Lymph node count is an independent prognostic factor for patients with pathological stage III gastric cancer

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ABSTRACT

The relationship between lymph node (LN) count and the outcome of patients with advanced gastric cancer (GC) is still not fully studied. In this study, a total of 3, 419 patients with pathological stage III GC from Surveillance, Epidemiology, and End Results Program (SEER) was analyzed. We found that the optimal cutoff value for retrieved LNs was 9 (χ^2 = 58.163, *P* < 0.001). Subgroup analysis showed that LN count was a prognostic factor in patients with pIIIA GC (χ^2 = 75.055, *P* < 0.001), pIIIB GC (χ^2 = 32.464, *P* < 0.001) and pIIIC GC (χ^2 = 6.903, *P* = 0.009). After adjusting variables, the number of LNs was also validated as an independent survival factor in pIIIA GC (LNs > 9, HR: 1.849, 95% CI: 1.571~2.176, *P* < 0.001), pIIIB GC (LNs > 9, HR: 1.414, 95% CI: 1.221~1.636, *P* < 0.001) and pIIIC GC (LNs > 9, HR: 1.306, 95% CI: 1.034~1.649, *P* = 0.025). In conclusion, our results demonstrated that LN count was an independent prognostic factor in patients with pathological stage III GC.

INTRODUCTION

Gastric cancer (GC) is the second most common cancer worldwide and the 4th leading cause of cancer-relative death [1–2]. The 5-year relative survival rates of GC is only approximately 30% and many patients are diagnosed in advanced stage [3–5]. The tumor node metastasis (TNM) staging system is considered as the gold standard for staging GC [6]. Lymph node (LN) metastasis is an important index for assessing TNM staging [7]. The 7th edition TNM staging system recommends that "≥ 16 LNs be assessed pathologically" [8]. In many Western and American cohorts where less extensive lymphadenectomies are performed and in which fewer LNs are examined [9–11]. Apparently, this stage based on absolute number of positive LNs is intrinsically susceptible to stage migration, particularly when understaging reflects insufficient lymph node retrieved [12]. Especially in pathological stage III GC, because the LN counts are its main components, stage migration is a very definite possibility. In 2005, David et al. [13] analyzed the relationships between the number of LNs examined and GC survival for the stage subgroups T1/2N0, T1/2N1, T3N0 and T3N1 based on the 6th edition TNM staging system, and reported that the overall survival was highly dependent on the number of LNs examined. However, the relationship between LN count and the outcome of pathological stage III GC patients is still not fully studied. The purpose of this study was to assess the relationship between LN count and the outcome of pathological stage III GC patients to determine the optimal number of LNs that should be examined.

RESULTS

Characteristics and clinical features of patients

From 2004 to 2010, a total of 3,149 patients with pathological stage III GC met our selection criteria, including 2,072 male and 1,347 female. The median age of

patients was 62 years (18–93). There were 1,004 patients with stage IIIA, 1,373 with stage IIIB and 1,042 with stage IIIC. The demographics and pathological features of patients are summarized in Table 1. The phase was closely correlated with race, primary site, grade, histologic type, marital status, LNs retrieved and mean of LNs dissected ($P < 0.05$).

The mean of LNs dissected was 17 (1–89), and there were 14 (1–79) LNs dissected in stage IIIA, 17 (1–89) in IIIB and 21 (3–80) in IIIC. The ratio of > 15/(≤ 15 + > 15) LNs examined was 43.87% in this cohort, and the ratio was 43.3% in IIIA, 55.4% in IIIB and 69.4% in IIIC.

Identification of cutoff points for the minimum number of LNs count in pIII GC patients

The 5-year cause specific survival (CSS) were calculated for patients with different LNs count. As shown in Table 2, LN count was a prognosis factor with the numbers from 2 to 24 (except for 1, $P = 0.183$). The optimal cutoff points for continuous variable LNs was identified by X-tile (Figure 1). The optimal cutoff value for retrieved LNs was 9 ($\chi^2 = 58.163$, $P < 0.001$) and then divided the patients into high and low risk subsets with the 5-year CSS of 15.6% and 24.4% respectively.

Impact of LNs count on CSS of GC patients in the SEER database

Univariate analysis showed that compared with their counterparts, patients in the group of year of diagnosis (2004–2007), age (≥ 60), race (white), grade (III/IV), histologic type (carcinoma), marital status (widowed), LNs retrieved (≤ 9) or AJCC stage (IIIC) had worse outcomes (all $P < 0.05$). Multivariate Cox proportional hazards model were used to assess the risk factors for CSS. We found that the year of diagnosis, sex, race, grade, histologic type, marital status, LNs retrieved (with an optimal cutoff value of 9) and AJCC stage were independent prognostic factors (all $P < 0.05$). LNs retrieved (> 9) had a significant impact on CSS of GC patients in the SEER database (HR: 1.530; 95% CI: 1.389–1.686, $P < 0.001$) (Table 3).

Subgroup analysis of impact of LNs count on CSS during each pIII stage

Subgroup analysis showed that LN count was a prognosis factor in pIIIA ($\chi^2 = 75.055$, $P < 0.001$), pIIIB ($\chi^2 = 32.464$, $P < 0.001$) and pIIIC ($\chi^2 = 6.903$, $P = 0.009$) (Figure 2) (Tables 4–6). After adjusting variables, the number of LNs was also validated as an independent survival factor in pIIIA (LNs > 9, HR: 1.849, 95% CI: 1.571~2.176, $P < 0.001$), pIIIB (LNs > 9, HR: 1.414, 95% CI: 1.221~1.636, $P < 0.001$) and pIIIC (LNs > 9, HR: 1.306, 95% CI: 1.034~1.649, $P = 0.025$) subgroups by multivariate Cox regression (Tables 4–6).

DISCUSSION

In 1997, the Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) redefined the pathologic N based on the number of involved nodes rather than the location, and thus reached an agreement that the cut-off points for the N classification should be as follows: N0 (no regional LN metastasis), N1 (1–6 nodes metastasis), N2 (7–15 nodes metastasis), and N3 (more than 15 nodes metastasis). In 2010, the 7th edition TNM staging system was changed to accommodate that N1 was set by 1–2 nodes metastasis, N2 by 3–6 nodes metastasis, and N3 by more than 7 nodes metastasis (N3a: 7~15, and N3b: more than 16) [8]. The total number of LNs retrieved is fundamental in the pathological staging systems for GC, which has direct implications on the survival of GC patients, validated in several large clinical series [12–17]. However, the optimal number of LNs to be removed to achieve an optimum reliability in stage assignment remains less clear.

Inadequate LN evaluation is related to worse outcomes in terms of tumor recurrence and patient survival [7]. Siewert et al. [10] showed that LN status was one of the most important prognostic factors in patients with resected GC and extended LN dissection did not increase the mortality or morbidity rate of resection for GC but markedly improved long-term survival in patients with stage II. Smith et al. [13] reported that 5-year survival with only one LN examined was 56% (T1/2N0), 35% (T1/2N1), 29% (T3N0), or 13% (T3N1); moreover for every 10 extra LNs dissected, survival improved by 7.6% (T1/2N0), 5.7% (T1/2N1), 11% (T3N0), or 7% (T3N1), and detected significantly superior survival differences for cut points at up to 40 LNs. Zheng et al. [12] demonstrated that the number of the retrieved LNs count was an independent prognostic factor for GC with no LN metastasis and the higher the LN count is, the better the survival would be; the longest CSS was observed in the group of LN count more than 14. Jiao et al. [18] found that patients with node-negative GC and LNs retrieved more than 15 had a better survival compared with those with LNs ≤ 15, and the cut-point analysis showed that T2-T4 patients with 11–15 LNs had a significantly longer mean overall survival than those with 4–10 LNs or 1–3 LNs. However, the relationship between LN count and pathological stage III GC has not been fully investigated. In this study, we revealed that the more LN count retrieved, the better the survival would be. LN count was a prognosis factor for patients with pIII GC. After using X-tile to identify 9 as the optimal cutoff value, LN count was found as an independent prognosis factor in pathological stage III GC. We suggest that LN count is a good supplement for current staging systems on evaluating the prognosis of these patients and it could be involved in practical prediction models.

The reason for the correlation between the LNs retrieved and survival has not been revealed. This is mainly due to stage-migration [12]. Lymphatic micrometastasis is

Table 1: Baseline demographic and tumor characteristics of patients with GC in SEER database and make comparison between pIIIA, pIIIB and pIIIC groups

Parameter	Characteristic	Total	IIIA	IIIB	IIIC	*P* value
		3419	1004	1373	1042	
Year of diagnosis						0.564
	2004–2007	2016	578 (57.6)	817 (59.5)	621 (59.6)	
	2008–2010	1403	426 (42.4)	556 (40.5)	421 (40.4)	
Sex						0.139
	Male	2072	606 (60.4)	857 (62.4)	609 (58.4)	
	Female	1347	398 (39.6)	516 (37.6)	433 (41.6)	
Age						0.086
	< 60	1274	347 (34.6)	519 (37.8)	408 (39.2)	
	≥ 60	2145	657 (65.4)	854 (62.2)	634 (60.8)	
Race						0.003
	White	2219	667 (66.4)	873 (63.6)	679 (65.2)	
	Black	480	163 (16.2)	190 (13.8)	127 (12.2)	
	Others	720	174 (17.3)	310 (22.6)	236 (22.6)	
Primary Site						0.000
	Cardia, NOS	764	264 (26.3)	317 (23.1)	183 (17.6)	
	Non-cardia	2361	664 (66.1)	937 (68.2)	760 (72.9)	
	Stomach, NOS	294	76 (7.6)	119 (8.7)	99 (9.5)	
Grade						0.000
	Grade I/II	683	252 (25.1)	278 (20.2)	153 (14.7)	
	Grade III/IV	2736	752 (74.9)	1095 (79.8)	889 (85.3)	
Histologic type						0.000
	Carcinoma	264	58 (5.8)	101 (7.4)	105 (10.1)	
	Adenocarcinoma	2142	681 (67.8)	897 (65.3)	564 (54.1)	
	Mucinous adenocarcinoma	117	44 (4.4)	42 (3.1)	31 (3.0)	
	Signet ring cell carcinoma	896	221 (22.0)	333 (24.3)	342 (32.8)	
Marital status						0.960
	Married	2150	622 (62.0)	873 (63.6)	655 (62.9)	
	Divorced	254	72 (7.2)	104 (7.6)	78 (7.5)	
	Single/Separated	521	163 (16.2)	200 (14.6)	158 (15.2)	
	Widowed	494	147 (14.6)	196 (14.3)	151 (14.5)	
LNs						0.000
	≤ 15	1500	569 (56.7)	612 (44.6)	319 (30.6)	
	> 15	1919	435 (43.3)	761 (55.4)	723 (69.4)	
LNs dissected		17 (1–89)	14 (1–79)	17 (1–89)	21 (3–80)	0.000

A value of $P < 0.05$ indicates statistical significance.

a key etiology of recurrence and metastasis after resection of GC, which is difficult to be found during operation [19–20]. We could retrieve more LNs to reduce the lymphatic micrometastases to improve the outcome of GC. We previously identified 12 negative LNs as the optimal cutoff value to divide the patients into high and low risk subsets in terms of survival rate and firmly demonstrated that negative LN count was an independent prognostic factor for patients with GC who received preoperative radiotherapy [21]. Zheng et al. [12] demonstrated the importantly prognostic value of LNs count on survival of patients with node-negative GC. It is suggested that increased LNs

Table 2: Univariate analysis of the influence of different LN count on CSS in patients with GC in ypIII stage

LNs	No.	5-year CCS	χ^2	*P* value	LNs	No.	5-year CCS	χ^2	*P* value
≤ 1	29	17.2%	1.777	0.183	≤ 13	1227	18.5%	38.929	0.000
> 1	3390	22.8%			> 13	2192	25.2%		
≤ 2	58	9.5%	5.557	0.018	≤ 14	1344	18.6%	38.774	0.000
> 2	3361	23.0%			> 14	2075	25.5%		
≤ 3	101	10.5%	15.961	0.000	≤ 15	1500	18.7%	39.233	0.000
> 3	3318	23.1%			> 15	1919	25.9%		
≤ 4	160	10.9%	29.447	0.000	≤ 16	1626	19.3%	31.726	0.000
> 4	3259	23.3%			> 16	1793	25.9%		
≤ 5	226	9.8%	48.842	0.000	≤ 17	1760	19.1%	39.316	0.000
> 5	3193	23.7%			> 17	1659	26.7%		
≤ 6	307	11.7%	47.631	0.000	≤ 18	1887	19.8%	33.128	0.000
> 6	3112	23.9%			> 18	1532	26.4%		
≤ 7	418	13.5%	52.991	0.000	≤ 19	1989	20.2%	28.815	0.000
> 7	3001	24.1%			> 19	1430	26.3%		
≤ 8	516	14.7%	52.228	0.000	≤ 20	2117	20.4%	26.896	0.000
> 8	2903	24.2%			> 20	1302	26.7%		
≤ 9	660	15.6%	58.163	0.000	≤ 21	2227	20.3%	27.737	0.000
> 9	2759	24.4%			> 21	1192	27.4%		
≤ 10	788	16.8%	50.955	0.000	≤ 22	2337	20.4%	27.517	0.000
> 10	2631	24.5%			> 22	1082	27.9%		
≤ 11	948	17.1%	47.893	0.000	≤ 23	2428	20.4%	31.490	0.000
> 11	2471	24.9%			> 23	991	28.6%		
≤ 12	1089	18.4%	37.425	0.000	≤ 24	2514	20.7%	27.814	0.000
> 12	2330	24.8%			> 24	905	28.6%		

A value of $P < 0.05$ indicates statistical significance.

retrieval would reduce the possibility of understaging, and thus then improve survival. In this study, we also found that the higher the LN count retrieved, the better survival would be in patients with pathological stage III GC.

The results of this study have some potential shortcomings. First, the SEER database does not include information of therapeutic options such as radical resection or palliative therapy, and detailed information of chemotherapy, which may also impact patients' prognosis [21]. Second, the information about recurrence and metastasis of GC and whether or not medical treatment on patients with recurrence or metastasis is given is still unknown in SEER database, which we cannot adjust in survival analysis [12]. Third, even different pathological doctors influence the number of LNs retrieval. But for the SEER database lacks these information, we cannot adjust for this.

In conclusion, our analysis of the SEER database revealed that the number of LNs retrieved (with an optimal cutoff value of 9) was an independent prognosis factor for patients with pathological stage III GC. Subgroup analysis showed that LN count was an independent prognostic factor in patients with pathological stage III GC (pIIIA, pIIIB and pIIIC).

MATERIALS AND METHODS

Patient selection

The current SEER database consists of 18 population-based cancer registries that represent approximately 26% of the population in the United States. Research Program, National Cancer Institute

Table 3: Univariate and multivariate analysis for evaluating the influence of LNs on CSS in patients with ypIII GC

Parameter	Characteristic	5-year CCS	Univariate analysis		Multivariate analysis	
			χ^2 test	*P* value	HR (95% CI)	*P* value
Year of diagnosis			10.205	0.001		0.036
	2004–2007	20.6%			Ref	
	2008–2010	26.3%			1.089 (1.006~1.180)	
Sex			3.391	0.066	NI	
	Male	23.3%				
	Female	21.9%				
Age			114.628	0.000		0.000
	< 60	31.0%			Ref	
	≥ 60	17.9%			0.640 (0.586~0.698)	
Race			24.086	0.000		0.000
	White	20.6%			Ref	
	Black	22.0%			1.318 (1.193~1.456)	0.000
	Others	29.9%			1.288 (1.123~1.478)	0.000
Primary Site			4.942	0.084	NI	
	Cardia, NOS	19.1%				
	Non-cardia	24.2%				
	Stomach, NOS	21.4%				
Grade			19.283	0.000		0.004
	Grade I/II	30.2%			Ref	
	Grade III/IV	20.9%			0.859 (0.773~0.954)	
Histologic type			15.995	0.001		0.009
	Carcinoma	17.3%			Ref	
	Adenocarcinoma	25.2%			1.092 (0.937~1.272)	0.260
	Mucinous adenocarcinoma	24.4%			0.887 (0.807~0.974)	0.012
	Signet ring cell carcinoma	18.1%			0.957 (0.765~1.197)	0.699
Marital status			50.020	0.000		0.000
	Married	24.4%			Ref	
	Divorced	17.6%			0.785 (0.703~0.877)	0.000
	Single/Separated	26.4%			0.975 (0.822~1.155)	0.768
	Widowed	14.8%			0.848 (0.732~0.982)	0.028
LNs			58.163	0.000		0.000
	≤ 9	15.6%			Ref	
	> 9	24.4%			1.530 (1.389~1.686)	
AJCC stage			154.496	0.000		0.000
	IIIA	33.2%			Ref	
	IIIB	22.5%			0.491 (0.442~0.545)	0.000
	IIIC	12.8%			0.708 (0.647~0.776)	0.000

A value of $P < 0.05$ indicates statistical significance.

Table 4: Univariate and multivariate analysis for evaluating the influence on CSS in patients with ypIIIA GC

Parameter	Characteristic	5-year CCS	Univariate analysis		Multivariate analysis	
			χ^2 test	*P* value	HR (95% CI)	*P* value
Year of diagnosis			4.721	0.030		0.491
	2004–2007	30.6%			Ref	
	2008–2010	36.5%			1.058 (0.901~1.241)	
Sex			0.847	0.357	NI	
	Male	34.1%				
	Female	31.9%				
Age			31.356	0.000		0.000
	< 60	44.1%			Ref	
	≥ 60	27.4%			0.668 (0.562~0.794)	
Race			22.006	0.000		0.002
	White	29.2%			Ref	
	Black	30.9%			1.510 (1.196~1.906)	0.001
	Others	50.7%			1.471 (1.106~1.957)	0.008
Primary Site			8.814	0.012		0.018
	Cardia, NOS	25.3%			Ref	
	Non-cardia	36.7%			1.208 (0.885~1.650)	0.234
	Stomach, NOS	30.0%			0.935 (0.700~1.247)	0.646
Grade			2.431	0.119	NI	
	Grade I/II	37.4%				
	Grade III/IV	31.7%				
Histologic type			0.366	0.947	NI	
	Carcinoma	34.8%				
	Adenocarcinoma	33.6%				
	Mucinous adenocarcinoma	30.6%				
	Signet ring cell carcinoma					
Marital status			11.732	0.008		0.061
	Married	35.1%			Ref	
	Divorced	21.6%			0.870 (0.697~1.085)	0.216
	Single/Separated	36.7%			1.265 (0.908~1.763)	0.165
	Widowed	26.4%			0.893 (0.675~1.182)	0.429
LNs			75.055	0.000		0.000
	≤ 9	18.3%			Ref	
	> 9	39.2%			1.849 (1.571~2.176)	

A value of $P < 0.05$ indicates statistical significance.

SEER*Stat software, was used to access the database. We searched for GC patients, at age ≥ 18 years, diagnosed between 2004 and 2010. Histological types were limited to adenocarcinoma (8140/3, 8144/3, 8255/3, 8211/3, 8260/3, 8263/3), signet ring cell carcinoma (8490/3) and carcinoma (8490/3). Patients were excluded if one accept neoadjuvant radiotherapy, or had more than one primary neoplasm, distant metastasis, no surgical resection, undefined TNM stage, unknown cause of death or survival months.

Patients' demographic and clinicopathological variables, including years of diagnosis, age, sex, race,

Table 5: Univariate and multivariate analysis for evaluating the influence on CSS in patients with ypIIIB GC

Parameter	Characteristic	5-year CCS	Univariate analysis		Multivariate analysis	
			χ^2 test	*P* value	HR (95% CI)	*P* value
Year of diagnosis			5.882	0.015		0.081
	2004–2007	19.8%			Ref	
	2008–2010	27.7%			1.119 (0.986~1.270)	
Sex			3.191	0.074	NI	
	Male	23.4%				
	Female	21.1%				
Age			72.076	0.000		0.000
	< 60	32.1%			Ref	
	≥ 60	16.8%			0.564 (0.490~0.650)	
Race			9.274	0.010		0.004
	White	20.9%			Ref	
	Black	20.3%			1.292 (1.108~1.507)	0.001
	Others	28.7%			1.274 (1.030~1.577)	0.026
Primary Site			2.666	0.264	NI	
	Cardia, NOS	17.3%				
	Non-cardia	24.0%				
	Stomach, NOS	25.9%				
Grade			8.971	0.003		0.002
	Grade I/II	30.7%			Ref	
	Grade III/IV	20.4%			0.768 (0.652~0.905)	
Histologic type			9.073	0.028		0.019
	Carcinoma	14.0%			Ref	
	Adenocarcinoma	24.8%			1.295 (1.016~1.651)	0.037
	Mucinous adenocarcinoma	21.2%			0.908 (0.781~1.055)	0.206
	Signet ring cell carcinoma	19.0%			1.024 (0.708~1.483)	0.898
Marital status			18.011	0.000		0.355
	Married	22.9%			Ref	
	Divorced	23.9%			0.874 (0.733~1.043)	0.135
	Single/Separated	26.4%			0.951 (0.720~1.258)	0.726
	Widowed	16.1%			0.976 (0.767~1.242)	0.845
LNs			32.464	0.000		0.000
	≤ 9	15.0%			Ref	
	> 9	24.5%			1.414 (1.221~1.636)	

A value of $P < 0.05$ indicates statistical significance.

primary site, grade, histologic type, marital status, pathological T or N stage, reginal LNs retrieval and metastasis were retrieved from the SEER database. The primary endpoint in this study was CSS, defined as the period from diagnosis to death due to GC. Data of patients who died from other causes or who were alive on the date of their last follow-up were censored. TNM classification was restaged according to the criteria described in the AJCC Cancer Staging Manual (7th edition, 2010).

Table 6: Univariate and multivariate analysis for evaluating the influence on CSS in patients with ypIIIC GC

Parameter	Characteristic	5-year CCS	Univariate analysis		Multivariate analysis	
			χ^2 test	*P* value	HR (95% CI)	*P* value
Year of diagnosis			0.219	0.640	NI	
	2004–2007	12.2%				
	2008–2010	14.0%				
Sex			0.003	0.955	NI	
	Male	12.4%				
	Female	13.7%				
Age			28.371	0.000		0.000
	< 60	18.3%			Ref	
	≥ 60	9.4%			0.754 (0.653~0.872)	
Race			4.091	0.129	NI	
	White	11.7%				
	Black	12.6%				
	Others	16.2%				
Primary Site			9.312	0.010		0.019
	Cardia, NOS	13.2%			Ref	
	Non-cardia	13.2%			0.715 (0.549~0.931)	0.013
	Stomach, NOS	9.0%			0.728 (0.580~0.913)	0.006
Grade			0.581	0.446	NI	
	Grade I/II	17.4%				
	Grade III/IV	12.0%				
Histologic type			3.187	0.364	NI	
	Carcinoma	9.8%				
	Adenocarcinoma	15.6%				
	Mucinous adenocarcinoma	12.9%				
	Signet ring cell carcinoma	9.0%				
Marital status			34.518	0.000		0.000
	Married	15.9%			Ref	
	Divorced	5.3%			0.652 (0.539~0.789)	0.000
	Single/Separated	15.0%			0.909 (0.685~1.206)	0.509
	Widowed	0%			0.712 (0.554~0.914)	0.008
LNs			6.903	0.009		0.025
	≤ 9	9.0%			Ref	
	> 9	13.2%			1.306 (1.034~1.649)	

A value of $P < 0.05$ indicates statistical significance.

Statistical analysis

The LNs cutoff points were analyzed using the X-tile program, identifying the cutoff with the minimum *P* values from log-rank χ^2 statistics for the categorical LNs in terms of survival. The Kaplan-Meier method was used to calculate the actual survival rate and to plot survival curves, followed by the log-rank test for clinical and histological variables. The Cox proportional hazard regression model was used to identify the variables that could independently influence survival in GC. Hazard ratios (HRs) and 95% confidence intervals (CI) were calculated. All statistical analyses were performed using SPSS ver.19.0 (SPSS Inc., Chicago, IL), and a value of $P < 0.05$ indicated statistical significance. All tests were 2 sided with $p < 0.05$ defined as statistically significant.

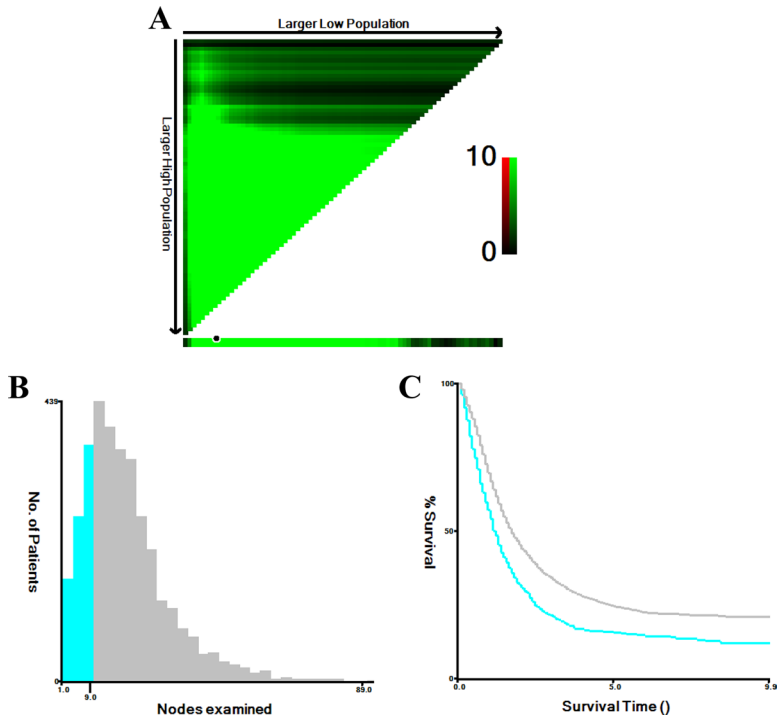

Figure 1: X-tile analysis of survival data from the SEER registry. X-tile analysis was performed using patients' data from the SEER registry, equally divided into training and validation sets. X-tile plots of the training sets are shown with plots of matched validation sets shown in the smaller inset (**A**). The optimal cut-point highlighted by the black circle in the left panels is shown on a histogram of the entire cohort (**B**), and a Kaplan-Meier plot (**C**). *P* values were determined using the cutoff point defined in the training set and applying it to the validation set. (The optimal cutoff value for LN count is 9, $\chi^2 = 58.163$, $P < 0.001$).

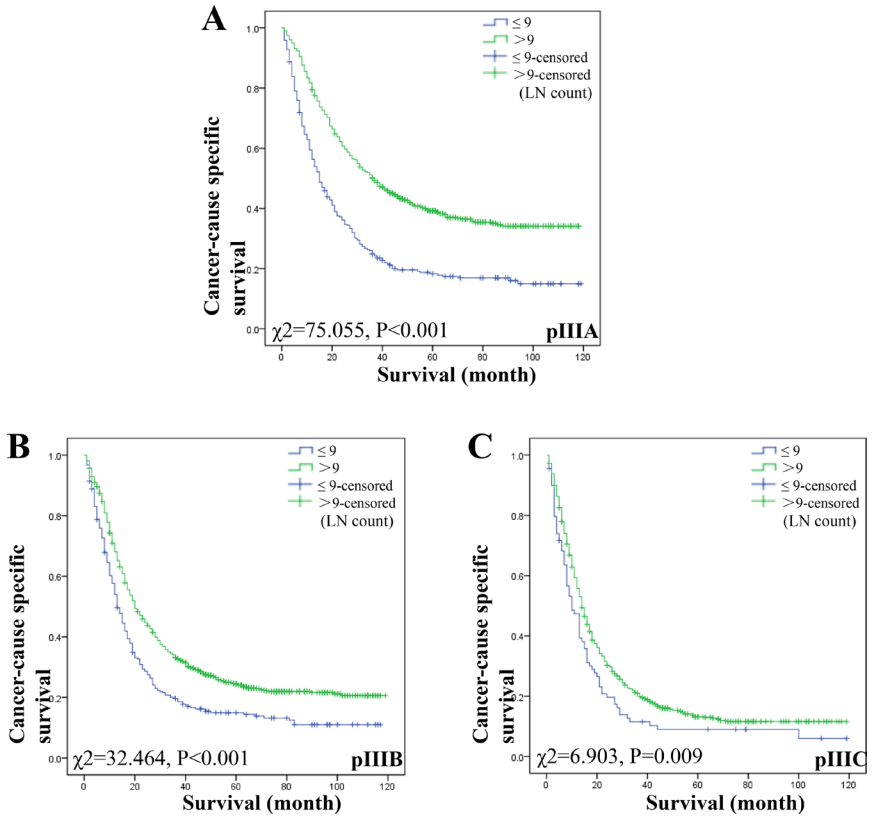

Figure 2: Log-rank tests of CSS comparing GC patients with LN count (≤ 9 VS > 9) for (**A**) stage pIIIA: $\chi^2 = 75.055$, $P < 0.001$; (**B**) stage pIIIB: $\chi^2 = 32.464$, $P < 0.001$; and (**C**) stage pIIIC: $\chi^2 = 6.903$, $P = 0.009$.

Author contributions

ZQH and XXL planned the study. WJW and HSY calculated statistics and analyzed the data. JY and HLW wrote the manuscript. XXL and XWL supervised the entire project. All authors reviewed the manuscript.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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