



Prognostic Value of the Number of Lymph Nodes Examined in Patients with Node-Negative Gastric Cancer

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Abstract

Background Our aim was to evaluate the prognostic value of the number of lymph nodes examined (eLNs) in patients with node-negative gastric cancer (GC) and further to adjust the American Joint Committee on Cancer (AJCC) 8th staging system based on the number of eLNs.

Methods Node-negative GC patients diagnosed during 1988–2015 from the Surveillance, Epidemiology, and End Results (SEER) database were included. On the basis of a primary cohort of 4159 node-negative GC patients, we built the adjusted AJCC 8th staging system, which was then internally validated by a bootstrap method, and externally validated with an independent cohort of 5565 node-negative GC patients.

Results The median number of eLNs was 10. For the training set, the optimal eLNs thresholds were determined to be 9 for node-negative GC patients. The adjusted AJCC 8th staging system for node-negative GC patients based on the number of eLNs had a significantly higher Harrell's concordance index than the initial AJCC 8th staging system (C-index, 0.635 versus 0.616; $P < 0.001$). Thus, the adjusted AJCC 8th staging system had superior prognostic stratification. Similar results were found in the validation set.

Conclusions For node-negative GC patients in the United States, the adjusted AJCC 8th staging system based on the number of eLNs predicted survival more accurately and discriminatively.

Keywords Gastric adenocarcinoma · Staging system · Overall survival

Introduction

Gastric cancer (GC) is the second leading cause of cancer-related death and the fifth most common cancer worldwide.¹ Although the incidence and mortality of GC has declined,² an estimated 26,240 GC diagnoses and more than 10,800 deaths

from GC are predicted in the United States (USA) in 2018.³ An accurate and discriminative staging system is necessary for doctors to make appropriate medical decisions and to assess their patients' prognoses. The most commonly used staging system for GC is the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) system, which stages patients on the basis of depth of primary tumor invasion (T), number of regional metastatic lymph nodes (N), and distant metastasis (M).⁴ The AJCC 8th staging system continues to base pN definitions on absolute number of regional metastatic lymph nodes and recommends that at least 16 regional lymph nodes be examined.⁵ However, half of the GC patients in the USA had fewer than 16 lymph nodes examined (eLNs).²

To better assess the prognosis of GC patients, especially for those with fewer than 16 eLNs, previous studies have proposed modifications to the AJCC staging system by including the positive lymph node ratio (LNR or Nr; i.e., positive lymph nodes divided by the number of eLNs) or log odds of positive lymph nodes (LODDS).^{6–8} However, the definition of the Nr0 classification is the same as that of the N0 classification which means that node-negative GC

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patients (approximately 40% of GC patients⁹) will not benefit from the Nr classification. The LODDS system is another node-based staging system. However, its performance for node-negative GC patients is only influenced by the number of eLNs. Moreover, the LODDS system is somewhat complex to explain and inconvenient for clinical practice.⁸ Thus, the two node-staging systems have limitations for node-negative GC patients.

In the light of these considerations, the purpose of our study was to evaluate the prognostic value of the number of eLNs in patients with node-negative GC and further to adjust the AJCC 8th staging system based on the number of eLNs.

Patients and Methods

We included patients in the Surveillance, Epidemiology, and End Results (SEER) database, who (1) were at least 18 years of age; (2) had histologically confirmed primary node-negative GC; (3) underwent resection of their primary site and regional lymph nodes; (4) had survival at least 1 month post-surgery; (5) had no distant metastases; and (6) had not undergone neoadjuvant therapy. The training set was composed of node-negative GC patients diagnosed between 1988 and 2015 from nine SEER registries (San Francisco-Oakland, Connecticut, Metropolitan Detroit, Hawaii, Iowa, New Mexico, Seattle-Puget Sound, Utah, and Atlanta). The validation set comprised two components: (1) patients diagnosed with node-negative GC in the period 1992–2015 from SEER directory of YR1992_2015.SJ_LA_RG_AK (Alaska, San Jose-Monterey, Los Angeles, and Rural Georgia) and (2) patients diagnosed with node-negative GC in the period 2000–2015 from SEER directory of YR2000_2015.CA_KY_LO_NJ and YR2005.LO_2nd_HALF (Greater California, Kentucky, Louisiana, New Jersey, and Greater Georgia). The median follow-up time for training and validation sets was 164 and 100 months, respectively.

Statistical Methods

The overall survival (OS) probabilities were calculated by Kaplan-Meier method and the different OS probabilities between groups were examined by log-rank test. The multivariate Cox proportional hazards regression was used to evaluate independently prognostic risk factors of OS and to calculate hazard ratio (HR) with 95% confidence intervals (CI). The eLNs cutoff points that determined the greatest actuarial survival difference were calculated by the X-tile program (<http://www.tissuearray.org>).¹⁰ The adjusted AJCC 8th staging system was built by combining the pT and pM with the adjusted pN. Harrell’s concordance index (C-index) was used to assess the relative discriminatory ability of the staging system; values closer to 1 indicated a higher predictive ability.¹¹ Additionally, the bootstrap technique with 1000 repetitions was used for internal validation and an independent cohort was used for external validation. The Akaike information criterion (AIC) within a Cox regression model was used to measure goodness of fit and discriminatory ability of the staging system; smaller AIC value indicated a more reasonable prognostic model.¹² All statistical analyses were performed using R-3.4 software (<http://www.r-project.org>). *P* < 0.05 (two-sided) was considered statistical significant.

Results

The included process for node-negative GC patients is shown in Fig. 1. Ultimately, 9724 node-negative GC patients were identified. Of whom, 4159 patients were classified into the training set and 5565 patients were classified into the validation set. The characteristics for node-negative GC patients are summarized in Table 1. The median number of eLNs of training set was 10 (interquartile range [IRQ], 5–17) and validation set was 10 (IRQ, 5–18). Only 30.61% of training set patients and 31.75% of validation set patients had more than 15 eLNs.

Fig. 1 Flowchart of node-negative gastric cancer patients included process. ^aICD-O-3: M-8140/3, M-8142/3 to M-8145/3, M-8210/3, M-8211/3, M-8255/3, M-8260/3 to M-8263/3, M-8310/3, M-8323/3, M-8480/3, M-8481/3, M-8490/3. eLNs lymph nodes examined

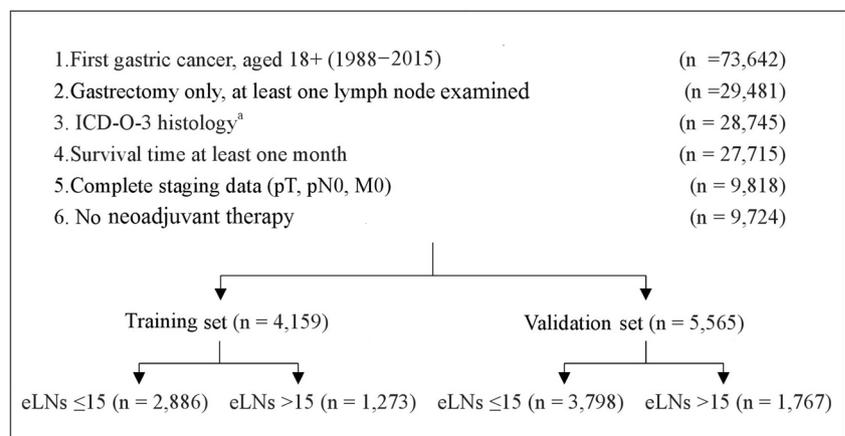


Table 1 The clinicopathological features for node-negative gastric cancer patients

Characteristic	All patients (<i>n</i> = 9724)	Training set (<i>n</i> = 4159)	Validation set (<i>n</i> = 5565)	<i>P</i> value ^a
Year of diagnosis				< 0.001
1988–2000	3092 (31.80)	2074 (49.87)	1018 (18.29)	
2001–2007	3171 (32.61)	1038 (24.96)	2133 (38.33)	
2008–2015	3461 (35.59)	1047 (25.17)	2414 (43.38)	
Age of diagnosis				0.024
≤ 70 years	4843 (49.80)	2016 (48.47)	2827 (50.80)	
> 70 years	4881 (50.20)	2143 (51.53)	2738 (49.20)	
Sex				0.994
Male	5397 (55.50)	2309 (55.52)	3088 (55.49)	
Female	4327 (44.50)	1850 (44.48)	2477 (44.51)	
Marital status				0.370
Single/others	3998 (41.11)	1732 (41.64)	2266 (40.72)	
Married	5726 (58.89)	2427 (58.36)	3299 (59.28)	
Ethnicity				0.672
White	5568 (57.26)	2374 (57.08)	3194 (57.39)	
Black	1411 (14.51)	617 (14.84)	794 (14.27)	
Asian or Pacific Islander	2620 (26.94)	1120 (26.93)	1500 (26.95)	
Others	125 (1.29)	48 (1.15)	77 (1.38)	
Origin				< 0.001
Non-Spanish-Hispanic	8004 (82.31)	3710 (89.20)	4294 (77.16)	
Spanish-Hispanic	1720 (17.69)	449 (10.80)	1271 (22.84)	
Location				< 0.001
Fundus of stomach	393 (4.04)	181 (4.35)	212 (3.81)	
Body of stomach	1169 (12.02)	455 (10.94)	714 (12.83)	
Gastric antrum	3561 (36.62)	1472 (35.39)	2089 (37.54)	
Pylorus	551 (5.67)	215 (5.17)	336 (6.04)	
Lesser curvature of stomach, NOS	1764 (18.14)	771 (18.54)	993 (17.84)	
Greater curvature of stomach, NOS	644 (6.62)	295 (7.09)	349 (6.27)	
Overlapping lesion of stomach	645 (6.63)	293 (7.04)	352 (6.33)	
Stomach, NOS	997 (10.25)	477 (11.47)	520 (9.34)	
Histology				< 0.001
Adenocarcinoma	7579 (77.94)	3331 (80.09)	4248 (76.33)	
Mucinous/signet ring cell	2145 (22.06)	828 (19.91)	1317 (23.67)	
Grade				< 0.001
Well differentiated	852 (8.76)	379 (9.11)	473 (8.50)	
Moderately differentiated	3029 (31.15)	1303 (31.33)	1726 (31.02)	
Poorly differentiated	5062 (52.06)	2066 (49.68)	2996 (53.84)	
Undifferentiated	171 (1.76)	85 (2.04)	86 (1.55)	
Unknown	610 (6.27)	326 (7.84)	284 (5.10)	
Tumor size				< 0.001
≤ 5 cm	6259 (64.37)	2565 (61.67)	3694 (66.38)	
> 5 cm	2209 (22.72)	1023 (24.60)	1186 (21.31)	
Unknown	1256 (12.92)	571 (13.73)	685 (12.31)	
AJCC 8th pT				0.005
T1	4283 (44.05)	1800 (43.28)	2483 (44.62)	
T2	1601 (16.46)	639 (15.36)	962 (17.29)	
T3	2510 (25.81)	1129 (27.15)	1381 (24.82)	
T4a	887 (9.12)	382 (9.18)	505 (9.07)	
T4b	443 (4.56)	209 (5.03)	234 (4.20)	
Surgery				0.793
Gastrectomy, NOS	8165 (83.97)	3487 (83.84)	4678 (84.06)	
Near total/total gastrectomy	1559 (16.03)	672 (16.16)	887 (15.94)	
Lymph nodes examined				0.237
≤ 15	6684 (68.74)	2886 (69.39)	3798 (68.25)	
> 15	3040 (31.26)	1273 (30.61)	1767 (31.75)	
Radiation therapy				< 0.001
Yes	1116 (11.48)	424 (10.19)	692 (12.43)	
No	8608 (88.52)	3735 (89.81)	4873 (87.57)	
Chemotherapy				< 0.001
Yes	1826 (18.78)	668 (16.06)	1158 (20.81)	
No, or unknown	7898 (81.22)	3491 (83.94)	4407 (79.19)	

Values are presented as number of patients (percentage of patients (%))

NOS, not otherwise specified

^a *P* value was calculated by Pearson's chi-squared test

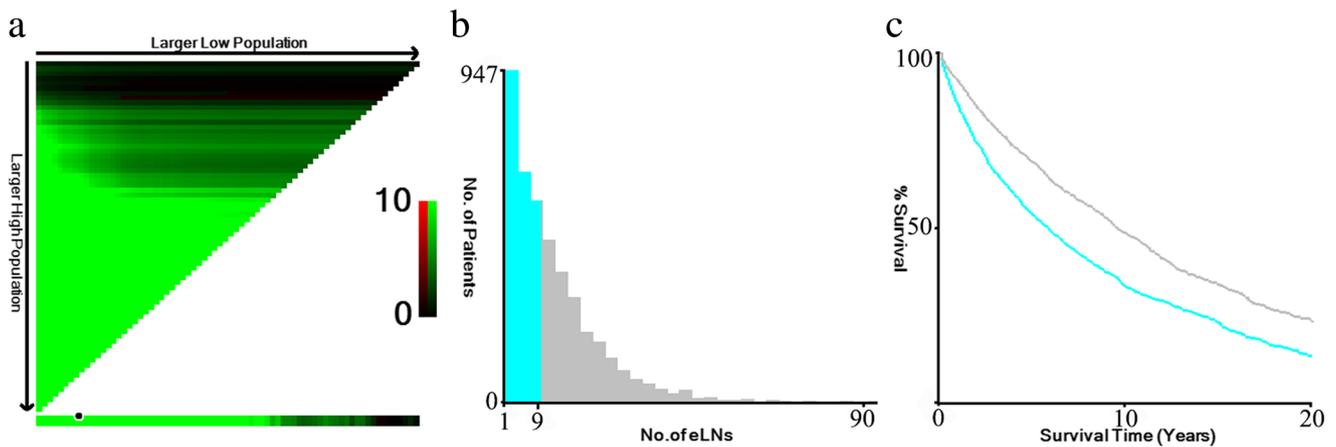


Fig. 2 X-tile analysis of survival data from the SEER registry. **a** X-tile plot. **b** Histogram plot. **c** Kaplan-Meier plot. The optimal cutoff point for node-negative gastric cancer patients was shown (number of 9, $P < 0.001$). eLNs lymph nodes examined

For the training set, the optimal eLNs thresholds that determined the most statistically survival difference for node-negative GC patients were found to be 9. Node-negative GC patients with more than 9 eLNs consistently had a better OS than those with 9 or fewer eLNs ($P < 0.001$; Fig. 2). We then reclassified the AJCC 8th stage pN0 based on the number of eLNs: adjusted pN0: eLNs > 9; adjusted pN1: eLNs ≤ 9. And the adjusted AJCC 8th staging system was established by combining the pT and pM with the adjusted pN (Supplemental Table 1).

For the training set, each AJCC 8th stage (IA–IIIA) was stratified into the adjusted AJCC 8th stages. After these stratifications, only stage IIIA was found to contain no subgroups of patients with significantly heterogeneous OS (Table 2). Similarly, when each adjusted AJCC 8th stage (IA–IIIB) was stratified into the original AJCC 8th stages, only adjusted stage IIA was found to contain subgroups of patients with

significantly heterogeneous OS (Table 2). These results indicated that the adjusted AJCC 8th staging system represented patients with more homogeneous OS compared with the original AJCC 8th staging system.

Survival curves for the original and adjusted AJCC 8th staging system are shown in Fig. 3. Furthermore, we compared prognostic performances for the original and adjusted AJCC staging systems and found the C-index for OS prediction of the adjusted AJCC 8th staging system was significantly higher than that of the original AJCC 8th staging system (C-index, 0.635 versus 0.616; $P < 0.001$; Table 3). The adjusted AJCC staging system also had a smaller AIC value and thus also represented a better prognostic stratification (Table 3).

To validate results from the training set, we conducted similar analyses on the validation set. Patients in each original AJCC 8th stage (IA–IIIA) showed statistically heterogeneous OS when stratified into the adjusted AJCC 8th stages

Table 2 Five-year overall survival based on the AJCC 8th stage and the adjusted AJCC 8th stage for the training set

AJCC 8th stage	Adjusted AJCC 8th stage						P value ^a
	IA 79.6% (915)	IB 70.6% (1229)	IIA 60.0% (898)	IIB 40.0% (727)	IIIA 33.6% (263)	IIIB 24.1% (127)	
T1N0M0/IA 74.3% (1800)	79.6% (915)	69.3% (885)					< 0.001
T2N0M0/IB 66.8% (639)		74.2% (344)	58.8% (295)				< 0.001
T3N0M0/IIA 50.0% (1129)			60.6% (603)	38.6% (526)			< 0.001
T4aN0M0/IIIB 37.9% (382)				43.9% (201)	32.5% (181)		0.001
T4bN0M0/IIIA 29.1% (209)					37.4% (82)	24.1% (127)	0.076
P value ^a	–	0.186	0.042	0.115	0.487	–	

Values are presented as 5-year overall survival (number of patients). Five-year overall survival was calculated by Kaplan-Meier method
AJCC, American Joint Committee on Cancer

^a P value was calculated by log-rank test. $P < 0.05$ indicates significant heterogeneity between subgroups

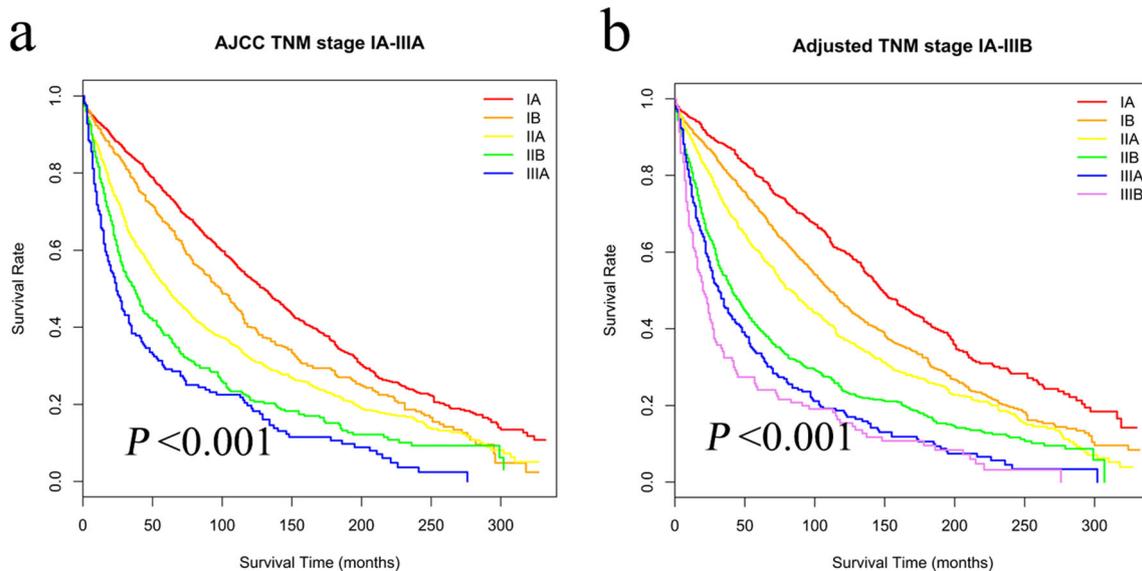


Fig. 3 Overall survival for different stages. **a** AJCC 8th staging system. Five-year overall survival for the AJCC 8th stages (IA–III A) was 74.3%, 66.8%, 50.0%, 37.9%, and 29.1%, respectively. **b** Adjusted AJCC 8th

staging system. Five-year overall survival for the adjusted AJCC 8th stages (IA–III B) was 79.6%, 70.6%, 60.0%, 40.0%, 33.6%, and 24.1%, respectively

(Table 4). Conversely, patients in each adjusted AJCC 8th stage (IA–III B) were found not to have statistically heterogeneous OS when stratified into the original AJCC 8th stages (Table 4). These results confirmed that the adjusted AJCC 8th staging system presented patients more homogeneous OS compared with the original AJCC 8th staging system. Furthermore, the adjusted AJCC 8th staging system offered better prognostic identification than the original AJCC 8th staging system (C-index, 0.647 versus 0.626; $P < 0.001$; Table 3).

Discussion

Recently, the AJCC 8th staging system made several modifications that were mainly based on recommendations from the International Gastric Cancer Association staging project, with 85% of cases collected from Japan and Korea.⁵ Although the

optimal number of eLNs remains controversial, the AJCC 8th GC staging system traditionally recommends that at least 16 lymph nodes should be examined. Notably, most patients in the Japan and Korea received more extensive lymphadenectomies ($\geq D2$) and had more eLNs.^{13, 14} In a study from Seoul National University Hospital in Korea, the median number of eLNs was 32.¹⁵ However, D2 lymphadenectomy had not been the standard procedure in Western countries in the past because of high perioperative complications and mortality.^{16, 17} Only about a third of the node-negative GC patients in our study had the AJCC recommended at least 16 eLNs, which meant that two thirds of the node-negative GC patients were inappropriately evaluated for the AJCC 8th staging system.

In this study, the number of eLNs was an independently prognostic factor for node-negative GC patients (Supplemental Table 2), which was consistent with the previous studies' results.^{18, 19} The dominant mechanism to explain

Table 3 Comparison of the performances of the two staging systems

	C-index (95% CI)	<i>P</i> value ^a	Validation ^b	AIC
Training set				
AJCC 8th staging system	0.616 (0.604–0.628)	Reference	0.616	39,333.842
Adjusted AJCC 8th staging system	0.635 (0.623–0.647)	< 0.001	0.635	39,229.953
Validation set				
AJCC 8th staging system	0.626 (0.614–0.638)	Reference	0.626	41,034.165
Adjusted AJCC 8th staging system	0.647 (0.635–0.659)	< 0.001	0.646	40,866.394

AJCC, American Joint Committee on Cancer; CI, confidence interval; AIC, Akaike information criterion

^a *P* value was calculated by R package “compareC”

^b Internal validation by bootstrap method ($n = 1000$)

Table 4 Five-year overall survival based on the AJCC 8th stage and the adjusted AJCC 8th stage for the validation set

AJCC 8th stage	Adjusted AJCC 8th stage						P value ^a
	IA 82.7% (1314)	IB 69.8% (1677)	IIA 61.7% (1244)	IIB 42.1% (863)	IIIA 35.4% (346)	IIIB 21.5% (121)	
T1N0M0/IA 75.9% (2483)	82.7% (1314)	69.2% (1169)					< 0.001
T2N0M0/IB 66.2% (962)		71.4% (508)	60.9% (454)				0.005
T3N0M0/IIA 53.3% (1381)			62.3% (790)	42.1% (591)			< 0.001
T4aN0M0/IIB 37.6% (505)				42.1% (272)	32.8% (233)		< 0.001
T4bN0M0/IIIA 31.1% (234)					41.8% (113)	21.5% (121)	< 0.001
P value ^a	–	0.861	0.193	0.080	0.160	–	

Values are presented as 5-year overall survival (number of patients). Five-year overall survival was calculated by Kaplan-Meier method

AJCC, American Joint Committee on Cancer

^a P value was calculated by log-rank test. P < 0.05 indicates significant heterogeneity between subgroups

the association between the number of eLNs and OS involves stage migration. The node-negative GC patients with few eLNs may not truly node negative but rather understaging, and an increased lymph node removal will reduce the chance of inappropriate understaging. Moreover, the isolated tumor cells and micrometastasis in lymph nodes are considered as the key factors that could increase the risk of recurrence and decrease the OS of GC patients.^{20, 21} Increased lymph node removal will reduce the chance of isolated tumor cells and micrometastasis lymph node residual and then improve survival.

In this study, the optimal eLNs thresholds that determined the most statistically survival difference for node-negative GC patients were found to be 9. The AJCC 8th stage pN0 with 9 or fewer eLNs consistently had a worse OS than that with more than 9 eLNs. Therefore, the AJCC 8th stage pN0 was classified into the adjusted pN0 and pN1 based on the number of eLNs: adjusted pN0: eLNs > 9; adjusted pN1: eLNs ≤ 9. In order not to further complicate an already complex staging model, the adjusted 8th staging system was established by combining the same T and the M with the adjusted pN instead of the AJCC 8th pN, which was similar to the AJCC 8th TNM staging system (Supplemental Table 1).

The adjusted AJCC 8th staging system satisfied three ideal models of stage conditions: (1) similar survival rates within a stage group (homogeneity), (2) decreased survival rates with increasing stage (monotonicity), (3) difference in survival between different stages (distinctiveness).¹⁷ Furthermore, the C-index of the adjusted AJCC 8th staging system to predict survival was significantly higher than that of the AJCC 8th staging system (C-index, 0.635 versus 0.616; P < 0.001). Then, the adjusted AJCC 8th staging system was subjected to internal and external validation. Similar results were found

that the adjusted AJCC 8th system was superior to the AJCC 8th staging system. Therefore, the adjusted AJCC 8th staging system should be taken into consideration when we are making medical decisions and evaluating the prognosis for node-negative GC patients.

It should be noticed that the optimal eLNs thresholds 9 did not mean that the number of 9 eLNs was adequate for node-negative GC patients, which only reflected the strongest impact of understaging may be observed with 9 or fewer eLNs. We should have more than 9 eLNs because of the fact that 5-year OS of the node-negative gastric patients always in favor of the higher number of eLNs. For the training set, 5-year OS increased from 53.4% (1 to 9 eLNs) to 86.2% (> 30 eLNs). An equal trend was encountered for the validation set; 5-year OS increased from 55.8 to 79.8% (Supplemental Table 3). Besides the dominant mechanism stage migration, another interpretation is that the number of lymph nodes itself may have a correlation with survival. Studies suggested that the number of lymph nodes might reflect the tumor-host relationship, and a higher number of lymph nodes dissected may simply reflect a host lymphocytic reaction to the tumor, which was associated with long survival.^{22–24}

Several limitations should be noticed in this study. Firstly, the optimal eLNs thresholds were determined to be 9 for node-negative GC patients based on a cohort with a median of 10 eLNs selected from the SEER database. The cutoff may not be the optimal for cohorts of patients with a far greater number of examined nodes, and modification of the eLNs intervals may be needed. Secondly, we only adjusted the AJCC 8th staging system for node-negative GC patients because of the fact that the LNR was confirmed suitable for node-positive GC patients, especially for those with limited eLNs.^{6, 25, 26} Thirdly, unlike neoadjuvant radiotherapy, we were unable to exclude

the patients who have received neoadjuvant chemotherapy. Before the publication of the MAGIC trial in 2006, the standard medical care in the United States was adjuvant chemotherapy according to the INT 0116 trial.^{27, 28} It was obvious that several patients may have received neoadjuvant chemotherapy in our study. To minimize the influence of the neoadjuvant chemotherapy, same analyses were conducted on the patients separated by the year of diagnosis in the training set. Similar result was found that the adjusted AJCC 8th staging system offered better prognostic identification than the AJCC 8th staging system for patients diagnosed before 2006 (C-index, 0.631 versus 0.613; $P < 0.001$), as well as for patients diagnosed after 2006 (C-index, 0.656 versus 0.635; $P < 0.001$) in the training set. Despite these limitations, the present study was significant because of that the adjusted AJCC 8th staging system based on the number of eLNs resulted in more node-negative GC patients being accurately and discriminatively staged without overcomplicating the existing staging system.

Conclusions

The optimal eLNs thresholds that determined the most statistically survival difference for node-negative GC patients were found to be 9. On this basis, we adjusted the AJCC stage pN0 for GC patients with 9 or fewer eLNs to pN1 and then combined the pT and pM with the adjusted pN to establish an adjusted AJCC 8th staging system that predicted survival more accurately and discriminatively. However, a validation set from another institution is warranted.

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Author Contributions Chun-Xi Wang and Ze-Long Yang had the concept for the study. Ze-Long Yang and Ming-Hua Zhu conducted data extraction and statistical analysis. Ze-Long Yang, Quan Shi, and Fu-Min Lu wrote the first draft. All authors edited and critically revised the final version of the manuscript.

Compliance with Ethical Standards

Conflict of Interest The authors declare that have no conflicts of interest.

Ethical Approval All patients in this study were collected from the SEER database, and we have got the permission of using the data.

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