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## Recent Advances in the Surgical Treatment of Advanced Gastric Cancer: A Review

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Gastric cancer is a common malignancy with a poor prognosis, and surgical treatment remains the first-line approach to treatment to provide a cure. Despite advances in surgical techniques, radiotherapy, chemotherapy, and neoadjuvant therapy, gastric cancer remains the second leading cause of cancer death worldwide. Although the 5-year survival rate of early gastric cancer can reach >90%, due to the low early diagnosis rate, most patients present with advanced-stage gastric cancer. Therefore, there has been increasing interest in improving surgical treatment of advanced gastric cancer. Lymph node dissection is an important part of the surgical treatment of advanced gastric cancer due to the high incidence of lymph node metastasis. Although prospective studies have confirmed the safety and feasibility of laparoscopic surgery for early gastric cancer, the relevant treatment models of advanced gastric cancer still need to be further explored and validated. This review aims to provide an update on the recent advances in the surgical treatment of advanced gastric cancer.

**MeSH Keywords:** **Laparoscopes • Lymph Node Excision • Stomach Neoplasms**

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## Background

Worldwide, gastric cancer is the fourth most common cancer and the second leading cause of cancer-related mortality and is associated with high morbidity [1]. The etiology and pathogenesis of gastric cancer remain to be established, and although some causal factors have been identified, primary prevention remains a challenge [2]. Currently, there are no screening methods to detect gastric cancer, and because patients with early gastric cancer are usually symptom-free, there is a low rate of early diagnosis of gastric cancer. Therefore, most patients (>70%) present with advanced gastric cancer [3].

Epidemiological studies have shown that the incidence of gastric cancer in young people is gradually increasing [4]. Therefore, it is particularly important to improve surgical treatment options for advanced gastric cancer. There has been recent progress in improving medical and surgical technology, and increased understanding of the pathogenesis of gastric cancer has resulted in approaches to the prevention of gastric cancer, and the development of targeted therapies [5]. However, despite the rapid development of radiotherapy, chemotherapy, and immunotherapy, surgical resection remains the only possible cure for gastric cancer [6–8]. Complete tumor resection and lymph node dissection combined with neoadjuvant chemotherapy and postoperative adjuvant radiotherapy and chemotherapy have been shown to significantly improve the postoperative survival time of patients with gastric cancer [9]. In particular, for the surgical treatment of gastric cancer, there continue to be studies that refine and compare open and laparoscopic gastric surgery [10]. This review aims to provide an update on the recent advances in the surgical treatment of advanced gastric cancer.

## The Extent of Lymph Node Dissection in Advanced Gastric Cancer

Lymph node dissection, performed during surgical resection for gastric cancer is used for staging but also has an important impact on patient prognosis. D1, D2, and D3 gastrectomy for gastric cancer include the perigastric Group 1, Group 2, and Group 3 lymph nodes, respectively. The current standard of care for curative surgery for gastric cancer is for D2 gastrectomy. Lymph node dissection is performed to determine the extent of lymph node involvement with metastases and to improve outcome from surgery. The benefit of lymph node dissection beyond D2 gastrectomy for advanced gastric remains controversial.

In addition to the D1, D2 and D3 lymph node dissection, different degrees of subclasses have been suggested such as D1 lymph node dissection with an additional seventh group

of lymph nodes (D1+ $\alpha$ ) and the simultaneous dissection of lymph nodes in groups 7, 8a and 9 D1 lymph nodes (D1+ $\beta$ ). If six groups of lymph nodes are found to contain metastases, then the dissection that removes 14v lymph nodes is called D2+ 14v. According to the latest guidelines, if cancer invades the duodenum, the lymph nodes behind the pancreatic head (13 groups) should be dissected and is defined as D2+13.

Inaki et al. suggested that D1+ $\alpha$  dissection was only suitable for early gastric cancer in which the tumor was located in the distal stomach. D1+ $\beta$  dissection is suitable for the treatment of early gastric cancer in the proximal stomach, but this type of lymph node dissection may not be suitable for the treatment of advanced gastric cancer [10]. To address the question regarding what extent of lymph node dissection is more beneficial for patients with gastric cancer, Songun et al. [11] showed in a 15-year follow-up study, that the local recurrence rate for patients undergoing D2 lymph node dissection was significantly lower than that of patients undergoing D1 resection, indicating that increasing lymph node dissection had survival benefits. However, Degiuli et al. performed a further stratified study that showed that D2 lymph node dissection did not improve the 5-year survival rate for patients with T1 gastric cancer [12]. In contrast, the 5-year survival rate of D2 lymph node dissection in patients with T2–T4 gastric cancer was greater than that in the D1 group (59% vs. 8%) [12]. In 2012, Seevaratnam et al. published a meta-analysis of D1 compared with D2 lymph node dissection and analyzed patient outcome in five randomized controlled trials [13]. Meta-analysis showed there was no statistical difference in the 5-year survival rate of patients with T1–T2 (55.4% in the D1 group and 52.3% in the D2 group) ( $P=0.46$ ) [13]. For patients with a higher T stage (T3–4), there was a trend towards survival benefits in favor of D2 (13.5% for D1 and 19.5% for D2) [13].

In a phase II trial conducted by the Japan Clinical Oncology Group (JCOG), patients with locally advanced gastric cancer and paragastric lymph node metastases and/or paraaortic metastases received neoadjuvant chemotherapy (S-1 plus cisplatin), followed by extended dissection of abdominal para-aortic lymph nodes (16 groups) [14]. The overall 3-year and 5-year survival rates were 59% and 53%, respectively [14]. Based on these results, Japanese surgeons now suggest that D2 gastrectomy plus para-aortic lymph node dissection after neoadjuvant chemotherapy may improve outcome in advanced gastric cancer with positive lymph nodes or extensive metastasis of N2 lymph nodes [15]. For lymph node dissection and prophylactic splenectomy, JCOG conducted the O110 clinical study and concluded that when there was no direct invasion of the spleen or splenic hilar lymph node metastasis under direct vision, splenectomy with the clearance of the splenic hilum, splenic artery, and lymph nodes was not necessary [16]. In 2014, a study showed that dissection of the superior mesenteric vein lymph

node (14v) combined with D2 gastrectomy improved prognosis in patients with stage III and IV distal gastric cancer, but this finding requires further verification with future controlled clinical studies [17].

Therefore, based on the above results, D2 lymph node dissection is recommended as a standard procedure in oncological surgery guidelines for the treatment of advanced gastric cancer, including guidelines from the Medical Oncology Society of Japan, South Korea, and Europe. The National Comprehensive Cancer Network (NCCN) in the US also recommends D1 or modified D2 lymph node dissection for advanced gastric cancer [18].

### Laparoscopic Surgery for Advanced Gastric Cancer

Laparoscopic surgery for the treatment of early gastric cancer is performed routinely worldwide and is recommended as a standard treatment in Japan and South Korea. The results from two prospective trials (KLASS 01 and JCOG 0703) have further confirmed the safety and feasibility of laparoscopic surgery for early gastric cancer [19,20]. There have been further studies that have supported the use of laparoscopy-assisted gastrectomy for advanced gastric cancer, but this type of surgery requires training and experience [21–23]. However, the use of minimally invasive techniques remains controversial for the treatment of advanced-stage tumors, mainly because of concerns about the adequacy of surgical resection and the ability to adequately perform surgical lymph node dissection [24].

A multicenter randomized controlled trial of stage II/III gastric cancer (JLSSG0901) from the Japanese Laparoscopic Surgery Study Group (JLSSG) was conducted in patients with advanced gastric cancer [10]. To evaluate whether laparoscopic surgery can achieve the same results as open surgery, the main endpoint of JLSSG0901 was relapse-free survival, pending the disclosure of level I evidence [10]. A phase III clinical trial (KLASS-02) from the Korea Laparoscopic Gastrointestinal Surgery Group was conducted to evaluate the long-term efficacy of laparoscopic D2 lymph node dissection in the treatment of advanced gastric cancer (cT2–T4a/cNO–N1) [25]. There was no significant difference in the short-term curative effect between the two methods, and showed that the average learning curve of laparoscopic gastric cancer surgery was 42 cases, which provided a useful reference [25]. A single-center study showed that the combination of laparoscopic gastrectomy and the Enhanced Recovery After Surgery (ERAS) protocol in patients with gastric cancer was feasible and resulted in good clinical outcome [26]. The Chinese Laparoscopic Gastrointestinal Surgery Research Group (CLASS) conducted a randomized controlled trial (LASS-01) of laparoscopic gastrectomy for gastric cancer in China and compared treatment with laparoscopy,

open distal gastrectomy, and D2 lymph node dissection [27]. The initial large multicenter retrospective cohort analysis was performed for stage T2–T4a gastric cancer with or without lymph node metastasis or distant metastasis [27]. The findings showed that laparoscopy was safe and effective [27]. As to whether D2 radical surgery increased the risk of postoperative complications, the CLASS team study showed that age  $\geq 65$  years (OR=1.72;  $P < 0.05$ ), accompanied by multiple complications (OR=2.76;  $P < 0.05$ ) increased the risk of postoperative complications after laparoscopic D2 radical gastrectomy for gastric cancer [27]. However, according to the number of complications, the study concluded that there was no statistical correlation between patient age  $\geq 65$  years and postoperative complications [27]. A meta-analysis also showed a laparoscopic approach for D2 total gastrectomy did not increase patient morbidity [28].

However, global clinical studies have mainly included laparoscopic distal gastrectomy and total gastrectomy, and there have been no randomized studies that have compared laparoscopic radical gastrectomy for distal gastric cancer, and laparoscopic-assisted total gastrectomy as an alternative to traditional surgical methods. The main reasons for the lack of studies are that the technique of total laparoscopic gastrectomy remains to be standardized, even by experienced surgeons and is a complex procedure, and also there is no standardized method for performing the anastomosis between the esophagus and the jejunum. Therefore, the use of laparoscopic methods for total gastrectomy for early gastric cancer and advanced gastric cancer remain rarely performed.

### Resection of the Lesser Omentum for Advanced Gastric Cancer

There remains controversy about whether or not to perform omental resection during radical gastrectomy for gastric cancer. The Japan gastric Cancer Association have recommended that only patients with gastric cancer with serous infiltration should be treated with omental resection [29]. In 2012, Fujita et al. reported the findings from a randomized controlled trial of the long-term outcome of omentectomy during standard total or distal D2 gastrectomy [30]. There was no significant difference in the 3-year cumulative survival rate between the omental resection group and the non-resection group (85.6% vs. 79.6%;  $P=0.443$ ) [30]. Subgroup analysis showed that the 3-year cumulative survival rate was 69.8% in the omental resection group, and 50.2% in the non-resection group ( $P=0.043$ ), and the incidence of abdominal metastasis in patients without omentectomy was significantly higher than that in patients who underwent omentectomy (13.2% vs. 8.7%) [30]. However, JCOG followed this study with a large multicenter randomized controlled trial (JCOG1001) that assessed the long-term benefits

of D2 lymph node dissection combined with omental resection in patients with T3–T4 advanced gastric cancer [31]. Compared with the omental preservation group, the operation time and intraoperative blood loss were significantly increased in the omental resection group, and the 3-year survival rates were 83.3% and 86.0%, respectively [31]. The findings from this study indicated that patients with stage T3 or T4 gastric cancer did not benefit from routine omental resection [31]. Yamamura et al. found that if gastric cancer micrometastases involved the omental sac, as confirmed by polymerase chain reaction (PCR), there was also likely to be tumor spread to the abdominal cavity, and omental resection was very unlikely to improve patient survival [32].

Currently, surgeons in Japan usually perform omental resection according to the recommendations from the Japanese guidelines and includes resection of the transverse mesocolon and pancreatic capsule (narrow omental sac resection). The advantage of omental sac resection during radical gastrectomy is the possible prevention of peritoneal dissemination, metastasis, and tumor recurrence. However, omental resection increases the surgical difficulty and the operation time, and there is a risk of damaging mesenteric vessels and the pancreas resulting in bleeding and pancreatic leak. Open gastrectomy also prolongs the operation time and requires the use of a general anesthetic with an increase in surgical and anesthetic complications.

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## Conclusions

Currently, patients with advanced gastric cancer are still mainly treated by surgery, combined with intraperitoneal chemotherapy and hyperthermic perfusion therapy, to improve surgical treatment. Because T and N staging before and during surgery is not very reliable, D2 lymphadenectomy is recommended. With the advent of individualized and personalized medicine, continued improvements in the treatment of advanced gastric cancer require support from randomized clinical trials, which are also needed to provide evidence to support D2 lymph node dissection following neoadjuvant chemotherapy. Most of the studies on the role of total laparoscopic gastrectomy and omental resection are have included small study populations and adequately powered controlled prospective studies are still required to reduce the limitations of selection bias and heterogeneity. Continued studies are required to determine the optimal approaches for the surgical treatment of patients with advanced gastric cancer.

## Conflict of interest

None.

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