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Review Article

Recent Evolution of Surgical Treatment for Gastric Cancer in Korea

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Gastric cancer is the most common malignancy and the incidence is steadily increasing in Korea. The principal treatment modality for gastric cancer is surgical extirpation of tumor along with draining lymph nodes. Gastrectomy with D2 lymph node dissection has been well established as a standard of surgery and improved the survival of gastric cancer patients. Recently, technological advances are drastically reshaping the landscape of surgical treatment of gastric cancer. One of the most notable trends is that minimal access surgery becomes dominating the treatment of early stage diseases. For advanced diseases, the standard access surgery is considered a reference treatment. Although there is a pilot study underway to evaluate the feasibility of the application of minimal access surgery to advanced gastric cancer (AGC), the evidence for oncological safety is not yet provided sufficiently. Based on the recent randomized controlled trials, the extent of surgery for AGC has re-defined as para-aortic lymph node dissection dose not add any survival benefit while increasing surgery-related morbidities. In addition, it is now accepted as a standard operation omitting unnecessary procedures such as splenectomy and/or distal pancreatectomy for prophylactic lymph node dissection. Conceptual and technical innovation has contributed to decreasing morbidity and mortality without impairing oncological safety. All these recent advances in the field of gastric cancer surgery would be concluded in maximizing therapeutic index for gastric cancer while improving quality of life.

Key Words: Stomach neoplasms, Therapeutics, Korea, General surgery

Introduction

Although the incidence of gastric cancer is decreasing worldwide, it is the most common cancer in Korea where the incidence is steadily increasing.(1,2) In Korea, malignancy is the leading cause of death and gastric cancer is the third site of cancer mortality.(1,2) The survival rate of gastric cancer has increased, from over 40% in 1990s to more than 60% in the early 2000s, indicating that there was notable progress in the field of gastric cancer diagnosis and treatment.(1)

The Information Committee of the Korean Gastric Cancer Association has performed nationwide survey to investigate the chronological changes and clinicopathological features of gastric cancer. The demographics and characteristics of patients with gastric cancer in 2000s compared to 1990s have changed substantially in that there are increase of older patients and early cancer proportions potentially due to the general population aging and heightened awareness of the checkup program, respectively. In addition, there was a trend of rise of upper gastric cancer and the number of patients with higher body mass index (BMI).(3,4)

All these changes and the progresses in the field of surgical treatment resulted in reshaping the landscape of surgical treatment of gastric cancer. In this review, we will discuss the recent trend, emerging concerns and future perspectives of gastric cancer treatment in Korea focusing on operative surgery.

Subject

The current standard treatment for operable gastric cancer is gastrectomy with D2 lymph node dissection which is a well-established practice in Korea as well as in Japan. The morbidity and

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mortality rates of this reference procedure is about 17~20% and 0.6~0.8%, respectively in Korea and Japan.(5,6) In two randomized controlled western studies, the morbidity was more than 40% and mortality was more than 10% in D2/D3 lymph node dissection. Moreover, because D2 gastrectomy showed no survival benefit over D1 gastrectomy, most western surgeons have been performed D1 dissection.(7,8)

Before minimal invasive access surgery has emerged, open surgery was a standard way to reach peritoneal cavity. After 2000s, minimal invasive techniques have been applied pushfully for patients with early gastric cancer (EGC) and the proportion of these techniques are increasing. In the fields of minimal invasive concept are endoscopic resection, laparoscopic surgery, robotic surgery, and sentinel lymph node detection. However, the fundamental principle that the oncological outcome and safety of minimally invasive techniques is comparable to the conventional method should be strictly followed.

Treatment of Early Gastric Cancer

1. Endoscopic resection

Endoscopic mucosal resection (EMR) is a treatment option for early gastric cancer with extremely low possibility of lymph node metastasis. The conventional worldwide indications of EMR are differentiated adenocarcinoma, a lesion < 2 cm in diameter, no ulceration within the tumor, and no lymphovascular involvement. Recently, due to the advances in endoscopic instrumentation and techniques, endoscopic submucosal dissection (ESD) became a main method of endoscopic treatment of early gastric cancer. ESD can achieve direct dissection of the submucosa without the limitation of tumor size. The large scaled multicenter trial in Korea showed the efficacy and safety of ESD, 95.3% of en-bloc resection and acceptable rate of complications (bleeding 15.6%, perforation 1%).(9) Considering the benefits of ESD in minimizing the amount of invasive procedure, it has the potential to extend its indication. Many studies have been carried out to evaluate the risk of lymph node metastasis in submucosal or undifferentiated early gastric cancers to establish the most appropriate treatment strategy. Gotoda et al.(10) demonstrated that the subgroup of patients with a size less than 3 cm, well differentiated histology, no lymphovascular invasion, and submucosal invasion depth of less than 500 μm showed no lymph node metastasis. They also showed there were no positive lymph nodes in EGC with undifferentiated lesions, no ulceration, and less than 2 cm. In Korea, there were some reports for subgroups of undifferentiated type EGC without lymph node metastasis which has a potential to extend the indication of endoscopic treatment.(11,12) However, because the number of patients included in these criteria is small, the oncological safety of extended application of ESD remains to be a matter of problem. Therefore, the standard treatment in EGC which are not included in conventional EMR criteria is still a surgical resection with appropriate lymph node dissection in Korea.(13)

2. Rapidly developing surgical treatment

One of the most notable trends is that minimal access surgery (MAS) becomes dominating the treatment of early stage diseases. Given that the equivalent procedures as standard surgery are delivered, the method of minimal invasive surgery would provide the comparable oncological outcomes in theory. With this premise, minimally invasive surgery (MIS) is now regarded as a viable alternative to standard access surgery for early gastric cancer. Moreover, the cosmetic advantage provided by the MIS/MAS is attractive to the patients, although this is way overly represented to the public.

Laparoscopy-assisted gastrectomy is representative procedure of MIS and accepted as a safe and feasible surgical procedure for early gastric cancer. The number of laparoscopy-assisted gastrectomy cases has increased rapidly for several years and more than 3,000 cases of laparoscopy-assisted gastrectomy were performed in Korea in 2009. The indication for laparoscopy-assisted gastrectomy has been limited to early gastric cancer, which are less likely to accompany lymph node metastasis due to the concern for incomplete lymph node dissection and the lack of long-term outcome results. Korean Laparoscopic Gastrointestinal Surgery Study (KLASS) group published several multicenter large-scale retrospective results of laparoscopy-assisted gastrectomy.(14-16) In those studies, laparoscopy-assisted gastrectomy showed similar long-term oncologic outcomes. The morbidity and mortality were similar to open surgery. In early gastric cancer, the application of laparoscopic surgery will be increasing in the future.

Robot surgery was invented to improve the difficulty and uncomfortability of laparoscopic surgery. In Korea, robot-assisted gastrectomy was rapidly adapted by experienced laparoscopic surgeons and until now in 20 institutes, about 30 robot systems have been installed.(17) There are several benefits for surgeons in robotic surgery, such as 3-D visualization, freedom of intraabdominal motion by EndoWrist, comfortable surgeon's position. They seem to be substantial for better and stable surgical circumstance and developing surgical techniques. Robot-assisted gastrectomy is a safe

procedure comparable to laparoscopic surgery. Considering high cost of patients or insurance pays, however, the efforts to identify patients' merits should be sought. In addition, the long-term outcome of robotic surgery should be evaluated.

As a function-preserving procedure, there have been many reports for pylorus-preserving gastrectomy (PPG) in Japan, but it has been performed limitedly in Korea. Park et al. reported that PPG has advantages over conventional distal gastrectomy with Billroth I anastomosis in gastric emptying, bile reflux, and gallstone.(18) However, the number of PPG is extremely limited, about 0.26 %, and the data is not enough in Korea.(3,4)

Proximal gastrectomy is a surgical option for EGC located at upper third of the stomach. The several reconstruction methods have been introduced, but the optimal method after gastrectomy remains controversial. In Korea, gastric tube esophagogastrostomy is mainly used because it is simple and fast and surgeons appear to be less favorable to jejunal or jejunal pouch interposition methods.(19,20) A large volume center reported that proximal gastrectomy was associated with a markedly higher rate of complications such as anastomotic stenosis and reflux esophagitis and to provide no benefit in terms of postoperative weight loss compared to total gastrectomy despite the surgical safety and curability were similar.(19) Therefore, proximal gastrectomy is not performed widely (1.1%) and total gastrectomy may be preferable in proximal EGC in Korea yet.(3,4)

Sentinel lymph node navigation surgery is a new paradigm shift in gastric cancer treatment. Sentinel lymph node is the first sites of metastasis through lymphatic drainage pathway from the primary tumor and it is a well established in breast cancer and melanoma. In gastric cancer, several surgeons in Japan performed many studies to develop surgical strategy based on sentinel lymph node status and the concept of lymphatic basin dissection and modified gastric resection for early gastric cancer without sentinel lymph node metastasis is appealing. However, skip metastasis and false negative rate are critical points for using it in clinical practice.(21)

3. Efforts for renovating current practices

As surgeons as well as patients have been interested in the patients' satisfaction and better life after surgery, the necessity of procedures afflicting patients was thought earnestly. Nasogastric tube insertion was a common practice in abdominal surgery including gastric surgery, because some surgeons believed that anastomotic leakage, intraluminal bleeding, or aspiration pneumonia would be aggravated or detected too late without nasogastric decompression.(22) However, a prospective study showed that gastric cancer surgery can be performed safely without nasogastric decompression and this uncomfortable and unpleasant procedure is not applied to patients any more in many hospitals in Korea.(22) In line with this thinking, we found that prophylactic drain placement would not offer additional benefit for patients undergoing gastric cancer surgery with standard lymph node dissection.(23) These data might contribute to mitigating inconvenience of gastric cancer patients by leaving out unnecessary procedures. Epidural or intravenous analgesia for postoperative pain relief also help patients tolerate well after surgery.

Surgical Treatment of Advanced Gastric Cancer

Conventional open surgery is the common approach method for advanced gastric cancer. Although the extent of lymph node dissection is controversial between eastern and western studies, radical gastrectomy with D2 lymph node dissection has been accepted as a standard procedure for advanced gastric cancer (AGC) in Korea and Japan.(24-26) Recently, with advances in technique and surgeon experience, the extended application of laparoscopy-assisted gastrectomy for patients with advanced gastric cancer has been tried by several experienced surgeons. In several studies, the long-term outcomes after laparoscopy-assisted gastrectomy for advanced gastric cancer were comparable to open surgery. However, these retrospective studies had small number of patients with selection bias.(27,28) The technical and oncological safety of D2 lymphadenectomy by minimally invasive approach should be proven. Therefore, multicenter prospective study will be undergoing in Korea.

The demand for better quality of lifes changes surgical procedures in detail achieving both of oncological safety and better quality of life. In these view, prophylactic splenectomy is not justified any more in Korea, which was a matter of debate in the past. Some authors showed that splenectomy for hilar lymph node dissection did not achieve oncological benefit even in locally advanced proximal gastric cancer.(29,30) A randomized clinical trial performed by several Korean surgeons showed splenectomy had no survival benefit in patients with metastatic lymph nodes at the hilum of the spleen.(31) Splenectomy for splenic hilar node dissection is not generally advised in Korea now.

Para-aortic lymph node dissection is also no longer performed for treatment of gastric cancer. In several randomized studies comparing D2 and D2+para-aortic lymph node dissection performed

in Japan, D2+para-aortic lymph node dissection did not improve survival rate but it increased postoperative complications.(5,32-34)

Recently, there was a discussion for the oncological benefit and the necessity of lymph node dissection along the superior mesenteric vein (no.14v). Lymph node no.14v is included in the D2 lymph node dissection, but not in the D1+β lymph node dissection for treatment of distal gastric cancer.(35) The clinical significance of lymph node no.14v metastasis was evaluated in a large-scaled Japanese study, and the prognostic impact of 14v lymph node metastasis seems to be strong.(36) The authors suggested that the prognosis of patients with 14v metastasis was similar to those with systemic metastasis and only some patients had a chance to be cured by 14v dissection. In a retrospective Korean study, authors suggested a subgroup of gastric cancer getting merits from 14v dissection.(37) There is no western study for lymph node no.14v metastasis or dissection and this issue seems not to be appealing to western surgeons. Although randomized controlled study could clarify the clinical impact of 14v dissection, it is difficult to make progress the study in Korea due to patients consent. After all, lymph node no. 14v will be excluded from the extent of conventional D2 lymph node dissection.

Concluding Remark

The unshakable principle in surgical oncology is to deliver the curative surgery with the intent to improve the survival of cancer patients. Although this principle in gastric cancer treatment remains unchanged, the way of delivering this principle, making R0 resection, has drastically changed over the last decade in Korea. There is little evidence to indicate that current technological innovations in surgical treatment of gastric cancer have been the product of biological principle. Rather, advances in technical engineering research and the resulting empiricism have brought new technical innovations to the clinical practice without noticeable resistance. Indeed, it is also recognized that even in the US, the early evolution of cancer surgery has been influenced by surgical technique and equipment innovations to a greater extent than by comprehension of the biology of cancer. Although current and future technological developments will continue to play a major role in the surgical treatment of gastric cancer, it needs to be stressed that the clinical and basic research should also be in parallel which dictates the future of gastric cancer and, ultimately, the fate of surgery.

Regardless, the current status and the main stream trend is that minimally invasive procedures are generally accepted in early gastric cancer treatment, while conventional access gastrectomy with D2 lymph node dissection is regarded as a standard surgical treatment in advanced gastric cancer. Recently, KLASS-02 trial (laparoscopy vs conventional access) is conceived and now undergoing to evaluate the oncological safety and quality of life (QoL) in advanced cancer patients treated with laparoscopy-assisted surgery. Although this trial would be one of the milestones in clinical trials for gastric cancer surgical treatment, it raises some controversies among some physicians and investigators. The prognosis of advanced stage diseases still needs to be improved. Unlike contemporary oncological trials in which the newer drugs are assessed for efficacy in prolonging the survival of AGC patients, most surgical trials in these days are clinging to the QoL of patients: even in patients with advanced diseases.

Although this would be a matter of viewpoint of many surgeons, we may need to reflect on ourselves and steer the right direction for further progress in surgical treatment of gastric cancer. It is foreseeable that studies for evaluating oncological safety and extending indication of minimal invasive techniques will be undergoing. Regardless, to improve the survival of gastric cancer, multimodal treatment including effective new agents in adjuvant or neoadjuvant setting should be more sought in parallel with current trends in surgical treatment of advanced cancer than now.

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