Review Article

Surgical treatment of gastric cancer: Current status and future directions

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Abstract

Surgery is the most important and effective method for the treatment of gastric cancer. Since the first gastrectomy in the early 19th century, surgical treatment of gastric cancer has undergone more than 100 years of development. With the increasing understanding of gastric cancer and the promotion of a series of clinical trials, the concept of gastric cancer surgery has evolved from the initial "bigger is better" to today's "standardized surgery" and is developing towards individualized surgery focusing on accurate resection and quality of life. This trend has had a tremendous impact on the development of surgical treatments, such as minimally invasive surgeries, function-preserving surgeries, and the optimal extent of lymph node dissection. Understanding the development and current status of gastric cancer surgery and exploring the remaining academic controversies are goals that every gastric surgeon should constantly pursue. However, how should gastric cancer surgery develop in the future? What opportunities and challenges will we encounter? In this review, we elaborate on the development and current status of gastric cancer surgery based on a series of clinical studies and discuss the controversy in the development of gastric cancer surgery.

Keywords: Gastric cancer; surgical treatment; minimally invasive surgery; function-preserving surgery; lymph node dissection; review

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Introduction

Gastric cancer ranks as the fifth most frequently diagnosed cancer and the third leading cause of cancer-related death worldwide, with more than 1,000,000 new cases and an estimated 783,000 deaths in 2018 (1). Surgical resection is considered to be the only curative therapeutic modality for early and some advanced forms of gastric cancer (2-4). Surgical treatment of gastric cancer began in the late 19th century (5). After more than a century of development, especially in the past two to three decades, with an accompanying series of clinical trials, today's surgical treatment of gastric cancer has made great progress.

In the late 19th century, Dr. Billroth performed the world's first gastrectomy and created the Billroth I and Billroth II gastrointestinal anastomosis, which represented the prelude to human exploration of gastric surgery. Several years later, the Swiss surgeon Karl Schlatter successfully performed the first total gastrectomy in a gastric cancer patient (5). In the years that followed, lymph node metastasis due to gastric cancer was gradually recognized by surgeons. Then, in 1942, T. Kajitani and his colleagues developed the original systemic lymph node dissection technique, the so-called D2 lymph node dissection (6). For a long time to come, the controversy regarding D1 surgery and D2 surgery as the best choice has been a hot topic in academia. The results of the British MRC trial suggested that D2 surgery, which preserves the body and tail of the pancreas and spleen, might be superior

to D1 surgery, but there is a lack of strong evidence-based medical evidence (7). It was not until the publication of the 15-year follow-up results of the Dunch trial in 2010 that D2 surgery officially became the current standard procedure for gastric cancer surgery (8).

Scientific and technological progress has also mediated great progress in surgical innovations. From the very beginning, surgeons could only rely on simple surgical instruments to complete the operation (5). Thanks to innovations in surgical instruments, laparoscopic and Da Vinci robotic surgery systems can be widely applied in clinical practice, and the concept of minimally invasive surgery has been introduced into the surgical treatment of gastric cancer, which has ushered in a new era (9,10).

With the increasing understanding of gastric cancer, the concept of gastric cancer surgery has evolved from the initial "bigger is better" to today's "standardized surgery" and is developing towards individualized surgery focusing on accurate resection and quality of life. This trend has had a tremendous impact on the development of surgical treatments, such as minimally invasive surgeries, function-preserving surgeries, and the optimal extent of lymph node dissection. However, how should gastric cancer surgery develop in the future? What opportunities and challenges will we encounter? Here, we introduce the current status and future development directions of gastric cancer surgery from these aspects.

Minimally invasive surgeries

With the development of medical instruments and the accumulation of surgical experience, surgeons began to consider the problems with conventional laparotomy and sought new solutions. The emergence of laparoscopy and its successful application in cholecystectomy provided a new direction for the exploration of gastric surgery. In 1992, Kitano performed the world's first laparoscopy gastrectomy in Japan, inaugurating the use of laparoscopic techniques in gastric surgery (9). Eight years later, another Japanese surgeon, Uyama, successfully performed the world's first laparoscopy-assisted total gastrectomy on a patient with advanced gastric cancer (11). Since then, endoscopic surgery for gastric cancer has flourished around the world, especially in Asia. After years of development, this minimally invasive concept has become deeply embedded in the treatment philosophy of most gastric surgeons.

The development of minimally invasive surgery has a great relationship with the improvement of early gastric cancer diagnosis rate during the past three decades. In Asian regions with a high incidence of gastric cancer, the rate of early gastric cancer diagnosis in Japan and Korea has reached very high levels (12-14). Surgeons in these two countries have shown high enthusiasm, initiative, and pioneering spirit for the application of minimally invasive technology. The Korean-led KLASS01 trial (15) and the Japanese-led JCOG0703 (16,17) and JCOG0912 trials (18,19) demonstrated that laparoscopic surgery is as safe and effective as laparotomy for the treatment of early distal gastric cancer. Furthermore, compared to laparotomy, laparoscopic surgery is less invasive, and patients recover more quickly during the perioperative period. In subsequent years, several clinical studies on laparoscopic total gastrectomy for early gastric cancer have successively published results. The JCOG1401 trial (20,21) in Japan, the KLASS03 trial (22,23) in Korea, and the CLASS02 trial (24) in China have all confirmed the safety and efficacy of laparoscopic total gastrectomy for gastric cancer. Since then, in areas where conditions permit, laparoscopic surgery has become the first choice for early gastric cancer treatment.

In the exploration of laparoscopic surgery for advanced gastric cancer, the Korean-led KLASS02 trial (25,26) is the first phase III randomized controlled trial to evaluate the safety and efficacy of laparoscopic D2 surgery in advanced gastric cancer. The trial included 1,050 patients with advanced gastric cancer, and the clinical T stage ranged from T2 to T4a (26). The recently published long-term follow-up results demonstrated that the 3-year overall survival (OS) rates of the laparoscopic and laparotomy groups were 90.6% and 90.3%, respectively, and the 3-year recurrence-free survival (RFS) rates were 80.3% and 81.3%, respectively. These differences were not significant. However, intraoperative blood loss, postoperative hospital stay, and postoperative complications in the laparoscopic group were reduced compared to the laparotomy group (25). In another clinical trial of laparoscopic advanced gastric cancer surgery conducted in China (CLASS01), 1,056 patients with advanced gastric cancer clinically staged from T2 to T4a were included (27). The long-term follow-up results published in 2019 showed that the 3-year disease-free survival (DFS) rates of patients in the laparoscopic or laparotomy group all performed by experienced surgeons were 76.5% and 77.8%, respectively. Furthermore, there were no significant differences in 3-year OS or 3-year DFS between the two groups (28). In

terms of current follow-up results, clinical trials in Korea and China have all confirmed that laparoscopic surgery for locally advanced gastric cancer is not only as safe and effective as traditional laparotomy but also has significant advantages in rapid postoperative recovery. However, we must also be aware that in the CLASS01 trial, differences in 3-year DFS between the laparoscopic and laparotomy groups increased with tumor stage, and although there was no significant difference, we believe that in patients with advanced gastric cancer with a later tumor stage, longer follow-up is needed to verify whether laparoscopic surgery and open surgery exhibit similar tumor security.

The application of laparoscopic technology ushered in the era of minimally invasive surgery, and the birth of the robotic surgery system has brought the era into a new stage. A meta-analysis of 24 nonrandomized controlled studies showed that the robotic surgery group had significantly longer operation time than the laparoscopic group, but it had an advantage in the number of lymph node dissections. Moreover, there was no significant difference in perioperative safety and long-term tumor survival (29). Another multicenter prospective single-arm clinical trial of robotic surgery for stage I gastric cancer in Japan included 326 patients who were enrolled and completed the clinical trial, with 253 (77.6%) patients undergoing distal gastrectomy. The median operation time and estimated blood loss were 313 mins and 20 mL, respectively. There were no deaths within 30 days, and the perioperative complication rate of the robotic surgery group was significantly lower than that of the historical control group (2.45% *vs*. 6.40%, P=0.0018) (30).

From traditional laparotomy to today's laparoscopic surgery, and then to robotic surgery, as an important means of gastric cancer treatment, surgical treatment has experienced a new revolution. However, we must also note that minimally invasive technology is only a means, not the endpoint we are pursuing. The safety of surgery and the effect of radical treatment of tumors are what surgeons should focus on. There is no doubt that minimally invasive surgery is a trend of future development. With the development of more prospective clinical trials, the scope of application of minimally invasive technology will be clearly defined, and surgeons will have a clearer choice of surgical methods in the future.

Function-preserving surgeries

With the continuous progress of clinical research, increasing evidence shows that expanding the scope of surgical resection does not benefit patients but rather increases postoperative complications and mortality. Maruyama and Katai believe that the development of gastric cancer surgery has shifted from "standard and expanded surgical resection" to "individual and precise surgery", pursuing the optimization of surgical safety and postoperative quality of life (6). In this context, several function-preserving surgeries have been proposed, including pancreas-preserving gastrectomy and pylorus- and nerve-preserving gastrectomy (PPG).

In the past, total gastrectomy required combined pancreatectomy. It is well known that removal of the distal pancreas often causes pancreatic fistulas, subdiaphragmatic abscesses and postoperative diabetes. In 1985, Maruyama first proposed "pancreas-preserving total gastrectomy" (31). The indications for this procedure are proximal cancer with no direct invasion of the pancreas and no obvious lymph node metastasis. Diabetic patients are especially recommended for this procedure. Compared to the combined pancreatic body and tail resection, the postoperative complication rate and mortality are lower, and it has an advantage in 5-year survival (32,33). Therefore, for proximal gastric cancer, if there is no direct invasion of the pancreas and there is no obvious lymph node metastasis, especially in diabetic patients, pancreatic body and tail resection are no longer routine when performing total gastrectomy and D2 lymph node dissection.

Preservation of the spleen is also a hot topic in gastric cancer surgery. Previously, surgeons would choose to remove the spleen for the dissection of No. 10 lymph nodes (34-37). However, the results of a series of prospective clinical trials published in recent years show that compared to spleen-preserving total gastrectomy, combined splenectomy does not improve long-term survival, instead conveying a higher incidence of complications (38-40). With the improvement of surgical technology and the advancement of surgical instruments, especially the emergence of laparoscopic technology, the technical threshold of No. 10 lymph node dissection that preserves the spleen has been greatly reduced, and spleen-preserving No. 10 lymph node dissection has gradually been recognized by surgeons unless the splenic hilum is directly invaded by the tumor or the splenic hilum enlarged lymph node envelops the splenic blood vessels. However, for tumors that invade the greater curvature of the stomach, although the guidelines still recommend splenectomy, it

remains to be seen whether lymph node dissection with spleen retention achieves the benefits of splenectomy. The Japanese-led JCOG1809 trial (UMIN000037580) is exploring the clinical efficacy of laparoscopic splenic preservation or splenectomy in the treatment of patients with proximal invasion of advanced gastric cancer at the greater curvature. It is believed that soon, we will have a clearer understanding of spleen-preserving surgery for advanced gastric cancer.

In the past, surgeons paid more attention to radical surgical treatment and less attention to gastric function preservation. In 1976, Maki *et al*. proposed PPG, which was originally designed to treat stomach ulcers (41). Studies have shown that PPG has a lower incidence of postoperative dumping syndrome than Billroth I surgery and has improved food storage function and the ability to prevent intestinal reflux (42,43). A Japanese retrospective study involving 3,646 patients with early-stage mid-gastric cancer found that the lymph node metastasis rate in the suprapyloric region was only 0.2%, providing theoretical support for the application of PPG surgery in early gastric cancer (42). In a clinical trial of 2,898 cT1N0 patients with early mid-gastric cancer published in 2018, researchers compared long-term outcomes of PPG surgery with distal gastrectomy. There was no significant difference between 3-year DFS (99.5% *vs*. 98.0%, P=0.12) or 5-year OS (98.4% *vs*. 96.6%, P=0.07) (33). Therefore, for small tumors located in the middle 1/3 of the stomach, PPG surgery should be promoted in areas where conditions allow.

Optimal extent of lymph node dissection

Whether to perform para-aortic lymph node dissection (PAND) during D2 surgery has been a controversial topic among surgeons in the past. The JCOG9501 trial led by Japanese scholars explored whether adding PAND based on standard D2 surgery benefits patients (44). A total of 523 gastric cancer patients were enrolled in this trial, 263 of whom received D2 surgery and 260 of whom received D2+PAND surgery. The 5-year follow-up results were published in 2008. The OS, progression-free survival (PFS), and risk of recurrence between the two groups were not significantly different. However, in the D2+PAND group, operation time, blood loss, and the probability of minor complications were increased (45). Therefore, D2+PAND is not recommended as a standard surgical procedure for radical gastric cancer. However, for patients with 16a2/b1 lymph node metastasis diagnosed by imaging before surgery, neoadjuvant therapy followed by radical surgery has proven effective in a series of trials (46-48). After neoadjuvant treatment, the radical resection rate of para-aortic lymph nodes can reach 82%, and the 5-year OS rate of patients reached 57% (47).

For non-greater curvature proximal advanced gastric cancer, spleen hilar lymph (No. 10) node dissection is no longer recommended as a routine requirement for D2 surgery in the Japanese gastric cancer treatment guidelines 2018 (5th edition) (49). This result comes from the JCOG0110 trial (50). In this trial, 505 patients with advanced gastric cancer on the proximal non-greater curvature side were randomly divided into a splenectomy group and a spleen preservation group at a ratio of 1:1. In the spleen-preserving group, spleen hilar lymph nodes were not routinely cleaned, and the surgeon made judgments based on the patient's condition. From the published long-term follow-up results, there was no significant difference between the two groups, but the complication rate in the splenectomy group was higher (30.3% *vs*. 16.7%, P=0.0004). In the splenectomy group, the lymph node metastasis rate of the spleen hilar lymph node was only 2.36%. Finally, the authors of this study concluded that when proximal gastric cancer does not invade the greater curvature, splenectomy should be avoided when performing total gastrectomy because it increases the incidence of surgery without improving survival. However, we believe that the JCOG0110 trial also has limitations, which include a large number of patients with early gastric cancer, nearly 70% of patients with stage I–II, and an enrollment rate of patients with stage T1 being higher than expected (14.1%). Therefore, it cannot fully reflect the regularity of the spleen hilar lymph node metastasis or the value of dissection in patients with proximal gastric cancer with the non-greater curve. In several retrospective studies, the lymphatic metastasis rate of the spleen hilar lymph node of proximal advanced gastric cancer was approximately 8.4%–27.9% (51-54). The prognosis of patients with spleen hilar lymph node metastasis has been reported to be significantly worse than that of patients without metastasis (55,56). Furthermore, Ikeguchi and Kaibara found that patients with splenic hilar lymph node metastasis, after splenic hilar lymph node dissection, the 5-year survival rate can be improved to the same level as those without splenic hilar lymph node metastasis (57). Therefore, in clinical practice, spleen hilar lymph node

dissection is still recommended for patients with tumor invasion to the greater curvature. The CLASS04 trial for spleen hilar lymph node dissection under laparoscopic surgery has completed patient enrollment, and results may bring new evidence in the future.

For early gastric cancer, if lymph nodes with metastasis risk can be cleaned in a targeted manner, instead of extensive standardized cleansing, then patient trauma and the incidence of perioperative complications can be greatly reduced. In this context, sentinel node navigation surgery (SNNS) is gradually coming to the attention of surgeons. The sentinel lymph node (SLN) is defined as the first lymph node that drains directly from the primary tumor (58). If the tumor's SLN is negative, lymph node dissection can be avoided. This concept has been applied to both melanoma and breast cancer surgery. The research on SLN in gastric cancer began in the early 21st century. Sano *et al*. (59) found that lymph node drainage of gastric cancer is a multi-directional and complex network, with only 62% of cases with the first metastatic lymph node around the primary site, and the probability of skipping metastasis is approximately 13%. Considering the complexity of the perigastric lymphatic drainage pipeline and the fact that there are usually multiple lymph nodes communicating with each other in one area, some scholars have proposed the concept of a sentinel lymphatic basin (SLB) (60). In a clinical trial comparing the rate of SLN detection with the removal of a single SLN or SLB, it was found that the removal of SLB significantly increased the rate of SLN detection (96.0% *vs*. 54.8%) (61). Therefore, the concept of SLB is widely used in current research to improve the detection rate of SLN.

Although the safety and efficacy of SNNS based on SLN technology have not yet reached a consensus in this field, with the improvement of technology and methods in recent years, an increasing number of studies have confirmed the reliability of SLN in early gastric cancer (62). A meta-analysis involving 21 studies showed that the sensitivity and accuracy of SLN detection for gastric cancer could reach as high as 85.4% and 94%, respectively (63). Based on this, Japanese surgeons initiated the JCOG0302 trial to evaluate the feasibility and accuracy of SNNS (64). Although the SLN detection rate in this study reached 97.8%, the false-negative rate was as high as 46.4%, which was far from the 5%–10% false-negative rate set at the beginning of the study, necessitating termination of the trial in advance. To avoid the influence of the false-negative rate in the frozen pathology examination on research, Japanese scholars initiated the SNNS trial (65). The trial used 99Tc and methylene blue double tracers for SLN visualization, and paraffin pathology was used to detect lymph node metastasis. Finally, in the enrolled 397 patients with cT1–2N0 stage and tumor diameter less than 4 cm, the sensitivity and specificity of SLN were 93% and 99%, respectively, which preliminarily confirmed the feasibility of applying SLN in gastric cancer surgery. In addition, the long-term survival results of a phase II, single-center clinical trial of early gastric cancer SNNS led by Korean scholars showed that there was no significant difference in the 3-year RFS or 3-year OS between the SLN positive and negative groups, indicating the feasibility of laparoscopic SNNS in early gastric cancer (66). Based on these results, in 2013, Korean scholars launched the SENORITA (Sentinel Node Oriented Tailored Approach) trial, which aims to evaluate the long-term tumor safety of laparoscopic gastric preservation surgery with SLB dissection (67). The study completed patient enrollment in 2016, and we expect its results to enable SNNS to play a more important role in early gastric cancer.

Conclusions

Surgery is the cornerstone of gastric cancer treatment, minimizing trauma and retaining digestive function on the premise of ensuring a radical cure of the tumor are the constant goals of surgeons. With these goals, minimally invasive surgery and function-saving surgery will be further developed, and the scope of more accurate lymph node dissection will become clearer with the continuous advancement of clinical trials. With the continuous advancement of targeting and immunotherapy, new treatment methods combined with surgery will give doctors more powerful tools to treat gastric cancer. In the era of precision treatment, accurately identifying the beneficiaries, and formulating an individualized surgical plan are the directions to which we should aspire in the next treatment revolution.

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Footnote

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