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Greater Lymph Node Retrieval Improves Survival in Node-Negative Resected Gastric Cancer in the United States

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ABSTRACT

Purpose: Guidelines in Western countries recommend retrieving ≥15 lymph nodes (LNs) during gastric cancer resection. This study sought to determine whether the number of examined lymph nodes (eLNs), a proxy for lymphadenectomy, effects survival in node-negative disease.
Materials and Methods: The US National Cancer Database (2003–2011) was reviewed for node-negative gastric adenocarcinoma. Treatment was categorized by neoadjuvant therapy (NAT) vs. initial resection, and further stratified by eLN. Kaplan-Meier and Weibull models were used to analyze overall survival.
Results: Of the 1,036 patients who received NAT, 40.5% had ≤10 eLN, and most underwent proximal gastrectomy (67.8%). In multivariate analysis, greater eLN was associated with improved survival (eLN 16–20: HR, 0.71; P=0.039, eLN 21–30: HR, 0.55; P=0.001). Of the 2,795 patients who underwent initial surgery, 42.5% had ≤10 eLN, and the majority underwent proximal gastrectomy (57.2%). In multivariate analysis, greater eLN was associated with improved survival (eLN 11–15: HR, 0.81; P=0.021, eLN 16–20: HR, 0.73; P=0.004, eLN 21–30: HR, 0.62; P<0.001, and eLN >30: HR, 0.58; P<0.001).
Conclusions: In the United States, the majority of node-negative gastrectomies include suboptimal eLN. In node-negative gastric cancer, greater LN retrieval appears to have therapeutic and prognostic value, irrespective of initial treatment, suggesting a survival benefit to meticulous lymphadenectomy.

Keywords: Stomach neoplasms; Lymph node excision; Gastric cancer; Survival

INTRODUCTION

In the United States, gastric cancer is a devastating disease, with a 5-year overall survival of only 30.6% [1]. Surgical resection with adequate oncologic margins and removal of regional lymph nodes (LNs) offers the best hope for long-term survival. LN status is an important prognostic indicator in gastric cancer, with positive LNs suggesting a poor prognosis [2,3]. However, patients with node-negative disease still have a 17% chance of disease recurrence, and a 5-year overall survival of only 53% [4].

Conflict of Interest

The National Cancer Data Base (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The CoC's NCDB and the hospitals participating in the CoC's NCDB are the source of the de-identified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

This study was selected and presented as a poster presentation at the Society for Surgery of the Alimentary Tract's Annual Meeting at Digestive Disease Week in Chicago, IL, May 6–9, 2017.

Extent of lymphadenectomy remains a controversial topic in surgical management of gastric cancer. In Japan, extended lymphadenectomy, referring to a D2 LN dissection, is standard of care [5]. However, initial data from randomized controlled trials in British and Dutch populations failed to find a significant survival benefit for D2 dissections over D1 dissections [6,7]. Long-term follow-up in the Dutch study found improved disease specific survival with D2 dissections [8]. In the United States, the National Comprehensive Cancer Network (NCCN) guidelines currently recommend gastrectomy with D1 or modified D2 LN dissection, with preservation of the distal pancreas and spleen; the surgeon should examine at least LNs [9]. Recent evidence from Asian populations demonstrates a survival benefit to increasing the number of examined lymph nodes (eLNs), even in node-negative disease [10-13]. However, this has not been explored in African, European, or North and South American populations. Given differences in gastric cancer between Asian and other populations, the results of these studies are not necessarily applicable to African, European, or North and South American populations. This study sought to determine whether number of eLN, a proxy for lymphadenectomy, effects survival in US patients with node-negative gastric cancer.

MATERIALS AND METHODS

Data

This was a retrospective cohort study using data from the National Cancer Data Base (NCDB). This clinical oncology database, jointly sponsored by the American College of Surgeons and the American Cancer Society, is sourced from hospital registry data collected from over 1,500 Commission on Cancer (CoC) accredited facilities. The NCDB captures over 70% of newly diagnosed cancer cases in the United States. The NCDB contains readily available de-identified data, and therefore this study was not subject to institutional review board approval or oversight.

Patient selection

The NCDB (2003–2011) was reviewed for patients diagnosed with clinical stages I–III gastric cancer, who underwent surgical resection, with or without systemic therapy. Patients with clinical stage IV disease or unknown stage were excluded. Clinical stage is coded in the NCDB according to standard practice at each individual institution. Patients who did not undergo surgical resection were excluded. Patients were categorized by receipt of neoadjuvant therapy (NAT) vs. initial resection, and further stratified by number of eLN: ≤10, 11–15, 16–20, 21–30, and >30.

Outcomes and covariates

The primary variable assessed was overall survival. Analyses controlled for patient and disease characteristics including age, sex, race, insurance type (private, Medicare, Medicaid and other government programs, unknown, and not insured), and the Charlson/Deyo comorbidity index (CCI), an index of 15 comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, diabetes, diabetes with chronic complications, hemiplegia or paraplegia, renal disease, moderate or severe liver disease, and acquired immunodeficiency syndrome) [14,15]. Median income of the patient's zip code was used as a proxy for socioeconomic status. Treatment facilities were characterized by type (community, comprehensive community, academic or research institution, other) and US geographic region (northeast, south, mid-west, west). Disease was characterized by the American Joint Committee on Cancer (AJCC) clinical stage, surgery type (proximal gastrectomy, total gastrectomy, distal gastrectomy, and surgery not otherwise specified), number of regional LNs removed, number of positive regional LNs, surgical margins (no residual tumor, residual tumor not otherwise specified, microscopic residual tumor, macroscopic residual tumor, and indeterminate and unknown margins), pathologic stage, and adjuvant therapy. The main covariate of interest was eLN, which was subdivided into 5 groups: ≤10, 11–15, 16–20, 21–30, and >30 LNs.

Statistical analysis

Statistical analyses were performed with Stata software (version 12.1; StataCorp., College Station, TX, USA). Patient, disease, and facility characteristics were compared within each cohort with analysis of variance for continuous variables and χ^2 tests for categorical variables. Kaplan-Meier analyses were performed for each clinical stage and treatment, and stratified by eLN. The proportional hazards assumption was violated, and thus multivariable survival analyses were performed for each initial treatment using a Weibull model, controlling for covariates described above.

RESULTS

From 2003 to 2011, the median number of eLN in node negative resected gastric cancer has steadily risen from 8 to 14 (**Fig. 1**).

Patient characteristics of NAT cohort

Of the 1,036 (27%) who received NAT, 40.5% (n=420) had ≤10, 21.8% (n=226) had 11–15, 16.8% (n=174) had 16–20, 13.4% (n=139) had 21–30, and 7.4% (n=77) had >30 eLN (**Fig. 2**). Of those who received NAT, 58.0% underwent a suboptimal lymphadenectomy as defined according to NCCN guidelines (<15 eLN).

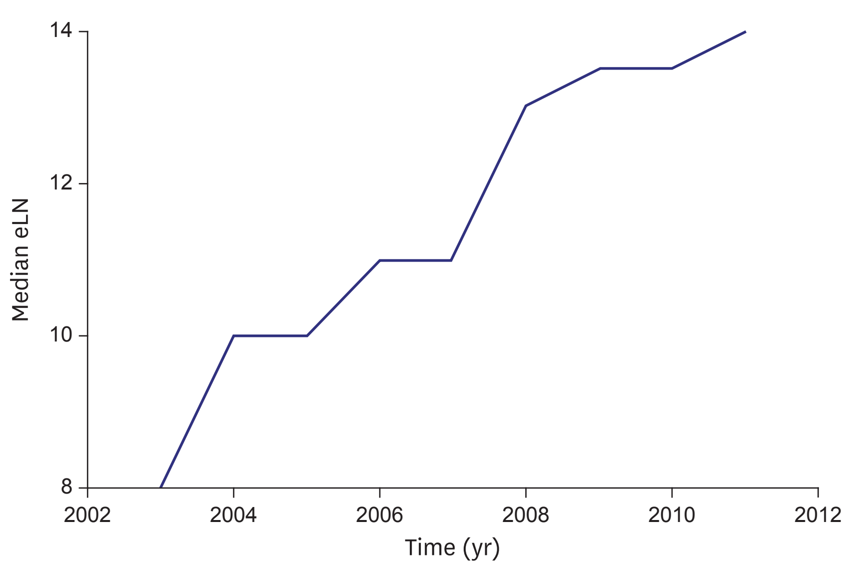

Fig. 1. Trends in median number of LN examined from 2003 to 2011.
LN = lymph node; eLN = examined lymph node.

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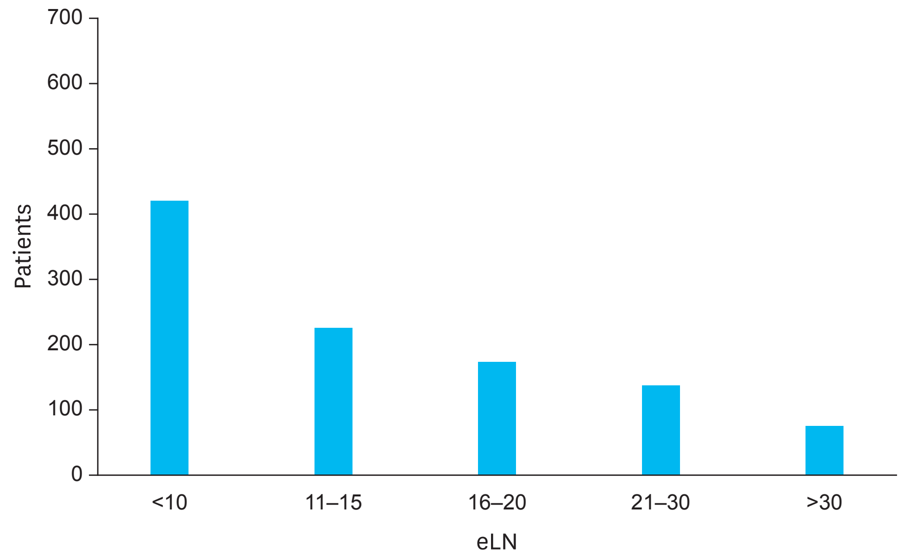

Fig. 2. Distribution of eLNs in NAT cohort.
eLN = examined lymph node; NAT = neoadjuvant therapy.

Patient, disease, and treatment characteristics of patients who received NAT, stratified by eLN, are presented in **Table 1**. Patients who received a suboptimal lymphadenectomy (eLN ≤10) tended to be male (P<0.001), were more likely to be treated at a comprehensive community center (P<0.001), and were more likely to undergo a proximal gastrectomy (P<0.001). Age (P=0.915),

Table 1. Patient, disease, and treatment characteristics of NAT cohort

Variable	≤10 (n=420, %)	11–15 (n=226, %)	16–20 (n=174, %)	21–30 (n=139, %)	>30 (n=77, %)	P-value
Age	61.5	61.4	60.9	62.0	61.0	0.915
18–59	41.2	39.4	38.5	38.8	45.5	
60–69	35.7	39.4	42.5	34.5	27.3	
70–79	20.7	19.5	18.4	23.7	24.7	
80–90	2.4	1.8	0.6	2.9	2.6	
Sex						<0.001
Male	82.1	85.8	83.3	68.3	68.8	
Female	17.9	14.2	16.7	31.7	31.2	
Race						0.395
White (non-Hispanic)	84.8	86.7	85.6	81.3	75.3	
Black (non-Hispanic)	4.0	3.5	2.9	7.9	6.5	
Other (non-Hispanic)	2.1	2.2	1.1	2.9	3.9	
Hispanic	9.0	7.5	10.3	7.9	14.3	
Insurance						0.260
Private	52.6	52.7	58.0	54.0	50.6	
Medicare	38.3	38.9	33.9	38.1	35.1	
Medicaid & other government	6.9	4.9	6.3	5.0	9.1	
Unknown	0.5	1.8	1.7	2.2	0.0	
Not insured	1.7	1.8	0.0	0.7	5.2	
Median income						0.561
<58,000	12.1	8.8	12.1	11.5	15.6	
58,000–74,000	21.4	25.7	27.6	20.9	19.5	
74,000–93,000	26.7	28.8	27.0	29.5	19.5	
>93,000	36.7	34.5	31.0	34.5	42.9	
Comorbidities						0.785
CCI score 0	73.3	75.7	76.4	75.5	79.2	
CCI score 1	22.1	20.4	21.8	20.9	19.5	
CCI score 2	4.5	4.0	1.7	3.6	1.3	

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Table 1. (Continued) Patient, disease, and treatment characteristics of NAT cohort

Variable	≤10 (n=420, %)	11–15 (n=226, %)	16–20 (n=174, %)	21–30 (n=139, %)	>30 (n=77, %)	P-value
Facility type						<0.001
Community	3.1	5.8	3.4	2.9	1.3	
Comprehensive community	42.4	32.3	26.4	22.3	31.2	
Academic/research	54.0	61.9	70.1	74.8	67.5	
Other	0.5	0.0	0.0	0.0	0.0	
Facility location						0.033
Northeast	18.8	22.1	25.9	30.2	29.9	
South	36.9	35.4	32.2	27.3	33.8	
Midwest	33.1	28.3	27.0	30.2	16.9	
West	11.2	14.2	14.9	12.2	19.5	
Clinical stage						0.901
Stage II	51.4	52.2	52.9	55.4	57.1	
Stage III	48.3	47.8	46.6	44.6	42.9	
Surgery type						<0.001
Proximal gastrectomy	74.0	69.9	67.8	54.7	50.6	
Total gastrectomy	19.0	23.0	24.7	40.3	40.3	
Distal gastrectomy	6.9	7.1	7.5	5.0	9.1	
Regional lymph nodes examined	6.2	13.0	17.7	24.5	39.0	<0.001
Surgical margins						0.225
No residual tumor	96.0	95.6	94.3	95.0	96.1	
Residual tumor, NOS	1.2	1.3	1.1	2.9	0.0	
Microscopic residual tumor	2.1	2.2	2.3	1.4	1.3	
Macroscopic residual tumor	0.0	0.0	0.0	0.0	1.3	
Indeterminate or unknown	0.7	0.9	2.3	0.7	1.3	
Pathological stage						0.124
Stage 0	3.3	3.5	7.5	2.9	2.6	
Stage 1	29.0	32.7	24.7	31.7	41.6	
Stage 2	36.9	36.7	37.4	34.5	32.5	
Stage 3	3.1	1.3	4.0	2.9	2.6	
Stage 4	0.5	0.4	0.0	0.0	2.6	
Unknown	23.6	23.9	22.4	23.7	13.0	

NAT = neoadjuvant therapy; CCI = Charlson/Deyo comorbidity index; NOS = not otherwise specified.

race (P=0.395), comorbidities (P=0.785), surgical margins (P=0.225), and clinical and pathological stages (P=0.901 and P=0.124, respectively) did not significantly differ among eLN groups.

Survival of NAT Cohort

Kaplan-Meier analyses of patients who received NAT are stratified by eLN and presented in **Fig. 3**. Inadequate lymphadenectomy (eLN ≤10) was associated with worse survival in clinical stage II and III disease; however, this association was only significant in stage III disease (P=0.020).

Results of a Weibull survival model of patients who received NAT are presented in **Table 2**. A greater number of eLN was associated with improved hazards of mortality (eLN 16–20: HR, 0.71; P=0.039, eLN 21–30: HR, 0.55; P=0.001). Treatment at an academic center was also associated with a reduction in mortality (HR, 0.52, P=0.005). Greater age (80–90: HR, 3.52; P<0.001) and coverage by Medicaid (HR, 1.59, P=0.019) were associated with increased hazards of mortality.

Patient characteristics of initial surgery cohort

Of the 2,795 patients who underwent initial surgery, 42.5% (n=1,187) had ≤10, 19.8% (n=553) had 11–15, 14.5% (n=404) had 16–20, 15.5% (n=432) had 21–30, and 7.8% (n=219) had >30 eLN (**Fig. 4**). Of those who underwent initial surgery, 58.6% underwent a suboptimal lymphadenectomy (<15 eLN).

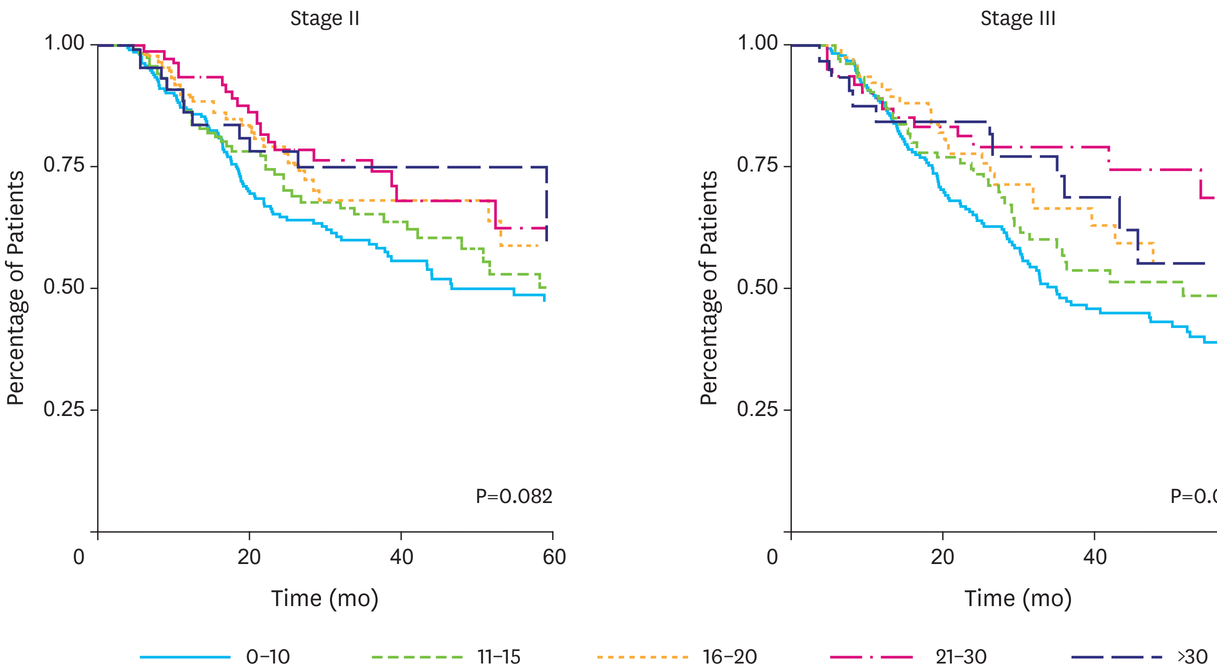

Fig. 3. Survival by eLNs in NAT cohort.
eLN = examined lymph node; NAT = neoadjuvant therapy.

Table 2. Factors impacting survival in NAT cohort

Variable	HR	95% CI		P-value
		Lower	Upper	
No. of lymph nodes examined				
≤10	Reference			
11–15	0.86	0.66	1.11	0.246
16–20	0.71	0.52	0.98	0.039
21–30	0.55	0.38	0.79	0.001
>30	0.75	0.48	1.17	0.203
Age				
18–59	Reference			
60–69	1.08	0.83	1.41	0.561
70–79	1.54	1.09	2.17	0.014
80–90	3.52	1.87	6.64	<0.001
Sex				
Male	Reference			
Female	0.96	0.74	1.25	0.757
Race				
White (non-Hispanic)	Reference			
Black (non-Hispanic)	0.71	0.41	1.24	0.227
Other (non-Hispanic)	0.67	0.29	1.54	0.348
Hispanic	1.05	0.75	1.48	0.777
Insurance				
Private	Reference			
Medicare	1.02	0.77	1.35	0.911
Medicaid & other government	1.59	1.08	2.35	0.019
Unknown	0.82	0.26	2.61	0.738
Not insured	1.67	0.77	3.65	0.195
Median income				
<58,000	Reference			
58,000–74,000	1.40	1.00	1.96	0.053
74,000–93,000	1.07	0.77	1.50	0.685
>93,000	0.92	0.66	1.29	0.645

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Table 2. (Continued) Factors impacting survival in NAT cohort

Variable	HR	95% CI		P-value
		Lower	Upper	
Comorbidities				
CCI score 0	Reference			
CCI score 1	1.22	0.96	1.55	0.100
CCI score 2	1.28	0.72	2.27	0.397
Facility type				
Community	Reference			
Comprehensive community	0.52	0.32	0.83	0.007
Academic/research	0.52	0.33	0.82	0.005
Other	1.05	0.14	8.14	0.961
Facility location				
Northeast	Reference			
South	1.18	0.89	1.56	0.249
Midwest	0.99	0.74	1.33	0.963
West	0.80	0.55	1.15	0.230
Surgery type				
Proximal gastrectomy	Reference			
Total gastrectomy	0.86	0.67	1.11	0.242
Distal gastrectomy	0.80	0.53	1.19	0.271
Surgical margins				
No residual tumor	Reference			
Residual tumor, NOS	2.05	1.05	4.01	0.035
Microscopic residual tumor	1.81	1.03	3.20	0.040
Macroscopic residual tumor	0.00	0.00	0.00	0.999
Indeterminate or unknown	1.09	0.39	2.99	0.874
Pathological stage				
Stage 0	Reference			
Stage 1	0.66	0.43	1.03	0.068
Stage 2	0.99	0.65	1.52	0.970
Stage 3	0.85	0.42	1.69	0.638
Stage 4	2.04	0.71	5.90	0.188
Unknown	0.62	0.39	0.98	0.041

NAT = neoadjuvant therapy; HR = hazard ratio; CI = confidence interval; CCI = Charlson/Deyo comorbidity index; NOS = not otherwise specified.

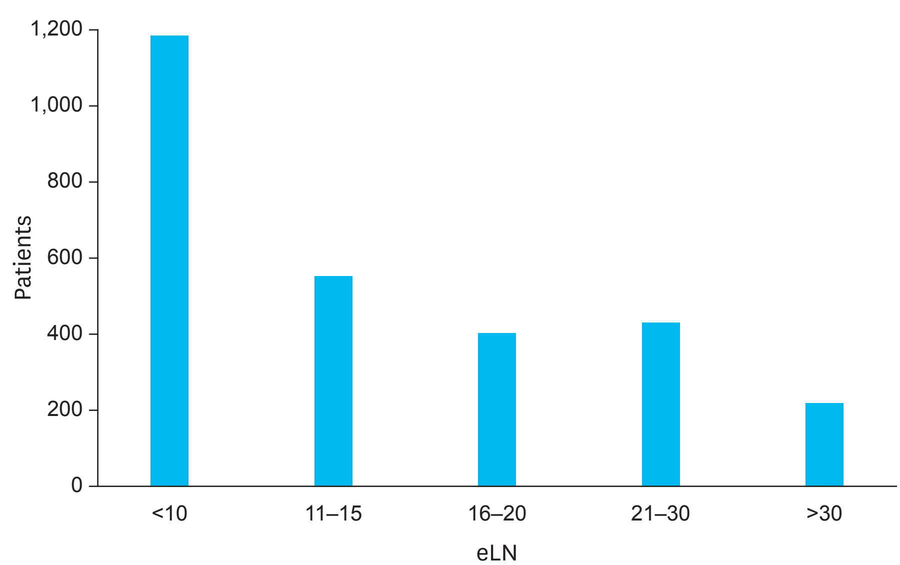

Fig. 4. Distribution of eLNs in initial surgery cohort.
eLN = examined lymph node.

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Patient, disease, and treatment characteristics of patients who underwent initial surgery are stratified by eLN and presented in **Table 3**. Patients who received a suboptimal lymphadenectomy (eLN ≤10) tended to be older (P<0.001), white (P<0.001), and treated at a comprehensive community center (P<0.001). They tended to undergo a proximal

Table 3. Patient, disease, and treatment characteristics of initial surgery cohort

Variable	≤10 (n=1,187, %)	11–15 (n=553, %)	16–20 (n=404, %)	21–30 (n=432, %)	>30 (n=219, %)	P-value
Age	67.8	66.8	66.3	64.9	65.1	<0.001
18–59	23.8	25.5	28.2	32.2	26.5	
60–69	27.0	32.0	28.7	28.2	35.2	
70–79	32.4	28.8	30.0	27.5	29.7	
80–90	16.8	13.7	13.1	12.0	8.7	
Sex						0.075
Male	68.0	72.7	68.6	67.4	62.6	
Female	32.0	27.3	31.4	32.6	37.4	
Race						<0.001
White (non-Hispanic)	73.3	68.4	70.3	68.3	59.4	
Black (non-Hispanic)	9.0	9.2	6.7	6.9	7.8	
Other (non-Hispanic)	5.1	7.8	7.2	10.6	12.3	
Hispanic	12.6	14.6	15.8	14.1	20.5	
Insurance						0.396
Private	33.6	35.4	39.6	39.8	39.3	
Medicare	58.0	54.4	52.2	50.5	48.9	
Medicaid & other government	5.4	6.1	5.7	5.8	8.2	
Unknown	1.0	1.1	0.7	1.4	1.4	
Not insured	2.0	2.9	1.7	2.5	2.3	
Median income						0.202
<58,000	15.5	15.9	14.1	13.7	13.7	
58,000–74,000	25.3	21.9	20.0	20.6	21.0	
74,000–93,000	23.5	26.0	26.2	29.2	25.1	
>93,000	32.8	33.3	38.4	35.0	38.8	
Comorbidities						0.076
CCI score 0	62.0	65.1	65.8	69.2	70.8	
CCI score 1	28.1	25.9	25.5	24.8	23.3	
CCI score 2	9.9	9.0	8.7	6.0	5.9	
Facility type						<0.001
Community	6.6	5.2	7.2	4.2	4.6	
Comprehensive community	48.8	38.3	35.4	31.5	25.1	
Academic/research	44.4	56.2	56.9	64.4	70.3	
Other	0.3	0.2	0.5	0.0	0.0	
Facility location						<0.001
Northeast	20.8	23.5	27.5	29.9	37.4	
South	39.9	33.3	30.2	23.4	22.4	
Midwest	23.0	25.5	27.0	27.5	19.2	
West	16.3	17.7	15.3	19.2	21.0	
Clinical stage						0.192
Stage I	71.7	74.1	70.3	71.1	73.5	
Stage II	15.2	13.7	19.8	16.9	17.4	
Stage III	6.4	6.7	5.7	8.6	5.5	
Surgery type						<0.001
Proximal gastrectomy	63.4	57.1	54.2	51.4	41.1	
Total gastrectomy	26.9	32.9	36.1	40.7	50.7	
Distal gastrectomy	9.8	9.9	9.7	7.9	8.2	
Regional lymph nodes examined	5.6	12.9	17.9	24.7	38.7	<0.001
Surgical margins						0.161
No residual tumor	93.7	95.8	96.0	96.5	96.3	
Residual tumor, NOS	1.1	1.1	0.7	0.9	0.5	
Microscopic residual tumor	4.2	2.2	1.5	1.6	2.3	
Macroscopic residual tumor	0.3	0.0	0.7	0.2	0.0	
Indeterminate or unknown	0.8	0.9	1.0	0.7	0.9	

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Table 3. (Continued) Patient, disease, and treatment characteristics of initial surgery cohort

Variable	≤10 (n=1,187, %)	11–15 (n=553, %)	16–20 (n=404, %)	21–30 (n=432, %)	>30 (n=219, %)	P-value
Pathological stage						0.024
Stage 0	4.5	3.3	2.5	2.5	2.3	
Stage 1	68.4	70.7	71.0	71.1	73.5	
Stage 2	14.9	14.6	19.1	16.7	16.9	
Stage 3	4.4	3.3	2.2	1.6	1.8	
Stage 4	1.4	0.7	0.7	0.5	0.9	
Unknown	5.0	6.1	4.0	6.7	4.1	
Adjuvant therapy						0.061
None	86.7	90.1	85.1	88.4	83.6	
Adjuvant therapy	13.3	9.9	14.9	11.6	16.4	

CCI = Charlson/Deyo comorbidity index; NOS = not otherwise specified.

gastrectomy (P<0.001), and have a more advanced pathological stage (P=0.024). Clinical stage (P=0.192), surgical margins (P=0.161), and adjuvant therapy (P=0.061) did not significantly differ among eLN groups.

Survival of initial surgery cohort

Kaplan-Meier analyses of patients who underwent initial surgery are stratified by eLN and presented in **Fig. 5**. Inadequate lymphadenectomy with eLN ≤10 was associated with worse survival in clinical stage I–III diseases; however, this association was only significant in stages I and II (P<0.001 and P=0.002, respectively).

Results of a Weibull survival model of patients who underwent initial surgery are presented in **Table 4**. A greater number of eLN was associated with improved hazards of mortality (eLN 11–15: HR, 0.81; P=0.021, eLN 16–20: HR, 0.73; P=0.004, eLN 21–30: HR, 0.62; P<0.001, and eLN >30: HR, 0.58; P=0.001). Female sex, Hispanic or other race, greater median income,

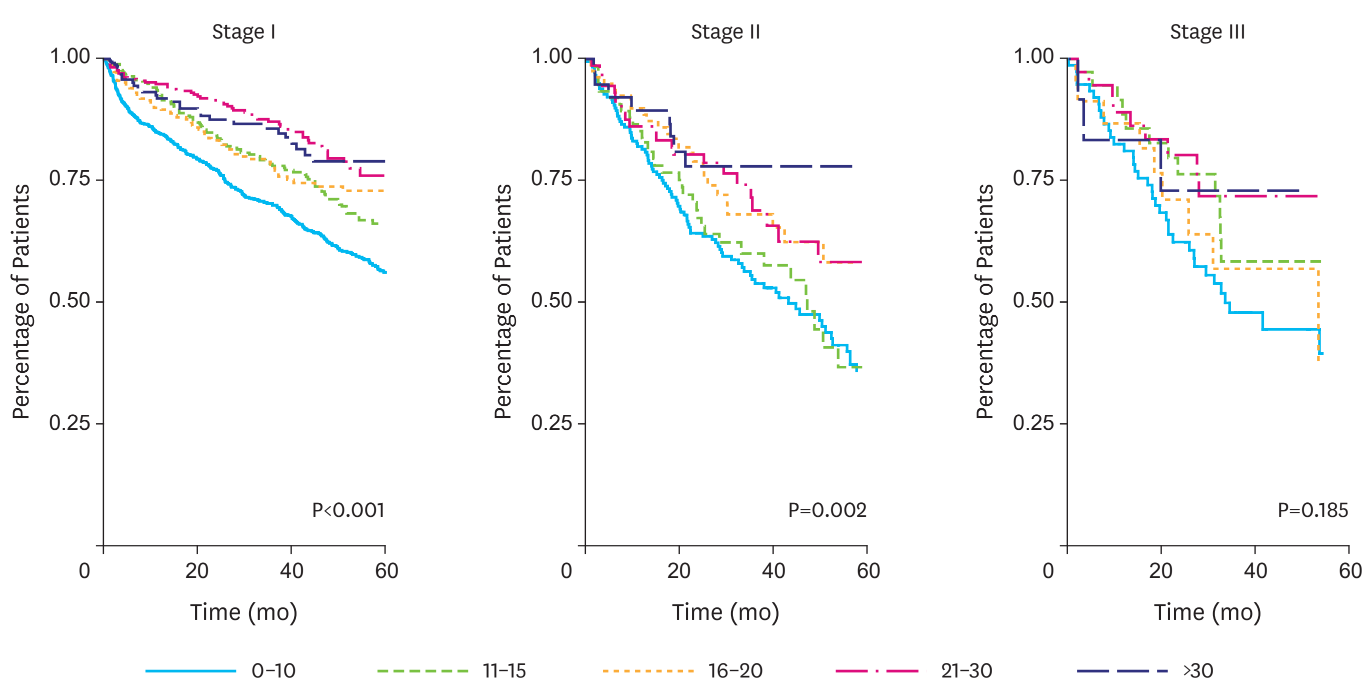

Fig. 5. Survival by eLNs in initial surgery cohort.
eLN = examined lymph node.

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Table 4. Factors impacting survival in initial surgery cohort

Variable	HR	95% CI		P-value
		Lower	Upper	
No. of lymph nodes examined				
≤10	Reference			
11–15	0.81	0.68	0.97	0.021
16–20	0.73	0.59	0.91	0.004
21–30	0.62	0.50	0.78	<0.001
>30	0.58	0.43	0.80	0.001
Age				
18–59	Reference			
60–69	1.25	1.00	1.57	0.054
70–79	1.74	1.37	2.21	<0.001
80–90	2.86	2.21	3.69	<0.001
Sex				
Male	Reference			
Female	0.83	0.72	0.97	0.015
Race				
White (non-Hispanic)	Reference			
Black (non-Hispanic)	0.88	0.68	1.14	0.347
Other (non-Hispanic)	0.54	0.38	0.75	<0.001
Hispanic	0.78	0.63	0.95	0.015
Insurance				
Private	Reference			
Medicare	1.28	1.06	1.54	0.011
Medicaid & other government	1.38	1.01	1.90	0.046
Unknown	2.62	1.49	4.62	0.001
Not insured	1.06	0.58	1.92	0.851
Median income				
<58,000	Reference			
58,000–74,000	0.96	0.78	1.17	0.656
74,000–93,000	0.77	0.62	0.94	0.012
>93,000	0.76	0.62	0.93	0.008
Comorbidities				
CCI score 0	Reference			
CCI score 1	1.16	1.00	1.35	0.054
CCI score 2	1.59	1.30	1.96	<0.001
Facility type				
Community	Reference			
Comprehensive community	0.81	0.62	1.05	0.117
Academic/research	0.72	0.56	0.94	0.016
Other	0.71	0.17	2.92	0.632
Facility location				
Northeast	Reference			
South	1.08	0.90	1.30	0.396
Midwest	0.93	0.77	1.14	0.495
West	0.88	0.71	1.10	0.276
Surgery type				
Proximal gastrectomy	Reference			
Total gastrectomy	1.31	1.13	1.51	<0.001
Distal gastrectomy	1.15	0.91	1.46	0.241

(continued to the next page)

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Table 4. (Continued) Factors impacting survival in initial surgery cohort

Variable	HR	95% CI		P-value
		Lower	Upper	
Surgical margins				
No residual tumor	Reference			
Residual tumor, NOS	2.14	1.29	3.55	0.003
Microscopic residual tumor	2.09	1.53	2.84	<0.001
Macroscopic residual tumor	2.98	1.21	7.34	0.017
Indeterminate or unknown	1.31	0.64	2.65	0.457
Pathological stage				
Stage 0	Reference			
Stage 1	1.66	1.10	2.48	0.015
Stage 2	3.11	2.04	4.76	<0.001
Stage 3	3.80	2.25	6.42	<0.001
Stage 4	5.87	3.15	10.97	<0.001
Unknown	1.90	1.16	3.10	0.011
Adjuvant therapy				
None	Reference			
Adjuvant therapy	0.77	0.62	0.96	0.02

HR = hazard ratio; CI = confidence interval; CCI = Charlson/Deyo comorbidity index; NOS = not otherwise specified.

treatment at an academic or research center, and receipt of adjuvant therapy were also associated with a reduction in mortality. Greater age, coverage by Medicaid or Medicare, receipt of total gastrectomy, positive surgical margins, and advanced pathological stage were associated with increased hazards of mortality.

DISCUSSION

Despite a near linear improvement in median eLN from gastrectomy over the past decade, most US patients with node-negative gastric cancer received operations that failed to meet NCCN guidelines of retrieving ≥15 LNs. This concerning statistic suggests that surgeons nationwide may not understand the correlation between the systemic potential of gastric cancer and clearance of regional LNs, thus failing to perform the meticulous LN dissection necessary to achieve an optimal LN yield. University facilities may adhere more strictly to NCCN guidelines, as a study on 7 US universities reported a mean of 16 eLN, and our current study found that academic centers were more frequently associated with adequate oncologic lymphadenectomy [4].

The effect of eLN on western patients was explored by Smith et al. [16] with a retrospective analysis of the Surveillance, Epidemiology, and End Results (SEER) database from 1973 to 1999. They reported an association between increased number of eLN and improved survival in patients with T1-3, N0-1 gastric cancer [16]. However, given the increased utilization of NAT, as well as improvement in lymphadenectomy techniques, this analysis also includes antiquated treatment protocols [17]. Jin et al. [4] evaluated factors associated with recurrence and survival in 317 patients with node-negative gastric cancer from 2000–2012, and reported that eLN ≥15 was associated with improvements in overall survival, but not disease recurrence. However, given the small sample size and inclusion of exclusively university facilities, the authors conceded that the analysis may have been insufficiently powered [4]. To our knowledge, this is the first study to evaluate national treatment patterns and outcomes of node-negative gastric cancer after the formation of the Meta-Analysis Group in Cancer (MAGIC) though it did include data from years prior to the publication of the trial by Cunningham et al. [17] in 2006 which established NAT as standard of care. It also includes the largest number of Western patients to undergo NAT or surgery for node-negative gastric cancer.

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In our study, both in patients who received NAT and in those who underwent initial surgery, a greater number of eLN was associated with improved survival. A study by Deng et al. [18] of 112 Chinese patients with node-negative gastric cancer reported that eLN >20 was associated with improved survival. Another study on 600 Chinese patients with node negative gastric cancer recently reported that eLN was the strongest independent prognostic predictor and urged eLN to be considered a mandatory requirement for improving prognostic evaluations [10]. An Italian study, pre-dating the MAGIC trial, of 301 node-negative patients from 1992–2002 reported an association between eLN >25 and improved survival [19]. These studies all advocate for meticulous LN dissection and optimizing the number of harvested nodes.

To our knowledge, this is the largest and most contemporary study on western patients with node-negative gastric cancer treated at a wide spectrum of CoC-accredited facilities. However, there are some important limitations which should be considered when interpreting the results. The NCDB is a database sourced from hospital registry data from diverse institutions across the United States, and data recording may vary slightly from facility to facility. Furthermore, though the NCDB was designed to collect oncologic data, it lacks chemotherapy regimen, disease recurrence, disease-specific death, and complications data. Given the retrospective nature of this study, there likely exists a selection bias, with patients with more severe presentations treated more aggressively. Additionally, node-negative disease was defined as patients with AJCC pathologic N0 disease. The database does not specify why patients received NAT, but it is possible that patients with clinically node positive disease converted to pathologic node negative disease following NAT and would thus be included in this study. While the NCCN recommends examination of at least 15 LNs, this study included patients with suboptimal lymphadenectomies to provide a more complete overview of US gastric cancer care. However, sub-optimal lymphadenectomy was controlled for in the multivariable Weibull survival analyses. Most patients in this study underwent proximal gastrectomy, which could include patients with gastroesophageal junction cancer, which current NCCN guidelines classify as esophageal tumors. However, this study used the NCDB gastric participant user file (PUF), not the esophagus PUF, to reduce possible misclassification. To further account for this, the multivariable Weibull analyses controlled for tumor location. Finally, it is important to consider the differences in pathologic specimen evaluation between Eastern countries and the United States [20]. While Eastern surgeons dissect out each LN station, Western surgeons typically submit specimens en bloc [21].

In conclusion, most US patients with node-negative gastric cancer receive a suboptimal lymphadenectomy. Even in node-negative disease, increasing the number of retrieved lymph nodes appears to have therapeutic and prognostic value, irrespective of initial treatment. This suggests a survival benefit to meticulous lymphadenectomy in Western patients with node-negative gastric cancer.

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