



# Effect of laparoscopic vs. open distal gastrectomy on 3-year disease free survival in patients with locally advanced gastric cancer: commentary on the class-01 randomized clinical trial

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## Introduction

Gastric cancer is a malignancy which displays a unique geographic distribution, with a high incidence in Eastern countries such as South Korea, Japan and China. Western countries, such as the United States and countries of Europe, do not have a high incidence. As such, treatment recommendations differ widely, with Western cancer guidelines adopting the recommendation for neoadjuvant chemotherapy in the treatment of locally advanced gastric cancer. Eastern countries, however, tend to utilize a surgery-first approach. Despite differences in treatment paradigms, focus on surgical approach and adequacy of oncologic resection has been meticulously evaluated, particularly in the East. Although D2 lymphadenectomy was widely performed in Eastern countries, Western countries struggled to prove survival benefit and demonstrated high initial complication rates (1). Fifteen-year follow-up of the Dutch D1D2 trial, however, showed lower local recurrence, regional recurrence and cancer-related deaths favoring D2 over D1, although overall survival was similar between groups (2). Further modification of the D2 lymphadenectomy to exclude pancreatectomy and splenectomy except when directly invaded has contributed to great improvement in morbidity and mortality with adequate node retrieval. This has prompted the recommendation in the U.S. (National Comprehensive Care Network Guidelines) and Europe

(European Medical Society of Oncology Guidelines) that D2 lymphadenectomy be performed in patients with localized, resectable gastric cancer, with an emphasis that surgery be performed in high volume, specialized centers (3,4).

Globally, minimally-invasive techniques, including laparoscopic and robotic platforms, have increased in utilization. Multiple specialties within surgery have shown improved recovery and function with a minimally-invasive approach, including urology, gynecology, and thoracic surgery. Minimally-invasive surgery for cancer, however, remains controversial. Laparoscopic colectomy for colon cancer, for example, has been retrospectively shown to improve short-term outcomes, have better compliance with adjuvant chemotherapy recommendations, and is non-inferior to open colectomy (5,6). The large, multi-national randomized trial, the Colon cancer Laparoscopic or Open Resection (COLOR) trial, did not show a difference in disease-free survival between laparoscopic and open colectomy and similar morbidity and mortality in 1,248 randomized patients (7). The Dutch cohort of the COLOR trial was reviewed at ten-years of follow-up. In the analyzed 256 patients, similar rates of disease-free survival, overall survival, and disease recurrence was observed at ten years, as compared to open surgery (8). Study of the minimally-invasive platform for gastric cancer is also ongoing. In April 2019, the Korean Laparoendoscopic Gastrointestinal

Surgery Study (KLASS) group published their multi-institutional study of over 1,400 patients with clinically-assessed stage 1 distal gastric cancer patients randomized to a laparoscopic or open surgical approach (9). At a median follow-up of 99.8 months, the overall and cancer specific survival were similar (9). Further study has been conducted on advanced gastric cancer, which is far more common in Western populations. This editorial comments on the current state of minimally-invasive surgery for gastric cancer and reviews the recent CLASS-01 trial.

### Eastern experience

The Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS) Group involved multiple centers throughout China, including multiple surgeons, and randomized patients with clinically staged advanced distal gastric cancer to either laparoscopic or open distal gastrectomy with D2 lymphadenectomy (10). This trial was conducted as a non-inferiority trial at 14 Chinese hospitals between September 2012 and December 2017. One thousand and fifty-six patients were clinically assessed as having T2-4aN0-3M0 gastric cancer and were randomized to either laparoscopic or open surgery. The primary outcome of disease-free survival was not different between groups and did not cross the pre-specified non-inferiority margin. However, in a subgroup analysis which excluded those with early stage tumors, the non-inferiority of disease-free survival became non-significant (10). Three-year overall survival, however, as well as cumulative incidence of recurrence did not significantly differ between groups.

This trial is one of few that enrolled a large number of patients with gastric cancer and randomized them to a laparoscopic or open approach. Given the geographic predisposition to stomach cancer, this study was conducted in China, which may limit its widespread applicability to Western patients. Another notable limitation is the large (nearly 24%) portion of enrolled patients who were found to have pathologic T1 tumors. In subgroup analyses that excluded pathological stage 1 patients, non-inferiority became non-significant, indicating that there may be a difference in operative platforms in early stage tumors. Three-year disease-free survival for pathologic stage 2, 3 and 4 patients, however, were not significantly different between the laparoscopic and open groups. This study, therefore, does demonstrate the non-inferiority of the laparoscopic approach for surgical resection in advanced gastric cancer. However, the large proportion of patients

with early stage gastric cancer does leave to question the pre-operative staging protocols utilized and the concern for overstaging patients.

The KLASS-01 trial showed similar long-term overall and cancer specific survival in a large randomized group of patients with early stage distal gastric cancer undergoing a laparoscopic distal gastrectomy. An ongoing randomized trial, the KLASS 02 trial comprises data from the same study group evaluating laparoscopic gastrectomy in advanced gastric cancer (11). The long-term results have yet to be published. The Japanese Laparoscopic Surgery Study Group (JLSSG) is also currently conducting a phase III trial JLSSG 0901 to evaluate the long-term outcomes of laparoscopic resection in advanced gastric cancer; this comes after proving the safety and low conversion to open surgery with the laparoscopic approach (12).

### Western experience

In Western countries, although the minimally-invasive platform has increased rapidly in utilization, its role in gastric resection for cancer remains undefined. One limitation is the low prevalence of gastric cancer as well as non-centralization of care. Another is the prevalence of more proximal tumors as well as the tendency for patients to present with more advanced cancer. It is not clear whether the Eastern experience should be extrapolated to Western patients, although large prospective, randomized trials in the West are lacking. A retrospective review of a prospectively maintained database at Memorial Sloan-Kettering Cancer Center reviewed 87 patients undergoing laparoscopic gastrectomy from 2005–2013 and compared them to a contemporaneous cohort undergoing open surgery (13). The laparoscopic approach was associated with longer operative times and a higher rate of microscopic margin positivity; however, less blood loss, decreased length of stay, and decreased minor complications were noted (13). Short-term follow-up showed comparable overall and recurrence-free survival (13). A multicenter, prospective randomized controlled trial is currently ongoing in the Netherlands comparing laparoscopic versus open gastrectomy for cancer (LOGICA-trial) (14). Results are eagerly awaited. Given the high numbers of patients undergoing neoadjuvant chemotherapy, another trial currently being conducted, also in the Netherlands, evaluates the role of minimally invasive surgery following chemotherapy for proximal or centralized gastric cancers versus open surgery (STOMACH trial) (15).

## Conclusions

Compared to the Western experience, Eastern surgeons and oncologists have been able to conduct robust clinical trials for comparison of the laparoscopic surgery platform relative to open surgery. In their hands, the morbidity/mortality and oncologic outcomes appear to be equivalent between platforms. This is less well defined in the West, where patients are more often obese, have more comorbidities, and more often have advanced disease and proximal tumors. However, as experience with the laparoscopic, and increasingly robotic, platform increases, the learning curve may be overcome in both the East and West in gastrectomy for cancer. The benefits of minimally-invasive surgery may ultimately allow for patients to recover faster and thus initiate adjuvant therapy; whether this allows for improved long-term outcomes, however, remains to be seen.

Given the results of KLASS-01 as well as CLASS-01, it seems reasonable to offer laparoscopic gastrectomy for patients with gastric cancer at experienced centers, particularly for distal gastric cancers. Further trials are ongoing to evaluate the role of minimally-invasive gastrectomy, for advanced tumors as well as following neoadjuvant chemotherapy, since these two factors are more prevalent in Western patients. Additional trials are evaluating the role of laparoscopic resection in proximal tumors, which generally necessitate a total gastrectomy. Robotic surgery is also increasing in utilization; however, its role has not yet been elucidated, whether it be comparable to laparoscopy or improved. This is an exciting time where technologic advances in minimally-invasive surgery may contribute to speedier and improved recovery; this may eventually translate not only to non-inferiority to open surgery but improved oncologic outcomes.

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## Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

*Ethical Statement:* The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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