Review Article

Laparoscopy-assisted gastrectomy following neoadjuvant chemotherapy for advanced gastric cancer - strategies for development

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Abstract: The established treatment for advanced gastric cancer is open gastrectomy with D2 lymph node dissection and postoperative adjuvant chemotherapy with S-1 or capecitabine plus oxaliplatin. However, the prognosis of patients with stage III disease is not satisfactory. More intensive chemotherapy is required to improve survival. Considering the patient compliance observed with intensive doublet or triplet chemotherapy, the administration of neoadjuvant chemotherapy is an attractive and promising approach. Many phase III trials to evaluate neoadjuvant chemotherapy in eastern Asia are now ongoing. On the other hand, surgical approaches have shifted to laparoscopic surgery. Several phase III trials to evaluate the efficacy of laparoscopy-assisted distal gastrectomy (LADG) have been performed in Japan and Korea, in both patients with early and advanced disease. Therefore, the candidates for future standard treatment consist of multimodality treatments, including neoadjuvant chemotherapy and subsequent LADG, for patients with advanced tumors located in the middle to lower third of the stomach. The feasibility, safety and long-term survival of laparoscopic gastrectomy following neoadjuvant chemotherapy must be guaranteed when neoadjuvant chemotherapy is the standard of care. Based on this background, we conducted a randomized phase II trial to compare LADG and open distal gastrectomy (ODG) after neoadjuvant chemotherapy for gastric cancer.

Key Words: Gastric cancer; laparoscopy; D2; gastrectomy; neoadjuvant chemotherapy

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Why should neoadjuvant chemotherapy be developed?

Gastric cancer is the second leading cause of cancer death worldwide and is the most common malignancy in Japan, South America, and Eastern Europe (1). Complete resection is essential for curing gastric cancer (2), however, the prognosis of patients with advanced disease treated with surgery alone is not satisfactory. Since 2000, surgery combined with adjuvant treatment has become the globally accepted standard of care for advanced gastric cancer. In the US, surgery followed by chemoradiotherapy has been established as the standard treatment based on the results of the INT-0116 phase III trial (3). In the UK and some European countries, pre- and postoperative chemotherapy with epirubicin, cisplatin and 5-fluorouracil is employed based on evidence from the MAGIC trial (4). However, surgery combined with adjuvant treatment was not optimized in the phase III trials performed in the US or Europe. After a long debate (5), D2 surgery, which was originally established in Japan, has been accepted as a standard surgery in Europe (6) and the US (7). The long-term observational report of the Dutch Phase III trial comparing D1 and D2 clearly demonstrated that

D2 reduces local recurrence after surgery and thereby contributes to survival (8).

In eastern Asia where D2 is the standard surgery, two pivotal phase III trials comparing D2 and D2 followed by postoperative adjuvant chemotherapy were conducted. The ACTS-GC phase III trial performed in Japan demonstrated the benefit of S-1 for 12 months after D2 (9), and the CLASSIC phase III trial performed primarily in Korea indicated the benefits of capecitabine and oxaliplatin for six months after D2 (10). Currently, D2 surgery combined with the administration of adjuvant chemotherapy is recommended as the standard treatment for advanced gastric cancer: D2 surgery followed by S-1 in Japan and D2 surgery followed by capecitabine and oxaliplatin in Korea and the US (11).

Nevertheless the survival of patients with advanced disease is not satisfactory even by means of D2 and postoperative adjuvant chemotherapy. To improve the prognosis, more effective but also more toxic treatments exceeding these regimens should be developed in the future. However, it is questionable whether a more toxic combination regimen administered after gastrectomy is feasible or safe. Concurrent doublet combination regimens including CDDP are not acceptable (12). Although S-1 induces mild toxicities, the proportion of time to treatment failure at 12 months after surgery was not satisfactory, namely it was only 65.8% in the ACTS-GC study (9). Generally, patients suffer from loss of appetite and decreased food intake following gastrectomy, which causes a loss of body weight and decreases the quality of life. These factors may influence compliance with chemotherapy. Recently, we examined the risk factors for discontinuing S-1 after gastrectomy and found weight loss after surgery to be a significant independent risk factor (13). More toxic regimens administered after gastrectomy generally lack feasibility and safety.

Different from post-operative adjuvant chemotherapy, the administration of more intensive chemotherapy is possible in the neoadjuvant setting. The MAGIC trial clearly showed a high rate of compliance of chemotherapy with chemotherapy due to low toxicities associated with neoadjuvant chemotherapy compared with post-operative adjuvant chemotherapy (4). Moreover, all patients who should receive chemotherapy can initiate chemotherapy before surgery. It is obvious that some patients are unable to start chemotherapy after surgery due to surgical morbidity and mortality. Moreover, tumor regression due to the effects of chemotherapy and the avoidance of unnecessary surgery as a result of progression during chemotherapy would contribute to high rates of substantial R0 resection.

Another reason is the theoretical advantage of neoadjuvant chemotherapy. The aim of adjuvant chemotherapy is to eradicate micrometastatic tumor cells that cannot be resected during surgery. No treatment for micrometastatic tumor cells is administered until the patient has recovered from surgery and postoperative chemotherapy is initiated. On the other hand, micrometastatic tumor cells are initially treated without delay in neoadjuvant chemotherapy regimens, which is another theoretical benefit of neoadjuvant chemotherapy.

On the other hand, over-diagnosis is a disadvantage of neoadjuvant chemotherapy. In the MAGIC trial, the target patients had clinical stage II-III disease and all patients had clinical T2-T4 disease (4). However, 8.3% of the patients had pathological T1 disease in the randomized surgery alone arm.

Current status of clinical trials for neoadjuvant chemotherapy

In Japan, a phase III trial conducted by the Japan Clinical Oncology Group (JCOG) is now on-going to evaluate the survival benefits of neoadjuvant chemotherapy consisting of S-1 plus CDDP followed by surgery and postoperative S-1 by comparing surgery and postoperative S-1 in patients with clinically resectable scirrhous type gastric cancer. More recently, several regimens and courses of neoadjuvant chemotherapy were tested among clinical T4 or clinical stage III patients in phase II trials (14,15). One of these trials is the COMPASS trial comparing neoadjuvant chemotherapy consisting of two and four courses of S-1 + CDDP, paclitaxel and CDDP for stage III gastric cancer by a two- by two-factorial design. The other is the COMPASS-D trial comparing neoadjuvant chemotherapy consisting of two and four courses of S-1 plus CDDP and S-1, CDDP and docetaxel for macroscopically resectable serosa-positive gastric cancer by a two- by two- factorial design (15).

In Korea, the PRODIGY phase III trial (NCT01515748) is now on-going to evaluate the survival benefit of neoadjuvant chemotherapy consisting of docetaxel, oxaliplatin, and S-1 followed by D2 and postoperative S-1 by comparing D2 and postoperative S-1 in patients with T2-3/N+ and T4 disease. In China, two different phase III trials are now on-going to evaluate the benefits of neoadjuvant chemotherapy by comparing surgery and

postoperative S-1 plus oxaliplatin. One study is being conducted to test neoadjuvant chemotherapy consisting of pre- and post operative S-1 plus oxaliplatin (RESONANCE phase III, NCT01583361), while the other is being performed to evaluate pre- and post operative S-1 plus oxaliplatin as well as pre- and post operative capecitabine plus oxaliplatin in three arms (the Hebei Medical University trial, NCT01516944). In the UK, perioperative bevacizumab combined with the MAGIC regimen was tested in the STO3 phase III study (NCT00450203).

Although new regimens such as S-1 followed by S-1 plus oxaliplatin, chemoradiation with S-1 or capecitabine with oxaliplatin, or S-1 plus docetaxel have been tested as post-operative adjuvant chemotherapy in phase III trials, no trials have evaluated the use of triplet regimen after surgery. In the future, it is obvious that post-operative adjuvant chemotherapy will shift to neoadjuvant chemotherapy.

Surgery combined with neoadjuvant chemotherapy

D2 gastrectomy is a feasible and safe procedure when performed by experienced surgeons. The morbidity and mortality were reported to be 20.9% and 0.8% (16), respectively, in the JCOG-9501 phase III trial performed in Japan. On the other hand, the feasibility and safety of D2 surgery following neoadjuvant chemotherapy has not been fully evaluated. In the MAGIC phase III trial, the surgical morbidity and mortality were 45.7% and 5.6%, respectively in the patients who received surgery following pre-operative chemotherapy and 45.3% and 5.9%, respectively in those who received primary surgery (4). In the FNCLCC/FFCD phase III study, the postoperative morbidity and mortality were 25.7% and 4.6%, respectively, in the patients who received neoadjuvant chemotherapy followed by surgery and 19.1% and 4.5%, respectively, in the patients who received primary surgery (17). In both trials, the surgical complications were similar regardless of whether the patients received primary surgery alone or surgery following the neoadjuvant chemotherapy, however, the surgical procedures were less than D2 in most cases in the MAGIC study and were not accurately described in the FNCLCC/FFCD phase III study.

Only one phase III study (EORTC 40954 study) has compared D2 surgery and preoperative 5-FU plus CDDP and D2 surgery (18). D2 surgery was performed in more than 90% of the patients in both arms. The overall morbidity was higher in the neoadjuvant group (27.1%) than in the surgery alone group (16.2%). Injury of a major blood vessel occurred in 4.3% of the patients in the neoadjuvant arm versus 1.5% of the patients in the surgery alone arm. In the surgery alone arm, one splenectomy was required to achieve hemostasis. Different from D1 and D0 surgery, the nodes along the pancreas and spleen should be dissected in D2 or more extended surgery. When the lymph nodes along the pancreas are enlarged, it may difficult to identify the branched arteries or drainage veins around the pancreas, which can be related to surgical difficulties.

On the other hand, several Japanese investigators have demonstrated that performing D2 or more extended surgery is feasible and safe, even after neoadjuvant chemotherapy, in single-arm phase II studies (19-21). Except for randomized studies, the complication rates in the single-arm studies are difficult to compare with other historical control data, due to differences in the population, chemotherapy regimen, duration of chemotherapy, and the terminology and definitions used to describe each complication were not strictly determined. In addition, surgical complications differ between total and distal gastrectomy.

Current status of laparoscopy-assisted distal gastrectomy (LADG)

Since Kitano reported the first case of LADG for gastric cancer in 1994 (22), LADG become widely performed in community hospitals to treat both early disease and 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. Thus far, many retrospective studies, in-house small prospective studies, and meta-analysis demonstrated the feasibility and safety of LADG for treating gastric cancer (23,24). Recently, Katai reported that the rate of Grade 3 or 4 morbidities evaluated according to the Clavien-Dindo classification was 5.1% among 176 patients and that the rate of anastomotic leakage and/or pancreatic fistula, the primary endpoint, was only 1.7% in a large-scale multicenter phase II study (25). Based on this study, Katai initiated a phase III study (JCOG-0912 study, UMIN000003319) to compare overall survival between LADG and open distal gastrectomy (ODG) for stage I gastric cancer (26). In Korea, Kim also reported that morbidity and mortality were not significantly different between LADG and ODG among 342 patients enrolled in a phase III study (KLASS-01 study, NCT00452751) (27).

The KLASS-01 study has recently completed patients recruitment (n=1,415) and will be opened in September 2015 (28). The JCOG-0912 and KLASS-01 studies will clarify that LADG exhibits non-inferior survival compared with ODG for early gastric cancer.

Moreover, a phase II/III trial is now on-going for advanced gastric cancer in Japan (JLSSG0901 trial, UMIN000003420). The phase II part of this trial has been completed, and the feasibility and safety of LADG with D2 dissection were confirmed for patients with advanced disease. In Korea, Lee also reported that performing LADG with D2 was found to be feasible and safe in a single-arm phase II study (29). In Korea, the KLASS-02 trial (NCT01456598) is also now on-going to compare D2 gastrectomy using the laparoscopic or open approach for T2-T3 gastric cancer. The JLSSG0901 and KLASS-02 studies will clarify whether LADG exhibits non-inferior survival compared with ODG for advanced gastric cancer.

Unlike LADG, performing total gastrectomy under the laparoscopic approach remains challenging and the technique has not been standardized.

Strategy to develop LADG following neoadjuvant chemotherapy

Considering the current status of the development of neoadjuvant chemotherapy and laparoscopic surgery for advanced disease as a primary treatment, the candidates for future standard treatment include multimodality treatments, such as neoadjuvant chemotherapy and subsequent LADG, when advanced tumors are located in the middle to lower third of the stomach. However, the efficacy of LADG following neoadjuvant chemotherapy has not yet been established. The feasibility, safety and long-term survival of laparoscopic gastrectomy following neoadjuvant chemotherapy must be guaranteed when neoadjuvant chemotherapy is the standard of care. This procedure has repeatedly been presented to be safe and feasible in some Japanese medical meetings (30). However, the use of LADG following neoadjuvant chemotherapy has not yet been tested in prospective clinical trials.

What should be evaluated in trials and how?

Surgical difficulties are affected by the extent of gastrectomy, the extent of dissection, disease progression, body composition, the duration and regimen of neoadjuvant chemotherapy and the approach of laparoscopy or open surgery. One ideal trial would be to evaluate whether safety and feasibility differ between LADG and ODG under the same conditions. Randomized trials to compare LADG and ODG following the same regimen of neoadjuvant chemotherapy would clarify this hypothesis. Another hypothesis is that the LADG following neoadjuvant chemotherapy is equally as feasible and safe as primary open surgery without neoadjuvant chemotherapy. Because a morbidity of 20.9% and a mortality of 0.8% were observed in the patients receiving primary D2 surgery (16), LADG following neoadjuvant chemotherapy must have either equivalent of lower rates of lower morbidity and mortality than these values. The hurdles for LADG appear to be too high in this setting. Based on this background, we conducted a randomized phase II trial to compare LADG and open distal gastrectomy (ODG) after neoadjuvant chemotherapy for gastric cancer (31).

LANDSCOPE trial

The purpose of this study was to evaluate the safety and efficacy of LADG compared with ODG for gastric cancer that is macroscopically resectable via D2 gastrectomy and to determine whether LADG can be used in a test arm in a future phase III trials to evaluate the non-inferiority of overall survival compared with ODG in patients who receive neoadjuvant chemotherapy. To minimize variability in chemotherapy regimens, we restrict to the subjects to the patients enrolled in a randomized phase II trial of neoadjuvant chemotherapy comparing a regimen of S-1 plus CDDP (SC) and S-1/CDDP/Docetaxel (SCD) as well as the duration of two and four courses of chemotherapy (COMPASS-D trial, UMIN000006378) (15).

This study is an open-label, randomized phase II clinical trial. The protocol has been approved by the Protocol Review Committee of the Kanagawa Standard Anti-cancer Therapy Support System (KSATTS). 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, R0R1 resection rate, conversion rate, efficacy and safety in patients who complete the surgery and the efficacy and safety in each subset.

The key eligibility criteria for the 1st enrollment before neoadjuvant chemotherapy included histologically proven adenocarcinoma of the stomach, clinical T4aN0-N3M0 disease, confirmed on upper gastrointestinal endoscopy or an upper gastrointestinal series, and abdominal CT and laparoscopy according to the method of Haberrmann (32),

an age ranging between 20 and 80 years and the patients who were enrolled in the COMPASS-D phase II trial. The key eligibility criteria for the 2nd enrollment included patients who received two or four courses of SC or SCD, as defined by the COMPASS-D trial, and the presence of gastric tumors that are macroscopically resectable via distal gastrectomy with D2 lymph node dissection. Resectability was evaluated using upper gastrointestinal endoscopy and CT seven to 21 days after the date when the anti-cancer drugs were administered.

Following the completion of neoadjuvant chemotherapy or when the tumors progress during treatment, the patients will proceed to surgery. The patients enrolled in this study will receive open or laparoscopic distal gastrectomy. In both groups, the intraperitoneal cavity will be assessed to determine whether R0 or R1 surgery is possible via D2 distal gastrectomy. When performing R0/R1 surgery is impossible, the protocol treatment will be stopped. After confirming resectability, dissection will be started.

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

The present study is a randomized phase II trial to evaluate the efficacy and safety of LADG compared to 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 promising for a subsequent phase III trial if the Bayesian posterior probability of "the difference in the 3-year disease-free survival (DFS) rate is less than a non-inferiority margin of 8%" is at least 50% (33). 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 a 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, and the 3-year DFS and its 95% confidence interval will be estimated. The 3-year DFS will be compared based on the normal approximation of the 3-year DFS rate (z test). The overall survival will also be analyzed in the same manner. The surgical morbidity and mortality, R0 resection rate, R0R1 resection rate, and conversion rate, will be calculated as proportions with exact confidence intervals, and compared using Fisher's exact test.

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