



The era of technology-focused gastric surgery is over: we should return to surgical oncology for gastric cancer – comment on the CLASS-01 randomized clinical trial

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The first laparoscopic gastrectomy was performed in 1991 (1). In the 30 years since then, laparoscopic gastrectomy has become one of the most important areas in gastric cancer surgery. At present, laparoscopic gastrectomies are performed not only in East Asia (2) but also worldwide (3). However, one clinical question that needs to be addressed is whether a laparoscopic gastrectomy counts as proper treatment. The paper “*Laparoscopic vs Open Distal Gastrectomy for Locally Advanced Gastric Cancer: Five-Year Outcomes From the CLASS-01 Randomized Clinical Trial*” by Huang *et al.* (4) answers this very question.

The most important aspect to be considered in radical surgical treatment for gastric cancer is safety, followed by curability. The safety of the laparoscopic gastrectomy has been extensively investigated and has been reported to be equivalent to that of open surgery (2,5). Some studies have reported fewer perioperative complications with laparoscopies than laparotomies (2,5-7). In addition, the non-inferiority of laparoscopic gastrectomies for early gastric cancer has been demonstrated in terms of curability (8-10). Thus, laparoscopic gastrectomy is widely used as the standard of care for early gastric cancer in East Asia (2). However, the success of laparoscopic gastrectomies in curing advanced gastric cancer has not been clarified. Advanced gastric cancer frequently metastasizes to regional lymph nodes and requires a gastrectomy with lymph node dissection (11). Unlike laparoscopic surgery for colorectal cancer (12), laparoscopic lymph node dissection for gastric cancer is complicated. However, through the tireless efforts

of pioneer surgeons, a laparoscopic technique for lymph node dissection has been developed.

Whether the curability by means of this procedure is equivalent to that of open surgery cannot be concluded adequately without a prospective randomized clinical trial. Large-scale, prospective trials have been conducted in China, South Korea, and Japan (4,6-10,13-16). A list of these trials is provided in *Table 1*. To date, studies from China and South Korea have been reported and have demonstrated the non-inferiority of a laparoscopic gastrectomy to open surgery for advanced gastric cancer. Unfortunately, in the previous CLASS-01 report on 3-year recurrence-free survival, the results of the subset analysis showed somewhat questionable equivalence in stage III patients (13); however, the current report has dispelled this concern (4). For the conclusion, we must wait for the result of the Japanese study (16). However, although unpublished, it has come to my knowledge that the Japanese trial also proved the same non-inferiority. Therefore, this will soon be the last piece of the puzzle to answer any remaining questions about the procedure. It has become clear that laparoscopic gastrectomy could be regarded as curative compared to conventional open gastrectomy.

Laparoscopic gastrectomy techniques have matured in terms of oncology, and the procedure should be considered as a common approach. For patients after a long period of surgeries, the only difference between a laparoscopic gastrectomy and a conventional open gastrectomy is in terms of the wound size. The laparoscopic gastrectomy will

Table 1 Nation-wide large-scale multicenter phase III prospective randomized clinical trials for survival prognosis of laparoscopic distal gastrectomy for gastric cancer

Stage	Trial code	cTNM	N	Postoperative adverse effects	Endpoint	Result	Country
cStage I	KLASS-01 (6,10)	cT1N0/cT1N1/cT2aN0	LDG 644, ODG 611	LDG < ODG	5-year OS	Non-inferiority	South Korea
	JCOG0912 (8,9)	cT1N0/cT1N1/cT2N0	LDG 457, ODG 455	LDG = ODG	5-year RFS	Non-inferiority	Japan
cStage II, III	CLASS-01 (4,13)	cT2-4a/N0-3/M0	LDG 510, ODG 502	NR	5-year OS	Non-inferiority	China
	KLASS-02 (7,14,15)	cT2-4a/N0-1/M0	LDG 248, ODG 254	LDG < ODG	3-year RFS	Non-inferiority	South Korea
	JLSSG0901 (16)	cT2-4a/N0-2/M0	LDG 248, ODG 254	LDG = ODG	5-year RFS	NR	Japan

LDG, laparoscopic distal gastrectomy; ODG, conventional open distal gastrectomy; OS, overall survival; RFS, relapse free survival; NR, not reported.

indeed continue to advance technologically. Therefore, it must be carried out more accurately and effortlessly. One approach is robotic surgery (17). However, laparoscopic and robotic gastrectomy are essentially the same. The perioperative safety, cost, surgeon stress, etc., will be points of comparison, but there will no longer be a need to compare the curative outcomes.

Is the current surgical treatment for gastric cancer perfect or complete? Perioperative adjuvant therapy for gastric cancer is undoubtedly advancing, with drastic improvements in chemotherapy and the changing role of immunotherapy (18,19). However, the essential contents of gastrectomies have not changed significantly. Distal gastrectomy was first developed in the 19th century, and lymph node dissection up to D2 in 1970. While laparoscopic surgery has made significant advances in approaches and devices, the content of the surgery is as old-fashioned as a standard D2 gastrectomy. The essential contents of surgical treatment must also be advanced. There are still several issues to be addressed regarding surgical treatment strategies. These include the choice of proper surgical treatment combined with chemotherapy (especially adjuvant preoperative immunochemotherapy), appropriate range of nodal dissection (11), and accurate intraoperative diagnosis of nodal and peritoneal micrometastasis. Laparoscopic gastrectomy has been the main point-of-interest in gastric surgery; however, oncology-based surgical treatment strategies have been neglected for the last 20 years. Of course, oncological approaches such as denial of bursectomy (20) and validation of the sentinel node concept (21) have also been accepted, but only a few were recognized. In the future, surgical treatment for gastric cancer should shift from a technology-focused approach to surgical oncology.

Some issues need to be noted. The inclusion criteria for the CLASS-01 study were T2-T4a/N0-3/M0, and patients with invasions to other organs or bulky regional nodes larger than 3 cm were excluded. Patients who received preoperative chemotherapy were also excluded (4,13). For reference, the inclusion and exclusion criteria for the KLASS-02 (14,15) and JLSSG0901 (16) studies are shown in *Table 2*. No patients who received preoperative chemotherapy were included in these studies. T4b patients were also excluded. It should also be noted that KLASS-02 and JLSSG0901 also excluded patients with suspected advanced lymph node metastasis at preoperative diagnosis. It is premature to conclude that all patients with advanced gastric cancer should be eligible for laparoscopic gastrectomy. It should be considered that patients with T4b or bulky N should be judged as out of indication, and that the oncological safety for T4a patients would also not be guaranteed.

It should also be noted that this was a non-inferior study, not a superiority study. Although laparoscopic gastrectomy is more widely used, it remains a complicated procedure. It is not clearly superior to conventional open gastrectomy, except for the size of the wound. It is possible that curative equivalence can only be achieved by a team capable of performing advanced laparoscopic surgery. This article (4) states that ‘finally, it will be difficult to generalize our findings to surgeons with less-intensive training’. There is no need to actively choose laparoscopic gastrectomy unless the surgeon is a specialized surgeon working at a high-volume center. In addition, real clinical data show that a laparoscopic gastrectomy is associated with more pancreatic complications than a conventional open gastrectomy (22). Today, most cholecystectomies and colectomies are performed by laparoscopic approach, but unlike these low-difficulty procedures, not all gastrectomies

Table 2 Details of inclusion and exclusion criteria of prospective studies

Trial code	Inclusion criteria	Exclusion criteria	Preoperative therapy	Postoperative adjuvant chemotherapy
CLASS-01 (4,13)	Patients who were expected to undergo distal gastrectomy with D2 for curative intent cT2-4a cN0-3 cM0 18–75 years old PS (ECOG) 0–1	Having bulky regional lymph nodes larger than 3 cm	No	LDG 37.0%, ODG 41.7%
KLASS-02 (7,14,15)	Patients with gastric cancer suitable for curative resection by distal subtotal gastrectomy cT2-4a cN0-1 (limited perigastric nodal metastasis) cM0 20–80 years old PS (ECOG) 0–1	Other malignancy diagnosed within the previous 5 years	No	LDG 60.6%, ODG 62.0%
JLSSG0901 (16)	Advanced gastric cancer could be treated by distal gastrectomy with D2 cT2-4a cN0-2 cM0 20–80 years old PS (ECOG) 0–1 BMI <30	Synchronous or metachronous (within 5 years) malignancies Bulky N2	No	Yes

LDG, laparoscopic distal gastrectomy; ODG, conventional open distal gastrectomy; PS, performance status; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index.

should be converted to laparoscopic approach. The significance of conventional open gastrectomy should be re-evaluated in terms of safety, difficulty, and uniformity. Surgeons should question if a laparoscopic gastrectomy is the best treatment approach for a patient on an individual level. Surgeons unfamiliar with advanced laparoscopic techniques should not hesitate to perform conventional open gastrectomy. Safety of the patient must be the highest priority in cancer surgery.

If ‘I’ were to be diagnosed with an advanced gastric cancer, I would prefer to undergo laparoscopic gastrectomy at a high-volume center. However, this would be the case only if it was located within the middle or lower side of the stomach, T3 or less, and with lymph node metastasis limited

to the perigastric nodes. For a more advanced cancer, I would prefer to receive preoperative immuno-chemotherapy followed by a conventional open R0 gastrectomy. On the other hand, if the tumor was on the proximal side, I would opt for an open proximal gastrectomy performed by a skilled surgeon (23).

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