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ORIGINAL ARTICLE

Evaluating Dissemination of Adequate Lymphadenectomy for Gastric Cancer in the USA

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Abstract

Background Adequate lymphadenectomy (AL) of 15+ lymph nodes comprises an important component of gastric cancer surgical therapy. Despite endorsement by the National Comprehensive Cancer Network and the Committee on Cancer, initial adoption of this paradigm has been relatively slow. The current analysis sought to perform an adjusted time-trend evaluation of the factors associated with AL and its dissemination.

Methods Utilizing the 2004–2015 National Cancer Database, 28,985 patients were identified who underwent gastrectomy for adenocarcinoma. An adjusted time-trend analysis was performed to estimate the adoption of AL overall. Multivariable logistic regression was utilized to assess factors associated with these observed trends. Interactions and stratified models determined disparate effects in vulnerable populations (older adults, ethnic minorities, low socioeconomic status).

Results The adjusted time-trend analysis demonstrated an overall 30% increase (28.8 to 58.7%) in receipt of AL (OR 1.10 increase/year; 95%CI 1.09–1.10) from 2004 to 2015. This trend persisted even after stratifying the models by age, race/ethnicity, and income (OR 1.07–1.12; $p < 0.05$). Slowest rates of adoption were seen amongst hospitals in the Midwest census region (OR 1.08, CI 1.06–1.90) and comprehensive community hospitals (OR 1.08, CI 1.06–1.91) and with African-American patients (OR 1.09, CI 1.06–1.11) (all $p < 0.05$).

Conclusion This multi-center evaluation demonstrates increased adoption of AL during gastric cancer surgery in the USA overall and amongst vulnerable populations, although regional and racial disparities were observed. Future studies are needed to investigate reasons underlying racial and regional differences in receipt of AL.

Keywords Gastric · Cancer · Lymphadenectomy · Outcomes · Disparity · Volume

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Introduction

Gastric cancer is the second leading cause of death worldwide despite decreasing incidence.[1] Surgical therapy (inclusive of margin-negative gastrectomy and adequate lymphadenectomy) remains the mainstay of operable gastric cancer care. Extended lymphadenectomy has been supported by level 1 evidence from Asia and Europe since the mid 1990s.[2,3] Adequate lymphadenectomy (AL), defined as 15 or more lymph nodes evaluated, is associated with improved staging accuracy[4,5] and long-term survival.[3–6] In 1997, AL evolved into a quality metric endorsed by the American Joint Committee on Cancer (AJCC)[7] and has since been further endorsed by the National Comprehensive Cancer Network (NCCN)[8] and the Committee on Cancer (CoC) of The American College of Surgeons (ACS).[9]

Despite these level 1–based endorsements followed by two decades to implement this practice, adoption of AL for gastric cancer in the United States (US) has been relatively slow. Earlier analyses found adoption rates ranging from 26 to 39% between 2001 and 2006.[10] Whether this slow adoption continues in the modern era remains largely unknown, as the most recent analysis examined trends of gastric lymphadenectomy up to 2009, nearly one decade ago.[11] Additionally, research on factors associated with AL beyond the early post-endorsement era is sparse. Filling these knowledge gaps in the modern era is important to inform quality improvement initiatives and policy implementation.

Given the prognostic and therapeutic importance of AL, and in light of the above knowledge gaps, this study aimed to evaluate adoption rates of AL for gastric cancer beyond its initial post-endorsement period. It was hypothesized that rates of AL have significantly improved since earlier evaluations. Given the strong body of evidence supporting AL, examination of these trends provides relevance with respect to future research, quality improvement, and policy-making.

Methods

Data Source

The analysis employed the 2004–2015 National Cancer Database Participant User File (NCDB PUF) provided by the ACS. The NCDB PUF is a large, nation-wide cancer database representing a collaborative effort administered by the American Cancer Society and ACS. This database contains information on patients treated at over 1500 CoC-accredited hospitals, spanning approximately 70% of all cancer cases in the US and containing over 34 million hospital records. These patient-, tumor-, treatment-, and hospital-level factors are collected and coded utilizing standard definitions (specified within the CoC Facility Oncology Registry Data Standards) by hospital cancer registrars.[12]

Study Population and Inclusion/Exclusion Criteria

The initial dataset was comprised of all gastric cancer patients aged 18 to 90 years treated between 2004 and 2015 (n = 183,204). Of these, patients were only included if they had a diagnosis of adenocarcinoma (ICD-O-3 histology codes 8140, 8260, 8211, 8480, 8255, 8560, n = 80,794) and underwent surgical resection (NCDB PUF surgical site codes 30, 31, 32, 33, 40, 41, 42, 50, 51, 52, 60, 61, 62, 63, n = 68,219). Patients were excluded if they were AJCC clinical stage IV or missing data (n = 5206). The final cohort was comprised of 28,985 patients, including 356 without lymphadenectomy data retained for sensitivity analysis.

Outcome (Dependent) Variable

The main outcome variable was receipt of AL, defined as 15 or more lymph nodes evaluated at the definitive surgical procedure. Procedures obtaining less than 15 were defined as inadequate. Evaluation of 0 lymph nodes was categorized and examined separately from inadequate lymphadenectomy, as this suggested no attempt to perform lymphadenectomy during the resection.

Independent Variables

Patient-, tumor-, treatment-, and hospital- level factors were compared and outlined in Table 1. Patient-level factors included age, race, sex, insurance, Charlson comorbidity index, travel distance to the treating hospital, rurality, income, and education. Income was defined as the median income for that patient's residential zip code using census tract. Similarly, education was ascertained indirectly as the percentage of population with no high school degree within the patient's residential zip code. Distance to the treating hospital equaled the great circle distance of the patient's zip code centroid to the treating facility. Tumor-level factors included TNM stage and grade. Hospital-level factors included facility type, US region of the facility, and hospital surgical volume.

Average annual hospital surgical volume was computed as the average number of procedures performed over a 3-year period for each hospital (2004–2006, 2007–2009, 2010–2012, and 2013–2015). After yearly volumes were summarized, these average hospital volumes per period were pooled and were ordered by volume. Hospitals were categorized as low- (LVHs), intermediate- (IVHs), or high-volume hospitals (HVHs) based on these thresholds, allowing hospitals to change volume category throughout the study period. Thresholds were set at terciles which grouped approximately the same number of patients as LVH, IVH, and HVH, rounded

Table 1 Bivariate analyses of patient-, tumor-, treatment-, and hospital-level factors by status of AL

Variable	Total ($n = 28,629$)	Inadequate lymphadenectomy (< 15 lymph nodes) ($n = 15,734$)	Adequate lymphadenectomy (15+ lymph nodes) ($n = 12,895$)	p value
Age (mean in years)	67.40	68.47	66.04	< 0.001
Sex (%)				0.405
Female	8646 (30.2%)	4719 (30%)	3927 (30.5%)	
Race (%)				< 0.001
White	19,844 (69.9%)	11,323 (72.5%)	8521 (66.7%)	
Asian	2239 (7.9%)	1008 (6.5%)	1231 (9.6%)	
Black	3909 (13.8%)	2088 (13.4%)	1821 (14.3%)	
Hispanic	2388 (8.4%)	1193 (7.6%)	1195 (9.4%)	
Insurance (%)				< 0.001
Medicare	15,969 (55.9%)	9260 (59.6%)	6521 (51.3%)	
Private	9818 (34.8%)	4959 (31.9%)	4859 (38.2%)	
Medicaid	1626 (5.8%)	810 (5.2%)	816 (6.4%)	
Not insured	741 (2.6%)	352 (2.3%)	389 (3.1%)	
Other government	279 (1%)	147 (0.9%)	132 (1%)	
Median income 2012 (%)				< 0.001
< $38,000	5320 (18.8%)	3052 (19.7%)	2268 (17.8%)	
$38,000–$47,999	6432 (22.8%)	3584 (23.2%)	2848 (22.3%)	
$48,000–$62,999	7600 (26.9%)	4240 (27.4%)	3360 (26.3%)	
$63,000+	8880 (31.5%)	4591 (29.7%)	4289 (33.6%)	
% no high school 2012 (%)				< 0.001
21% or more	5664 (20.1%)	3058 (19.8%)	2606 (20.4%)	
13–20.9%	7486 (26.5%)	4247 (27.4%)	3239 (25.4%)	
7–12.9%	9065 (32.1%)	5027 (32.5%)	4038 (31.6%)	
Less than 7%	6033 (21.4%)	3143 (20.3%)	2890 (22.6%)	
Distance to treating facility (mean)	35.36	31.3	40.28	< 0.001
Charlson comorbidity core (%)				< 0.001
0	18,646 (66.7%)	9867 (64.4%)	8779 (69.5%)	
1	7306 (26.1%)	4181 (27.3%)	3125 (24.7%)	
2+	2004 (7.2%)	1271 (8.3%)	733 (5.8%)	
Treating hospital rurality (%)				< 0.001
Metro: population > 1 million	15,542 (56.2%)	8162 (53.9%)	7380 (59%)	
Metro: population < 1 million	8157 (29.5%)	4727 (31.2%)	3430 (27.4%)	
Urban, adjacent to a metro area	2741 (9.9%)	1556 (10.3%)	1185 (9.5%)	
Urban, not adjacent to a metro area	1216 (4.4%)	709 (4.7%)	507 (4.1%)	
Facility type (%)				< 0.001
Academic research	13,120 (46.6%)	6139 (39.5%)	6981 (55.2%)	
Comprehensive community	10,097 (35.8%)	6341 (40.8%)	3756 (29.7%)	
Integrated network	3186 (11.3%)	1810 (11.7%)	1376 (10.9%)	
Community	1764 (6.3%)	1239 (8%)	525 (4.2%)	
Facility US region (%)				< 0.001
Midwest	6585 (23.4%)	3821 (24.6%)	2764 (21.9%)	
Northeast	6996 (24.8%)	3344 (21.5%)	3652 (28.9%)	
South	10,309 (36.6%)	6214 (40%)	4095 (32.4%)	
West	4277 (15.2%)	2150 (13.8%)	2127 (16.8%)	
Average annual number of procedures (mean)	26.18	19.97	33.77	< 0.001
Annual surgical volume, by tercile (%)				< 0.001
LVH: 00–07	7605 (26.6%)	5087 (32.3%)	2518 (19.5%)	
IVH: 08–22	8761 (30.6%)	5236 (33.3%)	3525 (27.3%)	
HVH: 23+	12,263 (42.8%)	5411 (34.4%)	6852 (53.1%)	
Regional nodes examined (mean)	15.00	7.56	24.08	< 0.001
Length of stay (mean, in days)	11.94	12.11	11.73	0.005
30-day unexpected readmission (%)	1955 (7.0%)	1097 (7.1%)	858 (6.8%)	0.256
30-day mortality (%)	1153 (4.4%)	779 (5.3%)	374 (3.3%)	< 0.001
90-day mortality (%)	2225 (8.6%)	1493 (10.3%)	732 (6.4%)	< 0.001

to the nearest integer, and were applied uniformly throughout the study period. Terciles were chosen this way because the thresholds were clinically meaningful (7–19 for intermediate, 20+ for HVH) while also having comparably the same number of patients in each level. Other quantiles including a priori thresholds such as those proffered by the Leapfrog group and volume as a continuous variable were also investigated for exploratory analysis and sensitivity.

Statistical Analysis

Patient-, tumor-, treatment-, and hospital-level factors were compared by statuses of AL. In order to detect if there was positive uptake of AL, a time-trend analysis was performed including locally weighted scatterplot smoothing, simple/multiple linear regression for average number of lymph nodes examined over time, and simple/multiple logistic regression for the odds of AL over time. Additionally, regression analysis was repeated after single value imputation of missing data with the mean value for continuous variables and the mode for categorical variables. By estimating multiple models with and without imputation, the time-trend in AL was able to be estimated by the stability of the effect across these multiple models.

After confirming the trend in AL, disparity in AL uptake rates was explored using stratified and interaction logistic regression analysis. Stratified regression allowed for testing if the uptake rate was statistically significant within various strata (age 70+ vs. under 70, race, median income of residence, facility type, and facility location). Interaction analyses were subsequently used to test if disparity existed between age, race, income, facility region, and facility type with respect to AL uptake rate (i.e., between-group comparisons). Main effects and interaction effects were combined for simultaneous inference to confirm the stability of the results of the stratified analysis, the within-group AL uptake rate.

Data was manipulated utilizing SAS 9.4 (SAS Institute, Cary, NC), and analysis was performed with R 3.4[13] using the ggplot2,[14] doBy,[15] RMS,[16] multcomp, and R2wd[17] packages.

Results

Baseline Cohort Characteristics

Characteristics of the overall cohort are outlined in Table 1. The average age of the sample was 67.4 years old. Most patients were male (69.9%), of white race (70%), and covered by Medicare (56%).

Of the total cohort, 45.1% received AL. The average number of nodes examined per procedure was 16. Only 1285 patients (4.8%) had 0 lymph nodes examined. The annual number of gastric cancer surgery performed for adenocarcinoma remained moderately stable throughout the study period, fluctuating around 2250/year (years 2004 to 2009) and increasing to 2600/year (after 2010).

Comparison of Adequacy of Lymphadenectomy Status (15+ vs. < 15 Lymph Nodes)

Patients who underwent AL were younger (66.0 vs. 68.5 years, respectively), had higher median income (33.6% from the uppermost quartile vs. 29.7%), were more educated (22.6% from uppermost quartile vs. 20.3%), and were more likely to be privately insured (38.2% vs. 31.9%) (for all, $p < 0.001$) than patients who did not undergo AL. White race had the lowest overall rates of AL (42%), while Asian race had the highest rate (54%, $p < 0.001$). Furthermore, academic research centers had the highest rate of AL while community hospitals had the lowest (55.2% vs. 4.2%, p < 0.001). Similarly, HVHs were more likely to perform AL than LVHs (53.1% vs. 19.5% p < 0.001). Patients who received AL traveled further to undergo surgery (40.28 vs. 31.3 miles, p < 0.001).

Overall Time-Trend of AL

At the beginning of the study window in 2004, only 28.8% of patients underwent AL. By 2015, the rate of AL increased to 58.7% (Fig. 1a). Unadjusted time-trend analysis indicated that the adherence to the guidelines for AL steadily increased over the 12-year period by a mean of 11.1% per year from the baseline (OR = 1.111, 95%CI [1.104–1.119], $p < 0.001$). Simple linear regression estimated that the average number of lymph nodes examined had increased by one node every 2 years ($\beta = 0.52.8$; Fig. 1b).

Factors Predictive of AL

Patient factors predictive of AL included female gender, Asian race, lower comorbidity score, higher income, and greater distance to the treating facility (for all, $p < 0.05$, Table 2). Patients had incrementally higher odds of AL with advanced stage (stage II: OR = 1.628, $p < 0.001$; stage III: OR = 2.649, $p < 0.001$) and higher grade disease (relative to well differentiated, moderately differentiated: OR = 1.308, $p < 0.001$; poorly differentiated: OR = 1.390, $p < 0.001$; undifferentiated: OR = 1.667, $p < 0.001$).

Hospital factors predictive of AL included facility region, facility type, and annual surgical volume (all $p < 0.05$). Relative to the Northeast, hospitals located in the Midwest (OR = 0.723, $p < 0.001$) or South (OR = 0.629, $p < 0.001$) were less likely to achieve AL. Hospital surgical volume demonstrated a dose-dependent relationship, such that relative to LVHs (0–7 cases per year), IVHs, and HVHs increasingly predicted AL (OR 1.147 and 1.889, respectively, $p < 0.001$ for both). As compared with community hospitals, patients who underwent gastric cancer surgery at academic/research hospitals had the highest base AL rate (OR = 1.516 relative to community hospitals, $p < 0.001$), followed by integrated network hospitals (OR = 1.396, $p < 0.001$) and comprehensive community hospitals (OR = 1.168, $p = 0.011$). All of the aforementioned variables similarly predicted mean pathologic lymph node yield after surgical resection (Supplementary Table 1).

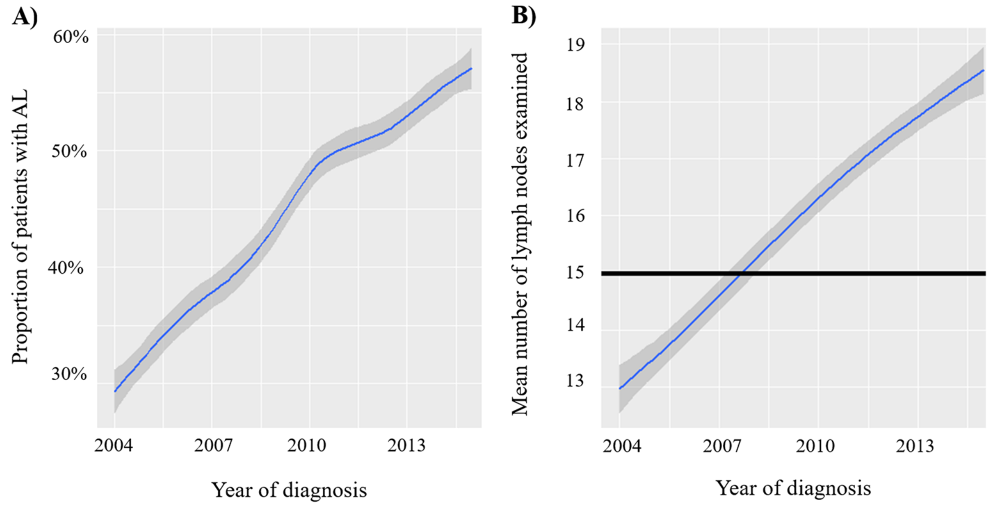

Fig. 1 **a** Time-trend analysis of AL from 2004 to 2015. **b** Time-trend analysis of mean number of lymph nodes examined from 2004 to 2015. *Dark line* demarcates 15 lymph nodes, correlating with current AJCC and NCCN guidelines

Factors Predicting Increased Rate of AL over Time

Stratified analysis tested whether the AL rate uptake was statistically significant within key population strata; it confirmed that AL increased over the study time period in every strata. AL rates ranged from an increase of 6.9% within Midwestern hospitals and up to 11.9% in Northeastern hospitals (Table 3, column 1).

Interaction analysis was used to test if the differential AL rates were statistically significant (Table 3, columns 2 and 3). The only statistically significant interactions were regional variables, where Midwestern and Southern hospitals had slower AL growth (OR 0.952, $p < 0.001$, and OR 0.969, $p = 0.002$, respectively) than hospitals in the Northeast. Other models had interactions with small p values but did not attain the critical level of alpha. Comparing AL growth rate by race, black patients had a slower rate than Asians (OR 1.031, $p = 0.072$) and Hispanic patients (OR 1.032, $p = 0.061$).

Effects of Race and US Region on AL

To better understand reasons behind the previously observed variations in AL by race and region, additional bivariate analyses evaluated association of patient and hospitals factors with AL stratified by race and region. With regard to the effects of region on AL, several relevant observations were detected. Amongst regions within the US, the Midwest and South had the lowest rates of AL (42.0% and 39.7%, respectively, $p < 0.01$; Table 4). These regions treated the fewest persons of Asian descent (4.0% Midwest, 4.6% South) and harbored more patients with 2 or more comorbid conditions (7.9% Midwest and 7.6% South) (all $p < 0.01$). The Midwest and South treated the highest proportions of patients at academic centers as compared with the other US regions (11% and 17%, respectively, $p < 0.01$). Patients from the Midwest and West traveled a significantly greater distance to undergo surgery (41.07 miles and 41.58 miles, respectively, $p < 0.01$).

With regard to the effect of race on AL, Asian race experienced the highest rate of AL as compared with all others (Table 5, 55%, $p < 0.01$). Compared with other races, Asian individuals had the fewest comorbidities (4.9%, Charlson index ≥ 2), were least likely to receive care at hospitals in US regions which lag in AL uptake (12% Midwest, 21.4% South), and had surgery at HVHs most frequently (45.3%)(for all, $p < 0.01$). Asian race was the least likely to receive gastric cancer surgery at academic center (9%, $p < 0.01$).

Discussion

This national multi-hospital evaluation demonstrated a steady improvement in the rates of AL for gastric adenocarcinoma, totaling a 29.9% increase (11.1% from the baseline rate, per year) in the US from 2004 to 2015. In addition to a consistent improvement in the rates of AL across multiple multivariate regression models, the current analysis also showed that more than half of surgically treated patients for gastric cancer received guideline-recommended care by the end of the study period. Furthermore, hospital-level factors (namely, academic centers and HVHs) were associated with the fastest growing rates of AL. Despite these improvements, this work also uncovered factors associated with a lag in the rate of adoption in community hospitals and in the Midwest/South US census regions, which might shed light on potential future interventions.

Earlier reports following endorsement of AL by the NCCN, AJCC, and CoC demonstrated slow adoption of AL in the US. Until recently, less than 40% of gastric cancer resections performed in the US were accompanied by AL. Results from the NCDB by Bilimoria and colleagues from 2003 to 2004 estimated AL rate at 23.2%.[18] Similarly,

Table 2 Multivariable regression analysis of factors predictive of AL (15+ lymph nodes)

Variable	OR	CI
Intercept	0.21	[0.16, 0.29]
Year	1.10	[1.09, 1.11]
Age	0.99	[0.99, 1.00]
Race		
White	-ref	
Asian	1.50	[1.36, 1.66]
Black	1.39	[1.28, 1.51]
Hispanic	1.28	[1.16, 1.42]
Female (referent male)	1.15	[1.08, 1.21]
Facility type		
Community	-ref	
Comprehensive community	1.17	[1.04, 1.32]
Academic research	1.52	[1.33, 1.73]
Integrated	1.40	[1.21, 1.61]
Facility US region		
Northeast	-ref	
Midwest	0.72	[0.67, 0.78]
South	0.63	[0.59, 0.68]
West	1.00	[0.92, 1.09]
Distance to treating facility	1.05	[1.03, 1.08]
Treating hospital rurality		
Metro: 1 million +	-ref	
Metro: under 1 million	0.94	[0.88, 1.00]
Non-metro: adjacent	0.93	[0.84, 1.04]
Non-metro: non-adjacent	0.92	[0.800, 1.06]
Median income		
Less than $38,000	-ref	
$38,000–$47,999	1.10	[1.01, 1.12]
$48,000–$62,999	1.00	[0.92, 1.10]
$63,000+	1.06	[0.95, 1.18]
% no high school diploma		
21% or more	-ref	
13–20.9%	0.94	[0.86, 1.02]
7–12.9%	0.93	[0.85, 1.02]
Less than 7%	1.03	[0.92, 1.15]
Charlson comorbidity score		
0	-ref	
1	0.91	[0.86, 0.97]
2+	0.77	[0.69, 0.85]
Insurance		
Private	-ref	
No insurance	0.86	[0.73, 1.02]
Medicaid	0.78	[0.65, 0.95]
Medicare	0.82	[0.69, 0.97]
Other	0.85	[0.63, 1.15]
AJCC stage		
0	-ref	
I	1.31	[1.09, 1.58]
II	1.63	[1.35, 1.96]
III	2.65	[2.12, 3.19]
Grade		
Well differentiated	-ref	
Moderately differentiated	1.31	[1.17, 1.46]
Poorly differentiated	1.39	[1.25, 1.55]
Undifferentiated	1.67	[1.29, 2.15]
Annual surgical volume (gastrectomies/year)		
LVH: 00–07	-ref	
IVH: 08–22	1.15	[1.07, 1.24]
HVH: 23+	1.89	[1.74, 2.05]
N	27,559	
C-statistic	0.694	

Baxter and colleagues demonstrated AL rates of 32% within the NCI-sponsored Surveillance, Epidemiology and End Results (SEER) Program Tumor Registries from 1998 to 2001.[19] A slower trend in growth was demonstrated by Le et al. in their analysis of SEER tumor registries from 1983 to 2002, with rates of AL having increased from 23 to 30% by the second half of the study period.[20] Similarly, Dubecz and others demonstrated a similar gradual uptake of AL from 33 to 41.6% from 1998 to 2009.[11] These previously published evaluations are in line with the rates of AL identified in the present analysis, with only 32% receiving AL in 2004. The current analysis has demonstrated that these rates have substantially increased (nearly doubled) to 58.7% by 2015.

Understanding reasons underlying the observed increased in adoption rates of AL is important, as it is likely to be multifactorial. First, the scientific rigor of research supporting and underscoring the importance of proper lymphadenectomy in the gastric cancer literature has increased as a result of several modern comparative trials that demonstrated clear benefits to survival with acceptable morbidity.[21–25] Work by Verlato and others, which examined the trends of published lymphadenectomy research between 2008 and 2012, demonstrated a substantial increase in the proportion of articles favoring D2 between 2010 and 2012 as compared with 2008–2010 (25 studies vs. 5 studies).[26] This paradigm shift has likely led to more generous lymphadenectomies. Second, centralization of gastric cancer care may translate to increasing numbers of patients attaining care at high-volume or academic centers. The current study identified that both high-surgical volume and academic research status predicted AL. Both of these findings are congruent with prior research by Dudeja,[10] Bilimoria,[18] and Morgan.[27] Further, patients who received AL during their procedure traveled significantly further to obtain surgical care in this study (40.28 miles vs. 31.30 miles). Increased travel distance can serve as a surrogate marker of regionalization of care,[28] and as such, modern trends of regionalization to high-volume and academic centers may be a large contributor to the observed improvement in recent AL rates. Third, there has been a concomitant emphasis on the performance of the pathologist to retrieve the maximal number of lymph nodes from the surgical specimen. The most current College of American Pathologists Cancer Protocol Template[29] for examination of gastric cancer resections now includes an advisory statement that at least 16 nodes should be removed and examined; previous versions of the template did not include this metric. In addition, gastric cancer AL was further emphasized to the pathology community upon the CoC releasing the related quality improvement standard measure in the Fall of 2014. Research has led to modern improvements in pathologic examination techniques which increase yield (including

Table 3 Interaction models comparing the rates of AL uptake amongst strata

	Logistic (stratified)	Logistic with interaction (ORs)[1]	Logistic with interaction (combined effects)[2]
Simple	1.11 [1.10, 1.12]	–	–
Multiple	1.10 [1.09, 1.10]	–	–
Multiple + missing	1.10 [1.09, 1.11]	–	–
Under 70	1.09 [1.08, 1.10]	0.99 [0.98, 1.01]	1.10 [1.09–1.11]
70+	1.10 [1.08, 1.11]	*1.10 [1.09, 1.12]**	1.10 [1.09–1.12]
Asian	1.11 [1.08, 1.15]	1.03 [1.00, 1.07]	1.12 [1.09, 1.15]
Black	1.09 [1.06, 1.11]	*1.08 [1.07, 1.11]**	1.09 [1.06–1.11]
Hispanic	1.12 [1.08, 1.15]	1.03 [1.00, 1.07]	1.12 [1.09, 1.15]
White	1.09 [1.08, 1.10]	1.01 [0.99, 1.03]	1.10 [1.09, 1.11]
High income	1.10 [1.09, 1.11]	*1.10 [1.09, 1.11]**	1.10 [1.09–1.11]
Low income	1.09 [1.07, 1.11]	1.00 [0.98, 1.02]	1.10 [1.08, 1.12]
Community	1.08 [1.05, 1.12]	*1.08 [1.05, 1.12]**	1.08 [1.05–1.12]
Comprehensive community	1.08 [1.06, 1.09]	1.00 [0.97, 1.04]	1.08 [1.07–1.10]
Academic research	1.10 [1.09, 1.12]	1.03 [1.00, 1.06]	1.11 [1.10–1.12]
Integrated network	1.12 [1.09, 1.14]	1.04 [1.00, 1.08]	1.12 [1.09–1.15]
Midwest	1.07 [1.05, 1.09]	0.95 [0.93, 0.97]	1.07 [1.06–1.09]
Northeast	1.12 [1.10, 1.14]	*1.13 [1.11, 1.15]**	1.13 [1.11–1.15]
South	1.09 [1.08, 1.11]	0.97 [0.95, 0.99]	1.09 [1.08–1.11]
West	1.10 [1.08, 1.13]	0.98 [0.96, 1.01]	1.11 [1.09–1.13]

[1] Multiple regression models were fit with time interacted with age, income, race, facility, type, and region. Italicized values with asterisks are ORs with 95%CIs for the reference strata, all other ORs test the interaction relative to the italicized reference strata

[2] Combined time effects were estimated from the main effect and interaction using *multcomp* package

micrometastases) such as systematic fat blocking[25] and ex vivo dissection of the specimen.[26]

Despite the demonstrable positive trends in AL over time, the current study has also uncovered factors associated with slow adoption of AL amongst racial/ethnic groups and US census region areas, highlighting potential areas for further improvement in gastric cancer surgery. Namely, racial disparities in receipt of AL have generally been variable in the literature to date, with no clear consensus. In line with findings by several prior studies,[19,20,27,30,31] Asian race was found to be predictive of AL. The current analysis extends this body of knowledge by demonstrating that non-Asian race exhibited slower uptake of AL over the study period, thus indicating a growing disparity gap. Further, on multivariate analysis, solely white race was predictive of inadequate lymphadenectomy. Potential hypotheses for these trends are that comorbid conditions portend a more difficult nodal dissection or predict more frequent attendance at LVHs. An association between greater comorbidities and inadequate AL was observed in this study and has been similarly illustrated by several others in gastric cancer.[28–31] Such a phenomenon may offer an explanation as to why Asian race (least comorbid) tends to consistently predict superior AL rates and why white race (most comorbid) has the worst AL rates in this analysis despite the advantage of high attendance at academic/HVHs. It was interesting to note that Asian race achieved the highest rates of AL despite the lowest attendance at academic centers. It may be possible that factors such as hospital volume and comorbidity status are more important and deserve further research attention.

Additionally, a lag in the uptake of AL was also identified for hospitals in the Midwest and Southern census regions of the US. Regional differences in AL rates have also been observed in two separate prior SEER studies by Baxter[19] and Le;[20] however, particular regional differences are difficult to compare amongst studies secondary to variable definitions of "region" and methods utilized in analysis. Regardless, these differences highlight that uniform uptake of AL has not yet been achieved and suggests these areas may lack high-volume, academic centers or that patients are unwilling to travel the distance necessary to attend these centers. Shorter travel distance and rural location were also associated with inadequate AL in this study. Alvino and others demonstrated that the majority of patients in California obtain gastrectomy at the center closest to their home (67%). Further, in their cohort, rurality predicted a lower likelihood to bypass to a more distant hospital. These "bypass hospitals" were more likely academic and HVHs, suggesting that unwillingness (or inability) to access a distant hospital may lead to lower quality care[32] and may partially explain the current study's findings (patients in the South traveled less distance than those in the West/

Table 4 Bivariate analysis of US regional effects

Variable	Northeast ($n = 6996$)	Midwest ($n = 6585$)	South ($n = 10,309$)	West ($n = 4277$)	p value
Race					< 0.01
White	5095 (73.6)	5301 (81.3)	6671 (65)	2549 (60.4)	
Asian	573 (8.3)	262 (4)	469 (4.6)	883 (20.9)	
Black	728 (10.5)	753 (11.6)	2186 (21.3)	161 (3.8)	
Hispanic	524 (7.6)	203 (3.1)	938 (9.1)	625 (14.8)	
Charlson comorbidity score					< 0.01
0	4506 (65.9)	4194 (65.6)	6518 (64.8)	3030 (72)	
1	1842 (26.9)	1698 (26.6)	2772 (27.6)	935 (22.2)	
2+	491 (7.2)	502 (7.9)	765 (7.6)	242 (5.8)	
Facility type					< 0.01
Community	332 (4.7)	499 (7.6)	620 (6)	313 (7.3)	
Comp community	1552 (22.2)	1951 (29.6)	4310 (41.8)	2284 (53.4)	
Integrated network	4684 (67.0)	3408 (51.8)	3626 (35.2)	1402 (32.8)	
Academic	428 (6.1)	727 (11)	1753 (17)	278 (6.5)	
Annual surgical volume, by tercile (%)					< 0.01
LVH: 00–07	1441 (20.6)	1968 (29.9)	2704 (26.2)	1389 (32.5)	
IVH: 08–22	1725 (24.7)	1923 (29.2)	3544 (34.4)	1425 (33.3)	
HVH: 23+	3830 (54.7)	2694 (40.9)	4061 (39.4)	1463 (34.2)	
Mean great circle distance (miles)	29.75 (118.79)	41.07 (133.94)	32.71 (67.3)	41.58 (151.12)	< 0.001
Mean nodes examined	16.69 (11.64)	14.31 (10.21)	13.6 (10.14)	16.43 (11.63)	< 0.001
Adequate LN n(p)					< 0.001
N	3344 (47.8)	3821 (58)	6214 (60.3)	2150 (50.3)	
Y	3652 (52.2)	2764 (42)	4095 (39.7)	2127 (49.7)	

Midwest and had the poorest rates of AL upon bivariate analysis).

The differences in uptake of AL amongst US census regions also highlight the potential importance of race/comorbidity status and suggest the interplay of patient-level and hospital-level variables is complex. It was interesting to note that race and comorbidity status consistently predicted both AL and mean lymph node yields. For example, Midwest and South hospitals (those lagging in rates of AL) treated *both* the lowest percentages of Asian patients (4% and 4.6%, respectively) and the highest percentages of severely comorbid patients (7.9% and 7.6%, respectively) as compared with Northeast and West hospitals. By contrast, hospital-level variables also shown predict AL (i.e., HVH status and academic center status), do not explain trends in AL by US region, and in fact contradict expected outcomes. For instance, hospitals in the West had the lowest percentage of HVHs (34.2%) and the lowest proportion of academic hospitals (34.2%), yet somehow managed to have the second highest AL rate and mean lymph node yield. Analysis by region demonstrated that West hospitals treat over five times more Asian patients than other regions (20.9%) as well as the least comorbid patient population (72% with no comorbidities)(Table 4). These findings suggest that the interplay of hospital-level variables (center volume, center experience, academic status) and patient-level variables (race, comorbidity) is more complicated than originally thought and patient-level variables play a significant role in prediction of AL.

The current study has several limitations in addition to those inherent to its retrospective design. First, the breadth of the analysis is limited to the variables contained within the NCDB PUF and cannot comment on important outcome markers such as disease-specific survival or local recurrence. Second, there is no data in the NCDB regarding the extent of lymphadenectomy (i.e., D1 vs. D2) performed. As a result, it is impossible to discern the relative contributions of the quality of lymphadenectomy as compared with the quality of pathologic analysis (although the two likely correlate well center to center and probably contribute similarly to either adequate or inadequate samplings). It is well illustrated in prior randomized trials that D2 lymphadenectomy consistently yields more lymph nodes on pathologic analysis;[22–24] thus, one can surmise that AL is achieved more frequently with aggressive lymphadenectomy. Third, the NCDB does not collect information on the experience of the individual surgeon or pathologist. Both have been shown to be independent predictors of lymph node yield[33] and as such should but cannot be controlled for in this analysis. Lastly, body mass index is not

Table 5 Bivariate analysis of the effect of race

Variable	White (n = 19,844)	Asian (n = 2239)	Black (n = 3909)	Hispanic (n = 2388)	p value
Charlson index					< 0.01
0	12,951 (66.8)	1575 (71.4)	2401 (63.2)	1540 (66.3)	
1	5049 (26.1)	523 (23.7)	1052 (27.7)	627 (27)	
≥ 2	1380 (7.1)	109 (4.9)	346 (9.1)	156 (6.7)	
Facility type					< 0.01
Community	1106 (5.6)	203 (9.3)	283 (7.4)	166 (7.2)	
Comp community	7029 (35.8)	759 (34.7)	1373 (35.9)	902 (39.4)	
Integrated network	9369 (47.8)	1028 (47)	1645 (43)	902 (39.4)	
Academic	2112 (10.8)	197 (9)	527 (13.8)	320 (14)	
US region					< 0.01
Midwest	5301 (27)	262 (12)	753 (19.7)	203 (8.9)	
Northeast	5095 (26)	573 (26.2)	728 (19)	524 (22.9)	
South	6671 (34)	469 (21.4)	2186 (57.1)	938 (41)	
West	2549 (13)	883 (40.4)	161 (4.2)	625 (27.3)	
Mean annual hospital volume by tercile					< 0.01
LVH (0–7 procedures)	5198 (26.2)	552 (24.7)	1208 (30.9)	620 (26)	
MVH (8–22 procedures)	5853 (29.5)	673 (30.1)	1321 (33.8)	871 (36.5)	
HVH (23+ procedures)	8793 (44.3)	1014 (45.3)	1380 (35.3)	897 (37.6)	
Mean great circle distance (miles)	41.07 (118.9)	24.16 (135.55)	19.22 (74.42)	18.75 (62.02)	< 0.01
Mean nodes examined	14.42 (10.46)	17.46 (12.16)	15.62 (11.33)	16.32 (11.36)	< 0.01
Adequate LN n(p)					< 0.01
N	11,323 (57.1)	1008 (45)	2088 (53.4)	1193 (50)	
Y	8521 (42.9)	1231 (55)	1821 (46.6)	1195 (50)	

measured in the NCDB and would have helped to elucidate the significance of obesity itself in relation to AL. Despite these shortcomings, results from the current paper stem from a large multi-hospital dataset which offers broad applicability on a national scale.

The current results have quality improvement and policy relevance. First, the overall increase in AL reinforces the importance of ongoing endorsement of cancer surgery quality measures defined by various quality programs such as the CoC and AJCC. Additional endorsement from key organizations such as the National Quality Forum and American Hospital Association might further accelerate these efforts. Second, explicit recommendations to centralize gastric cancer surgery and AL to academic/high-volume centers are paramount given the consistency of this finding in the literature. Unfortunately, gastric cancer has not received robust endorsement by programs such as Leapfrog in a manner similar to pancreatic or esophageal cancer.[34] Lastly, the observed regional disparities in performance of high-quality gastric cancer surgery activate state-level initiatives, in collaboration with the payers and regulators, to track and mitigate reasons behind low adoption of AL for operable gastric cancer.

Conclusions

This multi-institutional analysis demonstrated a consistent, nationwide improvement in AL after gastric cancer surgery in the current decade largely driven by hospital factors and locations. Academic and high-volume surgical centers continue to predict AL and highlight the need to further regionalize gastric cancer care to specialty centers to maximize patient survival. Understanding racial/ethnic and regional variations are important areas of future investigation and policy intervention to accelerate improvement in this important gastric cancer quality metric across US hospitals.

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