

The era of laparoscopic surgery for gastric cancer: what is the present territory and what will be next?

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Since its introduction, laparoscopic surgery has evolved from a new idea into a popular technique that is now the standard of care for many indications. In the treatment of gastric cancer, since Kitano *et al.* first reported a laparoscopic approach for gastric cancer resection in 1994 (1), laparoscopic techniques have become widely adopted by gastric cancer surgeons, beginning in Japan, Korea, and China, and now extending throughout the world. However, at the time laparoscopic techniques were being introduced, conservative surgeons expressed significant concerns about the use of laparoscopic techniques in the treatment of gastric cancer. In the past, many trials failed to show the benefit of chemotherapy for gastric cancer, thus it was considered to be a malignancy refractory to chemotherapy, making complete resection the only strategy for achieving a cure (2). As part of an attempt to completely remove all gastric cancer tumor cells, extended lymph node dissection was previously believed to provide survival benefits. Thus, surgeons were focused on more extended surgery for gastric cancer: a landmark clinical trial that compared D2 versus D2 plus para-aortic lymph node dissection was conducted from 1995 to 2001 (this period was the time that laparoscopic surgery was introduced for gastric cancer) to prove the benefit of extended lymph node dissection (3). Consequently, the argument that laparoscopic surgery might have limited applications in the treatment of gastric cancer because laparoscopic techniques do not permit adequate extended lymph node dissection was reasonable at that time. Even those circumstances, believing that laparoscopic approaches could be used to improve patients' quality of life after surgery with similar oncologic outcomes, smart and innovative surgeons have developed this laparoscopic technique for gastric cancer. These surgeons initially used

laparoscopic techniques to treat very early stage gastric cancers in which limited lymph node dissection would be performed, and over time multiple surgical techniques and new devices have been developed. Also, the advancement of laparoscopic gastric cancer treatment has been further aided by an active exchange of skills and knowledge not only between surgeons within countries (beginning mainly in Japan) but also extending across nations (Japan, Korea, and China). In addition, development and refinement of laparoscopic surgical techniques for the treatment of gastric cancer were further accelerated by the experiences of surgeons working in high volume centers in Korea, where these surgeons have accumulated substantial skill and experience within short periods of time (4). Laparoscopic treatments of gastric cancer have now been propagated across the world, and the use of these methods has been expanded to include even some cases of advanced gastric cancer.

These innovations are now yielding substantial clinical benefits. Interim results of the Korean Laparoscopic Gastrointestinal Surgery Study (KLASS) trial (5), a phase III multicenter, prospective, randomized trial, and the KLASS-01 trial (6) found no differences in mortality and fewer wound complications for laparoscopic surgery compared to conventional open surgery for early stage gastric cancer (clinical stage I). In addition, another large scale case-control and case-matched Korean multicenter study found that the long-term oncologic outcomes of laparoscopic surgery were comparable to those of open surgery (7). These results suggest that laparoscopic surgery may be considered as a standard procedure for the treatment of early gastric cancer, specifically in distal gastrectomy cases.

But would laparoscopic techniques be applied in cases

of advanced gastric cancer? The most recent study entitled “Morbidity and Mortality of Laparoscopic Versus Open D2 Distal Gastrectomy for Advanced Gastric Cancer: A Randomized Controlled Trial” investigating this question has been conducted in China: the Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS). The CLASS group has reported that short-term outcomes in their study cohort have been comparable for cases of advanced gastric cancer treated with laparoscopic surgery for D2 distal gastrectomy compared to cases treated with open surgery (8). To confirm the long-term oncologic outcomes of laparoscopic surgery for advanced gastric cancer, we must wait for the final reports of this and other ongoing trials in Korea, China, and Japan. However, if the quality of laparoscopic resection is the same as conventional open surgery, the expected result would be to find no difference in oncologic outcomes. In the recent CLASS trial and the KLASS II trial (NCT01456598), laparoscopic surgery quality was formally assessed using intraoperative videos and photos, therefore, their primary end point, the long term oncologic outcomes of laparoscopic surgery, would not be inferior to that of open surgery.

Following an extended debate, the D2 level has been set as the cutoff for lymph node dissection in cases of gastric cancer, and D2 lymph node dissection is the standard for gastric cancer treatment as part of either open or laparoscopic surgery, including robotic surgery (9,10). Thus, the maximum level for the application of laparoscopic techniques is D2, and some experienced surgeons are already achieving these technical end points with laparoscopic surgery. A separate problem, however, is that generalizing excellent results of laparoscopic procedures ultimately depend on whether the performance of this procedure can be standardized. The mortality rate for gastric cancer surgery is still high, even for open surgery in the West (11). And according to the United States (US) Graduate Medical Education General Surgery Report from 2012, current US general surgery residency graduates on average performed fewer than five gastrectomy procedures during their 5 years of residency training, suggesting limited exposure to gastric cancer surgery during their training (12). Even in East Asia, where gastric cancer is endemic and D2 gastrectomy has long been a standard surgery, only some qualified surgeons are capable of performing a complete D2 lymph node dissection using a laparoscopic approach. Therefore, one of the next challenges in laparoscopic gastric cancer surgery, which we must solve, will be standardizing how these procedures are performed.

Current trends in the surgical treatment of early gastric cancer have included minimizing the extent of surgery in highly selected patient (13), for example the use of endoscopic resection, sentinel lymph node navigation surgery, pylorus-preserving gastrectomy, or proximal gastrectomy. One of the aims of laparoscopic approaches in gastric cancer surgery is to minimize surgical extent and improve quality of life for patients, while achieving non-inferior oncologic outcomes. The major premise of all of these minimalist, less invasive surgeries is that there will be no remaining metastases in the lymph nodes in the non-dissected areas. Consequently, the development of methods to accurately predict the presence of lymph node metastases is a current research focus, and this issue must be addressed in order to actively propagate minimally invasive surgery for gastric cancer. Numerous prior studies have tried to predict lymph node metastases preoperatively using various clinical variables (14-16). However, the methods reported in these studies are not yet sufficiently accurate for translation into clinical use. The recent cutting edge technologies, including next generation sequencing (NGS), have enabled characterization of the genetic features of cancers, making it possible to further classify gastric cancers according to their molecular characteristics using multi-omics approaches (17,18). Different methods for treating each gastric cancer may then be applied according to the cancer subtype identified by its molecular characteristics. These genetic analysis methods will be (and in some cases already are) integrated into mainstream cancer research. In the near future, these approaches may make it possible to predict the presence of lymph node metastases at the time of preoperative planning, and such a diagnostic advancement would likely attach wings to the propagation of laparoscopic surgery for gastric cancer.

Last but not least, some of our surgeons must turn their attention to further improving the survival of patients with gastric cancer. Recent studies of gastric cancer surgery have mainly focused on using minimally invasive techniques to achieve non-inferior oncologic outcomes compared to conventional surgical approaches, rather than aiming to improve oncologic outcomes. Except in Korea and Japan, where nationwide screening systems have been established, most patients with gastric cancer are diagnosed at advanced stages. To improve survival in these patients, we need to collaborate with other disciplines and identify effective adjunctive treatment modalities, including advances in chemotherapy, radiotherapy, and immunotherapy coming from clinical and basic science research. Given that surgery

plays a central role in the treatment of gastric cancer and provides the only means of achieving cure, surgeons should acknowledge their pivotal role in conquering this deadly disease. Consilience between disciplines will guide us to victory in the war against gastric cancer.

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Footnote

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