Current status of extended 'D2 plus' lymphadenectomy in advanced gastric cancer (Review)

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Abstract. The extent of lymph node (LN) dissection has been a topic of interest in gastric cancer (GC) surgery. D2 lymphadenectomy is considered the standard surgical procedure for most resectable advanced GC cases. The value and indications of more extended lymphadenectomy than D2 remain unclear. Currently, the controversial stations beyond the D2 range are mainly focused on no. 14v, no. 16a2/b1 and no. 13 LN stations. The metastatic rate of no. 14v LN is relatively high in advanced distal GC, particularly in patients with suspicious no. 6 LN metastasis. D2 plus no. 14v LN dissection may be attributed to improved survival outcomes for patients with obvious no. 6 LN metastasis. Although GC with para-aortic lymph node (PALN) metastases is considered an M1 disease beyond surgical cure, patients with limited PALN metastases may benefit from the treatment strategy of adjuvant chemotherapy followed by D2 plus no. 16a2-b1 LN dissection. In addition, D2 plus no. 13 LN dissection may be an option in a potentially curative gastrectomy for GC with duodenal invasion. The present review discusses the current status and future perspectives of D2 plus lymphadenectomy.

Contents

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1. Introduction

Gastric cancer (GC) continues to be a major challenge facing the healthcare industry worldwide, particularly in East Asian countries, such as China, South Korea and Japan (1). Despite advancements in medical treatments, gastrectomy with regional lymph node (LN) dissection remains the primary treatment for patients with resectable GC (2-4). The extent of lymphadenectomy has been a topic of interest in GC surgery. Although controversy regarding the extent of LN dissection still exists between surgeons in East and West Asia, a consensus was achieved following the disclosure of several randomized clinical trials (5,6). The most influential study was the 15-year follow-up results of the Dutch trial, in which D2 lymphadenectomy was associated with lower locoregional recurrence and higher GC-associated mortality rates compared with D1 surgery (5). Based on the results of the Dutch trial, spleen preserving D2 lymphadenectomy is a recommended surgical approach for patients with resectable local advanced GC in Western guidelines (2,7). In East Asia, a standard therapeutic strategy for GC by stage has been established, and radical gastrectomy with D2 LN dissection is considered the standard surgical procedure for potentially curable T2-4 tumors, as well as $cT1N^{+}$ tumors (3). Theoretically, the removal of a wider range of LNs by extended dissection increases the chances for a cure, particularly for those with extensive LN metastases (8). It has been demonstrated that 'D2 plus' lymphadenectomy can obtain more LNs compared with standard D2 lymphadenectomy, and that increasing the number of LNs retrieved may contribute to adequate staging and survival benefits (8-10). Currently, controversial stations beyond D2 range are mainly focused on no. 14v, no. 16a2/b1 and no. 13 LN stations (4). Although no. 14v LN metastasis is considered an indicator of poor prognosis, some patients who are suspected of harboring metastasis to the no. 6 LN may benefit from curative D2 plus 14v dissection (11,12). For para-aortic lymph nodes (PALNs), the JCOG9501 trial was designed to investigate whether the addition of para-aortic nodal dissection (PAND) to D2 lymphadenectomy for stage T2, T3 or T4 tumors improved the survival of patients with GC (13). The results demonstrated that treatment with D2 lymphadenectomy plus PAND did not improve the survival rate in curable GC compared with D2 lymphadenectomy alone. Another randomized clinical trial from East Asia also demonstrated no survival benefit

using PAND (14). The involvement of PALNs is considered a metastatic disease, and PAND is not suggested in the prophylactic setting (4). LNs located posterior to the pancreatic head (no. 13) are often involved in advanced GC with duodenal invasion, and some researchers suggest that no. 13 LN dissection should be performed in distal GC, particularly in those with duodenal invasion (15-17). In the fourth edition of Japanese GC treatment guidelines (4), no. 13 LN involvement was considered a locoregional disease rather than distant metastasis for GC with duodenal invasion. Although gastrectomy with extended lymphadenectomy beyond the D2 range is classified as non-standard gastrectomy (3), its significance had been frequently assessed in clinical studies (8,10-12,14-17).

The present review discusses the current status of extended D2 plus lymphadenectomy compared with standard D2 lymphadenectomy.

2. No. 14v LN dissection for distal local advanced GC

According to the second English edition of the Japanese Classification of Gastric Carcinoma (18), 14v was referred to as LNs along the superior mesenteric vein and defined as regional GC LNs. 14v was included in D2 lymphadenectomy for distal advanced GC. However, the third English edition of the guideline excluded 14v from D2 gastrectomy (19), as several retrospective studies confirmed the poor survival outcomes of 14v-positive patients following curative resection (11,20). The guideline also emphasized that D2 plus 14v dissection may benefit patients who are suspected to harbor metastases to the no. 6 LNs (21). For 14v, the current fourth edition of the guideline is consistent with the previous version (4). The role of 14v lymphadenectomy in advanced GC is debatable. Some studies favor the removal of 14v in D2 gastrectomy for distal GC (10,12,22,23), while others do not (11,20).

The necessity of LN dissection is based on metastatic pathway, frequency and prognostic impact. 14v is anatomically downstream of no. 6 LN in the lymphatic flow in distal GC, and it receives the lymphatic flow from no. 6 LN, and subsequently flows to the no. 16 LN station. Theoretically, once the no. 6 LN is invaded, the 14v is at high risk of metastasis (12). It has been reported that no. 6 LN is a useful predictor for 14v metastasis, with high accuracy (99.0%) and low false negative rate (1.9%) (20). Several studies have confirmed that no. 6 LN metastasis is an independent risk factor for 14v metastasis (12,24). Our previous study (12) also investigated the risk factors for 14v metastasis, and it was demonstrated that 26.9% of patients with no. 6 LN metastasis also had 14v, and no. 4d [relative risk (RR), 2.615; 95% confident interval (CI), 1.068-6.402; P=0.035] and no. 6 (RR, 3.336; 95% CI, 1.387-8.024, P=0.007) LN metastases were independently associated with 14v metastasis. The frequency of 14v metastasis has ranged from 4.4-18.62% in previous studies (11,12,20,22,23) (Table I). It has been reported that the rate of 14v metastasis in T1a and T1b GC is lower, 0.0 and 0.7%, respectively (25). Masuda *et al* (11) reported that the incidence of 14v metastasis is merely 1.3% in early GC, which increases to 17.0% in T4 stage. In addition, An *et al* (20) demonstrated that the metastatic rates of 14v were 12.0 and 2.3% in patients with and without serosa invasion, respectively. According to our data (12), of the 60 patients with GC, with upper tumors, only two patients had 14v metastasis, and in tumors without serosal invasion, only one case exhibited 14v metastasis. However, in tumors that invaded serosa and adjacent structure, and were in the middle and lower sections of the stomach, the frequency of 14v metastasis was as high as 17.1%. The present review analyzes total metastatic rates of 14v from previous studies. Of the 4,525 patients with 14v dissection, 455 patients were affirmed with 14v metastasis, and the metastatic rate of 14v was 10.1%. The metastatic rates were 6.1 and 15.4% for those without and with serosal invasion, respectively (Table I). 14v is usually involved in patients with distal GC with serosal invasion, particularly those with no. 6 LN metastasis (11,12,20,22,23).

Previous studies have evaluated the prognosis of 14v-positive patients. A retrospective study in South Korea revealed that patients with GC with 14v metastasis have a significantly worse prognosis than those without 14v metastasis, and the survival of 14v-positive patients is worse than that of stage IV disease without 14v metastasis. Thus, the authors concluded that 14v should be excluded from regional LNs (20). Masuda *et al* (11) reported that patients with 14v metastasis have a significantly lower 5-year overall survival (OS) rate than those without 14v metastasis (11.9 vs. 39.3%; P<0.0001). However, the 5-year OS rate of 14v-positive patients without no. 16 LN metastasis was 17.5%, which indicated that some patients may benefit from curative D2 plus 14v dissection (11). Abe *et al* (26) reported that a patient with stage I GC with two LNs metastases to no. 6 LN station demonstrated early recurrence at the no. 14v LN station 4 months after $D1^+$ LN dissection; however, the patient survived without recurrence 5.5 years after resection of the recurrent LNs. This suggests that some patients with no. 6 LN metastasis may benefit from 14v dissection, even in early stage (26). Our previous study revealed that the OS rate of GC is significantly influenced by 14v status (12). The 3-year OS rates were 43.9 and 70.3% for patients with and without 14v metastasis, respectively. The status of 14v was an independent prognostic factor for stage III GC. The OS rate of patients with 14v metastasis following curative surgery was similar to that of patients at stage IIIc without 14v. Notably, our previous study demonstrated that the 3-year OS rates significantly decreased as LN metastasized to no. 6 LN (54.4%), to 14v (42.9%) and to distance (7.4%). Taken together, these findings suggest that there is a lymphatic flow from the no. 6 LN to the 14v station, and subsequently to distance. These studies (11,12,26) suggest that 14v metastasis is associated with poor prognosis and that 14v status is an independent prognostic factor for patients with GC. However, metastasis at station 14v does not always mean systemic metastasis that is beyond surgical cure. For patients with suspected 14v metastasis, those without other distant metastases may benefit from curative D2 plus 14v dissection.

Several retrospective studies (10,22,23,27,28) have confirmed that adding 14v to D2 dissection improves survival outcomes for patients with distal advanced GC (Table II). Eom *et al* (22) confirmed that 14v dissection improves the OS rates of patients with clinical stage III/IV GC in the middle or lower third of the stomach. Liang *et al* (10) demonstrated that adding 14v to D2 lymphadenectomy improves OS rates and lowers LN recurrence rates in patients with distal GC, with TNM IIIb/IIIc disease. Chen *et al* (23) demonstrated that laparoscopic-assisted radical distal gastrectomy with 14v

Table I. Incidence of 14v involvement based on serosa status and prognostic impact of 14v status.

Author, year	Country	Study design	N	Metastatic rate of 14v			OS rate, %		
				T1-3	T4	Total	14v negative	14v positive	P-value
Masuda *et al*, 2008	Japan	Retrospective study	2,513	8.0 (109/1,368)	17.0 (193/1,133)	12.1 (305[b]/2,513[c])	60.2 (5-year)	11.3 (5-year)	<0.001[a]
An *et al*, 2011	Korea	Retrospective study	1,104	2.3 (14/612)	12.0 (59/492)	6.6 (73/1,104)	74.1	9.0	<0.001[a]
Eom *et al*, 2014	Korea	Retrospective study	522	NA	NA	4.4 (23/522)	NA	NA	NA
Chen *et al*, 2018	China	Case control study	102	NA	NA	18.62 (19/102)	NA	NA	NA
Wu *et al*, 2018	China	Retrospective study	284	2.1 (1/47)	14.3 (34/237)	12.3 (35/284)	70.3 (3-year)	43.9 (3-year)	<0.001[a]
Total			4,525	6.1 (124/2,027)	15.4 (286/1,862)	10.1 (455[b]/4,525[c])	-	-	-

[a]P<0.001; [b]including 3 patients with T staging data missing; [c]including 12 patients with T staging data missing. N, number of patients who underwent gastrectomy with lymph node including 14v dissection; NA, not available; OS, overall survival.

dissection may improve the OS rate for clinical T2-3 lower third GC. Given that no random prospective trials have been performed to assess survival benefit of 14v dissection, no definite conclusions can be drawn. However, based on the results of previous studies, it can be concluded that considering the low incidence of 14v metastasis in early-stage disease, 14v dissection is not routinely recommended in these patients. For patients with distal GC, with serosal invasion, particularly those who are suspected to harbor metastasis to the no. 6 LN, the metastatic rate of 14v is relatively high (8,12). D2 lymphadenectomy plus 14v dissection may increase the possibility of curative resection, and thus contribute to improved OS outcomes.

3. PAND and its prognostic value in patients with locally advanced GC

In the third English edition of the Japanese Classification of Gastric Carcinoma, no. 16 LNs include 16a1 (PALN in the diaphragmatic hiatus), 16a2 (PALN between the upper margin of the origin of the celiac artery and the lower border of the left renal vein), 16b1 (PALN between the lower border of the left renal vein and the upper border of the origin of the inferior mesenteric artery) and 16b2 (PALN between the upper border of the origin of the inferior mesenteric artery and the aortic bifurcation) (19). Currently, controversy on extended lymphadenectomy for GC is mainly focused on the 16a2 and 16b1 LN subgroups. According to the current TNM classification, PALN metastasis is considered a systemic disease beyond surgical cure (4). However, long-term survival of patients with PALN metastasis is not uncommon after D2 plus PAND (29-31). It has been reported that some patients with limited PALN metastasis may benefit from curative D2 plus PAND (29-31).

Several studies have compared the surgical outcomes of patients who underwent D2 lymphadenectomy alone with those who underwent D2 plus PAND (13,14,30,32) (Table III). In these studies, the incidence of PALN metastasis was ~8.1-9.0% in patients with advanced GC. In addition, the incidence of PALN was up to 40.6% in patients at pT3 or pT4 stages, with 1-3 clinically involved para-aortic nodes (13,14,30,32). The results of the Japanese randomized controlled trial, JCOG9501 (13), demonstrated that the 5-year OS rate was 69.2% for the D2 lymphadenectomy alone group and 70.3% for the D2 lymphadenectomy plus PAND group. The rates of surgery-related complications among patients assigned to D2 lymphadenectomy alone and those assigned to D2 lymphadenectomy plus PAND were 20.9 and 28.1%, respectively (P=0.07). Based on these results, Sasako *et al* (13) concluded that treatment with D2 lymphadenectomy plus PAND does not improve the survival rate in curable GC compared with D2 lymphadenectomy alone. However, the conclusion of the trial was a controversial topic as patients with gross metastasis to the PALN were excluded according to the eligibility criteria. Despite this, the metastatic rate of PALN was as high as 8.5%, and the 5-year OS rate of patients with PALN metastasis was 18.5%, similar to that of patients at stage IIIc of the disease. In addition, >30% of patients lacked LN metastasis and more than half of the patients in each group did not have serosal invasion. Thus, the effect of D2 plus PAND may be obscured due to the lower incidence of PALN involvement and the higher ratio of patients without LN metastasis (13). Liang and Deng (33) deemed that the objective conclusion for the JCOG9501 trial should be that prophylactic PAND does not improve the survival outcome of patients with GC, with T2-3 and N1-2 disease. Subsequent studies have also suggested that D2 plus PAND does not benefit patient survival compared with standard D2 lymphadenectomy (14,32). A meta-analysis including eight studies demonstrated that D2

Table II. Impact of 14v dissection on OS of patients with GC.

Author, year	Country	Study design	Main inclusion criteria	Subgroup	D2		D2+14v		HR (95% CI) for D2+14v group	P-value
					Number of patients	3-year OS, %	Number of patients	3-year OS, %		
Eom *et al*, 2014	Korea	Retrospective study	Patients with advanced distal GC, patients accepted D2 dissection and patients who did not have distant metastasis	All	1,139	NA	522	NA		
				cI	788	NA	281	NA	1.160 (0.670-2.030)	0.594
				cII	147	NA	86	NA	0.930 (0.380-0.880)	0.777
				cIII/IV	199	NA	155	NA	0.580 (0.380-0.880)	0.010[a]
Chen *et al*, 2018	China	Case control study	Patients who underwent laparoscopic distal gastrectomy	All	655	70.4	102	64.7	0.938 (0.637-1.379)	0.743
				Matched patients	93	55.9	93	73.1	0.568 (0.344-0.937)	0.027[a]
				cT2-3	42	54.8	36	83.3	0.240 (0.080-0.700)	<0.050[a]
				14v negative					0.460 (0.265-0.798)	0.005[b]
Liang *et al*, 2015	China	Retrospective study	Patients with primary tumors located at middle or lower sections of the stomach	All	677	53.9	243	63.4		0.094
				I	86	94.2	23	100.0		0.776
				II	182	77.5	64	84.1		0.518
				IIIa	92	62.0	32	77.9		0.120
				IIIb	118	41.5	44	63.6		0.033[a]
				IIIc	152	22.4	59	37.3		0.016[a]
				IV	47	4.3	21	4.8		0.917

[a]P<0.05; [b]P<0.01. GC, gastric cancer; OS, overall survival; HR, hazard ratio; CI, confidence interval; NA, not available.

Table III. Incidence of PALN involvement and prognostic impact of PAND.

Author, year	Country	Study design	Main inclusion criteria	Metastatic rate of PALN, %	5-year OS of PALN positive patients, %	D2		*D2+PAND/D3		P-value
						Number of patients	5-year OS, %	Number of patients	5-year OS, %	
Sasako *et al*, 2008	Japan	Prospective randomized controlled study	Clinical T2b, T3 or T4 stage, absence of gross metastases to the PALN and no cytological observations in peritoneal-lavage fluid	8.5 (22/260)	18.2	263	70.3	260	69.2	0.85
Yonemura *et al*, 2008	Taiwan, Japan and Korea	Prospective randomized controlled study	Advanced and curable disease, absence of enlarged lymph nodes around the hepatoduodenal ligament or paraaortic region demonstrated by CT scan	9.0 (12/134)	25.0	135	52.6	134	55.0	0.801
Hu *et al*, 2009	China	Retrospective case-control study	Histologically proved curable gastric cancer	8.1 (5/62)	NA	55	66.1	62	65.8	0.946
Zhang *et al*, 2014	China	Retrospective study	1-3 involved PALNs diagnosed by preoperative CT and intraoperative investigation (pT3 or pT4 tumor)	40.6 (28/69)	15.6	88	31.8	69	43.7	0.044[a]

[a]P<0.05. *D2+PAND/D3, patients received D2 plus PALN dissection or D3 LN dissection. PALN, para-aortic lymph nodes; PAND, para-aortic nodal dissection; OS, overall survival; NA, not available.

plus PAND can be performed as safely as standard D2 dissection without increasing postoperative mortality, but failed to benefit OS in patients with advanced GC (34). Further analysis revealed that the eligibility criteria in these studies were similar to those of the JCOG9501 trial, and patients who had enlarged LNs around the para-aortic region exhibited via CT scans were excluded from the study. As a result, the metastatic rate of PALNs was low in these studies. Theoretically, PAND cannot improve OS outcomes in patients without LN metastasis around the para-aortic region. Zhang *et al* (30) evaluated PAND for locoregionally advanced GC with 1-3 involved para-aortic nodes diagnosed by preoperative CT and intraoperative investigation. In these studies, clinically positive nodes were considered when the maximum axial diameter was ≥10 or ≤10 mm, with abnormal contrast enhancement displayed in preoperative CT images, or hard texture was identified intraoperatively (13,30). They results demonstrated that the rate of PALN metastasis was 40.6%, and the 5-year OS rate was significantly higher in the D2 plus PAND group compared with the D2 alone group (43.7 vs. 31.8%; P=0.044). Thus, it was concluded that therapeutic PAND with D2 lymphadenectomy may be beneficial for patients with T3/T4 advanced GC, with 1-3 involved PALNs (30).

Although the prognosis of patients with para-aortic nodal involvement is poor (29), several studies have aimed to identify the indications for PAND (29,30,35-42) (Table IV). Nunobe *et al* (35) demonstrated that advanced GC with esophageal invasion is associated with a high rate of PALN metastasis (22.2%), and the therapeutic index of PALN was similar to that of the second-tier LNs. Thus, they recommended thorough dissection of the PALN in patients with esophageal invasion. de Manzoni *et al* (43) revealed that T3/T4 cancers located at the upper third of the stomach, and with stations no. 1 and no. 3 involved, were at high risk of PALN metastasis and can benefit from PAND. Wang *et al* (9) and Nomura *et al* (44) demonstrated that stations of no. 7 and no. 9 were significant indicators of PALN metastasis. Taken together, these findings are useful in assessing the pattern of lymphatic flow to the PALNs. Lymphatic flow is speculated to reach the PALNs as follows: i) Directly from the left paracardial LNs; ii) from the LNs along the splenic artery; iii) from the LNs around the celiac artery; iv) from the LNs along the superior mesenteric artery and v) from the LNs on the posterior surface of the pancreatic head and the LNs along the posterior common hepatic artery (44). The second and third routes of lymphatic drainage are considered the most frequent routes to the nodes surrounding the aorta in upper third GC (44). The status of no. 7 and no. 9 LNs is the most effective predictor of PALN metastasis (9,44). In addition, other potential risk factors for PALN metastasis were also investigated (29,39). Tokunaga *et al* (29) assessed 178 patients with pathologically positive PALN who underwent curative resection and demonstrated that the 5-year OS rate was merely 13.0%. However, the 5-year OS rate increased to 28.6% in patients with ≤15 positive nodes and macroscopic type other than type IV. Thus, it was concluded that R0 resection, including PAND, may be beneficial in carefully selected patients with pathologically positive PALNs. Kaito *et al* (39) reported that the 3- and 5-year OS rates of 65 pathologically PALN-positive GC patients who underwent PAND were 33.8 and 21.2%, respectively. Multivariate analysis

Table IV. Incidence of PALN involvement and prognosis of patients with PALN metastasis following D2 plus dissection.

Author, year	Country	Study design	Main inclusion criteria	NCT	Metastatic rate of PALN, %	5-year OS of PALN positive patients, %	D2+PAND/D3	
							Number of patients	5-year OS, %
Nunobe *et al*, 2008	Japan	Retrospective study	Advanced GC with esophageal invasion	-	22.2 (32/144)	21.9	144	-
Roviello *et al*, 2010	Italy	Retrospective study	Advanced pT2-4 tumors	-	12.9 (37/286)	17.0[a]	254[b]	52.00
Morita *et al*, 2016	Japan	Retrospective study	Radical gastrectomy	-	14.2 (33/232)	21.2	232	61.00
Marrelli *et al*, 2017	Italy	Retrospective study	R0 resection	-	10.8 (42/390)	11.0	390	NA
Tokunaga *et al*, 2010	Japan	Retrospective study	GC with pathologically positive PALN	-	100.0 (178/178)	13.0	178	28.60 (n=50)[c]
Kaito *et al*, 2017	Japan	Retrospective study	Advanced GC, R0 resection	-	100.0 (65/65)	21.2	65	21.20
Oyama *et al*, 2012	Japan	Retrospective study	Patients with pathologically positive PALN	DCS (n=16)	100.0 (44/44)	32.9 (no NCT)[d] 93.8 (with NCT)[d]	44	32.90 (no NCT)[d] 93.80 (with NCT)[d]
Tsuburaya *et al*, 2014	Japan	Prospective study	Clinically PALN and/or bulky N2 metastases	S-1+ cisplatin	51.0 (26/51)	57.0 (if no bulky N2) 17.0 (if bulky N2)	42[e]	50.00 (34-64)
Fujiwara *et al*, 2015	Japan	Retrospective study	Patients with clinically positive PALNs	SP, DCF, XP and S-1+ paclitaxel	100.0 (20/20)	65.0	20	65.00
He *et al*, 2016	China	Prospective study	Clinical presence of PALN metastasis, good clinical response for NCT (CR, PR)	Intravenous and intraarterial NCT	-	-	35[f]	40.63 (3-year)

D2+PAND/D3, patients received D2 plus PALN dissection or D3 LN dissection. [a]5-year OS of 43 patient with M1a disease, including 37 patients with PALN metastasis; [b]254 patients who underwent R0 resection; [c]5-year OS of patients with positives nodes ≤15 and not Borrmann type 4; [d]2-year OS; [e]eligible patients who underwent R0 resection; [f]D2 dissection was performed on patients who achieved PR or CR of the PALN, followed by 6 cycles of chemotherapy with XELOX regimen and radiotherapy to the region of PALN metastasis. PALN, para-aortic lymph nodes; GC, gastric cancer; NCT, neoadjuvant chemotherapy; CR, complete response; PR, partial response; PAND, para-aortic nodal dissection; OS, overall survival; DCS, Docetaxel+Cisplatin+S-1; SP, S-1+Cisplatin; DC, Docetaxel+Cisplatin+5-Fu; XP, Xeloda+Cisplatin.

indicated that the following were independent prognostic factors for poor survival: Nodal involvement around the celiac axis, tumor diameter ≥120 mm and ≥3 PALNs involved. It was confirmed that pathologically PALN-positive patients without these risk factors can achieve long survival rates (5-year OS, 87.5%) and the indications of PAND should be carefully considered (39). According to the results of these retrospective studies (9,29,30,35-44), PALNs are more likely to be involved in patients with the following characteristics: i) Upper third tumors, particularly those with esophageal invasion; ii) serosal invasion and iii) no. 1, no. 7 or no. 9 LNs metastases. Patients with GC with high risk for PALN metastasis may benefit from curative D2 plus PAND when <3 PALNs are involved, and the total number of metastatic LNs is ≤15.

It has been reported that neoadjuvant chemotherapy (NCT) can increase the possibility of curative resection and improve the OS rates of unresectable GC (45-47). Recently, several studies investigated a multidisciplinary approach for advanced GC with clinical PALN metastasis (31,40-42,47-49). Patients were arranged to receive NCT followed by D2 plus PAND. A prospective study from Japan revealed that 4-weekly S-1 plus cisplatin followed by D2 lymphadenectomy plus PAND was

Table V. Incidence of No.13 LN involvement and prognostic impact of D2 plus No.13 LN dissection.

Author, year	Country	Study design	Main inclusion criteria	Number of patients	Metastatic rate, %	5-year OS, %		
						Patients with No. 13 LN metastasis	Patients with DI or HR for patients who underwent No. 13 LN dissection	TVI
Kakeji *et al*, 1995	Japan	Retrospective study	Lesion within the gastric antrum	95 (with DI) and 555 (without DI)	16.00 (with DI) and 5.00 (without DI)	NA	35.40 (if R0 resection, 31 cases) 0 (if non-curative, 64 cases)	NA
Shen *et al*, 2008	China	Retrospective study	Lower third GC	158	2.53 (4/158)	NA	NA	NA
Tokunaga *et al*, 2009	Japan	Retrospective	Lower study	131 with DI and third AGC 264 without DI	23.90 (with DI) and 7.00 (without DI)	17.5	50.10 (with DI)	4.19
Eom *et al*, 2013	Korea	Retrospective study	Middle or lower third AGC	149 with No. 13 LN dissection and 379 without No. 13 LN dissection	6.70 (10/149)	NA	1.32 (0.77-2.24); P=0.310; cI/II[a] 0.55 (0.33-0.92); P=0.022; cIII/IV[a]	NA
Kumagai *et al*, 2018	Japan	Retrospective study	Advanced GC with DI	60	26.70 (16/60)	25.4	NA	6.8

[a]HR (95% CI) for patients who underwent No. 13 LN dissection compared with those without No. 13 LN dissection. DI, duodenal invasion; TVI, therapeutic value index; NA, not available; AGC, advanced gastric cancer; OS, overall survival; LN, lymph node.; HR, hazard ratio; CI, confidence interval.

effective for locally advanced GC with bulky LNs metastases along the celiac artery and its branches and/or PALN metastasis (40). Fujiwara *et al* (41) demonstrated that induction chemotherapy followed by curative surgery, including extended PAND, was a promising strategy for advanced GC with PALN metastasis as a sole distant metastasis. A Chinese study (42) included 46 patients with advanced with PALN metastasis who were given 2 cycles of intravenous and intraarterial NCT. Of these patients, 35 achieved a partial response (PR) or complete response (CR) in the PALN, and the response rate was 76.1%. A total of 32 patients also underwent D2 dissection followed by 6 cycles of chemotherapy with the XELOX regimen and radiotherapy to the region of PALN metastasis. The 3-year OS rate was 40.63% for surgical patients. The authors concluded that patients with advanced GC with PALN metastasis can obtain a survival benefit from NCT, subsequent surgery and radiotherapy (42). The results of these studies suggest that metastasis to PALN does not always indicate M1 disease, and it is not possible to totally deny the survival benefit of PAND when metastasis is restricted to the no. 16a2-b1 region, which is observed via preoperative imaging examination. In the Japanese gastric cancer treatment guidelines, a multidisciplinary approach, including surgery with PAND, has been proposed when PALN metastasis is confined to the no. 16a2-b1 region, provided other non-curative factors are absent (4). Based on current literature, the prophylactic para-aortic lymphadenectomy should be avoided, and the indications for PAND are as follows: i) Patients in good condition with no serious organ dysfunction; ii) patients with primary tumor located in the upper middle third or occupying more than one third of the stomach; iii) patients without peritoneal dissemination or liver metastasis; iv) PALN metastasis is the only factor that renders patients incurable; v) LN metastasis restricted to the no. 16a2-b1 region and vi) the involved PALN is ≤3 (9,29,30,33,35,44). Patients with GC with suspected PALN metastasis who meet these criteria should be treated with NCT. Those with a good response to chemotherapy can be treated with D2 plus PAND (40-42).

4. No. 13 LN dissection for distal GC with duodenal invasion

In the third English edition of the Japanese Classification of Gastric Carcinoma, no. 13 LNs are referred to as the LNs on the posterior surface of the pancreatic head cranial to the duodenal papilla. Metastasis to no. 13 LNs is classified as M1 (19). However, the guideline also points out that D2 plus no. 13 LN dissection may be an option in a potentially curative gastrectomy for tumors invading the duodenum (18,19).

Several retrospective studies have demonstrated that the incidence of no. 13 LN involvement is significantly associated with duodenal invasion (15-17,50,51) (Table V). The metastatic rates of

no. 13 LN were merely 2.43-7.00% in patients without duodenal invasion; however, they were as high as 16.0-26.7% in patients with duodenal invasion. Duodenal invasion is considered the only indication for high possibility of no. 13 LN involvement in distal advanced GC. Previous studies (16,17,52) used the therapeutic value index (TVI) to assess the benefit of no. 13 LN dissection. The TVI of LN dissection proposed by Sasako *et al* (53) was calculated by multiplication of the frequency of metastasis to the station by the 5-year survival rate of patients with metastasis to that station. This therapeutic index has been accepted worldwide and several studies have confirmed that the therapeutic index of no. 13 LN dissection in distal GC is equivalent to that of most second-tier LNs; thus, removal of no. 13 LN has been suggested (16,17,52). For example, Tokunaga *et al* (16) revealed the TVI of no. 13 LN dissection was 4.19, equivalent to that of the second-tier LNs, such as no. 9 and no. 11p LNs. Recently, a study in Japan specifically focused on patients with GC with duodenal invasion and demonstrated that the TVI of no. 13 LN dissection reached 6.8, equal to that of no. 9 and no. 7 LNs (17). The OS rates of patients with no. 13 LN metastasis were also evaluated in these studies. Tokunaga *et al* (16) reported that the 5-year OS rate was 17.5% in lower third advanced patients with no. 13 LN metastasis. In advanced GC with duodenal invasion, the 5-year OS rate of no. 13 LN-positive patients was as high as 25.4% (17). Considering that no. 13 LN-positive GC patients with long-term survival following curative resection is not uncommon in clinical practice, it can be concluded that distal GC with no. 13 LN metastasis does not always mean M1 disease, and some patients may benefit from curative D2 plus no. 13 LN dissection (16,17,50-52). A retrospective study (51) from South Korea evaluated the effects of additional no. 13 LN dissection on D2 gastrectomy for middle or lower third advanced GC, based on OS rate. It was demonstrated that that the incidence of no. 13 LN metastasis was 6.7% and the TVI of no. 13 LN was low. However, no. 13 LN dissection was demonstrated to be an independent prognostic factor in patients with distal GC patients, with clinical stage III/IV disease (51). Based on these retrospective studies, no. 13 LN is at a high risk of metastasis in patients with distal advanced GC with duodenal invasion, and it is suggested that D2 plus no. 13 LN dissection may improve survival outcomes.

5. Conclusions

In conclusion, patients with GC with LN metastases beyond the D2 range are common in clinical practice. The therapeutic strategy for such patients remains debatable. Gastrectomy with extended D2 plus lymphadenectomy may provide survival benefits for some patients with advanced GC. The indications for D2 plus lymphadenectomy include: i) D2 plus no. 14v LN dissection in patients with distal GC with serosal invasion, particularly those who are suspected of harboring metastasis to the no. 6 LN and those with 14v involvement by preoperative CT scan; ii) D2 plus no. 13 LN dissection for advanced GC with duodenal invasion and iii) D2 plus no. 16a2/b1 LN dissection for GC with limited PALN metastases. Currently, NCT followed by gastrectomy with extended D2 plus PAND may be the optimal treatment for these patients with PALN metastases. Although there are no data available about the efficiency of NCT prior to D2 plus 14v or no. 13 LN dissection, given the late staging and poor prognosis of patients with 14v or no. 13 LN metastasis, NCT should also be considered. However, the prognostic value of extended D2 plus lymphadenectomy requires verification via prospective studies.

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Authors' contributions

JQL, DH and YXL contributed to conception and design of the present study. JQL and YXL performed the literature review, and JQL and DH drafted the initial manuscript. JQL and YXL revised the manuscript for important intellectual content. Data sharing is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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