outcomes and postoperative quality of life (QOL).

Relapse-free survival is defined as days from randomization to relapse or death from any cause, and it is censored at the latest day when the patient is alive without any evidence of relapse. 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 the LADG arm. The proportion of conversion to open surgery is defined as the proportion of patients with conversion among the patients who are diagnosed before gastrectomy as clinical stage IA or IB. The short-term clinical outcomes consist of (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 5–10, (iii) the highest body temperatures during the first 3 days after the surgery and (iv) the highest body temperatures during hospitalization. Postoperative QOL is evaluated using EORTC QLQ-C30 and STO22. This QOL evaluation is performed only in four principal institutions due to the lack of resources in the other institutions. Primary analysis of QOL is performed using the global health status from EORTC QLQ-C30 in the 90th postoperative day.

ELIGIBILITY CRITERIA

INCLUSION CRITERIA

(i) Histologically proven gastric adenocarcinoma.
(ii) Clinical stage IA (T1N0) or IB [T1N1, T2(MP)N0] according to the Japanese Classification of Gastric Carcinoma, Second English edition (7).
(iii) In case without preceding endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), either ‘cN1’ or ‘cN0 and no indication of EMR’ is eligible.
(iv) In case with preceding EMR or ESD, the following conditions are fulfilled: (i) pathological findings require additional gastrectomy, (ii) within 91 days from EMR, (iii) no perforation by EMR and (iv) resection margin of EMR did not reach to the upper third of the stomach.
(v) Tumor located in the middle or lower third of the stomach, and curative resection is expected to be achievable by distal gastrectomy.
(vi) No invasion to duodenum.
(vii) Aged 20–80 years.
(viii) PS (ECOG) of 0 or 1.
(ix) A body mass index of <30.
(x) No history of upper abdominal surgery and no history of intestinal resection.
(xi) No prior treatment of chemotherapy or radiation therapy against any other malignancies.
(xii) Sufficient organ functions.
(xiii) Written informed consent.

EXCLUSION CRITERIA

(i) Synchronous or metachronous (within 5 years) malignancies other than carcinoma in situ.
(ii) Infectious disease with a systemic therapy indicated.
(iii) Body temperature of 38°C or more.
(iv) Women during pregnancy or breast-feeding.
(v) Severe mental disease.
(vi) Continuous systemic steroid therapy.
(vii) Unstable angina pectoris or history of myocardial infarction within 6 months.
(viii) Uncontrollable hypertension.
(ix) Uncontrollable diabetes mellitus or administration of insulin.
(x) Severe respiratory disease requiring continuous oxygen therapy.

**Randomization**

After the confirmation of the eligibility criteria, registration is made by telephone, fax or web-based system to the JCOG Data Center. Patients are randomized to either the ODG arm or the LADG arm by minimization method balancing the arms with institution and clinical stage (IA/IB).

**Treatment Methods**

The ODG or the LADG is performed in respective arms. All procedures are same except for the surgical approach. The extent of nodal dissection is decided according to the surgical T and N stage which is based on the third version of the Gastric Cancer Treatment Guideline in Japan (4). D1 or more dissection is applied for clinical stage IA tumor and D2 dissection is applied for clinical stage IB tumor. For clinical T1 gastric cancer having 4 cm or more margin from the pylorus, pylorus-preserving distal gastrectomy is allowed. Bursectomy is not allowed but preservation of omentum and/or vagus nerve is discretionary. The reconstruction method is not specified in this study.

In the LADG arm, > 6 cm of the mini-laparotomy incision is not allowed. If the intraoperative findings reveal a tumor stage of II or greater, the LADG is converted to an open surgery.

Only the surgeons credentialed by the study chair can be responsible for both LADG and ODG. In the ODG arm, the experience of 60 or more open gastrectomies is needed to be certified as a credentialed surgeon. In the LADG arm, the experience of 30 or more LADGs and the certification or its equivalent by the Japan Society for Endoscopic Surgery are needed. All the LADG procedures are centrally reviewed by photographs.

**Follow-Up**

Adjuvant chemotherapy with S-1 for 1 year is recommended for patients with curative resection and pathological stage II, IIIA or IIIB tumors.

All randomized patients are followed up for at least 5 years. Tumor markers, chest X-ray, upper gastrointestinal endoscopy and enhanced chest computed tomography is evaluated at least every year for the duration of the follow-up.

**Study Design and Statistical Analysis**

This randomized trial is designed to demonstrate that LADG is non-inferior to ODG in terms of overall survival. Some endpoints are adopted to evaluate the less invasiveness of LADG over ODG, but those endpoints are all considered to be exploratory. Thus, as long as the non-inferiority of LADG is confirmed, LADG will be concluded as one of the options of the standard treatments for clinical stage IA/IB gastric cancer.

According to the Schoenfeld and Richter’s method (8), the planned sample size is 920 patients, with 460 patients per arm. We anticipate 5 years of follow-up after 5 years of accrual, ensuring at least 80% power with a one-sided alpha of 5% and a non-inferiority margin of 5% in terms of 5-year survival. This assumes an expected 5-year overall survival of 90% in each arm.

The patients who are randomized to the LADG arm and are converted to ODG are included in the LADG population for the efficacy analyses based on the intention-to-treat principle. In the safety analyses, they are also regarded as the LADG population if the surgery starts as LADG but changes to ODG in the middle of the surgery, while they are included in the ODG population if the surgery starts as ODG from the beginning.

**Interim Analysis and Monitoring**

We plan to conduct two interim analyses, taking multiplicity into account using the Lan-DeMets method with the O’Brien and Fleming type alpha spending function. The Data and Safety Monitoring Committee of the JCOG will independently review the interim analysis reports and stop the trial early if necessary. In-house monitoring will be performed every 6 months by JCOG Data Center to evaluate and improve the progress and quality of the study.

**Participating Institutions (From North to South)**

Hakodate Goryoukaku Hospital, Iwate Medical University, National Hospital Organization Sendai Medical Center, Yamagata Prefectural Central Hospital, Tochigi Cancer Center, National Cancer Center Hospital East, National Cancer Center Hospital, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, Tokyo Medical and Dental University Hospital, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Toranomon Hospital, Kanagawa Cancer Center, Kitasato University School of Medicine, Yokohama City University Medical Center, Toyama Prefectural Central Hospital, Ishikawa Prefectural Central Hospital, Shizuoka General Hospital, Shizuoka Cancer Center, Aichi Cancer Center Hospital, Nagoya University School of Medicine, Fujita Health University, Osaka University Graduate School of Medicine, Kinki University School of Medicine, Osaka Prefectural Hospital Organization Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka Medical College, Kansai Medical University Hirakata Hospital, Hyogo Cancer Center, Wakayama Medical University School of Medicine, Shimane University School of Medicine, Hiroshima City Hospital, Fukuyama City Hospital, National Hospital Organization Shikoku Cancer Center, Oita University Faculty of Medicine.

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Conflict of interest statement

None declared.

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