Editorial Commentary

Less may be more: shifting paradigm toward minimally invasive gastrectomy for locally advanced gastric cancer

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Gastric cancer is the fifth most common malignancy and the third leading cause of cancer-related mortality worldwide (1). Despite evidence demonstrating improved outcomes with multimodality therapy (i.e., perioperative chemotherapy or adjuvant chemotherapy with/without radiotherapy), complete margin-negative surgical resection remains the mainstay of treatment (2). While open gastrectomy has remained the standard approach for gastric cancer resection globally, accumulating evidence over the last 2–3 decades from high-volume centers in Asia has indicated that minimally invasive gastrectomy (MIG) is an oncologically non-inferior approach in appropriately selected patients (3-8). The widespread adoption of MIG in Asia—particularly for early cancers located in the distal stomach—likely reflects a constellation of factors, such as higher incidence of gastric cancer, unique epidemiology (i.e., lower incidence of gastroesophageal junction tumors, lower rates of obesity-related cancers, higher *H. pylori* seroprevalence, etc.), and early detection screening programs (9). This paradigm shift also reflects a concerted effort by Asian surgeons to not only standardize the technical aspects of oncologic gastrectomy, but also translate these standards to the minimally invasive platform (10,11). While adoption of MIG for gastric cancer has been more tentative in the United States (US) (12), recent data from higher volume US institutions have corroborated its safety and oncologic adequacy, particularly for early distal tumors (13).

In the East, a substantial body of level I evidence supports MIG for early gastric cancers (i.e., T1-2) located in the middle/lower third of the stomach, for which distal gastrectomy with limited lymphadenectomy is recommended by consensus Asian guidelines. For such early distal tumors, several randomized controlled trials (RCT) have demonstrated the typical benefits of the minimally invasive approach—namely decreased intraoperative blood loss, decreased pain scores, reduced length of stay, and improved quality of life (3-5,6,11). Furthermore, the Korean KLASS-01 RCT demonstrated oncologic non-inferiority (i.e., overall and cancer-specific survival) of MIG (n=705) compared with open gastrectomy (n=711) for stage I gastric cancer. At a median follow-up of 100 months, 5-year cancer-specific survival was 97.1% in the laparoscopic group and 97.2% in the open surgery group (P=0.9) (5). As such, MIG for early distal gastric cancer has become standard of care in Asia.

These impressive data in early gastric cancer set the stage for exploration of MIG for locally advanced disease, for which formal D2 lymphadenectomy is mandated in Asia. Prior to reporting of 3-year survival data from the Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS)-01 trial (8), several retrospective case-control studies, meta-

analyses, and four other Asian RCTs (14-17) had indicated that MIG was technically feasible in locally advanced gastric cancer. The initial iteration of the CLASS-01 trial, designed to evaluate non-inferiority of laparoscopic compared with open distal gastrectomy in locally advanced gastric cancer, reported on short-term surgical outcomes. The trial randomized 1,056 patients with clinical stage T2-4aN0-3M0 gastric cancer to either laparoscopic or open gastrectomy with D2 lymphadenectomy between September 2012 and December 2014 at 14 high-volume institutions in China. Postoperative morbidity and mortality were identical and compliance with D2 lymphadenectomy were exceptionally high in both groups. Moreover, MIG was associated with lower blood loss, decreased hospital stay, and earlier time to first flatus at the expense of longer operative times. Approximately 40% of patients in either arm received adjuvant 5-FU-based chemotherapy (reserved for stage II disease or higher by design) (3). In the discussion section of the manuscript, an onus was placed on the vast experience, expertise, and high-volume practice of the surgeons participating in this trial. Nonetheless, these data invoked a renewed appreciation for the feasibility of MIG for locally advanced gastric cancer.

The reporting of 3-year survival data from this trial in *JAMA* earlier this year has catapulted this debate back into international dialog. At a median follow-up of nearly 38 months, the 3-year disease-free survival (DFS) rates were 76.5% in the laparoscopic group and 77.8% in the open group, with an absolute difference of –1.3% and a one-sided 97.5% CI that did not cross the prespecified non-inferiority threshold of –10%. These results were reproduced in their per-protocol analysis as well (i.e., after excluding patients who received total rather than distal gastrectomy, had inadequate D2 lymphadenectomy, or were switched to the other surgical approach preoperatively or intraoperatively). After adjusting for age, tumor size, pathologic T- and N-classification, and adjuvant chemotherapy receipt, a mixed-effects Cox regression yielded a non-significant HR of 1.1 (95% CI, 0.84–1.43) comparing laparoscopic with open distal gastrectomy. Moreover, the location and cumulative incidence of recurrence did not differ significantly between both arms. Three-year overall survival—a secondary outcome—was also similar between laparoscopic and open groups (83.1% *vs.* 85.2%, respectively). Although the absolute difference in gastric cancer-related death was 6.2% at 3 years favoring open gastrectomy, this did not reach statistical significance on post hoc exploratory analysis (8).

The CLASS consortium is to be congratulated on this impressive undertaking. These data represent the first level I evidence championing the oncologic non-inferiority of MIG in locally advanced gastric cancer. However, these data should be interpreted with two important caveats in mind: (I) a substantial proportion of patients were clinically overstaged; nearly a quarter of patients with clinical T2 tumors had pathologic T1 tumors, while nearly a third (29.7%) of patients actually had pathologic stage I disease; (II) a post hoc sensitivity analysis revealed that, upon exclusion of patients with pathologic stage I tumors, noninferiority became nonsignificant, with the lower bound of the 97.5% CI (–10.6%) crossing the pre-specified 10% noninferiority threshold. Clearly, the latter analysis is underpowered. Nonetheless, while acknowledging that clinical staging in Western/US centers is far from perfect, the applicability of these data to practice settings where endoscopic staging may be more robust is less certain.

Furthermore, the applicability of these data to Western and/or US patients remains unclear. First, management of locally advanced gastric cancer in the West/US is increasingly characterized by utilization of perioperative (even total neoadjuvant) chemotherapy, as evidenced in the FLOT4 (18) and MAGIC (19) trials. How translatable are these CLASS-01 data to the short-term (e.g., compliance with D2 lymphadenectomy and lymph node retrieval rates) and long-term (e.g., DFS and cancer-specific survival) oncologic outcomes in patients predominantly treated with neoadjuvant therapies? The German phase III Surgical Technique, Open versus Minimally-invasive gastrectomy After CHemotherapy (STOMACH) trial is currently underway, and will address this question (NCT02130726). Second, the incidence of proximal (i.e., cardia and gastroesophageal junction) gastric cancer is disproportionately on the rise in the West—particularly in North America. The CLASS-01 data cannot inform management for patients needing total gastrectomy. Third, the mean BMI in both arms in the CLASS-01 trial was 22.7 (8). With obesity rampant in the US, it is rare for even high-volume centers to see many patients with such BMIs. The impact of body habitus on the technical conduct of MIG cannot be overemphasized. These factors, in conjunction with the lower incidence of gastric cancer overall, the significant learning curve needed for technical proficiency in MIG (10), lack of centralization of gastric cancer to high-volume centers of excellence, and highly variable surgical and pathologic quality (12), may account for a rather tentative reception for these CLASS-01 data in

the West/US until more globally applicable data become available.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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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