Should the left gastric artery lymph node be considered as the predictive lymph node for extra-gastric lymph node metastases?

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Background: To validate the prognostic impacts of the left gastric artery lymph node (No. 7 LN) metastasis and investigate whether the No. 7 LN metastasis should be considered as the predictive LN for extra-gastric LN metastases.

Methods: Between January 2003 and December 2011, a total of 1,586 patients who underwent R0 gastrectomy were retrospected. Patients with LN metastases were divided into three groups: (I) patients with only peri-gastric LN metastases (peri-gastric group); (II) patients with peri-gastric and only No. 7 LN metastases (No. 7 group); and (III) patients with other extra-gastric LN metastases (extra-gastric group). Propensity score matching (PSM) was adopted to accurately evaluate prognoses of all patients after surgery.

Results: Of 1,586 patients, 235 (14.82%) were pathologically identified to present with the No. 7 LN metastases. Patients with the No. 7 LN metastases presented the significantly lower survival rate both before and after adjustment by pTNM stage, compared to those without the No. 7 LN metastases. Patients in the No. 7 group were identified to present the significant lower survival rate than those in the peri-gastric group, and to present the similar median overall survival (OS) to those in the extra-gastric group. In addition, patients with extra-gastric LN except No. 7 LN metastases failed to show any superiority of survival outcomes, compared with those with extra-gastric LN metastases including the No. 7 LN metastasis.

Conclusions: The No. 7 LN metastases had the crucial survival implications. Nevertheless, the No. 7 LN failed to be considered as the predictive LN for the extra-gastric LN metastases in gastric cancer (GC).

Keywords: Stomach; neoplasm; lymph node (LN); prognosis; left gastric artery

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Introduction

Gastric cancer (GC) has a tendency toward lymphatic metastasis due to the abundant lymphatic vessels in the stomach wall. Lymphadenectomy has an important clinical impact, and the extent of lymphadenectomy may directly influence the patients' survival outcome after radical gastronomy. The No. 7 station (along the left gastric artery) is a specific anatomic lymph node (LN) station located between peri-gastric LNs and other extra-gastric LNs in GC patients. In theory, the No. 7 LN station is not defined as one of the peri-gastric LN stations based on its anatomical location, despite the high incidence of metastatic

incidents occurring close to the peri-gastric LN stations (1,2). According to the latest Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) guidelines for GC (3), No. 7 station LNs should be considered while evaluating the extent of D2 lymphadenectomy. However, in the latest edition of the Japanese Gastric Cancer Treatment Guidelines (the 3rd edition) and the 14th edition of the Japanese General Rules for Gastric Cancer Study, the No. 7 LN station was assigned to the range of both D1 plus and D2 lymphadenectomy (4,5). That is to say, GC patients with cT1N0M0 stage disease might undergo different lymphadenectomies in different countries. Therefore, the clinical significance of the No. 7 station for GC patients remains controversial according to the current literature (1,6-9).

In order to evaluate precisely the range of LN metastasis, the concept of sentinel LNs (SLNs) arised, which was defined as the first draining LNs that obtain lymphatic flow from a primary tumor (10). The concept of SLNs is gradually being accepted and applied to GC, and novel techniques for SLN mapping have been developed, such as methods using dyes or radioisotopes (11-13). However, identifying specific SLNs in cases of GC is challenging, due to the complexity of lymphatic drainage from the gastric area (14,15). And SLNs seldom provides much benefit to predict the extra-gastric LN station or distant metastasis. Thus, new predictive factors are needed to identify the extra-gastric LN or distant metastasis. On the other hand, multiple recent studies have reported that the No. 7 LN station was the most common extra-gastric LN station to be involved in metastasis, regardless of tumor location (16-18). Taking anatomical location and high incidence of metastatic incidents of No. 7 LN station into account, we hypothesized that the No. 7 station should be on the main lymph routine and be a predictive LN for extra-gastric LN metastases. However, few studies have evaluated whether the No. 7 LN station might be considered as the predictive marker for determining the extent of lymphadenectomy in GC patients.

In this study, we aimed to demonstrate the prognostic impact of the No. 7 LN station and to validate whether the No. 7 LN should be considered as the predictive LN for other extra-gastric LN metastases in GC patients.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-19-4786a).

Methods

Patients

Between January 2003 and December 2011, a total of 1,923 GC patients who underwent R0 gastrectomy at Tianjin Medical University Cancer Institute and Hospital. The clinicopathologic date and fellow-up records of 1,923 GC patients were retrospectively reviewed after receiving Institutional Review Board approval. Eligibility criteria included: (I) proven histologically primary gastric carcinoma; (II) curative gastrectomy with pathologically negative resection margins (R0 resection); (III) remaining alive at the initial hospital stay and the first postoperative month. The exclusion criteria were: (I) distant metastases or peritoneal dissemination; (II) skip LN metastases; (III) posterior (No. 8p, No. 12b/p, No. 13, and No. 14v) or para-aortic (No. 16a2, and No. 16b1) LNs metastases; (IV) history of gastrectomy or other malignancies; (V) history of neoadjuvant chemotherapy; and (VI) loss of follow up.

Ultimately, 1,586 patients in total were included in this study (*Figure S1*). Of these 1,586 GC patients, 897 (56.56%) presented LN metastases, and 235 (14.82%) presented the No. 7 LN metastases. According to the range of LN involved, all included patients with LN involvement were divided into three groups of cases: (I) LN metastases limited to peri-gastric area (peri-gastric group), (II) peri-gastric LN metastases with only No. 7 LN metastases (No. 7 group), and (III) peri-gastric LN metastases with other extra-gastric LN metastases (extra-gastric group).

The study was approved by Tianjin Medical University Cancer Institute and Hospital ethics committees (No. bc2019087). All patients provided written informed consent before any enrolling procedures were initiated.

Surgical management

All included patients underwent the curative gastrectomy with lymphadenectomy for GC. Curative resection was defined as the complete absence of grossly visible tumor tissue and pathologically negative resection margins. The pT stage and pN stage were according to AJCC TNM staging system (19). The nodes staging system was defined according to the 13th edition of JCGC (Japanese Gastric Cancer Association, JCGC) (20). Peri-gastric LN stations were defined as n1-tire (from No. 1 to No. 6) LN station, whereas LN stations along the left gastric artery (No. 7),

along the common hepatic artery (No. 8a), the celiac axis (No. 9), the splenic hilar(No. 10), splenic artery (No. 11) and the proper hepatic artery (No. 12a) were defined as extra-gastric LN stations. Skip LN metastases were defined as the presence of a metastatic LN in an extra-gastric area without peri-gastric LN involvement (21).

Follow-up

After curative surgery for GC, all patients were followed-up every 3 or 6 months for 2 years, and annually, thereafter, until death or deadline. The median follow-up time for the entire cohort was 33 months (range, 2 to 148 months). The deadline of follow-up in this study was December 2015. At every visit, patients underwent ultrasonography, computed tomography, chest radiography, and endoscopy. Overall survival (OS) served as the primary end-point, and was defined as the time interval between the date of surgery and the date of either death as a result of GC or the last follow-up. During the follow-up period, 1,229 patients (77.49%) died.

Propensity score matching (PSM)

To overcome possible selection bias, one-to-one matching using PSM was performed in this study (22,23). The propensity score, defined as the conditional probability of patients being treated given the covariates, could be used to balance the covariates in two groups and therefore reduce such bias (24,25). It had also been reported that potential confounding variables that could be unrelated to the exposure but related to the outcome should be included in the propensity score model, and that this would decrease the variance of an estimated exposure effect without increasing the bias (26). The propensity scores were estimated by using a non-parsimonious multiple logistic regression model. In this study, the No. 7 LN metastases were significant correlated with pN stage (spearman r=0.424, P<0.001). Therefore, the following covariates were selected for the calculation of the propensity score: gender, age, tumor location, tumor size, pT stage, Borrmann type, Lauren type, vasculolymphatic invasion, neurological invasion and adjuvant chemotherapy.

Statistical analysis

The χ^2 or Fisher's exact test used for categorical variables, and a *t* test was used for continuous variables. Factors that showed significant difference in the univariate analysis (P<0.05) were included in the multivariate analysis. Multivariate analysis was performed using a logistic regression model for the evaluation of the predictive risk factors. OS was determined using the Kaplan-Meier method, and a log-rank test was used to evaluate significance. Multivariate analyses of OS were performed to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) through the Cox regression model. In all statistical analyses, significance was defined as P<0.05 (two-sided). All statistical analyses were performed using the statistical analysis program package SPSS version 24.0 (SPSS, Chicago, IL, United States).

Results

Survival analysis of the No. 7 station LN metastases

The prognostic impact of the No. 7 station LN metastases in patients was determined. During the follow-up, 1,229 patients died and 357 patients remained alive. Kaplan-Meier analyses showed a significant difference in terms of prognosis between the No. 7 LN-negative (no metastasis) and the No. 7 LN-positive (metastases) patients (HR 1.795, 95% CI: 1.545–2.086, P<0.001, *Figure 1A*). The median survival time of No. 7 LN-negative and No. 7 LN-positive patients was 38±1.757 *vs.* 18±1.730 months. That survival difference was also significant after stratification by pTNM stage (III stage with *vs.* without the No. 7 LN metastases: HR 1.225, 95% CI: 1.043–1.439, P=0.014, *Figure 1B*). Although the small-scale samples resulted in the non-significant difference in patients with II stage (II stage with *vs.* without the No. 7 metastases, HR 1.392, 95% CI: 0.763–2.539, P=0.281), the potential tendency of survival difference might be observed in the *Figure 1B*.

PSM among peri-gastric, the No. 7 and extra-gastric group

Table 1 showed the clinical characteristics of GC patients of peri-gastric group and the No. 7 group. Before PSM, some significant differences were observed between two groups: tumor location (P<0.001), and Borrmann type (P=0.119). The differences between peri-gastric and the No. 7 groups were well balanced after PSM: tumor location (P=0.858), and Borrmann type (P=0.425). Ultimately, 138pairs patients were analyzed after PSM. As *Table 2* showed, the differences between the No. 7 and extra-gastric group were also

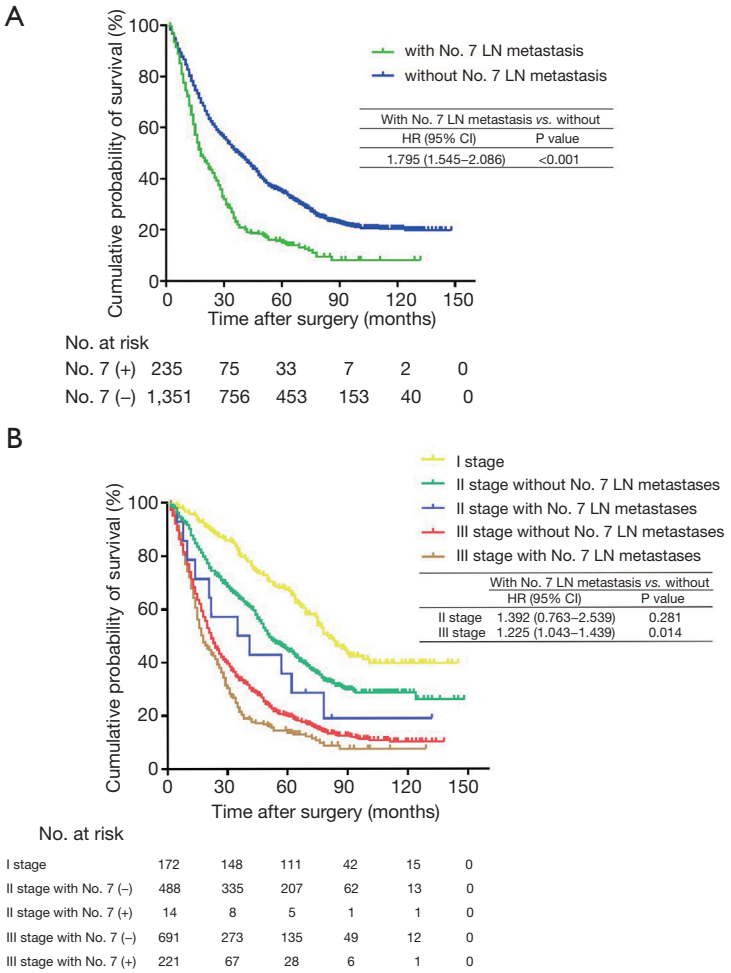

Figure 1 Kaplan-Meier curves for overall survival (A) between patients with No. 7 LN metastasis and patients without No. 7 LN metastasis; (B) after adjustment by pTNM stage. LN, lymph node. No. 7 LN, LN along the left gastric artery. No. 7 (+), with No. 7 LN metastasis; No. 7 (–), without No. 7 LN metastasis; HR, hazard ratio; CI, confidence interval.

immensely reduced after PSM: tumor location (before *vs.* after: P<0.001 *vs.* P=0.125), tumor size (before *vs.* after: P=0.104 *vs.* P=0.286), pT stage (before *vs.* after: P=0.071 *vs.* P=0.106), and Borrmann type (before *vs.* after: P<0.001 *vs.* P=0.207). Ultimately, 113 pair patients were enrolled after PSM.

Prognostic analysis before and after PSM

The prognostic analysis among peri-gastric, the No. 7 and extra-gastric groups was performed (*Figure 2A*). During the follow-up, the survival rates of these three groups were respectively: 15.4% (81/524), 13.04% (21/161) and 10.38% (22/212). And the median survival time were respectively: 24±1.381, 18±2.819, and 18±1.266 months. Before matching, Kaplan-Meier curve showed a significant difference in terms of prognosis between the No. 7 group and peri-gastric group (HR 1.227, 95% CI: 1.014–1.484, P=0.035, *Figure 2B*), but no significant difference in survival outcomes between the No. 7 group and extra-gastric group (HR 1.084, 95% CI: 0.872–1.349, P=0.467, *Figure 2C*). After PSM, the OS was also significantly poorer in the No. 7 group compared with peri-gastric group (HR 1.360, 95% CI: 1.051–1.761, P=0.020, *Figure 2D*). Similarly, the close survival rate between No. 7 group and extra-gastric group (HR 1.123, 95% CI: 0.851–1.482, P=0.411, *Figure 2E*) was observed after PSM.

Table 1 Clinical characteristics of patients of peri-gastric group and No. 7 group before and after propensity score matching

Characteristics	Entire cohort			Propensity score matching		
	Peri-gastric (n=524)	No. 7 (n=161)	P value	Peri-gastric (n=138)	No. 7 (n=138)	P value
Gender						
Male	372	119	0.472	108	99	0.211
Female	152	42		30	39	
Age (years)						
<60	217	64	0.708	47	56	0.263
≥60	307	97		91	82	
Tumor location						
Upper 1/3	156	77	<0.001**	55	59	0.858
Middle 1/3	39	8		9	8	
Lower 1/3	218	45		47	41	
More than 2/3	111	31		27	30	
Tumor size (cm)						
≤5.0	254	82	0.585	74	69	0.547
>5.0	270	79		64	69	
pT stage						
Pt1a	1	0	0.660[b]	1	0	0.962[b]
Pt1b	2	2		1	2	
Pt2	37	12		11	9	
Pt3	32	7		6	5	
Pt4a	436	137		116	119	
Pt4b	16	3		3	3	
Borrmann type						
I	30	13	0.119	12	6	0.425
II	148	58		43	49	
III	275	74		71	68	
IV	71	16		12	15	
Lauren type[c]						
Intestinal	273	79	0.683	70	66	0.858[b]
Diffuse	230	78		67	71	
Mixed	9	3		1	1	
Vasculolymphatic invasion						
No	519	157	0.273[a]	137	135	0.614[a]
Yes	5	4		1	3	
Neurological invasion[c]						
No	519	158	1.000[b]	135	136	0.481[a]
Yes	3	1		2	0	
Adjuvant chemotherapy						
No	204	60	0.704	61	55	0.464
Yes	320	101		77	83	

[a], continuity correction analysis; [b], fisher exact analysis; [c], some data missed; **, P<0.001. LN, lymph node.

Table 2 Clinical characteristics of patients of No. 7 group and extra-gastric group before and after propensity score matching

Characteristics	Entire cohort			Propensity score matching		
	No. 7 (n=161)	Extra-gastric (n=212)	P value	No. 7 (n=113)	Extra-gastric (n=113)	P value
Gender						
Male	119	156	0.943	84	86	0.758
Female	42	56		29	27	
Age (years)						
<60	64	97	0.246	54	46	0.284
≥60	97	115		59	67	
Tumor location						
Upper 1/3	77	35	<0.001**	34	33	0.125
Middle 1/3	8	28		5	12	
Lower 1/3	45	96		45	50	
More than 2/3	31	53		29	18	
Tumor size (cm)						
≤5.0	82	90	0.104	56	48	0.286
>5.0	79	122		57	65	
pT stage						
pT1a	0	1	0.071[b]	0	1	0.106[b]
pT1b	2	1		0	1	
pT2	12	7		9	6	
pT3	7	10		1	4	
pT4a	137	179		102	95	
pT4b	3	14		1	6	
Borrmann type						
I	13	8	<0.001**	4	8	0.207
II	58	44		34	22	
III	74	113		62	66	
IV	16	47		13	17	
Lauren type[c]						
Intestinal	79	90	0.250	48	43	0.170[b]
Diffuse	78	111		64	64	
Mixed	3	9		1	6	
Vasculolymphatic invasion						
No	157	210	0.449[a]	111	112	1.000[a]
Yes	4	2		2	1	
Neurological invasion[c]						
No	158	210	1.000[a]	112	111	0.481[a]
Yes	3	2		0	2	
Adjuvant chemotherapy						
No	60	78	0.925	44	37	0.332
Yes	101	134		69	76	

[a], continuity correction analysis; [b], fisher exact analysis; [c], some data missed; **, P<0.001. LN, lymph node.

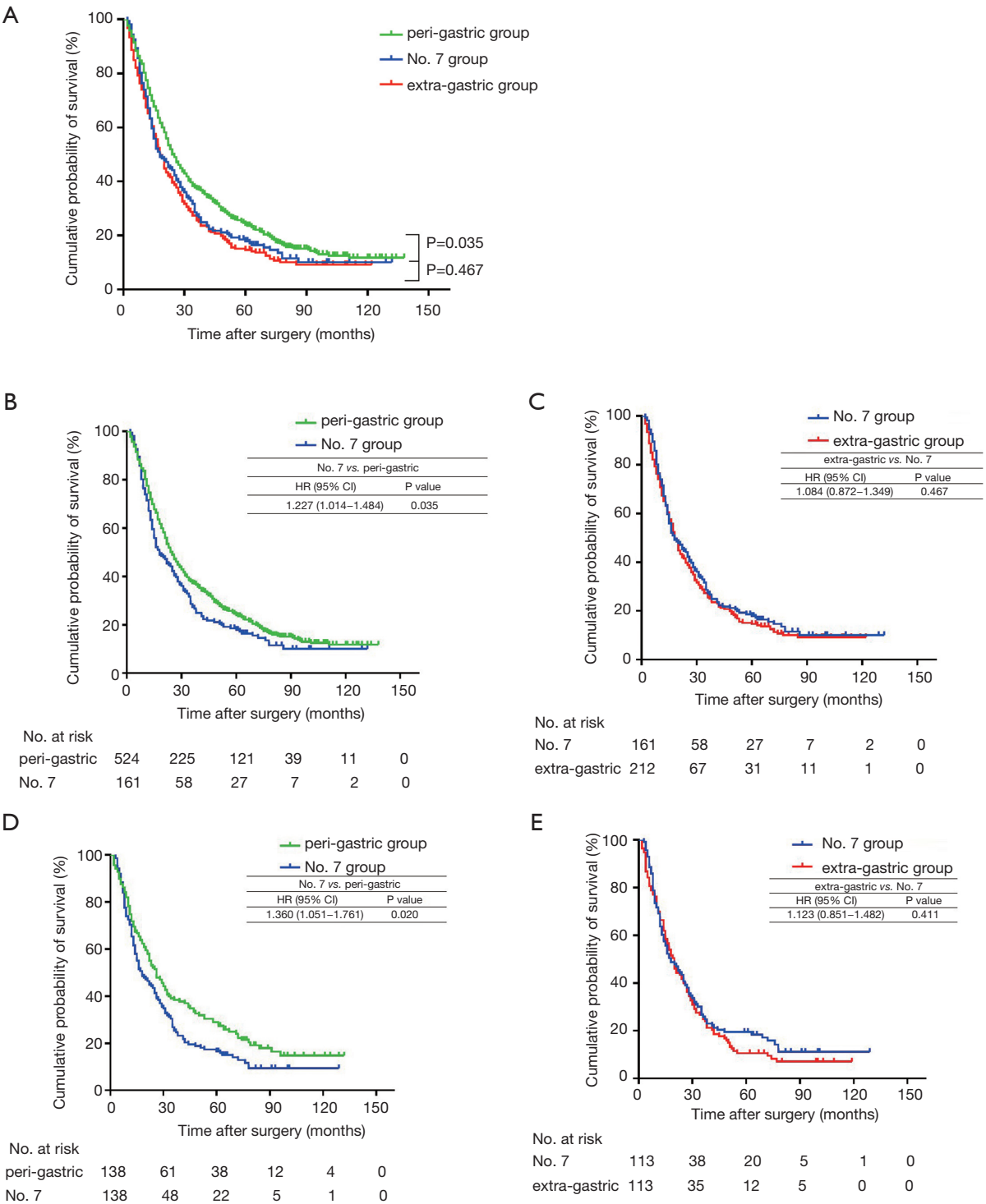

Figure 2 Kaplan-Meier curves for overall survival (A) among peri-gastric group, No. 7 group and extra-gastric group; (B) between peri-gastric group and No. 7 group before PSM; (C) between No. 7 and extra-gastric group before PSM; (D) between peri-gastric group and No. 7 group after PSM; (E) between No. 7 and extra-gastric group after PSM. PSM, propensity score matching; LN, lymph node; No. 7 LN, LN along the left gastric artery; HR, hazard ratio; CI, confidence interval.

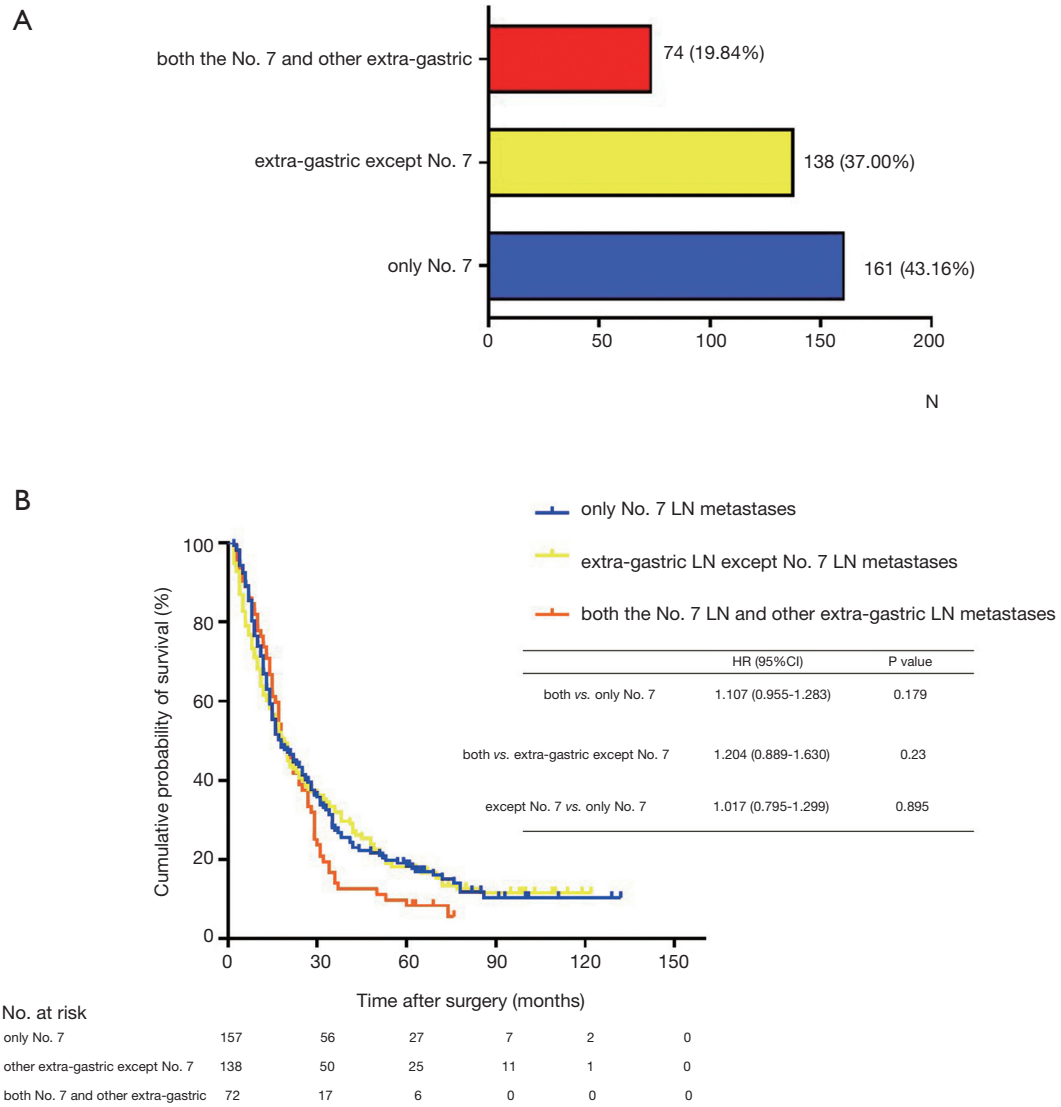

Figure 3 Survival analysis for patients with extra-gastric LN metastases. (A) Patients with extra-gastric LN metastases were subdivided into three subgroups: patients with only No. 7 LN metastases, patients with extra-gastric LN except No. 7 LN metastases, and patients with both No. 7 LN and other extra-gastric LN metastases; (B) Kaplan-Meier curves for overall survival among three subgroups. LN, lymph node; No. 7 LN, LN along the left gastric artery; HR, hazard ratio; CI, confidence interval.

Survival analysis for patients with extra-gastric LN metastases except the No. 7 LN

Patients in the extra-gastric group were further subdivided into two subgroups: 138 (37.00%) patients with extra-gastric LN except No. 7 LN metastases (No. 8a, No. 9, No. 10, No. 11, or No. 12a), and 74 (19.84%) presented with both the No. 7 LN and other extra-gastric LN metastases (*Figure 3A*). Patients without the No. 7 LN metastases failed to be elucidated to be significantly associated with the higher survival rate compared to other subgroups of patients (*Figure 3B*), which indicated the No. 7 LN should not be considered as the predictive LN for the extra-gastric LN metastases.

Correlation analysis of risk factors for the No. 7 LN metastases

Among 1,586 patients, 235 (14.82%) presented with the No. 7 LN metastases. The median number of the No. 7 LNs examined was 2 (range, 1 to 27). As shown in *Table 3*,

Table 3 Univariate and multivariate correlation analysis for the No. 7 LN metastases

Variable	Univariate analysis					Multivariate analysis		
	N	No. 7 LN metastases		χ^2 value	P	OR	95% CI	P
		No	Yes					
Gender								
Male	1,144	974	170	0.006	0.938			
Female	442	377	65					
Age								
Mean ± SD		60.68±11.48	61.68±11.19		0.217			
<60	698	597	101	0.119	0.73			
≥60	888	754	134					
Tumor location[b]								
Upper 1/3	484	394	90	10.605	0.014*			
Middle 1/3	134	112	22					
Lower 1/3	655	578	77					
More than 2/3	312	266	46					
Tumor size								
Mean ± SD		5.50±3.20	5.77±2.45		0.136			
≤5.0 cm	881	766	115	4.885	0.027*			
>5.0 cm	705	585	120					
Number of LNs examined								
Mean ± SD		14.79±10.00	19.13±10.52		<0.001**			
≤15	916	812	104	22.31	<0.001**			
16-30	536	436	100					
More than 30	134	103	31					
Pt stage								
Pt1a	21	21	0	17.776	0.003*			
Pt1b	31	29	2					
Pt2	183	167	16					
Pt3	107	98	9					
Pt4a	1,195	995	200					
Pt4b	49	41	8					
Pn stage								
Pn0	611	611	0	299.754	<0.001**	2.358	1.84–3.022	<0.001**
Pn1	288	270	18					
Pn2	355	265	90					

Table 3 (*continued*)

Table 3 (*continued*)

Variable	N	No. 7 LN metastases		χ^2 value	P	Multivariate analysis		
		No	Yes			OR	95% CI	P
Pn3a	248	156	92					
Pn3b	84	49	35					
Borrmann type								
I	114	98	16	2.725	0.436			
II	495	420	75					
III	749	631	118					
IV	228	202	26					
Lauren type[b]								
Intestinal	825	718	107	7.49	0.024*			
Diffuse	691	573	118					
Mixed	32	24	8					
Vasculolymphatic invasion								
No	1,571	1,341	230	4.113	0.096a			
Yes	15	10	5					
Neurological invasion[b]								
No	1,570	1,338	232	0.033	1.000a			
Yes	8	7	1					
No. 1 LN station metastases								
No	1,358	1,212	146	123.736	<0.001**			
Yes	228	139	89					
No. 2 LN station metastases								
No	688	580	108	20.317	<0.001**			
Yes	161	111	50					
No. 3 LN station metastases								
No	1,033	960	73	140.995	<0.001**	2.089	1.097–3.98	0.025*
Yes	553	391	162					
No. 4sa LN station metastases								
No	806	669	137	5.607	0.018*			
Yes	106	78	28					
No. 4sb LN station metastases								
No	1,379	1197	182	21.947	<0.001**			
Yes	207	154	53					

Table 3 (*continued*)

Table 3 (*continued*)

Variable	N	No. 7 LN metastases		χ^2 value	P	Univariate analysis	Multivariate analysis	
		No	Yes			OR	95% CI	P
No. 4d LN station metastases								
No	1558	1331	227	4.272	0.072a			
Yes	28	20	8					
No. 5 LN station metastases								
No	1,032	915	117	28.088	<0.001**	2.023	1.021–4.01	0.043*
Yes	147	107	40					
No. 6 LN station metastases								
No	869	792	77	62.354	<0.001**			
Yes	301	220	81					

[a], continuity correction analysis; [b], some data missed; *, P<0.05; **, P<0.001. LN, lymph node.

the univariate analysis showed that the No. 7 LN metastases were significantly related with thirteen clinicopathologic characteristics: tumor location (P=0.014), tumor size (P=0.027), number of LNs examined (P<0.001), pT stage (P=0.003), pN stage (P<0.001), Lauren type (P=0.024), No. 1 LN metastatic status (P<0.001), No. 2 LN metastatic status (P<0.001), No. 3 LN metastatic status (P<0.001), No. 4sa LN metastatic status (P=0.018), No. 4sb LN metastatic status (P<0.001), No. 5 LN metastatic status (P<0.001) and No. 6 LN metastatic status (P<0.001). However, pN stage [odds ratio (OR) 2.358, 95% confidence interval (CI): 1.840 to 3.022, P<0.001], No. 3 LN metastatic status (OR 2.089, 95% CI: 1.097 to 3.980, P=0.025), and No. 5 LN metastatic status (OR 2.023, 95% CI: 1.021 to 4.010, P=0.043) were identified as independent risk factors for the No. 7 LN metastases by using the multivariate logistic analysis.

Discussion

In this study, we found that the OS rate of patients with metastases in the No. 7 station in addition to peri-gastric stations was significantly lower than that of patients with metastases in only peri-gastric LN stations. Nevertheless, the survival rate for patients with peri-gastric and No. 7 station metastases was not significantly different from the survival rate for patients with peri-gastric and other extra-gastric LN metastases. Furthermore, among patients with both peri-gastric and extra-gastric LN metastases, there was no significant difference in survival rate between those with and without No. 7 station metastases. Metastasis in the No. 7 station did not appear to be essential for the development of other extra-gastric LN metastases, indicating that it should not be considered a predictive marker for predicting the invasion extent. Based on survival rate, the No. 7 station seems more closely aligned with the extra-gastric rather than peri-gastric stations.

LN metastases are extremely crucial for evaluating the prognostic outcomes of GC patients, and the precision of LN station staging is critical for deciding the treatment and for evaluating the OS. LN metastases in local peri-gastric area are mainly spreading via complicated lymphatic network and might fellow some orders from N1 station to N2 station LN, which gives us potential opportunities to find some mark LN stations to predict the extent of LN metastases and lymphadenectomy. Nevertheless, the skip LNs were reported as the presence of a metastatic LN in an extra-gastric area without peri-gastric LN involvement, which fortunately were relatively rare. In our entire 1923 GC patients, we observed the lower occurrence rate (65/1923, 3.38%) of skip metastases and highest frequency (32/65, 49.23%) of skip metastases of No. 7 LN station (*Figure S2*), which was consistent with most studies (27,28). As many previous studies reported (29,30), we found survival rate of patients with skip metastases was close to that of patients with only peri-gastric LN metastases (HR 0.965, 95% CI: 0.910–1.022, P=0.225), whereas was significantly superior

than that of NO. 7 group (HR 0.910, 95% CI: 0.839–0.986, P=0.021). Considering the specific clinical characteristic of skip metastases and the high frequency of skip metastases of No. 7 LN station, our study excluded this subgroup patients to obtain precise conclusion.

Currently, dissection of the No. 7 LN is deemed a part of the D1 LN dissection range (4), instead of the D2 dissection range (as per the previous definition) (20). In this study, the metastatic incident rate of the No. 7 LN station was 14.82% (235/1,586) in the entire cohort, which was the 3rd highest metastatic incident rate among all LN stations, only ranking lower than the rates of the No. 3 (544/1,586) and No. 6 (301/1,170) LN stations. Therefore, the No. 7 LN station might be considered as the main route of lymphatic drainage from the gastric area. Our previous study also reported a high metastatic incident rate in the No. 7 LN station in GC patients (2). Other researchers have similarly reported that the metastatic incident rate of the No. 7 LN station was comparable to or even higher than that of the peri-gastric LN stations (1,31). This high metastatic incident rate might be the reason that the No. 7 LN station was reclassified in the range of D1 LN dissection in the 3rd edition of the Japanese Gastric Cancer Treatment Guidelines and in the 14th edition of the Japanese General Rules for Gastric Cancer Study (4,5). However, it is still controversial whether the prognostic implication of the No. 7 LN station is similar to that of the peri-gastric LN stations or other extra-gastric LN stations and whether the No. 7 station might be considered as an SLN for extra-gastric LN metastases in GC patients.

In the entire cohort, No. 7 LN metastases showed a significant impact on OS rate (P<0.001). After stratification by pTNM stage, we observed similar results in patients with pIII stage (P=0.014). We also observed a similar non-significant trend in pII stage patients (shown in the *Figure 1B*), which might be a result of the small sample size of these GC patient subgroups. Our results were consistent with those reported by Chen (32). Nevertheless, another study reported contrasting results after adjustment for pN stage, because two-thirds of their patient population received preoperative therapy to downstage the pN stage (33). Furthermore, the small sample size might limit the credibility of the results of that study. In despite of those limitations, we also observed some tendency of poor outcome in patients with No .7 LN metastases (with No. 7 LN metastases *vs.* without No. 7 LN metastases, 3-year survival rate: N1, 75% *vs.* 79%; N2, 40% *vs.* 80%; N3, 20% *vs.* 33%). Thus, we could not deny that No. 7 LN station metastases might have a significant influence on the prognosis of GC patients.

To obtain more precise results, PSM was performed to balance the confounding factors between two groups. Both before and after PSM, the survival outcome of patients with No. 7 LN station metastases was similar to that of patients with extra-gastric LN station metastases (*Figure 2C,E*) and significantly poorer than that of patients with only peri-gastric LN station metastases (*Figure 2B,D*). Our results were consistent with those reported by Chen *et al.* (32). However, Murayama *et al.* reported that the prognostic impact of the No. 7 LN station was similar to that of peri-gastric LNs in patients with six or fewer positive LNs (6). This converse conclusion might be achieved result from enriching patients with lack of positive LNs. Based on our findings, we believe that the No. 7 LN station should be included in the range of D2 lymphadenectomy. If No. 7 LN involvement is highly suspected during the operation, D2 lymphadenectomy might be required. However, our study showed that metastases to extra-gastric LNs other than the No. 7 LN was observed in 37% (138/373) of patients, and this subgroup did not show a superior survival outcome. This result indicated that No. 7 LN metastasis was not essential for extra-gastric LN metastases and that the No. 7 LN should not be considered as the SLN for extra-gastric LN metastases. Further prospective large-scale studies are warranted to confirm this conclusion.

The results of multivariate analysis showed pN stage (P<0.001), No. 3 LN metastases (P=0.025), and No. 5 LN metastases (P=0.043) were independent risk factors for No. 7 LN metastases. Chen *et al.* also reported that metastases to the No. 7 LN station were associated with pN stage, pTNM stage, and No. 3 LN metastases, which is mostly consistent with our findings (32). In addition, previous studies have reported that No. 7 LN metastases are associated with aggressive biological behavior, such as large tumor size and vasculolymphatic invasion (34,35). These findings indicated that the No. 7 station might be a part of a crucial lymphatic route.

This study has several limitations. First, the endpoint in this study was OS; we did not investigate disease-free survival. Second, our study had a single-center retrospective design. Third, our study had a relatively small sample size. Third, the patients lost to follow up were excluded in this study, lesser than 10% of entire cohort, which might cause small amount of selection bias. Thus, there is a need for a multicenter study with a larger sample size to confirm our findings.

Conclusions

In conclusion, our study indicated the No. 7 LN station should be reclassified in the D2 dissection range due to its prognostic impact similar to that of extra-gastric LN station. If No. 7 LN involvement is highly suspected during the operation, D2 lymphadenectomy might be required. Nonetheless, our study proposed that the No. 7 LN station should not be considered a SLN as it does not appear to be essential for extra-gastric LN metastasis.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/atm-19-4786a

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-19-4786a
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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-19-4786a). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by Tianjin Medical University Cancer Institute and Hospital ethics committees (No. bc2019087). All patients provided written informed consent before any enrolling procedures were initiated.

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Supplementary

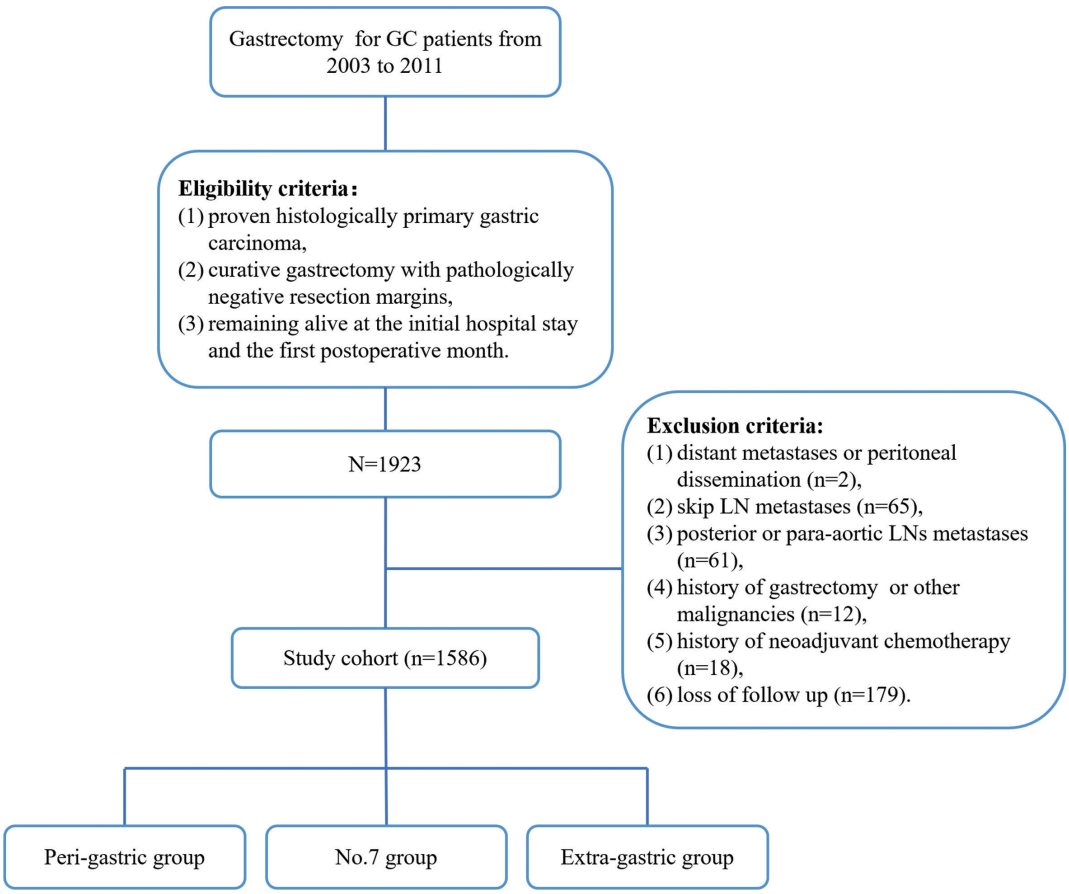
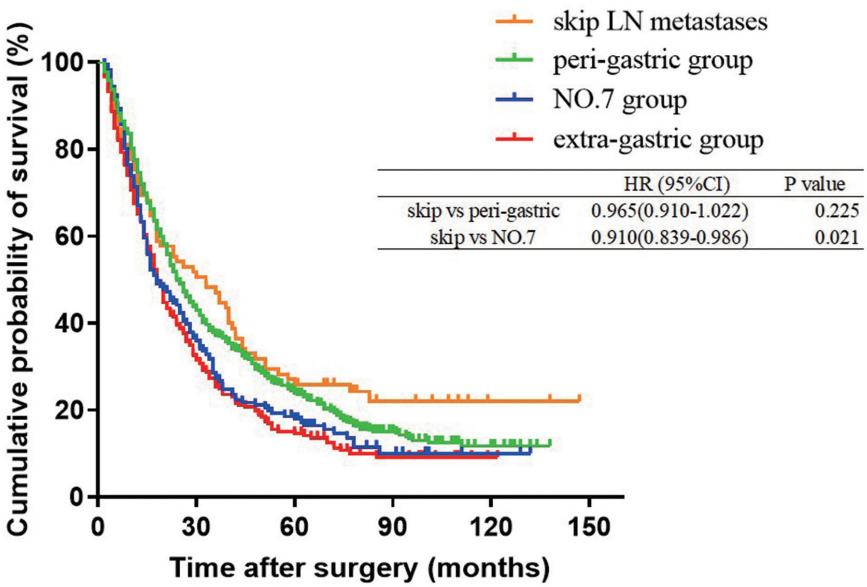


Figure S1 Patients flow diagram: eligibility criteria and exclusion criteria in this study. GC, gastric cancer; LN, lymph node.



	HR (95%CI)	P value
skip vs peri-gastric	0.965(0.910-1.022)	0.225
skip vs NO.7	0.910(0.839-0.986)	0.021

No. at risk						
skip LN	65	36	16	6	1	0
peri-gastric	524	225	121	39	11	0
NO.7	161	58	27	7	2	0
extra-gastirc	212	67	31	11	1	0

Figure S2 Survival analysis for patients with skip LN metastases. LN, lymph node; No. 7 LN, LN along the left gastric artery; HR, hazard ratio; CI, confidence interval.