The Current Status and Development of Lymph Node Dissection for Gastric Cancer

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Abstract

In 1962, according to the results concluding from specimens of gastric cancer, the Japanese Gastric Cancer Association produced the first edition of Japanese Classification of Gastric Carcinoma (JCGC), in which lymph nodes (LNs) associated with metastasis of gastric cancer (GC) were anatomically divided into groups. This clarified the gastric lymphatic circulation system in detail. The classification laid the theoretical foundation of systematic lymph node dissection for GC and also propelled its surgical treatment into a new era. Researchers in Japan had worked to ensure that the standard set by the JCGC realistically reflected the approach and extent of lymph node metastasis (LNM), to guide the reasonable extent of lymph node dissection. The JCGC has been steadily revised since 1962 with new understandings from continuously practices by Japanese researchers; they kept observing and summarizing the regularities of the distribution of positive metastatic LNs. In 2010 the 14th edition of the JCGC was published. It described the lymphatic system of the stomach from the perspective of anatomy and further revealed the regularity of LNM of GC and the method for evaluating the extent of LNM. Moreover, it established the integrated theoretical framework for systemic lymphadenectomy, in which the extent of lymph node dissection was verified by the stage of cancer. The TNM staging system of the Union for International Cancer Control (UICC) is another important international appraisal system for GC, which evaluates the extent of metastasis with only the number of metastatic LNs. It reflected the relationship between the number of metastatic LNs and the prognosis of the patient. However, with respect to the regularity of LNM, this system cannot reflect well. It can only be regarded as a way for assessing the post-

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Keywords
Lymphadenectomy • Gastric cancer • Laparoscopic surgery

In 1962, according to the results concluding from specimens of gastric cancer, the Japanese Gastric Cancer Association produced the first edition of Japanese Classification of Gastric Carcinoma (JCGC), in which lymph nodes (LNs) associated with metastasis of gastric cancer (GC) were anatomically divided into groups. This clarified the gastric lymphatic circulation system in detail. The classification laid the theoretical foundation of systematic lymph node dissection for GC and also propelled its surgical treatment into a new era. Researchers in Japan had worked to ensure that the standard set by the JCGC realistically reflected the approach and extent of lymph node metastasis (LNM), to guide the reasonable extent of lymph node dissection. The JCGC has been steadily revised since 1962 with new understandings from continuously practices by Japanese researchers; they kept observing and summarizing the regularities of the distribution of positive metastatic LNs. In 2010 the 14th edition of the JCGC was published. It described the lymphatic system of the stomach from the perspective of anatomy and further revealed the regularity of LNM of GC and the method for evaluating the extent of LNM. Moreover, it established the integrated theoretical framework for systemic lymphadenectomy, in which the extent of lymph node dissection was verified by the stage of cancer. The TNM staging system of the Union for International Cancer Control (UICC) is another important international appraisal system for GC, which evaluates the extent of metastasis with only the number of metastatic LNs. It reflected the relationship between the number of metastatic LNs and the prognosis of the patient. However, with respect to the regularity of LNM, this system cannot reflect well. It can only be regarded as a way for assessing the postoperative outcomes but not as a guide for determining the extent of surgery. Therefore, controversies on the extent of lymphadenectomy for GC almost center on the JCGC.

2.1 The Extent of Lymphadenectomy in Early Gastric Cancer (EGC)

The rate of EGC gradually increased in recent years, probably owing to improved detection [1–3]. More than 50.0 % of patients with GC in Japan, and more than 40.0 % of those in Korea, were diagnosed as EGC. These rates are expected to increase further as diagnostic techniques and public awareness of GC improve. Therefore, the correct surgical approach for EGC is especially important. Reportedly, among patients with EGC, only 2.4–16.7 % have metastatic nodes when the primary lesion is confined to the mucosa. However, if the tumor has invaded the submucosa, the rate increases to 16.0–46.7 % [2]. Therefore, if lymphadenectomy is not performed in patients with EGC, the risk of postoperative tumor residual and recurrence increases [4]. However, a D2 lymphadenectomy in accordance with radical gastrectomy for GC may be considered overtreatment. The most recent studies support limited (D1) dissection in EGC, as its 5-year survival rate is 98.0 %. Additionally, D2 dissections, when compared with D1 lymph node dissection, do not increase the overall 10-year survival rate or reduce the recurrence rate in EGC [5, 6]. The third edition of Japanese Gastric Cancer Treatment Guidelines [7] recommends the extent of lymphadenectomy for EGC as follows: (1) A D1 lymphadenectomy is indicated for cT1aN0 tumors that do not meet the criteria for endoscopic mucosal resection/endoscopic submucosal resection and

for tumors that are histologically of differentiated type and ≤1.5 cm in diameter. (2) A D1+ lymphadenectomy is indicated for cT1N0 tumors other than the above. (3) A D2 lymphadenectomy is indicated for cT1N+ tumors.

2.2 The Extent of Lymphadenectomy for Advanced Gastric Cancer

For advanced gastric cancer, Japanese researchers have recommended extended lymph node dissection (D2) for GC according to the study of lymphatic circulation system in JCGC since the 1960s. This recommendation was thereafter followed in Korea and China. Although most Asian researchers considered the D2 dissection was designed according to the feature of lymphatic drainage in GC, in which potentially metastatic LNs were removed to a great extent, it was also a relatively safe and effective radical treatment for GC. However, reports in Western countries were not so positive. In the 1980s, a multicenter prospective randomized controlled trial (RCT) of D1 and D2 lymphadenectomy for GC from Britain and the Netherlands found postoperative complications and in-hospital mortality of D2 lymphadenectomy to be higher than those of D1 procedures, but with similar survival rates. Therefore, D2 lymphadenectomy was regarded as unsafe [8, 9]. Nevertheless, the reasons of this result were various and complicated for some Western scholars in the early years. The Dutch trial involved 331 patients who underwent D2 dissection in 80 medical centers between August 1989 and July 1993; for a mean of 1.2 D2 lymphadenectomies per center, per year, the interval of each operation was too long, and the quality of operation was not well controlled. Besides, if doctors lacked experience of managing patients with D2 lymphadenectomy during the perioperative period, it also affected the recovery of patients. Therefore, Italian researchers in cooperation with Japanese researchers provided thorough training and strict control of surgeons' operating quality and found outcomes of D2 lymphadenectomies were closer to those of Asian reports [10]. The operative morbidity rate was 20.9 %, the postoperative in-hospital mortality was 3.1 %, and the postoperative 5-year survival rate was 65.9 %. Since then, Asian and Western researchers have continuously improved their technique for D2 lymphadenectomy through live surgical demonstrations and exchange of experience. Later RCTs which were scientific and well designed in Western countries showed that D2 and D1 lymphadenectomy did not significantly differ in postoperative morbidity or in-hospital mortality, but the postoperative 5-year survival rate of D2 lymphadenectomy was obviously higher than that of D1. A 15-year follow-up of the Dutch research reported in 2010 showed D2 lymphadenectomy to be superior to D1 in postoperative survival rate, morbidity, and recurrence rate [11]. However, Asian and Western researchers have not yet reached a complete consensus. The NCCN2010 GC guidelines point out that D2 dissection for GC should be performed by surgeons with significant degree of training and expertise. And it is considered a recommended but not required surgery. Thus the acceptance of D2 lymphadenectomy as a standard procedure for stage II and III GC is occurring gradually. The guidelines defined a standard gastrectomy as resection of at least two-thirds of the stomach with a D2 lymph node dissection.

Extensive lymphadenectomy beyond D2 is controversial. Although Sano T et al. suggested that D2 plus No. 16 lymph node dissection would not increase major surgical complications [12], the JCOG9501 study in 2008 denied that preventative No. 16 lymph node dissection had a curative effect [13]. The study additionally reported that although patients with No. 16 LNM or those with no other non-radical factors could undergo R0 resection, their prognosis remains poor.

A consensus as to whether No. 14v LNs are regional has not been formed. Although in the past No. 14v LNs were divided into N3 LNs and were not dissected in standard radical gastrectomy in the JCGC of the edition before 13th, they were thereafter placed within the extent of D2 procedures in the 13th edition. Then in the 14th edition, they were once again placed outside of D2 procedures, as patients with No. 14v LNM were thought to have a worse survival rate. However, No. 14v lymph node dissection is

recommended for patients with GC with potential distal No. 6 LNM.

2.3 The Application of Laparoscopic Techniques in Lymphadenectomy

Through the aforementioned discussion about the extent of lymphadenectomy, laparoscopic radical gastrectomy (LRG) would be a standard surgical mode for GC, if it can follow the rules of open curative resection to achieve the goal of thorough lymph node dissection. In EGC, LRG can meet the requirements of negative margins and can determine the extent of systematic lymphadenectomy according to the depth of tumor invasion. Since the first report of its use by Kitano in 1994 [14], LRG for EGC has become widely used all over the world. Currently, LRG is considered a standard procedure with a maturing technique and is associated with good outcomes in EGC [15, 16]. In 1997, Goh et al. [17] first reported laparoscopy-assisted gastrectomy (LAG) with D2 lymphadenectomy for advanced GC, and the safety and feasibility of which have been shown in multiple studies [18–21]. However, indications for laparoscopic approaches are controversial. Although techniques in LRG with D2 lymphadenectomy continue to develop, most of the surgeons accept that one of the indications is the advanced tumor that has not perforated the visceral peritoneum [22]. Some surgeons suggest that LRG has similar curative resection and oncologic outcomes to open approaches and LRG with D2 lymphadenectomy can be performed exploratively for tumors that penetrate the visceral peritoneum $\leq 10\ cm^2$ [23]. Improper manipulations in laparoscopic surgery may be associated with increased risk of the tumor spreading to the abdominal wall, immune function disturbance, and changes in the peritoneal structure. These increased the risk of tumor cell distribution and implantation metastasis at the incision [24, 25]. Thus LAG was unsuitable for GC that penetrated the visceral peritoneum $>10\ cm^2$, LNM surrounding important vessels, or when there is extensive invasion of adjacent structures. LRG is also not suited for extremely complicated lymphadenectomies, such as LNM that requires super extended (D3) lymphadenectomy.

Although the most striking feature of LRG was its minimal invasiveness [20, 26–29], its oncologic outcomes are the focus of our attention. The number of dissected LNs was the most important surrogate marker of the "radical surgery." Miura et al. [30] reported that significantly fewer LNs were harvested by an LRG than by conventional open surgery, particularly for No. 4, 6, 9, and 11 LNs. However, Huscher et al. [31] reported that the two methods did not significantly differ in lymph node retrieval. Song et al. [18] compared surgical outcomes of LRG with D2 dissection and conventional open gastrectomy (OG) for patients with EGC (75 patients, of whom 44 underwent LAG and 31 underwent OG) and found no significant differences in the total number of retrieved LNs (37.2 vs. 42.4; $P>0.05$) or node stations ($P>0.05$) between the two groups. We found that skilled laparoscopic surgical technique and thorough palpation of anatomical layers under laparoscopy are the key to lymph node dissection. Laparoscopic amplification elaborately shows the finer structures of the vasculature, nerves, and fascia, which helps the surgeon identify specific fascial planes and facilitates lymph node dissection within the vascular sheath. Furthermore, the ultrasonic scalpel is an effective instrument for cutting, providing hemostasis, and minimizing damage to surrounding tissues, which is suitable for vascular separation and lymph node dissection. We previously reported a study that compared 506 patients who received LRG with 428 who received OG. The mean number of dissected LNs was 29.1 ± 10.4 per patient, showing that there were no significant differences between LRG group and OG group ($P<0.05$). However, significantly more No. 7 and 8 LNs were retrieved in the LRG group than in the OG group. And no significant difference in other groups of LNs was observed [19]. We also performed a retrospective matched-cohort study to compare LRG and OG for advanced GC without serosa invasion ($n=83$ for both groups). We found no significant difference

in the number of dissected LNs between these two groups during the same period [32]. Hence, LRG for GC is apparently as curative as the open approach.

Long-term outcomes are an important measure of curative effect. In Korea and Japan, the proportion of LRG for EGC has increased. Some retrospective analyses and small sample RCTs reported that long-term outcomes from laparoscopic surgery for EGC are similar with those from open surgery. Mochiki et al. [33] reported a retrospective study of 89 patients who underwent LRG, compared with 60 who underwent conventional OG; the two groups did not significantly differ in their 5-year survival rates (98.0 % vs. 95.0 %). A multicenter study of oncologic outcomes after laparoscopic surgery for early gastric cancer in Japan [34] showed that among 1,294 patients who were treated curatively (median follow-up: 36 months), only six cases were of recurred disease; the 5-year disease-free survival rate was 99.8 % for stage IA disease, 98.7 % for stage IB disease, and 85.7 % for stage II disease; the results indicated that laparoscopic surgery treatment for early gastric cancer has a good long-term outcomes. Although few studies focus on long-term outcomes of patients with advanced GC, reports of results from laparoscopic surgery for advanced GC were not inferior to those from open surgery. Shuang et al. [35] reported a case-control study of laparoscopy-assisted and open distal gastrectomy for advanced GC. Cumulative survival of the two groups was similar after 50 months of follow-up. Ibanez et al. [36] and Azagra et al. [37] reported that laparoscopy-assisted gastrectomy for locally advanced cancer is equivalent to laparotomy as far as long-term oncological results are concerned. Recently, a study to verify the long-term safety of laparoscopic gastrectomy for GC compared with open conventional gastrectomy was conducted across multiple institutions in Korea. The researchers analyzed long-term follow-up data of a large number of patients and found, after matching with a propensity scoring system, that overall survival, disease-specific survival, and recurrence-free survival rates did not significantly differ at each stage (median follow-up period: 70.8 months) [38]. However, all of the aforementioned results should be confirmed by large well-designed prospective RCTs. Currently, some countries such as China, Japan, and Korea have carried out RCTs focused on the efficacy of laparoscopic and open conventional surgery for patients with advanced GC. These RCTs will offer strong evidence of evidence-based medicine for the further application of laparoscopic surgery for gastric cancer.

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