Advances in Gastric Cancer Surgical Management

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KEYWORDS

• Minimally invasive gastrectomy • Robotic gastrectomy • Laparoscopic gastrectomy • Gastric cancer surgery • Gastric cancer • Stomach cancer • Total gastrectomy

KEY POINTS

- Gastric cancer should be resected with a negative microscopic margin.
- D2 lymph node dissection has been proven superior but should be done by experienced surgeons.
- Minimally invasive techniques for appropriately selected patients have equivalent oncologic outcomes with reduced hospital stay, less pain, less blood loss, faster return to work/life activities, and fewer adhesions. This approach also may facilitate sooner adjuvant systemic treatment.
- Endoscopic resection is supported for properly selected T1a N0 cancers due to lower risk of nodal metastasis.
- We are moving toward individualized treatments based on molecular/genetic features.

INTRODUCTION

Gastric cancer has been declared a public health concern by the World Health Organization and is the fifth most common cancer worldwide and the third most common cause of mortality.[1] Although not as prevalent as in the East, the United States has an estimated 26,380 new cases each year with 11,090 deaths,[2] and incidence in the West is rising in younger populations (ages 25–39 years).[3] Surgery remains the mainstay of treatment. In the past 30 years, the surgical approach has evolved with the advent of laparoscopic and robotic surgery. The debate regarding the extent of lymphadenectomy has been settled with the acceptance of D2 lymph node (LN) dissection as superior. However, reconstructive methods are still being investigated with no single

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preferred method. As we look toward the future, tailoring treatment to genetic and molecular subtypes will further guide our approach to surgery.

FUNDAMENTALS IN TECHNIQUE

As with other forms of oncologic surgery, negative resection margin and lymphadenectomy are fundamentally important to surgical technique. Negative resection margins constitute a critical factor in gastric resection, as positive resection margin is an independent predictor of poor survival.[4,5] Therefore, the goal of surgery is successful R0 resection (microscopically negative surgical margin) to reduce chances of local recurrence, which has been observed in 16% of patients with a positive surgical margin.[4] Owing to the importance of R0 resection, intraoperative frozen sections can be used to verify a negative resection margin and reduce the risk of local recurrence.[6] The diagnostic accuracy of frozen sections in esophagogastric adenocarcinoma ranges from 93% to 98%, though caution should be used in cases of signet ring cell (SRC) cancer due to a higher prevalence of false negatives in this subtype.[7,8] Previously the National Comprehensive Cancer Network (NCCN) guidelines recommended a 4 cm gross surgical margin; however, the 2023 guidelines have been updated to recommend a negative microscopic margin only.[9,10] Of course, as previously stated caution should be taken with diffuse or SRC cancers due to their propensity to spread within the submucosa and cause false-negative margins.[7,8] Therefore, resections should be planned with either subtotal or total gastrectomy as needed to obtain negative margins.

Although the extent of lymphatic dissection has been extensively debated, the importance of positive and total number of resected LNs after pathologic review has been established as one of the most important prognostic factors for gastric cancer.[11] It improves the accuracy of staging[11] and is associated with increased survival.[12] The ideal number of LN to be retrieved during lymphadenectomy has also been debated, with literature ranging from 15[11] to 29,[12] and the current NCCN guidelines recommend at least 16 for localized resectable gastric cancer.[9,10]

To inform the extent of lymphadenectomy, LN stations have been grouped into 3 levels: D1, D2, and D3. D1 dissection consists of the perigastric LNs only (stations 1–7).[13] A D2 dissection includes stations 1 to 12a and adds the hepatic, left gastric, celiac, and splenic nodes.[13] D3 dissection includes stations 1 to 16 and adds the porta hepatis and periaortic nodes to D2 dissection.[13] The appropriate method of LN dissection has been debated, and incongruence remains between approaches in the East and West. However, after years of randomized controlled trials (RCTs) D2 dissection has emerged as superior. Although initial studies indicated increased morbidity and mortality,[14,15] Western studies (Dutch and Italian) with 15 year follow-up have confirmed that D2 LN dissection has been found to have a significantly improved disease-specific survival, a lower risk of gastric cancer-related death, and lower locoregional recurrence versus D1 without significant increase in rate of complications.[16,17] It has also been shown that there is no benefit to D3 dissection, given no evidence of survival benefit with possible increased morbidity especially with pancreatectomy and splenectomy, which is no longer recommended except in cases of direct tumor extension/vascular encasement.[18–20] The NCCN guidelines currently recommend D1 or modified D2 dissection for localized resectable gastric cancer, again with the goal of $\geq$16 LN.[9] They recommend D2 dissection be completed by experienced surgeons in high-volume centers.[9]

TRANSITION TO MINIMALLY INVASIVE SURGERY

Surgical treatment of gastric cancer has now evolved beyond open gastrectomy, although it still may remain necessary in cases with considerable adhesions, patients

with significant comorbidities, or with inaccessible tumor location. Regarding gastric conservation, studies established that subtotal gastrectomy, when feasible to achieve R0 resection, had identical long-term survival to total gastrectomy with possible lower morbidity and mortality rates.[21,22]

After the advancement of laparoscopic surgical techniques in the 1980s, the first laparoscopic gastrectomy was performed in Japan in 1994,[23] proving the feasibility of laparoscopic resection for gastric cancer. Several RCTs followed from 2005 to 2010 showing the oncological safety of laparoscopic resection, as well as suggesting that minimally invasive surgery (MIS) techniques lead to reduced blood loss, reduced time to oral intake, and earlier discharge than open surgery.[24–27] To examine use in early cancer, two large RCTs were published, KLASS-01[28] and JCOG-0912,[29] confirming the oncologic equivalency of laparoscopic gastrectomy versus open surgery along with the added benefits of a minimally invasive approach. These studies were followed by RCTs for advanced gastric cancer: the CLASS-01,[30] JLSSG0901,[31] KLASS-02,[32] and STOMACH[33] trials. Once again these RCTs revealed technical safety without significant difference in disease-free survival between laparoscopic and open surgery.[30–32] Laparoscopic D2 resection was also confirmed to be equivalent to its counterpart in open surgery.[34] Many studies investigating the benefits of laparoscopic surgery for both early and late cancer have been performed in the East as well as the West, resulting in a wealth of data supporting oncologic equivalency with improved outcomes from MIS including: fewer complications, decreased hospital stay, decreased pain, less blood loss, and faster recovery.[35–49] Patients who had laparoscopic surgery were also significantly more likely to receive adjuvant chemotherapy when indicated.[45]

However, there is a learning curve associated with laparoscopic gastrectomy, with studies determining that 40 to 100 surgeries were needed to achieve decreased operative times.[50–53] Long-term outcomes remained equivalent during this learning stage.[50] After the learning was completed, operative times became comparable to open surgery.[52]

With the advent of robotic surgery, several RCTs investigated outcomes of robotic versus laparoscopic gastric resections. Robotic surgery was found to have fewer postoperative complications, with better LN dissection, faster recovery, and more prompt initiation of adjuvant chemotherapy.[47,54,55] In 2021, a single institution in Korea reviewed its 2000 robotic gastrostomies proving safety and feasibility at a high-volume center with equivalent long- and short-term outcomes.[56] This transition from open to MIS gastrectomy is summarized in **Fig. 1**. Currently, the NCCN guidelines state that laparoscopic or robotic approaches can be considered if the surgeon is experienced in MIS approaches and MIS lymphadenectomy.[9,10] Open surgery is still recommended if the tumor is T4b or there is bulky N2 disease.[9,10]

In regard to reconstruction after gastrectomy, no single method has emerged as superior. Reconstruction after proximal gastrectomy can be achieved with esophagogastrostomy, jejunal interposition, or double-tract reconstruction, a technique that is currently being evaluated in a randomized, prospective trial. Meta-analysis suggests that although esophagogastrostomy carried a higher risk of reflux esophagitis, it had a shorter operating time and hospital stay as well as lower risk of anastomotic stenosis and obstruction when compared with jejunal interposition.[57] Double-tract reconstruction was found to be comparable to esophagogastrostomy with fundoplication in terms of postoperative complications and may help prevent extreme body weight loss.[58] Double-tract reconstruction continues under investigation; however, the KLASS 05 study confirmed the short-term outcomes of laparoscopic proximal gastrectomy with double-tract reconstruction to be comparable to total laparoscopic

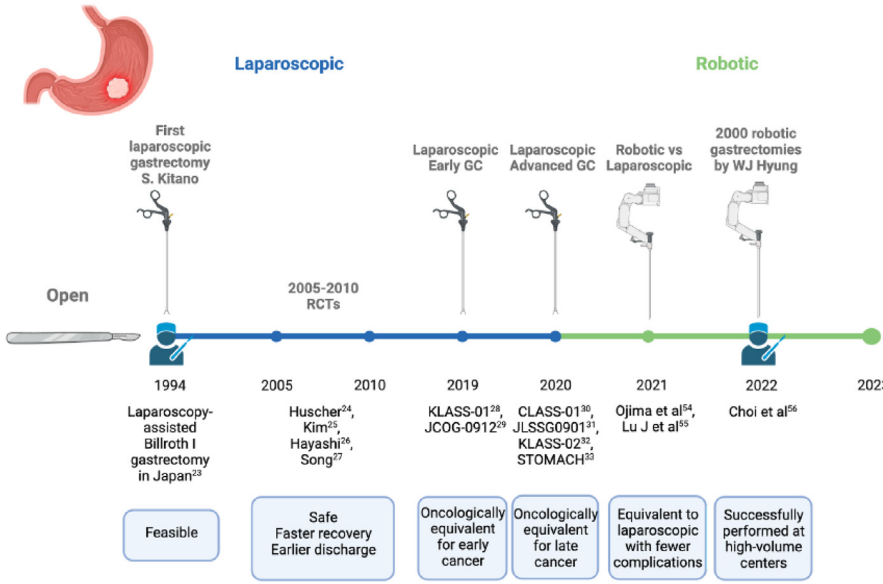

Fig. 1. Timeline depicting the progress from open to laparoscopic to robotic surgery with pertinent studies and conclusions. (Created with BioRender.com.)

gastrectomy.[59] Distal gastrectomy can be reconstructed with Billroth I, Billroth II, or Roux-en-Y. Outcomes from Roux-en-Y and Billroth II are similar, though Billroth II may be associated with a higher incidence of heartburn symptoms.[60] Meta-analysis suggests that complications and overall outcomes are similar between all three methods, though Roux-en-Y carried a lower risk of remnant gastritis.[61] Reconstruction after total gastrectomy can be achieved with Roux-en-Y, jejunal interposition, jejunal pouch, or Billroth II. One study suggested that jejunal pouch may be associated with improved quality of life when compared with Roux-en-Y, though overall both groups had similar outcomes.[62] The optimal method of reconstruction continues to be debated.

Along with the transition to laparoscopic and robotic surgery for gastrectomy, the role of diagnostic laparoscopy (DL) in staging and restaging has been well established. Positive peritoneal cytology was found to be the most predictive preoperative factor of gastric cancer mortality.[63] Therefore, DL allows identification of a population that is at high risk for early recurrence and death. The NCCN guidelines recommend DL for middle- and late-stage disease, and positive cytology as well as gross metastasis should direct care toward initial treatment with systemic therapy.[9,10] After chemotherapy, DL has been shown to be useful in restaging to determine which patients may be considered for subsequent primary tumor resection.[64]

Laparoscopy also has a role in several forms of intraperitoneal chemotherapy, though these remain controversial. Hyperthermic Intraperitoneal Chemotherapy (HIPEC) continues to be under investigation with several RCTs still enrolling.[65] The GASTRIPEC study has been completed and examined therapeutic HIPEC treatment in patients with peritoneal carcinomatosis.[66] They found no difference in overall survival with HIPEC added to treatment compared with cytoreductive surgery and systemic chemotherapy alone; however, progression-free survival and metastasis-free survival were significantly improved by a few months.[66] Pressurized

intraperitoneal aerosolized chemotherapy (PIPAC) was initially developed in Germany and uses nebulized chemotherapy injected into the abdomen at high pressure during laparoscopic surgery. No large RCTs have been completed at this time, though PIPAC VEROne is currently recruiting.[67] A systematic literature review suggests a possible survival benefit.[68] Early postoperative intraperitoneal chemotherapy involves installation of chemotherapy via catheters immediately after gastrectomy. Studies have revealed differing results, with a potential for prolonging survival but a higher degree of morbidity.[69,70] A systematic literature review reveals that although limited, the improvement in overall survival for patients with gastric cancers may be statistically significant.[71] Intraperitoneal chemotherapy remains under investigation, and ongoing clinical trials will help to identify its role in gastric cancer treatment.

NEW TECHNIQUES AND TECHNOLOGY

Developments in endoscopic techniques have allowed for safe and effective endoscopic resection of T1a N0 lesions, supported by the NCCN guidelines.[9,10] Endoscopic submucosal dissection compared with surgery was shown to be less expensive with less trauma and faster recovery, but there was no significant difference in overall or disease-specific survival when strict selection criteria were applied.[72,73]

Along with the development of the surgical robot, technology has allowed for near-infrared fluorescence imaging with indocyanine green (ICG) which can be used to improve visualization and identification of LNs. This technique can assist in LN identification and retrieval without adding significant operative time (<10 minutes in one study).[74] The use of this technology has the potential to allow less extensive resections, with more LN retrieval and better staging to guide treatment. It also can play a role in teaching, to help better guide trainees during lymphadenectomy.

GENETICS AND MOLECULAR SUBTYPES

The Cancer Genome Atlas Project proposed 4 molecular subtypes: tumors positive for Epstein–Barr virus, microsatellite unstable tumors (microsatellite instability [MSI]-high), genomically stable tumors, and those with chromosomal instability.[75] This new understanding has led to research investigating subtype-based treatment response and outcome. A secondary analysis of the MAGIC trial revealed that MSI-high patients treated with surgery alone had superior survival compared with patients with microsatellite stable cancers and actually worse survival when treated with chemotherapy.[76] Analysis of the CLASSIC RCT also confirmed that there was no benefit from adjuvant chemotherapy in MSI-high patients over surgery alone.[77] This evidence suggests that patients with MSI-high tumors could go straight to surgery if early or middle stage. As MSI-high cancers respond well to immune checkpoint inhibitors, there are now clinical trials of these agents as preoperative therapy. Preliminary reports indicate high rates of pathologic complete response to immune checkpoint inhibitor therapy.[78] Surgical care will continue to follow scientific discovery as medicine moves toward more molecular and genetic-based treatment models.

Another example of scientific advances determining surgical management is our understanding of the CDH1 gene. Pathogenic mutations in this gene increase the risk of diffuse gastric cancer characterized by SRCs. The current recommendation for patients with pathogenic CDH1 mutations and a family history who are appropriate surgical candidates is total gastrectomy.[79] Minimally invasive approaches are also feasible for prophylactic total gastrectomy.[79]

DISCUSSION

As technological advances have unlocked minimally invasive methods, fundamentals in technique such as negative resection margin and adequate lymphadenectomy continue to apply. MIS approaches have been proven to be oncologically equivalent with improved recovery, and surgery will continue to move toward less invasive techniques for the appropriately selected patient. No one clear method of reconstruction has been deemed superior, and further RCTs are necessary. Endoscopic techniques are now supported for T1a N0 tumor resection. The impact of intraperitoneal chemotherapy is not yet clear and continues to be investigated. ICG imaging of LNs may allow for a more limited LN dissection in the future, though this also requires further study. Given new understanding of genetic drivers and molecular subtypes, surgical management will have to evolve to become a part of personalized and precision cancer care.

SUMMARY

Gastric cancer resection requires a microscopically negative resection margin and D2 lymphadenectomy. Minimally invasive techniques (laparoscopic and robotic) have been proven to be equivalent for oncologic care, yet with faster recovery. Endoscopic resection can be used for T1a N0 tumor resection. Better understanding of hereditary gastric cancer and molecular subtypes has led to specialized recommendations for MSI-high tumors and patients with pathogenic CDH1 mutations. In the future, surgical management will support MIS approaches and personalized cancer care based on subtype.

CLINICS CARE POINTS

- Gastric cancer should be resected with a negative microscopic margin.
- D2 lymph node dissection has been proven superior but should be done by experienced surgeons.
- Minimally invasive techniques have equivalent oncologic outcomes with reduced hospital stay, less pain, less blood loss, faster return to work/life activities, and fewer adhesions.
- Endoscopic resection is supported for T1aN0 cancers that meet appropriate criteria.
- Care is moving toward treatment based on molecular/genetic subtypes, if MSI-high consider taking directly to surgery or enrolling on an immunotherapy trial.
- The current recommended treatment for carriers of pathogenic CDH1 mutations who are appropriate surgical candidates with positive family history is total gastrectomy.

DISCLOSURES

Dr V.E. Strong has recieved speaking honoraria from AstraZeneca.

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