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Original Article

Survival prognosis and clinicopathological features of the lymph nodes along the left gastric artery in gastric cancer: implications for D2 lymphadenectomy

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Abstract: The Japanese Gastric Cancer Treatment Guidelines (third edition) have assigned No. 7 station left gastric artery lymph nodes (LNs) to the D1 range of lymphatic dissection. We investigated the clinicopathological characteristics, survival impact, and appropriateness of ascribing No. 7 station LNs to D1 lymphadenectomy in gastric cancer. Patients (n=608) undergoing radical resection with No. 7 station LN dissection were recruited between January 1997 and June 2008. They were subdivided into four groups: N0, no LN metastasis; D1, LN without No. 7 station LN metastasis in the D1 lymphadenectomy region; No. 7, No. 7 station LN without LN metastasis in the D2 lymphadenectomy region; and D2, LN without No. 7 station LN metastasis in the D2 lymphadenectomy region. Of these, 17.2% (n=105) were positive for No. 7 LN metastasis, an important, independent prognostic factor associated with poor clinicopathological parameters, advanced tumor stage, and reduced survival. Tumor behavior in the No. 7 group was similar to that in the D2 group, but poorer than in the D1 group in terms of advanced tumor stage, with 5-year survival rates of 34.3%, 25.9% and 54.6%, respectively. Five-year survival rates in the No. 7 group were comparable to those in the D2 group (P>0.05), but significantly lower than in the D1 group (P<0.05). Logistic multivariate regression analysis established No. 3 and 9 station LN metastasis, node classification, and tumor-node-metastasis stage as independent risk factors for No. 7 station LN metastasis. Thus, No. 7 station LNs should be ascribed to D2 lymphadenectomy in gastric cancer.

Keywords: Gastric cancer, lymph nodes, left gastric artery, clinicopathological features, survival

Introduction

Gastric cancer is one of the most common causes of malignancy-related deaths in China. According to the World Health Organization (2008), estimated incidence rates of stomach cancer in China are 30.1/10,000 for males and 14.6/10,000 for females, respectively [1]. As lymphatic metastasis is one of the most important factors influencing both treatment and prognosis, the level of lymph node (LN) dissection affects the prognosis of patients with gastric cancer. Although LN dissection is the most important part of gastric cancer radical resection, it remains a controversial issue.

The 1st edition of the Japanese Gastric Cancer Treatment Guidelines (treatment guidelines in short in the remainder of this article), published in March 2001 [2], summarizing the long-term experience of the Japanese Gastric Cancer Association (JGCA), attracted a great deal of attention, and was widely implemented around the globe. The second edition [3] of the treatment guidelines was considered to be representative of the optimal treatment strategy available at that time. The latest, third edition published in 2010 [4], contains several revisions made to the academic concepts and technological innovations mentioned in the 14th edition of the Japanese General Rules for Gastric Cancer Study [5]. In this newest edition, the No. 7 station LNs along the left gastric artery have been assigned to the D1 rather than the D2 range of lymphatic dissection in gastric cancer.

Most surgeons in Asian countries have reported D2 lymphadenectomy to be associated with survival benefits in patients with gastric cancer.

Table 1. Comparison of clinicopathological parameters in gastric cancer patients with or without No. 7 LN metastasis after radical resection

	No. 7 LN (-)	No. 7 LN (+)	*P* value
Age			0.969
≤60 year	272 (54.1%)	57 (54.3%)	
>60 year	231 (45.9%)	48 (45.7%)	
Sex			0.357
Male	346 (68.8%)	77 (73.3%)	
Female	157 (31.2%)	28 (26.7%)	
Tumor location			0.043
Upper 1/3	148 (29.4%)	44 (41.9%)	
Middle 1/3	108 (21.5%)	19 (18.1%)	
Lower1/3	247 (49.1%)	42 (40.0%)	
Tumor diameter			<0.001
≤5 cm	338 (67.2%)	45 (42.9%)	
>5 cm	165 (32.8%)	60 (57.1%)	
Gross type			<0.001
Borrmann I+II	210 (41.7%)	20 (19.0%)	
Borrmann III+IV	293 (58.3%)	85 (81.0%)	
Histologic grade			0.006
G1+G2	186 (37.0%)	24 (22.9%)	
G3+G4	317 (63.0%)	81 (77.1%)	
T stage (7^{th})			<0.001
T1	104 (20.7%)	4 (3.8%)	
T2	75 (14.9%)	2 (1.9%)	
T3	118 (23.5%)	8 (7.6%)	
T4	206 (41.0%)	91 (86.7%)	
N stage (7^{th})			<0.001
N0	304 (57.0%)	0 (0.0%)	
N1	113 (21.2%)	19 (18.1%)	
N2	67 (12.6%)	55 (52.4%)	
N3	49 (9.2%)	31 (29.5%)	
TNM stage (7^{th})			<0.001
I	146 (29.0%)	0 (0.0%)	
II	112 (22.3%)	4 (3.8%)	
III	245 (48.7%)	101 (96.2%)	
CEA level			0.061
≤5 mg/ml	468 (93.0%)	92 (87.6%)	
>5 mg/ml	35 (7.0%)	13 (12.4%)	

LN: lymph node.

Table 2. Comparison of clinicopathological parameters between gastric cancer patients in No. 7 group and D1 group after radical resection

	No. 7 group	D1 group	*P* value
Age			0.984
≤60 year	35 (54.7%)	85 (54.8%)	
>60 year	29 (45.3%)	70 (45.2%)	
Sex			0.096
Male	52 (81.2%)	109 (70.3%)	
Female	12 (18.8%)	46 (29.7%)	
Tumor location			0.048
Upper 1/3	31 (48.4%)	48 (31.0%)	
Middle 1/3	8 (12.5%)	29 (18.7%)	
Lower1/3	25 (39.1%)	78 (50.3%)	
Tumor diameter			0.481
≤5 cm	33 (51.6%)	88 (56.8%)	
>5 cm	31 (48.4%)	67 (43.2%)	
Gross type			0.349
Borrmann I+II	15 (23.4%)	46 (29.7%)	
Borrmann III+IV	49 (76.6%)	109 (70.3%)	
Histologic grade			0.410
G1+G2	19 (29.7%)	55 (35.5%)	
G3+G4	45 (70.3%)	100 (64.5%)	
T stage (7^{th})			<0.001
T1	3 (4.7%)	10 (6.5%)	
T2	1 (1.6%)	25 (16.1%)	
T3	7 (10.9%)	43 (27.7%)	
T4	53 (82.8%)	77 (49.7%)	
N stage (7^{th})			<0.001
N0	0 (0.0%)	0 (0.0%)	
N1	20 (32.2%)	67 (43.2%)	
N2	21 (32.8%)	69 (44.5%)	
N3	23 (35.9%)	19 (12.3%)	
TNM stage (7^{th})			0.004
I	0 (0.0%)	0 (0.0%)	
II	3 (4.7%)	31 (20.0%)	
III	61 (95.3%)	124 (80.0%)	
CEA level			0.986
≤5 mg/ml	59 (92.2%)	143 (92.3%)	
>5 mg/ml	5 (7.8%)	12 (7.7%)	

LN: lymph node.

Gastrointestinal surgeons in Western countries, however, tend to hold the opposite belief, based on results from several clinical trials that have supported D1 lymphadenectomy as the standard of care operation strategy. In light of these contrasting views, it is important to clarify the assignment of the No. 7 station LNs to their appropriate range of lymphatic dissection. Therefore, in this study we aimed to explore the characteristics and clinical significance of the No. 7 station LNs in order to assign them to the most appropriate range of lymphatic dissection in gastric cancer.

Materials and methods

Between January 1998 and June 2006, 608 patients with primary gastric cancer underwent

Table 3. Comparison of clinicopathological parameters between gastric cancer patients in No.7 group and D2 group after radical resection

	No. 7 group	D2 group	*P* value
Age			0.490
≤60 year	35 (54.7%)	69 (60.0%)	
>60 year	29 (45.3%)	46 (40.0%)	
Sex			0.024
Male	52 (81.2%)	75 (65.2%)	
Female	12 (18.8%)	40 (34.8%)	
Tumor location			0.264
Upper 1/3	31 (48.4%)	44 (38.3%)	
Middle 1/3	8 (12.5%)	24 (20.9%)	
Lower1/3	25 (39.1%)	47 (40.9%)	
Tumor diameter			0.299
≤5 cm	33 (51.6%)	50 (43.5%)	
>5 cm	31 (48.4%)	65 (56.5%)	
Gross type			0.590
Borrmann I+II	15 (23.4%)	23 (20.0%)	
Borrmann III+IV	49 (76.6%)	92 (80.0%)	
Histologic grade			0.237
G1+G2	19 (29.7%)	25 (21.7%)	
G3+G4	45 (70.3%)	90 (78.3%)	
T stage (7^{th})			0.757
T1	3 (4.7%)	4 (3.5%)	
T2	1 (1.6%)	5 (4.3%)	
T3	7 (10.9%)	11 (9.6%)	
T4	53 (82.8%)	95 (82.6%)	
N stage (7^{th})			0.563
N0	0 (0.0%)	0 (0.0%)	
N1	20 (32.2%)	45 (39.1%)	
N2	21 (32.8%)	32 (27.8%)	
N3	23 (35.9%)	38 (33.0%)	
TNM stage (7^{th})			0.251
I	0 (0.0%)	0 (0.0%)	
II	3 (4.7%)	2 (1.7%)	
III	61 (95.3%)	113 (98.3%)	
CEA level			0.287
≤5 mg/ml	59 (92.2%)	100 (87.0%)	
>5 mg/ml	5 (7.8%)	15 (13.0%)	

LN: lymph node.

radical gastrectomy at the Division of Gastrointestinal Surgery Center of The First Affiliated Hospital of Sun Yat-sen University. Patients recruited to the study had at least 15 LNs harvested; those with distal metastasis or who had received neoadjuvant chemotherapy were excluded. Surgeons with standardized radical operation training, who had completed at least 50 cases of prior radical gastrectomy, performed the surgeries. D2 lymphadenectomy was considered the standard treatment for all gastric cancer patients in our department. None of the 608 patients received D1 lymphadenectomy. The area of D2 lymphadenectomy was defined according to the 13th edition of the JGCA, whereas, dissection of perigastric LNs defined D1 lymphadenectomy. LNs along the left gastric artery (station No. 7), common hepatic artery (station No. 8a), celiac axis (station No. 9), splenic hilar (station No. 10), splenic artery (station No. 11), and proper hepatic artery (station No. 12a) were all defined as part of the D2 range. Based on the location of the primary gastric carcinoma, modifications were applied to the scale of lymphadenectomy. Two types of gastrectomy (total and distal) were performed, with total gastrectomy used for patients with cardiac cancer.

Gastroscopic examination, tumor marker assessment, chest radiography, and computed tomography (or abdominal ultrasound examination) were performed for all patients. The last follow-up was in December 2011. Patients were monitored until death, or for a minimum of 5 years. Fewer than one in 20 patients (4.4%) were lost during follow-up.

Patients with gastric cancer were subdivided into four groups: N0, no LN metastasis; D1, LN without No. 7 station LN metastasis in the D1 lymphadenectomy region; No. 7, No. 7 station LN without LN metastasis in the D2 lymphadenectomy region; and D2, LN without No. 7 station LN metastasis in the D2 lymphadenectomy region.

Mann-Whitney U and chi-squared (χ^2) tests were used to compare individual variables between groups. All survival data shown represents cancer-specific survival, whilst deaths not attributed to gastric cancer were recorded as lost during follow-up. Survival curves were analyzed using the Kaplan-Meier method, with differences in survival compared by applying a log-rank test. Overall, cumulative survival rates were calculated from the date of diagnosis to the date of death, or the date of the last follow-up. A Cox (proportional hazards) regression model and forward logistic regression (LR) procedure were applied for univariate and multivariate analyses, respectively. Only prognostic factors with statistical significance ($P<0.05$) in

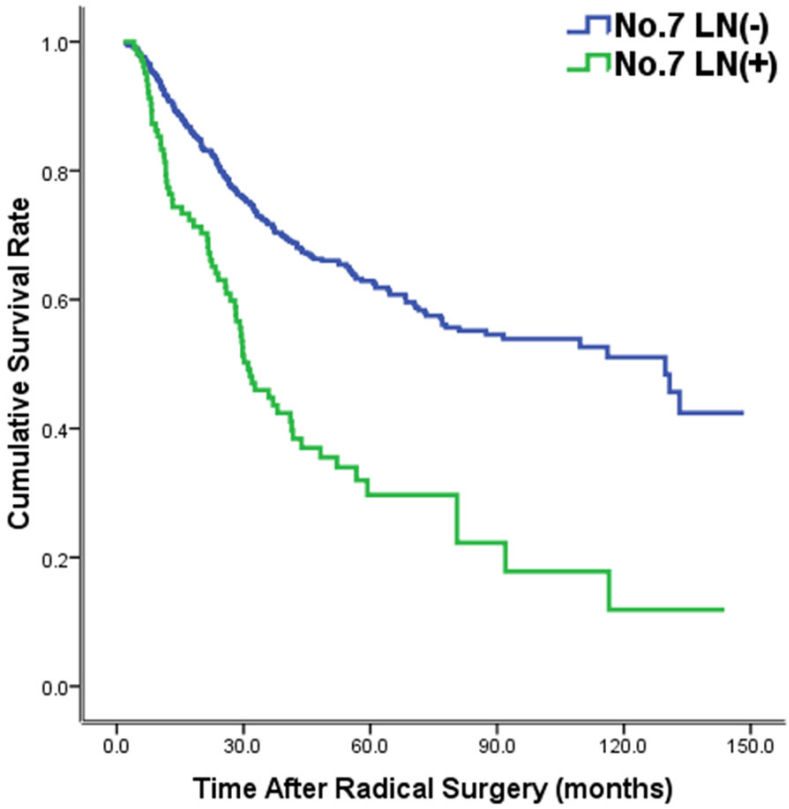

Figure 1. Kaplan-Meier survival curves for patients with gastric cancer according to the status of the No. 7 station lymph nodes (LNs). Differences in the survival rates among the three different subgroups were considered statistically significant (P<0.001).

the univariate analysis were considered for further multivariate analysis. All statistical values were computed using Statistical Package for Social Sciences (SPSS) for Windows, Version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Analysis of clinicopathological parameters pertaining to No. 7 station LN metastasis

Among the 608 patients with gastric cancer who underwent radical resection, metastatic positive No. 7 station LNs were harvested postoperatively in 105 cases (17.3%) that met the criteria for inclusion. The average number of positive No. 7 station LNs was 2.23 ± 1.63.

No statistical differences were associated with age or sex between patients with positive or negative No. 7 station LNs (P>0.05). Patients with metastatic cancer in the No. 7 station LNs, however, were reported to have significantly larger tumors, with poorer differentiation, greater vascular lymphatic invasion, and more advanced tumor (T), node (N), as well as, tumor-node-metastasis (TNM) stages (P<0.05). There was also a significant distribution of tumor location between patients with or without metastatic positive No. 7 station LNs (P<0.05; **Table 1**).

Analysis of clinicopathological parameters among the D1, No. 7, and D2 groups

There were 274 (45.1%), 155 (25.5%), 115 (18.9%) and 64 (10.5%) cases in the N0, D1, No. 7, and D2 groups. Epidemiological characteristics, including age, sex, tumor size, gross type, and histological type were similar between cases in the D1 and No. 7 groups. There was no distribution of carcinoembryonic antigen (CEA) level between these two groups. No. 7 cases had more advanced T, N, and TNM stages compared to D1 cases, and a statistically significant distribution difference in tumor location was observed between the two groups (P<0.05; **Table 2**).

The No. 7 positive and D2 positive groups, however, shared similar clinicopathological features, except for sex, that were not statistically significant (P>0.05; **Table 3**).

Prognostic analysis of metastatic No. 7 station LNs

Kaplan-Meier survival curves of patients with or without No. 7 station LN metastasis are depicted in **Figure 1**. Five-year survival rates for the 105 cases included in this study were 29.8% and 62.9%, respectively. Differences in survival between metastatic positive and metastatic negative No. 7 station LNs was statistically significant (P<0.05; **Figure 1**).

The 5-year survival rates of patients in the N0, D1, No. 7, and D2 groups were as follows: 76.6%, 54.6%, 34.3% and 25.9%, respectively (P<0.05; **Figure 2**). The survival rate of the D1

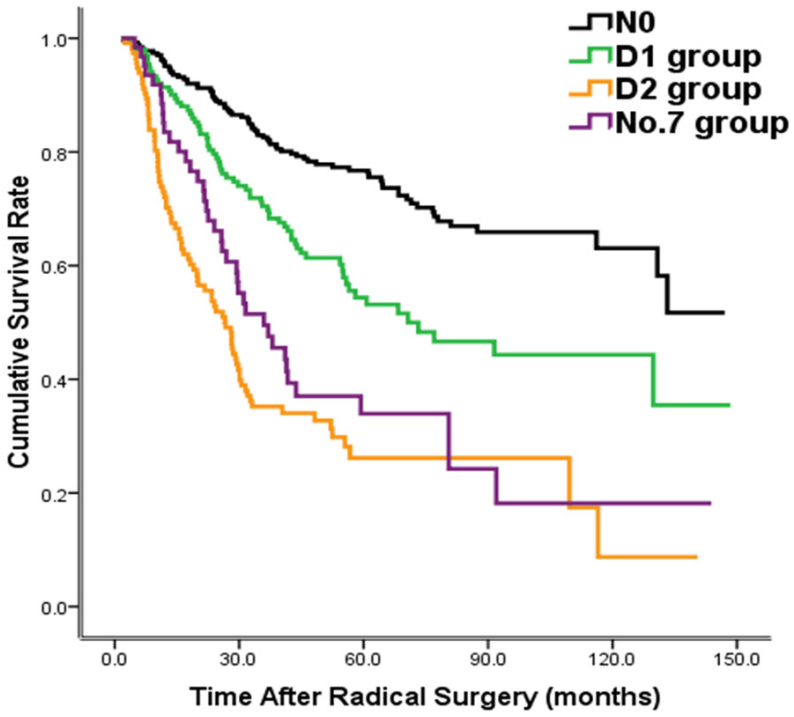

Figure 2. Comparison of the overall survival rate among four subgroups comprising N0, D1, No. 7, and D2 patients. Differences in survival rates among the groupings were considered statistically significant (P<0.001). Survival curves were constructed using the Kaplan-Meier method.

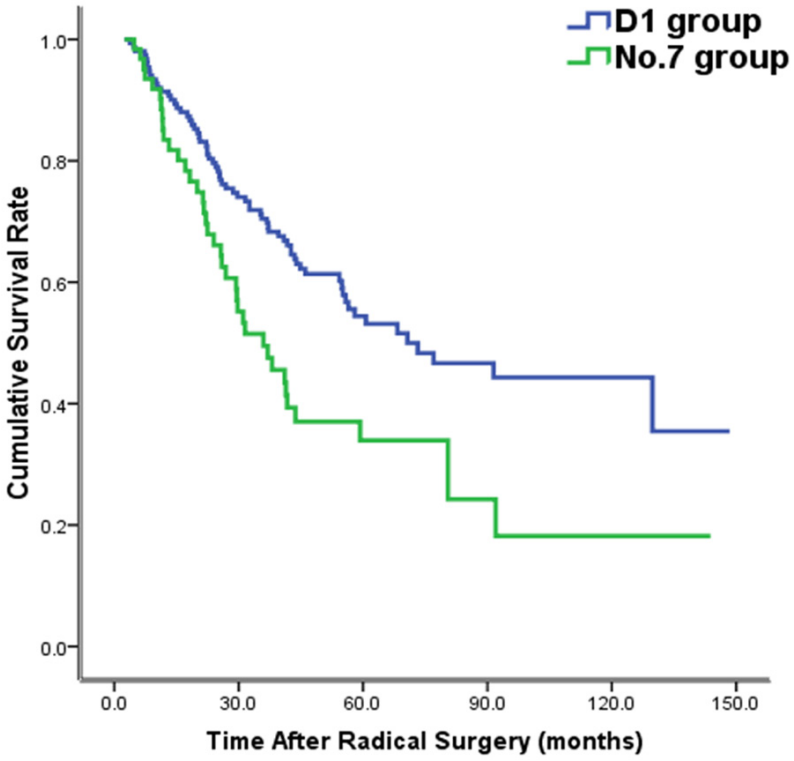

Figure 3. Comparison of overall survival rates between D1 and No. 7 patients. Differences in survival rates between the two subgroupings were considered statistically significant (P<0.001). Survival curves were constructed using the Kaplan-Meier method.

group was reported to be significantly higher than that of the No. 7 group (P<0.05; **Figure 3**). Conversely, no significant differences in survival were observed between patients in the D2 and No. 7 groups (P>0.05; **Figure 4**).

Survival regression analysis of No. 7 station LN metastasis

According to the univariate regression analysis data presented in **Table 4**, factors associated with No. 7 station LN metastasis that influenced the survival outcome for patients with gastric cancer included: tumor location and size; gross type; histological type; as well as, T, and N stages. Moreover, No. 7 station LN metastasis was an independent prognostic factor for survival based upon further multivariate regression analysis.

Risk factor analysis of No. 7 station LN metastasis

According to univariate LR analysis gross type, histological type, tumor size, T, N and TNM stages, as well as, No. 1-6, 8a, 9, and 11 station LN metastasis all correlated with No. 7 station LN metastasis (**Table 5**). Moreover, the results of multivariate LR analysis revealed that only No. 3 and No. 9 station LN metastasis, along with, N and TNM stages were risk factors for No. 7 station LN metastasis (**Table 6**).

Discussion

Surgical procedures have long been considered a primary treatment option for

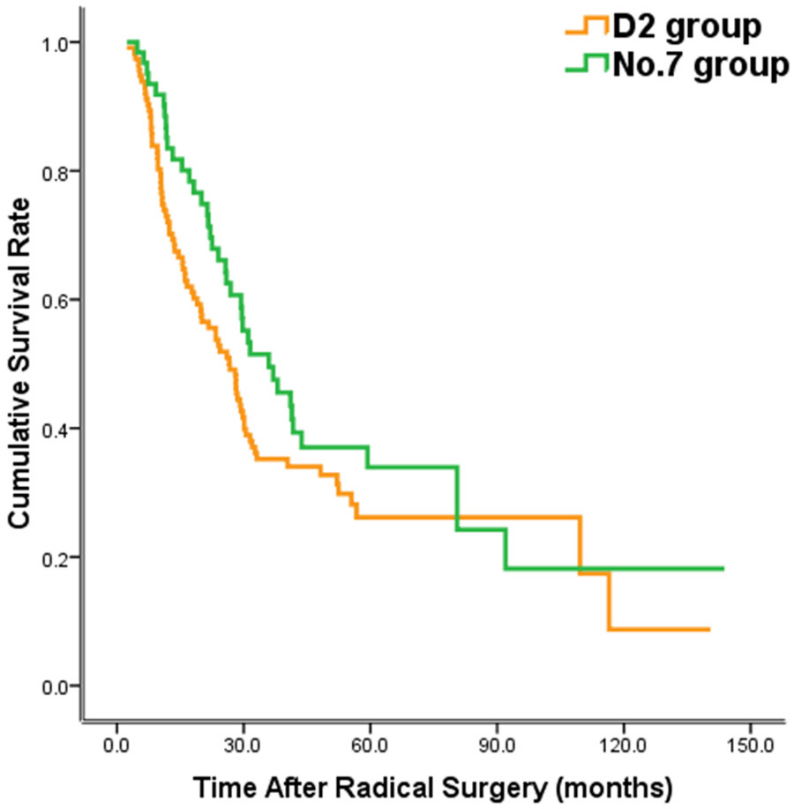

Figure 4. Comparison of overall survival rates between D2 and No. 7 patients. Differences in the survival rates between the two subgroupings were considered no statistically significant (P>0.05). Survival curves were constructed using the Kaplan-Meier method.

gastric cancer patients. The first successful case of gastrectomy and gastrojejunostomy for gastric cancer patients, performed by Billroth in 1881, was marked as a milestone in gastric carcinoma surgery. Throughout the 80 years that followed, tumor lesion resection and digestive reconstruction were also applied as standard treatments for gastric cancer. Since the 1960s, the concept of standard LN dissection has been proposed, based on studies pertaining to the lymphatic metastasis of gastric cancer. In European countries, the earliest randomized clinical trials for gastric cancer, including the Medical Research Council (MRC) trial in the United Kingdom [6], the Dutch trial in the Netherlands [7, 8], and the Italian Gastric Cancer Study Group (IGCSG) trial in Italy [9], did not show any superiority of D2 as compared to D1 lymphadenectomy. Despite these initial findings, however, D2 lymphadenectomy has emerged as a better long-term procedure with both a lower local recurrence rate and lower tumor-special mortality rate, based on data from a 15-year follow-up study on patients from the Dutch trial [10] and the Wu et al [11] study in Taiwan, China. The National Comprehensive Cancer Network (NCCN) guidelines, which are widely accepted, both in Eastern and Western countries, recommend gastrectomy with modified D2 lymphadenectomy for patients with T2 or greater, or LN involvement, whilst D1 dissection is only considered appropriate for T1N0 patients [12, 13].

The lack of a standardized definition for the extent of D2 lymphadenectomy range in Eastern and Western guidelines is problematic and needs to be resolved. The No. 7 station LNs classified as part of the D2 lymphadenectomy range in Western countries, were based upon the latest NCCN/AJCC (American Joint Committee on Cancer) guidelines for gastric cancer [14]. In the most recent (3rd) edition of the Japanese Gastric Cancer Treatment Guidelines, and the 14th edition of the Japanese General Rules for Gastric Cancer Study, however, the No. 7 station LNs were reclassified as part of the D1, rather than D2, lymphadenectomy range. In future surgeries, No. 7 station LNs will be removed in patients with cT1N0 disease, in Japan, as part of a D1 dissection based on Japanese guidelines. In Western countries, D1 dissection does not include the No. 7 station LNs and, thus, “D1 dissection” patients in Eastern and Western reports will not be comparable. Therefore, further clinical studies on the clinicopathological features and survival outcomes of No. 7 station LNs are needed.

Japanese experts in gastric cancer have posited that lymphatic metastasis of gastric cancer occurs along vessels surrounding the primary tumor lesion in a radial style [15]. They named

Table 4. The survival univariate and multivariate regression data of gastric cancer patients

	Univariate regression analysis				Multivariate regression analysis			
	χ^2 value	OR	95% CI	*P* value	χ^2 value	OR	95% CI	*P* value
Age	7.603	1.407	1.104-1.794	0.006*	8.701	1.441	1.131-1.838	0.003*
Sex	2.755	-	-	0.097				
Tumor location	10.454	0.795	0.692-0.914	0.001*				
Tumor size	71.171	2.862	2.241-3.653	<0.001*	26.683	1.932	1.505-2.481	<0.001*
Histological type	4.733	1.338	1.029-1.740	0.030*				
Gross type	41.139	2.553	1.917-3.400	<0.001*				
T stage	89.306	2.063	1.776-2.398	<0.001*	56.620	1.842	1.571-2.159	<0.001*
N stage	37.911	1.390	1.251-1.543	<0.001*				
No.7 metastasis	38.008	2.403	1.818-3.175	<0.001*	4.445	1.365	1.022-1.824	0.035*
Chemotherapy	0.438	-	-	0.508				
CEA level	7.494	1.730	1.169-2.562	0.006*				

OR: Odd ratio; CI: Confidential interval. *: With statistical significance.

Table 5. Univariate logistic regression analysis of the No.7 station LN metastasis

	χ^2 value	HR value	95% CI	*P* value
Age	0.002	-	-	0.969
Sex	0.848	-	-	0.357
Tumor location	5.228	0.757	0.597-0.961	0.022*
Histological classification	7.464	1.980	1.213-3.233	0.006*
Gross type	17.739	3.046	1.814-5.115	<0.001*
Tumor diameter	21.073	2.731	1.779-4.195	<0.001*
UICC T stage	40.105	3.227	2.246-4.638	<0.001*
UICC pN stage	75.483	2.305	1.909-2.782	<0.001*
UICC TNM stage	29.872	13.839	5.394-35.505	<0.001*
No. 1 station LN metastasis	20.755	2.965	1.858-4.732	<0.001*
No. 2 station LN metastasis	18.271	3.680	2.025-6.687	<0.001*
No. 3 station LN metastasis	65.855	6.490	4.131-10.196	<0.001*
No. 4 station LN metastasis	28.296	3.763	2.309-6.131	<0.001*
No. 5 station LN metastasis	15.537	3.016	1.742-5.221	<0.001*
No. 6 station LN metastasis	25.195	3.254	2.053-5.158	<0.001*
No. 8a station LN metastasis	26.606	4.236	2.447-7.331	<0.001*
No. 9 station LN metastasis	16.113	6.423	2.590-15.927	<0.001*
No. 10 station LN metastasis	1.599	-	-	0.206
No. 11 station LN metastasis	14.458	4.864	2.152-10.991	<0.001*
No. 12 station LN metastasis	21.899	5.849	2.791-12.255	<0.001*

LN: lymph nodes; HR: Hazard ratio; CI: Confidential interval. *: With statistical significance.

each station of LNs according to the adjacent vessels, recommending that LNs be harvested postoperatively, and that regional LNs be dissected according to neighboring vessels. Although this method was considered strenuous, anatomical information could be recorded for further study. Therefore, surgeons in our department began to perform LN dissection postoperatively in 1994.

According to the literature, a larger tumor size [16], poorer differentiation [17], greater vascular lymphatic invasion [18], as well as, more advanced T, N, and TNM stages are evidence of aggressive biological behavior that predicts an unfavorable prognosis. In the current study, metastasis to No. 7 station LNs was very unlikely in early-stage gastric cancer patients. This may be explained as the jumping mode of the lymphatic system in gastric cancer. Additional findings pertaining to the biological behavior of tumors in this current study were in good concordance with the aforementioned tumor characteristics.

Few studies have been conducted on No. 7 station LNs prior to ours. Murayama et al reported that the survival rate of patients with No. 7 station LN metastasis was similar to that of patients with N1 stage, but higher than that of patients with N2 stage regional gastric cancer (Japanese Research Society for Gastric Cancer [JRSGC]) [19]. Conversely, the results of this study have

Table 6. Multivariate logistic regression analysis of the No. 7 station LN metastasis

	χ^2 value	HR value	95% CI	*P* value
Age				
Sex				
Gross type				
Histological classification				
Tumor location				
Tumor diameter				
UICC T stage				
UICC pN stage	8.799	1.407	1.123-1.763	0.003*
UICC TNM stage	17.919	7.542	2.959-19.220	<0.001*
No. 1 station LN metastasis				
No. 2 station LN metastasis				
No. 3 station LN metastasis	9.264	2.315	1.348-3.974	0.002*
No. 4 station LN metastasis				
No. 5 station LN metastasis				
No. 6 station LN metastasis				
No. 8a station LN metastasis				
No. 9 station LN metastasis	5.522	3.174	1.211-8.320	0.019*
No. 10 station LN metastasis				
No. 11 station LN metastasis				
No. 12 station LN metastasis				

LN: lymph nodes; HR: Hazard ratio; CI: Confidential interval. *: With statistical significance.

indicated that the survival rate of patients with No. 7 station LN metastasis is similar to that of patients with the JRSGC N2 stage, but substantially poorer than that of patients with the JRSGC N1 stage. Since No. 7 station lymphadenectomy is associated with a significant benefit to survival following radical resection in our study, we propose that No. 7 station LNs should be considered part of the D2 range of lymphatic dissection as they are in the current NCCN consensus guidelines, and as they were in previous Japanese classifications.

Limitations of this current study include its retrospective design, as well as, inclusion of D2 lymphadenectomy patients only. Therefore, we could not address the likelihood of No. 7 station LN metastasis occurring in D1 lymphadenectomy patients.

In conclusion, the clinical characteristics and prognoses of patients with No. 7 station LN metastasis were similar to that in the D2 group, but significantly poorer than that of the D1 group. Thus, No. 7 station LNs should be considered part of the D2 rather than the D1 range of lymphatic dissection in gastric cancer.

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Disclosure of conflict of interest

None.

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