Review Article

Ongoing clinical studies of minimally invasive surgery for gastric cancer in Japan

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Abstract: Since the development of laparoscopy-assisted distal gastrectomy (LADG) with lymph node dissection for gastric cancer in Japan, this type of surgery is improving and evolving. To establish high-quality evidence of laparoscopic gastrectomy (LAG) in the field of gastric cancer treatments, two large-scale, prospective randomized controlled trials have been performed in Japan; the Japan Clinical Oncology Study Group (JCOG) 0912 for early disease and the Japanese Laparoscopic Surgery Study Group (JLSSG) 0901 for advanced disease. Analyses using mega-data from the National Clinical Database (NCD) have also been carried out as a clinical study to clarify the safety of LAG. Furthermore, as advanced laparoscopic techniques have been developed, prospective clinical studies are being performed with regard to laparoscopy-assisted total gastrectomy (LATG), robotic gastrectomy, and minimally invasive surgery with sentinel node (SN) navigation. This review summarizes the current status of minimally invasive surgeries for gastric cancer based on the latest ongoing clinical trials in Japan.

Keywords: Laparoscopic gastrectomy (LAG); randomized clinical trials (RCTs); advanced gastric cancer (AGC)

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Introduction

Since laparoscopy-assisted distal gastrectomy (LADG) with lymph node dissection for early gastric cancer (EGC) was developed in 1991 in Japan, the number of patients treated using LAG has gradually increased (1,2). In January 2011, the National Clinical Database (NCD) in Japan started to prospectively collect data on surgical procedures. According to the NCD data base, the ratio of LADG and laparoscopy-assisted total gastrectomy (LATG) has reached 45% and 20% of total number of the cases undergone gastrectomy for gastric cancer, respectively.

Initially, major efforts were made to improve the technical safety and improve the standardization of laparoscopic gastrectomy (LAG) (3-7). For the purpose of improving the laparoscopic technique, the Japan Society for Endoscopic Surgery (JSES) established the Committee for the Endoscopic Surgical Skill Qualification System in 2001 (8,9). With regard to the clinical relevance of this examination, Mori *et al*. demonstrated that surgical complications were significantly fewer in those who passed the examination compared with those who failed (8). Thus, this assessment system may contribute to the standardization of laparoscopic techniques and enhance surgical skills in the field of LAG.

Although advances in techniques and improvement of instruments have led to the standardization of LAG with lymph node dissection among experienced surgeons, surgeons should valuate as to whether the laparoscopic approach to gastric cancer is adequate and beneficial for

cancer treatment. Therefore, large-scale, prospective studies are needed to answer several clinical questions.

Here we review ongoing clinical studies of LAG for gastric cancer in Japan, and introduce the current status of the latest studies.

Current indication of LAG for gastric cancer according to the Japanese gastric cancer guidelines (version 4)

Since the Japanese gastric cancer treatment guidelines were established in 2001, LAG has been indicated as an investigational treatment even though the number of LAG rapidly increased in Japan (10). Small-scale randomized controlled trials, a non-randomized study and retrospective studies have demonstrated that LAG has superior short-term and comparable long-term outcomes to open gastrectomy (11-17). As a result, the guidelines were revised based on the latest evidence and trends of cancer treatments in 2014. According to the recent guidelines (version 4), LAG is recommended as an optional treatment for cStage IA gastric cancer not indicated for endoscopic treatment and cStage IB gastric cancer.

However, there are several limitations in this statement. First, the only study with a high level of evidence is a single, small-scale, randomized clinical trial (RCT). Recently, a Japanese phase II clinical trial performed by the Japan Clinical Oncology Study Group (JCOG0703) in patients with cStage IB (including SS, N0) gastric cancer demonstrated that LADG can be performed safely with a minimal risk of anastomotic insufficiency or pancreatic fistula, although most of the patients had cStage IA cancer (18). The technical feasibility of LADG could be statistically proven; on the other hand, data on long-term outcome are not available yet. Second, it should be noted that in the Japanese trial, LADG was performed by surgeons with a high level of relevant experience. Therefore, the indication should be considered in each institution by taking into account not only surgeon' skills but also surgical team organization. Third, the technical safety of LATG is still controversial, particularly in terms of anastomotic complications. Although LAG including distal gastrectomy (DG) and total gastrectomy is covered by Japanese health insurance, LAG currently means LADG in most cases.

Thus, the statements on LAG in the latest guidelines mainly pertain to LADG. Taking the above limitations into consideration, the statements in these guidelines are applicable to practice.

Ongoing clinical studies of LAG for gastric cancer in Japan

To provide answers to the clinical questions, prospective clinical studies are ongoing in Japan. These contain multicenter prospective randomized trials and a large-scaled prospective cohort study.

Current studies of LADG for EGC

Since LADG for EGC was introduced in 1991, the technical and oncological feasibility of LAG has been evaluated worldwide. However, most of these studies were limited by having a small sample size, and a short-term follow-up period.

Therefore, a retrospective, multicenter study was performed by the Japanese Laparoscopic Surgery Study Group (JLSSG) to evaluate preliminary short- and long-term outcomes of LAG for EGC (19). A total of 1,294 patients (872 men, 422 women) undergoing laparoscopic surgery were enrolled in this study from 1994 to 2003. The overall morbidity and mortality rates associated with these operations were 14.8% and 0%, respectively. This study showed that the 5-year disease-free survival rate was 99.8% for stage IA disease, 98.7% for stage IB disease, and 85.7% for stage II disease. Although these data may be considered preliminary, they appear to indicate that LAG for EGC yields good short- and long-term oncologic outcomes. In addition, morbidity and mortality rates following LADG are identical to or less than those observed following open distal gastrectomy (ODG) as per the published small randomized clinical trials (RCTs) (14-17).

With regard to prospective studies in Japan, a phase III study (JCOG0912) was performed to confirm the non-inferiority of relapse-free survival of LADG to ODG in patients with the same inclusion criteria used in the phase II study (JCOG0703) (20). Regarding short-term outcome, there were no significant differences between two groups in terms of intra-operative adverse events (G3–4) and in-hospital, non-hematological adverse events (G3–4) (21). The authors concluded that LADG performed by the credentialed surgeons was safe as ODG for cStage I cancer. A large-scale, multicenter randomized trial (KLASS01) regarding the safety of LADG for cStage I cancer from Korea has mentioned that this procedure confers the benefit of a lower occurrence of wound complications compared with conventional ODG (22). Therefore, LADG is safe in terms of short-term outcomes, at least for patients with

cStage I cancer. Regarding the non-inferiority of LADG in terms of long-term outcome, the result should be anticipated from each country.

To establish a risk model for DG in Japanese patients with gastric cancer, the NCD was constructed for risk determination in gastric cancer-related gastrectomy using data from 33,917 cases (1,737 hospitals) (23). As a result, the 30-day, in-hospital, and operative mortality rates were 0.52%, 1.16%, and 1.2%, respectively. The morbidity rate was 18.3%. This study demonstrated that this risk model developed using nationwide Japanese data on DG including both laparoscopic and open approaches for gastric cancer can predict surgical outcomes. Regarding LAG, JSES and JLSSG have performed a nationwide prospective survey to verify the feasibility and safety of LAG (NaSLAG) in 2014. The estimated enrollment number was approximately 8,300, and patient enrollment was finished in September 2015. The short-term surgical outcomes of LAG compared with OG are being evaluated using a propensity score-matched analysis. These results based on mega-data from Japan will be expected to cover the fields of exclusive criteria in our prospective RCT for LAG, such as age (elderly patients), and high BMI.

Current studies of LADG for advanced gastric cancer (AGC)

The extent of lymph node dissection in AGC remains controversial. In Asian countries, D2 lymph node dissection is routinely carried out in AGC, the main advantages of D2 lymph node dissection being considered to include prolonged survival and improved staging accuracy (24,25). Techniques for D2 lymph node dissection were recently developed for laparoscopic surgery and used in several Asian institutions (5,26,27). Recent retrospective studies and meta-analysis comparing laparoscopic D2 gastrectomy and open D2 gastrectomy for AGC demonstrated that the laparoscopic procedure may be feasible (11-13,17). However, several questions remained to be answered because the evidence from large-scaled, prospective study is yet to be established. Therefore, a randomized, controlled phase II trial was performed in Japan to confirm the feasibility of LADG in terms of technical safety, and short-term surgical outcomes (registered number, UMIN 000003420, www.umin.ac.jp/ctr/) (28). In this study, the eligibility criteria included pre-operatively diagnosed AGC that could be treated using DG with D2 lymph node dissection; MP, SS, SE without the involvement of other organs; N0–2 and M0. Patients aged 20–80 years were pre-operatively randomized. To proceed to a phase III trial developed to identify the potential non-inferiority of LADG to ODG in terms of short- and long-term outcomes, the safety of LADG with D2 lymph node dissection should be established through a preliminary step, which determines the occurrence of anastomotic leakage and pancreatic fistula as primary endpoints in a phase II trial. For quality control in this study, surgeons operating on patients in the laparoscopic arm had to be certified by the Endoscopic Surgical Skill Qualification System. This accreditation system for gastrointestinal surgery was established in 2004, and the surgical skill assessment system has contributed to the standardization of the laparoscopic technique and has enhanced the surgical skills of laparoscopic surgeons in Japan (8,9). In addition, a central review of the surgical procedure was carried out on the basis of photographs taken after lymph node dissection for all patients and video footage for arbitrarily selected patients (29). This review system may enable surgical standardization in terms of D2 lymph node dissection.

As a result, among the 91 patients in the laparoscopic arm, 86 underwent LADG according to study protocol. Regarding the primary endpoint of the phase II trial, the proportion of patients with either anastomotic leakage or pancreatic fistula was 4.7% (4/86). The morbidity rate of grade 3 or higher, including systemic and local complications, was 5.8%. Conversion to open surgery was required for one patient (1.2%), in the absence of any intra-operative complications. The post-operative mortality rate was 0 and no patient required readmission for surgical complications within 6 months following initial discharge. Hence, the technical safety of LADG with D2 lymph node dissection for locally AGC was demonstrated. A phase III trial to confirm the non-inferiority of this procedure to open gastrectomy in terms of long-term outcomes is ongoing. In East Asia, large-scale, multicenter RCTs are currently ongoing not only in Japan, but also in Korea (KLASS 02: NCT01456598) and China (CLASS 01: NCT01609309). Regarding to short-term outcome from the Chinese trials including CLASS01 study, favorable outcome in LADG as well as ODG for AGC has been demonstrated (30,31). These data in combination will be beneficial for determining the role of LAG.

Current studies of LATG for gastric cancer

LATG for upper gastric cancer is performed at a limited number of hospitals in Japan because of its technical

difficulty, particularly for esophagojejunostomy, and concerns regarding subsequent complications. According to the 12th JSES survey in 2014, the incidence of intraoperative and postoperative complications in LADG was 1.1% and 7.5%, respectively. On the other hand, the incidence of intraoperative and postoperative complications in LATG was 1.9% and 20.1%, respectively. With regard to the laparoscopic procedure in LATG, Uyama *et al*. first reported in Japan on Roux-en-Y anastomosis using a laparoscopic linear stapler in 1999 (32), and Tanimura *et al*. reported a good outcome for intracorporeal anastomosis using a conventional circular stapling device (33). Kunisaki *et al*. also reported that LATG using the Or-Vil™ system (Covidien, Mansfield, MA, USA) was a technically feasible procedure (34). However, no RCT data on LATG are available in Japan, because the standardization of techniques for esophagojejunal anastomosis has proved difficult even for experienced surgeons.

Recently, a multicenter, non-randomized confirmatory study of LATG with lymph nodal dissection for clinical stage I gastric cancer (JCOG1401) was carried out in terms of technical safety-, and short-term surgical outcomes (registered number, UMIN 000017155). The primary endpoint of the study was the proportion of anastomotic leakage because anastomosis-associated complications are great concern in LATG.

In Korea, a feasibility study of LATG in EGC (KLASS03) was performed, and patient enrollment has already finished (NCT01584336). The primary endpoint of the KLASS03 study was to evaluate the incidence of postoperative morbidity and mortality. These studies will lead to the confirmation of the technical safety of LATG for EGC. On the other hand, several issues related to the technical and oncological feasibility still exist regarding LATG for AGC. Recently, Nakauchi *et al*. demonstrated that totally laparoscopic total gastrectomy for AGC performed by expert surgeons is sufficiently feasible and safe, although combined resection of the spleen or distal pancreas for R0 resection was included in their retrospective, single institute study (35). For standardization of these procedures, it will be needed to expand the indication of LATG step by step at this moment.

Current studies of robotic gastrectomy for gastric cancer

Robotic surgery in cholecystectomy was first performed in 1997 by Cadière *et al*. (36). Since then, this system has been broadly applied in various fields including not only gastrointestinal surgery but also urological surgery and other surgical specialties (37). Recently, the clinical relevance of robot-assisted gastrectomy for gastric cancer was reported. The small series of cases have demonstrated that robot-assisted gastrectomy for the treatment of gastric cancer is a feasible and safe procedure in the hands of experienced laparoscopic surgeons (38-41). In contrast, Yoon *et al*. demonstrated that robotic gastrectomy offered no apparent benefit, in terms of surgical and oncological outcomes, given its present technological status (42). A recent meta-analysis of robotic gastrectomy used in 1,875 patients demonstrated that it was similar to that of LAG in terms of short-term outcomes and number of harvested lymph nodes, and it had a longer operative time and lower estimated blood loss (43).

In Japan, Uyama *et al*. demonstrated that this approach using a robotic system can facilitate D2 nodal dissection, particularly in suprapancreatic lymph node dissection (44). Suda *et al*. also showed the short-term outcomes of robotic gastrectomy in a single institutional retrospective cohort study (41). In the robotic surgery group, morbidity and duration of hospitalization following surgery were significantly improved, although the operative time and estimated blood loss were slightly greater. As the number of robotic systems is rapidly increasing in Japan, robotic surgery has spread into many institutions. However, several issues remain to be solved regarding clinical indication, short- and long-term outcomes, cost-effectiveness, and stress of surgeons. Recently, a multi-institutional historically controlled prospective cohort study was conducted to clarify the feasibility, safety, effectiveness, and economical efficacy of robotic gastrectomy for resectable gastric cancer (registered number, UMIN000015388). The primary endpoint of this study includes postoperative complications greater than grade 3 according to the Clavian-Dindo classification. Inclusion criteria with regards to indication are cStage I or II gastric cancer, curably treated by total, distal or proximal gastrectomy with D1+ or D2 lymph node dissection. The estimated enrollment number is 330, and this study is ongoing. The results from the Japanese study are expected to inform decisions on the future direction of robotic gastrectomy for gastric cancer.

Current studies of minimally invasive surgery for gastric cancer based on sentinel node (SN) navigation

The SN concept has been focusing on gastric cancer surgery, and many studies, mainly from Japan, have demonstrated the results of SN biopsy for EGC (45,46). A multicenter,

single-arm, phase II study of SN mapping for gastric cancer showed a SN detection rate of 97.5% (387/397), and the accuracy of nodal evaluation for metastasis was 99% (383/387) (47). Only four false-negative SN biopsies were observed. Next, a study of SN navigation surgery for EGC was launched to assess the availability and safety of individualized gastrectomy based on the SN concept for the EGC (registered number, UMIN000014401). The primary endpoint of this study is postoperative 5-year recurrence free survival (RFS) ratio. In this study, strategy of treatment based on SN mapping relied on the division of patient into three groups. Among these, the minimized gastrectomy and sentinel basin resection group included patients whose SNs were negative by intraoperative pathological diagnosis and spread within the confines of the resection range of minimized surgery involved laparoscopic local resection or gastrectomy. Although several issues remain to be resolved for the validation of the SN concept, the combination of less invasive laparoscopic surgery and SN navigation appears contribute to the improvement of long-term quality of life after gastric surgery.

Future perspective

Since the first LADG for gastric cancer was introduced in Japan, many surgeons have made efforts to improve the technical and oncological safety of LAG. With a view to standardizing LAG, multicenter clinical studies have also been launched to establish high-quality evidence not only in Japan but also in Korea and China. The fruitful data from these studies are expected to decide future directions for the use of LAG for gastric cancer. International cooperation and sharing of information on current issues regarding LAG for gastric cancer will be required.

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Footnote

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