Adherence with operative standards in the treatment of gastric cancer in the United States

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Abstract

Background Despite multiple clinical trials and practice guidelines for the treatment of gastric cancer, oncologic outcomes have not improved in the United States. One potential reason could be differences in the quality of surgery as performed in a controlled trial versus in practice.

Methods Using the National Cancer Database, rates of adherence with operative standards for gastrectomy for cancer were analyzed. Of the numerous evidence-based operative standards outlined in the manual, two were reliably measured in the NCDB: (1) achieving an R0 resection, and (2) having > 16 lymph nodes examined. Univariable and multivariable Cox proportional hazard modeling and logistic regression were performed.

Results A total of 28,705 patients with gastric adenocarcinoma who underwent curative-intent gastrectomy during 2004–2014 were identified. Only 36.5% of stage 0/I patients, and 41.8% of stage II/III patients, met minimum standards. Predictors for meeting standards included age < 65, fewer comorbidities, Asian/Pacific Islander race, and treatment at academic and high-volume centers. Patients who met standards had longer OS (stage 0/I: 104.9 versus 66.6 months; stage II/III: 40.6 versus 26.0 months; $p < 0.001$ for both). Meeting standards was a significant predictor for improved OS for both stage 0/I and II/III patients (HR = 0.665 and HR = 0.747, respectively, $p < 0.001$ for both).

Conclusions For standards that are measurable in the NCDB, adherence is poor. Improved adherence with operative standards may improve survival for gastric cancer patients in the U.S. There is a need for better measuring of, and adherence with, operative standards in gastrectomy for cancer.

Keywords Gastric cancer · National Cancer Database · NCDB · Operative standards

Introduction

Evidence-based guidelines for the treatment of cancer are formulated as a means of summarizing and disseminating clinical trial results and expert consensus recommendations. The Operative Standards for Cancer Surgery (OSCS) is a publication jointly produced by the American College of

Surgeons and the Alliance for Clinical Trials in Oncology that focuses on the surgical treatment of various cancers and clearly defines technical aspects of surgery that are likely to directly impact oncologic outcomes. This comprehensive manual is compiled by experts and is based on comprehensive literature review with grading of strength of evidence. The first volume of this series was published in 2015 and covered breast, colorectal, pancreatic, and lung cancers [1]. The second volume was published in 2018 and covered thyroid, esophageal, gastric, and rectal cancers, and melanoma [2].

Gastric cancer is a particularly aggressive solid organ cancer. It is currently the third leading cause of cancer death worldwide and the seventh leading cause in the United States (U.S.) [3]. If diagnosed and treated at an early stage, it can be cured with complete surgical resection. When locally advanced, recurrence rates are high and multi-modality therapy is necessary to optimize outcomes. When metastatic,

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treatment is palliative, as cure is not possible. In the U.S., the majority of patients have locally advanced or metastatic disease at presentation, because screening is not performed and symptoms generally occur late in the natural history of gastric cancer.

Gastric cancer is unique in that despite promising results from multiple prospective, randomized trials of multidisciplinary treatment regimens showing improved survival [4–8], there has been little-to-no improvement in clinical outcomes for this disease in decades. Reasons for this phenomenon are not clear, but one reason may be the quality of surgery as performed on a controlled trial, as opposed to in the real-world setting. We hypothesized that compliance with operative standards may be suboptimal, and improved compliance may be a means to improve outcomes in this aggressive disease. In this study, we aimed to evaluate baseline rates and predictors of compliance with the evidence-based operative standards recommended in the OSGS Volume II for the treatment of gastric cancer at Commission on Cancer (CoC)-accredited centers, and to determine if compliance with the standards is associated with overall survival.

Methods

Patients and minimum surgical standards

The National Cancer Database (NCDB) is a national oncology outcomes database that is jointly sponsored by the American College of Surgeons and the American Cancer Society. It contains clinical oncology data sourced from over 1500 CoC-accredited centers. Patients diagnosed

with gastric adenocarcinoma between 2004 and 2014 were included in this analysis.

Surgical standards recommended for the treatment of gastric cancer in the OSGS Volume II were identified. The NCDB participant user file was then evaluated to determine which of the standards can be assessed with existing collected variables. Certain standards were not measurable without making large assumptions or the data were not available in NCDB (e.g. endoscopic resection for flat or superficially elevated lesions, proximal margin length, reconstruction methods after resection). Potentially evaluable and non-evaluable standards are shown in Table 1. Specific patient cohorts were created to analyze each potentially evaluable recommendation, as detailed below. For all cohorts, patients who underwent curative-intent gastrectomy without metastatic disease were included.

1. Staging laparoscopy that includes peritoneal lavage and acquisition of fluid for cytologic examination should routinely be performed for patients with operable gastric cancer (stage T1b or greater) prior to gastrectomy or preoperative therapy.

Patients with clinical stage T0 were excluded. To satisfy this standard, a surgical exploration must be performed separately from the definitive resection (defined by “days from first surgical procedure” that is less than “days from definitive surgery”). The number of these patients underwent any type of surgical exploration and diagnostic procedure (excluding endoscopic diagnostic procedures, aspiration, and biopsies) prior to gastrectomy or neoadjuvant therapy was analyzed.

2. Partial gastrectomy is recommended for cancers of the middle or distal third of the stomach, and total gastrectomy for cancers of the proximal third.

Table 1 Evaluable and non-evaluable operative standards

Potentially evaluable operative standards

1. Staging laparoscopy with peritoneal lavage for operable disease prior to gastrectomy or preoperative therapy
2. Partial gastrectomy for cancers of the middle or distal third; total gastrectomy for cancers of the proximal third
3. Minimally invasive surgery is a suitable alternative to open surgery when surgeon’s expertise is adequate
4. R0 resection should be performed
5. At least 16 regional nodes should be removed and examined at gastrectomy. A D2 dissection is the minimum lymph node dissection that would enable routine resection and assessment of at least 16 regional nodes

Non-evaluable operative standards

1. Endoscopic resection for patients with flat or superficially elevated lesions < 2 cm
2. For patients with early stage cancers of the distal stomach, the primary tumor should be resected with intent to achieve a final proximal margin of 3 cm or more. For patients with later stage distal cancers or those with proximal tumors, data do not support extension of the margin to any specific length
3. Esophagojejunostomy with Roux-en-Y anastomosis is recommended for reconstruction after total and subtotal gastrectomy for cancer. Either Roux-en-Y or Billroth II is acceptable for distal gastrectomy
4. Intraperitoneal drains and small bowel feeding tubes should not routinely be placed at the time of gastrectomy for cancer. The use of small bowel feeding tubes may be justified in select patients at the highest risk of anastomotic leak and/or malnutrition, such as those undergoing total gastrectomy

Tumors of the cardia and fundus were defined as proximal third, and those of the body, antrum, and pylorus were defined as middle/distal third. Tumors located in the lesser curve, greater curve, overlapping tumors, and tumor locations that were not otherwise specified were excluded from this analysis. The type of gastrectomy performed was compiled into partial or total gastrectomy. The NCDB does not specify if a gastrectomy was proximal or distal, only if it was partial or total. The type of gastrectomy performed for each tumor location was then analyzed.

3. Minimally invasive surgery is a suitable alternative to open surgery in gastrectomy for cancer when surgeon expertise is adequate.

Patients with clinical stage group 0 to III who had any type of gastrectomy were identified. Patients who had conversions to open surgery were considered as having undergone a minimally invasive approach in an “intent-to-treat” analysis. Analysis was then performed to determine how many patients underwent a minimally invasive gastrectomy (including laparoscopic and robotic approaches) since 2010, as this was the first year these data were collected in the NCDB. It should be noted that this recommendation does not state that minimally invasive surgery is *superior* to open surgery, but rather that the current evidence supports the use of a minimally invasive approach in gastric cancer surgery.

4. R0 resection should be performed.

The proportion of patients who had a microscopically negative surgical margin (R0) versus a microscopic or grossly positive margin (R1 or R2) was identified.

5. D2 lymphadenectomy should be performed with at least 16 lymph nodes removed and examined.

There is no variable in the NCDB defining a D2 lymphadenectomy, but the number of lymph nodes examined in surgical specimens is collected. Examination of at least 16 lymph nodes is required for adequate staging. The proportion of patients who had at least 16 lymph nodes examined was determined and was used as a surrogate for D2 lymphadenectomy.

6. Intraperitoneal drains and small bowel feeding tubes should not routinely be placed at the time of gastrectomy for cancer. The use of small bowel feeding tubes may be justified in select patients at the highest risk of anastomotic leak and/or malnutrition, such as those undergoing total gastrectomy.

The use of drains and feeding tubes is not recorded in the NCDB. Additionally, the selective use of drains and tubes is considered appropriate.

Variables

The American Joint Committee on Cancer (AJCC) Stage Group was used by the NCDB for staging (6th edition of the AJCC cancer staging manual for 2004–2009, 7th edition for 2010–2014). Patient age was dichotomized to < 65 and ≥ 65. As reported in the NCDB, Charlson/Deyo comorbidity scores (CDCS) were categorized into 0, 1, or ≥ 2. Race was categorized into white, black, Asian/Pacific Islander, American Indian, and other. Rurality of the patient’s domicile was dichotomized into urban/metro versus rural. Median household income of the patient’s domicile was dichotomized into < \$48,000 and ≥ \$48,000. In the NCDB, education of the patient’s domicile is measured by the percentage of the population with no high-school diploma. This variable was dichotomized into < 13% and ≥ 13%. Dichotomized median household income and education level represent the median within the NCDB dataset. Patient insurance was categorized into no insurance, private insurance, or government insurance (e.g. Medicaid, Medicare, and other governmental insurance). Tumor size was categorized by centimeters up to 5 cm. Tumor grade was divided into well-differentiated, moderately differentiated, poorly differentiated, and undifferentiated/anaplastic, as per the NCDB. Hospital volume was determined by annualizing the total number of gastrectomies performed for adenocarcinoma per facility, as identified by the unique facility code within NCDB. This was then dichotomized into high- and low-volume centers at the 50th percentile. Facility type was dichotomized into community (community, comprehensive community, integrated network cancer programs) versus academic center.

Statistical analyses

Patients were stratified into clinical stage 0/I or stage II/III disease. For both cohorts, Kaplan–Meier analysis was performed to compare the overall survival (OS) of patients who met minimal standards versus those who did not by the log-rank test. Minimum standards were chosen based on evaluability in the NCDB. Of the evaluable standards, only two were felt to be reliably measured and were included in survival analyses as minimum standards: (1) ≥ 16 LNs examined, and (2) achieving an R0 resection. We examined adherence rates to these standards stratified by region in the United States for both stage 0/I and II/III patients. For all regression analyses, a univariable model was performed for all predictors with inclusion criteria for entry into the multivariable model set at $p < 0.20$. For both stage 0/I and II/III patients, Cox proportional hazard ratio analysis was performed to identify independent predictors of OS and logistic regression analysis was performed to identify predictors for meeting minimum surgical standards. Lastly, a Cox proportional hazard ratio analysis was performed that

included all testable standards (except the partial versus total gastrectomy standard). For this model, all testable standards were forced into the multivariable model. All analyses were performed using SPSS (IBM Corp, Version 24, Armonk, NY). All comparisons were two-sided and considered to be significant at $p < 0.05$.

Results

A total of 28,705 patients with gastric adenocarcinoma who underwent curative-intent gastrectomy during this time period were identified. Patient demographics are shown in Table 2.

Adherence to operative standards

Adherence to operative standards is shown in Table 3. As defined in this study, a staging laparoscopy was performed prior to initiating any therapy in 1143 (4.0%) patients with stage cT1 or greater disease who underwent a curative-intent gastrectomy. Of patients with proximal tumors, 7555 (59.4%) underwent a partial gastrectomy, while 5171 (40.6%) underwent a total gastrectomy. For patients with distal tumors, 6748 (83.0%) underwent a partial gastrectomy, while 1379 (17.0%) underwent a total gastrectomy. Since 2010, a total of 10,814 (71.4%) patients underwent an open curative-intent gastrectomy, while 4329 (28.6%) underwent a minimally invasive gastrectomy. A total of 24,664 (92.6%) patients had negative (R0) resection margins. Lastly, 12,578 (44.5%) of patients who had curative-intent gastrectomy had at least 16 lymph nodes examined.

Minimum standards and survival

Adherence rates to minimum standards and Kaplan–Meier survival curves for clinical stage 0/I and II/III patients are shown in Fig. 1. For patients with clinical stage 0/I disease, 4139 (36.5%) met minimum standards of at least 16 lymph nodes examined and an R0 resection. The median OS for those who met the minimum standards was 104.9 months (95% CI 93.5–116.4), which was significantly longer compared to those who did not (66.6 months, 95% CI 62.9–70.3, $p < 0.001$). For patients with stage II/III disease, 6735 (41.8%) met the minimum standards of at least 16 lymph nodes examined and R0 resection. The median OS for those who met standards (40.6 months, 95% CI 38.2–42.9) was significantly longer than those who did not (26.0 months, 95% CI 25.1–26.9, $p < 0.001$). Adherence to minimum standards also varied by region within the United States (Appendix 1), with the highest rates of adherence in the Middle Atlantic region and the lowest rates of adherence in the East South Central region.

Table 2 Demographic information of stage 0/I and II/III patients who underwent curative-intent gastrectomy

Demographic	Stage 0/I patients	Stage II/III patients
Number of patients	11,708	16,997
Median age (range)	69 (19–≥ 90)	65 (19–≥ 90)
Female sex (%)	4369 (37.3)	5051 (29.7)
Race (%)		
White	8689 (75.0)	13,473 (79.9)
Black	1535 (13.3)	2000 (11.9)
American Indian	49 (0.4)	56 (0.3)
Asian/Pacific Islander	1180 (10.2)	1099 (6.5)
Other	128 (1.1)	224 (1.3)
Charlson/Deyo Score (%)		
0	7569 (64.6)	12,051 (70.9)
1	2966 (25.3)	3791 (22.3)
≥ 2	1173 (10.0)	1155 (6.8)
Tumor size (%)		
0–1 cm	1784 (17.6)	511 (3.6)
1.1–2 cm	2330 (23.0)	1332 (9.4)
2.1–3 cm	1987 (19.6)	2269 (16.0)
3.1–4 cm	1343 (13.3)	2384 (16.9)
4.1–5 cm	933 (9.2)	2204 (15.6)
> 5 cm	1739 (9.2)	5440 (38.5)
Tumor differentiation (%)		
Well	1196 (11.2)	494 (3.1)
Moderate	3834 (35.8)	4425 (28.1)
Poor	5518 (51.5)	10,527 (66.9)
Undifferentiated	157 (1.5)	295 (1.9)
Insurance (%)		
None	246 (2.1)	553 (3.3)
Government	7351 (64.1)	9176 (55.1)
Private	3873 (33.8)	6930 (41.6)
High-volume center (%)	6323 (54.0)	9436 (55.5)
Academic center (%)	5404 (47.2)	8187 (49.6)
Chemotherapy		
Neoadjuvant	1157 (33.5)	6737 (55.9)
Adjuvant	2027 (58.7)	3579 (29.7)
Perioperative	267 (7.7)	1729 (14.4)

For patients with stage 0/I disease, meeting minimum standards was a significant predictor of improved OS after adjusting for other possible predictors (Table 4). Additional independent predictors of OS included age, gender, race, CDCS, tumor size, tumor grade, and treatment at an academic center (Table 4). Predictors for meeting minimum standards for stage 0/I patients are shown in Table 5. Independent predictors for meeting standards included age < 65, lower CDCS, Asian/Pacific Islander race (reference: white), median income of domicile ≥ \$48,000, increasing tumor size (reference 0–1 cm), and treatment at high-volume and academic centers.

Table 3 Adherence rates to operative standards

Operative standards	+ Standards (%)	– Standards (%)	Total patients
1. Staging laparoscopy with peritoneal lavage for operable disease prior to gastrectomy or preoperative therapy	1143 (4.0%)	27,222 (96.0%)	28,365
2a. Partial gastrectomy for cancers of the middle or distal third	6748 (83.0%)	1379 (17.0%)	8127
2b. Total gastrectomy for cancers of the proximal third	5171 (40.6%)	7555 (59.4%)	12,726
3. Minimally invasive surgery is a suitable alternative to open surgery	4329 (28.6%)	10,814 (71.4%)	15,143
4. R0 resection should be performed	24,664 (92.6%)	1969 (7.4%)	26,633
5. D2 lymphadenectomy should be performed and at least 16 lymph nodes should be removed and examined	12,578 (44.5%)	15,687 (55.5%)	28,265

Meeting minimum surgical standards was also an independent predictor of improved OS for patients with stage II/III after controlling for other possible predictors (Table 3). Additional independent predictors of OS in this cohort included age, race, CDCS, tumor size, tumor grade, minimally invasive approach, and treatment at academic and high-volume centers. Predictors for meeting minimum standards for stage II/III patients are shown in Table 4. Independent predictors for meeting standards included female gender, lower CDCS, black and Asian/Pacific Islander race (reference: white), and treatment at high-volume and academic centers. Tumor sizes of 1.1–2 cm were associated with not meeting standards. Cox analysis including all measurable standards are shown in Appendix 2 for stage 0/I patients and Appendix 3 for stage II/III patients.

Discussion

The development of evidence-based guidelines and expert consensus recommendations are a means of summarizing and succinctly disseminating clinical trial results and original research findings. The OSGS is a unique publication in that it focuses on the technical aspects of surgery that impact oncologic outcomes. Many other high-impact guidelines focus more on the optimal multidisciplinary treatment of cancer with surgery as a component, and high-quality surgery is assumed [9, 10]. Early clinical trials for gastric cancer had poor surgical quality control and this was a subject of critique following their publication [7, 11]. The more recent randomized, prospective trials in gastric cancer that provided the rationale for current multidisciplinary treatment recommendations had strict surgical quality control [4, 5, 12, 13]. High-quality surgery is, therefore, necessary if these study results are to be achieved outside of the clinical trial setting.

The American College of Surgeons/Alliance for Clinical Trials in Oncology OSGS clearly defines minimum surgical standards that should be met in cancer operations to optimize oncologic outcomes. These minimum standards were

determined with rigorous methodology after systematic review of the literature [2]. The aim of the current study was to evaluate the baseline adherence rates with the OSGS recommendations for the operative treatment of gastric cancer at CoC-accredited centers.

Five of the nine standards for gastric cancer surgery were thought to be potentially measurable in the NCDB (Table 1), but only two could be reliably assessed. Staging laparoscopy with peritoneal lavage is not specifically measured. Four percent of patients who underwent curative-intent gastrectomy had a separate surgical staging procedure prior to gastrectomy, so it is estimated that staging laparoscopy was performed in only 4% of cases or less. While it is possible that some patients are undergoing diagnostic laparoscopy immediately prior to their gastrectomy, the current recommendation requires cytology to be performed, which requires a separate diagnostic procedure [10]. The recommendation for partial gastrectomy for distal tumors and total gastrectomy for proximal tumors was also difficult to assess, because in over 25% of cases, tumor location was coded as “NOS”, or “overlapping sites”. It is noteworthy, however, that of patients with proximal tumors, only 41% had a total gastrectomy. The remaining 59% had some form of partial gastrectomy, either a subtotal which would likely have an inadequate proximal margin, or a proximal gastrectomy, which is not recommended [2, 14, 15].

The recommendation for minimally invasive approach simply states that it is “a suitable alternative to open surgery when surgeon experience is adequate”, but it is not considered superior to open surgery. Minimally invasive gastrectomy has been associated with potential benefits of decreased blood loss, postoperative pain, complications, and a higher likelihood of receiving adjuvant therapy when indicated [16–18]. These data show that utilization of minimally invasive approach is less than 30%. This may be due to surgeon inexperience with the technique. Data on minimally invasive versus open gastrectomy were only collected from 2010 onward, so whether or not this factor is associated with survival can be evaluated in the future. For now, performance of open gastrectomy is not considered sub-standard.

Fig. 1 Kaplan–Meier survival curve and rates of adherence to standards for stage 0/I and II/III patients. In stage 0/I patients, median overall survival for patients who met standards was significantly longer than those who did not meet standards (104.9 versus 66.6 months, $p < 0.001$). In stage II/III patients, median over-

all survival for patients who met standards was significantly longer than those who did not meet standards (40.6 versus 26.0 months, $p < 0.001$). Adherence rates to operative standards were 36.5% and 41.8% for stage 0/I and II/III patients, respectively. Red = + standards, Blue = – standards

The standards of an R0 resection and ≥ 16 LNs examined were the only two that could be reliably assessed in the NCDB. Adherence rates with these minimum operative standards was low, at 36.5% for patients with stage 0/I disease and 41.8% for those with stage II/III disease. Rates of

R0 resection were $> 90\%$ in both groups. While a positive margin is sometimes unavoidable and has been shown to be a marker of aggressive disease biology, it is important everything possible is done to avoid a positive margin [16–19]. The finding that nearly 60% of patients with proximal tumors

Table 4 Effect of minimal standards and other predictors on overall survival in stage 0/I and II/III patients

Variable	Univariable analysis			Multivariable analysis		
	Hazard ratio	95% CI	<i>P</i> value	Hazard ratio	95% CI	<i>P</i> value
Stage 0/I patients						
Age > 65	1.590	1.489–1.698	<0.001	1.522	1.329–1.743	<0.001
Female sex	0.872	0.819–0.929	<0.001	0.837	0.739–0.948	0.005
Race						
White	Ref.	–	<0.001	Ref.	–	<0.001
Black	–	–	0.658	–	–	0.300
American Indian	–	–	0.138	–	–	0.912
Asian/Pacific Islander	0.491	0.430–0.559	<0.001	0.555	0.433–0.711	<0.001
Other	0.577	0.389–0.855	0.006	0.351	0.157–0.784	0.011
Charlson/Deyo Score						
0	Ref.	–	<0.001	Ref.	–	0.005
1	1.159	1.081–1.244	<0.001	–	–	0.656
≥ 2	1.619	1.475–1.776	<0.001	1.331	1.118–1.585	0.001
Tumor size						
0–1 cm	Ref.	–	<0.001	Ref.	–	<0.001
1.1–2 cm	1.382	1.218–1.568	<0.001	–	–	0.120
2.1–3 cm	1.887	1.666–2.137	<0.001	1.874	1.495–2.350	<0.001
3.1–4 cm	2.232	1.959–2.543	<0.001	2.367	1.868–2.998	<0.001
4.1–5 cm	2.297	1.996–2.645	<0.001	2.298	1.767–2.989	<0.001
> 5 cm	2.921	2.588–3.296	<0.001	3.344	2.668–4.192	<0.001
Tumor differentiation						
Well	Ref.	–	<0.001	Ref.	–	<0.001
Moderate	1.310	1.163–1.475	<0.001	–	–	0.069
Poor	1.570	1.400–1.761	<0.001	1.553	1.247–1.934	<0.001
Undifferentiated	1.585	1.221–2.057	0.001	2.073	1.247–3.448	0.005
High-volume center	0.708	0.666–0.752	<0.001	–	–	0.127
Academic center	0.742	0.697–0.789	<0.001	0.801	0.698–0.919	0.002
Staging laparoscopy	–	–	0.336	–	–	–
Minimally invasive gastrectomy	0.875	0.773–0.991	0.035	–	–	0.782
Met minimum surgical standards ^a	0.687	0.642–0.736	<0.001	0.665	0.584–0.757	<0.001
Stage II/III patients						
Age > 65	1.425	1.365–1.487	<0.001	1.383	1.281–1.492	<0.001
Female sex	–	–	0.434	–	–	–
Race						
White	Ref.	–	<0.001	Ref.	–	<0.001
Black	–	–	0.072	–	–	0.051
American Indian	–	–	0.822	–	–	0.358
Asian/Pacific Islander	0.721	0.655–0.794	<0.001	0.727	0.618–0.855	<0.001
Other	0.684	0.547–0.857	0.001	0.610	0.404–0.920	0.019
Charlson/Deyo Score						
0	Ref.	–	<0.001	Ref.	–	<0.001
1	1.187	1.129–1.249	<0.001	1.157	1.062–1.261	0.001
≥ 2	1.451	1.339–1.572	<0.001	1.369	1.204–1.557	<0.001
Tumor size						
0–1 cm	Ref.	–	<0.001	Ref.	–	<0.001
1.1–2 cm	–	–	0.364	–	–	0.096
2.1–3 cm	–	–	0.960	–	–	0.318
3.1–4 cm	1.162	1.004–1.347	0.045	–	–	0.647

Table 4 (continued)

Variable	Univariable analysis			Multivariable analysis		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
4.1–5 cm	–	–	0.068	–	–	0.466
> 5 cm	1.433	1.246–1.648	<0.001	1.393	1.130–1.718	0.002
Tumor differentiation						
Well	Ref.	–	<0.001	Ref.	–	<0.001
Moderate	–	–	0.102	–	–	0.136
Poor	1.598	1.390–1.837	<0.001	1.712	1.359–2.158	<0.001
Undifferentiated	1.634	1.338–1.995	<0.001	1.878	1.295–2.724	0.001
High-volume center	0.789	0.757–0.823	<0.001	0.866	0.794–0.944	0.001
Academic center	0.797	0.763–0.832	<0.001	0.881	0.809–0.960	0.004
Staging laparoscopy	–	–	0.958	–	–	–
Minimally invasive gastrectomy	0.831	0.770–0.897	<0.001	–	–	0.068
Neoadjuvant therapy	–	–	0.312	–	–	–
Met minimum surgical standards ^a	0.691	0.660–0.724	<0.001	0.747	0.691–0.807	<0.001

^aNegative resection margin and ≥ 16 lymph nodes examined

underwent a partial gastrectomy raises the concern that this is not being done, and that at least part of this survival discrepancy may be due to surgical technique. There were also large variations in adherence to operative standards when stratified by regions in the U.S. Adherence was highest in the Middle Atlantic region (which includes New York, Pennsylvania, and New Jersey) and lowest in the East South Central region (which includes Kentucky, Tennessee, Alabama, and Mississippi). The high variability in adherence among regions in the United States is likely related to a multitude of factors including case volume and distribution of center types, and will be a focus of future research.

Performance of a D2 lymphadenectomy was defined as examination of ≥ 16 lymph nodes in a surgical specimen, and adherence with this recommendation was poor ($< 50\%$). While a D2 lymphadenectomy has long been the standard-of-care in high-incidence countries such as Japan and South Korea, it has been more controversial in Western countries and has only recently been definitively accepted as standard-of-care [10, 17–23]. It is important to note that performance of a D2 lymphadenectomy is not measured in the NCDB. The number of lymph nodes in the specimen was used as a surrogate for D2 lymphadenectomy for purposes of this study. The number of lymph nodes is also dependent on the pathologist, however, so it is possible that more patients underwent a D2 lymphadenectomy, but fewer than 16 nodes were found on pathologic examination of the specimens. While using the number of LNs examined is likely a reasonable surrogate, future iterations of the NCDB would ideally include the extent of lymphadenectomy as described by the surgeon as a variable.

For patients with stage 0/I disease, median OS was over 8 years for those who met standards, and for those with stage

II/III disease, it was over 3 years. After controlling for multiple variables, meeting operative standards was independently associated with improved OS. Predictors for meeting operative standards in both stage 0/I and II/III patients were similar, and included age < 65 , lower CDCS, Asian/Pacific Islander race, and treatment at an academic and high-volume center. Of these predictors for meeting operative standards, the only modifiable predictor is treatment at an academic and high-volume center. As such, this may be a potential avenue to improve adherence rates in the United States. Larger tumors were associated with increased adherence in stage 0/I patients. In stage II/III patients, there was not a clear association with tumor size, however, median tumor size was much larger for this group. Black race was associated with meeting standards in stage II/III patients only. Based on this data, efforts can be focused at patients who are at increased risk for not meeting standards.

Limitations

Limitations of this study include the retrospective design and possible selection bias in which patients did and did not meet standards. It is not possible to determine the reasons why operative standards were or were not met for individual patients. Clinical decision-making cannot be assessed and it may be that extensive lymphadenectomy or aggressive resections were not performed in older or more frail patients. To attempt to address these limitations, multivariate analyses were performed and showed that meeting minimum operative standards of R0 resection and ≥ 16 nodes examined were independent predictors of OS after adjusting for multiple factors. Patients with missing data were excluded from analysis. This may be a potential source of bias, but the

Table 5 Predictors for meeting minimum standards in stage 0/I and II/III patients

Variable	Univariable analysis			Multivariable analysis		
	Odds ratio	95% CI	<i>P</i> value	Odds ratio	95% CI	<i>P</i> value
Stage 0/I patients						
Age < 65	1.437	1.329–1.554	< 0.001	1.282	1.146–1.434	< 0.001
Female sex	–	–	0.459	–	–	–
Charlson/Deyo Score						
≥ 2	Ref.	–	< 0.001	Ref.	–	< 0.001
0	1.511	1.319–1.730	< 0.001	1.356	1.166–1.578	< 0.001
1	1.285	1.108–1.491	0.001	1.228	1.042–1.447	0.014
Race						
White	Ref.	–	< 0.001	Ref.	–	< 0.001
Black	–	–	0.808	–	–	0.718
American Indian	–	–	0.936	–	–	0.875
Asian/Pacific Islander	1.843	1.628–2.086	< 0.001	1.693	1.470–1.951	< 0.001
Other	–	–	0.145	–	–	0.149
Median income of domicile ≥ \$48,000	1.240	1.146–1.343	< 0.001	1.184	1.064–1.316	0.002
Urban domicile	–	–	0.544	–	–	–
No high-school diploma < 13%	1.129	1.045–1.220	0.002	–	–	0.885
Insurance						
Government	Ref.	–	< 0.001	Ref.	–	0.322
None	1.460	1.125–1.897	0.005	–	–	0.164
Private	1.383	1.275–1.500	< 0.001	–	–	0.385
Tumor size						
0–1 cm	Ref.	–	< 0.001	Ref.	–	< 0.001
1.1–2 cm	1.142	1.001–1.303	0.048	1.219	1.060–1.402	0.006
2.1–3 cm	1.225	1.069–1.403	0.003	1.348	1.167–1.559	< 0.001
3.1–4 cm	1.482	1.277–1.719	< 0.001	1.766	1.507–2.070	< 0.001
4.1–5 cm	1.346	1.140–1.967	< 0.001	1.562	1.308–1.866	< 0.001
> 5 cm	1.711	1.488–1.967	< 0.001	2.103	1.811–2.444	< 0.001
Occult	–	–	0.114	–	–	0.124
High-volume center	2.151	1.987–2.328	< 0.001	1.873	1.694–2.072	< 0.001
Academic center	1.778	1.645–1.923	< 0.001	1.308	1.184–1.444	< 0.001
Stage II/III patients						
Age < 65	1.156	1.086–1.231	< 0.001	–	–	0.239
Female sex	1.128	1.054–1.208	0.001	1.116	1.029–1.209	0.008
Charlson/Deyo Score						
≥ 2	Ref.	–	< 0.001	Ref.	–	< 0.001
0	1.382	1.215–1.572	< 0.001	1.351	1.168–1.564	< 0.001
1	1.239	1.077–1.426	0.003	1.202	1.026–1.407	0.023
Race						
White	Ref.	–	< 0.001	Ref.	–	< 0.001
Black	1.261	1.145–1.390	< 0.001	1.251	1.118–1.401	< 0.001
American Indian	–	–	0.938	–	–	0.880
Asian/Pacific Islander	1.599	1.409–1.814	< 0.001	1.398	1.206–1.619	< 0.001
Other	1.384	1.045–1.835	0.024	–	–	0.494
Median income of domicile ≥ \$48,000	1.121	1.051–1.196	0.001	–	–	0.074
Urban domicile	1.407	1.089–1.818	0.009	–	–	0.771
No high-school diploma < 13%	–	–	0.406	–	–	–
Insurance						
Government	Ref.	–	0.001	Ref.	–	0.377

Table 5 (continued)

Variable	Univariable analysis			Multivariable analysis		
	Odds ratio	95% CI	<i>P</i> value	Odds ratio	95% CI	<i>P</i> value
None	–	–	0.823	–	–	0.169
Private	1.131	1.060–1.207	<0.001	–	–	0.878
Tumor size						
0–1 cm	Ref.	–	<0.001	Ref.	–	<0.001
1.1–2 cm	0.712	0.576–0.879	0.002	0.764	0.609–0.957	0.019
2.1–3 cm	0.785	0.644–0.957	0.017	–	–	0.078
3.1–4 cm	–	–	0.160	–	–	0.553
4.1–5 cm	–	–	0.414	–	–	0.899
> 5 cm	–	–	0.716	–	–	0.665
Occult	–	–	0.281	–	–	0.599
High-volume center	1.998	1.873–2.132	<0.001	1.641	1.507–1.787	<0.001
Academic center	1.873	1.756–1.997	<0.001	1.483	1.363–1.614	<0.001

large sample size and use of multivariable regression should provide enough statistical rigor to overcome this limitation. Our multivariable model may be subject to some collinearity for certain predictors. However, we believe that these predictors represent unique populations of patients and should not be excluded from the multivariable model. It is possible that stage migration is contributing to the differences found in our analysis due to improved staging after examining ≥ 16 LNs. However, this effect was minimized by initially stratifying patients by clinical, not pathologic, stage.

Conclusions

Baseline adherence rates with American College of Surgeons/Alliance for Clinical Trials in Oncology operative standards for the treatment of gastric cancer at CoC-accredited centers are poor. It is possible that adherence rates are even lower at non-CoC-accredited centers. These data suggest that improved adherence with surgical standards may lead to improved OS in gastric cancer patients in the U.S. Additionally, most of the surgical standards are not currently adequately measured in the NCDB, particularly staging laparoscopy, degree of lymphadenectomy, margin length, type of gastrectomy for given tumor location, and type of reconstruction.

The importance of high-quality surgery in cancer care cannot be overstated. There are important considerations and steps in cancer surgery that are not typically performed in operations on the same organs for benign disease but can affect long-term oncologic outcomes. Considering that a large proportion of cancer surgery in the U.S. is performed by surgeons not specifically trained in oncology, it is critical to highlight the importance of these steps and to have a means of assessing the quality of cancer surgery being

performed. As operative standards are developed for gastric and other cancer types, it is important that they be measured in the NCDB and other cancer databases so that adherence and quality of care can be assessed, targets for improvement can be determined, and improved patient outcomes can be achieved.

Compliance with ethical standards

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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