



Clinicopathological features and prognostic impact of splenic hilar lymph node metastasis in proximal gastric carcinoma



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ABSTRACT

Background: Lymph nodes (LNs) at the splenic hilum (no. 10) are treated as regional LNs in proximal gastric carcinoma. However, patients with no.10 LN metastasis show a poor prognosis after curative surgery. This study aimed to investigate the prognostic impact of no.10 LN metastasis in proximal gastric carcinoma.

Methods: We retrospectively reviewed 665 proximal gastric carcinoma patients who underwent total gastrectomy and D2 LN dissection. Clinicopathological features were compared between patients with and without no.10 LN metastasis. The prognostic value of no.10 LN metastasis was examined using Cox prognostic model.

Results: There were 63 (9.5%) patients with no. 10 LN metastasis. No. 10 LN metastasis only existed in stage III/IV, and was significantly associated with greater curvature/circumferential tumor location, larger tumor size, B4 gross type, undifferentiated histology, lymphovascular invasion. The 5-year survival of no.10 LN metastasis group was 26%, which was significantly lower than those without no.10 LN metastasis (79%, $p < 0.001$). Patients with no. 10 LN metastasis also showed a significantly worse survival than those without in each tumor stage (stage III = 45% vs. 66%, $p = 0.044$, stage IV = 13% vs. 33%, $p = 0.024$). In the multivariate cox model, no.10 LN metastasis was an independent poor prognostic factor when adjusting for TNM stage and other prognostic factors.

Conclusion: The prognosis of no.10 LN metastasis is as poor as that of distant metastasis. This suggests that no. 10 LN should rather be considered as non-regional LNs in the treatment of proximal gastric carcinoma.

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Introduction

Gastric carcinoma is one of the leading causes of cancer-related death in Asian countries [1]. Despite the decreasing global incidence of the disease as a whole, the incidence of proximal gastric carcinoma, including gastric cardia cancer, has gradually increased in Western countries [2], and this trend has also been observed in Korea and Japan [3]. The standard surgery for proximal gastric carcinoma is total gastrectomy and regional lymph node (LN) dissection. LNs at the splenic hilum (no.10) are regarded as regional

LN group for proximal gastric carcinoma [4], and for complete removal of no. 10 LNs, splenectomy has been commonly performed along with total gastrectomy as a standard surgery for proximal gastric carcinoma [5]. However, several studies have demonstrated that splenectomy increased morbidity and mortality without survival benefits [6–11]. More recently, many gastric surgeons perform no. 10 LN dissection preserving the spleen (spleen-preserving method), which has been reported to reduce operative morbidity maintaining adequate oncological outcomes [12].

Metastasis to no.10 LNs is reported to occur in 10%–26% of proximal gastric carcinoma cases [13]. In many studies, patients with no.10 LN metastasis showed a poor prognosis even when they underwent a curative surgery [14–16]. In addition, the survival benefit of prophylactic no.10 LN dissection for proximal gastric carcinoma still remains controversial [17]. In a recent large randomized controlled trial in Japan, it has been found that adding splenectomy for no. 10 LN dissection did not increase patient

Abbreviations: LN, lymph node; TNM staging, tumor node metastasis staging; HR, hazard ratio; CI, confidence interval.

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survival compared with total gastrectomy alone in proximal gastric carcinoma [18]. Therefore, the prognostic implication of metastasis to no.10 LNs needs to be determined for proper treatment plan of proximal gastric carcinoma. In this study, we investigated the clinicopathological features associated with no.10 LN metastasis, and analyzed the prognostic impact of no.10 LN metastasis in proximal gastric carcinoma.

Methods

Patients

We retrospectively reviewed a prospectively constructed database of gastric carcinoma patients who underwent surgery between 2006 and 2014 at our institution (Chonnam National University, South Korea). From the database, we selected patients who underwent total gastrectomy with D2 LN dissection for middle or upper third gastric carcinoma. In our institution, we carried out D2 LN dissection for the tumors that were diagnosed as \geq cT2 (proper muscle) or cN+ in the preoperative staging as recommended in the Japanese gastric cancer treatment guideline [19]. We excluded patients who underwent less than D2 LN dissection, had other malignancies, or received preoperative chemotherapy. We identified 1131 patients who underwent total gastrectomy for gastric carcinoma in our database, and 665 patients were finally included in the study (Fig. 1). This study was performed with the approval of the institutional review board at our institution, which waived the requirement for informed consent.

Data collection and definitions

All data about demographic and clinicopathological characteristics of patients were retrieved from our prospectively constructed database. Demographic data included age, sex, body mass index,

and medical history. Clinicopathological data included preoperative work-up, operative results, tumor characteristics, and pathological stage. Postoperative outcomes included hospital stay, complications, and mortality. Classification of the tumor characteristics was recorded based on the Japanese classification of gastric carcinoma (3rd English edition) [4]. Pathological staging followed the 7th edition of the Union for International Cancer Control's (UICC) tumor node metastasis (TNM) classification. Distant metastasis (M1) refers to metastatic tumor in the liver, lung, peritoneum surface, or nonregional/distant lymph nodes. Non-curative surgery was defined as coexisting distant metastasis or incomplete resection with residual disease.

Survival data of patients were obtained from the death registry of the Korean national statistical office. Overall survival was defined as the time from surgery to death of any cause. Patient survival was ascertained until December 2016, and the median follow-up time was 52 months (range 19–108 months).

Surgical procedures and follow-up

All surgeries were performed by 4 surgeons who were specialized for gastric cancer surgery. We performed D2 LN dissection as described in the Japanese treatment guidelines, which involves removing the LNs at the splenic hilum (no.10), splenic artery (no.11), and proper hepatic artery (no.12a), in addition to the perigastric and celiac lymph nodes [19]. We usually performed no. 10 LN dissection preserving the spleen; however, splenectomy was carried out when there were direct spleen invasion or suspicious no.10 LN metastasis. Immediately after surgery, an attending surgeon dissected LNs from the resected specimen and grouped it into each lymph node station.

Postoperatively, patients with \geq stage 2 received adjuvant chemotherapy using S-1 monotherapy or capecitabine/oxaliplatin combination therapy, as appropriate. Patients who had undergone

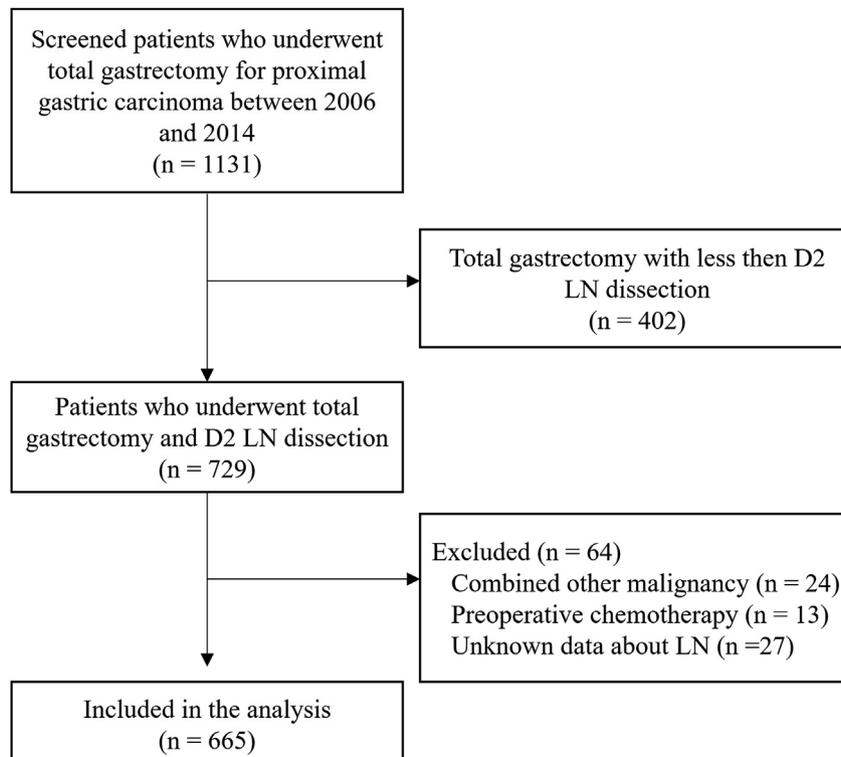


Fig. 1. Study flow chart.

non-curative surgery received palliative chemotherapy, comprising a platinum and 5-fluoropyrimidine-based regimen (with or without trastuzumab based on the presence or absence of human epidermal growth factor 2 expression). Patients were regularly followed up every 6 months until postoperative 5 years. During the follow-up, we performed abdominal computed tomography scan every 6 months, and endoscopy annually along with blood tests including tumor marker measurements (carcinoembryonic antigen and cancer antigen 19-9).

Statistical analysis

Continuous variables were compared using a *t*-test, and categorical variables were compared using the chi-square test. Survival curves were plotted using the Kaplan-Meier method and were compared with the log-rank test. A multivariate prognostic model was generated using the Cox proportional hazard model. Statistically significant variables ($p \leq 0.05$) in the univariate analysis were selected as candidates for the multivariate model. The proportionality assumption of the Cox model was ascertained using the log-log survival plot. All statistical analyses were performed using SPSS version 23.0 (IBM Corp. NY., USA). Throughout the analyses, two-sided *P* values of <0.05 were considered statistically significant.

Results

The study group consisted of 439 men and 226 women with a mean age of 60.5 years. D2 LN dissection was performed via the spleen-preserving method in 475 (71.4%) patients, and 190 (28.6%) patients underwent splenectomy or pancreaticosplenectomy with total gastrectomy. Curative and non-curative surgery were performed in 576 (86.6%) and 89 (13.5%) patients, respectively. Post-operative morbidity and mortality were 17.4% and 0.5%, respectively. In the final pathological examination, the mean number of harvested LNs was 52 ± 22 (range, 11–169); ≥ 25 LNs were obtained from 619 (93.1%) patients. There were 199 (29.9%) patients with stage I disease, 148 (22.3%) with stage II, 229 (34.4%) with stage III, and 81 (12.2%) with stage IV. Eight patients underwent incomplete resection (R2 surgery) without distant metastasis. Of patients, 450 (67.7%) received adjuvant chemotherapy.

Clinicopathological features associated with no.10 LN metastasis

There were 63 (9.5%) patients who had no.10 LN metastasis. Table 1 shows the clinicopathological characteristics of patients with no.10 LN metastasis. No.10 LN metastasis was found to only exist in highly advanced pT and pN stages. All patients with no.10 LN metastasis had \geq pT3 or pN2 disease, while there was no no.10

Table 1
Clinicopathological characteristics of patients with no.10 LN metastasis.

	Total (n = 665)	No.10 LN metastasis		P
		Present (n = 63)	Absent (n = 602)	
Age (years)		58.1 \pm 13.1	60.8 \pm 12.1	0.094
Sex				0.316
Male	439	38 (8.7)	401 (91.3)	
Female	226	25 (11.1)	201 (88.9)	
Tumor location				<0.001
Anterior	62	5 (8.1)	57 (91.9)	
Posterior	176	13 (7.4)	163 (92.6)	
Lesser curvature	282	10 (3.5)	272 (96.5)	
Greater curvature	36	7 (19.4)	29 (80.6)	
Circumferential	109	28 (25.7)	81 (74.3)	
Gross type				<0.001
Superficial	155	0	155 (100)	
Borrmann 1	39	1 (2.6)	38 (97.4)	
Borrmann 2	101	8 (7.9)	93 (92.1)	
Borrmann 3	274	28 (10.2)	246 (89.8)	
Borrmann 4	96	26 (27.1)	70 (72.9)	
Tumor size (mm)		95 \pm 41	55 \pm 35	<0.001
Lymphatic/vascular invasion	321	56 (17.4)	265 (82.6)	<0.001
Histologic differentiation				0.002
Differentiated	222	10 (4.5)	212 (95.5)	
Undifferentiated	443	53 (12.0)	390 (88.0)	
Tumor invasion				<0.001
pT1	165	0	165 (100)	
pT2	65	0	65 (100)	
pT3	161	9 (5.6)	152 (94.4)	
pT4a	236	40 (16.9)	196 (83.1)	
pT4b	38	14 (36.8)	24 (63.2)	
Nodal metastasis				<0.001
pN0	288	0	288 (100)	
pN1	92	0	92 (100)	
pN2	93	6 (6.5)	87 (93.5)	
pN3	192	57 (29.7)	135 (70.3)	
Distant metastasis	81	31 (38.3)	50 (61.7)	<0.001
Tumor stage				<0.001
Stage I	199	0	199 (100)	
Stage II	148	0	148 (100)	
Stage III	229	31 (13.5)	198 (86.5)	
Stage IV	81	31 (38.3)	50 (61.7)	

The numbers in parentheses are percentages.

LN metastasis in patients with \leq pT2 or \leq pN1 disease. Consequently, all patients with no.10 LN metastasis were classified as stage III or IV. Of patients with no.10 LN metastasis, 31 (49.2%) patients had concomitant distant metastasis, including paraaortic lymph nodes (n = 16), peritoneum (n = 13), and liver (n = 2).

In addition to the advanced pT and pN stage, no.10 LN metastasis was also significantly more common in the tumors of the greater curvature or circumferential location, Borrmann 4 gross type, larger tumor size, undifferentiated histology, and lymphovascular invasion (Table 1).

Survival of patients with no.10 LN metastasis

The 5-year overall survival of all patients with no.10 LN metastasis was 26%, which was significantly worse than that of patients without no. LN 10 metastasis (Fig. 2a). When the survivals were compared in the same stage, patients with no.10 LN metastasis showed significantly worse survival than those without no. 10 LN metastasis in stage III (5-year, 45% vs. 66%, $p = 0.044$, Fig. 2b) and stage IV (5-year, 13% vs. 33%, $p = 0.024$, Fig. 2c).

Fig. 3 compares survival of no.10 LN metastasis group (n = 63) with patients with distant metastasis in no.10 LN negative group (n = 50). The 5-year survival of no.10 LN metastasis group did not significantly differ from that of patients with distant metastasis (26% vs. 31%, $p = 0.559$, Fig. 3a). To exclude the effect of coexisting distant metastasis on survival of no.10 LN metastasis group, the survival of no.10 LN metastasis group without distant metastasis (n = 32) was compared with distant metastasis group. The 5-year survival of the no.10 LN metastasis group without distant metastasis also did not significantly differ from that of the distant metastasis group (43% vs. 31%, $p = 0.249$, Fig. 3b).

Prognostic value of no.10 LN metastasis in the multivariate prognostic model

To investigate the prognostic impact of no.10 LN metastasis, we performed analysis of prognostic factors in 576 patients excluding patients with non-curative surgery or distant metastasis. In the univariate analysis, tumor location (whole stomach), tumor size, lymphovascular invasion, splenectomy, adjuvant therapy, tumor

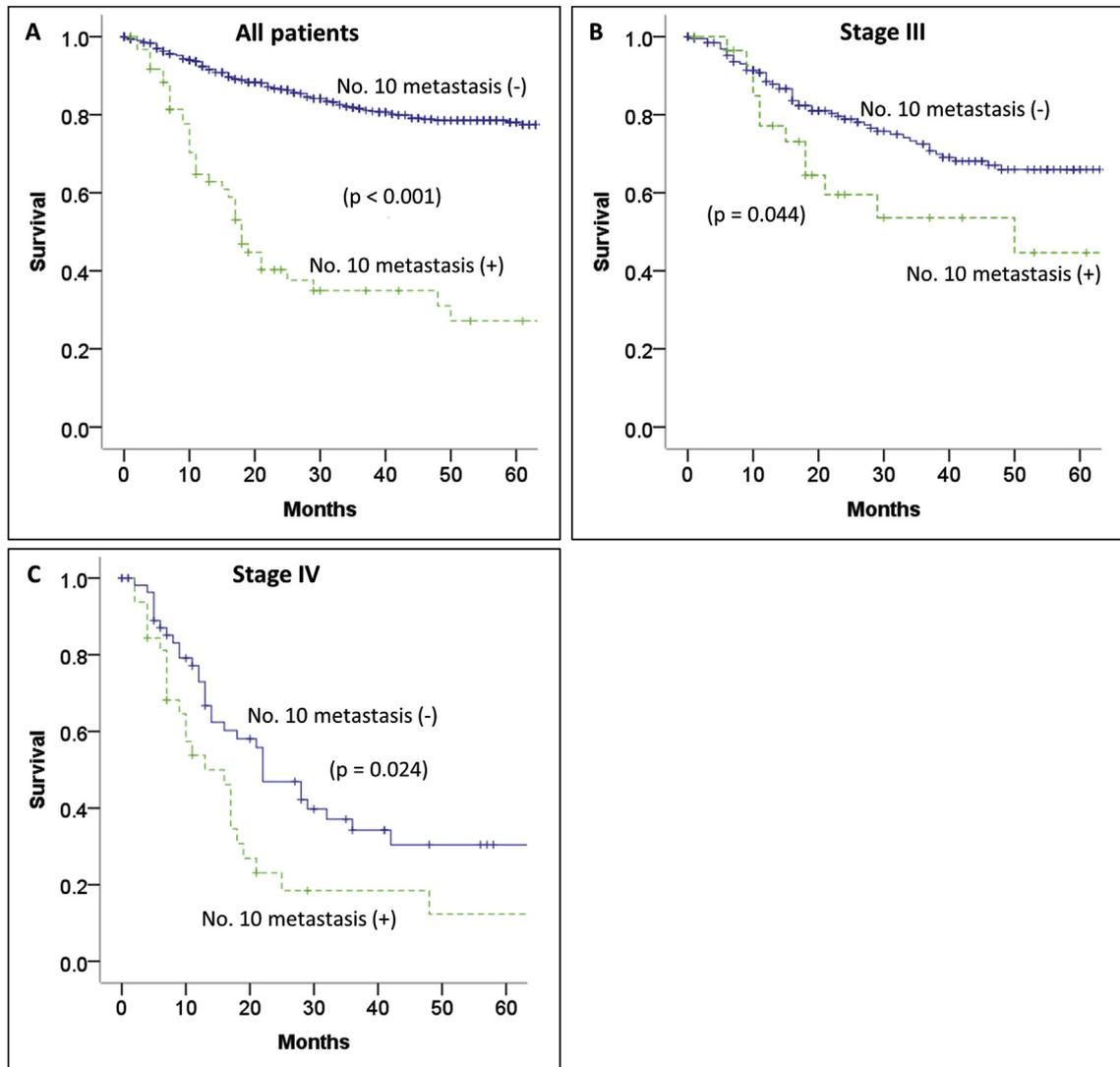


Fig. 2. Survival of patients with no.10 LN metastasis. Patients with no.10 LN metastasis showed a significantly worse survival than those without metastasis across all patients (a) and among those with the same disease stage (b and c).

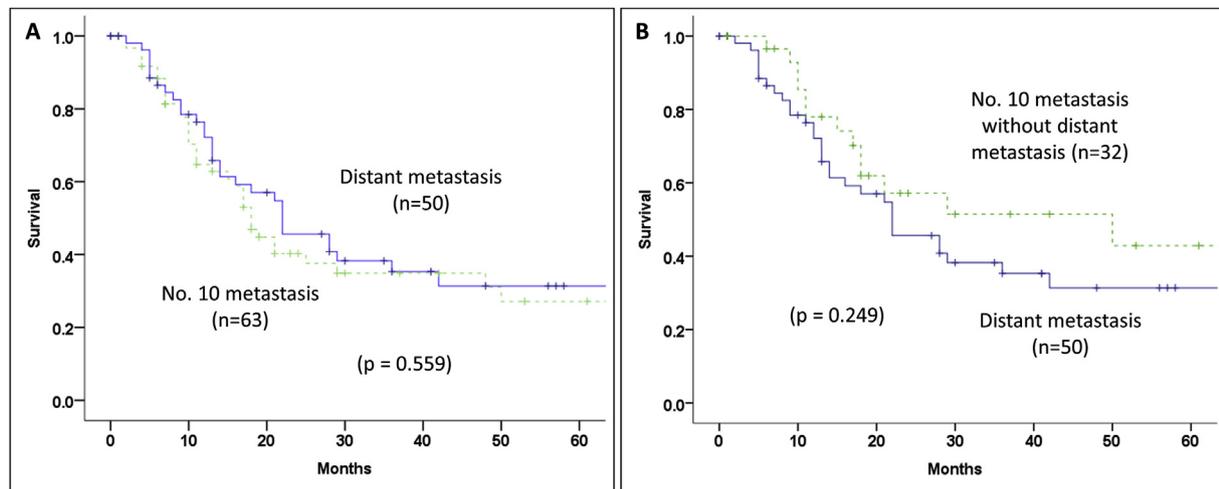


Fig. 3. Survival of patients with no.10 LN metastasis compared with those with distant metastasis. (a) Survival of the no.10 LN metastasis group versus the distant metastasis group. (b) Survival of no.10 metastasis without coexisting distant metastasis versus the distant metastasis group.

invasion (pT), and nodal metastasis (pN) were significantly associated with survival. Multivariate analysis with adjustment for these factors showed that no. 10 LN metastasis remained an independent poor prognostic factor (hazard ratio = 1.90, 95% confidence interval = 1.02–3.57) when adjusting tumor stage and other prognostic factors (Table 2).

Therapeutic index of extra-perigastric lymph nodes

Table 3 shows therapeutic indexes of extra-perigastric lymph nodes. Therapeutic index of lymph nodes was calculated by multiplying the frequency of lymph node metastasis by 5-year survival rate in each lymph node station. The therapeutic index of no.10 LN was the second lowest (2.5), followed by no.12a LN. When therapeutic index was analyzed according to involvement of the greater curvature, therapeutic index of no.10 LN was higher in tumors involving the greater curvature than those without (4.4 vs. 2.0).

Discussion

Standard surgery for proximal gastric carcinoma is total gastrectomy and adequate regional LN dissection. Although no.10 LNs are treated as the regional LNs for proximal gastric cancer, patients with no.10 LN metastasis often show poor prognosis even after curative surgery. To the best of our knowledge, this is the largest study that investigated the prognostic impact of no.10 LN metastasis in proximal gastric carcinoma. We have found that no. 10 LN metastasis only existed in very advanced tumor stage (stage III or IV), and the 5-year survival was only 26%, which was as poor as that of distant metastasis group. Poor prognostic impact of no. 10 LN metastasis was also verified in the multivariate prognostic model adjusting TNM stage and other prognostic factors. Therefore, our results suggest that no. 10 LNs should rather be considered as non-regional LNs in the treatment of proximal gastric carcinoma. No. 10 LN dissection should be indicated for selected cases, such as \geq pT3N2 and greater/circumferential location, for diagnostic

Table 2
Univariate and multivariate analysis of prognostic factors.

Variables	Univariate			Multivariate			
	HR	95% CI	P	Adjusted HR	95% CI	P	P
No.10 LN metastasis	3.97	2.016–7.32	<0.001	1.90	1.02–3.57	0.035	
Age (years)	1.01	0.99–1.03	0.294				
Sex (male)	1.44	0.91–2.30	0.124				
Tumor location (whole stomach)	3.85	2.09–7.10	<0.001	1.44	0.73–2.85	0.291	
Tumor size (cm)	1.15	1.09–1.21	<0.001	1.03	0.96–1.10	0.437	
Undifferentiated tumor	1.53	0.97–2.41	0.065				
Lymphovascular invasion	2.95	1.92–4.53	<0.001	1.41	0.87–2.30	0.169	
No. harvested lymph nodes	0.99	0.98–1.01	0.267				
Splenectomy	2.29	1.52–3.45	<0.001	1.299	0.892–1.892	0.172	
Tumor invasion (vs. pT1)			<0.001			0.014	
pT2	1.61	0.58–4.43		1.34	0.48–3.76		
pT3	2.80	1.34–5.87		1.55	0.68–3.54		
pT4	6.35	3.22–12.52		2.89	1.30–6.44		
Nodal metastasis (vs. pN0)			<0.001			0.001	
pN1	2.15	1.08–4.27		1.62	0.78–3.35		
pN2	3.22	1.71–6.06		2.16	1.07–4.34		
pN3	6.90	4.08–11.65		3.71	1.94–7.12		
Adjuvant chemotherapy	4.34	2.37–7.97	<0.001	1.31	0.31–5.58	0.713	

HR, hazard ratio; CI, confidence interval.

Table 3
Therapeutic index of extra perigastric lymph nodes.

Lymph node station	All patients (n = 665)			Greater curvature involvement					
				Yes (n = 145)			No (n = 520)		
	Frequency (%)	5-ysr (%)	Therapeutic index ^a	Frequency (%)	5-ysr (%)	Therapeutic index	Frequency (%)	5-ysr (%)	Therapeutic index
LN 7	17.7	40	7.1	31.0	24	7.4	14.0	48	6.7
LN 8a	11.1	29	3.2	24.1	24	5.8	7.5	56	4.2
LN 9	13.7	39	5.3	26.2	22	5.7	10.2	50	5.1
LN 10	9.5	26	2.5	24.1	18	4.4	5.4	36	2.0
LN 11	8.7	30	2.6	22.1	20	4.5	5.0	36	1.8
LN 12a	2.4	36	0.9	5.5	46	2.5	1.5	43	0.6

5-ysr, 5-year survival rate.

^a Therapeutic index was calculated by multiplying the frequency of metastasis by 5-year survival rate in each lymph node station.

purpose, and more intensive adjuvant therapy or postoperative surveillance would be required for no. 10 LN metastasis.

Poor prognosis associated with no.10 LN metastasis has been reported in many studies. In the study analyzing 265 proximal gastric carcinoma patients, the 5-year survival of patients with no.10 LN metastasis was only 8.6% after curative surgery, and this was nearly similar to the survival of patients undergoing R1–2 surgery [14]. In another study by Shin et al. [15], the 5-year survival of the no.10 LN metastasis group was 11.4%, and patients with no.10 LN metastasis showed significantly worse survival than patients with the same stage. Chen et al. [16] analyzed long-term outcomes of 205 patients with D2 total gastrectomy and reported that no.10 LN metastasis was significantly associated with a poor prognosis when adjusting for tumor invasion, nodal metastasis, and R0 resection.

In the past, splenectomy was commonly performed as a standard procedure for complete removal of no. 10 LNs for proximal gastric carcinoma. However, many subsequent studies have revealed that splenectomy only increased morbidity and mortality with no survival benefit [20–22]. Recently, no. 10 LN dissection preserving the spleen (spleen-preserving method) is widely performed as a feasible surgical option in our region. In a randomized controlled trial comparing the spleen-preserving method and splenectomy for upper gastric carcinoma in Korea, splenectomy was associated with higher morbidity and mortality, but did not increase long-term survival compared to spleen-preserving method [12]. However, this technique necessitates substantial experience of gastric cancer surgery to obtain technical proficiency.

The survival benefit of no.10 LN dissection for proximal gastric carcinoma is still controversial. Some studies have shown that combined splenectomy for no.10 LN dissection did not increase patients' survival compared with total gastrectomy alone; however, they are mostly limited by the selection bias of performing splenectomy in a more advanced disease stage [11,22]. In a small randomized trial by Csendes et al. [17], they compared total gastrectomy alone and total gastrectomy plus splenectomy for advanced proximal gastric carcinoma. The long-term survival of the total gastrectomy alone group did not significantly differ from that of patients undergoing total gastrectomy plus splenectomy. Most recently, Japanese surgeons performed a large multicenter randomized controlled trial to compare total gastrectomy plus splenectomy and total gastrectomy alone for proximal gastric carcinoma [18]. In their study, total gastrectomy alone group showed non-inferiority of survival compared with total gastrectomy plus splenectomy group (5-year, 75.1% vs. 76.4%, hazard ratio = 0.88, 1-sided P value for non-inferiority = 0.025). However, this study included a relatively large number of early stage disease and excluded the tumors at the greater curvature and B4 gross type. Therefore, the therapeutic efficacy of prophylactic no. 10 LN

dissection for proximal gastric carcinoma may require to be further investigated.

Meanwhile, some surgeons have insisted the usefulness of no.10 LN dissection in selected patients. Aoyagi et al. [23] reported a high incidence of no.10 LN metastasis in the tumors at the greater curvature or in the case of no.4a, no.4sb, or no.11 LN metastasis. They suggested the necessity of no.10 LN dissection for R0 surgery under these conditions. Kosuga et al. [24] examined the survival index of each lymph node station in proximal gastric carcinoma [25], and reported a relatively high survival index of no. 10 LN metastasis in B4 type tumors and tumors at the greater curvature. Similarly, Watanabe et al. [26] showed the possible survival benefit of no.10 LN dissection in tumors involving the greater curvature. These studies indicate a tailored surgical approach to no.10 LN dissection rather than routine prophylactic lymphadenectomy.

Tailored surgical approach for no. 10 LN dissection may necessitate appropriate patient selection. Advanced tumor stage, tumor location (greater curvature) and size, and gross type (Borrmann 4 type) were the main factors that were associated with no. 10 LN metastasis in the previous studies [15,16,23,24]. In our study, we have found that no. 10 LN metastasis only existed in \geq pT3 or \geq pN2 disease. Also, tumor location (greater curvature or circumferential location), size, and gross tumor type (Borrmann 3 or 4) were significantly associated with no. 10 LN metastasis. Therefore, we suggest that these tumor characteristics should be considered when deciding the candidates for no. 10 LN dissection.

There are some limitations in this study. First, misclassification and diagnosis of no. 10 LN metastasis can be problematic. In this study, experienced gastric cancer surgeons who perform more than 200 gastric cancer surgeries each year carried out LN retrieval and grouping from the resected specimen. Second, splenectomy was more frequently performed in patients with no.10 LN metastasis, which could influence the survival of patient with no. 10 LN metastasis. To solve this problem, we included splenectomy in the multivariate prognostic model, and found that no.10 LN metastasis was an independent poor prognostic factor when adjusting for splenectomy. Lastly, this study did not provide detailed data about disease recurrence in no.10 LN metastasis cases. This could be helpful in drafting suitable plans for adjuvant therapy, and needs to be investigated further.

Conclusions

We have found that the prognosis of no.10 LN metastasis was as poor as that in patients with distant metastasis. No. 10 LN metastasis was an independent poor prognostic factor when adjusting for tumor stage and other prognostic factors. Our results suggest that no. 10 LNs should rather be treated as non-regional LNs in treatment of proximal gastric carcinoma.

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Conflicts of interest

All authors declare no conflicts of interest. No external grants or funding was received for this study.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.ejso.2018.10.531>.

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