



Laparoscopic for advanced gastric cancer – minimally invasive for maximal results?

Mickael Chevally, Charles-Henri Wassmer, Marco Bonino, Stefan Mönig

Department of Visceral Surgery, Geneva University Hospital, Geneva, Switzerland

Correspondence to: Mickael Chevally. Department of Visceral Surgery, Geneva University Hospital, Geneva, Switzerland. Email: mlcy@hcuge.ch.

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We have read with great interest the article from Yu *et al.* (1). This randomized clinical trial presents the long term oncological and survival results comparing laparoscopic and open distal gastrectomy for advanced gastric cancer.

Minimally invasive approach has always aroused enthusiasm in oncological surgery.

The concept to minimize the surgical stress in order to fasten the recovery and start as soon as possible the adjuvant treatment is appealing. However, this should not be at the cost of a surgical compromise. The fundamental oncological principles of complete resection and adequate lymph node retrieval should be respected.

For early distal gastric cancer, laparoscopic approach has been proved to be equivalent to the open procedure by several randomised trial. The Korean randomized trial, KLASS-01 (2), which compared laparoscopic and open gastrectomy for early distal gastric cancer, has shown similar 5-year cancer-specific survival rates between the 2 groups (97.1% in the laparoscopic and 97.2% in the open group).

Japanese randomized trial had the same conclusion in short- and long-term results with similar surgical complication, no mortality in either arm (3). They found the same long-term results in their 921 patients in term of recurrence and survival (4).

Laparoscopic approach is established as one of the standard treatments for early gastric cancer.

However, the question for advanced tumors is still pending. The major difference with early cancer is the need for a proper D2 lymphadenectomy. Laparoscopic approach could jeopardize the ability to perform this procedure and can explain the surgeon's restraint in adopting it for advanced tumors.

The Chinese Laparoscopic Gastrointestinal Surgery

Study (CLASS) group conducted several multicenter retrospective studies on the feasibility, safety, and oncologic outcomes of laparoscopic gastrectomy with extended lymphadenectomy for advanced cancer.

Their conclusion was that minimally invasive approach was safe with a low mortality (0.1%), morbidity (10.2%) and acceptable long-term results (3-year overall survival: 75.3%, disease-free survival: 69.0%) (5).

The CLASS Group, in a randomized trial, compared then laparoscopic and open distal gastrectomy for advanced gastric cancer. One thousand and fifty-six patients were divided in laparoscopic and open group for clinical stage T2-4aN0-3M0 gastric cancer. They reported a similar postoperative morbidity (15.2% in the laparoscopic *vs.* 12.9% in the open group) and a mortality rate (0.4% for the laparoscopic *vs.* 0% in the OG group) with no statistically difference. The rate of positive margins and number of lymph nodes retrieved were similar for both laparoscopic and open gastrectomy groups (6).

Building on these short-term results, the CLASS group presents in this article the long-term results at 3 years. Each group had 500 patients from 14 centers in China. All patients had an advanced tumor at the preoperative staging, meaning tumor cT2-4a N0-3 M0 according to the Japanese classification. A mini laparotomy was performed during minimally invasive procedure in order to extract the specimen and perform the anastomosis. The primary endpoint was 3-year disease-free survival and the secondary end points were 3-year overall survival and recurrence patterns.

The follow up included a medical history, physical examination with carcinoembryonic antigen ant cancer antigen 19-9 testing, abdominal Ct Scan and upper

gastrointestinal endoscopy annually for 3 years.

Each arm had more than 500 patients with few non-resectable tumors (only 8 patients in the laparoscopic group and 7 in the open group). Although all patients were diagnosed pre-operatively for clinical stage of T2 or higher, 23.9% patients had a final histologic diagnostic of T1 tumors.

The authors reported a 3 years disease free survival rates of 76.5% in the laparoscopic group and 77.8% in the open group. The overall survival as secondary outcomes showed 83.1% in the laparoscopic group and 85.2% in the open group with no difference after controlling for age, tumor size, pathologic T stage, and pathologic N stage. The sites of recurrence were similar between the 2 groups (local, peritoneum, liver and other sites).

When the two studies are taken into account, the CLASS group conclude that the short-term and long-term results in high volume centers are similar for distal gastrectomy using either of the two approaches when performed by expert surgeons.

We must recognize the good methodology of this study. Randomized surgical studies are rare and therefore valuable. The follow-up is also excellent with no drop out from the 36-month follow-up.

As highlighted by the authors, there was an over staging in the cancer evaluation. As there was no neoadjuvant treatment, down staging cannot explain these results. This population of stage I tumor, mitigate the overall results. In deed, if the subgroup of early cancer patients was excluded from the analysis, the non-inferiority threshold was crossed, favouring the open group. The subgroup analysis for disease free survival rates showed better results in the open group for stage III and IV. As the stage is higher, the difference is significantly larger and favours the open group.

This difference should not only be attributed to the surgical approach. Adjuvant chemotherapy was not standardized and the choice of regimen and treatment duration was left at the discretion of the local oncological team. Few patients received adjuvant chemotherapy with 37% in the laparoscopic group and 41.7% in the open group. The absence of systematic perioperative treatment could be one of the explanations for the results in stage III–IV patients.

In Korea, the long-term results of two randomized trial showed similar results.

For the early outcomes, the Randomized KLASS-02 trial (7) compared open and laparoscopy for advanced tumor in 1,050 patients and showed non inferiority of the laparoscopic group with lower complication rate, faster

recovery, and less pain compared with open surgery. The mean number of totally retrieved lymph nodes was similar in both groups.

The COACT 1001 (8) randomized trial showed that there was no difference in the 3 years disease free survival between laparoscopic and open approach. However, in higher stage, there was a significant difference in the compliance of the lymphadenectomy, with a greater proportion of patients with more than 1 empty lymph node station in the laparoscopic group.

In stage III patients, the rate of non-compliant D2-lymphadenectomy was 52% versus 25% in the open group. The subgroup analysis of stage III patients found a disease-free survival at 3 years of 64.3% in the open group and 56.6% in the laparoscopic group.

We found also here that at higher pathological stage, laparoscopic seems to be inferior to the open approach. But again, the perioperative treatment could play a part with 21 patients in LADG group and 20 in ODG group did not receive adjuvant chemotherapy.

Concerning the gastric tumors, the Western and Eastern populations differ on several points (Body Mass Index, localization of the tumor, initial stage) (9). In the Western population, two pioneer studies showed the feasibility and safety of laparoscopic gastrectomy for gastric cancer.

The first is from Italy with Huscher *et al.* (10) in 2005 and their randomized trial for open or laparoscopic subtotal gastrectomy. They showed reduced blood loss, shorter time for oral intake and earlier discharge from the hospital. The long-term results showed also no difference of five-year overall and disease-free survival rates. In each group, 25% of the patients had an advanced gastric tumor.

The second is a retrospective study from Strong *et al.* (11) in 2009 comparing open and laparoscopic subtotal gastrectomy approach for gastric cancer. In regard of oncologic principles, this study showed equivalent results in term of margin status, lymph node retrieval and equivalent short-term recurrence-free survival with a median follow up of 11 months.

Specifically for advanced tumor, a Canadian retrospective study (12) showed the results of 21 patients with laparoscopic gastrectomy for advanced gastric cancer and compared with open gastrectomy. All patients were enrolled during the adjuvant treatment. They showed a similar rate of recurrence (38.1% in the laparoscopic group *vs.* 36.8% in the open group).

The 3 years survival was also similar. One observation of great interest was the fact that 71% of the laparoscopic

group had no delay in the initiation of the adjuvant treatment compared with the 57% of the open group.

A study from Chile by Moisan *et al.* (13) compared retrospectively laparoscopic with matched on histological side with open gastrectomy. They compared 31 laparoscopic gastrectomy with 31 open procedures. In each group, half had advanced gastric cancer. The 3 years survival was similar when the subgroup of advanced gastric cancer was analyzed. Three-year disease-free survival was 77.8% in the LG and 68.8% in the OG.

For future evidence, an ongoing trial, LOGICA-trial (14), plan to compare open and laparoscopic gastrectomy in randomized trial. This will add evidence for the western population and the analysis of the advanced disease group will be of great interest.

In conclusion, the long-term results from the CLASS group are encouraging for the future of minimally invasive surgery. This approach must be part of a multidisciplinary management in order to obtain a tumor profile favourable to complete resection. This could improve the long-term disease-free survival, especially in stage III–IV patients. With the addition of newer, better-tolerated chemotherapy regimens for perioperative therapy, such as FLOT (fluorouracil plus leucovorin calcium, oxaliplatin, and docetaxel) (15), we can hope to see even more patients undergo surgical resection.

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Footnote

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