



Treatment burden of robotic gastrectomy for locally advanced gastric cancer (LAGC): a single western experience

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Background: This study compares standard of care (SOC) open and robotic D2-gastrectomy for locally advanced gastric cancer (LAGC) in the Western context of low disease prevalence, reduced surgical volume, and neoadjuvant chemotherapy (NAC). We hypothesized that robotic gastrectomy (RG) after NAC reduces treatment burden for LAGC across multiple outcome domains *vs.* SOC.

Methods: Single institution, interrupted time series comparing SOC (2008–2013) for LAGC (T2–4Nany/TanyN+) *vs.* NAC + RG (2013–2018). Treatment burden was a composite metric of narcotic consumption, oncologic efficacy, cumulative morbidity, and 90-day resource utilization. Predictors were evaluated via multivariate modeling. Learning curve analysis was done using CUSUM.

Results: After exclusions, 87 subjects with equivalent baseline characteristics, aside from male sex, were treated via SOC (n=55) or NAC + RG (n=32). All four domains of treatment burden were significantly reduced in the NAC + RG cohort compared to SOC (P=0.003). The odds ratio for excess treatment burden in the NAC/RG was 0.23 (95% CI: 0.07–0.72, P=0.0117) *vs.* SOC upon multivariable modeling, whereas the extent of resection (total/subtotal), tumor size, T-stage, sex, and early learning curve had no effect. Differences in treatment burden persisted in subgroup analysis for NAC (n=51).

Conclusions: NAC + RG was associated with decreased treatment burden relative to SOC for LAGC. Frequencies of unfavorable hospitalization, adverse oncological outcomes, major morbidity, and narcotic consumption all decreased in this interrupted time series.

Keywords: Stomach neoplasms; robotic surgical procedures; neoadjuvant therapy

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Introduction

Gastric cancer is the third-leading cause of cancer death worldwide (1). In western countries without routine surveillance, nearly two-thirds of patients present with locally-advanced gastric cancer (LAGC) (2). Although radical gastrectomy with D2 lymphadenectomy is potentially curative, the expected five-year survival rate is only 25% with multimodality treatment (3-7). These unfortunate survival outcomes emphasize the relative importance of treatment burden and quality of life as metrics of comparative effectiveness between different surgical strategies.

Recent phase III trials comparing surgical approaches to early gastric cancer demonstrate superior short-term outcomes after minimally-invasive gastrectomy compared to open gastrectomy (8) with equivalent overall and 5-year cancer-specific survival rates (9). The randomized KLASS-02 trial expanded inclusion criteria to locally-advanced gastric cancer and reported lower complication rates, faster recovery, and less pain after laparoscopic-assisted radical gastrectomy with extended lymphadenectomy for advanced resectable gastric cancer (2). However, these data have important limitations in the Western context of LAGC where preoperative chemotherapy was excluded. Furthermore, study accrual occurred in countries with a high prevalence of gastric cancer where the volume of surgical resection promotes the technical proficiency required for more advanced stages of disease among patients more likely to have adverse preoperative risk factors.

We hypothesized that the short-term benefits of robotic D2 gastrectomy can be demonstrated for LAGC at Western centers despite the hurdles of technical complexity, low surgical volume, and elevated morbidity after extended lymphadenectomy (2,10-13). The aim of this study was to compare the effect of surgical approach: robotic gastrectomy (RG) versus standard of care (SOC) open surgery in the treatment burden of radical gastrectomy for LAGC using a single Western center experience. We hypothesized that robotic D2-gastrectomy after neoadjuvant chemotherapy (NAC) provides immediate reduction in treatment burden relative to standard treatment despite its volume-driven learning curve. We present the following article in accordance with the STROBE reporting checklist (available at <https://dx.doi.org/10.21037/atm-21-1054>).

Methods

Study design

This single institution interrupted time series compared SOC and robotic D2 gastrectomy for LAGC between 2008–2018. The SOC cohort underwent open D2 gastrectomy and received preoperative chemotherapy according to SOC recommendations between 2008–2013. The robotic cohort (2013–2018) underwent robotic D2 gastrectomy after universal preoperative chemotherapy and encompassed the entire institutional learning curve starting with case #1. Outcomes were analyzed according to the intended surgical approach regardless of conversion. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Review Board of the Beth Israel Deaconess Medical Center and Dana Farber Cancer Institute (IRB No. 15-249) and individual consent for this retrospective analysis was waived.

Primary outcome

The primary outcome was ninety-day treatment burden defined by component variables across four critical domains: (I) treatment efficiency: duration of index hospital stay exceeding the 75th percentile for the entire cohort and 90-day readmissions; (II) oncological efficacy: positive resection margin (R1/R2) and lymph nodes harvest below the American Joint Committee on Cancer (AJCC) minimum requirement (≤ 16) (14); (III) cumulative major morbidity: all events Clavien-Dindo $\geq 3A$, unplanned reoperation within 90 days, and 90-day comprehensive complication index (CCI) (15,16); (IV) narcotic consumption ≥ 75 th percentile for the cohort.

Study population

Locally-advanced gastric cancer was defined as cT2-T4a, Nx, M0 after a thorough literature search to identify a consensus definition (Table S1) (2). A prospectively maintained institutional database identified consecutive patients with LAGC who underwent intended surgical resection between 2008–2018 (Figure 1). All diagnostic imaging was subjected to blinded central radiology review (K.S.) at the time of enrollment as well as prior to surgery

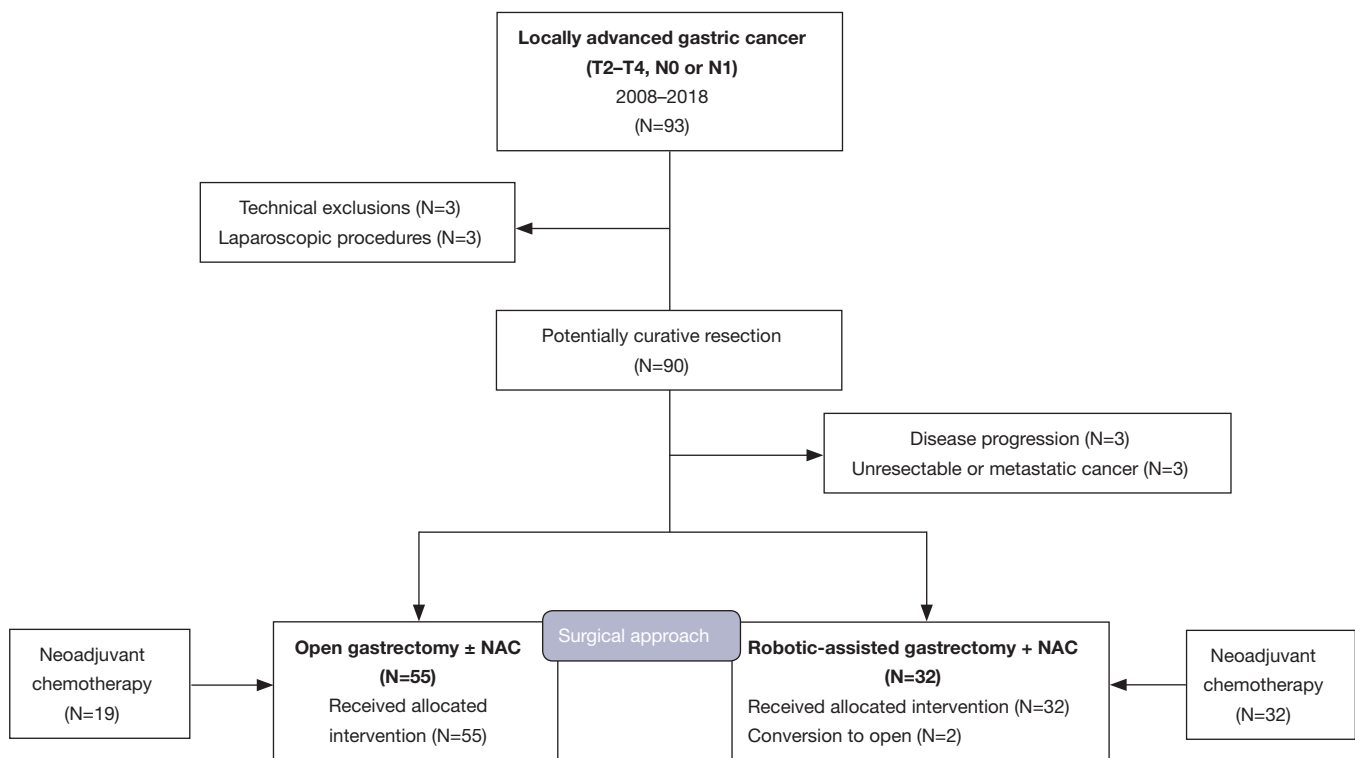


Figure 1 Study flow-chart based on CONSORT guidelines for study design. NAC, neoadjuvant chemotherapy.

(upon completion of NAC) according to precise TNM clinical staging criteria to prevent unmeasured confounding by stage between cohorts.

Inclusion required: (I) histologically confirmed gastric adenocarcinoma; (II) clinical tumor stage cT2–cT4a (tumor invading the muscularis propria to exposed serosa) documented by preoperative endoscopic ultrasound and/or abdominal computed tomography; (III) nodal stage cN0 or cN1 (invasion of perigastric lymph nodes or lymph nodes along the left gastric artery); (IV) no detectable metastasis; and (V) total or subtotal D2 gastrectomy with Roux-Y reconstruction with curative intent (17); and (VI) age ≥ 18 years. Exclusion criteria included: (I) suspected distant metastasis at diagnosis; (II) metastases detected during staging laparoscopy at the time of planned resection; (III) history of previous gastric surgery; (IV) total laparoscopic procedures due to their low frequency ($n=3$).

NAC

The administration of NAC, agent selection, and duration of treatment was determined were decided according to the evolving SOC and recorded. All candidates for robotic-

assisted D2 gastrectomy received NAC regardless of the potential extent of resection.

Description of the surgical procedure

The technique for robotic D2 total gastrectomy has been previously reported by our group (18). Patients are placed supine in 15 degrees anti-Trendelenburg position. Four robot ports are placed and one assistant port across the above midline of the abdomen in both quadrants. The location of the primary tumor dictated the extent of resection, however, all procedures included omentectomy, *en bloc* resection of involved adjacent structures, and division of the left gastric artery with D2 lymph node dissection. Initially, dissection of the great curvature was started by division of the gastrocolic ligament with entering the lesser sac. The right gastro-omental vessels were identified and divided at their root along with associated lymph nodes. After ligation of the right gastric vessels, dissection was extended to retrieve lymph nodes around the left gastric vessels. Duodenum was circumferentially dissected and transected distal to the pylorus.

Subsequently, D2 lymphadenectomy included removal

of nodes from the left gastric artery (station 7), common hepatic artery (station 8), celiac trunk (station 9), splenic hilum and splenic artery (station 10 and 11), as well as D1 nodal basins of the right and left cardia lymph nodes (station 1–2), lymph nodes along the lesser and greater curvature (stations 3–4), lymph nodes along the short gastric vessels, left gastroepiploic, and right gastroepiploic (station 4), including the supra and infrapyloric lymph nodes (station 5–6). Splenectomy was not routinely performed. Fully robotic reconstruction included an antecolic Roux-en-Y esophago- or gastrojejunostomy. Surgical drains were used after total gastrectomy.

Data collection

In addition to baseline demographic characteristics, body mass index (BMI), American Society of Anesthesiologists (ASA) performance score (19) and age-adjusted Charlson Comorbidity Index (ChCI) (20) were computed. Clinical and pathological staging were obtained from the SOC pathology and radiology reports available during surgical consultation and classified according to the clinical TNM and AJCC staging systems (14). Standard operative outcomes, conversions to open, and anastomotic leaks were recorded. All complications (minor or major) were recorded and graded according to Clavien-Dindo (21) for 90 days and used to calculate the CCI (15) as a measure of adverse event frequency and severity contributing to composite treatment burden. Total opioid consumption was measured during the index hospital stay after surgery. Total administration was the sum of epidural, oral, intravenous (IV) and patient control analgesia (PCA). Cumulative inpatient narcotic consumption was converted to IV morphine milligram equivalents (MME) using the Stanford morphine equivalency calculator (22). Epidural conversion to IV administration was performed using equianalgesic conversion rules (23–25). Two-year actuarial survival was estimated based on Kaplan Meier.

Learning curve analysis

Operating time was plotted by CUSUM methodology as a surrogate measure of operative performance between 2008–2018 (26) for both open and RG to evaluate the entire learning curve. Because every operative procedure contributes to learning, learning curve analysis incorporated all elective total and subtotal gastrectomies with Roux-en Y reconstruction performed within the study period regardless

of exclusion criteria.

Statistical analysis

Descriptive statistics were reported as counts and proportions for categorical data and mean/standard deviation (SD) or median/inter quartile range (IQR) for continuous data based on tests of normality. Comparisons between groups were performed via Student's *t*-test, Chi-square test, Mann-Whitney U test, or Fisher's exact test as appropriate. An alpha <0.05 was used to indicate statistical significance. A multivariable model was constructed to analyze Treatment Burden after adjustment for pre-specified confounders at enrollment including sex, BMI, tumor size, clinical T stage, procedure approach and extent of gastric resection. A subgroup analysis was performed among patients that received NAC. Two-year overall survival was estimated using the Kaplan-Meier method and compared using the log-rank test. Data were analyzed by an independent biostatistician (K.K.) using STATA version 15.0 (Copyright 1996–2016 Stata Corp LP, 4905 Lake Way Drive, College Station, TX 77845, USA).

Results

We identified 93 patients with biopsy-proven cT2–T4aNxM0 LAGC between January 2008 and November 2018. After study-specific exclusions, 87 patients met eligibility (CONSORT diagram *Figure 1*).

Baseline characteristics

The treatment cohorts were equivalent with respect to all demographic measures and indices of comorbidity except male sex (68% RG *vs.* 32% SOC, *P*=0.023). Preoperative TNM stage and tumor size were also equally distributed between cohorts as confirmed by central radiology review (*Table 1*). Radiographic measures of technical difficulty were similarly equivalent: mean tumor diameter; frequency of T3/T4 tumors at enrollment (75% RG; 58.2% SOC), and suspected node positive disease 59.4% RG *vs.* 49.1% SOC.

Surgical intervention

Laparoscopic staging was performed in all 90 evaluable participants, of whom three (3.3%) were found to have previously undetected distant metastases or unresectable primary tumors. The SOC cohort consisted of 55 (63.2%)

Table 1 Baseline characteristics

Characteristics	Robotic (n=32)	Open (n=55)	P value
Sociodemographic			
Age, mean \pm SD, years	63.3 \pm 10.3	64.9 \pm 14.5	0.573
Sex, male, No. (%)	22 (68.80)	24 (43.60)	0.023
Race, No. (%)			0.738
Asian	11 (34.40)	17 (30.90)	
Black	7 (21.90)	8 (14.5)	
Hispanic	1 (3.10)	3 (5.50)	
White	13 (40.6)	27 (49.10)	
BMI, mean \pm SD, kg/m ²	26.6 \pm 4.3	24.6 \pm 5.2	0.061
Smoker, No. (%)	8 (25.00)	8 (14.50)	0.224
ASA-classification, No. (%)			0.814
2	6 (18.80)	12 (21.80)	
3	25 (78.10)	40 (72.70)	
4	1 (3.10)	3 (5.50)	
ChCI age-adjusted, median [IQR]	5 [4–6.5]	4.5 [3–6]	0.213 [‡]
Preoperative tumor staging			
Tumor size, mean \pm SD, cm	3.65 \pm 2.00	3.16 \pm 2.00	0.300
CBD, No. (%)	1 (3.12)	9 (15.52)	
Clinical tumor stage*, No. (%)			0.114
T2	8 (25.00)	23 (41.80)	
T3/T4	24 (75.00)	32 (58.20)	
N-stage, No. (%)			0.276
Negative (N0)	13 (40.60)	29 (52.70)	
Positive (N1, N2, N3)	19 (59.40)	26 (47.30)	

*, staging based on CT criteria and EUS according to AJCC; †, based on the Wilcoxon rank-sum test. SD, standard deviation; BMI, body mass index; ASA, American Society of Anesthesiologists; ChCI, Charlson Comorbidity Index; IQR, inter quartile range; CBD, can't be determined; CT, computed tomography; EUS, endoscopic ultrasonography; AJCC, American Joint Committee on Cancer.

completed SOC D2 gastrectomy with 32 (36.8%) robotic-assisted gastrectomy and 2 conversions (6.2%) due to failure to progress. The frequencies of total gastrectomy/esophagojejunostomy were equivalent (RG 34.4%; SOC 50.9%; $P=0.3$).

Univariate analysis

Univariate analysis is shown in *Table 2*. Standard measures of surgical outcomes demonstrated low estimated blood loss and rates of transfusion within 72 hours of surgery in both

groups, including similar adverse event frequencies through 90 days such as anastomotic leak (6.3% *vs.* 5.5%, $P=0.877$), major complications (Clavien-Dindo IIIa–IV), and the cumulative intensity of complications (CCI). There were no deaths.

Final pathologic examination revealed equivalent TNM and AJCC staging between cohorts, significantly reducing the risk of unmeasured confounding during treatment selection. Proportions of pT0–pT2 tumors (43.8% RG; 41.8% SOC), pT3/T4 tumors (53.1% RG; 54.8% SOC) as well as proportions of positive lymph nodes (50% RG;

Table 2 Univariate analyses

Perioperative and postoperative variables	Robotic (n=32)	Open (n=55)	P value
Perioperative			
Extent of resection, No. (%)			0.135
Subtotal + gastrojejunostomy	21 (65.60)	27 (49.10)	
Total + esophagojejunostomy	11 (34.40)	28 (50.90)	
R0 resection, No. (%)	30 (93.80)	44 (80.00)	0.082
Lymph node harvest, median [IQR]	22.5 [16–31.5]	18 [12–24]	0.056 [‡]
Estimated blood, median [IQR], mL	150 [100–225]	200 [100–300]	0.489 [‡]
Blood transfusion within 72 h, No. (%)	3 (9.40)	9 (16.40)	0.361
Operative time, mean \pm SD, mins	520.3 \pm 61.6	297.2 \pm 80.7	<0.001
Length of stay, mean \pm SD, days	8 \pm 3	10.5 \pm 6	0.043
Surgical pathology			
Tumor size, mean \pm SD, cm	3.50 \pm 2.8	4.27 \pm 2.2	0.272
CBA, No. (%)	9 (28.10)	11 (20.00)	
Tumor stage, No. (%)			0.980
pT0–T2	14 (43.80)	23 (41.80)	
pT3/4	17 (53.10)	30 (54.60)	
pTx	1 (3.10)	2 (3.60)	
N-stage, No. (%)			0.596
Negative (pN0)	16 (50.00)	23 (41.80)	
Nx	0 (0.00)	1 (1.80)	
Positive (pN1, pN2, pN3)	16 (50.00)	31 (56.40)	
Morbidity			
Anastomotic leaks [‡] , No. (%)	2 (6.30)	3 (5.50)	0.877
90-day Clavien-Dindo*, No. (%)			0.363
0–II	25 (78.20)	38 (69.10)	
IIIa–IVa	7 (21.80)	17 (30.90)	
V (Death)	0 (0.00)	0 (0.00)	
CCI 90 days, median [IQR]	20.9 [0–27.9]	20.9 [8.7–34.6]	0.101 [‡]
90-day reoperation, No. (%)	0 (0.00)	4 (6.90)	0.129
90-day readmission, No. (%)	7 (21.88)	14 (24.14)	0.808

*, Clavien-Dindo classification of complications; [‡], Wilcoxon rank-sum test; [‡], defined as either radiographic or clinical. IQR, inter quartile range; SD, standard deviation; CBA, could not be assessed; CCI, comprehensive complication index.

Table 3 Composite outcomes

Outcomes	Robotic (n=32)	Open (n=55)	P value
Hospital utilization, No. (%)	12 (37.5)	28 (50.9)	0.226
Readmission within 90-day	7 (21.9)	14 (25.5)	0.116
LOS >75th percentile	7 (21.9)	21 (38.2)	0.706
Oncological efficacy, No. (%)	10 (31.3)	30 (54.5)	0.035
Positive margin (R1/R2)	2 (6.3)	11 (20.0)	0.082
<16 lymph node resected	8 (25.0)	24 (43.6)	0.082
Major morbidity, No. (%)	7 (21.8)	20 (36.3)	0.159
Clavien-Dindo \geq 3A	7 (21.9)	17 (30.9)	0.363
CCI \geq 32	5 (15.6)	17 (30.9)	0.114
Reoperation within 90 days	0 (0.0)	4 (7.3)	0.118
Narcotic use, No. (%)			
>75th percentile	3 (9.4)	20 (37.0)	0.005
Composite treatment burden, No. (%)	18 (56.3)	47 (85.5)	0.003

*, Clavien-Dindo classification of complications. LOS, length of stay; CCI, comprehensive complication index.

56.4% SOC) were virtually identical despite universal administration of NAC in the RG group. Univariate analysis demonstrated a statistical trend in favor of RG for the following outcomes: margin negative resection rate (93.8% vs. 80%, $P=0.082$) and lymph node harvest (22.5 vs. 18, $P=0.056$).

Primary outcome

As shown in *Table 3*, the frequency of excess treatment burden was 86% in the SOC group compared to 56% after robotic D2 gastrectomy ($P=0.003$). Favorable comparisons were observed in three of four component metrics for oncological efficacy, narcotic administration, and hospital resource utilization, whereas the frequency of major postoperative adverse events was similar despite universal administration of chemotherapy prior to RG. In terms of cancer outcomes, 68.7% of participants obtained negative surgical margins and lymph node harvest exceeding AJCC standards after RG compared to 45.5% in the SOC group ($P=0.035$). The duration of hospital stay was strongly associated with both total narcotic consumption and surgical approach. Only 9.4% of RG patients exceeded the 75th percentile for narcotic consumption compared to 37% of participants in the SOC group ($P=0.005$).

Improved metrics of hospital utilization included: significantly reduced median length of stay in the RG group (8 vs. 10.5 days; $P=0.043$) as well as trends toward reduced 90-day rates of readmission (21.9% vs. 25.5%, $P=0.116$) and reoperation (0% vs. 7.3%; $P=0.118$). The maximum grade (Clavien-Dindo \geq 3A) and cumulative severity (CCI) of 90-day postoperative adverse events were equivalent. We observed no evidence that early discharge in the NAC + RG group masked adverse events within the 90-day postoperative monitoring period.

These differences between cohorts persisted after adjustment for pre-specified predictors of adverse outcome, including sex, BMI, extent of gastric resection (total vs. subtotal), tumor diameter, and clinical T-stage. After controlling for these potential confounders, multivariable analysis demonstrated a significantly reduced risk of treatment burden (OR 0.23; 95% CI: 0.07–0.72, $P=0.0117$) in the robot gastrectomy cohort compared to SOC.

Learning curve

Figure 2 shows the time course for adopting robot gastrectomy and preoperative chemotherapy between 2008–2018. CUSUM analysis (*Figure 3*) showed no consistent deviation from mean operating time during the SOC phase

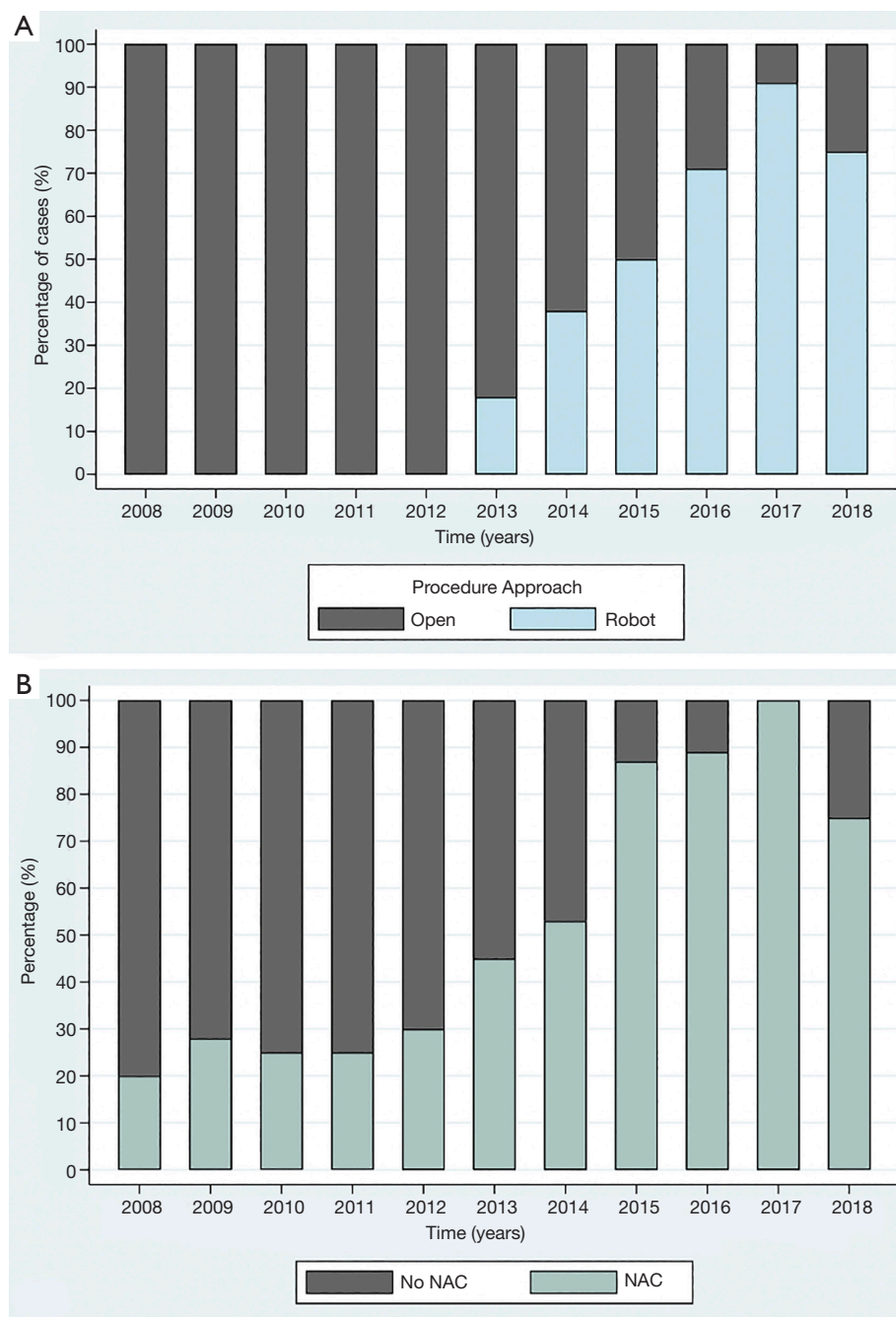


Figure 2 Institutional adoption of surgical approach and NAC over time for LAGC. (A) Surgical approach of radical gastrectomy for LAGC between January 2008 and November 2018. Robotic-assisted gastrectomy was implemented in August 2013. (B) Administration of NAC for LAGC between 2008–2018. NAC, neoadjuvant chemotherapy; LAGC, locally advanced gastric cancer.

of the study (297 min; cases #1–55) demonstrating stable implementation. In contrast, the CUSUM plot of the first 32 RG (cases #56–87) exhibited accumulating operating time above the mean (520.3 *vs.* 297.2 mins, $P < 0.001$) as

expected of a surgical procedure that has not achieved optimization. The learning curve therefore offset favorable metrics of hospital utilization at the rate of 90 minutes of excess OR time per day of reduced hospital stay.

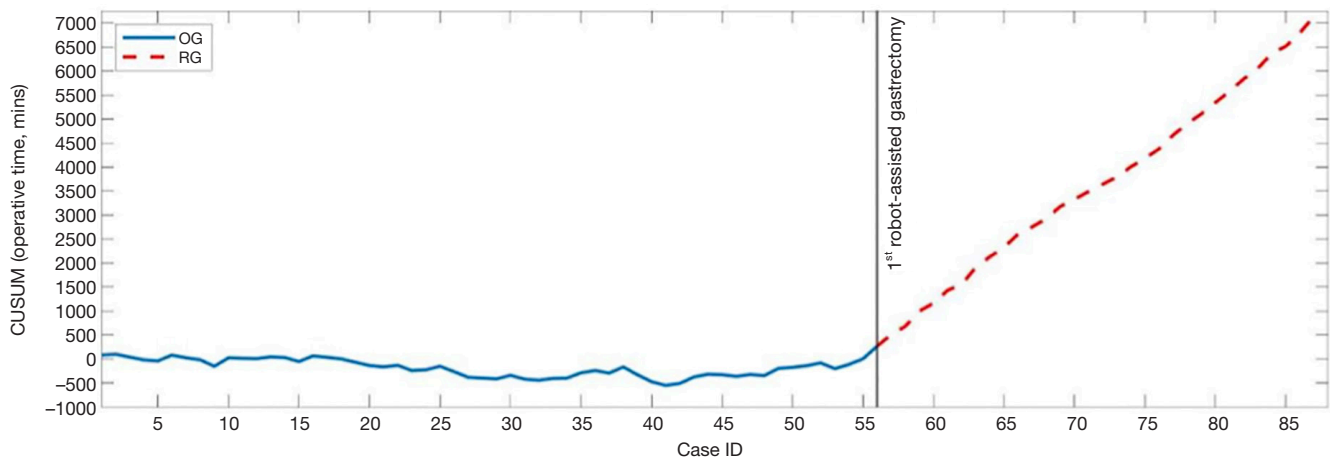


Figure 3 CUSUM analysis of operative time before and after implementation of robotic-assisted gastrectomy in 2013. CUSUM demonstrates stable implementation of open D2 gastrectomy (blue), whereas robotic D2 gastrectomy demonstrates accumulating OR time indicative of accumulating experience during phase 1 of the learning curve. RG, robotic gastrectomy.

Neoadjuvant subgroup analysis

The adoption of neoadjuvant treatment for LAGC is a measured confounder during this interrupted time series (27). The administration of NAC increased from 20% in 2008 and changed from 3 months neoadjuvant/3 months adjuvant treatment in the SOC group to 6 months' total NAC ($P=0.023$) in the robotic group. We performed subgroup analysis of the 51 participants that received NAC to determine whether preoperative chemotherapy was associated with unmeasured bias affecting the selection of surgical approach. Subgroup analysis demonstrated significantly reduced treatment burden in the RG arm (56%) compared to 95% in the SOC arm ($P=0.003$) associated with persistent reductions in narcotic utilization and length of hospital stay (Table S2). Kaplan-Meier analysis of 2-year actual survival demonstrated no detrimental effect ($P=0.133$; log rank test) of RG within the 24-month observation period (Figure S1).

Discussion

This study compared the effectiveness of robotic and SOC radical gastrectomy for LAGC at a US cancer center using a quasi-experimental design. The design maximized generalizability of results from this modest single institution series of Western gastric cancer. An interrupted time series was used to minimize selection bias associated with enrollment date. The definition of LAGC and associated

staging requirements were derived from an objective review of published data. Blinded central radiology analysis confirmed that inclusion criteria reflected the pre-specified TNM definition of LAGC to minimize unmeasured confounding and treatment selection bias in these non-randomized cohorts. NAC was permitted to emulate “real world” SOC treatment in accordance with published standardized regimens from landmark studies (4) or resulting modifications (28-30). Finally, robotic outcomes were analyzed according to intention to treat and spanned the entire learning curve to maximize early detection of serious, unanticipated adverse events associated with adoption of the new procedure.

The surgical technique for robot-assisted D2 radical gastrectomy (18) adapts the open technique for extended lymphadenectomy around the celiac trunk and esophageal reconstruction to a minimally-invasive approach (12). The technique incorporates three-dimensional vision, tremor filtration, motion scaling and wristed motion necessary for dissection and reconstruction of the esophagus through the diaphragmatic hiatus (31). Meta-analyses of eastern series of patients have already been published demonstrating the feasibility and safety of this intervention (32-34).

These data demonstrated a statistically significant association between robot-assisted gastrectomy and 90-day composite treatment burden measuring oncological efficacy, narcotic consumption, hospital utilization, and major morbidity. The use of multiple competing outcome domains provided a broader assessment of healthcare

quality (35) as suggested by the Institute of Medicine and was supported by comprehensive ninety-day postoperative event monitoring, chemotherapy subgroup analyses, and Kaplan-Meier survival estimates to improve detection of unmeasured bias in this non-randomized series.

The odds ratio for composite treatment burden after robotic radical gastrectomy was 0.23 (95% CI: 0.07–0.72) compared to SOC regardless of preoperative chemotherapy or esophageal reconstruction. These differences were detected during the early learning curve as evidenced by accumulating excess operative time on CUSUM analysis. We therefore speculate that the reported effect size of robotic radical gastrectomy is a low estimate that may improve as technical proficiency is achieved.

The composite primary outcome incorporated metrics to assess the separate interests of involved stakeholders and was not selected merely as a method to increase statistical power in a study with limited sample size. RG was associated with significantly improved rates of positive surgical margins and substandard lymph node harvest according to published outcome standards (14,36-39). No corresponding increases in the frequency or severity of major 90-day postoperative complications, anastomotic leaks, readmissions, or blood transfusion were observed as a consequence of the low 6.2% conversion rate. Total narcotic use declined by approximately 73% in robotic cohort as a single powerful measure of patient-centered concern about perioperative pain. Hospital length of stay improved by one day for every 90 minutes of increased operating time during RG without increased 90-day readmission or reoperation rates. Overall, participants in the robotic cohort were therefore significantly more likely to experience an “ideal” surgical outcome (44%) than the SOC cohort (15%).

Previously published studies of MIS gastrectomy for gastric cancer have been conducted in Asian centers with high gastric cancer incidence and correspondingly high volumes of surgical resection for early-stage disease. These enabling factors provide Asian surgeons a mechanism to acquire technical proficiency necessary to resect complicated tumors in higher risk patient populations with advanced disease stages. As a result, large randomized trials of laparoscopic gastrectomy for early-stage and locally-advanced gastric cancer have demonstrated superior short-term outcomes compared to open (2,8,9,40).

These data suggest that robotic D2 gastrectomy can be implemented effectively by lower volume gastric surgeons in Western centers serving an older population with higher

BMI and measures of comorbid conditions. However, the composite outcomes demonstrate a significant misalignment of interests. If validated by randomized studies, patients will become clear beneficiaries of this new innovation through improved short-term outcomes, faster recovery, and less pain. Hospital systems will benefit from steady improvements in resource utilization and operative time as surgeons gain proficiency. The benefit for the surgeon learner is less obvious. The learning curve in practice exceeds thirty cases in this series and may be as long as 95 cases (41,42). Increased operative time for surgeons to surmount the learning curve represents lost revenue opportunity in the US system, an important factor may be a key driver for slow adoption of minimally invasive gastric surgery.

The study methods attempted to minimize the limitations of single institution non-randomized design. The cohorts were well-matched in terms of their baseline demographics and tumor characteristics as validated by central radiology review. Despite the potential for unmeasured confounding and selection bias, the quasi-experimental features of an interrupted time series equilibrated known risk factors. Outcomes were analyzed according to intention to treat and adjusted for variables widely available to other cancer centers considering adoption. Despite having a prolonged learning curve, robotic radical gastrectomy demonstrated significant reductions in treatment burden without significant risk of undetected harm at 90 days or signal for adverse survival outcomes at two years. Moreover, NAC was administered, and the esophagus reconstructed, without undue risk for life-threatening leaks or conversions.

These nonrandomized data suggest that robot assisted D2 gastrectomy was associated with improved treatment burden relative to open gastrectomy despite modest surgical volume for this complex procedure. Frequencies of unfavorable resource utilization, adverse oncological outcomes, major morbidity, and narcotic consumption all improved after RG even in the earliest phase of the learning curve. Current prospective international western registries (UGIRA) are in the process of collecting uniform data to gain further insight into optimal surgical techniques and outcomes. Prospective randomized trials for LAGC are needed to elucidate long-term comparative effectiveness of this novel procedure as compared to other minimally invasive approaches but face significant accrual hurdles in the Western context of this challenging disease.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Review Board of the Beth Israel Deaconess Medical Center and Dana Farber Cancer Institute (IRB No. 15-249) and individual consent for this retrospective analysis was waived.

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Table S1 Definition of locally advanced gastric cancer*

Author, year	Type of study	Country (E/W)	Patients	Staging method	Definition
Yu <i>et al.</i> 2019 (43)	RCT	China (E)	1,056	Histology, EUS, CT scan	cT2–4a, N0–3, M0
Li <i>et al.</i> 2019 (44)	RCT	China (E)	96	Histology, CT/MRI, or diagnostic laparoscopy	cT2–4a, N+, M0
Lee <i>et al.</i> 2019 (45)	RCT	Korea (E)	1,050	Histology, EUS, CT scan	cT2–4a, N0–1, M0
Guo <i>et al.</i> 2019 (46)	RCT	China (E)	550	Histology, CT scan or diagnostic laparoscopy	cT3/4, Nany, M0
Wang <i>et al.</i> 2019 (47)	RCT	China (E)	446	Histology, EUS, CT scan	cT2–4aN0–3M0
Shi <i>et al.</i> 2019 (48)	RCT	China (E)	328	Histology, EUS, CT scan	cT2–4aN0–3M0
Zhao <i>et al.</i> 2018 (49)	RCT	China (E)	114	Histology, CT scan	cT2–4aN0–3M0
Shi <i>et al.</i> 2018 (50)	RCT	China (E)	328	Histology, EUS, CT scan	cT2–3, N0–3, M0
Wang <i>et al.</i> 2016 (28)	RCT	China (E)	73	Histology, CT scan	cT2–cT4, N+, M0
He <i>et al.</i> 2016 (51)	RCT	China (E)	105	Histology, EUS, CT scan	cT3–4N1–3M0
Hwang <i>et al.</i> 2015 (52)	RCT	Korea (E)	136	Histology, CT scan	Clinical stage IIA–IIIC (M0)
Ma <i>et al.</i> 2015 (53)	RCT	China (E)	80	Histology, CT scan	cT3–4, N1–3, M0
Inaki <i>et al.</i> 2015 (54)	RCT	Japan (E)	180	Histology, CT scan	cT any, N0–2, M0
Ahn <i>et al.</i> 2014 (55)	RCT	Korea (E)	51	Histology, CT scan	Clinical stage IB, II, IIIA, or IIIB
Tsuburaya <i>et al.</i> 2013 (56)	RCT	Japan (E)	52	Histology, EUS, CT scan	Clinical stage III–IV (M0)
Inoue <i>et al.</i> 2012 (57)	RCT	Japan (E)	27	Histology, CT scan	cT2–3N2–3M0 or cT4NanyM0
Shi <i>et al.</i> 2012 (58)	RCT	China (E)	158	Histology, CT scan	Clinical stage III–IV(M0)
Lee <i>et al.</i> 2012 (59)	RCT	Korea (E)	31	Histology, CT scan	Clinical stage T2N+, T3–T4 and/or N+
Batista <i>et al.</i> 2015 (60)	Prospective	Brazil (W)	16	Histology, CT scan	cT3–4 and/or N+, M0
Trip <i>et al.</i> 2014 (61)	Prospective	Netherlands (W)	25	Histology, EUS, CT scan, PET scan	Clinical stage IB–IV(M0)
Badakhshi <i>et al.</i> 2013 (62)	Prospective	Germany (W)	25	Histology, CT scan, EUS or diagnostic laparoscopy	cT2–4 and N2–3, M0
Schuhmacher <i>et al.</i> 2010 (63)	RCT	Germany (W)	144	Histology, CT scan	Clinical stage III and IV (cM0)
Orditura <i>et al.</i> 2010 (64)	RCT	Italy (W)	29	Histology, CT scan	Clinical stages III–IV (M0)
Biffi <i>et al.</i> 2010 (65)	RCT	Italy (W)	70	Histology, CT scan or diagnostic laparoscopy	cT3–4 any NM0 or any T, N1–3, M0

*, high grade evidence studies were included if histologically proven adenocarcinoma of the stomach and clinically staged using AJCC staging system. RCT, randomized clinical trial; (E), Eastern country; (W), Western country; EUS, endoscopic ultrasound; CT, computed tomography; AJCC, American Joint Committee on Cancer.

Table S2 Subgroup analysis NAC treatment burden

Composite outcomes	Robotic + NAC (n=32)	Open + NAC (n=19)	P value
Efficiency	7 (21.9)	8 (42.1)	0.125
Readmission within 90-day, No. (%)	7 (21.9)	7 (36.8)	0.246
LOS > 75th percentile, No. (%)	7 (21.9)	9 (47.4)	0.057
Oncological efficacy	10 (31.3)	8 (42.1)	0.432
Positive margin (R1/R2), No. (%)	2 (6.3)	2 (10.5)	0.582
<16 lymph node resected, No. (%)	8 (25.0)	6 (31.6)	0.610
Major morbidity	7 (21.8)	8 (42.1)	0.125
Clavien-Dindo \geq 3A, No. (%)	7 (21.9)	8 (42.1)	0.432
CCI \geq 32, No. (%)	5 (15.6)	7 (36.8)	0.084
Reoperation within 90-day, No. (%)	0 (0.0)	2 (10.5)	0.061
Narcotic use			
Narcotic use > 75th percentile, No. (%)	3 (9.4)	8 (44.0)	0.004
Composite treatment burden, No. (%)	18 (56.3)	18 (94.7)	0.003

*, Clavien-Dindo classification of complications. NAC, neoadjuvant chemotherapy; LOS, length of stay; CCI, Comprehensive Complication Index.

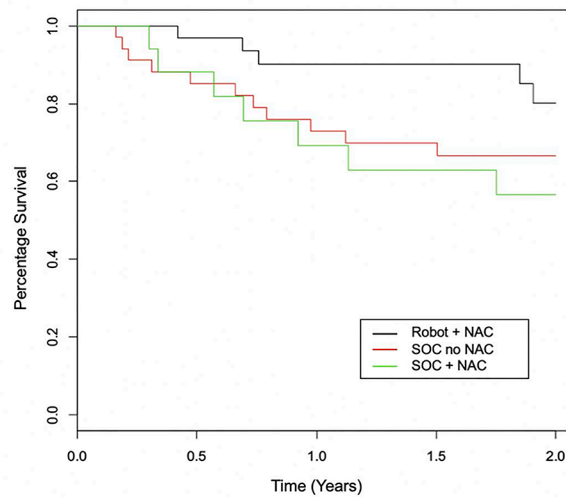


Figure S1 Kaplan-Meier curves illustrating percentage survival at 2-year for the robotic + NAC, SOC + NAC subgroups and SOC no NAC respectively. NAC, neoadjuvant chemotherapy; SOC, standard of care.

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