Review article

Current practice of gastric cancer treatment

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Objective The aim of this review was to overview the current practice of gastric cancer treatment including surgery and other adjuvant modalities.

Data sources The review was based on data obtained from the published articles and main guidelines in the East and West.

Study selection Articles with high level of evidence or current best evidence in each issue were selected to be reviewed.

Results Although varied adjuvant modalities have been proved to be benefit for treating gastric cancer, surgery is still the most important treatment strategy against gastric cancer. Actively adapting to new technology is important but it should be balanced with an effort to establish sound scientific rationale that adheres to oncologic principles.

Conclusions Future treatment of gastric cancer will be focused on tailored, personalized therapy. For achieving it, collaboration across disciplines is essential. Also the philosophy of caring for the patients with gastric cancer should be rooted in the realization of true patient benefit regardless of who is providing the care. With these philosophies, we can shift the scientific and technological advances toward triumph over gastric cancer.

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Gastric cancer is a major health issue worldwide, with 989 000 newly diagnosed cases (7.8% of the total malignancy) and 737 000 deaths annually (9.7% of total cancer deaths).[1] Half of all gastric cancer patients are from Eastern Asia (463 000 gastric cancer patients in China alone), and approximately two-thirds of all cases occur in developing countries.

Gastrectomy with lymph node dissection has been established as a standard treatment for gastric cancer.[2] Traditionally, the surgeon assumes responsibility in determining operability and the extent of surgery required using histologic and radiologic information. With recent advances in both knowledge and available technology, however, therapeutic strategies for gastric cancer have been diversified. Surgical instruments and devices have been improved, and chemotherapeutic drugs as well as targeted agents have become more advanced as we gain a more comprehensive understanding of cancer biology. The epidemiology of gastric cancer has also been changing due to mass screening programs and improved survival rates. Further, recent progress in molecular biology research has been promising for personalized cancer therapy. In this new era, the role of physicians who treat gastric cancer is to rapidly translate these advances, thereby providing the best possible patient care.

This review focuses on basic oncologic and technical principles of gastric cancer surgery to date. We also discuss adjuvant modalities for treatment of gastric cancer and the future directions of these treatments.

Basic oncologic principle of gastric cancer surgery

Complete surgical resection of macro and microscopic tumors (R0) with en-block lymphadenectomy is the gold standard for cancer treatment. In patients with gastric cancer, radical gastrectomy is considered to be the only curative treatment option. In order to realize the clinical benefits of this definitive surgery, several oncologic principles should be maintained. During surgery, frequent manipulation of the tumor itself could lead to direct spillage of tumor cells.[3] Thus, a "no touch technique" that entails wrapping the lesion, especially in cases of serosa-positive tumors, to prevent iatrogenic peritoneal seeding during the operation should be applied. Also, careful hemostasis to avoid bleeding and lymphatic leakage is important as well.

Lymph node dissection for gastric cancer surgery

Gastric cancer can spread along both the lesser and greater curvatures of the stomach via an abundant and complicated lymphatic network system. Thus, standard lymph node dissection is essential during radical gastrectomy. The extent of lymph node dissection in cases of gastric cancer is determined via the D-level criteria, while the D level is decided according to the type of gastrectomy performed. N1 lymph nodes commonly refer to the lymph nodes around the stomach, while N2 lymph nodes refer to those around the major vessels that supply blood to the stomach.[4] Thus, D1 gastrectomy refers to gastrectomy with lymph node dissection at the N1 level only, while D2 lymph node dissection indicates removal of lymph nodes at the N2

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level.

The appropriate extent of lymph node dissection for gastric cancer treatment has long been debated. Japanese surgeons previously proposed that more extensive lymph node dissection leads to an improved survival benefit in patients with advanced gastric cancer (AGC). Under this premise, D3 lymph node dissections (D2 lymph node dissection including para-aortic area) were routinely performed. More recently, however, a prospective randomized controlled study by Japanese researchers showed that D3 surgery was associated with more complications without survival benefit compared with D2 surgery.[5,6] Based on these randomized clinical trial results, D2 lymphadenectomy has been adopted as the standard of care in Eastern countries.

In the 1990s, phase III randomized controlled trials (RCTs) in Western countries showed that D2 lymph node dissection did not offer a survival benefit over D1,[7,8] but was associated with a higher incidence of surgery-related morbidity and mortality. Consequently, limited D0 or D1 lymph node dissection with perioperative chemotherapy or postoperative chemoradiotherapy was adopted as the standard of care in Western countries.[9-12] A subsequent Dutch trial that included 15 years of follow-up data, however, showed that D2 lymph node dissection was beneficial in terms of preventing loco-regional recurrence and gastric cancer-related death compared with D1 surgery.[13] In addition, an RCT from Taiwan reported a survival benefit without any surgery-related mortality in patients who underwent D2 lymph node dissection.[14] Currently, the most commonly used Western guidelines, the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology guidelines, recommend D2 gastrectomy as the standard of care when performed at specialized centers only[15,16] due to the high rates of morbidity and mortality when performed by inexperienced surgeons.

Omentectomy with bursectomy

The omentum is a visceral peritoneum which hangs from the stomach and defends against inflammation within the abdominal cavity.[17] The omentum has milky spots which act as a gateway for cancer seeding in the early stages of peritoneal metastasis.[18] Therefore, complete removal of the greater omentum is considered to be essential for successful gastric cancer surgery. Recent studies have reported that outcomes were similar between partial and complete omentectomy in patients with early gastric cancer (EGC)[19] as well as AGC.[20] However, the safety of partial omentectomy for AGC has yet to be confirmed by an RCT. Thus the current Japanese guidelines recommend complete removal of the greater omentum when gastric cancer invades the subserosal layer (T3) and permits partial omentectomy, preserving a 3 cm distal portion of the gastroepiploic arcade if invasion involves less than the proper muscle layer.[4]

Dissection and removal of the anterior membrane of the transverse mesocolon with the capsule of pancreas, also known as "bursectomy", has been considered the standard procedure in conjunction with total omentectomy during radical gastrectomy for AGC in Eastern countries.[21] The reasoning behind this procedure is that removing the membrane that covers the posterior stomach cavity which may include free cancer cells or micrometastasis could decrease cancer recurrence.[22] It was previously suggested that bursectomy was a futile procedure without clinical benefit[23] and a recent NCCN guideline excluded bursectomy from the definition of D2 dissection.[15] However, based on the interim results of an RCT conducted in Japan,[24,25] bursectomy is recommended for serosa-positive gastric cancer because it could offer survival benefit.[4] Long-term follow-up results and the on-going large-scale multicenter RCT (JCOG 1001) will provide more concrete evidence on this issue in the future.

Organ-preserving gastrectomy

Historically, surgeons thought that pancreatico-splenectomy should be performed in cases of proximal gastric cancer since lymph nodes along the upper border of the pancreas and splenic hilum needed to be resected for curative surgery.[26] Thus total gastrectomy for proximal gastric cancer had meant total gastrectomy with distal pancreatectomy and splenectomy. One of the common complications of distal pancreatectomy is pancreatic leak resulting in subphrenic abscess formation.[27] In 1995, Maruyama et al[28] reported that pancreas-preserving total gastrectomy could be performed with a lower incidence of morbidity and mortality. An RCT which compared the effects of D2 gastrectomy with those of D1 gastrectomy reported that splenectomy with lymph node dissection was associated with high morbidity and a worse prognosis compared to spleen- and pancreas-preserving gastrectomy, and pancreatico-splenectomy with lymph node dissection had the highest morbidity and worst prognosis.[29] In addition, Noh et al presented the technique of spleen-preserving total gastrectomy with splenic hilar lymph node dissection at the Second International Gastric Cancer Congress and reported that splenectomy resulted in poor short-term outcomes with similar long-term outcomes compared to spleen-preserving gastrectomy.[30,31] As a result, splenectomy for the purpose of lymph node dissection is not routinely practiced in cases of proximal gastric cancer,[15] and this change has decreased the morbidity and mortality associated with gastrectomy. It is important, however, that appropriate lymph node dissection (D2 gastrectomy) is performed in conjunction with spleen-preserving gastrectomy.

Adequate resection margins

The type of gastrectomy performed is determined according to the location of the tumor with the goal of achieving an adequate macroscopic and microscopic resection margin. The current Japanese guidelines recommend a gross resection margin of greater than 2 cm for EGC and 3–5 cm for AGC.[4] NCNN guidelines, on the other

hand, recommend a resection margin of 4 cm.[15] If there is direct tumor invasion into adjacent organs such as the transverse colon or pancreas, en-block combined resection is necessary. When the resection margin is ambiguous, histopathologic confirmation on frozen sections is required.

Reconstruction after gastrectomy

After achieving a safe resection margin, the pathway for food passage should be reconstructed. The most commonly used reconstruction techniques are the Billroth I (gastroduodenostomy), Billroth II (gastrojejunostomy), and Roux-en-Y gastrojejunostomy (or esophagojejunostomy). The Billroth I anastomosis offers advantages such as maintenance of physiologic food passage, use of a single anastomosis, and simplicity of surgical technique.[32] A recent study reported on the benefit of maintaining iron metabolism when a Billroth I anastomosis is utilized.[33] However, the extent of gastric resection is limited and at times tension at the anastomosis site is problematic. Anastomosis leak is one of the more serious complications of gastrectomy, which can have a negative impact on patients' prognosis.[34] To decrease the risk of leak after Billroth I, a modified double stapling technique which avoids stapling on the staple line is helpful.[35]

The Billroth II anastomosis permits a wider range of gastric resection than Billroth I and is quicker to perform than the Roux-en-Y reconstruction. The Billroth II technique is associated with postoperative reflux symptoms, however, and as a result may decrease the quality of life (QOL) of patients and increase the risk of developing cancer in the stomach remnant.[36] The Roux-en-Y reconstruction was designed to reduce bile reflux, which in turn lowers the risk of associated gastritis or esophagitis compared with the Billroth methods.[37,38] Roux-en-Y reconstruction is more time intensive, the risk of leakage is high due to a greater number of anastomoses, and Roux stasis can occur.[39] A recent meta-analysis showed that Roux-en-Y reconstruction did not increase postoperative complications such as leakage,[40] and an RCT reported no difference in postoperative QOL and nutritional status between the reconstruction techniques.[37] Because each reconstruction method has its own distinct advantages and disadvantages, surgeons are able to tailor the treatment method to the needs of the patient.

Strategies for improving quality of life and decreasing complications

Historically, the use of large incisions, nasogastric tubes, and placement of drains were common practice during surgery for gastric cancer. This often resulted in discomfort for the patient, however, due to incisional pain, sore throat due to nasogastric tube insertion, and drain site infection. Consecutive studies have shown that routine insertion of nasogastric tubes and drains is not necessary,[41,42] and that trimming of the lesser curvature and greater curvature using a "Bovie" instead of a "clamp and tie" technique can reduce the operative time and increase cost effectiveness.[43] In addition, if wound traction is appropriate, a small incision less than 15 cm in length that does not extend below the umbilicus is large enough for total gastrectomy. These small changes may help to improve the QOL of patients undergoing gastrectomy for gastric cancer.

Role of minimally invasive surgery for gastric cancer

Minimally invasive surgery (MIS) such as laparoscopic or robotic surgery has become the standard procedure in many surgical fields including oncologic surgery. In gastric cancer patients, laparoscopic distal gastrectomy with lymph node dissection[44] has become widely used for EGC without evidence of lymph node metastasis, especially in Korea and Japan. Although the short-term benefits such as small incision size, improved QOL, and shorter hospital stay are well established,[45,46] there have been concerns that MIS does not achieve adequate D2 lymph node dissection. Thus, to evaluate the oncologic safety of laparoscopic gastrectomy for EGC, multicenter randomized trials are ongoing in both Korea (KLASS trial)[46] and Japan (JCOG 0912 trial).[47] While several studies[48,49] have reported that laparoscopic gastrectomy offers similar long-term outcomes to those of open gastrectomy for EGC, results from these ongoing trials are needed for further confirmation. To evaluate whether laparoscopic gastrectomy can be used in cases of AGC, a multicenter RCT (KLASS II) is ongoing in Korea.

Robotic surgery has several potential advantages over laparoscopic surgery including three-dimensional viewing, a tremor filter, and articulated movements of robotic arms.[50,51] Several recent studies have reported that robotic gastrectomy was associated with less blood loss and decreased incidence of ileus or obstruction than open or laparoscopic gastrectomy during short-term follow-up.[52,53] The cost of robotic surgery is very high, however, and the practical advantages over laparoscopic surgery have yet to be proven. Moreover there have been no studies that have examined long-term outcomes. Thus, future trials are needed to further assess the role of robotic surgery in the treatment of gastric cancer.

The development of endoscopic mucosal resection has transformed the role of endoscopy from a diagnostic tool into a treatment option for gastric cancer. Endoscopic submucosal dissection permits complete removal of large, deep tumors due to advanced endoscopic instruments and techniques when the probability of lymph node metastasis is very low.[54,55] Because endoscopic treatment has the advantage of not requiring gastrectomy, its indications have been expanded.[4,56] This technique carries its own risks, however, including gastric perforation and bleeding.[57] Additionally, the long-term oncologic outcomes of endoscopic treatment of gastric cancer have not yet been established. As a result, surgical resection with adequate lymph node dissection remains the standard treatment

for EGC yet. In the future, with the development of tools which can clearly identify whether there are lymph node metastases, the use of endoscopic treatment could be greatly expanded.

Sentinel lymph node navigation and tailored surgical approaches

Although radical gastrectomy with D2 lymph node dissection is the standard surgical treatment for AGC, more extensive lymph node dissection results in greater morbidity and mortality,[7,8,29] and gastrectomy itself could decrease the QOL of patients. Therefore, if we can predict the status of the primary tumor and regional lymph nodes before the operation, tailored gastrectomy such as wedge resection and limited lymph node dissection may be possible.

Sentinel lymph node biopsy for predicting whether there are metastatic lymph nodes has been widely used in patients with breast cancer and melanoma. In patients with gastric cancer, the use of sentinel lymph node biopsy to establish a tailored surgical approach for lymph node-negative EGC has been studied. This method is not widely used to date, however, since there are no established data regarding standardized techniques or accuracy. Fluorescent surgical imaging has recently emerged as well and has been widely studied in other types of cancers in combination with laparoscopic or robotic surgery.[58-62] This new technique is expected to guide the possibility of tailored, limited surgery for gastric cancer.

Adjuvant therapy for gastric cancer

Surgery is the oldest but most important treatment strategy for patients with gastric cancer, without which patients rarely get cured. In conjunction with surgery, additional adjuvant treatment strategies such as chemotherapy and radiotherapy help to increase the chance of cure.

In Eastern countries, many surgeons believed that D2 gastrectomy alone can cure gastric cancer, since results from those patients were better than those of Western countries that utilized surgery combined with perioperative chemotherapy or postoperative chemoradiation therapy. However, others were curious about the effect of adjuvant chemotherapy after D2 gastrectomy, and a large patient-level meta-analysis by the GASTRIC group suggested that postoperative adjuvant chemotherapy may have a survival benefit compared with surgery alone.[63] To test this hypothesis, two monumental phase III multicenter RCTs were conducted: the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) in Japan[64,65] and the Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC) in multiple Eastern countries.[66]

The results of the ACTS-GC trial showed that adjuvant S-1 chemotherapy after D2 gastrectomy had a survival benefit in terms of overall survival and relapse-free survival compared with surgery alone. As a result, the latest Japanese Gastric Cancer Association treatment guidelines[4] recommend adjuvant S-1 chemotherapy as a standard regimen for patients with stage II or III gastric cancer (according to Japanese classification).[67] The interim results of the CLASSIC trial supported the positive effects of adjuvant chemotherapy with the XELOX regimen (capecitabine with oxaliplatin) after D2 gastrectomy. Their results showed that adjuvant XELOX after D2 gastrectomy resulted in better 3-year disease-free survival compared with the group that underwent surgery alone.

Although D2 gastrectomy is now recommended by Western guidelines,[15,16] it has not been a practical standard surgery due to its high morbidity and mortality. Thus, the role of perioperative chemotherapy or postoperative chemoradiation therapy with a more limited surgery has been evaluated and practiced in Western countries. In Europe, based on the Medical Research Council Adjuvant Gastric Infusional Chemotherapy trial (MAGIC trial),[9] perioperative chemotherapy in conjunction with surgery has been the standard treatment for AGC. Their results showed that perioperative chemotherapy improved not only resectability, but also disease-free survival and overall survival compared to surgery alone. However, this study was limited by the inclusion of patients with lower esophageal cancer and esophago-gastric junction cancer. Additionally, the trial lacked a standard preoperative staging system.

In the United States, adjuvant chemoradiation therapy after gastrectomy with limited lymph node dissection (D0 or D1) has been the standard treatment for AGC based on the results of the intergroup 0116 trial.[10,11] That study showed promising results using chemoradiation therapy after surgery, with better overall survival and relapse-free survival compared with the surgery alone group. The role of radiation is to control loco-regional tumors after insufficient lymph node dissection. However, Eastern studies have shown that appropriate lymph node dissection (D2 dissection) can offer controlled loco-regional tumor growth with lower morbidity and mortality than chemoradiation therapy after surgery. Thus the effects of radiation therapy after D2 gastrectomy were thought to be negative, and this has been supported by the results of a clinical trial from Korea (the Adjuvant Chemoradiation Therapy in Stomach Cancer, ARTIST trial).[68] However, there have been some suggestions from Eastern studies that radiotherapy would be helpful in decreasing logo-regional recurrence in specific patients even after D2 gastrectomy.[69,70] A recent study reported that radiation therapy after D2 gastrectomy with chemotherapy improves loco-regional recurrence-free survival compared with D2 gastrectomy with chemotherapy in patients with stage III gastric cancer.[71] To determine the efficacy of radiation therapy after D2 gastrectomy, further RCTs are needed.

Prognosis and treatment responses are sometimes different even within groups of patients with the same stage of cancer. Thus, further understanding of cancer biology will

help to develop new strategies for approaching gastric cancer. The Trastuzumab for Gastric Cancer (ToGA) trial[72] showed potential success for targeted therapy in gastric cancer, which has encouraged investigators to seek other targeted biological pathways. Trastuzumab (Herceptin) is a humanized monoclonal antibody which interferes with human EGFR type 2 (HER-2/neu, ErbB-2). The ToGA trial showed that trastuzumab combined with chemotherapy provides a survival benefit in patients with HER-2-positive AGC. Recent advances in genomics and multiomics-based high-throughput biology are helping to pave a new road toward personalized cancer treatment. Molecular assays as well as integrated genomic scale data will allow for tailoring of the therapeutic decision-making process for patients within the same TNM stage groups.

Although adjuvant treatment strategies for gastric cancer are far more advanced today than in past decades, the quality of surgery still strongly affects patient survival. Thus, it is important to not only identify specific indications for various adjuvant therapies and new treatment strategies, but also standardize the type of gastric cancer surgery as D2 gastrectomy.

Concluding remarks

In recent years, we have made great strides in the treatment of gastric cancer. Surgical treatment of gastric cancer has improved and been standardized, and new technologies and instruments are continuously being developed and adapted. In order to achieve minimal invasiveness, the roles of endoscopic, laparoscopic, and robotic approaches have been evaluated and established, and the indications for chemotherapy and radiation therapy have also been determined. Actively adapting to new technology is an important part of delivering optimal care in patients with gastric cancer, though this should be balanced with an effort to establish sound scientific rationale that adheres to oncologic principles.

In the future, treatment of gastric cancer will be focused on tailored, personalized therapy. To achieve this, collaboration across disciplines will be necessary. Thus surgeons and physicians should envision a future featuring genomic precision oncology. The philosophy of caring for patients with gastric cancer should be rooted in the realization of true patient benefit regardless of who is providing the care. If we keep these philosophies in mind, we can shift these scientific and technological advances toward triumph over gastric cancer.

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