



Minimally invasive gastrectomy and the risk of pancreas-related morbidity

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For most of the last century, open gastrectomy (OG) has been the standard approach for gastric cancer. However, in recent years there has been growing acceptance of laparoscopic gastrectomy (LG), first performed by Kitano in 1994 (1), as an alternative and equally effective approach. In fact, LG has many advantages over the open approach including less blood loss, shorter time to bowel function, improved pain control, earlier oral intake, shorter length of stay, decreased postoperative morbidity and overall improved quality of life and patient satisfaction. Importantly, it has been shown to have similar oncologic outcomes compared to an open approach (2-4).

Several randomized controlled trials (RCT) have now established the short-term safety and oncologic equivalency of LG compared to OG. One of the first randomized trials comparing LG to OG approach for early gastric cancer (EGC) was conducted by Kitano *et al.* in 2002 (5). From October 1998 to March 2001, 28 patients (14 in each arm) with EGC were randomized to either laparoscopy or open surgery. All patients underwent a Billroth I reconstruction. They demonstrated earlier recovery, less pain, no reduction in curability with laparoscopy. In 2007, they performed a retrospective analysis of their laparoscopic cases from 1994 to 2013, including the previously randomized patient and again demonstrated good short-term and long-term outcomes (6).

Results from the JCOG0912 trial, a large multi-institutional RCT from Japan evaluating outcomes in patients with clinical stage 1 cancer of the middle or lower third of the stomach was completed between March 2010

and November 2013, enrolling 921 patients (462 LG and 459 OG). Although long term outcomes are yet to be analyzed, initial findings demonstrate no differences in short-term outcomes (7). Similarly, the KLASS-1 study randomized 1,416 patients with EGC to either LG versus OG. While no significant differences were observed in major complications or mortality, the overall complication rate was significantly lower in the LG group (8). Additional studies (KLASS-02, KLASS-03, KLASS-04, KLASS-05, KLASS-07 and KLASS-07), which include patients with more advanced disease are underway (9). Similar results have been demonstrated in non-randomized trials, single center studies and retrospective reviews.

Results in the West, though less compelling, have been similar. Huscher *et al.* randomized 59 patients with distal gastric cancer to either LG or OG. There were no differences postoperative in morbidity rates, 5-year disease free survival and overall 5-year survival. Patients in the laparoscopic arm had reduced blood loss, shorter time to resumption of oral intake, and shorter length of hospital stay (10). Although there have been no randomized trials in the United States, institutional and national database reviews have shown similar findings (11-13). The LOGICA trial, a multi-institutional prospective randomized superiority trial of LG versus OG opened in the Netherlands in 2014, and is currently recruiting with an expected study completion date is January 2023 (14).

Despite the evidence to support the use of LG for gastric cancer and its increasing adoption, some specific concerns remain. For example, there has been some concern that

LG may be associated with a higher incidence of post-gastrectomy pancreas-related morbidity, particularly acute pancreatitis (AP) and pancreatic fistula (PF) formation (15-18). Pancreas-related morbidity following gastrectomy is a rare but potentially devastating complication. While there may be several mechanistic explanations for how PF occurs following gastrectomy, the most likely etiology is violation of the pancreatic parenchyma during infrapancreatic dissection of the gastroepiploic lymph node basins or suprapancreatic dissection of the celiac axis branches. Furthermore, AP may occur as a result of ischemic, compressive, thromboembolic, or thermal injury.

Fortunately, the incidence of pancreas-related morbidity following gastric resection is low. Guerra *et al.* recently performed a systematic review and meta-analysis of the existing literature and found a pooled incidence of approximately 1%. While the authors conclude that LG is associated with a higher incidence of pancreas-related complications, it is important to note that no statistically significant differences were found between the OG and LG groups. Specifically, using RCT data only, pancreas-related complications occurred in about 1.24% of laparoscopic gastrectomies and about 0.91% of open gastrectomies ($P=0.42$). Of 11 studies reporting AP, 11 patients in the minimal invasive group developed AP, compared to six patients in the OG group ($P=0.03$). PF was reported in 35 patients in the minimal invasive group compared to 27 patients in the open group ($P=0.44$) (16).

Overall, these data are encouraging as some surgeons theorized that LG may lead to a higher rate of pancreas-related complications given the increased use of thermal energy devices. Nevertheless, these data must be interpreted cautiously since the methodological designs in these studies demonstrated significant heterogeneity. How were PF and AP defined and what criteria were used to make these diagnoses? How was perioperative drain placement standardized? What other technical or surgeon differences may have existed between patients who received an open versus minimally invasive approach?

To overcome these limitations, it may be most appropriate to focus attention on prospective RCTs and well-controlled cohort studies. Indeed, the JCOG0912 trial, a multi-institutional RCT of EGC, found similar rates of PF (0.4%) in patients undergoing LG and OG (7). Similar findings were reported in RCTs published by Aoyama *et al.* (1/13 in OG *vs.* 0/13 in LG group) (19), Hu *et al.* (0% OG *vs.* 0.4% LG, $P=0.249$) (20). The RCTs reported by Huscher *et al.* (10) and Kim *et al.* (8) did not note the

occurrence of any PF but each reported 1 case of AP in the LG group.

LG remains a technically challenging procedure, whose success is largely driven by the experience of the surgeon. Some have estimated a learning curve that includes at minimum 40 cases (21), and possibly up to 100 cases (22), to achieve optimal success. It is, therefore, not surprising that some of the studies with smaller case numbers had a trend towards increased pancreas-related complications in the laparoscopic group. It is, however, worth noting in a majority of the cases, these differences did not reach statistical significance. Regardless of surgical approach, AP and PF lead to significant morbidity and therefore the identification of risk factors and effective mitigation strategies are strongly justified. Jiang *et al.* reviewed some of the risk factors associated with PF formation including higher mean body mass index and longer operation time (15). Yu *et al.* equally identified D2 lymphadenectomy, total gastrectomy, splenectomy or distal pancreatectomy as being associated with higher PF rates (17). Future studies should attempt to identify comprehensive risk scores and prevention strategies as has recently been done for PF following pancreatectomy (23,24).

In summary, pancreas-related morbidity, including PF and AP, remain important considerations for surgeons performing LG or OG. Fortunately, the incidence of these events is rare and does not appear to be influenced by the use of minimally invasive approaches. Future studies should work to more accurately identify risk factors so that effective prevention strategies can be developed. In the meantime, meticulous surgical technique and rigorous attention to postoperative care will hopefully minimize the occurrence and impact of this dreaded complication.

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