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ORIGINAL ARTICLE

Gastric Cancer Surgery in the US: a Contemporary Trend Analysis of Lymphadenectomy and the Impact of Minimally Invasive Approaches

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Abstract

Background The National Comprehensive Cancer Network guidelines recommend harvesting 16 or more lymph nodes for the adequate staging of gastric adenocarcinoma. This study examines the rate of adequate lymphadenectomy over recent years, its predictors, and its impact on overall survival(OS).

Study design The National Cancer Database was utilized to identify patients who underwent surgical treatment for gastric adenocarcinoma between 2006–2019. Trend analysis was performed for lymphadenectomy rates during the study period. Logistic regression, Kaplan-Meier survival plots, and Cox proportional hazard regression were utilized.

Results A total of 57,039 patients who underwent surgical treatment for gastric adenocarcinoma were identified. Only 50.5% of the patients underwent a lymphadenectomy of ≥ 16 nodes. Trend analysis showed that this rate significantly improved over the years, from 35.1% in 2006 to 63.3% in 2019 ($p < .0001$). The main independent predictors of adequate lymphadenectomy included high-volume facility with ≥ 31 gastrectomies/year (OR: 2.71; 95%CI:2.46–2.99), surgery between 2015–2019 (OR: 1.68; 95%CI: 1.60–1.75), and preoperative chemotherapy (OR:1.49; 95%CI:1.41–1.58). Patients with adequate lymphadenectomy had better OS than patients who did not: median survival: 59 versus 43 months (Log-Rank: $p < .0001$). Adequate lymphadenectomy was independently associated with improved OS (HR:0.79; 95%CI:0.77–0.81). Laparoscopic and robotic gastrectomies were independently associated with adequate lymphadenectomy compared to open, OR: 1.11, 95%CI:1.05–1.18 and OR: 1.24, 95%CI:1.13–1.35, respectively.

Conclusion Although the rate of adequate lymphadenectomy improved over the study period, a large number of patients still lacked adequate lymph node dissection, negatively impacting their OS despite multimodality therapy. Laparoscopic and robotic surgeries were associated with a significantly higher rate of lymphadenectomy ≥ 16 nodes.

Keywords Gastric cancer · Gastrectomy · Lymphadenectomy

Introduction

Although the incidence of gastric cancer has decreased over the last decades, it remains the fourth most common cause of cancer-related death worldwide.[1] In the United States,

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gastric cancer is responsible for more than 11,000 deaths each year.[2] Gastrectomy with adequate lymphadenectomy is the mainstay therapy of the multimodality treatment of gastric cancer.[3–8] Historically, the extent of lymphadenectomy has been a subject of intense debate in Western countries, and two large European clinical trials seemed to have addressed this controversial topic.[9,10] The United Kingdom Medical Research Council trial showed that D2 lymphadenectomy compared to D1 was associated with higher postoperative morbidity and mortality, and similar overall survival.[9] Likewise, the Dutch Gastric Cancer Group trial demonstrated that patients who underwent D2 lymphadenectomy had higher postoperative morbidity and mortality with a similar 5-year overall survival.[10] However, the 15-year follow-up of the Dutch trial revealed that D2 lymphadenectomy was associated with lower locoregional recurrence and gastric cancer-related mortality.[11] Therefore, the authors concluded that spleen-preserving D2 gastrectomy in high-volume centers is the recommended surgical approach for resectable gastric cancer. Based on the current evidence, the National Comprehensive Cancer Network (NCCN) gastric cancer guidelines recommend gastrectomy with a D1 or a modified D2 lymph node dissection, with a goal of examining 16 or more lymph nodes.[12]

Previous studies have reported a suboptimal rate of adequate lymphadenectomy during the resection of gastric cancer in the United States.[13,14] However, these studies evaluated a cohort of patients who underwent surgery up to 2016, before the 8th Edition American Joint Commission on Cancer (AJCC) publication in 2017, which recommended lymphadenectomy of 16 or more lymph nodes for gastric cancer.[15] Herein, we aim to perform a contemporary trend analysis of the adherence to the recommendation of lymphadenectomy of 16 or more nodes, determining the factors associated with its achievement and its impact on overall survival.

Methods

Data Source and Study Cohort

This is a retrospective cohort study that used the 2019 participant user file (PUF) of the National Cancer Database (NCDB). NCDB is a nationwide hospital-level database that captures 70% of the cancers in the United States in more than 1500 Commission on Cancer accredited facilities.[16] Eligibility criteria included patients with a diagnosis of gastric adenocarcinoma, without metastatic disease, and who underwent subtotal, total, or en bloc gastrectomy between 2006 and 2019. Patients with gastric adenocarcinoma were identified using the following histologic codes, as previously described:[17] 8020, 8070, 8071, 8140, 8142, 8144, 8145, 8210, 8211, 8244, 8245, 8255, 8260, 8261, 8262, 8263, 8323, 8480, 8481, 8490, 8560 and 8574. Site-specific surgery codes were defined as per the Facility Oncology Registry Data Standards (FORDS).[18] Following the descriptions of the NCDB data dictionary PUF 2019, facility types were defined as Academic/Research Cancer Programs, Integrated Network Cancer Programs, while Community Programs and Comprehensive Community Programs were grouped together as Community Cancer Programs. Presence of comorbid conditions was captured using the Charlson-Deyo Score for administrative data available in the NCDB database.[19] Surgical approach was defined as per PUF 2019 as open, laparoscopic and robotic. Converted cases were considered open. Patients without complete information on surgical margins, lymph node status, AJCC stage group, and receipt of chemotherapy or radiation therapy were excluded. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[20]

Variables and Outcomes

The variables of interest included the following: patient's demographics, year of diagnosis, type of surgery, receipt of preoperative, perioperative or adjuvant chemotherapy, receipt of preoperative, perioperative or adjuvant radiation therapy, clinical nodal stage, lymph node examination status, number of lymph nodes examined, number of positive lymph nodes, surgical margins, AJCC group stage, survival length, and vital status. Pathological stages were characterized utilizing the AJCC staging system, 6th edition before 2009, 7th edition between 2009 to 2016, and 8th edition between 2017 to 2019.[21–23] Hospital volume was defined as low (1–10 gastrectomies/year), intermediate (11–30 gastrectomies/year), and high (≥ 31 gastrectomies/year), adapted from the previous definition by Claassen et al.[24]

Statistical Analysis

Patients' demographic and clinicopathological data were reported as a mean with standard deviation for continuous variables and frequency for categorical variables. Cochran-Armitage trend test was utilized to evaluate the association between the rate of lymphadenectomy of ≥ 16 nodes and time (years of the study period). Somer's D test examined the association between the number of lymph nodes examined (0, 1–15, and ≥ 16 nodes) and time. Univariable and multivariable logistic regression analyses were performed to identify factors independently associated with lymphadenectomy with the removal of 16 or more lymph nodes. Survival analysis was performed using the Kaplan-Meier method, and comparisons were performed with the log-rank test. Univariable and multivariable Cox proportional hazard regression

analyses were performed to evaluate the association between clinicopathological factors and overall survival. A complete case analysis was utilized for missing data. Statistical comparisons were 2-sided and a P-value < 0.05 was considered significant. The SAS version 9.4 was used for the statistical analysis (SAS Institute Inc). This study was submitted to the Texas Tech University Health Sciences Center Internal Review Board (IRB), which waived further review as the project utilizes retrospective and de-identified data.

RESULTS

Patient and Clinicopathological Characteristics

A total of 57039 patients underwent gastrectomy for gastric adenocarcinoma between 2006 and 2019 and met the study's inclusion criteria. The demographics and clinicopathological characteristics of the entire cohort are outlined in Table 1. The mean age was 67 years [Standard deviation (SD): ± 11.3], and the majority of the patients were male ($n = 37600$, 65.9%), Caucasian ($n = 42111$, 73.8%), and had no comorbidities ($n = 37529$, 65.8%). Most surgeries were performed in Academic Research Cancer Programs ($n = 25461$, 44.6%) and low-volume hospitals ($n = 36656$, 64.2%). Subtotal gastrectomy was the most common operation ($n = 27390$, 48.0%), followed by total gastrectomy ($n = 24210$, 42.4%). Just over half of the patients who underwent gastrectomy for gastric cancer had 16 or more lymph nodes examined ($n = 28818$, 50.5%) during the study period, and the rate of positive surgical margin was 11.3% ($n = 6439$). Most patients had AJCC stage group III ($n = 21431$, 37.6%). The 90-day mortality was 7% ($n = 3726$) and the median follow-up was 34.5 months (IQR: 15.4 – 67.8 months).

Trend Analysis of the Lymphadenectomy for Gastric Cancer Between 2006 to 2019

The rate of lymphadenectomy of ≥ 16 nodes and the number of lymph nodes removed during gastrectomy for gastric cancer significantly improved during the study period (Table 2). The rate of lymphadenectomy of ≥ 16 nodes was 63.3% in 2019 compared to 35.1% in 2006 and 50.3% in 2013; Cochran-Armitage trend test: $P < 0.0001$ (Fig. 1A). Similarly, the number of lymph nodes examined significantly increased from 2006 to 2019, Somer's D test: $P < 0.0001$ (Fig. 1B). Despite this increase, still 36.7 to 38.3% of the patients who underwent gastrectomies after 2016 had a lymphadenectomy with less than the recommended 16 lymph nodes (Table 2).

Table 1 Patient demographics and clinicopathological characteristics of patients who underwent gastrectomy for adenocarcinoma of the stomach between 2006–2019

Variable	$N = 57039$
Age, years (SD)	67 (11.3)
Male, No. (%)	37600 (65.9)
Race, No. (%)	
Caucasian	42111 (73.8)
African American	8021 (14.1)
Asian	3790 (6.6)
Other	3117 (5.5)
Charlson-Deyo Score (%)	
0	37529 (65.8)
1	13292 (23.3)
2	4057 (7.1)
≥ 3	2161 (3.8)
Era of diagnosis	
2006–2009	14200 (25.0)
2010–2014	22165 (38.8)
2015–2019	20674 (36.2)
Facility (%)	
Academic Research Cancer Program	25461 (44.6)
Integrated Network Cancer Program	10885 (19.1)
Community Cancer Program	20693 (36.3)
Facility Volume – gastrectomies/year (%)	
1–10	36656 (64.2)
11–30	17489 (30.7)
≥ 31	2853 (5.1)
AJCC Stage Group	
0	534 (0.9)
I	18773 (32.9)
II	16301 (28.6)
III	21431 (37.6)
Gastrectomy type (%)	
Subtotal	27390 (48.0)
Total	24210 (42.4)
En bloc	5439 (9.6)
Lymph node examination (%)	
0	1972 (3.5)
1–15	26249 (46.0)
≥ 16	28818 (50.5)
Positive lymph nodes (%)	
0	27200 (47.7)
1–2	10532 (18.5)
3–6	8664 (15.2)
≥ 6	10643 (18.6)
Surgical Margins (%)	
Negative	50600 (88.7)
Positive	6439 (11.3)
Systemic therapy (%)	
None	22975 (40.3)
Pre-operative	15749 (27.6)

Table 1 (continued)

Variable	*N* = 57039
Post-operative	13634 (23.9)
Pre and Post-operative	4633 (8.2)
Radiation therapy (%)	
None	35541 (62.3)
Pre-operative	10783 (18.9)
Post-operative	10626 (18.6)
Pre and Post-operative	89 (0.2)
90-day mortality (%)	3726 (7)
Median follow-up (IQR)	34.5 (15.4—67.8)

SD: Standard deviation, IQR: Interquartile Range; AJCC: American Joint Committee on Cancer

Factors Associated with the Receipt of Adequate Lymphadenectomy

Clinical factors associated with the receipt of adequate lymphadenectomy are depicted in Table 3. The multivariable logistic regression analysis showed that the factors independently associated with the receipt of lymphadenectomy with 16 or more nodes included: age younger than 65 (OR: 1.14, 95% CI: 1.09–1.18), female gender (OR: 1.10, 95% CI: 1.06–1.15), race [African Americans (OR: 1.12, 95% CI: 1.06–1.19), Asians (OR: 1.69, 95% CI: 1.56–1.84) and Other races (OR: 1.25, 95% CI: 1.14–1.37) when compared to Caucasians], absence of comorbidities (OR: 1.29, 95% CI: 1.16–1.43), receipt of surgery between 2015–2019 (OR: 1.68, 95% CI: 1.60–1.75), surgery in Academic Research Cancer Program (OR: 1.15, 95% CI: 1.09–1.22), surgery in intermediate-volume (OR: 1.57, 95% CI: 1.49–1.65) and high-volume facilities (OR: 2.71, 95% CI: 2.46–2.99), positive clinical nodal status (Node positive: OR: 1.42, 95% CI: 1.36–1.49), total gastrectomy (OR: 1.49, 95% CI: 1.43–1.56) and en bloc gastrectomy (OR: 1.69, 95% CI: 1.57–1.82), and receipt of preoperative chemotherapy (OR: 1.49, 95% CI: 1.41–1.58).

Impact of the Lymphadenectomy of 16 or more Nodes on Overall Survival

The Kaplan-Meier survival analysis demonstrated that the removal of 16 or more lymph nodes during gastrectomy for gastric cancer was associated with improved overall survival when compared to patients who did not receive adequate lymphadenectomy, with a median survival of 59 months vs 43 months, respectively (Log-rank test: $P < 0.0001$) (Fig. 2). After adjusting for age, gender, race, Charlson-Deyo score, the era of diagnosis, type of treatment facility, hospital volume, AJCC stage group, gastrectomy type, surgical margins, nodal status, histological grade, receipt of chemotherapy, and receipt of radiation therapy, patients with lymphadenectomy of ≥ 16 nodes had a decreased mortality compared to patients who lacked adequate lymphadenectomy, Hazard ratio (HR): 0.79, 95% CI: 0.77–0.81. Other factors independently associated with overall survival are shown in Table 4.

Table 2 Lymph node examination rate by year among patients who underwent gastrectomy for adenocarcinoma of the stomach between 2006–2019

Year	Rate of adequate lymphadenectomy (≥ 16 nodes)[a]	Number of lymph nodes examined[b]		
		0	1–15	≥ 16
2006 (*n* = 3442)	1209 (35.1%)	169 (4.9%)	2064 (60.0%)	1209 (35.1%)
2007 (*n* = 3480)	1292 (37.1%)	168 (4.8%)	2020 (58.0%)	1292 (37.2%)
2008 (*n* = 3546)	1320 (37.2%)	149 (4.2%)	2077 (58.6%)	1320 (37.2%)
2009 (*n* = 3732)	1505 (40.3%)	160 (4.3%)	2067 (55.4%)	1505 (40.3%)
2010 (*n* = 4150)	2007 (48.3%)	152 (3.7%)	1991 (48.0%)	2007 (48.3%)
2011 (*n* = 4463)	2076 (46.5%)	169 (3.8%)	2218 (49.7%)	2076 (46.5%)
2012 (*n* = 4353)	2108 (48.4%)	147 (3.4%)	2098 (48.2%)	2108 (48.4%)
2013 (*n* = 4596)	2312 (50.3%)	155 (3.4%)	2129 (46.3%)	2312 (50.3%)
2014 (*n* = 4603)	2416 (52.5%)	151 (3.3%)	2036 (44.2%)	2416 (52.5%)
2015 (*n* = 4480)	2496 (55.7%)	137 (3.0%)	1847 (41.2%)	2496 (55.7%)
2016 (*n* = 4385)	2681 (61.1%)	89 (2.0%)	1615 (36.8%)	2681 (61.2%)
2017 (*n* = 4364)	2695 (61.7%)	77 (1.7%)	1592 (36.5%)	2695 (61.7%)
2018 (*n* = 3870)	2438 (63.0%)	135 (3.5%)	1297 (33.5%)	2438 (63.0%)
2019 (*n* = 3575)	2263 (63.3%)	114 (3.2%)	1198 (33.5%)	2263 (63.3%)
Total (*n* = 57039)	28818 (50.6%)	1972 (3.4%)	26249 (46.0%)	28818 (50.6%)

[a]Cochran-Armitage trend test: $P < .0001$

[b]Somer's D test: $P < .0001$

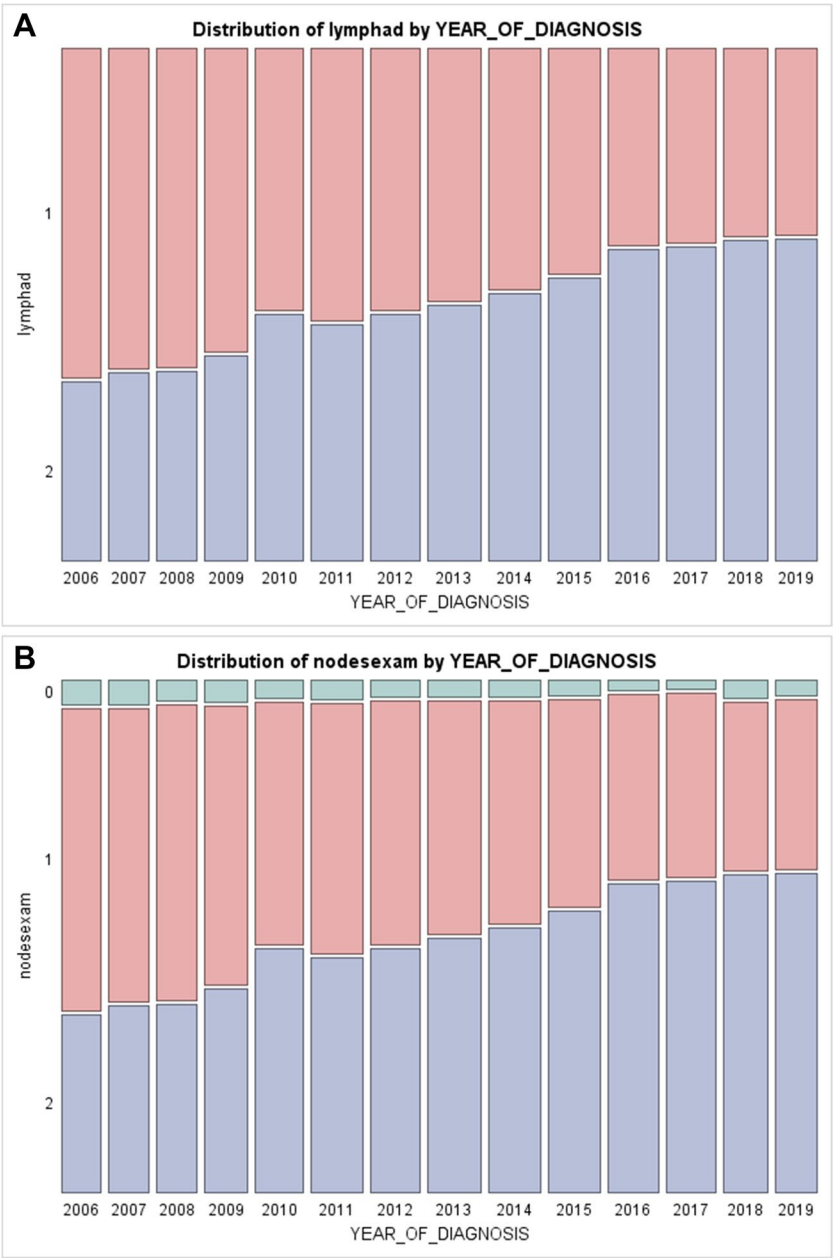

Fig. 1 Mosaic plots showing the increased rate of adequate lymphadenectomy and number of lymph nodes retrieved over the years. **A** – Cochran-Armitage trend test: $P < .0001$. **B** – Somer's D test: $P < .0001$. Footnote: **A:** Lymphadenectomy: Group 1: < 16 nodes; Group 2: ≥ 16 nodes. **B:** Group 0 = 0 nodes examined, Group 1 = 1–15 nodes examined, Group 2: ≥ 16 nodes examined

Subgroup Analysis of Patients with known Surgical Approach Data

A total of 37150 patients who underwent gastrectomy for gastric cancer during the study period had complete data on the surgical approach, detailing whether the surgery was performed open, laparoscopically, or robotically. After adjusting for other factors associated with receipt of lymphadenectomy of ≥ 16 nodes, including age, gender, race, Charlson-Deyo score, era of diagnosis, facility type, hospital volume, clinical nodal stage, gastrectomy type, preoperative radiation, and preoperative chemotherapy, laparoscopic and robotic surgeries were associated with higher odds of adequate lymph node examination when compared to the open approach, OR: 1.11, CI 95%: 1.05–1.18 and OR: 1.24, 95% CI: 1.13–1.35, respectively (Table 5). Furthermore, laparoscopic and robotic approaches were associated with improved overall survival when compared to open surgery, with a median survival of 73 months and 74.8 months, versus 48 months, respectively (Log-rank test: $P < 0.0001$) (Fig. 3). Multivariable analysis revealed that patients who underwent laparoscopic and robotic gastrectomy had significantly lower mortality compared to patients who underwent open surgery, HR: 0.90, 95% CI: 0.86–0.93 and HR: 0.88, 95% CI: 0.82–0.95, respectively (Table 6).

Table 3 Univariable and multivariable logistic regression analysis for factors associated with the receipt of lymphadenectomy of ≥ 16 nodes

Variable	Unadjusted		Adjusted[b]	
	OR (95% CI)[a]	P-value	OR (95% CI)	P-value
Age < 65 years	1.28 (1.24, 1.32)	< .0001	1.14 (1.09, 1.18)	< .0001
Female	1.07 (1.03, 1.11)	< .0001	1.10 (1.06, 1.15)	< .0001
Race				
Caucasian	Ref		Ref	
African American	1.11 (1.06, 1.17)	< .0001	1.12 (1.06, 1.19)	0.0001
Asian	1.79 (1.67, 1.91)	< .0001	1.69 (1.56, 1.84)	< .0001
Other	1.55 (1.44, 1.67)	< .0001	1.25 (1.14, 1.37)	< .0001
Charlson-Deyo Score				
≥ 3	Ref		Ref	
2	0.91 (0.82, 1.01)	0.08	1.02 (0.90, 1.16)	0.68
1	1.07 (0.97, 1.17)	0.15	1.15 (1.03, 1.29)	0.01
0	1.31 (1.20, 1.43)	< .0001	1.29 (1.16, 1.43)	< .0001
Era of diagnosis				
2010–2014	Ref		Ref	
2015–2019	1.60 (1.53, 1.66)	< .0001	1.68 (1.60, 1.75)	< .0001
2006–2009	0.62 (0.59, 0.64)	< .0001	0.63 (0.59, 0.66)	< .0001
Facility				
Integrated Network Cancer Program	Ref		Ref	
Academic Research Program	1.56 (1.49, 1.63)	< .0001	1.15 (1.09, 1.22)	< .0001
Community Cancer Program	0.85 (0.81, 0.89)	< .0001	0.92 (0.87, 0.97)	0.004
Facility Volume – gastrectomies/year (%)				
1–10	Ref		Ref	
11–30	1.78 (1.72, 1.85)	< .0001	1.57 (1.49, 1.65)	< .0001
≥ 31	2.95 (2.72, 3.20)	< .0001	2.71 (2.46, 2.99)	< .0001
Clinical Nodal Status				
Negative	Ref		Ref	
Positive	1.39 (1.34, 1.45)	< .0001	1.42 (1.36, 1.49)	< .0001
Gastrectomy type				
Subtotal	Ref		Ref	
Total	1.41 (1.36, 1.46)	< .0001	1.49 (1.43, 1.56)	< .0001
En bloc	1.69 (1.59, 1.79)	< .0001	1.69 (1.57, 1.82)	< .0001
Preoperative Radiation				
No	Ref		Ref	
Yes	0.77 (0.74, 0.81)	< .0001	0.39 (0.37, 0.42)	< .0001
Preoperative Chemotherapy				
No	Ref		Ref	
Yes	1.43 (1.38, 1.48)	< .0001	1.49 (1.41, 1.58)	< .0001

[a]derived from logistic regression

[b]adjusted for variables with an unadjusted $p < 0.10$. OR: Odds ratio; CI: Confidence interval

Discussion

The role of surgery with adequate lymphadenectomy in the multimodality treatment of gastric cancer is well established.[3–8,11] Despite the AJCC and NCCN recommendations on lymphadenectomy for gastric cancer surgery,[12,15] the actual rate of adequate lymphadenectomy during gastrectomies for gastric cancer has been reported to be suboptimal in the US.[13,14] This contemporary analysis of a large cohort found that this remains a challenge in the US, where still a significant number of patients who underwent gastrectomy for gastric cancer lacked adequate lymphadenectomy. This study is the first to include patients who had surgery after the publication of the AJCC 8th edition guidelines on gastric cancer in 2017.[21] The current analysis is the first to demonstrate that there were still 36.7 to 38.3% of patients, who underwent surgery after the new AJCC recommendations, lacking the recommended lymphadenectomy of ≥ 16 nodes.

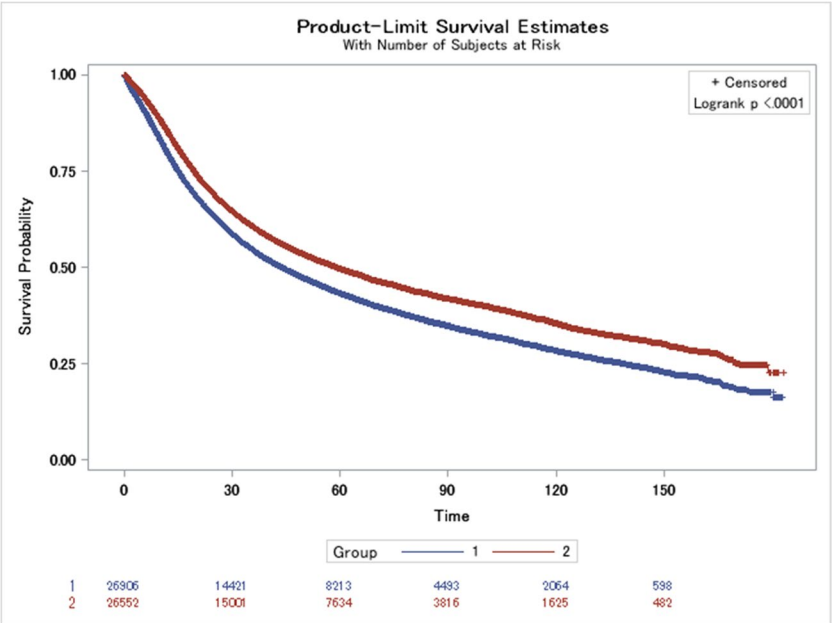

Fig. 2 Kaplan-Meier plot comparing the overall survival between patients who underwent gastrectomy for adenocarcinoma with and without adequate lymphadenectomy. Footnote: **1:** Lymphadenectomy < 16 nodes; **2:** Lymphadenectomy ≥ 16 nodes

Table 4 Univariable and multivariable Cox proportional hazard regression analysis for predictors of overall survival

Variable	Unadjusted		Adjusted[b]	
	HR (95% CI)[a]	P-value	HR (95% CI)[a]	P-value
Age < 65 years	0.68 (0.67, 0.70)	< .0001	0.68 (0.67, 0.70)	< .0001
Female	0.94 (0.91, 0.96)	< .0001	0.95 (0.93, 0.97)	< .0001
Race				
Caucasian	Ref		Ref	
African American	0.94 (0.90, 0.97)	< .0001	0.99 (0.96, 1.03)	0.85
Asian	0.62 (0.59, 0.66)	< .0001	0.71 (0.68, 0.75)	< .0001
Other	0.65 (0.61, 0.69)	< .0001	0.75 (0.71, 0.80)	< .0001
Charlson-Deyo Score				
0	Ref		Ref	
1	1.14 (1.11, 1.17)	< .0001	1.11 (1.08, 1.14)	< .0001
2	1.33 (1.28, 1.40)	< .0001	1.29 (1.24, 1.34)	< .0001
≥ 3	1.51 (1.43, 1.60)	< .0001	1.51 (1.43, 1.60)	< .0001
Era of diagnosis				
2010–2014	Ref		Ref	
2015–2019	0.84 (0.81, 0.86)	< .0001	0.88 (0.85, 0.91)	< .0001
2006–2009	1.09 (1.06, 1.11)	< .0001	1.13 (1.10, 1.16)	< .0001
Facility				
Integrated Network Cancer Program	Ref		Ref	
Academic Research Program	0.79 (0.77, 0.82)	< .0001	0.93 (0.90, 0.96)	< .0001
Community Cancer Program	1.07 (1.04, 1.10)	< .0001	1.01 (0.98, 1.05)	0.38
Facility Volume – gastrectomies/year (%)				
1–10	Ref		Ref	
11–30	0.76 (0.74, 0.78)	< .0001	0.87 (0.85, 0.90)	< .0001
≥ 31	0.65 (0.61, 0.69)	< .0001	0.76 (0.71, 0.81)	< .0001
AJCC Stage Group				
0	Ref		Ref	
I	0.99 (0.86, 1.14)	0.93	0.84 (0.72, 0.96)	0.01
II	1.71 (1.49, 1.97)	< .0001	1.47 (1.28, 1.70)	< .0001
III	3.03 (2.64, 3.48)	< .0001	2.31 (2.01, 2.67)	< .0001

Table 4 (continued)

Variable	Unadjusted		Adjusted[b]	
	HR (95% CI)[a]	P-value	HR (95% CI)[a]	P-value
Gastrectomy type				
Subtotal	Ref		Ref	
Total	1.17 (1.14, 1.20)	< .0001	1.14 (1.11, 1.17)	< .0001
En bloc	1.31 (1.26, 1.36)	< .0001	1.20 (1.15, 1.25)	< .0001
Lymphadenectomy ≥ 16 LN				
No	Ref		Ref	
Yes	0.81 (0.79, 0.83)	< .0001	0.79 (0.77, 0.81)	< .0001
Negative Nodal Involvement				
No	Ref		Ref	
Yes	0.45 (0.44, 0.46)	< .0001	0.66 (0.64, 0.68)	< .0001
Negative Surgical Margins				
No	Ref		Ref	
Yes	0.38 (0.37, 0.39)	< .0001	0.53 (0.52, 0.55)	< .0001
Grade				
Poorly Differentiated/Anaplastic	Ref			
Well/Moderately Differentiated	0.72 (0.70, 0.74)	< .0001	0.83 (0.81, 0.86)	< .0001
Preoperative Radiation				
No	Ref		Ref	
Preoperative	1.13 (1.10, 1.17)	< .0001	1.17 (1.12, 1.22)	< .0001
Postoperative	1.06 (1.03, 1.09)	0.0001	0.88 (0.84, 0.92)	< .0001
Pre and Postoperative	1.71 (1.33, 2.20)	< .0001	1.53 (1.18, 1.99)	0.001
Systemic Chemotherapy				
No	Ref		Ref	
Preoperative	1.02 (0.99, 1.05)	0.12	0.71 (0.69, 0.75)	< .0001
Postoperative	1.01 (0.99, 1.04)	0.19	0.60 (0.58, 0.63)	< .0001
Pre and Postoperative	0.87 (0.83, 0.91)	< .0001	0.60 (0.57, 0.63)	< .0001

[a]derived from logistic regression

[b]adjusted for variables with an unadjusted $p < 0.10$. HR: Hazard ratio; CI: Confidence interval; LN: Lymph nodes; AJCC: American Joint Committee on Cancer

The lack of adequate lymphadenectomy negatively impacted the overall survival of these patients, even after adjusting for the receipt of perioperative or adjuvant chemotherapy and other factors associated with survival. Furthermore, this analysis is unique in demonstrating that receipt of preoperative chemotherapy was independently associated with an increased rate of adequate lymphadenectomy. Conversely, the receipt of preoperative radiation therapy was associated with decreased odds of a lymphadenectomy of ≥ 16 nodes. Other factors found to be strongly associated with adequate lymphadenectomy included younger age, female gender, Asian race, lack of comorbidities, surgery during more recent years in intermediate to high-volume institutions, and positive clinical nodal status.

The patients who received preoperative chemotherapy, alone or as part of perioperative chemotherapy protocol, were possibly treated in intermediate/high-volume centers and/or in Academic Research Programs, which were also associated with better lymphadenectomy. The changes in the operative field caused by radiation therapy could explain the decreased rate of adequate lymphadenectomy among the patients who received preoperative radiation therapy. The improved survival observed among patients with adequate lymphadenectomy is likely a result of better staging, prognostication and multimodality cancer care, provided in intermediate and high-volume centers, which were independently associated with lymphadenectomy ≥ 16 nodes. Age, gender, race and lack of comorbidities might have an effect in the patients' body habitus, which could have influenced the lymph node dissection during the gastrectomy. The lack of more granular data limits the certainty of this explanation. This highlights the need for large cancer databases to collect and make available indicators of intra-operative complexity, such as body habitus, anatomic variations and previous

Table 5 Multivariable logistic regression analysis for factors associated with the receipt of lymphadenectomy among patients with documented surgical approach ($n = 37150$)

Variable	Adjusted[a]	
	OR (95% CI)	P-value
Age < 65 years	1.13 (1.07, 1.18)	< .0001
Female	1.12 (1.06, 1.18)	< .0001
Race		
Caucasian	Ref	
African American	1.17 (1.09, 1.25)	< .0001
Asian	1.64 (1.49, 1.82)	< .0001
Other	1.30 (1.17, 1.44)	< .0001
Charlson-Deyo Score		
≥ 3	Ref	
0	1.26 (1.12, 1.41)	< .0001
1	1.14 (1.01, 1.29)	0.03
2	1.02 (0.89, 1.17)	0.76
Era of diagnosis		
2010–2014	Ref	
2015–2019	1.63 (1.55, 1.71)	< .0001
Facility		
Integrated Network Cancer Program	Ref	
Academic Research Cancer Program	1.16 (1.09, 1.24)	< .0001
Community Cancer Program	0.90 (0.84, 0.97)	0.004
Facility Volume – gastrectomies/year (%)		
1–10	Ref	
11–30	1.70 (1.61, 1.80)	< .0001
≥ 31	2.73 (2.43, 3.05)	< .0001
Clinical Nodal Status		
Negative	Ref	
Positive	1.43 (1.36, 1.51)	< .0001
Gastrectomy type		
Subtotal	Ref	
Total	1.53 (1.45, 1.61)	< .0001
En bloc	1.79 (1.65, 1.96)	< .0001
Surgical approach		
Open (69.9%)	Ref	
Laparoscopic (22.4%)	1.11 (1.05, 1.18)	0.0002
Robotic (7.7%)	1.24 (1.13, 1.35)	< .0001
Preoperative Radiation		
No	Ref	
Yes	0.37 (0.35, 0.40)	< .0001
Preoperative Chemotherapy		
No	Ref	
Yes	1.50 (1.41, 1.60)	< .0001

[a]adjusted for variables with an unadjusted $p < 0.10$. OR: Odds ratio; CI: Confidence interval

abdominal surgeries. These indicators of intra-operative complexity could facilitate individualization of procedure choices and allow a better understanding of the influence of such factors in surgical outcomes.

Villano et al. examining an NCBD cohort of patients who underwent surgery for gastric cancer between 2004–2015, also demonstrated that there was an increase in the rate of lymphadenectomy over their study period.[13] However, they focused on the removal of 15 or more nodes and not the current standard of ≥ 16 nodes.[12,15] Similar to this study, they found that female gender, Asian race, and lower comorbidity index were associated with higher odds of lymphadenectomy of ≥ 15 nodes. However, they did not demonstrate the impact of pre or perioperative chemotherapy on the adequacy of the lymphadenectomy. Zhao et al. studying the adherence to operative standards for gastric cancer, which included lymphadenectomy ≥ 16 nodes and negative margins in patients who underwent gastrectomies between 2004–2014, reported an adherence rate of only 41.8%.[14] The authors reported the factors associated with adherence to high-quality surgical standards were age < 65, female gender, Asian race, low comorbidity index, surgery high-volume centers, and Academic facilities. These findings corroborate with the results of the current study. However, they utilized an older cohort of patients who underwent surgery up to 2014, which likely explains why they did not study the impact of perioperative chemotherapy and surgical approaches as predictors of lymph node yield.

In light of the increased use of minimally invasive approaches in the surgical treatment of gastric cancer, the adequacy of lymphadenectomy has never been so relevant. As surgeons progress through their learning curves, while adopting minimally invasive approaches, it is paramount that the quality of the oncological resection is not compromised. Therefore, a subgroup analysis was performed to evaluate how laparoscopic and robotic approaches were performed in regards to lymphadenectomy of 16 or more nodes. This analysis showed that both laparoscopic and robotic surgeries were associated with a significantly higher rate of removal of 16 or more lymph nodes than open gastrectomy, which translated into a better overall survival. Salehi et al. compared the oncologic surgical quality and outcomes of laparoscopic versus open gastrectomy for gastric cancer using the NCDB database. They reported a higher lymph node yield for the laparoscopic group and no difference in overall survival.[25] Conversely, the current study showed that laparoscopic and robotic gastrectomies were associated with improved overall survival compared to open surgery. This difference in overall survival between these studies might be explained by the different study period of these analyses. Salehi et al. studied patients who underwent surgery between 2010–2016, of which only 3170 had laparoscopic surgery. The present study included patients who underwent

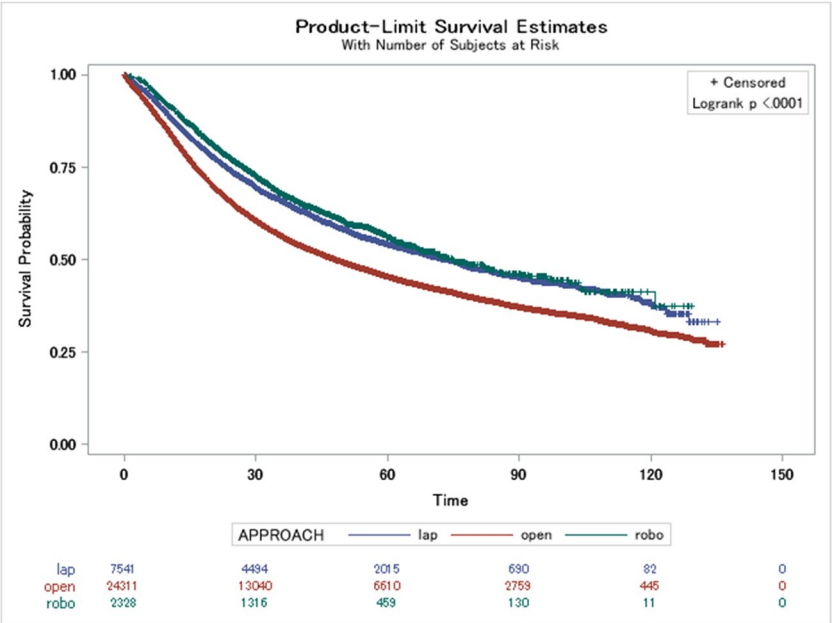

Fig. 3 Kaplan-Meier plot comparing the overall survival by surgical approach among patients who underwent gastrectomy for adenocarcinoma. Footnote: Lap**:** laparoscopic gastrectomies; Open: open gastrectomies; Robo: robotic gastrectomies

surgery up to 2019, of which 8320 underwent laparoscopic gastrectomies and 2853 robotic gastrectomies. The first multicenter Western randomized clinical trial comparing laparoscopic versus open gastrectomy for gastric cancer showed no difference in postoperative complications, length of stay, lymph node yield, 1-year overall survival, and quality of life.[26] Those findings were aligned with the Eastern multicenter randomized clinical trials, which compared laparoscopic versus open distal gastrectomy for stage I and locally advanced gastric cancers.[27–29] These large clinical trials included high-volume tertiary centers with experienced surgeons in both surgical approaches in the Netherlands and Korea. This large NCDB cohort study also included low-volume centers with different levels of surgical expertise in community and academic settings, which likely explains the different findings of the current analysis regarding lymph node yield and overall survival between minimally invasive approaches and open gastrectomy.

The debate between D1 versus D2 lymphadenectomy seemed to be settled after two Western randomized clinical trials showed that D2 lymphadenectomy had no overall survival advantage and was associated with increased postoperative morbidity.[9,10] However, the 15-year follow-up of the Dutch clinical trial showed lower locoregional recurrence and cancer-related mortality for the D2 lymphadenectomy patients compared to D1.[11] Furthermore, the Dutch adjuvant chemoradiation clinical trial showed that compared to surgery alone, adjuvant chemoradiation led to a lower local recurrence rates for patients who underwent D1 lymphadenectomy but not for those undergoing D2 lymphadenectomy, which indirectly suggested the D1 patients had suboptimal locoregional control.[30] With this evidence, postoperative chemoradiation therapy is currently recommended for patients who received less than a D2 lymphadenectomy.[12] Aligned with this evidence, the present study showed that patients who underwent gastrectomy with lymphadenectomy ≥ 16 nodes had improved survival independently of the receipt of postoperative radiation therapy and postoperative chemotherapy.

This study has several limitations that are inherent to its retrospective design and the use of administrative data, that is subject to potential coding and abstraction errors. Potential selection bias exists when determining which patients received adequate lymphadenectomy, chemotherapy, radiation therapy, and type of surgical approach. Furthermore, there is no data on surgeon's volume and experience. The unmeasured characteristics, such as intra-operative complexity (such as patient's body habitus, anatomic variation and history of previous abdominal surgeries), postoperative complications, the extent of the lymphadenectomy in terms of D1 and D2, locoregional recurrence and cancer-related mortality could not be analyzed as they are not available in the NCDB database. Some of these limitations were mitigated by the large number of patients included in this study, and for taking into account the hospital volume and facility type in the multivariable analysis.

Conclusions

Although the rate of lymphadenectomy ≥ 16 nodes has increased over time, a significant number of patients still lack adequate lymph node dissection during gastrectomy for gastric cancer in the US. The failure to

Table 6 Multivariable Cox proportional hazard analysis for predictors of overall survival among patients with documented surgical approach ($n = 37150$)

Variable	Adjusted[a]	
	HR (95% CI)	P-value
Age < 65 years	0.71 (0.68, 0.73)	< .0001
Female	0.94 (0.91, 0.97)	0.0002
Race		
Caucasian	Ref	
African American	1.00 (0.96, 1.05)	0.97
Asian	0.70 (0.65, 0.76)	< .0001
Other	0.74 (0.68, 0.79)	< .0001
Charlson-Deyo Score		
0	Ref	
1	1.09 (1.05, 1.12)	0.0004
2	1.23 (1.16, 1.30)	< .0001
≥ 3	1.51 (1.40, 1.62)	< .0001
Era of diagnosis		
2010–2014	Ref	
2015–2019	0.90 (0.87, 0.93)	< .0001
Facility		
Integrated Network Cancer Program	Ref	
Academic Research Program	0.89 (0.86, 0.94)	< .0001
Community Cancer Program	0.99 (0.95, 1.03)	0.66
Facility Volume – gastrectomies/year (%)		
1–10	Ref	
11–30	0.87 (0.84, 0.90)	< .0001
≥ 31	0.78 (0.72, 0.84)	< .0001
AJCC Stage Group		
0	Ref	
I	0.81 (0.67, 0.96)	0.02
II	1.52 (1.28, 1.82)	< .0001
III	2.44 (2.04, 2.91)	< .0001
Surgical Approach		
Open (69.9%)	Ref	
Laparoscopic (22.4%)	0.90 (0.86, 0.93)	< .0001
Robotic (7.7%)	0.88 (0.82, 0.95)	0.0006
Gastrectomy type		
Subtotal	Ref	
Total	1.13 (1.09, 1.17)	< .0001
En bloc	1.23 (1.17, 1.29)	< .0001
Lymphadenectomy ≥ 16 LN		
No	Ref	
Yes	0.80 (0.78, 0.83)	< .0001
Negative Nodal Involvement		
No	Ref	
Yes	0.65 (0.63, 0.68)	< .0001
Negative Surgical Margins		
No	Ref	
Yes	0.52 (0.50, 0.54)	< .0001
Grade		
Poorly Differentiated/Anaplastic	Ref	
Well/Moderately Differentiated	0.83 (0.80, 0.86)	< .0001
Preoperative Radiation		
No	Ref	
Preoperative	1.25 (1.18, 1.31)	< .0001
Postoperative	0.88 (0.83, 0.93)	< .0001
Pre and Postoperative	1.71 (1.23, 2.37)	0.001
Systemic Chemotherapy		
No	Ref	
Preoperative	0.70 (0.67, 0.74)	< .0001
Postoperative	0.60 (0.56, 0.63)	< .0001
Pre and Postoperative	0.59 (0.55, 0.63)	< .0001

[a]adjusted for variables with an unadjusted $p < 0.10$. HR: Hazard ratio; CI: Confidence interval; AJCC: American Joint Committee on Cancer

achieve this surgical standard is associated with worsened overall survival despite multimodality therapy. Because surgery is the cornerstone of gastric cancer treatment and the only chance for cure, every measure to improve the quality of the surgical technique should be sought out. Laparoscopic and robotic surgery provided a higher rate of adequate lymphadenectomy, leading to better overall survival when compared to open gastrectomy. These findings highlight the urgent need for taking advantage of modern minimally invasive platforms to enhance our surgical technique and lymph node dissections.

Authors Contribution Felipe B Maegawa: study design, analysis, interpretation of data, writing the manuscript, approving the final version.

Ankit D. Patel: conception, drafting and approving the final version of the manuscript.

Federico J. Serrot: conception, drafting and approving the final version of the manuscript.

Snehal G. Patel: conception, drafting and approving the final version of the manuscript.

Jamil L. Stetler: conception, drafting and approving the final version of the manuscript.

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Iman Ghaderi: conception, drafting and approving the final version of the manuscript.

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Yazan Ashouri: conception, analysis, and approving the final version of the manuscript.

Juan M. Sarmiento: conception, drafting and approving the final version of the manuscript.

Ioannis T. Konstantinidis: design, acquisition of the data, drafting and approving the final version of the manuscript.

Edward Lin: design, drafting, and approving the final version of the manuscript.

All authors are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability The National Cancer Database is available through the American College of Surgeons.

Declarations

Conflict of Interest Authors have no conflicts of interest to disclose.

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