Laparoscopic or Open Distal Gastrectomy After Neoadjuvant Chemotherapy for Operable Gastric Cancer, a Randomized Phase II Trial (LANDSCOPE Trial)

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This randomized Phase II trial will compare the efficacy and safety of laparoscopy-assisted D2 distal gastrectomy and open distal D2 gastrectomy after neoadjuvant chemotherapy for patients with macroscopically resectable serosa-positive gastric cancer. When R0/R1 surgery is achieved, patients receive S-1 chemotherapy for 1-year post-operatively. The primary endpoint is the 3-year disease-free survival. The sample size to test the hypothesis of the non-inferiority of laparoscopy-assisted D2 distal gastrectomy to open distal D2 gastrectomy is 80. This trial will be able to appraise the use of the laparoscopic approach as a curative D2 distal gastrectomy after neoadjuvant chemotherapy for gastric cancer.

Key words: gastric cancer – laparoscopy – D2 – gastrectomy – neoadjuvant chemotherapy

INTRODUCTION

Gastric cancer is the second leading cause of cancer death in the world and is the most common malignancy in Japan, South America and Eastern Europe (1). Complete resection is essential for the cure of gastric cancer (2). Even after macroscopic complete resection, more than half of T3 and T4 tumors recur. Recently, adjuvant chemotherapy with S-1 (1 M tegafur—0.4 M gimestat—1 M ostat potassium) for 12 months has been established as the standard treatment after D2 gastrectomy in Japanese patients with Stage II or III disease based on a large Phase III study (3). Nonetheless, even with adjuvant S-1 chemotherapy, the prognosis for serosa-positive tumors was not satisfactory.

Pre-operative (neoadjuvant) chemotherapy followed by extended surgery has some theoretical benefits when compared with post-operative chemotherapy (4). Several European Phase III trials have demonstrated that neoadjuvant chemotheraphy, followed by curative surgery and adjuvant chemotherapy, improved the survival for gastric cancer patients (5,6). In Japan, a Phase III trial conducted by the Japan Clinical Oncology Group (JCOG) is now ongoing to evaluate the efficacy of neoadjuvant chemotherapy followed by surgery and post-operative S-1 for clinically resectable scirrhous type gastric cancer. More recently, several regimens and courses of neoadjuvant chemotherapy were tested in clinical T4 or clinical stage III patients in Phase II trials (7).

After neoadjuvant chemotherapy, patients generally receive a D2 gastrectomy with curative intent. For many years, gastrectomy has been performed under laparotomy. Since Kitano et al. (8) reported the first case of laparoscopy-assisted distal gastrectomy (LADG) for gastric...
cancer in 1994, LADG has been widely performed in community hospitals not only for early disease but also for advanced tumors. Laparoscopic surgery provides a good quality of life in addition to cosmetic benefits. LADG is often selected when the tumors are located in the middle to the lower third of the stomach. Unlike LADG, total gastrectomy remains challenging under the laparoscopic approach and the technique has not been standardized.

The feasibility and safety of LADG was confirmed for T1 and T2N0 disease in Japanese Phase II (9) and Korean Phase III (KLASS trial, NCT00452751) trials (10). The non-inferiority of long-term survival will be confirmed in Japanese (JCOG-0912 trial, UMIN000003319) and Korean Phase III trials. Moreover, a Phase II/III trial is ongoing for advanced gastric cancer in Japan (JLSSG0901 trial, UMIN000003420). The Phase II part of this trial was finished, and the feasibility and safety of LADG was confirmed for advanced disease.

Thus, candidates for future standard treatment are multimodality treatments including neoadjuvant chemotherapy and LADG, when advanced tumors are located in the middle to the lower third of the stomach. However, LADG after neoadjuvant chemotherapy has not been evaluated in Phase II trials, although it has been presented to be safe and feasible in some Japanese medical meetings repeatedly (11).

Based on these, we conducted a randomized Phase II trial to compare LADG and open distal gastrectomy (ODG) after neoadjuvant chemotherapy for gastric cancer.

**PROTOCOL DIGEST OF THE STUDY**

**PURPOSE**

The purpose of the study is to evaluate the safety and efficacy of LADG compared with ODG for gastric cancer which is macroscopically resectable by D2 gastrectomy, to determine whether LADG can be a test arm for a future Phase III trial to evaluate the non-inferiority of overall survival compared with ODG in patients who receive neoadjuvant chemotherapy. To minimize the variability of chemotherapy regimens, we restrict to the patients who are enrolled in the Phase II trial of neoadjuvant chemotherapy (COMPASS-D trial, UMIN000006378) (12).

**STUDY SETTING AND PROTOCOL REVIEW**

The study is an open-label, randomized Phase II clinical trial. The protocol has been approved by the Protocol Review Committee of Kanagawa Standard Anti-cancer Therapy Support System (KSATTS).

**RESOURCES**

Research grants are from the KSATTS.

**ENDPOINTS**

The primary endpoint is the 3-year progression-free survival (PFS) rate. The secondary endpoints are the overall survival, surgical morbidity and mortality, R0 resection rate, R0/R1 resection rate, conversion rate, efficacy and safety in patients who complete the surgery, and efficacy and safety in each subset.

**ELIGIBILITY CRITERIA FOR THE FIRST ENROLLMENT**

The tumors are staged according to the 14th edition of the Japanese Gastric Cancer Classification (13).

The inclusion criteria are as follows:

(i) Histologically proven adenocarcinoma of the stomach.
(ii) Clinical T4aN0-N3 disease, confirmed by upper gastrointestinal endoscopy or an upper gastrointestinal series, and abdominal computed tomography (CT) and laparoscopy. The T and N stages are determined by the method of Habermann et al. (14).
(iii) The gastric tumors are located in the middle to lower third of the stomach, are macroscopically resectable by distal gastrectomy with D2 lymph node dissection, and R0 or R1 resection can be achieved.
(iv) No bulky lymph node metastasis is detected by abdominal CT.
(v) No pleural effusion, no ascites exceeding the pelvis and no metastasis to the peritoneum, liver or other distant organs are confirmed by abdominal pelvic CT.
(vi) No clinically apparent distant metastasis.
(vii) Age ranging between 20 and 80 years.
(viii) ECOG performance status 0–1.
(ix) Sufficient oral intake.
(x) No previous treatment with chemotherapy or radiation therapy for any tumors.
(xi) No previous surgery for the present disease.
(xii) The patients were enrolled in the COMPASS-D Phase II trial comparing neoadjuvant chemotherapy with two and four courses of S-1 plus cisplatin (SC) or S-1 plus cisplatin and docetaxel (SCD) by a two-by-two factorial design for patients with macroscopically resectable serosa-positive gastric cancer, and receive neoadjuvant chemotherapy.
(xiii) Written informed consent.

The exclusion criteria are as follows:

(i) Past history of upper abdominal surgery.
(ii) Past history of surgery for the gastrointestinal tract.
(iii) Body mass index exceeding 30 kg/m².

**ELIGIBILITY CRITERIA FOR THE SECOND ENROLLMENT**

(i) Patients received two or four courses of SC or SCD defined by the COMPASS-D trial.
(ii) The gastric tumors are macroscopically resectable disease by distal gastrectomy with D2 lymph node
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REGISTRATION

Reduced port surgery is prohibited. The length of the skin dissection is started. After confirming the resectability, whether R0 or R1 surgery is possible by D2 distal gastrectomy. When R0/R1 surgery is impossible, the protocol treatment regimen when the anti-cancer drugs were given.

Group A: ODG with D2 lymph node dissection

Group B: Laparoscopic distal gastrectomy with D2 lymph node dissection

In both groups, the intraperitoneal cavity is checked to see whether R0 or R1 surgery is possible by D2 distal gastrectomy. When R0/R1 surgery is impossible, the protocol treatment is stopped. After confirming the resectability, dissection is started.

For Group B, the number of trocars is limited to 5 or 6. Reduced port surgery is prohibited. The length of the skin incision is limited to ≤6 cm. When a longer skin incision is necessary, the case is regarded to require conversion to open surgery. The protocol prohibits laparoscopic total gastrectomy and laparoscopic extended surgeries such as lymphadenectomy exceeding D2 and combined resection of other organs. When these types of surgery are necessary to achieve an R0/R1 resection, the surgeon must convert to open surgery. The operators of laparoscopic surgery are limited to the surgeons whose skills for laparoscopic distal gastrectomy are qualified by Japan Society for Endoscopic Surgery.

More invasive surgeries such as pancreatoduodenectomy or Appleby’s surgery are prohibited. The protocol treatment is to be stopped if curative surgery is not performed. When R0/R1 surgery is achieved, S-1 of 80 mg/m² p.o. daily for 28 days, every 6 weeks, is initiated within 6 weeks after surgery, and was continued for 1 year. After the completion of the protocol treatment, no other treatment is permitted until recurrence is noted.

STUDY DESIGN AND STATISTICAL METHODS

The present study is a randomized Phase II trial to evaluate the efficacy and safety of LADG compared with ODG. This study is primarily designed to evaluate the 3-year DFS rate of LADG and to demonstrate that it is not inferior to that of ODG. LADG will be considered to be promising for a subsequent Phase III trial if the Bayesian posterior probability of ‘the difference of the 3-year DFS rate is less than the non-inferiority margin of 8%’ is at least 50% (15). For safety, the point estimate of treatment-related death (TRD) is expected to be ≤5% in each group.

The planned sample size is 80, with 40 cases per arm. This sample size provides 76% chance of satisfying the above criteria, under the hypothesis that the expected 3-year disease-free survival rate in each arm is 50%.

The primary analysis in this study aims to estimate the 3-year DFS rate. The DFS curves are constructed as time-to-event plots by using the Kaplan–Meier method (14), and the 3-year DFS and its 95% confidence interval are estimated. The 3-year DFS is compared based on the normal approximation of the 3-year DFS rate (z-test). The overall survival is also analyzed in the same manner. The surgical morbidity and mortality, R0 resection rate, R0R1 resection rate and conversion rate are calculated as proportions with exact confidence intervals and compared with the Fisher’s exact test.

INTERIM ANALYSIS AND MONITORING

The Data and Safety Monitoring Committee (DSMC) independently review the report of trial monitoring regarding the efficacy and safety data from the present study. Based on the monitoring, the DSMC can consider early termination of a treatment regimen when the TRD exceeds 5% (three patients) in each group during the enrollment. The protocol
compliance, safety, and on-schedule study progress are also monitored by the DSMC.

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**Conflict of interest statement**

None declared.

**References**