Review Article

Current status of lymph node dissection in gastric cancer

Bin Ke, Han Liang

Department of Gastric Cancer, Tianjin Medical University Cancer Institute and Hospital, Tianjin Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, National Clinical Research Center for Cancer, Tianjin 300060, China

Correspondence to: Han Liang. Department of Gastric Cancer, Tianjin Medical University Cancer Institute and Hospital, Tianjin Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, National Clinical Research Center for Cancer, Tianjin 300060, China. Email: tjlianghan@126.com.

Abstract

Gastrectomy with lymph node (LN) dissection has been regarded as the standard surgery for gastric cancer (GC), however, the rational extent of lymphadenectomy remains controversial. Though gastrectomy with extended lymphadenectomy beyond D2 is classified as a non-standard gastrectomy, its clinical significance has been evaluated in many studies. Although hard evidence is lacking, D2 plus superior mesenteric vein (No. 14v) LN dissection is recommended when harbor metastasis to No. 6 nodes is suspected in the lower stomach, and dissection of splenic hilar (No. 10) LN can be performed for advanced GC invading the greater curvature of the upper stomach, and D2 plus posterior surface of the pancreatic head (No. 13) LN dissection may be an option in a potentially curative gastrectomy for cancer invading the duodenum. Prophylactic D2+ para-aortic nodal dissection (PAND) was not routinely recommended for advanced GC patients, but therapeutic D2 plus PAND may offer a chance of cure in selected patients, preoperative chemotherapy was considered as the standard treatment for GC with para-aortic node metastasis. There has been no consensus on the extent of lymphadenectomy for the adenocarcinoma of the esophagogastric junction (AEG) so far. The length of esophageal invasion can be used as a reference point for mediastinal LN metastases, and the distance from the esophagogastric junction to the distal end of the tumor is essential for determining the optimal extent of resection. The quality of lymphadenectomy may influence prognosis in GC patients. Both hospital volume and surgeon volume were important factors for the quality of radical gastrectomy. Centralization of GC surgery may be needed to improve prognosis.

Keywords: Gastric cancer; lymphadenectomy; lymph node; prognosis

Submitted Jan 31, 2021. Accepted for publication Mar 01, 2021.
doi: 10.21147/j.issn.1000-9604.2021.02.07
View this article at: https://doi.org/10.21147/j.issn.1000-9604.2021.02.07

Introduction

Gastric cancer (GC) is one of the most common malignancies worldwide accounting for 1.2 million new cancer cases and 783,000 deaths in 2008 (1). Nearly 40% of the global GC cases occur in China, 80% of which are diagnosed at an advanced stage, and the 5-year overall survival (OS) rate is less than 50% (2). At present, the comprehensive treatment based on surgery is the standard treatment modalities for GC (3,4). Gastrectomy with lymph node (LN) dissection is currently considered to be the standard procedure for the treatment of GC; however, the extent of lymphadenectomy remains controversial, and there is no worldwide consensus.

A rational lymphadenectomy can contribute to improve patient outcomes and reduce complication rates. According to Japanese Gastric Cancer Treatment Guideline (JGCTG), the extent of lymphadenectomy is classified by the D-level criteria into D1, D1+ or D2, and the extent of systematic lymphadenectomy is defined as follows according to the type of gastrectomy conducted (*Table 1*) (4). For early GC, D1 or D1+ lymph node dissection is recommended as the standard treatment. For advanced tumors, according to the results of several trials, D2

Table 1 Extent of lymph node dissection

Surgery	D0	D1	D1+	D2
Total gastrectomy	<D1	No. 1–7	D1+ No. 8a, 9, 11p, *No. 110	D1+ No. 8a, 9, 11p, 11d, 12a *No. 19, 20, 110, 111
Distal gastrectomy	<D1	No. 1, 3, 4sb, 4d, 5, 6, 7	D1+ No. 8a, 9	D1+ No. 8a, 9, 11p, 12a
Proximal gastrectomy	<D1	No. 1, 2, 3a, 4sa, 4sb, 7	D1+ No. 8a, 9, 11p, *No. 110	
Pylorus-preserving gastrectomy		No. 1, 3, 4sb, 4d, 6, 7	D1+ No. 8a, 9	

*, Esophagus is invaded.

lymphadenectomy is recommended as a standard treatment worldwide (5). However, there is currently no consensus on the optimal extent of D2 lymphadenectomy. Some regional LNs such as No. 13 and No. 14V, which have a high risk of metastasis, are outside the extent of D2 LN dissection. Several previous researches indicated that D2+ lymphadenectomy can improve surgical outcomes in some patients. Therefore, to explore the appropriate extent of LN dissection for GC is an important clinical and research focus.

In this review, we focus on the issues that remain controversial in the extent of LN dissection for GC and try to provide answers on these issues based on the most recent available literature. We hope this review can provide new insights on the optimal extent of LN dissection.

Superior mesenteric vein (No. 14v) LN dissection for local advanced GC

LNs along the superior mesenteric vein are referred to as No. 14v LN. According to the Japanese Classification of Gastric Carcinoma (2nd English edition), No. 14v LN was defined as regional GC LN, and No. 14v LN was included in D2 lymphadenectomy for distal advanced GC (6). However, the third English edition of JGCTG excluded No. 14v LN from D2 lymphadenectomy (7), though it was still defined as regional gastric LN (8), and the guideline state that D2+ No. 14v lymphadenectomy may be beneficial for cancer with metastasis to No. 6 LN. Whether to add the No. 14v lymphadenectomy to D2 lymphadenectomy is a hot spot in the field of GC surgery.

Previous articles have reported that the metastatic rate of No. 14v node was 4.3%–18.5% (9-13). In the study by Masuda *et al.* (9), the incidence of No. 14v node metastasis was 12.1%, and the metastatic rate was 1.3% in early GC, 19.7% in advanced GC. The No. 6 node status can predict the status of No. 14v node metastasis. An *et al.* (10) reported that the incidence of No. 14v node metastasis was 6.6%, and the frequency of No. 14v node metastasis was high in patients with advanced TNM stage and poor histological differentiation. The No. 6 node metastasis was a useful predictive factor for No. 14v node metastasis with high accuracy (99.0%) and low false-negative rate (1.9%). The study of Han *et al.* (13) showed that the No. 14v node metastatic rate was 4.3%. The No. 14v node metastasis was rare in early stage, especially in T1 cancer (<1%), but metastasis rate increased to 5%–10% in advanced cancer with T2 or higher T category. In N1 patients, there was no No. 14v LN metastasis, but 5% of N2 and 19% of N3 patients had No. 14v LN metastasis. The metastasis in No. 6 and No. 11p nodes may indicate the necessity of No. 14v node dissection. According to our data (11,12), the metastatic rate for No. 14v node was 12.3%–18.5% in patients with advanced GC. No patients with stage I disease had No. 14v node metastasis. The frequency of No. 14v node involvement was 1.6%, 6.3%, 20.5% and 32.2%, respectively in stages II, IIIa, IIIb and IIIc, and it rose to 66.7% in stage IV disease. No. 14v node metastasis was found to correlate significantly with the tumor location (region including the lower third of the stomach), the depth of invasion (muscularis propria or deeper) and N stage. The above references suggested that the middle and lower GC with serosal invasion, or with No. 6 node metastasis has a higher rate of No. 14v node metastasis.

The prognostic impact of No. 14v lymphadenectomy on GC is controversial. Several previous studies had identified that patients with No. 14v LN metastasis had poor survival even after curative resection. The study by An *et al.* (10) demonstrated that the survival of No. 14v node positive patients was similar with that of patients with M1 disease and No. 14v node should be excluded from regional gastric LN. On the contrary, data from other studies showed that the dissection of No. 14v node could improve the OS of distal GC patients. Masuda *et al.* (9) reported that patients with No. 14v LN metastasis had a poor prognosis (5-year OS: 11.3%), similar to those with systemic metastasis, while patients without No. 16 node metastasis may benefit from a curative resection. Eom *et al.* (14) reported that the

No. 14v node dissection did not affect OS in stage I/II GC; in contrast, the No. 14v LN dissection seems to be associated with improved OS of patients with clinical stage III/IV GC in the middle or lower third of the stomach. Data from our center (11,12) showed that the OS of GC patients with No. 14v node metastasis was significant decreased compared with those without (3-year OS: 42.9% *vs.* 70.3%, P<0.001), and D2+ No. 14v lymphadenectomy can improve OS and lower LN recurrence rate for distal GC patients with IIIb/IIIc disease. There were several reasons to support this point of view. First of all, the incidence of No. 14v node metastasis in stage III GC was relatively high, and No. 14v lymphadenectomy decreases the possibility of local regional tumor residual and increases the chance of curable resection, which may account for improved OS. In addition, Xu *et al.* (15) reported that the incidence of micro-metastasis in No. 14v node was up to 29.5%, systemic dissection of that area could be helpful to avoid metastasis to adjacent retroperitoneal LNs. What's more, No. 14v lymphadenectomy might make the No. 6 LN dissection more complete in cases with No. 6 LN metastasis.

The necessity of LN dissection was based on metastatic pathway, frequency and its impact on survival. Sasako *et al.* (16) reported a simple index which was estimated by multiplying the number of metastasized LN by 5-year survival rate of patient with metastasis at that station to evaluate the therapeutic value of LN dissection. The therapeutic index of No. 14v node was 2.1, which was similar to that of No. 1 (1.6) and No. 12a (2.7). Our data (12) showed that the therapeutic index of No. 14v node (5.3) was similar to that of No. 5 (5.6) and No. 9 (9.5) LNs, and it was reasonable to add No. 14v node dissection to D2 category.

Until now, the necessity of No. 14v node dissection is still controversial in GC surgery. In order to further clarify the necessity of No. 14v node dissection for local advanced GC, Tianjin Medical University Cancer Institute and Hospital conducted a multi-center prospective randomized clinical trial (NCT02272894) to elucidate the potential impact of No. 14v node dissection on long-term survival of GC patients. We are looking forward to the research results and hope it could provide more clinical evidence for this question.

Splenic hilar (No. 10) LN dissection with or without splenectomy for proximal GC

The role of No. 10 node dissection with or without splenectomy for GC of the upper-third stomach had long been an issue of controversy. In the earlier editions of JGCTG, the No. 10 LN needed to be removed during standard D2 surgery for total gastrectomy (17). However, according to the results of JCOG0110 trial (18), the latest JGCTG concluded that No. 10 lymphadenectomy should not be recommended for advanced GC when the tumor is not infiltrated into the greater curvature (4).

According to previous reports, the incidence of metastasis to No. 10 LN in advanced proximal GC is from 7.3% to 27.9% (19-22). Son *et al.* (21) reported that the incidence of No. 10 node metastatic rate was 14.5% in advanced GC with total gastrectomy, and the therapeutic value of No. 10 node was 3.5, which was similar to index values for LN dissection at other extra-perigastric LNs. Yura *et al.* (22) reported that the incidence of No. 10 node metastasis was 8.1%, and the metastatic rate of No. 10 LN was relatively high for patients with advanced proximal GC invading the greater curvature (greater curvature group 15.1% *vs.* non-greater curvature group 4.2%). The therapeutic value for No. 10 LN was 7.1 in the greater curvature group, exceeding the indices for No. 6, 8a, 9, 11p, and 11d. The No. 10 node metastasis was frequently observed in advanced proximal GC and tumors located in the greater curvature, the No. 10 lymphadenectomy may be reconsidered as a treatment option for these patients based on its high metastatic rate and therapeutic index.

In several researches, patients with No. 10 node metastasis showed a poor prognosis even when they underwent a curative surgery. Jeong *et al.* (23) showed that the 5-year OS of all patients with No. 10 node metastasis was 26%, which was significantly worse than that of patients without No. 10 node metastasis, as poor as that of distant metastasis. In addition, the survival benefit of prophylactic No. 10 lymphadenectomy for proximal gastric carcinoma still remains controversial. The study of Kosuga *et al.* (24) showed that there was no significant difference in survival between patients with No. 10 node metastasis and those without such metastasis (51.3% and 42.1%, respectively). However, the results of subgroup analysis showed that patients with tumors localized on the greater curvature and Borrmann type 4 cancers might obtain survival benefits from No. 10 node dissection by splenectomy. Huang *et al.* (25) showed that, in stage III patients, the No. 10 node dissection group had better survival than patients without No. 10 node dissection (3-year OS: 52.6% *vs.* 41.0%, P=0.016), the No. 10

lymphadenectomy can improved the long-term survival of patients. Previously, a splenectomy during total gastrectomy was performed for complete removal of No. 10 LN. However, many studies had demonstrated that splenectomy increased morbidity and mortality without survival benefits. The JCOG 0110 trial (18) showed that the 5-year survivals were 75.1% and 76.4% in the splenectomy and spleen preservation group, respectively and the results revealed no benefit of splenectomy in terms of operative safety and survival. The final results of Dutch trail (5) showed that there was no survival benefit from a splenectomy in patients with D2 gastrectomy, whereas morbidity and mortality were significantly increased. Researchers believed that spleen-preserving lymphadenectomy may had a better therapeutic effect. As such, many gastric surgeons perform No. 10 lymphadenectomy preserving the spleen, which has been reported to reduce operative morbidity maintaining adequate oncological outcome. Oh *et al.* (26) showed that splenectomy patients had a poorer short-surgical outcome than spleen-preservation patients, and the survival analysis indicated that the 5-year OS of the spleen-preservation group was significantly higher than that of the splenectomy group in pN0 advanced GC patients. Zhong *et al.* (27) study indicated that laparoscopic spleen-preserving No. 10 node dissection for GC was safe and feasible, and the 3-year OS of D2+ No. 10 group was better than that of the D2 group (74.4% *vs*. 42.1%; P=0.005). In summary, we believe that spleen-preserving No. 10 lymphadenectomy could be recommended for patients with tumor invading the greater curvature or local advance proximal GC. The prophylactic splenectomy for No. 10 node dissection should be avoided.

Posterior surface of pancreatic head (No. 13) LN dissection for distal advanced GC

LNs on the posterior surface of the pancreatic head cranial to the duodenal papilla are defined as No. 13 LN. According to the JGCTG (5th edition) (4), the No. 13 node was not required to be dissected during standard D2 lymphadenectomy. Metastases to the No. 13 node should be classified as the distant metastasis (M1). However the Japanese classification of gastric carcinoma was still defined the No. 13 node as the regional LNs for cancer with duodenal invasion (8). The guidelines state that D2+ No. 13 lymphadenectomy could be considered for a potentially curative gastrectomy for tumors invading the duodenum.

The metastatic rate of No. 13 node for patients with lower-third advanced GC was reported from 2.53% to 23.9% (28-32). In advanced GC with duodenal invasion, the No. 13 node was susceptible to metastasis because of their proximity to duodenum. Tokunaga *et al.* (29) reported that the incidence of No. 13 node metastasis was significantly higher in patients of advanced GC with duodenal invasion (23.9%) compared to the same type patients but without duodenal invasion (7%, P<0.0001). The study of Kumagai *et al.* (31) showed that the No. 13 node metastatic rate was 26.7% in advanced GC with duodenal invasion, and the therapeutic value of No. 13 node was 6.9 which was equal to or better than those of second-tier LNs (No. 7, 9 and 11p). A study from our institute (33) suggested that No. 13 node metastatic rate was 12.8% in advanced distal GC. The therapeutic value as 5.1 for No. 13 node, which was better than some LNs station in D2 lymphadenectomy region, such as No. 7 (3.4), No. 8a (5.0) and No. 9 (3.4). These references indicated that the metastatic ratio and therapeutic value of No. 13 node were relatively high in advanced distal GC with duodenal invasion.

Some studies reported that metastasis of No. 13 node was correlated with poor prognosis (30-32), however, the effect of additional No. 13 LN dissection during D2 gastrectomy on survival has remained controversial. The study of Xue *et al.* (30) indicated that GC patients with No. 13 LN metastasis had significantly poorer prognosis than those without No. 13 LN metastasis (3-year OS: 15% *vs.* 69%, P<0.001). The study conducted by Eom *et al.* (32) demonstrated that there was no significant difference in morbidity or mortality between the No. 13 node dissection group and the No. 13 node non-dissection group. However, the subgroup analysis the No. 13 LN dissection can improve OS in stages III/IV GC. Kumagai *et al.* (31) reported that the 5-year OS rate was 25.4% in patients with No. 13 node metastasis, and there may be survival benefit in dissection of No. 13 node in a potentially curative gastrectomy for GC with duodenal invasion. Our data (34) showed that the 5-year OS in patients with D2+ No.13 lymphadenectomy group (46.0%) was higher than standard D2 group (36.5%, P<0.05). It is necessary to dissect the No. 13 node for II/III stage lower-third GC. These researches suggested that additional No. 13 node dissection beyond a D2 gastrectomy might be favorable for survival in patients with the advanced middle or lower-third GC with duodenal invasion.

Para-aortic node (PAN) dissection for advanced GC

PAN is defined as LNs between the aortic hiatus and the aortic bifurcation. The PAN was considered as the terminal regional nodes of gastric lymphatic drainage, and defined as distal metastasis (M1 nodes) according to the Japanese classification of gastric carcinoma (8). The necessity of para-aortic nodal dissection (PAND) remains controversial for patients with advanced GC.

It was reported that the incidence of metastasis to PAN was present in 18%–40% of advanced GC (35-37). When considering the incidence of micro-metastases, Natsugoe *et al.* (38) reported that the micro-metastasis rate was up to 64%. Our data (39) showed that the PAN metastatic rate was 27.0%. The correlation analysis indicated that pathologic N stage was a significant risk factor for PAN metastasis. The higher the pathologic N stage, the greater the incidence of PAN metastases. The No. 9 node metastasis was identified as indicators for a high incidence of PAN metastasis.

In the past, prophylactic D2+PAND was considered to be a necessary procedure in order to achieve R0 resection. However, some researches did not show survival benefit after D2+PAND. The JCOG 9501 trail showed that there was no survival benefit from surgery with D2+PAND. The 5-year OS rate was found to be similar in the groups D2 lymphadenectomy and D2+PAND (69.2% *vs*. 70.3%, P=0.85). However, there were some limitations to this research, the results revealed that there were only 2.5% for patients with T4 enrolled in this study. Therefore, whether D2+PAND could result in better survival for patients with T4 disease needs more research. Evidence from some studies showed that GC patients with PAN involvement alone were found to have better survival than other advanced GC patients with multiple organ sites metastasis (40), and some researches indicated a strong possibility that the D2+PAND can benefit selected patients with GC. The study conducted by Zhang *et al.* (41) showed that the 5-year OS rate was significantly higher in patients underwent D2+PAND surgery than in those performed D1 surgery (37.4% *vs*. 48.7%, P=0.027). They recommend D2+PAND lymphadenectomy for patients with curable GC except for patients with Borrmann I disease. Roviello *et al*. (42) showed that the 5-year OS was 17% for patients with non-regional LN metastasis who underwent R0 resection. The study indicated that D2+ PAND could be considered for curative surgery of advanced GC, especially for upper third tumors. To sum up, these considerations suggest the possibility that prophylactic D2+PAND can offer a chance of cure in selected patients with advanced GC.

Systemic chemotherapy is regarded as the standard treatment for GC with PAN involvement, extended gastrectomy with neoadjuvant chemotherapy is weakly recommended from the guideline (4). Many clinical trials were implemented to investigate the safety and efficacy of neoadjuvant chemotherapy followed by gastrectomy with D2+PAND for GC with PAN metastasis. In the JCOG1001 (43), patients received irinotecan and cisplatin chemotherapy before surgery. The results showed a good 3-year survival of 27.0%, but the study was terminated due to three treatment-related deaths among the 55 enrolled patients. In the JCOG0405 trial (44), neoadjuvant cisplatin and S-1 (CS) was administered to patients with GC with PAN metastasis. The investigators showed an excellent response rate of 64.7% and a 3-year survival of 58.8% with no treatment-related deaths. The JCOG1002 study (45) showed that adding docetaxel to CS in preoperative chemotherapy improved neither short-term outcomes nor long-term survival. Since then, CS chemotherapy has been considered the current standard for patients with PAN metastasis by Japanese guideline. Likewise, a Chinese phase II trial (46) indicated that neoadjuvant chemotherapy with xeloda and oxaliplatin was demonstrated a good response rate, and a sufficient R0 resection rate, with acceptable toxicities for GC patients with PAN involvement. These studies indicate that preoperative chemotherapy followed by gastrectomy with D2+PAND was considered as the standard treatment for GC with PAND metastasis. Further investigations on appropriate regimens and suitable durations of perioperative chemotherapy should be used in clinical practice for better survival.

Taken together, prophylactic D2+PAND was not routinely recommended for advanced GC patients, but therapeutic D2+PAND may offer a chance of cure in selected patients. At present, a multidisciplinary discussion may help in choosing the appropriate therapy for patients with PAN metastasis. In future, more clinical trials are needed to identify the role of PAND in GC.

Lymphadenectomy for adenocarcinoma of esophagogastric junction (AEG)

The incidence of AEG is rising dramatically in the past few decades. AEG is usually classified into 3 categories based on the location of the epicenter of the tumor. The optimal

surgical management of AEG is challenging and complex. It is generally acknowledged that Siewert I and III carcinomas are to be treated as esophageal and gastric tumors, respectively (47). The optimal surgical approach for Siewert II tumor remains debated.

The metastatic rate of mediastinal LNs for Siewert II patients was 18%−40% (48-50). A Japanese multicenter prospective study (50) indicated that the mediastinal LN metastasis was correlated with the length of esophageal involvement. Subgroup analysis according to the length of esophageal involvement (≤1.0 cm, 1.1−2.0 cm, 2.1−3.0 cm, 3.1−4.0 cm, and >4.0 cm) showed that the rate of No. 110 node metastasis was 0.9%, 6.4%, 10.8%, 20.8% and 28.6%, respectively. The authors indicated that if esophageal invasion of >3 cm was noted, the upper and middle mediastinal LNs should be harvested. Kurokawa *et al.* (49) showed similar results in their study. These results suggested that the mediastinal LN dissection was unnecessary for Siewert II tumor of esophageal involvement of less than 2.0 cm. D2+ No. 110 lymphadenectomy via transabdominal esophageal hiatus approach was recommend in cases of esophageal involvement from 2.0−4.0 cm. Thorough mediastinal LN dissection via a transthoracic approach may provide a therapeutic benefit when the distance was more than 4 cm.

Abdominal LN metastasis was also very common in patients with Siewert II tumors. A Japanese nationwide retrospective study (51) indicated that for patients with AEG, the incidence of metastasis was high in the upper half of perigastric LNs (No. 1, 2 and 3) and the second-tier LNs (No. 7, 9 and 11), whereas it was especially lower in the lower perigastric LNs (No. 4d−6). Mine *et al.* (52) showed that the distance from the esophagogastric junction to the distal end of the tumor was related to the distribution of involved abdominal LN in Siewert II tumors. When the distance was 0−3 cm, 3−5 cm, and >5 cm, the incidence of abdominal LN involvement was 2.2%, 8.0% and 20.0%). A gastric tube or proximal gastrectomy may be a surgical option when this distance was less than 3 cm. In contrast, a total gastrectomy should be considered for abdominal lymphadenectomy when this distance was >5 cm. However, when the distance was 3−5 cm, the choice of proximal gastrectomy or total gastrectomy should be made based on the necessity of thoracic lymphadenectomy and the extent of esophageal resection.

In summary, these studies indicated that AEG mainly metastasizes to the abdominal LN around the stomach. A preoperative evaluation of the distance from the esophagogastric junction to the distal end of the tumor is essential for determining the optimal extent of resection. The lower mediastinal compartment is the most common site of mediastinal LN metastases. The length of esophageal invasion can be used as a reference point for mediastinal LN metastases.

Quality control of lymphadenectomy

During the 1990s, European surgeons organized some large trials in which patients were randomly assigned to either D1 or D2 lymphadenectomy (5). This was soon found out to be due to the surgeons who were carrying out the operations lacked the necessary training in extended lymphadenectomy (performing less than 5 cases per year). The extended lymphadenectomy yielded a very high postoperative mortality (9.7% in the Dutch). The Dutch trials indicated that surgeons with limited experience in extended lymphadenectomy made them very difficult to perform the procedure safely and effectively.

Several studies showed that the hospital volume had a positive association with surgical outcome of patients with resectable GC. Mahar *et al.* (53) reported a systematic review of the effect of the institution-surgeon factor on surgical outcomes for GC. In this review, it reported that the hospital-surgeon factor did influence the outcomes for patients received the GC surgery. High hospital volume on the procedure was associated with low procedure-related mortality. Iwatsuki *et al.* (54) studied the national data from Japan, and it reported that hospital volume has a crucial impact on postoperative morbidity and mortality after distal gastrectomy. Operative mortality rate was 1.9% in low-volume hospital, and the mortality rate decreased to 0.5% in high-volume hospitals. A significant reduction in mortality rate was observed according to hospital volume (P<0.001). These findings suggest that centralization may improve outcomes of GC patients after gastrectomy.

Compared with hospital volume, the surgeon factor can better predict the surgical outcome in a given center. Indeed, many studies have affirmed the positive influence of surgeon specialty on survival for GC. Maciej *et al.* (55) reported that the perioperative morbidity and mortality were 37.5% and 8.9% for surgeons performing less than two gastrectomies per year and 16% and 0.9% for surgeons performing more than two resections annually (P=0.002 and 0.003). Patients operated by surgeons performing less

than two gastrectomies per year were associated with more frequent distant metastases or peritoneal spread. The surgeon was a significant predictive factor of morbidity and mortality following gastrectomy for GC. A study from our group reported the similar results (56). Patients operated by specialized group demonstrated a significantly higher 5-year OS rate than those operated by the non-specialized group (50.7% *vs.* 37.2%, P=0.001). In this study, the specialized surgeons were defined as the surgeons from Department of Gastric Cancer and whose annual GC surgery volume was more than 50 with proven experience in D2 LN dissection confirmed by intraoperative photographs, while non-specialized surgeons were from the Department of Hepatobiliary Cancer, Colorectal Cancer and Pancreatic Cancer. It was suggested that GC patients should be treated by specialized surgeons in a large-volume center.

We believed that skill and experience of surgeons was one of the key factors to improve the quality of surgery for GC. Centralization of GC surgery may improve outcomes for GC.

Conclusions

To explore the appropriate extent of LN dissection for GC is an important clinical and research focus. Several previous researches indicated that D2+ No. 10, 13 and 14v lymphadenectomy can improve surgical outcomes in some patients. D2+PAND after preoperative chemotherapy may be an option for GC with PAN metastasis. The length of esophageal invasion and the distance from the esophago-gastric junction to the distal end of the tumor may be helpful to determine the operative approach of AEG. The quality of lymphadenectomy may influence prognosis of GC patients. Centralization of GC surgery may be needed to improve prognosis.

Acknowledgements

This study was supported by the National Natural Science Foundation of China (No. 81401952), National Key Research and Development Program "major chronic non-infectious disease research" (No. 2016YFC1303202), National Key Research and Development Program "precision medicine research" (No. 2017YFC0908304), and Science and Technology Research Projects of Tianjin Municipal Health Bureau (No. 2014KZ082).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Yang L, Zheng R, Wang N, et al. Incidence and mortality of stomach cancer in China, 2014. Chin J Cancer Res 2018;30:291-8.
3. National Health Commission of the People's Republic of China. Chinese guidelines for diagnosis and treatment of gastric cancer 2018 (English version). Chin J Cancer Res 2019;31:707-37.
4. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). Gastric Cancer 2021;24:1-21.
5. Hartgrink HH, van de Velde CJ, Putter H, et al. Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial. J Clin Oncol 2004; 22:2069-77.
6. Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma (2nd English Edition). Gastric Cancer 1998;1:10-24.
7. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer 2011;14:113-23.
8. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer 2011;14:101-12.
9. Masuda TA, Sakaguchi Y, Toh Y, et al. Clinical characteristics of gastric cancer with metastasis to the lymph node along the superior mesenteric vein (14v). Dig Surg 2008;25:351-8.
10. An JY, Pak KH, Inaba K, et al. Relevance of lymph node metastasis along the superior mesenteric vein in gastric cancer. Br J Surg 2011;98:667-72.
11. Liang Y, Wu L, Wang X, et al. Positive impact of adding No.14v lymph node to D2 dissection on survival for distal gastric cancer patients after surgery with curative intent. Chin J Cancer Res 2015;27:

580-7.
12. Wu L, Zhang C, Liang Y, et al. Risk factors for metastasis to No.14v lymph node and prognostic value of 14v status for gastric cancer patients after surgery. Jpn J Clin Oncol 2018;48:335-42.
13. Han WH, Joo J, Eom BW, et al. Factors associated with metastasis in superior mesenteric vein lymph node in subtotal gastrectomy for gastric cancer: Retrospective case control study. Chin J Cancer Res 2020;32:43-50.
14. Eom BW, Joo J, Kim YW, et al. Improved survival after adding dissection of the superior mesenteric vein lymph node (14v) to standard D2 gastrectomy for advanced distal gastric cancer. Surgery 2014;155: 408-16.
15. Xu KF, Zhou YB, Li Y, et al. Study on metastasis and micrometastasis in No.14v lymph nodes of patients with lower third gastric cancer. Zhonghua Wei Chang Wai Ke Za Zhi (in Chinese) 2011;14:125-7.
16. Sasako M, McCulloch P, Kinoshita T, et al. New method to evaluate the therapeutic value of lymph node dissection for gastric cancer. Br J Surg 1995;82:346-51.
17. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer 2017;20:1-19.
18. Sano T, Sasako M, Mizusawa J, et al. Randomized controlled trial to evaluate splenectomy in total gastrectomy for proximal gastric carcinoma. Ann Surg 2017;265:277-83.
19. Kunisaki C, Makino H, Suwa H, et al. Impact of splenectomy in patients with gastric adenocarcinoma of the cardia. J Gastrointest Surg 2007;11:1039-44.
20. Zhu GL, Sun Z, Wang ZN, et al. Splenic hilar lymph node metastasis independently predicts poor survival for patients with gastric cancers in the upper and/or the middle third of the stomach. J Surg Oncol 2012; 105:786-92.
21. Son T, Kwon IG, Lee JH, et al. Impact of splenic hilar lymph node metastasis on prognosis in patients with advanced gastric cancer. Oncotarget 2017;8: 84515-28.
22. Yura M, Yoshikawa T, Otsuki S, et al. The therapeutic survival benefit of splenic hilar nodal dissection for advanced proximal gastric cancer invading the greater curvature. Ann Surg Oncol 2019; 26:829-35.
23. Jeong O, Jung MR, Ryu SY. Clinicopathological features and prognostic impact of splenic hilar lymph node metastasis in proximal gastric carcinoma. Eur J Surg Oncol 2019;45:432-8.
24. Kosuga T, Ichikawa D, Okamoto K, et al. Survival benefits from splenic hilar lymph node dissection by splenectomy in gastric cancer patients: relative comparison of the benefits in subgroups of patients. Gastric Cancer 2011;14:172-7.
25. Huang CM, Chen T, Lin JX, et al. The effects of laparoscopic spleen-preserving splenic hilar lymphadenectomy on the surgical outcome of proximal gastric cancer: a propensity score-matched, case-control study. Surg Endosc 2017;31:1383-92.
26. Oh SJ, Hyung WJ, Li C, et al. The effect of spleen-preserving lymphadenectomy on surgical outcomes of locally advanced proximal gastric cancer. J Surg Oncol 2009;99:275-80.
27. Zhong Q, Chen QY, Xu YC, et al. Reappraise role of No. 10 lymphadenectomy for proximal gastric cancer in the era of minimal invasive surgery during total gastrectomy: a pooled analysis of 4 prospective trial. Gastric Cancer 2021;24:245-57.
28. Shen DF, Chen DW, Quan ZW, et al. Dissection of No. 13 lymph node in radical gastrectomy for gastric carcinoma. World J Gastroenterol 2008;14:936-8.
29. Tokunaga M, Ohyama S, Hiki N, et al. Therapeutic value of lymph node dissection in advanced gastric cancer with macroscopic duodenum invasion: is the posterior pancreatic head lymph node dissection beneficial? Ann Surg Oncol 2009;16:1241-6.
30. Xue L, Chen XL, Zhang WH, et al. Risk factors and prognostic significance of retropancreatic lymph nodes in gastric adenocarcinoma. Gastroenterol Res Pract 2015;2015:367679.
31. Kumagai K, Sano T, Hiki N, et al. Survival benefit of "D2-plus" gastrectomy in gastric cancer patients with duodenal invasion. Gastric Cancer 2018;21:296-302.
32. Eom BW, Joo J, Kim YW, et al. Is there any role of additional retropancreatic lymph node dissection on D2 gastrectomy for advanced gastric cancer? Ann Surg Oncol 2013;20:2669-75.
33. Sun W, Deng J, Zhang N, et al. Prognostic impact of

D2-plus lymphadenectomy and optimal extent of lymphadenectomy in advanced gastric antral carcinoma: Propensity score matching analysis. Chin J Cancer Res 2020;32:51-61.
34. Jiao XG, Liang H, Deng JY, et al. The significance of No.13 lymph node dissection in D2 gastrectomy for lower-third advanced gastric cancer. Zhonghua Wai Ke Za Zhi (in Chinese) 2013;51:235-9.
35. Morita S, Fukagawa T, Fujiwara H, et al. The clinical significance of para-aortic nodal dissection for advanced gastric cancer. Eur J Surg Oncol 2016;42: 1448-54.
36. Mengardo V, Bencivenga M, Weindelmayer J, et al. Para-aortic lymphadenectomy in surgery for gastric cancer: current indications and future perspectives. Updates Surg 2018;70:207-11.
37. Dong YP, Deng JY. Advances in para-aortic nodal dissection in gastric cancer surgery: A review of research progress over the last decade. World J Clin Cases 2020;8:2703-16.
38. Natsugoe S, Nakashima S, Matsumoto M, et al. Paraaortic lymph node micrometastasis and tumor cell microinvolvement in advanced gastric carcinoma. Gastric Cancer 1999;2:179-85.
39. Wang L, Liang H, Wang X, et al. Risk factors for metastasis to para-aortic lymph nodes in gastric cancer: a single institution study in China. J Surg Res 2013;179:54-9.
40. Park IH, Kim SY, Kim YW, et al. Clinical characteristics and treatment outcomes of gastric cancer patients with isolated para-aortic lymph node involvement. Cancer Chemother Pharmacol 2011;67: 127-36.
41. Zhang H, Liu C, Wu D, et al. Does D3 surgery offer a better survival outcome compared to D1 surgery for gastric cancer? A result based on a hospital population of two decades as taking D2 surgery for reference. BMC Cancer 2010;10:308.
42. Roviello F, Pedrazzani C, Marrelli D, et al. Super-extended (D3) lymphadenectomy in advanced gastric cancer. Eur J Surg Oncol 2010;36:439-46.
43. Yoshikawa T, Sasako M, Yamamoto S, et al. Phase II study of neoadjuvant chemotherapy and extended surgery for locally advanced gastric cancer. Br J Surg 2009;96:1015-22.
44. Tsuburaya A, Mizusawa J, Tanaka Y, et al. Neo-adjuvant chemotherapy with S-1 and cisplatin followed by D2 gastrectomy with para-aortic lymph node dissection for gastric cancer with extensive lymph node metastasis. Br J Surg 2014;101:653-60.
45. Takahari D, Ito S, Mizusawa J, et al. Long-term outcomes of preoperative docetaxel with cisplatin plus S-1 therapy for gastric cancer with extensive nodal metastasis (JCOG1002). Gastric Cancer 2020;23: 293-9.
46. Wang Y, Yu YY, Li W, et al. A phase II trial of Xeloda and oxaliplatin (XELOX) neo-adjuvant chemotherapy followed by surgery for advanced gastric cancer patients with para-aortic lymph node metastasis. Cancer Chemother Pharmacol 2014;73: 1155-61.
47. Mariette C, Piessen G, Briez N, et al. Oesophago-gastric junction adenocarcinoma: which therapeutic approach? Lancet Oncol 2011;12:296-305.
48. Pedrazzani C, de Manzoni G, Marrelli D, et al. Lymph node involvement in advanced gastro-esophageal junction adenocarcinoma. J Thorac Cardiovasc Surg 2007;134:378-85.
49. Kurokawa Y, Hiki N, Yoshikawa T, et al. Mediastinal lymph node metastasis and recurrence in adeno-carcinoma of the esophagogastric junction. Surgery 2015;157:551-5.
50. Kurokawa Y, Takeuchi H, Doki Y, et al. Mapping of lymph node metastasis from esophagogastric junction tumors: a prospective nationwide multicenter study. Ann Surg 2019. [Epub ahead of print]
51. Yamashita H, Seto Y, Sano T, et al. Results of a nation-wide retrospective study of lymphadenectomy for esophagogastric junction carcinoma. Gastric Cancer 2017;20(1 suppl):69-83.
52. Mine S, Kurokawa Y, Takeuchi H, et al. Distribution of involved abdominal lymph nodes is correlated with the distance from the esophagogastric junction to the distal end of the tumor in Siewert type II tumors. Eur J Surg Oncol 2015;41:1348-53.
53. Mahar AL, McLeod RS, Kiss A, et al. A systematic review of the effect of institution and surgeon factors on surgical outcomes for gastric cancer. J Am Coll Surg 2012;214:860-8.
54. Iwatsuki M, Yamamoto H, Miyata H, et al. Effect of

hospital and surgeon volume on postoperative outcomes after distal gastrectomy for gastric cancer based on data from 145,523 Japanese patients collected from a nationwide web-based data entry system. Gastric Cancer 2019;22:190-201.
55. Ciesielski M, Kruszewski WJ, Walczak J, et al. Analysis of postoperative morbidity and mortality following surgery for gastric cancer. Surgeon volume as the most significant prognostic factor. Prz Gastroenterol 2017;12:215-21.
56. Liang Y, Wu L, Wang X, et al. The positive impact of surgeon specialization on survival for gastric cancer patients after surgery with curative intent. Gastric Cancer 2015;18:859-67.

Cite this article as: Ke B, Liang H. Current status of lymph node dissection in gastric cancer. Chin J Cancer Res 2021;33(2):193-202. doi: 10.21147/j.issn.1000-9604.2021.02.07

