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Morbidity and Mortality of Total Gastrectomy: a Comprehensive Analysis of 90-Day Outcomes

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Abstract

Background Total gastrectomy (TG) is a complex procedure that carries a high risk of morbidity and mortality and in which patients may experience post-operative sequelae well past the standard 30-day follow-up period. Large studies from high-volume centers with detailed 90-day follow-up data are needed to provide benchmarks for high-quality care for this complex procedure.
Methods Single-institution, retrospective review of a comprehensive gastric cancer database of 148 patients undergoing curative intent TG from 2000 to 2017. Clinicopathologic and treatment factors were analyzed for their impact on 90-day outcomes.
Results The median age of the cohort was 66 years, and 61% were male. Neoadjuvant chemotherapy and radiation therapy were delivered to 32% and 11% of patients, respectively. Open and laparoscopic TG were performed in 93% ($n = 137$) and 7% ($n = 11$) of patients, respectively. Extended lymphadenectomy, pancreatectomy, and splenectomy were performed in 37%, 4.7%, and 19% of patients, respectively. The 30- and 90-day mortality rates were 2.0% and 3.4%, respectively. At least one 90-day complication was experienced by 43.9% ($n = 65$) of patients, and 14% ($n = 21$) experienced a Clavien–Dindo grade 3 or 4 complication. Anastomotic leak occurred in 5.4% ($n = 8$) of patients, half of which required an invasive intervention. Median length of stay was 8 days. The readmission rate was 22%, and most readmissions were due to dehydration and/or nutritional compromise.
Conclusions This study defines 30- and 90-day post-operative outcomes after total gastrectomy in a high-volume center. These outcomes data are critical to the improvement of the informed consent process and as benchmarks for future quality improvement initiatives.

Keywords Gastric cancer · Total gastrectomy · Morbidity · Mortality · Outcomes

Introduction

Gastric cancer is the fifth most common malignancy worldwide, and, until the mid-1990s, it was the leading cause of cancer-related deaths.[1] In recent decades, the incidence and mortality rates of gastric cancer have decreased, yet it still remains the third leading cause of cancer-related mortality.[1] The prognosis and overall approach to the treatment of gastric cancer varies widely throughout the world due to geographic variations in the incidence, biology, and stage at presentation of the disease. The Japanese Gastric Cancer Association has published clear guidelines on the treatment approach to gastric cancer in an effort to standardize their care regimens based on the best available data from their high-volume institutions.[2] Further, this has allowed for further risk stratification of post-operative outcomes and identification of patients at risk for morbidity.[3] In the United States, the National Comprehensive Cancer Network (NCCN) guidelines define the standard of care for the treatment of gastric cancer.[4] However, there remain challenges in reaching this type of standardization with the limited experience of most Western centers. Extrapolation from the experience at high-volume Eastern centers to the West is limited by significant differences in patient characteristics, stage of disease at presentation, and volume of cases. As such, studies from large, high-volume Western centers are critically important to report in order to offer a more accurate benchmark with which to compare outcomes from other Western institutions.

Though subtotal gastrectomy is the preferred surgical approach to gastric cancer whenever possible in order to limit

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post-operative morbidity and to optimize quality of life,[5] the primary goal of surgery is to accomplish a complete resection with microscopically negative margins (R0 resection), and, in many cases, a total gastrectomy (TG) is necessary to achieve this goal. Indeed, for tumors that diffusely involve the stomach (as with *linitis plastica*), as well as for prophylactic resections in patients with the Hereditary Diffuse Gastric Cancer Syndrome due to a germline CDH-1 mutation, TG is necessary.[4, 6] TG is a complex procedure that carries a significant risk of post-operative morbidity and mortality and in which patients may continue to experience adverse events beyond the standard 30-day follow-up period after surgery. Our study thus focuses on 90-day post-operative outcomes, which has been proposed as the preferred measure of perioperative outcomes in other types of complex oncologic surgery.[7, 8]

Prior authors from large Western centers have reported a rather high degree of variability in post-operative outcomes after TG,[9–12] with some authors[12] limiting their analyses to only in-hospital complications and others to 30-day outcomes.[9, 10] Bartlett et al. queried the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database from 2005 to 2011 for all patients with a gastric neoplasm undergoing TG and reported 30-day morbidity and mortality rates of 36 and 4.7%, respectively.[9] Papenfuss et al., using the same database to identify patients undergoing TG for malignancy from 2005 to 2010, reported a 30-day serious morbidity rate of 29% and a 30-day mortality rate of 5.4%.[10] Pacelli et al. published their single-institution experience with 400 patients with gastric cancer undergoing TG from 1981 to 2005, in which the in-hospital morbidity and mortality rates were 24 and 3.5%, respectively, for patients undergoing potentially curative TG.[12] Lastly, Selby et al. reported their outcomes on 238 gastric cancer patients undergoing TG with curative intent from 2003 to 2012 and reported 90-day morbidity and mortality rates of 62 and 2.9%, respectively, including an esophageal anastomotic leak rate of 14%.[11] This latter study comprehensively defined the post-operative morbidity and mortality after TG using the Clavien–Dindo classification,[13] and, furthermore, they included 90-day outcomes in order to collect a more comprehensive picture of post-operative adverse events after TG. Utilizing this prior study as a benchmark, we sought to analyze our 90-day outcomes after TG with curative intent for gastric cancer at our high-volume, Western center.

Methods

The protocol for this retrospective study (IRB 2008P000578) was approved by the Institutional Review Board (IRB) of Partners Healthcare. A comprehensive institutional database was queried for all patients who underwent TG with curative intent for gastroesophageal cancer at the Massachusetts General Hospital from 2000 to 2017. Whether and when to obtain a routine upper gastrointestinal swallow study after TG were at the discretion of the attending surgeon. Post-operative adverse events were collected from the database and/or from the medical record itself, and all adverse events that occurred within 90 days of the procedure were recorded and then classified according to the Clavien–Dindo (CD) severity classification, with major events defined as CD grade 3 or higher.[13] All patients were seen in outpatient follow-up at approximately 1–3 weeks after hospital discharge, and, for those with nutritional difficulties (e.g., on supplemental jejunostomy tube feedings) and/or complications (e.g., a superficial wound infection), additional post-operative visits were scheduled at weekly or bimonthly intervals until the issue at hand was resolved. All patients had a multidisciplinary oncologic follow-up visit with staging computed tomography scans of the chest, abdomen, and pelvis at approximately 3 months after surgery. Only patients who had at least 90 days of post-operative follow-up were included in this study.

The extent of lymph node dissection was determined by a careful review of the operative note and was defined by the Japanese Gastric Cancer Association guidelines.[3] In these guidelines, D1 and D2 lymph node dissections vary depending on the location of the tumor. For a D1 dissection, some or all of the lymph nodes in stations 1, 2, 3, 4sa, 4sb, 4d, 5, 6, and 7 were included, depending on the location of the tumor. For a D2 dissection, a D1 dissection was performed along with some or all of the lymph nodes in stations 8a, 9, 10, 11p, 11d, and 12a, again depending on the location of the tumor. A "D1+" dissection was defined as a lymph node dissection which typically included all but one of the lymph node stations resected as part of a standard D2 dissection (e.g., leaving the splenic hilar nodes in station 10 undissected during the course of a total gastrectomy for an advanced proximal gastric cancer). Hospital readmission was defined as re-hospitalization within 30 days of discharge from the index hospitalization. Clinicopathologic and treatment factors were analyzed for their impact on morbidity and mortality. Patient characteristics were compared using the Wilcoxon rank-sum test for continuous variables and Pearson's chi-squared test for categorical variables. Odds ratios for post-operative complications and mortality were estimated using univariate and multivariate logistic regression. Results are reported as odds ratios (ORs) with 95% confidence intervals (95% CIs). P values < 0.05 were considered significant. Data were analyzed using MatLab and R statistical software.

Results

Patient Characteristics

The clinicopathologic characteristics of the patients included in this study are detailed in Table 1. A total of 148 patients met

Table 1 Clinicopathologic characteristics of the patients

Demographic	Overall (n = 148) n or median	% or IQR
Age	66	54–77
Male sex	90	60.8
Race		
White	131	88.5
Asian	6	4.1
Hispanic	7	4.7
Black	3	2.0
Unrecorded	2	1.4
Prior comorbidities		
Diabetes	27	18.2
Coronary artery disease	25	16.9
Hypertension	67	45.2
Arrhythmia	21	14.2
Asthma	9	6.1
COPD	6	4.1
Smoking history	70	40.3
Alcohol history	41	27.7
Prior gastric resection	15	10.1
Neoadjuvant chemotherapy	47	31.8
Neoadjuvant radiation therapy	16	10.8
Tumor site		
Proximal	85	57.4
Body	47	31.8
Distal	12	8.1
Diffuse	4	2.7
8th ed. AJCC—T status		
ypCR	19	12.8
ypT1	31	20.9
ypT2	24	16.2
ypT3	53	35.8
ypT4	21	14.2
8th ed. AJCC—N status		
ypN0	79	53.4
ypN1	13	8.8
ypN2	18	12.2
ypN3a	30	20.3
ypN3b	8	5.41
8th ed. AJCC—TNM stage		
yp0	19	12.8
ypIA	27	18.2
ypIB	13	8.8
ypIIA	19	12.8
ypIIB	15	10.1
ypIIIA	22	14.9
ypIIIB	20	13.5
ypIIIC	6	4.1
ypIV	7	4.7

the inclusion criteria for this study (Fig. 1) and had a median age of 66 years (range, 54–77 years); 60.8% were male. At least one co-morbidity was observed in 76% of patients, the most common of which were hypertension (45%), coronary artery disease (34%), and diabetes mellitus (18%). A smoking history was reported in 70 (40.3%) patients. Forty-seven (32%) patients received neoadjuvant chemotherapy, and 16 (11%) underwent neoadjuvant radiation therapy (Table 1). Fifteen patients had a prior gastric resection, all of which were distal or subtotal gastrectomies with Billroth II reconstruction. The majority of the patients (51%) had pT3 or pT4 disease, and 48% had regional nodal metastases on final pathologic analysis.

Operative Details

The operative details are summarized in Table 2. The majority of total gastrectomies were completed via an open surgical approach (93%, n = 137), while 7% (n = 11) were performed laparoscopically. Since 2011, approximately 90% of all TGs at our institution were performed by one of three gastrointestinal surgeons. D1 lymphadenectomies were performed in the majority of patients (62.8%, n = 93), whereas D1+ and D2 lymphadenectomies were performed in 11% (n = 17) and 26% (n = 38) of patients, respectively. The median number of lymph nodes examined was 18 (IQR 11–22 nodes) for a D1 dissection, 23 (IQR 17–32 nodes) for a D1+ dissection, and 30 (IQR 18–40 nodes) for a D2 dissection. All patients had a Roux-en-Y esophagojejunostomy reconstruction. A hand-sewn anastomosis was performed in 65.5% (n = 97) of patients, and a stapled end-to-end anastomosis was performed in 34.5% (n = 51) of the patients. The vast majority of esophagojejunal anastomoses since 2010 have been performed with an EEA stapler. In 23.6% of the patients, a

Table 2 Operative details

Operative variable	Overall (n = 148) n	% or IQR
Operative approach		
Open	137	92.6
Laparoscopic	11	7.4
Lymph node dissection		
D1	93	62.8
D1+	17	11.5
D2	38	25.7
Anastomotic method		
Hand-sewn	97	65.5
Stapled	51	34.5
J-tube placement	59	39.9
Additional pancreatectomy	7	4.7
Additional splenectomy	28	18.9

concomitant pancreatectomy and/or splenectomy was performed. A feeding jejunostomy tube was placed in 39.9% ($n = 59$) of the patients.

Post-Operative Outcomes

Post-operative outcomes were collected over a 90-day period in order to more accurately capture the true risk of a total gastrectomy and are summarized in Table 3. A total of 65 (43.9%) patients experienced one or more complications in the 90-day post-operative period after TG, including 42 (28.4%) patients who had one post-operative complication and 21 (14.2%) patients who had two or more complications. Most (62%) complications were minor (Clavien–Dindo class I or II), whereas 21 patients, representing 14% of the entire cohort, had a major complication, defined as requiring surgical or radiologic intervention (Clavien–Dindo class III or IV). The most common 90-day complications, affecting 16.2% of the entire cohort, were respiratory in nature, including pneumonia, pleural effusion, hemothorax, and reintubation. Anemia requiring blood transfusion and new-onset cardiac arrhythmias were the next most commonly experienced complications. As expected, older age and N3 nodal disease were positive predictive factors for major adverse events (Clavien–Dindo grade 3 or higher) on both univariate and multivariate analyses (Table 4). No other factors, including surgical approach (open versus laparoscopic), treatment with preoperative chemotherapy or radiotherapy, or baseline comorbidities, predicted the likelihood of suffering a severe post-operative complication (Table 4).

A routine upper gastrointestinal swallow study to evaluate for anastomotic leak after TG was obtained in 78.4% ($n = 116$)

Table 3 The 90-day post-operative outcomes

	n or median	% or IQR
Complication severity (Clavien–Dindo)		
0	85	57.4
I	13	8.8
II	26	17.6
III	15	10.1
IV	6	4.1
V	5	3.4
Specific complications		
Respiratory complication	24	16.2
Arrhythmia	16	10.7
Anemia	19	12.8
Jejunostomy tube leak or obstruction	11	7.4
Anastomotic leak (esophageal)	8	5.4
Duodenal stump leak	1	0.7
Pancreatic leak	1	0.7
Abscess	8	5.4
Wound dehiscence or infection	4	2.7
Renal dysfunction	3	2.0
Hemorrhage	3	2.0
Length of stay (days)	8	7–11
30-Day readmission	33	22.3
Mortality		
30 days	3	2.1
90 days	5	3.4

Table 4 Univariate and multivariate predictors of 90-day severe complications

	Univariate		Multivariate	
	Risk ratio	*P* value	Risk ratio	*P* value
Age	1.04	0.022	1.04	0.029
Male sex	0.71	0.439		
Race				
White	Ref	Ref		
Asian	0.98	0.987		
Hispanic	< 0.001	0.991		
Black	2.45	0.471		
Prior comorbidities				
Diabetes	2.12	0.982		
Coronary artery disease	2.40	0.090		
Hypertension	2.28	0.074		
Arrhythmia	1.76	0.321		
Asthma	0.63	0.665		
COPD	1.03	0.982		
Smoking history	1.07	0.881		
Alcohol history	0.81	0.680		
Year of surgery				
2000–2005	Ref	Ref		
2006–2010	0.90	0.848		
2011–2017	0.60	0.388		
Prior resection	2.04	0.261		
Neoadjuvant chemotherapy	1.66	0.269		
Neoadjuvant radiation	1.21	0.781		
Laparoscopic procedure	1.15	0.863		
Additional pancreatectomy	0.85	0.881		
Additional splenectomy	1.53	0.419		
Lymph node dissection				
D1	Ref	Ref		
D1+/D2	1.00	0.992		
Anastomotic method				
Hand-sewn	Ref	Ref		
Stapler	0.74	0.535		
Site				
Body	Ref	Ref		
Proximal	1.01	0.991		
Distal	2.79	0.165		
Diffuse	< 0.001	0.990		
8th ed. AJCC—T stage				
ypCR	Ref	Ref		
ypT1	1.8e+7	0.991		
ypT2	3.0e+7	0.991		
ypT3	2.4e+7	0.991		
ypT4	4.6e+7	0.991		
8th ed. AJCC—N stage				
ypN0	Ref	Ref	Ref	Ref
ypN1	1.59	0.587	1.26	0.793
ypN2	2.50	0.177	2.40	0.208
ypN3	3.13	0.030	2.93	0.044

of the patients. A total of 8 (5.4%) patients experienced a leak at the esophageal anastomosis, and Table 5 summarizes the surgical details, methods of discovery, treatments rendered, and outcomes of these 8 patients. All 8 anastomotic leaks were diagnosed during the index hospitalization, and one patient was readmitted on POD#22 for continuing symptoms of regurgitation of food. Three of the 8 anastomotic leaks were managed conservatively with restriction of oral intake and total parenteral nutrition (TPN) and were thus classified as CD grade I or II complications. Four of the anastomotic leaks were additionally managed with percutaneous drain placement by radiology. One patient required reoperation after failing conservative management, including lung decortication and buttressing the anastomosis with an intercostal muscle flap, and a drain was placed at the site. There was one death associated with sepsis secondary to anastomotic leak. The patient elected for comfort measures only and subsequently expired on POD#18 (Table 5). In addition, one patient experienced a duodenal stump leak requiring readmission and management with a percutaneous drain for 4 days, and one patient experienced a pancreatic leak, which was diagnosed by an elevated amylase level in a closed suction drain placed at the time of surgery. This patient remained asymptomatic and was successfully managed with eventual removal of this drain without further intervention.

On multivariate analysis, the occurrence of anastomotic leak was not significantly correlated with prior chemotherapy or radiation therapy ($P = 0.82$). Additionally, patient demographics, comorbidities, and operative details were not significantly associated with the incidence of anastomotic leak. Of note, 7 of the 8 anastomotic leaks were hand-sewn as opposed to stapled; however, this finding was not statistically significant ($P = 0.21$) and may have more to do with differences in the year in which the surgical procedure was performed, as all of the leaks occurred in the years 2001–2012. The use of a circular stapler for construction of the esophagojejunal anastomosis has become increasingly common in the more contemporary timeframe, and, so, other factors that have changed over time, such as surgeon skill in their ascent of the learning curve and limiting the performance of total gastrectomy to a smaller subset of specialized, high-volume surgeons, have likely had a greater impact on the anastomotic leak rate.

The overall median length of stay (LOS) of the cohort was 8 days. However, the LOS increased for an individual patient as the number of adverse events they experienced post-operatively increased, with one patient staying a total of 121 days after suffering five post-operative complications (Fig. 2). LOS was also prolonged up to 13 additional days due to specific post-operative adverse events, the most significant being anastomotic leak, for which the median LOS was 22 days (range 14–46 days) (Fig. 3). A total of 33 (22.3%) patients were readmitted within 30 days of hospital discharge. The most common cause of readmission was a complication related to the feeding jejunostomy tube (12.1%, $n = 4$). Additional causes of readmission were nausea/vomiting, abdominal discomfort, abscess, *Clostridium difficile* infection, and nutritional difficulties ($n = 3$ each). Less common causes of readmission ($n = 2$ each) included pneumonia and small bowel obstruction.

Table 5 Summary of patients with esophageal anastomotic leaks

Patient	Surgery year	Anastomotic method	Leak discovery	Leak symptoms	Intervention	Leak outcome
Patient #1	2001	Hand-sewn	Symptomatic	Bleeding, sepsis	Comfort measures only	Death
Patient #2	2008	Hand-sewn	Discovered on UGI swallow (POD#4)	Fever, tachycardia (110–120 bpm), pleural effusion	IR intervention: drain placement	Full recovery
Patient #3	2008	Hand-sewn	Discovered on UGI swallow (POD#5)	SOB, pulmonary edema, anemia	NPO status, TPN	Self-limited
Patient #4	2008	Hand-sewn	Discovered on UGI swallow (POD#5)	Tachycardia, crampy abdominal pain	NPO status, TPN	Self-limited
Patient #5	2009	Hand-sewn	Negative UGI swallow (POD#7, #25), fluid collection discovered on CT	Nausea, vomiting	IR intervention: drain placement	Full recovery
Patient #6	2010	Stapler	Discovered on UGI swallow (POD#7)	Abdominal pain	Surgical intervention: decortication with muscle flap and coverage of perforation	Full recovery
Patient #7	2011	Hand-sewn	Discovered on UGI swallow (POD#7)	Fever, tachycardia, insomnia, pleural effusion	IR intervention: drain placement	Full recovery
Patient #8	2012	Hand-sewn	Discovered on UGI swallow (POD#4)	Hypertension, elevated WBC	NPO status	Full recovery

UGI, upper gastrointestinal

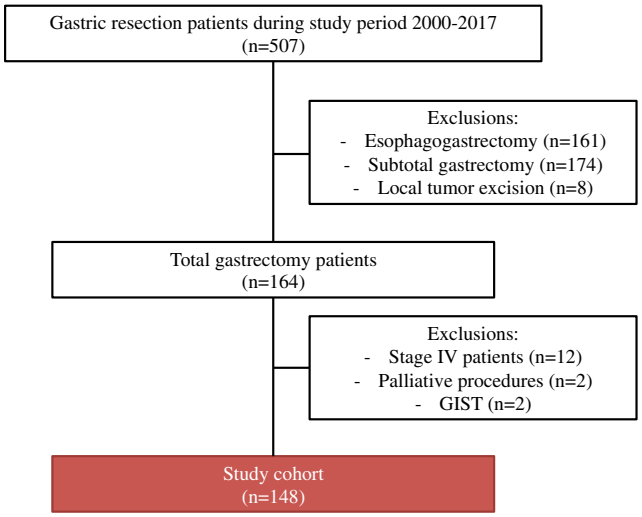

Fig. 1 Study design

The overall 30- and 90-day mortality rates were 2.0% ($n = 3$) and 3.4% ($n = 5$), respectively (Table 3). There were no patient or treatment factors which were predictive of either 30-day or 90-day mortality. Over the past 6 years of this study (2012–2017), there have been no 90-day deaths, which may reflect the fact that over this time period our institution has moved towards a policy that complex surgical procedures, such as total gastrectomy, are performed by a smaller subset of specialized, high-volume surgeons.

Discussion

Gastric cancer remains one of the most common malignancies worldwide, and its surgical treatment often entails the performance of a total gastrectomy. Total gastrectomy (TG) is a complex procedure that carries a high risk of morbidity and mortality and in which patients may experience post-operative sequelae well past the standard 30-day follow-up period. Large studies from high-volume centers with detailed 90-day follow-up data are needed to provide benchmarks for high-quality care for this complex procedure. Thus, as a high-volume, academic referral center, we sought to carefully collect and analyze our 90-day outcomes after TG with curative intent for gastric cancer.

First, and perhaps most importantly, we observed 30- and 90-day mortality rates of 2.0 and 3.4%, respectively, after TG. The fact that there was a nearly 75% increase in the post-operative mortality rate when considering 90-day outcomes reflects the importance of measuring outcomes as important as death well beyond the traditional reporting period of 30 days, as these data are critical to the informed consent process. These 30- and 90-day post-operative mortality rates after TG are in line with those reported by Selby et al.[11] at the Memorial Sloan Kettering Cancer Center (2.5 and 2.9%, respectively) and compare favorably with the 30- and 90-day mortality rates reported by Fedeli et al.[14] in their analysis of the outcomes after TG in more than 1000 patients from the Veneto region in Italy (~4 and ~8.5%, respectively). Our 30-day mortality rate of 2.0% also compares favorably with the rate of 3.5% reported by Pacelli et al.[12] in 312 patients undergoing potentially curative TG and the rate of 4.7% reported in the NSQIP database from 2005 to 2011.[9] In contrast to the study by Bartlett et al. summarizing the NSQIP database outcomes,[9] in which age > 70 years, weight loss, albumin < 3.0 g/dL, and pancreatectomy were all found to be predictive of 30-day mortality, we did not find any risk factor to be independently predictive of either 30-day or 90-day mortality, likely due to the very small number of events in this study.

Second, it should be noted that the risk for complications after TG is substantial, as we report a 43.9% morbidity rate, including a 14% rate of serious morbidity (CD classes III and IV). These rates are similar to those reported by other authors, including a morbidity rate of 36% reported by Bartlett et al. in the NSQIP database,[9] a rate of 24% reported by Pacelli et al. in patients undergoing curative TG,[9] and a rate of 62% (including a 28% rate of serious complications) reported by Selby et al. at MSKCC.[11] Though most patients in our series had just one post-operative complication, 33% of them had two or more complications, and they not surprisingly had a much longer length of stay than those of the 8-day median LOS of

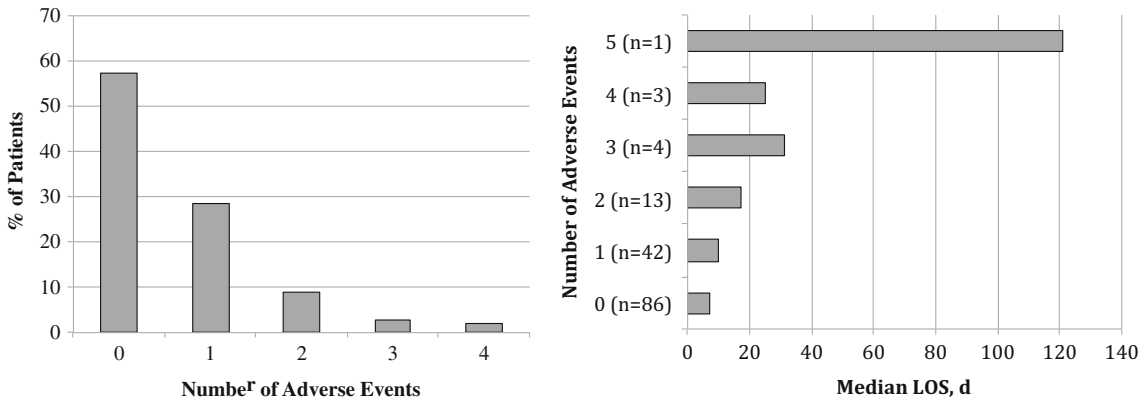

Fig. 2 Percentages of patients experiencing adverse events, and the effect of the number of adverse events on the median length of stay (LOS) in days (d)

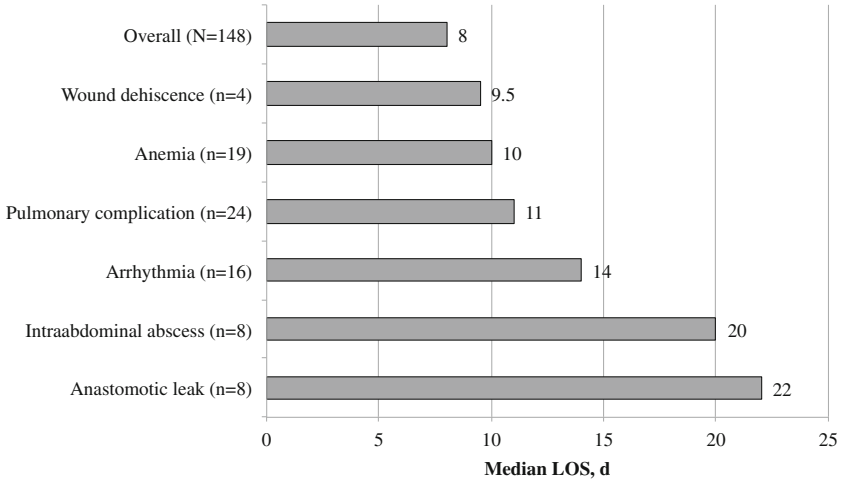

Fig. 3 Effect of specific complications on median length of stay (LOS) in days (d)

the entire cohort. Note that the median length of stay in our series compares favorably to those reported by Selby et al.[11] (9 days) and Bartlett et al.[9] (10 days).

In recent years, many studies have demonstrated the advantages of a minimally invasive gastrectomy over the traditional open gastrectomy, including improved efficacy, shorter length of hospital stay, and fewer complications.[15–17] Conversely, other studies have shown no significant differences in morbidity based on the surgical approach.[18, 19] The vast majority (92.6%) of total gastrectomy procedures performed at our institution have been done, and continue to be done, in the traditional open fashion (92.6%), as this is the approach favored by our most experienced, high-volume surgeons. We find that an open total gastrectomy is the most appropriate choice for the majority of our patients since most of them present with advanced gastric cancers, often with bulky regional nodal disease, and are heavily pre-treated with neoadjuvant chemotherapy and chemoradiation therapy. Furthermore, our outcomes with this approach, as reported herein, have been excellent. That being said, more recently, we have been doing more laparoscopic gastrectomies in highly selected patients, such as those undergoing prophylactic total gastrectomy or those who present with early-stage disease. Note that the purpose of our study was not to compare minimally invasive total gastrectomy to open total gastrectomy given the small number of laparoscopic procedures in our cohort; nonetheless, we identified no significant differences in post-operative morbidity or mortality between the two groups.

One of the most serious, and thus feared, complications of TG is anastomotic leak at the esophagojejunal anastomosis. Since anastomotic leak rates are not collected in the NSQIP database, Bartlett et al.[9] were not able to report on this particular outcome, which illustrates the advantages of single-institution studies and their granular patient outcome data. In prior single-institution studies, Selby et al.[11] and Pacelli et al.[12] reported esophageal anastomotic leak rates of 14.7 and 8.6%, respectively. We identified an anastomotic leak rate of just 5.4% in this series, and the vast majority of these were successfully managed with conservative measures, including bowel rest, antibiotics, and percutaneous drainage. Only one leak required surgical intervention, and one leak lead to an early death in a patient who was made comfort measures only. When examined more closely, our low anastomotic leak rate compared to those reported in series from other high-volume centers is likely not due to any one particular factor. Given how clinically significant this complication is, one would be unlikely to "miss" an anastomotic leak, either with or without a routine upper GI contrast study in the post-operative period. All of the leaks in this study were discovered during the index hospitalization, between post-operative days 4 and 7, and all patients were symptomatic. This is consistent with the findings of Selby et al., who noted that the majority (71%) of their anastomotic leaks were discovered during the inpatient stay, at a median of 7.5 days.[8] One factor that may explain our relatively low anastomotic leak rate, especially over the past 5 or so years, is that increasingly our institution has moved towards a policy that complex surgical procedures, such as total gastrectomy, are performed by a smaller subset of specialized, high-volume surgeons, all of whom have already ascended the learning curve for this procedure.

It is important to note that one of our anastomotic leaks was missed on two separate upper gastrointestinal (GI) swallow studies. It is well-recognized that an UGI barium swallow study is not a very sensitive test for the detection of anastomotic leak after esophagectomy, with a reported sensitivity of only ~45%.[20] Furthermore, this study is not without risk, including aspiration of the contrast material. As such, it may be most reasonable to forego routine imaging to rule out an anastomotic leak after TG in favor of selectively obtaining a more senstitive study, such as a computed tomography (CT) scan with oral contrast, only for those patients exhibiting signs and symptoms worrisome for a leak (i.e., fever, tachycardia, pain, leuocucytosis).[12] Of course, once recognized, an anastomotic leak must be treated expediently to achieve an optimal

outcome.[21] Not surprisingly, anastomotic leak after TG significantly impacts the length of hospital stay, as we found that the median LOS increased by 13 days on average for patients who experienced an anastomotic leak. Sierzega et al.[22] reported an increase in the median LOS of 18 additional days for anastomotic leaks treated conservatively and 48 days for those treated surgically.[22] Similar to the findings of Selby et al.,[11] we were unable to identify any significant predictors of anastomotic leak, including receipt of neoadjuvant therapy or anastomotic technique (hand-sewn versus stapled), again likely the result of too few "events" to achieve statistical significance.

Another feared complication after TG is leakage from the duodenal stump, as this is associated with a very high post-operative mortality rate. We identified only one duodenal stump leak (0.7%), and this was successfully managed with a percutaneous drain. Pacelli et al.[12] reported a similar duodenal stump leak rate of just 1%, whereas Selby et al.[11] identified 9 (3.8%) duodenal stump leaks, three of which lead to patient deaths. The authors of this latter study surmised that the higher mortality rate associated with duodenal stump leaks compared to esophageal anastomotic leaks may be related to the difference in effluent between the two sites as well as the difficulty in accessing the duodenal stump to achieve adequate drainage of the leak. An additional reason may be the challenge in diagnosing these leaks in a timely fashion after surgery.

A final point worth noting in this analysis is the relatively high readmission rate (22.3%) after TG. We have previously reported that patients undergoing TG have a readmission rate nearly twice that of patients undergoing either a subtotal gastrectomy or an esophagogastrectomy,[23] and nutritional difficulties emerged as the leading cause of readmission. Similarly, in this current study, we again identified that nutritional difficulties and feeding jejunostomy tube complications together accounted for the majority of readmissions. We have taken a selective approach to the placement of feeding jejunostomy tubes at the time of TG, as evidenced by the fact that only 40% of our patients undergoing TG had a feeding jejunostomy tube placed. We typically place feeding jejunostomy tubes in those patients who are nutritionally tenuous at the time of TG, such as those undergoing a protracted course of neoadjuvant therapy prior to TG or at highest risk for such compromise after TG, such as those with a low body mass index prior to surgery. The reasons that we have been selective in the placement of feeding jejunostomy tubes is due to the high risk of complications related to these tubes, including clogging of the tube, tube dislodgement, leakage around the tube, bowel obstruction, abdominal cramping, bloating, and diarrhea related to enteral tube feed administration. Patel et al.[24] reported a similarly high complication rate related to feeding jejunostomy tubes and thus have likewise concluded that such tubes should be placed selectively in those patients at highest risk of nutritional compromise after TG.

Though our study provides robust outcomes data on a cohort of patients undergoing TG, it is not without significant limitations. First, the size of our patient cohort is relatively small, and, so, the incidence of important complications like anastomotic leak and death is correspondingly small, limiting our ability to identify potentially important predictors of these outcomes. Second, our study does not capture many of the well-described, longer-term complications of TG, such as anastomotic stricture, dumping syndrome, Roux stasis syndrome, and malnutrition, all of which can dramatically impact the quality of life of patients after TG. Lastly, as a small, single-center study, our findings are unlikely to be generalizable to other institutions across the United States or beyond.

In conclusion, in this study, we comprehensively define the 30- and 90-day post-operative outcomes after total gastrectomy in a relatively high-volume, Western center. These outcomes data are critical to the improvement of the informed consent process and as benchmarks for future quality improvement initiatives. It is imperative for all centers to critically examine their own outcomes after complex surgical procedures, such as TG, as part of a continuous effort to improve the care that we deliver each day to our patients.

Author Contributions All three authors (Li, Costantino, and Mullen) made substantial contributions to the conception and design of this study, including acquisition, analysis, and interpretation of the data. All three authors drafted and critically revised the manuscript and have granted final approval to this final version to be published. All three authors agree to be accountable for all aspects of this manuscript in ensuring that questions related to the accuracy or integrity of any part of it are appropriately investigated and resolved.

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