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Western population-based study of oncologic surgical quality and outcomes of laparoscopic versus open gastrectomy for gastric adenocarcinoma

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Abstract

Background While studies have reported improved morbidity of laparoscopic (LG) compared with open gastrectomy (OG), it remains unclear whether comparable oncologic outcomes can be achieved. This study aims at comparing not only short-term outcomes, including 30- and 90-day mortality, but also survival of LG vs OG.

Methods The National Cancer Database was searched for adult patients with histologically proven gastric cancer and complete information regarding M0 disease, tumor size, differentiation grade, T stage, nodal status, comorbidities, type of hospital, hospital stay, type of surgery, oncological treatment and survival data were included. Logistic regression analyses were performed to analyze margin status, 30- and 90-day mortality, and 30-day re-admission rate. Linear regression was performed for length of hospital stay and lymph node yield. Kaplan–Meier survival analyses were performed to evaluate median survival. Cox multivariable regression models were created to correct for confounders and identify factors affecting survival.

Results A query of the National Cancer Database identified 13,538 patients with complete dataset. A significant regression equation favoring LG for lymph node yield, hospital stay, and unplanned re-admission rate was identified. There was no significant effect of surgical approach on R1 margin rate, 30-day mortality, or 90-day mortality. Median survival was comparable between LG and OG (44.8 vs 40.2 months, $p = 0.804$).

Conclusion LG offers a safe surgical approach to gastric cancer with shorter hospital stay and lower re-admission rates than OG, and also similar and sometimes improved operative oncologic quality parameters (margin, lymph node yield). More importantly, this Western series demonstrates that equivalent long-term outcomes of LG vs. OG are being achieved.

Keywords Laparoscopic gastrectomy · Open gastrectomy · Gastric adenocarcinoma · Oncologic outcomes · NCDB

Today, the short-term benefits of laparoscopic gastrectomy (LG) are well established [1]. These short-term benefits include reduced complication rates (15.5% vs. 28.2% for LG vs. open gastrectomy (OG), faster time to oral intake and ambulation, less analgesic requirement, reduced intra-operative blood loss of > 100 cc, and shorter length of hospital stay. These advantages extend even to at-risk patient

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populations such as the elderly patients [2, 3], cirrhotic patients [4], and patients following neoadjuvant chemotherapy [5, 6]. Despite these encouraging reports, these findings are not consistent across studies. In this context, LG has been reported to be associated with longer operative times [7], worse rates of anastomotic leak and stenosis [8], pancreatitis, pancreatic fistula [9], bleeding, and reoperation [10].

Regardless of most reporting reduced morbidity, it remains unclear whether the benefits of LG extend to long-term outcomes. While there are randomized controlled trials demonstrating equivalent 5-year overall survival (OS) and disease-free survival (DFS), these studies have limitations such as single institution design, small cohort size, inconsistent follow up, or limited extent of gastrectomy performed [11, 12]. However, reports of quality of oncologic surgery of LG vs OG are inconsistent. Some have shown similar or improved lymph node harvest [1, 11, 13–15], rates of D2 lymphadenectomy [16], positive margin rate [17], and completion of adjuvant chemotherapy [14] for LG, while others have reported improved extent of lymph node dissection [13] and lymph node yield [7, 18] (particularly in D2 resections [1]) for OG. Furthermore, LG may only be oncologically safe and effective in specific settings, such as high-volume academic centers [19]. Moreover, many of the reports on this topic are from Eastern centers, which may have differences in gastric cancer tumor biology, operative experience, or earlier tumor stage at time of discovery due to screening programs. Additionally, past studies rarely report short-term mortality (30-day and 90-day) and re-admission rate differences in a comparative fashion.

Therefore, our objective was to compare short-term outcomes, 30-day mortality, 90-day mortality, and survival of LG to OG in Western gastric cancer patients while controlling for clinical and demographic factors associated with potential selection bias.

Patients and methods

Database and cohort selection

According to institutional protocol, this national database study is exempt from institutional review board approval. The National Cancer Database (NCDB) between years of 2010–2016 was utilized as the data source. These dates were chosen due to availability of surgical approach data beginning in 2010. Inclusion criteria were histologically proven gastric adenocarcinoma, age 18–79, M0 disease with complete information on tumor size, grade, TNM (American Joint Committee on Cancer 7th edition staging system [20]), comorbidities, type of hospital (academic vs integrated network vs comprehensive community vs community), length of hospital stay, type of surgery, oncological treatment, surgical approach, procedure data (distal, total, proximal gastrectomy) and survival data. A custom computer script (Python 3.8) was developed to check for discrepancies in the NCDB records. A waiver of informed consent and a waiver of authorization is requested in this retrospective database review.

Statistical analysis and outcomes

The impact of surgical approach on perioperative outcomes including 30-day mortality, 90-day mortality, margin status, and unplanned 30-day re-admission was evaluated using binary logistic regression models. The impact of laparoscopic approach on lymph node yield and hospital stay was evaluated using linear regression models. The results were corrected for possible confounders: age, sex, comorbidities, T stage, N stage, grade, type of surgery, and type of institution.

Survival analysis

Kaplan–Meier survival analysis with log rank test was performed to analyze the impact of approach on survival. Cox multivariable regression models were constructed to identify the factors affecting survival and to correct for confounders of age, sex, T stage, N stage, grade, comorbidities, margin status, adjuvant chemotherapy, type of surgery, facility type and hospital length of stay. Statistical analyses were performed using SPSS 26 (IBM Corp., Armonk, N.Y., USA). A *P*-value of 0.05 was deemed significant.

Results

The NCDB query identified 13,538 patients fitting the inclusion criteria. 3170 (23.4%) underwent LG while 10,368 (76.6%) had OG. Mean age was 68.1 years (67.9 LG, 68.1 OG). Patient demographics and surgical characteristics are summarized by operative approach in Table 1. Laparoscopic and Open cohorts had significant differences in factors of sex, T stage, N stage, tumor size, lymph node yield, type of surgery, positive margins, unplanned 30-day re-admission, 30-day mortality, 90-day mortality, facility type, and hospital length of stay.

Perioperative outcomes

The effect of laparoscopic approach on perioperative outcomes is reported in Table 2. 30-day mortality was 3.5% (2.5% LG, 4.4% OG) and 90-day mortality was 6.7% (4.9% LG, 7.3% OG). After correcting for confounders, no difference was seen between OG and LG for 30-day mortality (OR 0.858, $p = 0.239$) and 90-day mortality (OR 0.882,

Table 1 Patient demographics and clinical characteristics

Patient factors	All patients		Laparoscopic		Open		*P* value
Total patients (*n* %)	13,538	100	3170	23.4	10,368	76.6	
Age (mean-range)	68.1	18–90	67.9	22–90	68.1	18–90	0.07
Sex (female)	4562	33.7	1008	31.8	3554	34.3	**0.01**
Comorbidities							0.453
0	8516	62.9	2007	63.3	6509	62.8	
1	3585	26.5	848	26.8	2737	26.4	
2	1007	7.4	215	6.8	792	7.6	
> 2	430	3.2	100	3.2	330	3.2	
T Stage							**0.02**
T1	3817	28.2	1153	36.4	2664	25.7	
T2	2238	16.5	544	17.2	1694	16.3	
T3	4991	36.9	1086	34.3	3905	37.7	
T4	2492	18.4	387	12.2	2105	20.3	
Tumor size mm (mean-range)	43.22	4–141	38.02	4–123	44.81	5–141	**0.01**
N Stage							**0.04**
N0	6360	47	1688	53.2	4672	45.1	
N1	2605	19.2	605	19.1	2000	19.3	
N2	2142	15.8	453	14.3	1689	16.3	
N3	582	4.3	115	3.6	467	4.5	
N3A	1106	8.2	173	5.5	933	9	
N3B	441	3.3	48	1.5	393	3.8	
NX	302	2.2	88	2.8	214	2.1	
Lymph node yield (mean-range)	17.24	0–79	18.3	0–79	16.92	0–79	**0.03**
Grade of differentiation							0.09
1 (well)	1062	7.8	297	9.4	765	7.4	
2 (moderate)	4969	36.7	1258	39.7	3711	35.8	
3 (poor)	7329	54.1	1580	49.8	5749	55.4	
4 (undifferentiated)	178	1.3	35	1.1	143	1.4	
Type of surgery							**0.01**
Distal	7112	52.5	1574	49.7	5538	53.4	
Proximal	3388	25	1003	31.6	2385	23	
Total	3038	22.4	593	18.7	2445	23.6	
Positive margins	1557	11.5	276	8.7	1281	12.4	**< 0.001**
Re-admission	996	7.4	205	6.5	791	7.6	**0.01**
30-day mortality	475	3.5	78	2.5	3.8	4.4	**0.02**
90-day mortality	909	6.7	155	4.9	754	7.3	**< 0.001**
Cancer center							**< 0.001**
Community	887	6.6	106	3.3	781	7.5	
Comprehensive comm	4796	35.4	926	29.2	3870	37.3	
Academic	6156	45.5	1777	56.1	4379	42.2	
Integrated network	1456	10.8	307	9.7	1149	11.1	
Hospital stay (mean-range)	9.4	5–168	7.6	5–166	9.9	6–168	**0.02**

P values in bold were significant ($P < 0.05$)

$p = 0.187$). R1 margin rate was 11.5% (8.7% LG, 12.4% OG), however, after correction, no difference was seen (OR 0.956, $p = 0.557$). Lymph node yield was 17.24 nodes (18.3 LG, 16.9 OG); after correcting for confounders, linear regression analysis showed a significant equation favoring LG ($p < 0.001$, constant 16.6, beta 1.234). Length of hospital stay was 9.4 days, (7.6 LG, 9.9 OG); similarly, after correcting for confounders, linear regression analysis showed a significant equation favoring LG ($p < 0.001$, constant 8.99, beta -1.131). Unplanned 30-day re-admission rate was 7.4% (6.5% LG, 7.6% OG). After correcting for

Table 2 Effect of laparoscopic approach on perioperative outcomes after correcting for confounding factors

Outcomes	OR	95% CI		*P* value
		Lower	Upper	
Margin status	0.956	0.824	1.110	0.557
Readmission	0.838	0.712	0.987	**0.035**
30-day mortality	0.858	0.665	1.107	0.239
90-day mortality	0.882	0.732	1.063	0.187
Outcomes	Constant	Beta		*P* value
Hospital stay	8.988	−1.131		**<0.001**
Lymph node yield	16.614	1.234		**<0.001**

P values in bold were significant ($P < 0.05$)

OR odds ratio, *CI* confidence interval

confounders, LG was associated with improved unplanned re-admission rates (OR 0.838, CI 0.712–0.987, $p = 0.035$).

Survival analysis

Kaplan Meier survival analysis showed mean survival of 43.79 months (44.8 months LG, 40.2 months OG). A significant difference was seen between the LG and OG groups (log rank $p < 0.001$) (Fig. 1A, Table 3). However, after correcting for confounders by cox multivariable regression models, no difference was seen between LG and OG groups (HR 1.009, 95%CI 0.938–1.085, $p = 0.804$) (Fig. 1B).

The results of a multivariate Cox regression hazard model for factors affecting survival are shown in Table 4. Age, male sex, ≥ 2 comorbidities, Grade ≥ 3, T stage ≥ 2, N stage X or ≥ 1, total or proximal gastrectomy (compared to distal), positive margins, larger tumor size and increased hospital stay were associated with worse survival (all $p < 0.022$). Conversely, surgical management at an academic institution (compared to at a community hospital) and adjuvant chemotherapy administration were associated with better survival

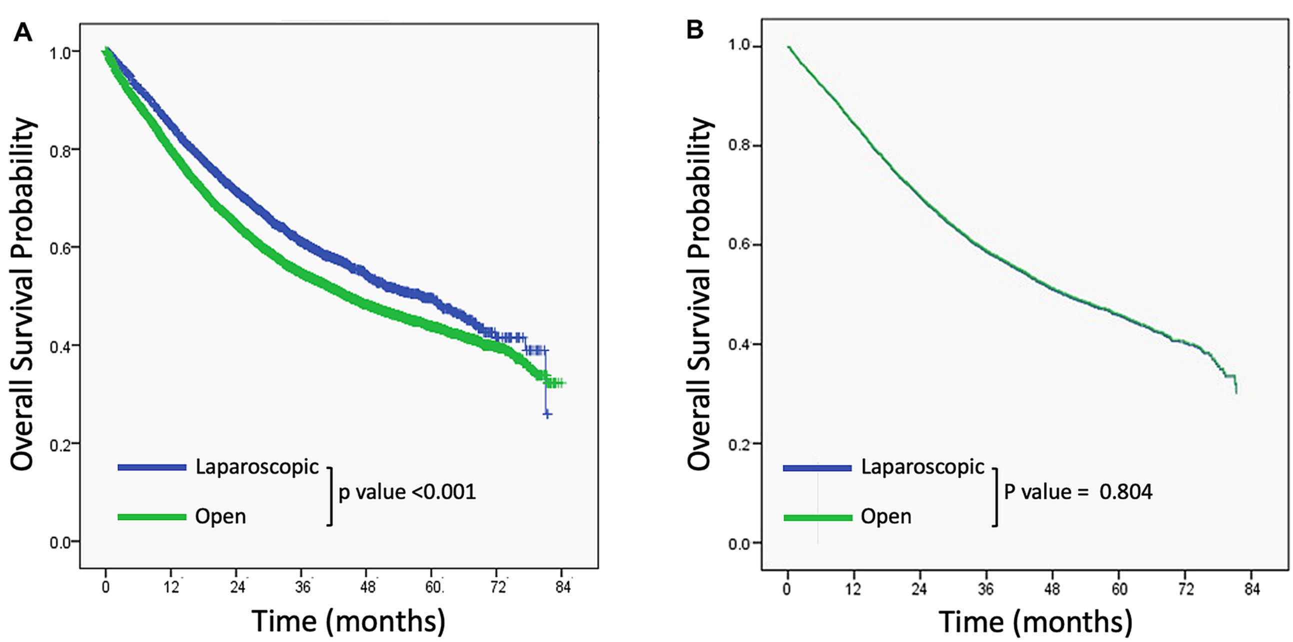

Fig. 1 **A** Kaplan–Meier survival curve based on surgical approach (blue: laparoscopic; green: open); Overall mean survival: 43.793 months (95%CI 43.361–44.225), Laparoscopic mean survival: 44.891 months (95%CI 44.391–45.391), Open mean survival: 40.24 months (95%CI 39.407–41.074), Log rank: $p < 0.001$. **B** Kaplan–Meier survival curve based on surgical approach after adjusting for cofounding (blue: laparoscopic; green: open); Laparoscopic vs Open gastrectomy hazard ratio 1.009 (95%CI 0.938–1.085, $p = 0.804$) (Color figure online)

Table 3 Kaplan Meier means and medians of survival time in months

Approach	Mean	95% CI		Median	95% CI		*P* value
		Lower	Upper		Lower	Upper	
Overall	43.793	43.361	44.225	43.04	42.281	43.799	–
Open	40.240	39.407	41.074	38.70	37.477	39.923	–
Laparoscopic	44.891	44.391	45.391	44.85	43.949	45.751	**< 0.001**

P values in bold were significant ($P < 0.05$)

CI confidence interval

(all $p \leq 0.001$). Other factors that did not significantly impact survival either positively or negatively included: surgery at a comprehensive community or integrated network facility, 1 comorbidity, and grade 2 tumor.

Discussion

In this Western study, LG was not statistically different from OG in negative margin rates, 30-day mortality, 90-day mortality, and overall survival. Moreover, LG was significantly superior to OG regarding hospital stay, re-admission rates, and lymph node yield. Regardless of approach, age, male sex, ≥ 2 comorbidities, Grade ≥ 3, T stage ≥ 2, N stage X or ≥ 1, total or proximal gastrectomy, positive margins, larger tumor size and prolonged hospital stay were associated with worse survival, whereas academic institutions and adjuvant chemotherapy conferred better survival.

To date, only few studies exist comparing LG to OG in Western patients, as most randomized clinical trials on LG are from Eastern Asia. In this context, while this study yielded 13,538 patients with resected gastric cancer over a 10-year span, Eastern countries, such as Japan, report almost 60,000 cases in an even narrower time span of 7 years [8]. Despite such volume disparity, 23.4% of resectable gastric cancer cases undergo LG in our cohort, which is comparable to Eastern reported rates. This implies comparable training and comfort level with LG in Western institutions. In addition, re-admission rates in the Western cohort are possibly improved compared to Eastern studies. This study showed re-admission was 6.5% for LG and 7.6% for OG compared to rates of 7.7% for LG and 10.3% for OG in a large Eastern series [8]. Compared to studies from Europe, this study has similar results regarding mortality, morbidity, margin positivity and improved hospital stay between LG and OG; however, lymph node yield was improved in LG compared to recent Western studies, possibly due to higher experience level that has accumulated over time [21, 22].

Optimal prognostication in patients with gastric adenocarcinoma is correlated with optimal lymph node sampling. The 8th edition AJCC staging's highest N stage (N3B) is 16 positive lymph nodes, thereby defining the minimal number of an optimal lymph node dissection. In this context, while our findings did not demonstrate a survival difference between LG and OG, a significantly higher lymph node yield was seen in LG. This is even more impressive given LG patients had significantly earlier N stage than OG patients. Higher lymph node yield leads to a more accurate AJCC N category and prognostication. This is particularly important in gastric cancer as varying nodal stages are independently associated with survival, consistent with our findings; in addition, studies have demonstrated increased lymph node yield to be associated with prolonged survival after curative gastrectomy without increase in postoperative mortality [23] which may support increased use of LG. Nonetheless, previous studies have found no difference in lymph node harvest between LG and OG [13] which may suggest flattening of the learning curve for laparoscopic lymphadenectomy.

A recent publication addressed the concepts of our work [24], while reaching a different conclusions. Using the same database, the previous study demonstrated that minimally invasive surgery improved survival at 5 years compared to open gastrectomy. This is inconsistent with our findings which demonstrate equivalent survival between LG and OG. In contrast to the previous study, this study includes patients with complete dataset only, leading to a smaller study and more reliable cohort of 13,538 patients (compared to 17,449 in the previous report). In addition, the previous report used clinical (preoperative) staging, while here pathologic (postoperative) staging was used. The discrepancy between clinical and pathological staging methods have been reported to be has high as ~ 30%, which can contribute to selection bias. Furthermore, the previous report limited the survival analysis to 5 years, whereas this study's survival analysis extends beyond 7 years. This is important, since the survival curves of LG versus OG converge after 5 years (Fig. 1A). Therefore, (A) inclusion of patients with complete datasets only, (B) the use of pathological rather than clinical staging and (C) obtaining survival data beyond 5 years, may have contributed to the difference in conclusions.

This and the previous investigation (discussed in the paragraph above) revealed clinical differences between LG vs. OG patients. OG patients had higher T and N stages, larger tumor size, more frequently total gastrectomy, and more perioperative chemotherapy, suggesting more aggressive gastric cancer in the open cohort. Therefore,

Table 4 Factors affecting survival after correcting for confounders

Factors	HR	95% CI		*P* value
		Lower	Upper	
Age	1.024	1.021	1.027	**<0.001**
Sex (male vs female)	1.127	1.060	1.197	**<0.001**
Comorbidities				
0	Reference	–	–	1
1	1.026	0.962	1.094	0.436
2	1.200	1.083	1.330	**<0.001**
>2	1.512	1.299	1.759	**<0.001**
T Stage				
T1	Reference	–	–	1
T2	1.440	1.297	1.599	**<0.001**
T3	1.877	1.712	2.059	**<0.001**
T4	2.465	2.216	2.742	**<0.001**
Tumor size	1.003	1.001	1.006	**0.019**
N Stage				
N0	Reference	–	–	1
NX	1.725	1.587	1.875	**<0.001**
N1	1.912	1.593	2.294	**<0.001**
N2	2.055	1.882	2.245	**<0.001**
N3A	2.484	2.231	2.766	**<0.001**
N3B	2.847	2.518	3.219	**<0.001**
Grade of differentiation				
1 (well)	Reference	–	–	1
2 (moderate)	1.227	0.940	1.601	0.132
3 (poor)	1.176	1.023	1.351	**0.022**
4 (undifferentiated)	1.367	1.191	1.570	**<0.001**
Type of surgery				
Distal	Reference	–	–	1
Proximal	1.190	1.108	1.277	**<0.001**
Total	1.283	1.195	1.377	**<0.001**
Laparoscopic vs open approach	1.009	0.938	1.085	0.804
Positive margins	1.671	1.545	1.807	**<0.001**
Hospital stay	1.017	1.015	1.019	**<0.001**
Adjuvant chemotherapy	0.896	0.878	0.914	**<0.001**
Facility type				
Community	Reference	–	–	1
Comprehensive comm	1.086	0.949	1.242	0.23
Integrated network	1.077	0.980	1.185	0.125
Academic	0.851	0.774	0.936	**0.001**

P values in bold were significant ($P < 0.05$)

HR Hazard ratio, *CI* Confidence interval

despite correcting for these confounders through regression analyses, unmeasured influences on patient selection cannot be fully excluded [24]. Nevertheless, our findings of LG's superior short-term and equivalent long-term outcomes after addressing confounders give credibility to this burgeoning technique.

Current NCCN guidelines for gastric cancer staging and perioperative care recommend upfront surgery for clinically staged T1b or lower, followed by adjuvant chemotherapy for pathologically staged ≥ T2 or node positive disease; clinically staged ≥ T2 gastric cancer or concern for nodal dissemination requires perioperative chemotherapy and surgery based on response [25]. The guidelines also state postoperative radiation is appropriate for patients receiving less than a D2 nodal dissection or R1/R2 resection if no preoperative radiation was administered. Per NCCN, surgical goals include negative margins through adequate gastric resection and harvest of at least 16 lymph nodes. This study's findings corroborate these recommendations, as adjuvant chemotherapy was associated with improved survival, and may help frame future guidelines, particularly with respect to better survival in academic centers possibly supporting centralization of gastric cancer surgery. Although no definitive guideline for LG vs OG exists, LG's improved nodal yield may better meet the NCCN surgical goals outlined for higher quality resection and less reliance on postoperative radiation, and thus may be incorporated into guidelines in coming years.

Although this study of the NCDB is one of the largest Western studies comparatively investigating perioperative and oncologic outcomes in gastric cancer based on surgical approach and tumor location, limitations exist. First, the study is retrospective, thus prone to inherent and unmeasured biases, especially with respect to patient selection, despite correction for confounders. While an RCT would be optimal to exclude unmeasured biases, this may not be feasible due to cost, unwillingness of surgeons and patients to randomize or be randomized, number of gastric cancers in the US, diffusion of laparoscopic technique and other factors. Second, due to the limitations of the NCDB, several factors such as surgeons' learning curve and experience, as well as lack of short-term data on complications, is not fully accounted for. Third, our study is limited to a 6-year period; while this doesn't encompass much of the overall timeframe of laparoscopic gastrectomy beginning in the early 1990s [26], it does help control for historical bias. In addition, our analysis includes facility type to better relate this US study to the centralization of gastric cancer surgery seen in Europe [27, 28].

Conclusion

LG offers a safe surgical approach to gastric cancer with similar surgical oncologic safety and survival. LG's benefits include shorter hospital stay, lower re-admission rates, and improved lymph node yield and no significant difference in R1 margin rate, 30-day mortality, or 90-day mortality and median survival.

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Compliance with ethical standards

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