Modified vs. standard D2 lymphadenectomy in distal subtotal gastrectomy for locally advanced gastric cancer patients under 70 years of age

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Abstract. The present study was conducted to investigate the prognosis and survival of patients with locally advanced gastric cancer who underwent distal subtotal gastrectomy with modified D2 (D1+) and D2 lymphadenectomy, under 70 years of age. The five-year overall survival rates of 390 patients were compared between those receiving D1+ and D2 lymphadenectomy. Univariate and multivariate analyses were used to identify factors that correlated with prognosis and lymph node metastasis. Tumor size (P=0.039), pT stage (P=0.011), pN stage (P<0.001), and lymphadenectomy (P=0.004) were identified as independent prognostic factors. Furthermore, tumor size (P=0.022), pT stage (P=0.012), and lymphadenectomy (P=0.028) were proven as independent factors predicting lymph node metastasis. In conclusion, cancers of larger size, higher pT stage, and with D1+ lymphadenectomy had a higher risk of lymph node metastasis. Standard D2 lymphadenectomy removes sufficient lymph nodes to improve staging accuracy and survival. Therefore, D2 lymphanectomy is recommended in distal subtotal gastrectomy for locally advanced gastric cancer, especially for cancers of larger size and higher pT stage.

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Abbreviations: UICC, International Union Against Cancer; AJCC, American Joint Committee on Cancer; JGCA, Japanese Gastric Cancer Association; NCCN, national comprehensive cancer network; R0, negative resection margins; OS, overall survival; RR, relative risk; SD, standard deviation; 95% CI, 95% confidence interval; LN, lymph node; LVI, lymphovascular invasion; D1+, modified D2 lymphadenectomy; D2, standard D2 lymphadenectomy; CEA, carcino-embryonic antigen; CT, computer tomography

Key words: prognostic significance, gastric cancer, TNM staging system, lymph nodes, lymphadenectomy, standard D2, modified D2 (D1+)

Introduction

Gastric cancer is common and remains a major public health problem around the world (1-3). The incidence of gastric cancer has declined recently; however, it remains the fifth most frequently diagnosed cancer and the second leading cause of cancer-related death globally (4). Unfortunately, gastric cancer is often diagnosed at an advanced stage in China, and this is associated with poor survival. Radical surgery remains the primary potentially curative therapy for patients with resectable gastric cancer.

It is known that the number of metastatic lymph nodes (LNs) is one of the most important prognostic factors for patients with gastric cancer. Both the International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC) and the Japanese Gastric Cancer Association (JGCA) recommend a goal of ≥15 LNs examined for optimal staging (3,5). A more extensive LN dissection helps to improve staging accuracy and survival outcomes of patients with advanced gastric cancer (6-8). However, the beneficial survival outcome of more extensive LN dissection may only be associated with stage migration or staging accuracy; its direct contribution to improved survival remains unclear (9,10). Moreover, more extensive LN dissection may increase operation-related morbidity and mortality.

The efficacy of various types of LN dissection remains controversial (11-14). In the West, D1 or a modified D2 lymphadenectomy (i.e., D1+) for gastrectomy has been identified as the gold standard treatment for localized resectable gastric cancer, and standard D2 lymphadenectomy is considered only a recommended but not a required procedure (3,6,13,15,16). In eastern Asia, especially in Japan and China, standard D2 lymphadenectomy has been the standard surgical therapy for curable gastric cancer. However, D2 lymphadenectomy requires a significant degree of surgical expertise and knowledge. In addition, D1+ lymphadenectomy helps to retrieve more LNs for optimal staging than D1 lymphadenectomy, and with lower postoperative mortality and morbidity than D2 lymphadenectomy. Thus, the efficacy of D1+ lymphadenectomy during gastrectomy, in comparison with D2 lymphadenectomy, in eastern Asia remains unclear. The incidence of gastric cancer in China is the highest in the world (17).

The average lifespans of men and women in China are 74 and 77 years, respectively. Therefore, the long-term effect of curative gastrectomy for gastric cancer may not be evaluable in such elderly patients (18). In the light of these considerations, we conducted this study to investigate the prognosis and survival outcomes, comparing D1+ and standard D2 lymphadenectomy in distal subtotal gastrectomy for locally advanced patients under 70 years of age in China.

Patients and methods

Patients. Between May 1987 and February 2014, patients with advanced gastric cancer, who underwent subtotal gastrectomy in the Department of Gastrointestinal Surgery of the Fourth Affiliated Hospital and Cancer Research Institute of China Medical University, were entered into a retrospectively maintained database. In total, 397 patients with locally advanced gastric cancer underwent distal subtotal gastrectomy with D1+ or D2 lymphadenectomy. All patients achieved a potentially curative resection for histologically proven gastric adenocarcinoma. This study was approved by the Ethics Committee of the Fourth Affiliated Hospital, China Medical University. All patient records and information were anonymized and de-identified prior to analysis. Research was conducted in accordance with the principals of the 1964 Declaration of Helsinki and its later amendments.

Included and excluded standards. The inclusion criteria were as follows: Patients under 70 years of age; histologically proven adenocarcinoma; cancers in pT2-4aN0-3M0 stage; negative resection margins (R0); potentially curable, and a curative operation was performed; complete medical records were available; with D1+ or D2 lymphadenectomy. The exclusion criteria were as follows: Preoperative adjuvant therapy; previous or concomitant other cancer; emergency surgery; and patients lost to follow-up.

Follow-up. The follow-up of the entire study population was complete until death or the cutoff date (October 2014). All the patients gave a history and underwent physical examination, and their carcino-embryonic antigen (CEA) levels were assessed every 3 to 6 months for the first postoperative year, and every 6 to 12 months thereafter. Seven patients were lost to follow-up and therefore were excluded. The rate of follow-up was 98.2%. Therefore, a total of 390 patients with locally advanced gastric cancer were included in this study.

Clinicopathologic characteristics. The clinicopathologic features that were investigated for prognostic significance included sex, age, previous history, family history of carcinoma, tumor size, blood loss, macroscopic type, histologic grade, lymphatic vessel invasion (LVI), number of LNs retrieved, depth of invasion (pT stage), number of regional LN metastases (pN stage), reconstruction type, inadequate or adequate LNs retrieved, LN metastasis, locoregional recurrence, distant recurrence, and chemotherapy. Among the 390 patients included, 114 (29.2%) patients underwent D1+ lymphadenectomy, with an average of 7.94±6.86 LNs retrieved and 2.85±4.15 LN metastases; 276 (70.8%) patients underwent D2 lymphadenectomy, with an average of 17.58±9.24 LNs retrieved and 4.43±4.91 LN metastases (Table I).

D1+ and D2 lymphadenectomy. According to the Japanese Gastric Cancer Treatment Guidelines of the Japanese Gastric Cancer Association (JGCA), D1 lymphadenectomy for distal gastrectomy includes stations Nos. 1, 3, 4sb, 4d, 5, 6, 7; D1+ lymphadenectomy includes D1 and stations Nos. 8a, 9; D2 lymphadenectomy includes D1 and stations Nos. 8a, 9, 11p, 12a (5).

Pathology. Two pathologists independently examined the histologic sections, and disagreements were resolved by discussion to determine the final diagnosis. The carcinoma lesions together with the surrounding gastric wall were fixed in formalin and cut into multiple 5 mm slices, which were parallel to the lesser curvature. As many LNs as possible were retrieved for adequate staging. According to the current guidelines for gastric cancer, examining at least 15 LNs is strongly recommended for adequate staging (6,13). The 8th Edition of the AJCC TNM staging classification for carcinoma of the stomach was applied to re-stage the cancers of all patients in this study. The pathology report generally included tumor size, pT, pN, status of margin, LVI, status of mucosa, status of LNs, number of LNs retrieved, macroscopic type, and histologic grade.

Statistical analysis. Five-year overall survival (OS) rates were calculated using Kaplan-Meier survival analysis. The number at risk was also shown in all Kaplan-Meier curves. Two-sided χ^2 tests or two-tailed t-tests were performed for comparison of clinicopathologic features between patients who underwent D1+ and D2 lymphadenectomy. The log-rank (Mantel-Cox) test was conducted in the univariate analysis to identify independently significant prognostic factors and prognostic factors correlated with LN metastasis. Multivariate analysis was applied to identify significant factors correlated with prognosis, including lymphadenectomy and all significant factors identified by univariate analysis. Univariate analysis was firstly applied to find the potential prognostic factors. Then multivariate analysis was applied to identify significant factors correlated with prognosis, including all significant factors identified by the univariate analysis and the factor lymphadenectomy. Moreover, scatter-plots and population pyramid

Table I. Clinicopathologic features of patients who underwent D1+ and D2 lymphadenectomy (*n*=390).

Variables	D1+ lymphadenectomy *n*=114 (%)	D2 lymphadenectomy *n*=276 (%)	P-value
Sex			0.276
Female	30 (26.3)	88 (31.9)	
Male	84 (73.7)	188 (68.1)	
Age (years)	59.24±11.17	58.59±11.88	0.621
Previous history			0.799
Gastritis and (or) ulcer	32 (28.1)	74 (26.8)	
None	82 (71.9)	202 (73.2)	
Family history of carcinoma			0.058
Yes	26 (22.8)	41 (14.9)	
No	88 (77.2)	235 (85.1)	
Tumor size (cm)	5.89±3.78	4.87±2.17	0.001[a]
Blood loss			0.048[a]
<200 ml	57 (50.0)	108 (39.1)	
≥200 ml	57 (50.0)	168 (60.9)	
Macroscopic type			0.014[a]
Borrmann 1	6 (5.3)	5 (1.8)	
Borrmann 2	35 (30.7)	56 (20.3)	
Borrmann 3	65 (57.0)	201 (72.8)	
Borrmann 4	8 (7.0)	14 (5.1)	
Histologic grade			<0.001[a]
Well differentiated	32 (28.1)	41 (14.9)	
Moderately differentiated	23 (20.2)	50 (18.1)	
Poorly differentiated	50 (43.8)	178 (64.5)	
Undifferentiated	9 (7.9)	7 (2.5)	
Lymphatic vessels invasion			0.881
Negative	90 (78.9)	216 (78.3)	
Positive	24 (21.1)	60 (21.7)	
Number of LNs retrieved	7.94±6.86	17.58±9.24	<0.001[a]
pT stage			0.269
pT2	15 (13.2)	55 (19.9)	
pT3	59 (51.7)	136 (49.3)	
pT4a	40 (35.1)	85 (30.8)	
pN stage			<0.001[a]
pN0	44 (38.6)	53 (19.2)	
pN1	36 (31.6)	75 (27.2)	
pN2	17 (14.9)	85 (30.8)	
pN3	17 (14.9)	63 (22.8)	
Number of metastatic LNs	2.85±4.15	4.43±4.91	0.003[a]
Reconstruction type			<0.001[a]
Billroth I	64 (56.1)	225 (81.5)	
Billroth II	50 (43.9)	51 (18.5)	
Number of LNs retrieved			<0.001[a]
Inadequate (n <15)	88 (77.2)	99 (35.9)	
Adequate (n ≥15)	26 (22.8)	177 (64.1)	
LN metastasis			<0.001[a]
No	44 (38.6)	53 (19.2)	
Yes	70 (61.4)	223 (80.8)	
Locoregional recurrence			0.072
Absent	87 (76.3)	232 (84.1)	
Present	27 (23.7)	44 (15.9)	

Table I. Continued.

Variables	D1+ lymphadenectomy *n*=114 (%)	D2 lymphadenectomy *n*=276 (%)	P-value
Distant recurrence			0.208
Absent	82 (71.9)	215 (77.9)	
Present	32 (28.1)	61 (22.1)	
Chemotherapy			0.117
No	78 (68.4)	210 (76.1)	
Yes	36 (31.6)	66 (23.9)	

[a]Two tailed t-tests of mean ± standard deviation; *n*, number of patients; LNs, lymph nodes.

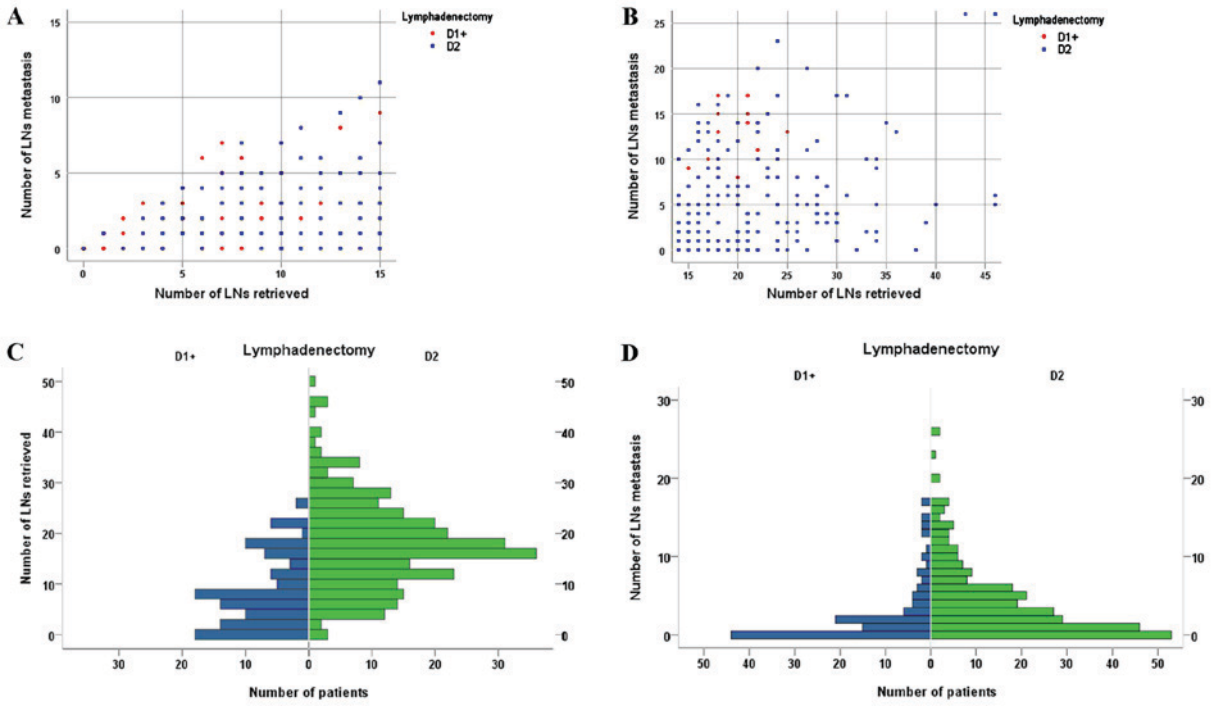

Figure 1. (A) The distribution of the number of metastatic LNs according to the number of LNs retrieved for patients with ≤15 LNs retrieved, comparing D1+ with D2 lymphadenectomy. (B) The distribution of the number of metastatic LNs according to the number of LNs retrieved for patients with >15 LNs retrieved, comparing D1+ with D2 lymphadenectomy. (C) The number of patients according to the number of LNs retrieved, comparing D1+ with D2 lymphadenectomy. (D) The number of patients according to the number of metastatic LNs, comparing D1+ with D2 lymphadenectomy.

figures were used to compare the distribution of metastatic LNs and retrieved LNs between patients who underwent D1+ and D2 lymphadenectomy. A P-value of less than 0.05 was defined as statistically significant. IBM SPSS v.22.0 statistical software was used for all statistical analyses (SPSS Inc., Chicago, IL, USA).

Results

In total, 390 patients with locally advanced gastric cancer who underwent distal subtotal gastrectomy were assessed for eligibility in this study. The age of the entire population ranged from 30 to 70 years. Of these patients, 114 patients underwent D1+ lymphadenectomy and 276 patients underwent D2 lymphadenectomy. Among the patients who underwent D1+ lymphadenectomy, 30 (26.3%) were female and 84 (73.7%) were male; among those who underwent D2 lymphadenectomy, 88 (31.9%) were female and 188 (68.1%) were male.

Clinicopathologic features. The two groups (D1+ vs. D2 lymphadenectomy) were well balanced in sex (P=0.276), age (P=0.621), previous history (P=0.799), family history of carcinoma (P=0.058), and chemotherapy (P=0.117) (Table I). The median number of LNs retrieved was significantly higher with D2 than D1+ lymphadenectomy (17.58±9.24 vs. 7.94±6.86; P<0.001). A significant difference could be found in the number of LN metastases when comparing D2 and D1+ lymphadenectomy (4.43±4.91 vs. 2.85±4.15, P=0.003). Similarly, significant differences were found with regard to tumor size (P=0.001), blood loss (P=0.048), macroscopic type (P=0.014), histologic grade (P<0.001), pN stage (P<0.001), reconstruction type (P<0.001), and LN metastasis (P<0.001) when comparing D2 and D1+ lymphadenectomy. No significant difference could

Table II. Univariate and multivariable analysis of prognostic factors for the entire study population (*n*=390).

	Univariate analysis			Multivariate analysis		
Variables	*n* (%)	5-YSR (%)	P-value	RR	95% CI	P-value
Sex			0.706			
Female	118 (30.3)	45.8				
Male	272 (69.7)	40.6				
Age (years)			0.308			
<65	245 (62.8)	40.9				
≥65	145 (37.2)	50.1				
Tumor size (cm)			0.003[a]	1.429	1.017-2.007	0.039[a]
<4	87 (22.3)	52.9				
≥4	303 (77.7)	41.7				
Macroscopic type			0.279			
Borrmann 1	11 (2.8)	39.0				
Borrmann 2	91 (23.3)	52.7				
Borrmann 3	266 (68.2)	41.7				
Borrmann 4	22 (5.7)	37.3				
Histological grade			0.400			
Well differentiated	73 (18.7)	55.9				
Moderately differentiated	73 (18.7)	34.3				
Poorly differentiated	228 (58.5)	44.8				
Undifferentiated	16 (4.1)	34.7				
Lymphatic vessels invasion			0.068			
Negative	306 (78.5)	46.0				
Positive	84 (21.5)	37.8				
pT stage			0.005[a]	1.279	1.059-1.545	0.011[a]
pT2	70 (17.9)	60.2				
pT3	195 (50.0)	47.0				
pT4a	125 (32.1)	31.6				
pN stage			0.008[a]	1.302	1.139-1.487	<0.001[a]
pN0	97 (24.9)	50.2				
pN1	111 (28.5)	49.5				
pN2	102 (26.1)	46.1				
pN3	80 (20.5)	25.0				
Reconstruction type			0.012[a]			
Billroth I	289 (74.1)	47.1				
Billroth II	101 (25.9)	36.2				
Lymphadenectomy			0.018[a]	0.653	0.490-0.870	0.004[a]
D1+	114 (29.2)	35.7				
D2	276 (70.8)	48.2				
Number of LNs retrieved			0.057			
Inadequate (n <15)	187 (47.9)	40.8				
Adequate (n ≥15)	203 (52.1)	48.9				
LN metastasis			0.170			
No	97 (24.9)	50.2				
Yes	293 (75.1)	42.1				
Locoregional recurrence			0.274			
Absent	319 (81.8)	45.1				
Present	71 (18.2)	38.4				
Distant recurrence			0.238			
Absent	297 (76.2)	45.3				

Table II. Continued.

	Univariate analysis			Multivariate analysis		
Variables	*n* (%)	5-YSR (%)	P-value	RR	95% CI	P-value
Present	93 (23.8)	40.8				
Chemotherapy			0.057			
No	288 (73.8)	50.3				
Yes	102 (26.2)	36.1				

[a]*n*, number of patients; LNs, lymph nodes; RR, relative risk; 95% CI, 95% confidence interval; 5-YSR, five-year overall survival rate (%).

be found in LVI (P=0.881), pT stage (P=0.269), locoregional recurrence (P=0.072), and distant recurrence (P=0.208) when comparing D2 and D1+ lymphadenectomy (Table I).

Fig. 1 shows the distribution of the number of LN metastases according to the number of LNs retrieved for patients with ≤15 LNs retrieved and >15 LNs retrieved, comparing D1+ with D2 lymphadenectomy. Fig. 1 also shows the number of patients distributed according to the number of LNs retrieved and the number of LN metastases, comparing D1+ with D2 lymphadenectomy.

Outcomes. As far as we are concerned, lymphadenectomy is very important for patients with gastric cancer surgery, which refers to the removal of regional LNs. And lymphadenectomy may be classified as D0, D1, D1+, or D2 depending on the extent of LNs removed at the time of gastrectomy. More extensive lymph node dissection helps to better accurate staging. Patients with accurate staging may receive ideal postoperative treatments, which may contribute to survival benefit. Therefore, identifying the best lymphadenectomy type for every patient will be of great importance.

To identify which factors were correlated with prognosis and were independent prognostic factors for the entire study population. We firstly conducted univariate analysis to find the potential prognostic factors and then multivariate analysis was applied to identify significant factors correlated with prognosis, including all significant factors identified by the univariate analysis and the factor lymphadenectomy. Firstly, univariate analysis identified tumor size (P=0.003), pT stage (P=0.005), pN stage (P=0.008), reconstruction type (P=0.012), and lymphadenectomy (P=0.018) as potential factors correlated with prognosis for the entire study population (Table II, Fig. 2). Secondly, multivariate analysis demonstrated that tumor size (RR 1.429, 95% CI 1.017-2.007, P=0.039), pT stage (RR 1.279, 95% CI 1.059-1.545, P=0.011), pN stage (RR 1.302, 95% CI 1.139-1.487, P<0.001) and lymphadenectomy (RR 0.653, 95% CI 0.490-0.870, P=0.004) were independent prognostic factors for the entire study population (Table II). Five-year overall survival rates are also shown (Table II).

To identify which factors were correlated with LN metastasis, we firstly conducted univariate analysis to find the potential factors correlated with LN metastasis and then multivariate analysis was applied to identify significant factors correlated with LN metastasis, including all significant factors identified by the univariate analysis and the factor lymphadenectomy. Firstly, univariate analysis identified tumor size (P=0.006) and pT stage (P=0.002) as potential factors correlated with LN metastasis (Table III). Secondly, multivariate analysis demonstrated that tumor size (RR 1.486, 95% CI 1.059-2.087, P=0.022), pT stage (RR 1.247, 95% CI 1.055-1.540, P=0.012), and lymphadenectomy (D1+ vs. D2, RR 0.740, 95% CI 0.565-0.969, P=0.028) were independent prognostic factors predicting LN metastasis (Table III). Survival curves comparing tumor size, pT stage, reconstruction type, and lymphadenectomy are shown in Fig. 3.

Comparisons of prognosis for patients who underwent D1+ and D2 lymphadenectomy are shown in Table IV, as stratified by pT stage, pN stage, and the number of LNs retrieved. As shown, D2 lymphadenectomy helped to achieve a higher 5-year OS rate, compared with D1+ lymphadenectomy for the entire sample of patients (35.7% for D1+, 48.2% for D2) and for patients in stage pT2 (51.9% for D1+, 63.0% for D2), pT3 (38.3% for D1+, 51.8% for D2), pT4a (25.9% for D1+, 34.3% for D2), pN0 (36.6% for D1+, 63.9% for D2), pN1 (42.7% for D1+, 52.7% for D2), pN2 (32.7% for D1+, 49.2% for D2), and pN3 (17.7% for D1+, 27.7% for D2), as well as patients with adequate (34.3% for D1+, 46.9% for D2) or inadequate LN retrieval (44.7% for D1+, 49.6% for D2). Importantly, a statistically significant difference in 5-year OS rate could be found in the entire study population (35.7% for D1+, 48.2% for D2, log-rank test, P=0.018), and especially for patients with pN0 cancer (36.6% for D1+, 63.9% for D2, log-rank test, P=0.021).

Discussion

Radical surgery is still the primary potentially curable treatment for resectable gastric cancer, and R0 resection is recommended as the gold standard. For patients with distal gastric cancer, subtotal gastrectomy is preferred for its similar outcomes and fewer complications, when compared with total gastrectomy (19). Therefore, in this study, only patients with locally advanced gastric cancer who underwent subtotal gastrectomy were included. In addition, the average lifespans of men and women in China are 74 and 77 years, respectively. Therefore, if we include patients older than age of 70 years, the long-term effect of curative gastrectomy for gastric cancer may not be evaluable; thus, we only included patients under age of 70 years in this study.

Recently, D1 or D1+ lymphadenectomy for gastrectomy has been identified as the gold standard treatment for

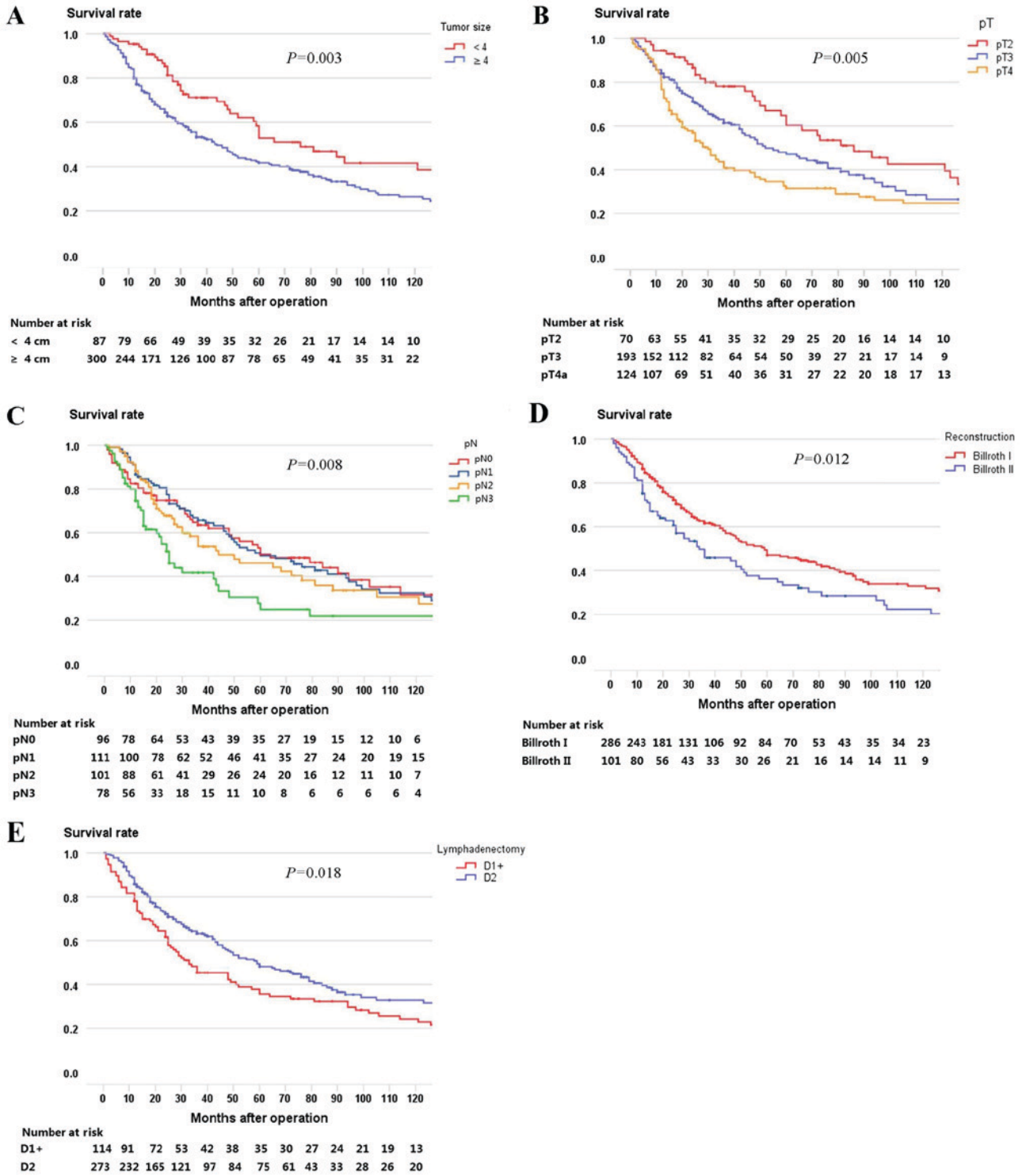

Figure 2. (A) Kaplan-Meier curve for the entire study population according to tumor size (P=0.003). (B) Kaplan-Meier curve for the entire study population according to pT stage (P=0.005). (C) Kaplan-Meier curve for the entire study population according to pN stage (P=0.008). (D) Kaplan-Meier curve for the entire study population according to reconstruction type (P=0.012). (E) Kaplan-Meier curve for the entire study population according to lymphadenectomy (P=0.018).

localized resectable gastric cancer in the West; however, D2 lymphadenectomy is considered only a recommended but not a required procedure, which may only contribute to accurate staging (3,6,13,15,16). In addition, its contribution to survival benefit is under debate and may be due to the effect of 'stage migration'. D2 lymphadenectomy has been a standard therapy for curable gastric cancer in eastern Asia; however, it was reported to be associated with significantly higher postoperative mortality and morbidity, when compared with D1 lymphadenectomy (11). As far as we are concerned, D1+ lymphadenectomy helps to retrieve more LNs for optimal staging than D1 lymphadenectomy, and D1+ lymphadenectomy may be associated with lower postoperative mortality and morbidity than D2 lymphadenectomy. Thus, the efficacy

Table III. Univariate and multivariate analysis of factors predicting LN metastasis (*n*=293).

	Univariate analysis			Multivariate analysis		
Variables	LN metastasis (+)	5-YSR (%)	P-value	RR	95% CI	P-value
Sex			0.475			
Female	93 (31.7)	37.5				
Male	200 (68.3)	44.1				
Age (years)			0.527			
<65	190 (64.8)	39.1				
≥65	103 (35.2)	47.9				
Tumor size (cm)			0.006[a]	1.486	1.059-2.087	0.022[a]
<4	65 (22.2)	50.7				
≥4	228 (77.8)	39.6				
Previous history			0.939			
Gastritis and (or) ulcer	76 (25.9)	42.5				
None	217 (74.1)	41.6				
Family history of carcinoma			0.432			
No	246 (84.0)	43.3				
Yes	47 (16.0)	35.0				
Macroscopic type			0.197			
Borrmann 1	8 (2.7)	35.0				
Borrmann 2	66 (22.5)	50.5				
Borrmann 3	201 (68.6)	39.7				
Borrmann 4	18 (6.2)	34.4				
Histological grade			0.737			
Well differentiated	50 (17.1)	54.1				
Moderately differentiated	48 (16.4)	34.6				
Poorly differentiated	188 (64.1)	41.4				
Undifferentiated	7 (2.4)	28.6				
Lymphatic vessels invasion			0.228			
Negative	221 (75.4)	43.1				
Positive	72 (24.6)	39.9				
pT stage			0.002[a]	1.274	1.055-1.540	0.012[a]
pT2	70 (23.9)	60.2				
pT3	135 (46.1)	40.8				
pT4a	88 (30.0)	28.8				
Reconstruction type			0.204			
Billroth I	219 (74.7)	43.6				
Billroth II	74 (25.3)	37.6				
Lymphadenectomy			0.085	0.740	0.565-0.969	0.028[a]
D1+	70 (23.9)	34.9				
D2	223 (76.1)	44.3				
Number of LNs retrieved			0.351			
Inadequate (n <15)	122 (41.6)	41.7				
Adequate (n ≥15)	171 (58.4)	42.4				

[a]*n*, number of patients; LN, lymph node; RR, relative risk; 95% CI, 95% confidence interval; 5-YSR, five-year overall survival rate (%).

of D1+ lymphadenectomy in eastern Asia is still under debate. D1+ lymphadenectomy in total gastrectomy has been shown to be effective for gastric carcinoma with LN metastasis, but this requires further validation (20,21). This study was conducted to investigate survival outcomes, comparing D1+ and standard D2 lymphadenectomy in distal subtotal

Table IV. Comparison of prognosis for all patients comparing D1+ and D2 lymphadenectomy (*n*=390).

Variables	D1+ lymphadenectomy		D2 lymphadenectomy		P-value
	n	5-YSR (%)	*n*	5-YSR (%)	
For the entire population	114	35.7	276	48.2	0.018[a]
pT stage					
pT2	15 (13.2)	51.9	55 (19.9)	63.0	0.820
pT3	59 (51.7)	38.3	136 (49.3)	51.8	0.074
pT4a	40 (35.1)	25.9	5 (1.8)	34.3	0.131
pN stage					
pN0	44 (38.6)	36.6	53 (19.2)	63.9	0.021[a]
pN1	36 (31.6)	42.7	75 (27.2)	52.7	0.166
pN2	17 (14.9)	32.7	85 (30.8)	49.2	0.642
pN3	17 (14.9)	17.7	63 (22.8)	27.7	0.138
Number of LNs retrieved					
Inadequate (n ≥15)	26 (22.8)	44.7	177 (64.1)	49.6	0.403
Adequate (n <15)	88 (77.2)	34.3	99 (35.9)	46.9	0.149

[a]*n*, number of patients; LNs, lymph nodes; RR, relative risk; 95% CI, 95% confidence interval; 5-YSR, five-year overall survival rate (%).

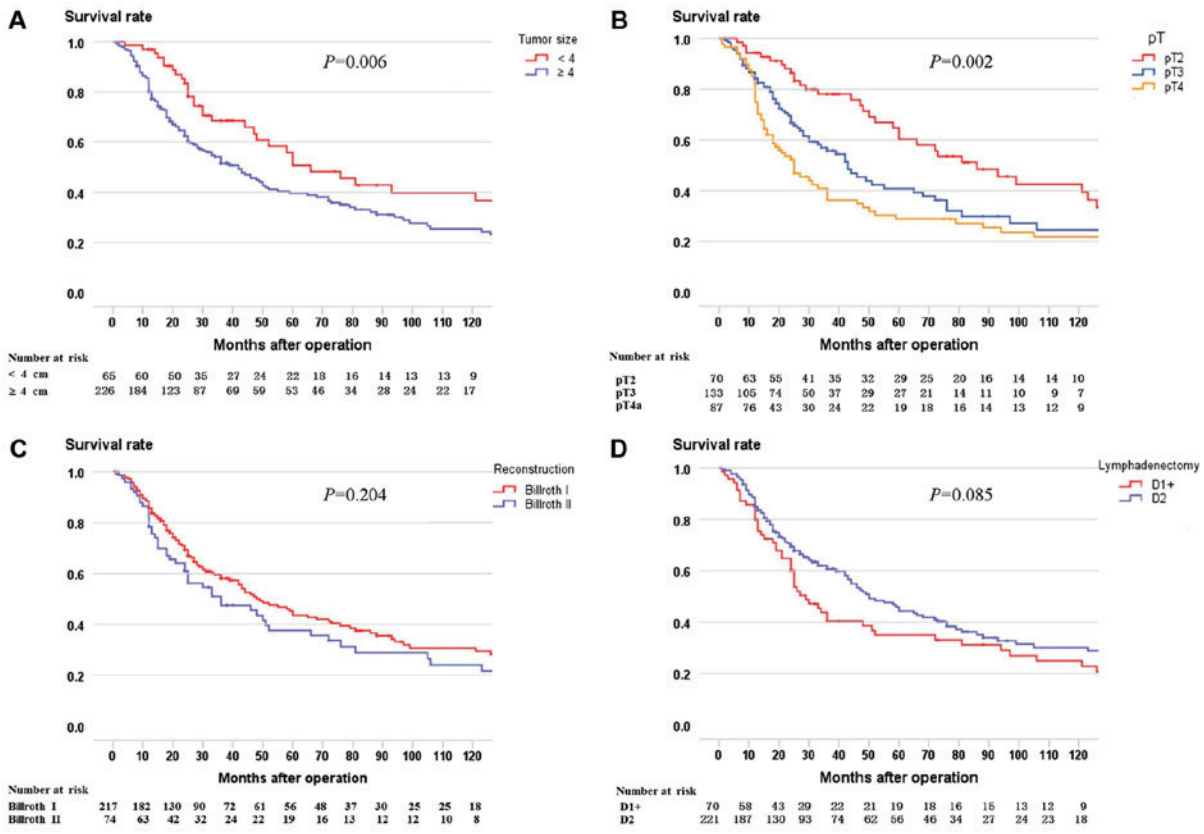

Figure 3. (A) Kaplan-Meier curve for patients with metastatic LNs according to tumor size (P=0.006). (B) Kaplan-Meier curve for patients with metastatic LNs according to pT stage (P=0.002). (C) Kaplan-Meier curve for patients with metastatic LNs according to reconstruction type (P=0.204). (D) Kaplan-Meier curve for patients with metastatic LNs according to lymphadenectomy (P=0.085).

gastrectomy, for patients with locally advanced gastric cancer.

Recurrences were classified as locoregional and distant recurrence. Locoregional recurrence was identified as any cancer recurrence in the gastric bed, anastomotic sites, and regional LNs. Distant recurrence was identified as visceral metastases, peritoneal metastases, and LN metastases beyond the regional LNs. All recurrences were diagnosed clinically

or radio-graphically, with histopathologic testing or radiography, including computer tomography (CT) scan (head, chest, abdomen, and pelvis) and bone scans; positron emission tomography CT (PET/CT) would be applied if necessary. According to the findings of these examinations, the incidence of recurrence was comparable between patients who underwent D1+ and D2 lymphadenectomy.

To investigate the independent prognostic factors for the entire study population, both univariate and multivariate analyses were performed. We finally identified that tumor size (P=0.039), pT stage (P=0.011), pN stage (P<0.001), and lymphadenectomy (P=0.004) as independent prognostic factors. Our result is similar to those of many previous studies concerning independent factors for locally advanced gastric cancer.

Both the UICC and JGCA recommend that a sufficient number and level of LNs should be retrieved. A minimum of 15 LNs retrieved is recommended for both the UICC and JGCA staging systems. Insufficient LN retrieval may lead to residual positive LNs. In our study, the median number of LNs retrieved for patients with D1+ lymphadenectomy was significantly less than that of patients with D2 lymphadenectomy (7.94±6.86 for D1+ lymphadenectomy vs. 17.58±9.24 for D2 lymphadenectomy, P<0.001). The 5-year OS rate of patients with D1+ lymphadenectomy was significantly lower than that of patients with D2 lymphadenectomy (35.7% for D1+ lymphadenectomy vs. 48.2% for D2 lymphadenectomy, P=0.018). The number of LNs retrieved for patients with D1+ lymphadenectomy is inadequate (7.94±6.86), which is much fewer than the minimum of 15 LNs as recommended by the UICC and JGCA staging system; therefore, down-staging may occur as a result of residual positive lymph nodes. More extensive lymph node dissection helps to better accurate staging. Thus, patients with accurate staging may receive ideal postoperative treatments, which may contribute to survival benefit. These results indicate that patients would benefit from D2 lymphadenectomy, which helps to retrieve adequate LNs for optimal staging and to improve survival outcomes.

Lymph node metastasis is a poor prognostic factor for gastric cancer and the number of regional LN metastases will influences survival significantly (22). In this current cohort, tumor size (P=0.022), pT stage (P=0.012), and lymphadenectomy (P=0.028) were proved as independent prognostic factors predicting LN metastasis. Accordingly, patients with larger tumor size (≥4 cm), higher pT stage, and who underwent D1+ lymphadenectomy had a higher risk of LN metastasis and shorter survival times. It is not surprising that patients with larger tumor size, higher pT stage, and D1+ lymphadenectomy would have a worse survival outcome. Larger cancers with higher pT stage are more locally advanced, and may have a higher risk of LN metastasis; therefore, D2 lymphadenectomy is strongly recommended, especially for larger cancers with higher pT stage. As many LNs should be retrieved as possible to avoid residual LNs (as least 15 LNs were recommended), especially for patients with larger tumor size and higher pT stage. However, the results of our study should be interpreted with caution and need to be clarified in further studies.

To evaluate prognosis, 5-year OS rates for patients who underwent D1+ and D2 lymphadenectomy were calculated. According to our study, D2 lymphadenectomy helped to achieve higher 5-year OS rates for the entire study population, patients in pT2-4a and pN0-3 stages, and patients with adequate or inadequate LNs retrieved. Statistically significant differences in 5-year OS rate could be found for the entire study population, and for patients in pN0 stage. Recent studies have shown that D2 lymphadenectomy is associated with fewer postoperative complications and a trend toward an improved OS rate when performed in high-volume centers with sufficient experience of the operation and postoperative management (23-25). Therefore, we believed that standard D2 lymphadenectomy helps to retrieve adequate LNs and improve staging accuracy and survival outcomes; however, it should be performed by experienced surgeons in high-volume centers.

However, limitations still exist in the present study. First, this retrospective study was based on a follow-up that varied from operation to operation and has changed during the past 27 years. During this large time frame, the effects of surgical progress, surgical techniques, surgical skill and adjuvant therapy may have changed, which may have produced bias. Second, our study lacked the investigation of safety outcomes, such as operation-related morbidity, mortality, and so on, which are also very important and need to be investigated in future studies. Third, it is necessary to note that selection bias may exist because this study was not a randomized controlled trial. Therefore, our study still needs to be validated by future prospective and randomized controlled studies.

In conclusion, cancers of larger size, higher pT stage, and with D1+ lymphadenectomy have higher risk of LN metastasis. This study demonstrated that standard D2 lymphadenectomy helps to retrieve adequate LNs to improve staging accuracy and survival. Therefore, we recommend standard D2 lymphadenectomy in distal subtotal gastrectomy for locally advanced gastric cancer, especially for cancers of larger size and higher pT stage of patients younger than age of 70 years. However, standard D2 lymphadenectomy requires surgeons to have undergone an appropriate learning curve and needs to be performed by experienced surgeons in high-volume centers.

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