

Original Article



OPEN ACCESS

Received: Aug 5, 2017

Revised: Oct 24, 2017

Accepted: Nov 20, 2017

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Conceptualization: N.S.A, S.G.I.; Data curation: N.S.A, S.G.I.; Formal analysis: N.S.A.; Investigation: N.S.A, S.G.I.; Methodology: N.S.A, S.G.I.; Project administration: S.G.I.; Resources: N.S.A, S.G.I.; Supervision: S.G.I.; Validation: N.S.A, S.G.I.; Visualization: N.S.A, S.G.I.; Writing - original draft: N.S.A.; Writing - review & editing: N.S.A, S.G.I.

Extensive Lymph Node Dissection Improves Survival among American Patients with Gastric Adenocarcinoma Treated Surgically: Analysis of the National Cancer Database

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ABSTRACT

Introduction: The extent of lymphadenectomy in the surgical treatment of gastric cancer is a topic of controversy among surgeons. This study was conducted to analyze the American National Cancer Database (NCDB) and conclude the optimal extent of lymphadenectomy for gastric adenocarcinoma.

Methods: The NCDB for gastric cancer was utilized. Patients who received at least a partial gastrectomy were included. Patients with metastatic disease, unknown TNM stages, R1/R2 resection, or treated with a palliative intent were excluded. Joinpoint regression was used to identify the extent of lymphadenectomy that reflects the optimal survival. Cox regression analysis and Bayesian information criterion were used to identify significant survival predictors. Kaplan-Meier was applied to study overall survival and stage migration.

Results: 40,281 patients of 168,377 met the inclusion criteria. Joinpoint analysis showed that dissection of 29 nodes provides the optimal median survival for the overall population. Regression analysis reported the cutoff ≥ 29 to have a better fit in the prognostic model than that of ≥ 15 . Dissection of ≥ 29 nodes in the higher stages provides a comparable overall survival to the immediately lower stage. Nonetheless, the retrieval of ≥ 15 nodes proved to be adequate for staging without a significant stage migration compared to ≥ 29 nodes.

Conclusion: The extent of lymphadenectomy in gastric adenocarcinoma is a marker of improved resection which reflects in a longer overall survival. Our analysis concludes that the dissection of ≥ 15 nodes is adequate for staging. However, the dissection of 29 nodes might be needed to provide a significantly improved survival.

Keywords: Gastric cancer; Lymphadenectomy; Survival; Cancer staging

INTRODUCTION

In the past decade, gastric cancer (GC) was the fifth most common cancer and the third leading cause of cancer-related death worldwide, with an estimated incidence of one million new cases yearly, and a case fatality rate of 60%–70% with a 2-fold male preponderance

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

[1]. More than 40% of GC cases occur in East Asia [2]. In the United States, approximately 26,370 new cases and 10,730 deaths from GC occurred in 2016 [3]. Meanwhile, Korea has the highest incidence rate in the world relative to the population, with 33,000 new cases of GC annually [4] and an annual mortality rate of up to 8,000 [5]. The incidence and mortality rates increased to 74,000 and 34,000 in Japan and to 283,500 and 221,500 in China, respectively [4]. This discrepancy in epidemiology may have contributed to the significant differences in the surgical expertise concerning this cancer between the eastern and the western hemispheres as well as a subsequent controversy about the adequate extent of lymphadenectomy.

D2 lymphadenectomy is considered the standard treatment for GCs beyond the T1 depth in East Asia, with numerous reports demonstrating a survival improvement in the D2 vs. D1 group dissections [6-8]. The Western stance against extensive nodal dissection stems from the results of large prospective, randomized trials in the United Kingdom [9] and the Netherlands [10] in the 1990s. Despite the efforts taken to standardize the procedures in these trials, a noteworthy high rate of morbidity and mortality was documented compared to the Eastern trials, without a significant survival benefit in the D2 arm. These results guided the Western surgeons to refrain from aggressive nodal dissections in GC surgeries.

The National Comprehensive Cancer Network (NCCN) currently recommends the retrieval of at least 15 nodes in GC to achieve proper staging and avoid stage migration [11]. However, the Surveillance, Epidemiology, and End Results (SEER) analysis demonstrated that the median number of examined nodes in the United States is 11 [12]. Importantly, evidence shows that even compliance with the current NCCN guidelines may lead to understaging, with an evident stage migration in approximately one-third of the patients whose nodal stages were upstaged as the number of retrieved nodes increased [13,14].

In this study, we used the National Cancer Database (NCDB), which is a large population-based cancer registry collected and maintained by the American College of Surgeons Committee on Cancer and records approximately 70% of the cancer cases nationwide. We aimed to analyze the NCDB for GC, study the impact of the extent of lymphadenectomy on staging and overall survival (OS) in an exclusively western patient population, and determine the level of nodal dissection that provides the optimal outcome in both staging and OS.

MATERIALS AND METHODS

The NCDB contains records of 168,377 patients diagnosed with GC between 2004 and 2014. Multiple steps of inclusion/exclusion were implemented to ensure proper selection for the purposes of the study as follows:

- 1) All patients with metastatic disease identified through data items **CS_METS_AT_DX** and **ANALYTIC_GROUP_STAGE** were excluded from the study. Selected patients were confirmed not to have any evidence of metastatic disease through data items **CS_METS_LIVER**, **CS_METS_LUNG**, **CS_METS_BRAIN**, and **CS_METS_BONE**.
- 2) All patients who were reported to receive any treatment modality with a palliative intent (data item **PALLIATIVE_CARE**) were excluded.
- 3) Patients who did not receive surgical treatment or “limited” resection such as “local destruction” or “local excision” as reported in data item **RX_SUMM_SURG_PRIM_SITE**

- were excluded. Only patients who received surgical intervention reported to be at least partial gastrectomy were included in the analysis.
- 4) Only patients who underwent R0 resection confirmed microscopically were included in the analysis (data item **RX_SUMM_SURGICAL_MARGINS**).
 - 5) Only patients confirmed to have gastric adenocarcinoma on final pathology were included. Other pathologies were excluded (data item **HISTOLOGY** using the International Classification of Diseases for Oncology-3).
 - 6) All patients who had a missing T stage (missing pathology report) or N stage (unknown number of resected nodes or positive nodes) were excluded (data items **TNM_PATH_T** and **TNM_PATH_N**).
 - 7) Patients with stage 0 gastric adenocarcinoma were removed from the dataset.
 - 8) All patients were staged according to the 7th edition of the American Joint Committee on Cancer (AJCC) staging classification of GC.

SPSS version 22.0 (IBM Corp., Armonk, NY, USA) was used to conduct the statistical analysis. Cox univariate and multivariate logistic regressions were utilized to determine significant predictors of survival. Joinpoint analysis was applied using the Joinpoint regression software 4.4.0.0 produced by the surveillance research program of the National Cancer Institute (Calverton, MD, USA). The median survival for each number of resected nodes, the number of resected nodes, and tumor, node, and metastasis (TNM) stage were incorporated in the model as the dependent factor, independent factor, and by-variable, respectively. The analysis was conducted to the node resection range between 1 and 40. For nodal resections >40, the number of cases at each point was <0.5% of the entire dataset. This limitation in size rendered the medians “unreached,” thus inapplicable in the analysis. Kaplan-Meier method was used to determine patients' survival according to the TNM stage and the extent of lymphadenectomy. Bayesian information criterion (BIC) was used to determine the optimal nodal cutoff in the models created based on the results of multivariate regression. Statistical significance was set at $P < 0.05$ throughout the analysis.

RESULTS

Dataset description

After the application of the inclusion/exclusion criteria, 40,281 patients with stage 1–3 gastric adenocarcinoma and having a known number of resected and positive lymph nodes, approached with no palliative intent, who underwent at least partial gastrectomy as a surgical treatment with R0 resection were included. The mean patient age was 66.33 ± 12.63 years, and 64.9% of the patients were men. **Table 1** summarizes the patients' demographic and perioperative characteristics.

Dataset validation

To validate the selection, a survival analysis was conducted on the selected group of patients based on their AJCC TNM stages. The analysis showed a median survival of 79.64 ± 1.66 , 50.01 ± 0.98 , and 22.57 ± 0.37 months for stages I, II, and III, respectively. **Fig. 1** demonstrates the results of the survival analysis. The 5-year survival rates in the selected population were: stage IA: 66.0%; stage IB: 48.2%; stage IIA: 44.1%; stage IIB: 34.5%; stage IIIA: 24.8%; stage IIIB: 16.8%; and stage IIIC: 11.9%, which is in accordance with the survival rates of patients with GC following surgery as reported by the American Cancer Society [15].

Table 1. Summary of the patients' demographic and perioperative characteristics as reported in the NCDB

Characteristics	Values
Age	66.33±12.63
Sex	Male 26,137 (64.9) Female 14,144 (35.1)
Race	White 29,639 (73.6) Black 6,047 (15.0) Other 4,595 (11.3)
Charlson score	0 27,112 (67.3) 1 9,735 (24.2) ≥2 3,434 (8.5)
Grade	Well-differentiated 2,616 (6.5) Moderately differentiated 11,879 (29.5) Poorly differentiated 23,386 (58.0) Not reported 2,400 (6.0)
Location	Cardia (C16.0) 13,793 (34.2) Fundus (C16.1) 1,308 (3.2) Corpus (C16.2) 3,149 (7.8) Antrum (C16.3) 8,842 (22.0) Pylorus (C16.4) 1,255 (3.1) Lesser curvature (C16.5) 3,786 (9.4) Greater curvature (C16.6) 1,681 (4.2) Overlapping lesion (C16.8) 2,343 (5.8) NOS (C16.9) 4,124 (10.2)
Mean No. of resected nodes (median)	16.04±10.92 (14)
No. of patients with ≥15 nodes retrieved	20,815 (51.7)
Mean No. of positive LN (median)	2.68±4.56 (1)
Mean LOH	11.23±10.99
30-day mortality	1,302 (3.2)
Chemotherapy	20,858 (51.8)
Radiation	14,682 (36.4)
AJCC Stage	I 12,655 (31.4) II 19,116 (47.5) III 8,510 (21.1)
T stage (7th edition)	T1 9,941 (24.7) T2 11,590 (28.8) T3 14,444 (35.9) T4 4,306 (10.7)
N stage (7th edition)	N0 (0 positive nodes) 19,564 (48.6) N1 (1–2 positive nodes) 8,189 (20.3) N2 (3–6 positive nodes) 6,695 (16.6) N3 (>7 positive nodes) 5,833 (14.5)

All values are expressed as mean±standard deviation or number (%) not otherwise specified. NCDB = National Cancer Database; NOS = Not Otherwise Specified; LN = lymph node; LOH = length of hospitalization; AJCC = American Joint Committee on Cancer.

Joinpoint regression

Joinpoint analysis was applied as described above to determine the optimal number of nodal resection for improved median survival. Regression analysis showed that the resection of 29 nodes yielded the optimal survival benefit for the entire population. Subgroup analysis indicated that 16, 28, and 29 nodes were the optimal numbers of retrieved nodes for improved survival in stages I, II, and III, respectively. **Fig. 2** shows the results of the Joinpoint analysis.

Regression analysis

The results of Cox univariate and multivariate regression analyses showed that age, presence of ≥2 comorbidities according to the Charlson score, tumor grade, higher nodal stage, and cardiac tumors were poor prognostic factors, whereas female sex, chemotherapy, radiation,

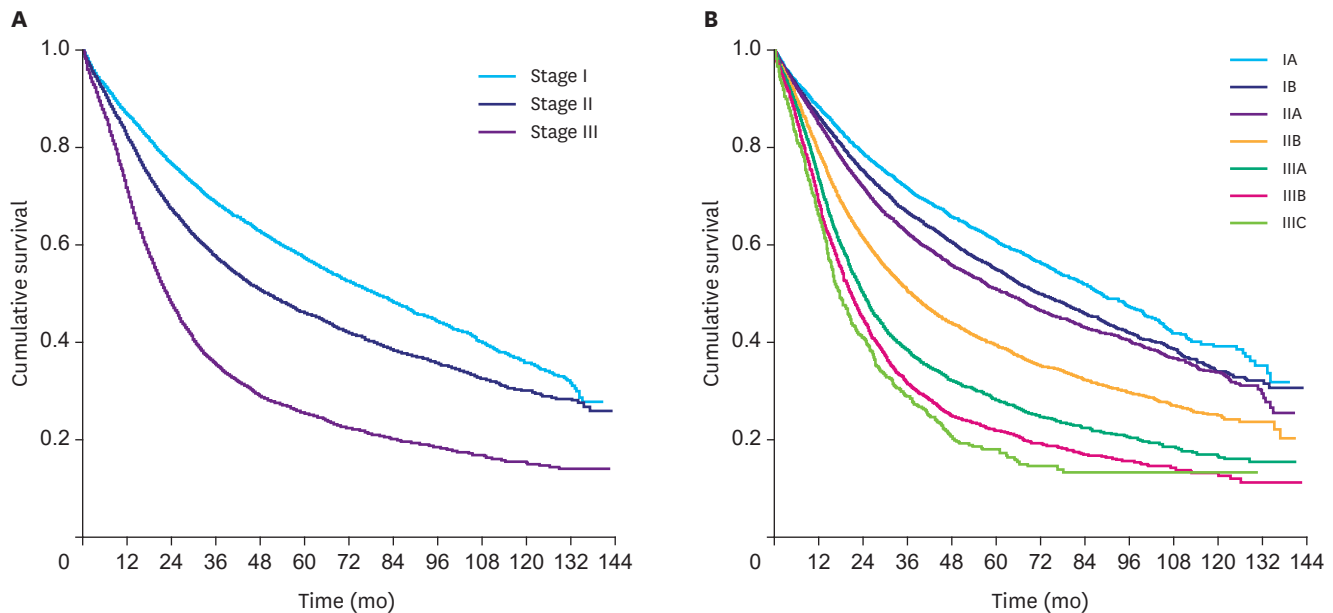


Fig. 1. Kaplan-Meier for OS according to the AJCC stage. (A) Stage I (median, 79.64±1.66 months); stage II (median, 50.01±0.98 months); and stage III (median, 22.57±0.37 months). (B) Stage IA (median, 89.07±2.80 months); stage IB (median, 72.74±2.02 months); stage IIA (median, 63.47±1.59 months); stage IIB (median, 37.32±0.89 months); stage IIIA (24.25±0.54 months); stage IIIB (median, 20.73±0.58 months); and stage IIIC (median, 17.81±1.06 months). OS = overall survival; AJCC = American Joint Committee on Cancer.

and the number of resected nodes (as a continuous variable) were favorable prognostic predictors of OS. **Table 2** demonstrates the results of the Cox univariate and multivariate regression analyses with the reported hazard ratios.

BIC

Based on the results of regression analysis, 2 models were created including the entire population and using the significant survival predictors, in addition to 2 nodal dissection cutoffs: ≥15 nodes per the current NCCN guidelines and ≥29 nodes based on our Joinpoint analysis. A total of 20,815 patients (51.7%) had ≥15 nodes retrieved as recommended by the NCCN, whereas 4,640 (11.5%) had ≥29 nodes resected. The BIC for the model with ≥15 nodes was 21,860.426. This was significantly higher than the one with the cutoff of ≥29 nodes, which was at 19,705.648, indicating a better fit when the latter cutoff is used.

Survival benefit

The survival benefit was compared for each AJCC stage based on the 2 dissection cutoffs: ≥15 nodes in compliance with the current NCCN guidelines and ≥29 nodes in compliance with the present NCDB Joinpoint. Notably, using ≥15 nodes as a cutoff did not improve survival in late-stage disease compared to the immediately lower stage. However, compliance with the ≥29 node cutoff provided a comparable median survival toward the immediately lower stage in IB (compared to IA), IIA (compared to IB), IIIC (compared to IIIB), and a trend in IIIA (compared to IIB), suggesting that the tumor is surgically downgraded in these stages when ≥29 nodes are retrieved during lymphadenectomy. The results are summarized in **Table 3**. Moreover, Kaplan-Meier curves demonstrated an increased survival between noncompliance with the nodal dissection guidelines (<15 nodes), compliance with the NCCN guidelines but not the NCDB Joinpoint (15–28 nodes), and compliance with both (≥29 nodes) as shown in **Fig. 3**.

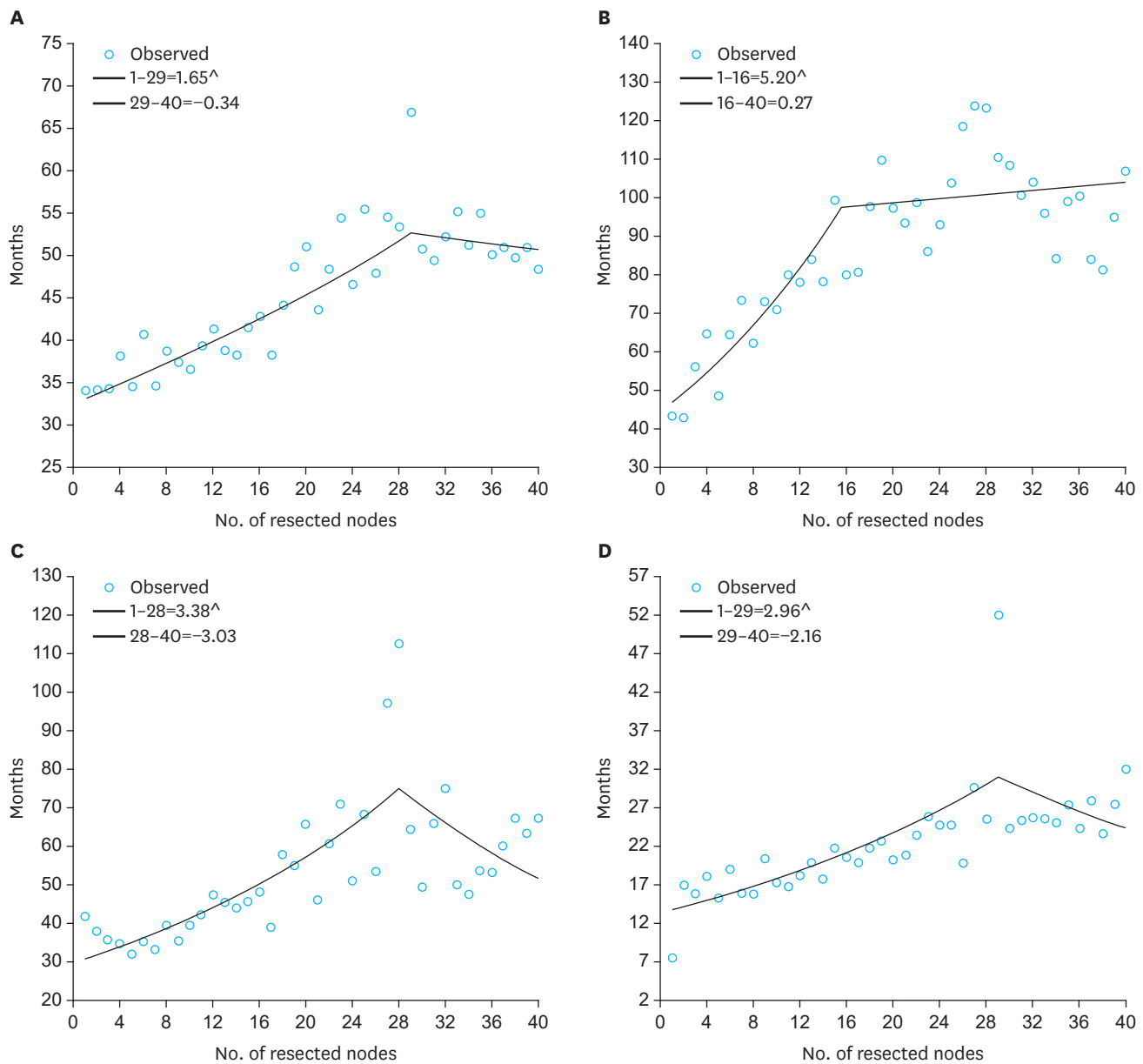


Fig. 2. Joinpoint analysis to determine the optimal node resection for median survival. (A) Overall: Joinpoint determined at 29 nodes. (B) Stage I: Joinpoint determined at 16 nodes. (C) Stage II: Joinpoint determined at 28 nodes. (D) Stage III: Joinpoint determined at 29 nodes.

Stage migration

To demonstrate the effect of stage migration in these survival curves, the rate of each N stage and the mean number of metastatic nodes were compared for each T stage. Remarkably, the retrieval of <15 nodes resulted in an evident nodal understaging throughout the T stages.

Also, the results show that the nodal sampling of ≥15 nodes is adequate for nodal staging in T1-T3 given the correspondence in N stages compared to ≥29 nodes, which indicates that the survival benefit between groups is truly attributed to a better disease control and not stage migration.

Table 2. Results of univariate and multivariate Cox regression analyses for significant predictors of survival in gastric adenocarcinoma

Characteristics	Univariate analysis		Multivariate analysis	
	HR (CI)	P	HR (CI)	P
Age	1.021 (1.019–1.024)	<0.001	1.025 (1.023–1.026)	<0.001
Sex				
Male	Reference		Reference	
Female	0.911 (0.882–0.968)	<0.001	0.908 (0.880–0.937)	<0.001
Race				
White	Reference			
Black	0.999 (0.994–1.061)	0.152	NS	NS
Other	0.990 (0.964–1.044)	0.118	NS	NS
Charlson score				
0	Reference		Reference	
1	1.122 (1.091–1.163)	<0.001	1.083 (1.046–1.120)	<0.001
≥2	1.455 (1.407–1.496)	<0.001	1.407 (1.340–1.478)	<0.001
Grade				
Well-differentiated	Reference		Reference	
Moderately differentiated	1.588 (1.439–1.766)	<0.001	1.304 (1.211–1.404)	<0.001
Poorly differentiated	2.111 (1.883–2.241)	<0.001	1.624 (1.511–1.746)	<0.001
Tumor location				
Non-cardiac adenocarcinoma	Reference		Reference	
Cardiac adenocarcinoma	1.128 (1.100–1.151)	<0.001	1.396 (1.352–1.441)	<0.001
Chemotherapy	0.859 (0.838–0.875)	<0.001	0.844 (0.809–0.880)	<0.001
Radiation	0.931 (0.907–0.944)	<0.001	0.921 (0.844–0.960)	<0.001
No. of resected nodes	0.989 (0.988–0.991)	<0.001	0.978 (0.977–0.980)	<0.001
Nodal stage				
N0	Reference		Reference	
N1	1.742 (1.678–1.808)	<0.001	1.896 (1.821–1.975)	<0.001
N2	2.379 (2.292–2.469)	<0.001	2.841 (2.724–2.963)	<0.001
N3	3.301 (3.181–3.426)	<0.001	4.511 (4.313–4.719)	<0.001

HR = hazard ratio; CI = confidence interval; NS = not significant.

Table 3. Survival benefit based on the AJCC TNM stages and compliance with either the current NCCN guidelines (≥15 nodes) or with the NCDB Joinpoint (≥29 nodes)

AJCC TNM stages	Stage IA	Stage IB	Stage IIA	Stage IIB	Stage IIIA	Stage IIIB	Stage IIIC
Compliance with the NCCN guidelines (≥15 nodes retrieved)							
Median survival (mon)	126.95±9.56	94.26±4.83	91.17±3.65	42.58±1.82	28.12±0.97	22.67±0.79	20.01±1.43
P	<0.001	0.019	<0.001	<0.001	<0.001	<0.001	0.029
Compliance with the current NCDB Joinpoint (≥29 nodes retrieved)							
Median survival (mon)	127.51±33.82	126.26±26.13	114.46±22.95	52.93±4.34	43.22±3.09	25.13±1.97	23.56±4.26
P	0.116	0.340	<0.001	0.030	<0.001	0.881	

AJCC = American Joint Committee on Cancer; TNM = tumor, node, and metastasis; NCCN = National Comprehensive Cancer Network; NCDB = National Cancer Database.

In T4, however, more than 29 nodes are required to achieve a more accurate nodal staging, suggesting a combined effect of adequate dissection and stage migration on the survival difference. The results are shown in **Table 4**.

Operative outcomes

The NCDB reports on the length of hospitalization (LOH), 30-day readmission, and 30-day mortality as the main surgical outcomes. The resection of ≥29 nodes was associated with a significantly higher 30-day mortality (4.3%) compared to resection of 15–28 nodes and <15 nodes (3.0% and 2.1%, respectively; P<0.001). Other outcomes were not different between the groups of node dissection (<15, 15–28, and ≥29 nodes), including 30-day readmission rates (6.6%, 6.0%, and 6.7%, respectively; P=0.097), and mean LOH (11.54, 10.63, and 11.15 days, respectively; P=0.198).

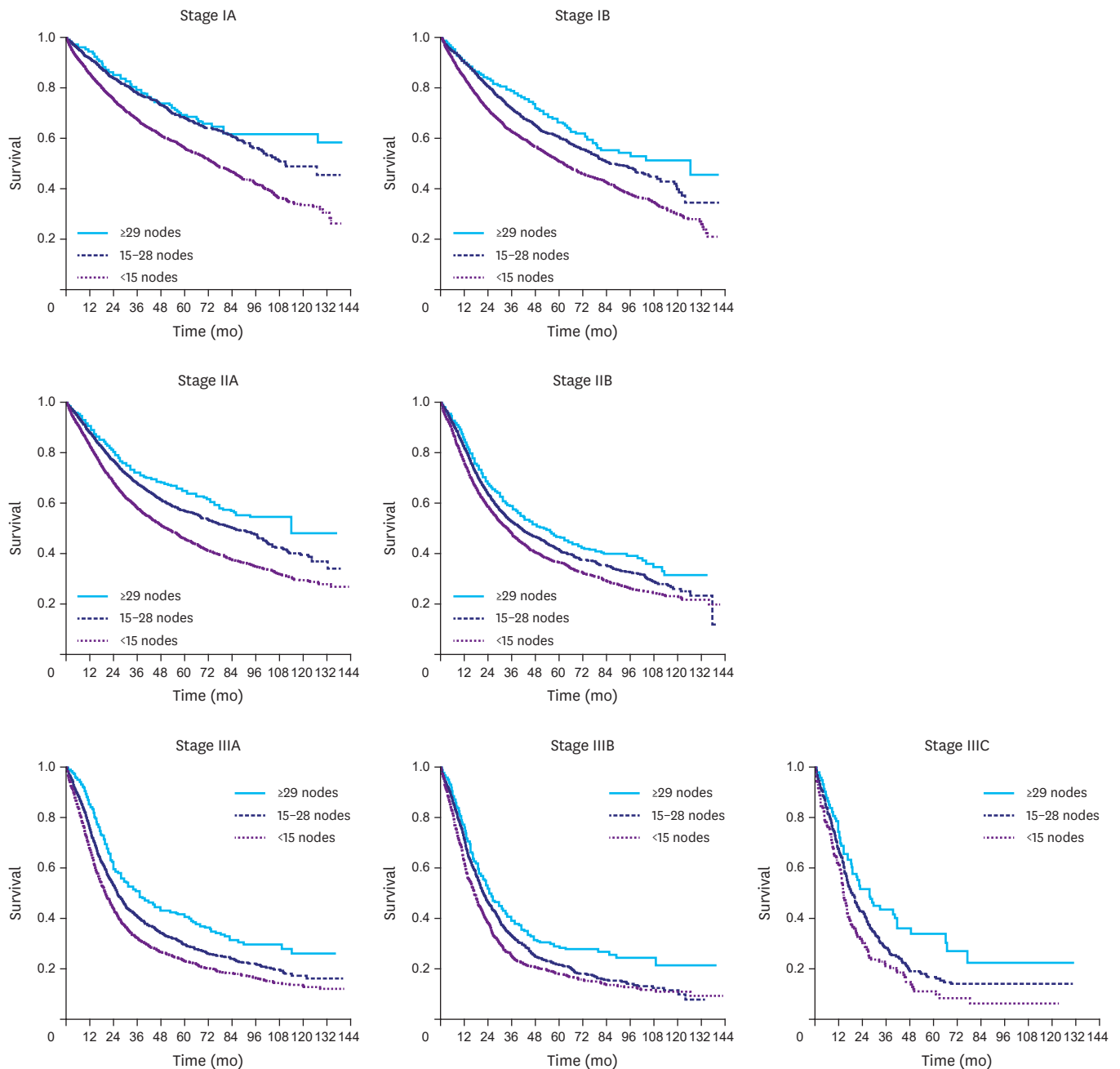


Fig. 3. Kaplan-Meier curves demonstrating the survival benefit for each TNM stage based on the cutoff of retrieved nodes. TNM = tumor, node, and metastasis.

DISCUSSION

The standard extent of lymphadenectomy in GC surgery is yet to be established among western surgeons. The current western practice is mostly influenced by the concern of the high morbidity and mortality following D2 lymphadenectomy, without a significant survival benefit based on the British [9] and Dutch trials [10], despite some positive evidence of the role of extensive node dissection in other studies [16,17]. Increasing evidence shows that the morbidity in D2 lymphadenectomy can be significantly reduced by performing spleen- and

Table 4. Comparison of the 3 lymphadenectomy cutoffs of inadequate nodal sampling (<15 nodes), compliance with the NCCN guidelines but not NCDB Joinpoint (15–28 nodes), and compliance with both (≥29 nodes) to demonstrate the effect of nodal stage migration as the number of retrieved nodes increases

T stage		<15 nodes retrieved	15–28 nodes retrieved	≥29 nodes retrieved	P	
					<15 nodes retrieved vs. 15–28 nodes retrieved	15–28 nodes retrieved vs. ≥29 nodes retrieved
T1	Rate of N0 (%)	79.9	73.6	71.8	<0.001	0.281
	Rate of N1 (%)	11.4	15.2	15.3		
	Rate of N2 (%)	7.8	9.8	11.6		
	Rate of N3 (%)	0.9	1.4	1.3		
	Positive nodes	0.54±1.56	0.99±2.73	1.16±3.24	<0.001	0.080
T2	Rate of N0 (%)	48.2	38.9	37.8	<0.001	0.207
	Rate of N1 (%)	26.5	23.2	21.6		
	Rate of N2 (%)	19.6	19.6	20.3		
	Rate of N3 (%)	5.7	18.3	20.3		
	Positive nodes	1.69±2.52	3.23±4.10	3.48±5.33	<0.001	0.074
T3	Rate of N0 (%)	32.3	23.0	22.8	<0.001	0.162
	Rate of N1 (%)	30.7	23.8	22.0		
	Rate of N2 (%)	25.1	29.3	30.5		
	Rate of N3 (%)	11.9	23.9	24.7		
	Positive nodes	2.88±3.35	5.20±5.31	6.90±8.55	<0.001	<0.001
T4	Rate of N0 (%)	30.8	16.1	11.7	<0.001	0.031
	Rate of N1 (%)	34.9	19.0	18.3		
	Rate of N2 (%)	21.9	34.7	34.4		
	Rate of N3 (%)	12.4	30.2	35.6		
	Positive nodes	3.58±4.19	7.96±6.99	13.86±13.01	<0.001	<0.001

All values are expressed as mean±standard deviation or percentage.

NCCN = National Comprehensive Cancer Network; NCBD = National Cancer Database.

pancreas-sparing nodal dissections [6,18-20], causing an important shift in the modern practice since the completion of the above-mentioned trials.

For staging purposes, the retrieval of at least 15 nodes was reported to be adequate [21,22], a guideline currently adopted and recommended by the NCCN. Nevertheless, the impact of lymphadenectomy on survival is not clearly stated in the current guidelines.

In our analysis, we used the Joinpoint regression to detect the extent of lymphadenectomy that yields the optimal survival and concluded that the retrieval of 29 nodes is the “Joinpoint” for the overall population, which is in exact agreement with the results of a recent analysis of the combined SEER and Yonsei University databases [23].

Joinpoint is a statistical software for the analysis of trends using joinpoint models; it takes trend data (e.g., incidence, rates, survival, and among others) and fits the simplest joinpoint model that the data allow to detect a change or modification in the behavior of the trend [24]. Interestingly, our subgroup analysis demonstrated that the survival benefit of lymphadenectomy for stage I cancers relapses to an insignificant slope after 16 nodes. On the other hand, stages II and III demonstrate an obvious survival benefit from a more extensive nodal dissection of up to 28 and 29 nodes, respectively. In the randomized trial by the Italian Gastric Cancer Study Group, a similar conclusion was made, indicating that extensive lymphadenectomy may only provide longer survival in the late stages of GC [25].

With regard to staging, our results support that the retrieval of ≥15 nodes is adequate to establish an accurate nodal stage as recommended by the NCCN, despite a trend toward the need for more nodes in T4 cancers to avoid stage migration into a better prognosis category and a false inflation of the survival in this group of patients. Notably, the rate of compliance

with the NCCN guidelines to retrieve at least 15 nodes in the NCDB was only 48%. Many national registry studies demonstrated that <40% of gastrectomies were compliant with these guidelines in the United States and the United Kingdom [12,26,27].

The same analysis also proved that the survival benefit associated with more extensive nodal dissection is attributed to aggressive disease control rather than stage migration. However, an aggressive approach in surgery for upper gastrointestinal cancer in western populations has been accompanied by a high rate of morbidity and mortality, mainly due to the low volume and limited surgeon experience. A “large-volume” center for GC in the United States is defined to perform >20 gastrectomies per year [28,29] compared to the Eastern experience where large tertiary care centers perform at least 200 GC surgeries yearly [30]. As a result, poorer surgical outcomes were noted in western populations, with inpatient mortality rates of 4%–9% per Medicare data [29] compared with the <1% mortality rate in Korean and Japanese trials [31,32]. The NCDB 2004–2014 reports a 30-day mortality of 3.4% in gastrectomies performed with curative intent for stages I–III gastric adenocarcinoma, with higher rates in more extensive lymphadenectomies.

The limitations of the current analysis originate from its retrospective nature, data loss and misreport, and lack of detailed surgical inputs and outcomes, all of which are inherent shortcomings of registry-based data banks. Therefore, we were not able to study the impact of certain factors known to influence the outcome, such as incidental splenectomy and distal pancreatectomy as part of the extensive lymphadenectomy. Another criticism often highlighted in such analyses is patient selection. We applied very strict inclusion/exclusion criteria to achieve a proper selection of the cases of interest and validated the dataset with epidemiologic and survival analyses that matched the nationally reported oncologic data. These steps were taken to ensure that the selected patients represent the population of the surgically treated gastric adenocarcinoma and that the conclusions of this analysis would provide a clinical relevance to the management of these patients.

The extent of lymphadenectomy in gastric adenocarcinoma is a marker of an improved disease control that results in longer OS. The results of our analysis indicated that retrieval of ≥ 15 nodes is adequate for staging. However, 29 nodes might be needed to achieve an optimal survival benefit throughout the AJCC TNM stages. Extensive lymphadenectomy in western populations continues to demonstrate high rates of postoperative mortality; thus, extrapolation of the current data should be done with caution with regard to patient selection for more extensive lymphadenectomy.

ACKNOWLEDGMENTS

We acknowledge Dr. Jinsong Chen from the Department of Biostatistics, University of Illinois College of Medicine, for his guidance during the statistical analysis of this work.

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