

# Prognostic significance of suprapancreatic lymph nodes and its implication on D2 dissection

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## Abstract

There have been few studies on the prognostic significance of suprapancreatic lymph nodes (SPLNs), which are targeted in D2 dissections in patients with gastric cancer. The aim of this study was to investigate the prognostic significance of SPLNs by determining whether treatment outcomes of SPLN-positive gastric cancer are comparable to that of SPLN-negative cancer.

This study enrolled patients with node-positive gastric cancer, who underwent curative surgery with D2 dissection, at the Samsung Medical Centre from 2007 to 2009. The survival outcomes of patients with and without metastatic SPLNs were analyzed.

The total number of patients was 1086, with 377 patients (34.7%) having metastatic SPLNs. SPLN positivity was associated with a more advanced tumor status and the 5-year survival rate of the SPLN-positive group was significantly lower than that of the SPLN-negative group (59.5% vs 81.2%,  $P < .001$ ). However, the survival was not significantly different between the 2 groups when comparing SPLN status within a given disease stage. Cox multivariate analysis revealed that SPLN metastasis was not an independent prognostic factor.

SPLNs were not different from perigastric lymph nodes in terms of prognostic significance and SPLN metastasis should be regarded as a locoregional disease. Complete removal of SPLNs by D2 dissection is recommended for the locoregional control of gastric cancer.

**Abbreviations:** IGCSG = Italian Gastric Cancer Study Group, RCT = randomized controlled trial, SPLN = suprapancreatic lymph node.

**Keywords:** D2 dissection, gastric cancer, stage migration, suprapancreatic lymph node

## 1. Introduction

In gastric cancer surgery, D2 dissection typically consists of a standard resection of the perigastric lymph nodes (D1) and resection of suprapancreatic lymph nodes (SPLNs), which includes the celiac, hepatic, and splenic lymph nodes. There has been controversy between Eastern and Western countries regarding the outcome of D2 dissection in patients with gastric cancer. According to several randomized controlled trials (RCTs), reported mainly in Western countries, the benefits of D2 dissection remain unclear.<sup>[1–6]</sup>

It is difficult to compare the clinical benefits of D1 and D2 dissection precisely; in cases of early tumors, metastatic lymph nodes usually remain in the perigastric region and D2 dissection would not be advantageous compared with D1 dissection. To determine any potential benefit after D2 dissection, a comparison between D1 and D2 dissection should be performed for tumors with metastatic lymph nodes existing in the suprapancreatic region. However, a true comparison of D1 and D2 dissection by selecting tumors with positive SPLNs is challenging in practice. There is no precise method to identify the exact number of metastatic SPLNs preoperatively. After surgery, it is impossible to identify metastatic SPLNs in the D1 group because SPLNs are not resected and SPLN positivity is not guaranteed.

D2 dissection may provide more favorable locoregional control and more accurate cancer staging than D1 dissection. Although it is difficult to clarify the clinical benefit of D2 dissection over D1 dissection by direct comparison, the implication of the locoregional control from D2 dissection could be evaluated by addressing the prognostic significance of metastatic SPLNs. Previous studies have reported that advanced gastric cancer patients with metastatic SPLN had poor prognosis, even after D2 dissection, suggesting that SPLN positivity may be associated with systemic disease.<sup>[7,8]</sup> However, these studies were based on a relatively small number of patients and it is unclear whether metastatic SPLNs are different from perigastric lymph nodes in terms of stage-specific survival.

The necessity of D2 dissection would be minimal if metastatic SPLNs are comparable to systemic disease, but could be justified if metastatic SPLNs are comparable to locoregional disease. In this study, we compared the survival outcomes between gastric cancer patients with metastatic SPLNs and those without, to

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All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent was not required owing to the retrospective nature of this study.

The authors declare that they have no conflict of interest.

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evaluate the prognostic significance of SPLNs, which is the target of D2 dissection.

## 2. Methods

### 2.1. Study population

From 2007 to 2009, the retrospective data of 1086 node-positive (N1-N3b) gastric cancer patients who underwent curative surgery with D2 lymph node dissection at the Department of Surgery, Samsung Medical Centre, were reviewed. Adjuvant chemotherapy was usually recommended after surgery, except for patients with stage T1N0 or T2N0 cancers. Patients who underwent neo-adjuvant chemotherapy before surgery were excluded.

Clinicopathological factors such as age, sex, extent of resection, tumor location and size, histologic types, depth of invasion, lymph node metastasis, pathologic stage, lymphatic invasion, venous invasion, and perineural invasion were reviewed using data from medical records and pathology reports. Histological type was categorized as “differentiated” or “undifferentiated.” Well or moderately differentiated cases were classified into the differentiated group, with cases of poorly differentiated tubular adenocarcinoma, signet ring cell type, and mucinous adenocarcinoma were assigned to the undifferentiated group. The pathologic stage was classified according to the 7th edition of AJCC classification. Survival data were obtained from patients’ medical records and the Korean cancer registry. The study protocol was approved by the institutional review board of Samsung Medical Centre, Seoul, Korea (SMC 2016-08-007).

Lymph nodes were harvested and classified according to each lymph node station shortly after specimen collection. SPLNs were classified as those along the common hepatic artery (station 8a), around the celiac artery (station 9), along the splenic artery (station 11p and/or 11d), and around the proper hepatic artery (station 12a).

Stage migration effect was evaluated by assuming the patients had undergone hypothetical D1 dissection. In the simulated D1 dissection group, stages were redefined by deleting the SPLN data and the proportion of downstaging phenomena was calculated in each stage.

### 2.2. Statistical analysis

The differences in clinicopathological parameters between patients with and without metastatic SPLNs were determined by the Chi-square ( $\chi^2$ ) test. The 5-year survival rate was calculated using the Kaplan–Meier method, and the log-rank test was used to determine the significance of the clinicopathological variables previously listed. Variables with  $P < .05$  in univariable analysis were included in the multivariable analysis. Multivariable analysis was carried out using a Cox proportional hazards model with the logistic regression method to identify independent risk factors of patient survival. The associated hazard ratios and 95% confidence intervals were calculated. A  $P$  value of  $< .05$  derived from a 2-tailed test was considered statistically significant. Statistical analysis was carried out using SPSS version 23.0 statistical software for Windows (SPSS, Chicago, IL).

## 3. Results

### 3.1. Patients characteristics

Among the 1086 gastric cancer patients analyzed, 377 (34.7%) had SPLN metastasis with a mean ( $\pm$  standard deviation) follow-up

**Table 1**

**Clinicopathological characteristics of the patients with and without metastatic suprapancreatic lymph nodes.**

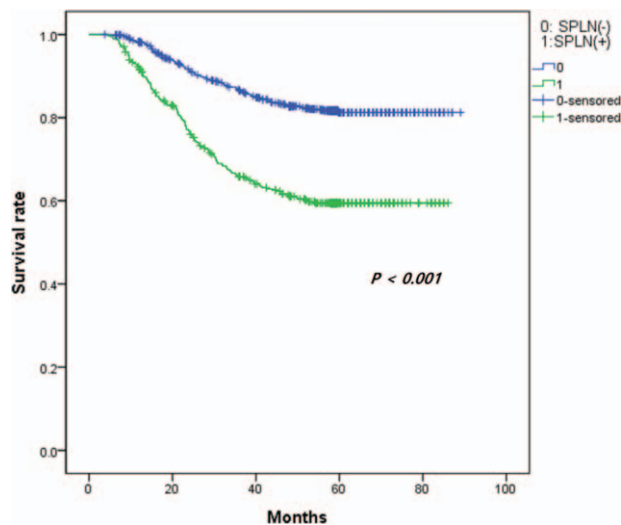
	Suprapancreatic LN positive (n=377)	Suprapancreatic LN negative (n=709)	$P^{\dagger}$
Age, y	57.40 ( $\pm$ 11.92)	56.22 ( $\pm$ 12.09)	.612
Sex			.791
Male	242 (64.2%)	449 (63.3%)	
Female	135 (35.8%)	260 (36.7%)	
Extent of resection			.009
Total	136 (36.1%)	200 (28.2%)	
Subtotal	241 (63.9%)	509 (71.8%)	
Tumor location			<.001
Upper third	66 (17.5%)	91 (12.8%)	
Middle third	98 (26%)	283 (39.9%)	
Lower third	186 (49.3%)	320 (45.1%)	
Whole	27 (7.2%)	15 (2.1%)	
Tumor size, cm			<.001
$\leq 6$	205 (54.4%)	490 (69.1%)	
$> 6$	172 (45.6%)	219 (30.9%)	
Histologic type			.056
Differentiated	93 (24.7%)	215 (30.3%)	
Undifferentiated	284 (75.3%)	494 (69.7%)	
Depth of invasion			<.001
T1	33 (8.8%)	145 (20.5%)	
T2	51 (13.5%)	156 (22.0%)	
T3	150 (39.8%)	263 (37.1%)	
T4	143 (37.9%)	145 (20.5%)	
LN metastasis			<.001
N1	34 (9.0%)	359 (50.6%)	
N2	79 (21.0%)	207 (29.2%)	
N3	264 (70.0%)	143 (20.2%)	
Pathologic stage*			<.001
IB	8 (2.1%)	96 (13.5%)	
IIA	27 (7.2%)	149 (21.0%)	
IIB	40 (10.6%)	164 (23.1%)	
IIIA	55 (14.6%)	130 (18.3%)	
IIIB	119 (31.6%)	102 (14.4%)	
IIIC	128 (34.0%)	68 (9.6%)	
Lymphatic invasion			<.001
Absent	45 (11.9%)	179 (25.2%)	
Present	332 (88.1%)	530 (74.8%)	
Vascular invasion			<.001
Absent	288 (76.4%)	611 (86.2%)	
Present	89 (23.6%)	98 (13.8%)	
Perineural invasion			<.001
Absent	162 (43.0%)	412 (58.1%)	
Present	215 (57.0%)	297 (41.9%)	

Values in parentheses are percentages. LN=lymph node.

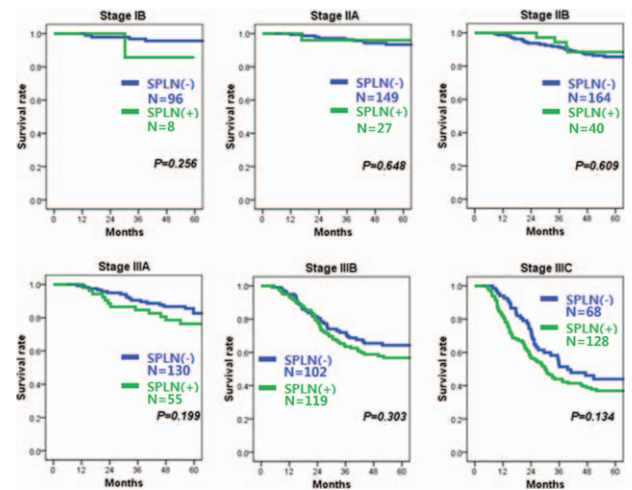
\* According to the seventh edition of the American Joint Committee on Cancer classification.

$\dagger$  Chi-square test.

duration of 48.7 ( $\pm$  20.5) months. There were significant differences in terms of the extent of resection, tumor location, tumor size, depth of invasion, lymph node metastasis, pathologic stage, and presence of lymphatic, vascular, and perineural invasion between the patients with and without metastatic SPLNs (Table 1). SPLN positivity was associated with a more advanced tumor stage and pathological diagnosis of lymphatic, vascular, or perineural invasion. The 5-year overall survival rate of the SPLN-positive group was significantly lower than that of the SPLN-negative group (59.5% vs 81.2%,  $P < .001$ ) (Fig. 1). However, in the comparison of 5-year stage-specific survival rates, there was no significant difference between the 2 groups with the same stage (Fig. 2).



**Figure 1.** Comparison of the 5-year survival rates between gastric cancer patients with and without metastatic suprapancreatic lymph nodes.



**Figure 2.** Comparison of 5-year survival rates between the gastric cancer patients with and without metastatic suprapancreatic lymph nodes according to each TNM stage.

### 3.2. Prognosis factors for overall survival

Univariate analysis revealed the following parameters to be significantly associated with survival: age, extent of resection, tumor location and size, depth of invasion, lymph node metastasis, lymphatic invasion, vascular invasion, perineural

invasion, and SPLN positivity. Multivariate Cox regression analysis identified age, tumor location, depth of invasion, lymph node metastasis, vascular invasion, and perineural invasion as independent prognostic indicators, but SPLN positivity itself was not an independent prognostic factor (Table 2).

**Table 2**  
Univariate and multivariate logistic regression analysis of prognostic factors.

	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Age, y				
≤60	1		1	
>60	1.928 (1.516~2.453)	<.001	1.876 (1.469~2.396)	<.001
Extent of resection				
Subtotal	1	<.001		
Total	1.605 (1.256~2.052)			
Tumor location				
Lower third	1		1	
Middle third	0.684 (0.506~0.925)	.014	0.746 (0.550~1.012)	.059
Upper third	1.462 (1.051~2.032)	.024	1.336 (0.960~1.860)	.086
Whole	5.392 (3.606~8.063)	<.001	2.402 (1.596~3.616)	<.001
Tumor size, cm				
≤6	1			
>6	1.936 (1.522~2.463)	<.001		
Depth of invasion				
T1	1		1	
T2	3.254 (1.319~8.026)	.010	2.422 (0.978~5.999)	.056
T3	7.541 (3.300~17.230)	<.001	3.957 (1.695~9.237)	.001
T4	21.248 (9.386~48.104)	<.001	8.059 (3.409~19.053)	<.001
LN metastasis				
N1	1		1	
N2	1.164 (0.760~1.781)	.484	0.881 (0.573~1.356)	.566
N3	4.689 (3.409~6.451)	<.001	2.242 (1.580~3.180)	<.001
Lymphatic invasion				
Absent	1			
Present	1.686 (1.196~2.378)	.003		
Vascular invasion				
Absent	1		1	
Present	2.366 (1.818~3.078)	<.001	1.615 (1.236~2.112)	<.001
Perineural invasion				
Absent	1		1	
Present	2.638 (2.041~3.409)	<.001	1.372 (1.043~1.806)	.024
Suprapancreatic LN				
Negative	1			
Positive	2.628 (2.064~3.346)	<.001		

CI=confidence interval, LN=lymph node, OR=odds ratio.

\* Log-rank test.

† Cox proportional hazards model with the forward logistic regression method. Bold values indicate statistical significance (e.g.,  $P < .05$ ).

**Table 3**

**Comparison of 5-year survival rates between the groups with and without metastatic suprapancreatic lymph nodes according to each T and N stage.**

	5-y survival rates (%)		P*
	Suprapancreatic LN positive (n=377)	Suprapancreatic LN negative (n=709)	
T1			
N1	85.7 (8)	95.6 (96)	.256
N2	100.0 (14)	100.0 (45)	
N3	90.0 (11)	100.0 (4)	.450
T2			
N1	92.3 (13)	90.5 (104)	.872
N2	100.0 (18)	86.5 (40)	.125
N3	75.0 (20)	82.5 (12)	.729
T3			
N1	66.7 (11)	84.8 (120)	.153
N2	81.9 (33)	92.3 (82)	.158
N3	56.1 (106)	69.9 (61)	.561
T4			
N1	0.0 (2)	65.5 (39)	<.001
N2	57.1 (14)	54.2 (40)	.991
N3	37.2 (127)	44.5 (66)	.149

LN=lymph node.

\* Log-rank test.

### 3.3. Comparison of 5-year survival rates

Patients were classified in more detailed subgroups according to each T and N category, with survival outcomes compared between the patients with and without metastatic SPLN in each subgroup. No significant difference in survival rates was observed between the 2 groups except for the T4N1 subgroup (Table 3).

Additional findings included a simulated D1 dissection, which demonstrated stage migration in 7.7% (84 of 1086) of the patients, as well as the percentage of migration according to each stage, which is summarized in Table 4.

## 4. Discussion

This study investigated the prognostic significance of SPLNs, which are the target of D2 dissections in gastric cancer patients, by examining the treatment outcomes of SPLN-positive gastric cancer. The role of D2 dissection is still debatable despite previous RCTs from Western countries failing to show a survival benefit for D2 over D1 dissection. Earlier studies have been criticized for high morbidity and mortality rates, which were attributed to pancreatic-splenectomy, as well as other possible factors, such as inadequate clinical experience of surgeons due to

low case volumes.<sup>[9]</sup> Later, another RCT from the Italian Gastric Cancer Study Group (IGCSG) not only showed low morbidity and mortality rates but also failed to reveal any difference in 5-year overall survival between D1 and D2 dissection.<sup>[5,10]</sup> However, this study's interpretation was limited due to several problems such as harvesting of incorrect lymph node stations and a higher prevalence of early tumors in the D1 arm.

Meanwhile, several reports have argued in favor of D2 dissection. A RCT from Taiwan first reported a significant survival benefit with extended lymph node dissection.<sup>[11]</sup> The 15-year follow-up of the Dutch D1D2 trial also demonstrated that D2 dissection is associated with lower locoregional recurrence, as well as gastric cancer related death rates, than D1 surgery.<sup>[12]</sup> Subgroup analysis of the IGCSG study showed a trend toward improvement in both overall survival and disease-specific survival for extended surgery in patients with locally advanced gastric cancer and positive nodes. Another retrospective study also demonstrated that a more extensive lymphadenectomy was associated with prolonged survival in patients with stage IA–IIIA disease, possibly due to superior locoregional control.<sup>[13]</sup>

To determine any therapeutic benefit, D2 dissection should be compared with D1 dissection in patients with positive SPLNs, as there is no expected advantage of D2 dissection in patients without metastatic SPLNs. However, the actual stage-by-stage comparison of D1 and D2 dissection in patients with a definite SPLN positivity is impossible because SPLN information cannot be acquired from D1 patients.

As an indirect way to address the importance of D2 dissection, we investigated the prognostic significance of SPLNs. Our data revealed that metastatic SPLNs were not associated with a worse prognosis than metastatic perigastric lymph nodes for each TNM stage and in subgroup analysis of stage by T and N categories. Significant difference in survival was only observed for T4N1 stage, but its implication is limited due to a small number of SPLN-positive patients. On the basis of our findings, the prognostic significance of SPLN metastasis seems to be similar to that of perigastric lymph node metastasis.

If SPLN positivity was associated with systemic disease, then the importance of D2 dissection would decrease. However, our result implies that SPLN positivity is comparable to a locoregional disease, implying that it is advantageous to remove metastatic SPLNs by D2 dissection during gastric cancer surgery. Performing only D1 dissection and not resecting SPLNs appears to be a suboptimal treatment course when considering the SPLN-positive rate of 34.7% in our study.

Another significant phenomenon caused by lymph node dissection is stage migration. A more complete lymphadenectomy may shift survival curves without a real survival benefit by

**Table 4**

**Effect of simulated D1 dissection on stage migration.**

Simulated D1 TNM stage	D2 TNM stage					
	IB (104)	IIA (176)	IIB (204)	IIIA (185)	IIIB (221)	IIIC (196)
IA (4)	4					
IB (116)	100	16				
IIA (177)		160	17			
IIB (206)			187	19		
IIIA (184)				166	18	
IIIB (213)					203	
IIIC (186)						10
Migration (%)	3.85	9.09	8.33	10.27	8.14	5.10

Values in parentheses are number of patients.



upstaging patients.<sup>[14,15]</sup> However, the increase in upstaged gastric cancer patients after D2 dissection can also lead to more efficacious multimodality treatments further affecting the survival difference.<sup>[16]</sup> In the analysis of simulated D1 dissection, our data demonstrated 7.7% of the patients were downstaged compared with real D2 dissection due to a lower count of metastatic SPLNs in staging. D2 dissection has advantages in not only resecting metastatic SPLNs but also by preventing this downstaging problem.

This study has fundamental limitations in that it is a retrospective, single-center analysis, with patients treated in an Eastern country. The difference in biology, diagnosis, epidemiology, and treatment between Eastern and Western countries is beyond the scope of this study. It may be necessary to analyze the significance of metastatic SPLNs by integrating data of multicenter group of east and west in the future. Moreover, the benefit of D2 dissection was not examined by direct comparison between D1 and D2 dissection in this study. However, direct comparison studies have their own limitations. It should also be noted that adjuvant chemotherapy could control metastatic SPLNs and may therefore invalidate the necessity of D2 dissection. However, it is difficult to assure that adjuvant chemotherapy can routinely provide an optimal locoregional control of metastatic SPLNs. Therefore, it appears more appropriate to perform D2 dissection for patients with advanced gastric cancer.

In conclusion, SPLN positivity itself was not associated with a worse prognosis than perigastric lymph node positivity. The complete removal of metastatic SPLNs by D2 dissection is important for locoregional control of advanced gastric cancer.

### Author contributions

**Conceptualization:** Min-Gew Choi.

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**Formal analysis:** Man Ho Ha.

**Investigation:** Man Ho Ha.

**Methodology:** Man Ho Ha.

**Project administration:** Man Ho Ha.

**Resources:** Man Ho Ha.

**Software:** Man Ho Ha.

**Supervision:** Min-Gew Choi, Tae Sung Sohn, Jae Moon Bae, Sung Kim.

**Validation:** Min-Gew Choi, Tae Sung Sohn, Jae Moon Bae, Sung Kim.

**Writing – original draft:** Man Ho Ha.

**Writing – review & editing:** Min-Gew Choi.

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