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•Gastric Cancer Column•

Some problems in the surgical treatment of gastric cancer

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Abstract Gastric cancer is one of the most common cancers in the world. Surgery is the most important therapy for gastric cancer, individual treatment strategies for patients suffering from gastric cancer according to the different tumor node metastasis (TNM) stage would improve the survival rate in a maximum degree, and improve the patient quality-of-life. This article reviewed some problems in the surgical treatment of gastric cancer.

Key words: Gastric neoplasm, surgery therapy

Gastric cancer is one of the most common malignant tumors with new onset cases exceeding one million annually all over the world, among which 41% of all cases are in China. Up to eight hundred thousand patients died from gastric cancer globally every year and Chinese patients account for 35%. Surgery remains the mainstay treatment for patients with gastric cancer. Recently, with the development of surgical techniques, the survival rate of patients with gastric cancer after radical gastrectomy has markedly improved. This article aims to review some problems in the surgical treatment of patients with gastric cancer.

Advances of gastric cancer staging

On August 19, 2008, members from the American Joint Committee on Cancer (AJCC), the International Union Against Cancer (UICC), and the International Gastric Cancer Association (IGCA) convened a meeting in Buffalo, New York, aiming to revise and reach a consensus on gastric cancer staging. At the meeting, Japanese experts were first invited to draft the tumor node metastasis (TNM) staging system of gastric cancer. The following third edition of Japanese gastric cancer criteria show that a consensus of gastric cancer staging has been reached among the three systems of the UICC, AJCC and Japan Gastric Cancer Association (JGCA), which provides criteria for the transverse assessment of the treatment of gastric cancer across the world and will greatly contribute to the progress of clinical investigations on gastric cancer treatment.

The most important feature of the new edition (7th edition) of the gastric cancer TNM staging system is that the original N stages have been greatly revised. The original N1 (1–6 lymph node metastases) has been divided into N1 (1–2 lymph node metastases) and N2 (3–6 lymph node metastases). The original N2 (7–15 lymph node metastases) has been assigned to N3a in the new edition, and the original N3 (> 15 lymph node metastases) has been designated N3b in the new edition.

The 81th session of the symposium of Japanese Gastric Cancer Research Committee was held on March 4, 2009 in Tokyo. The revision of gastric cancer treatment criteria at the symposium is a milestone that will unify the gastric N stage with that of the UICC and TNM staging systems in the new edition (3rd edition) guidelines of Japanese gastric cancer treatment expected to be published at the beginning of 2010. However, the N staging in this guideline is somewhat different from the UICC/AJCC. The new Japanese criteria define N3 as those with more than 7 lymph node metastases, including N3a and N3b in the UICC/AJCC.

In previous studies, although both the currently used TNM staging and JGCA N staging can predict clinical outcomes for patients with gastric cancer with different N stages to some extent, they have their own disadvantages1,2. Consistently with more recent studies, our study showed that the rate of lymph node metastasis was an alternative for predicting the clinical outcomes due to different numbers of resected lymph nodes3. Additionally, the current TNM staging system treats positive extranodal metastasis (EM) as lymph node metastasis. However, our study showed that EM is an independent factor for the prognosis of gastric cancer and should be defined as a metastatic pattern between lymph node metastasis and peritoneal seeding4. Etoh et al.5 also showed that with EM increases, the 5-year survival rate of patients with gastric cancer declined rapidly, and the curve was not linear. In contrast to the
lymph node metastasis, EM is more like peritoneal metastasis, except that patients with peritoneal metastasis have no opportunity to recover, whereas those with EM could achieve long-term survival. That is the difference. Therefore, Etoh suggested that EM was closely associated with tumor progression and its prognosis, and thus it should be included in the TNM staging system.

Appropriate treatment of early gastric cancer

Early gastric cancer (EGC) was first proposed by the Japanese Cancer Research Association in 1963, which was defined as adenocarcinoma limited to the mucous or submucous irrespective of lymph node metastasis. The diagnosis of EGC is primarily dependent on endoscopy and pathology. The prognosis of EGC is favorable with a 5-year survival rate above 90%. Appropriate management of EGC according to its growth pattern, infiltration depth, lymph node metastasis, and differentiation can maximally improve the survival rate, as well as patient quality-of-life. Treatment of EGC includes the following several strategies.

Endoscopic treatment of EGC

Two approaches to endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are most commonly used. As endoscopic techniques have progressed, the indications of endoscopic management have also changed. The candidates for EMR include those less likely to have lymph node metastasis and completely resectable lesions: (1) diameter of the lesion < 2 cm; and diagnosed as intramucosal cancer by endoscopy; (2) highly differentiated cancer; and (3) no ulceration formed on the surface of the depressed lesion. Since EMR resects the lesion into separate pieces, the major problem is incomplete resection or low resection rate. The rate of complete resection is approximately 56.0%, and residual lesions or recurrence are likely to occur with a 3-year recurrence rate of 7.5%. [8]

The development of ESD makes complete resection of the whole mass possible and has extended the indications of endoscopic treatment of patients with EGC. Indications for ESD include: (1) differentiated intramucosal carcinoma at any size and without ulceration; (2) if differentiated carcinoma is accompanied by ulceration, the tumor size should be < 3 cm; (3) undifferentiated intramucosal carcinoma without ulceration and with a diameter < 2 cm; and (4) differentiated minimal submucosal carcinoma with a diameter < 3 cm, without ulceration or lymphatic and vascular invasion [7,8]. With the strict selection of candidates, the 5-year survival rates among patients receiving open surgery and endoscopic surgery are insignificantly different (> 90%) [8-10]. Oda et al. [8] summarized 714 patients with EGC in 11 centers with an average follow-up of 3.2 years, and found that the 3-year disease-free and total survival rates were 94.4% and 99.2%, respectively. The survival rate of ESD was significantly higher than that of EMS. The major complications of EGC endoscopic surgery are bleeding and perforation. Chung et al. [11] reported on 952 patients with EGC that underwent endoscopic resection at 6 centers in North Korean and found that the incidence of bleeding, perforation, and other surgery-related complications were 15.6%, 1.25%, and 0.2%, respectively.

Reduced operations for EGC

The incidence of lymph node metastasis in patients with EGC range from 8.4% - 20.1%, with the first lymph node at 9.6% - 16.0%, the second lymph node at 4.0% - 6.0% and the third lymph node at 0.3% - 1.0% [10-13]. Thus, radical gastrectomy may unnecessarily resect some lymph nodes in a certain number of patients. If the extent and degree of lymph node metastasis can be determined pre- and intra-operatively, the lymph node resection can be more appropriate, ensuring the radical resection and the safety of the operation, as well as the reduction of surgical impact and improvements of quality-of-life. Based on the TNM system, EGC can be categorized into stage IA (T1N0), stage IB (T1N1), and stage II (T1N2). The JGCA 2002 standardized the indications for the reduced operations in the treatment of EGC [14]. For intramucosal carcinoma (IA stage), except for those of differentiated types, with a diameter < 2 cm and without ulceration, which underwent EMR, the rest of the patients should undergo modified gastrectomy (MGA) (D1+No7a). Those with IB stage and a diameter < 2 cm should undergo modified standard gastrectomy (MGB) (D2, D1+No7, 8a,9), and the rest should undergo D2 gastrectomy. Submucosal carcinoma (IA stage) of the differentiated type should undergo MGA and the rest should undergo MGB. Those at IB stage and with a diameter < 2 cm should undergo MGB and the rest should undergo D2 gastrectomy. Patients with stage II should undergo D2 gastrectomy. Moreover, other approaches can be considered in performing reduced gastrectomy for EGC, such as pylorus and vagus preserving methods and laparoscopy. Numerous studies demonstrate that the EGC prognosis is associated with lymph node metastasis [17-18]. Some patients with negative lymph node as examined by routine pathology may have lymph node micrometastasis [19]. Therefore, reduced operations for patients with EGC must be based on precise preoperative staging and strict candidate selection, and insufficient treatment should be avoided.

Standard radical gastrectomy

Most authors agree that standard radical gastrectomy (D2) is the standard method for treating patients with stage II and IIIA gastric cancer [20]. The popularization of D2 radical gastrectomy has greatly improved the 5-year survival rates of patients with gastric cancer in the past 20 years. Such changes also occur beyond Asia. Recent experience from the UK shows that the 5-year survival rate of patients with gastric cancer increased from 15% to 41% in this period, and that of the radical resection increased from 33% to 73% [21]. An randomized clinical trial (RCT) from Italy conducted by Hartgrink et al. [22] showed that D2 lymphadenectomy in patients with N2 disease was positively associated with an improved survival rate, and D2 radical gastrectomy can remarkably improve the outcomes of patients with stage II and IIIA gastric cancer. Recently, more and more
Western authors support the idea of using D2 as the standard approach for advanced gastric cancer. They found that the complications were associated with the experience of the surgeon, which decreased with increasing experiences. Recent studies further demonstrated that the survival rate increased with increased number of lymphadenectomy. Huang et al. examined 211 patients with gastric cancer without lymph node metastasis who underwent D2 gastrectomy and found that the total 5-year survival rate was 82.2%; with the same depth of invasion, and the survival increased with increased numbers of lymphadenectomy: T1–2 stage, the number of lymphadenectomies was more than 15; T3–4 stage, patients who had more than 20 lymphadenectomies had more survival benefits. These results indicate that the number of lymphadenectomies is an independent factor for the prognosis of gastric cancer. Our study also showed that, in D2 gastrectomy, those that underwent more than 20 lymphadenectomies had better survival rates than those with below 20, although it was not statistically significant.

The new edition of the Japanese gastric cancer treatment guidelines, which is expected to be released at the beginning of 2010 and is based on data on lymph node metastasis rates and resection efficacy, defines the extent of lymphadenectomy as D1/D2 and establishes the extent of lymphadenectomy according to different gastrectomy approaches. For conditions of excessive or insufficient lymphadenectomy, it should be noted as follows: D1+No.8a,D2-No.10; total gastrectomy D2: D1+No.8a,9,10,11,12a; distal gastrectomy D2: D1+No.8a,9,11p,12a; and proximal gastrectomy D2: D1+No.8a,9,10,11. Additionally, No.20 should be added to esophagus-involved total gastrectomy, and proximal gastrectomy D1 and D2 should be added with No.19,20,110,111. Carcinoma above stage T2 should undergo D2 lymphadenectomy. Moreover, because numerous studies have demonstrated a high metastasis rate of the No.7 lymph node, in the new guidelines, it is included in the D1 extent. For carcinoma involving the lower part of the stomach, the No.14v lymph node is no longer included in regional lymph nodes in the new edition. Thus, those with No.14v metastasis should be recorded as M1. However, patients with No.14v metastasis who have long-term survival are not uncommon. Therefore, the importance of lymphadenectomy of this lymph node is remarkable. Those that have undergone No.14v lymphadenectomy can be recorded as D2+No.14v for future analysis. Total gastrectomy and proximal gastrectomy attach great importance to No. 10, and the pancreas preservation and splenectomy are recommended in this circumstance to achieve complete lymphadenectomy. However, some experienced centers and surgeons are more likely to adopt No.10 lymphadenectomy while preserving the spleen. Zhang et al. reported that the No.10 and No.11 lymphadenectomies while preserving the spleen and separating the spleen and the body and tail of the pancreas was effective. For carcinomas involving cardia and fundus, spleen preservation not only can reduce surgical complications, but also can improve the 5-year survival rate (38.7% vs. 16.95%, P < 0.01). Only stage-III and -IV lesions with spleen involvement should undergo splenectomy.

Extended radical gastrectomy

It is well known that D2 radical gastrectomy is the standard approach for patients with advanced gastric cancer. However, whether extended radical gastrectomy can benefit some patients with advanced gastric cancer remains unclear, and the indications and complications related to extended radical gastrectomy require further investigation. Radical gastrectomy includes extended lymphadenectomy and organ resection.

Extended lymphadenectomy

Currently, the indications for extended lymphadenectomy include: (1) the tumor involves gastric serosa or neighboring organs while sparing the liver, the peritoneum, and other distal organs; (2) leather cysts of the stomach; (3) those with a second or third positive lymph node; (4) the surgeon is familiar with the radical gastrectomy involving D2 and D3; and (5) the patient can tolerate the D3 operation and should be younger than 70 years.

Yoshikawa et al. demonstrated that para-aortic lymph node metastasis rates of patients with N1(+), N2(+), and N3(+) were 1%, 20%, and 43%, respectively. Those of patients with stage IIIA, stage IIIB, and stage IV were 9%, 19%, and 56%, respectively. They contended that the D2 operation plus para-aortic lymph node resection can determine the lymph node metastasis more precisely and improve the accuracy of outcome predictions. A RCT from Chinese Taiwan showed that the D3 operation can improve clinical outcomes compared with the D2 operation. Zhan et al. conducted D2 or D3 radical gastrectomies plus para-aortic lymph nodes resection in 73 patients (PALD group) and found that the mean survival time was (56 ± 3) months, compared to the (42 ± 4) months of 85 patients in the non-PALD group. The median survival times were significantly different (62 ± 6) months vs. (29 ± 3) months (P < 0.01). At the Eighth World Gastric Cancer Conference, two cancer centers from Italy reported the efficacies of their treatment for gastric cancer. Until 2008, 60% of their patients received D2* gastrectomies with an average number of lymphadenectomies at 50, and surgery-related mortality was 2.1%. Takashi et al. contended that, for patients who were likely to have lymph node metastasis with tumor mass at certain sites, selective para-aortic lymph node resection was an alternative strategy in treating patients with advanced gastric cancer. Therefore, we recommend that the No.16 lymph node should be routinely explored in advanced gastric cancer. If lymphadenopathy is identified, lymphadenectomy should be performed with no metastatic lymph node left. Extended lymphadenectomy performed by experienced surgeons will not increase complications or mortality.

Extended organ resection

Extended organ resection refers to when the gastric cancer infiltrates its neighboring organs, the combined resection of related organs can achieve radical resection. Prophylactic cystectomy does not belong to extended organ resections. We will discuss radical gastrectomy combined with splenectomy and pancreaticoduodenectomy in the following sections.
As mentioned previously, the new edition of Japanese gastric cancer treatment guidelines mentions that in total or proximal gastrectomies, splenectomy can be considered to ensure complete resection of the No.10 lymph node. Additionally, those with splenic hilar lymph node or parasplenic artery lymph node involvement and are likely to have residual cancer lesions should be considered to perform combined splenectomy. However, the clinical efficacy of gastrectomy combined with splenectomy is controversial. Ikeguchi et al. reported that the combined splenectomy was mandatory when advanced gastric cancer involved gastric serosa and local lymph nodes. The incidence of splenic hilar lymph node metastasis was 20.9%, and those that were not completely resected showed poor prognosis; while those received radical resection had a similar prognosis to those without metastasis. Zhang et al. examined 108 patients with cardia and fundus carcinoma who underwent radical surgery and compared the clinical outcomes of patients with and without splenectomy. The result showed that the 5-year survival rates of patients that underwent spleen preserving procedures and splenectomy were 38.7% and 16.9%, respectively (P = 0.008), indicating poorer prognosis in patients who underwent splenectomy. Therefore, the spleen should be preserved when metastatic lesions are not involved. Conclusively, there is no evidence whether pancreas-preserving extended surgeries should be performed for T2 or T3 gastric carcinoma that involves the upper part of the stomach. Currently, most authors think that for patients without direct involvement of the pancreas or No.11 lymph node metastasis, the pancreas should be preserved and the spleen should be resected. In this circumstance, splenectomy is performed by cutting the splenic artery at its root or at the bifurcation of the dorsal pancreatic artery, and the splenic vein is preserved to the pancreatic tail. This approach can reduce complications, such as pancreatic fistula, peritoneal infection, and impaired glucose tolerance, while preserving the therapeutic efficacy compared with those who undergo pancreas resection.

The clinical application of radical gastrectomy combined with pancreaticoduodenectomy, due to its high rates of complications and substantial mortality, is controversial. Previous literature has reported that the mortality of this approach was 5%–7% with a 5-year survival rate of 5%–8%, though these figures have improved in recent years. Currently, the recommended indications for this approach include: (1) antral carcinoma invading the duodenum or the pancreatic head directly; (2) pyloric metastatic lymph node involving the pancreatic head; and (3) lymph node metastasis limited to D2, without distal organ involvement (liver, peritoneum). Zhan et al. performed radical gastrectomy combined with pancreaticoduodenectomy in 14 patients with advanced gastric cancer that had pancreatic head or duodenal involvement. They found that postoperative complications occurred in 28.5% patients, the median survival time was 29.7 months, and survival rates at 1 year and 3 years were 60.9% and 36.5%, respectively. Whereas 9 patients who underwent palliative surgery showed a median survival time of 2.7 months, and only 22.2% patients survived more than half a year. Thus, they contended that gastrectomy combined with pancreaticoduodenectomy was safe and could prolong the median survival time compared to palliative operations. This approach is worthy of being generalized. The National Cancer Center of Japan reported on pancreaticoduodenectomy for 23 patients with advanced gastric cancer that had pancreatic head involvement between 1970 and 2001, including 18 patients with primary gastric cancer and 5 patients with residual cancer. Distal gastrectomy was performed for patients with primary gastric cancer and total gastrectomy was performed for patients with residual cancer, with the median surgical time of 8 h (6–13 h). Postoperative complications occurred in 73.9% patients, while no surgery-related deaths were reported, and the 5-year total survival was 34.3%. Additionally, none of the 8 patients that could not undergo radical surgery survived beyond 5 years. The reasons why they could not undergo radical surgery included para-aortic lymph node metastasis, positive cytology of peritoneal lavage, and peritoneal dissemination. Min et al. reported on 12 patients with gastric pyloric carcinoma involving the pancreatic head or the duodenum who underwent pancreaticoduodenectomy and contended that one of the indications of pancreaticoduodenectomy was gastric pyloric carcinoma involving the pancreatic head or the duodenum. Clinical outcomes of those with D1 and D2 lymph node metastasis were favorable after surgery, and this operation was safe. D3 lymph node metastasis should be considered to be a contraindication of pancreaticoduodenectomy. Therefore, with the strict selection of candidates, radical gastrectomy combined with pancreaticoduodenectomy is an appropriate approach for patients with gastric pyloric carcinoma involving the pancreatic head or duodenum and can be performed in some centers by experienced surgeons.

In conclusion, with the development of strategies of gastric cancer evaluation and treatment, as well as surgical operations, the survival rate for patients with gastric cancer will increase year by year. Long survival times and optimal quality-of-life can be achieved for patients with gastric cancer by accurate preoperative staging, individualized treatment, and appropriate surgical approaches.

References


