

Postoperative Mortality Rates following Total Gastrectomy for Gastric Cancer: Experience of a Single Surgical Team

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Abstract: *Objective:* Total gastrectomy is a complex surgical procedure that is characterized by significant postoperative morbidity and mortality rates and the patients may continue to experience adverse events beyond the standard 30-day follow-up period after surgery. The aim of this study is to investigate postoperative complication and 30-day/90-day mortality rates following total gastrectomy in a cohort of patients and highlight the possible ways that can improve the short-term outcome of this surgical procedure.

Material and Methods: 401 patients underwent total gastrectomy for gastric carcinoma by a single surgical team from January 2001 till December 2021. The patients stratified in 3 groups based on the time period when surgery was performed, hospital- and treatment-related objective factors: group I (61 patients); group II (163 patients) and group III (177 patients).

Results: Esophagojejunal anastomotic leakage rate varied with periods and ranged from 1.1% to 3.3%, 1.7% in total. Differences were insignificant in complication and death rates between the patients aged ≤ 70 years and > 70 years ($p > 0.05$). Postoperative death rate within 90 days was higher by 42% compared to that in standard 30-day follow-up period. Neoadjuvant chemotherapy was not found to be associated with an increased rate of 30-day postoperative mortality ($p > 0.05$).

Conclusion(s): Total gastrectomy for gastric cancer may be associated with minimal rates of esophagojejunal anastomotic leakage and mortality when performed by specialized and experienced high-volume surgeons. 90-day mortality rate after total gastrectomy is 42% higher compared to 30-day mortality that warrants more intense monitoring of the relevant patients within 3 months after surgery.

Keywords: Gastric cancer, gastrectomy, total gastrectomy, esophagojejunal anastomosis, anastomotic leakage.

INTRODUCTION

Gastric cancer is the fifth most common malignancy worldwide (excluding non-melanoma skin cancer) and the third leading cause of cancer-related death [1]. Radical intent surgery is the only treatment option offering cure to patients with gastric carcinoma. Gastrectomy for cancer is considered an extensive surgery. Even in cases of an uneventful postoperative course, such procedure may deteriorate multiple physical and psychological functions and significantly worsen the quality of life. Therefore, the outcome prediction and patient selection for such surgery becomes challenging and requires better recognition [2].

Recent studies have demonstrated that 30-day mortality rates range from 3.7% to 12.8% among patients with gastric cancer undergone total gastrectomy. This is almost twice as high as the postoperative mortality rate in patients with rectal cancer, which ranges from 0.9% to 7.5% [3].

The aim of this study is to investigate postoperative complication rates and 30-day/90-day mortality rates following total gastrectomy and highlight the possible

ways that can improve the short-term outcome of this surgical procedure. Using the prior available studies as a benchmark, we analyzed our 30 day and 90-day outcomes after curative-intent total gastrectomy for gastric cancer at our high-volume center.

MATERIAL AND METHODS

762 patients (m – 534, f – 228) underwent gastrectomy (total and subtotal) for gastric carcinoma in Oncologic Clinic, Azerbaijan Medical University from January 2001 till December 2021 (Table 1). All cases of gastrectomy were performed by single surgical team. The age range of the patients was 24-82 years (mean 57.8 years). The patients are grouped in 3 groups based on the hospital-related objective factors that included modernization of the surgical rooms and the intensive care unit, alterations in treatment approaches, as well as rise in the number of patients undergone surgery. So the patients were grouped according to the following time periods: group I – 191 patients, with 61 patients (31.9%) undergone total gastrectomy (operated from January 2001 till December 2007); group II – 269 patients, with 163 (60.6%) patients undergone total gastrectomy (operated from January 2008 till December 2014), and group III – 302 patients, with 177 patients (58.6%) undergone total gastrectomy (operated from January 2015 till December 2021).

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Table 1: Characteristics of Patients and Surgical Procedures Related to Different Periods.

	Group I (N=191)	Group II (N=269)	Group III (N=302)	Total (N=762)
Men/Women	2.5	2.3	2.3	2.3
Mean age (range), years	57.8 (24-78)	58.4 (26-82)	60.4 (26-82)	59 (24-82)
Age >70 year (n, %)	24 (12.6%)	32 (11.9%)	27 (8.9%)	83 (10.9%)
Tumor location				
proximal third (n, %)	48 (25.1%)	83 (30.9%)	121 (40.0%)	252 (33.1%)
middle third (n, %)	30 (15.7%)	80 (29.7%)	57 (18.9%)	167 (21.9%)
distal third (n, %)	113 (59.2%)	106 (39.4%)	124 (41.1%)	343 (45.0%)
Types of the surgical procedure				
total gastrectomy (n)	61	163	177	401
D1 lymph node dissection (n, %)	43 (70.5%)	0	0	43 (10.7%)
D2 lymph node dissection (n, %)	7 (11.5%)	163 (100%)	177 (100%)	347 (86.5%)
D3 lymph node dissection (n, %)	11 (18.0%)	0	0	11 (2.7%)
proximal gastrectomy (n)	17	0	1	18
D1 lymph node dissection (n, %)	13 (76.5%)	0	0	13 (72.2%)
D2 lymph node dissection (n, %)	0 (0%)	0	1 (100%)	1 (5.5%)
D3 lymph node dissection (n, %)	4 (23.5%)	0	0	4 (22.3%)
distal subtotal gastrectomy (n)	113	106	124	343
D1 lymph node dissection (n, %)	93 (82.3%)	0	0	93
D2 lymph node dissection (n, %)	12 (10.6%)	106 (100%)	124	242
D3 lymph node dissection (n, %)	8 (7.1%)	0	0	8

In group I, not all patients underwent extended lymph node dissection (however, in 11 of these patients, D3 extent was performed) and neoadjuvant chemotherapy had never been used. This group of patients underwent surgery when our surgical team had just begun performing total gastrectomy and had not had enough experience on this surgery as well as on extended lymph node dissection. During the period corresponding to group I, 8-9 total gastrectomies were executed per year.

All patients in group II underwent D2 lymph node dissection. The number of harvested lymph nodes was more than 25 in all cases (mean, 26 lymph nodes). Neoadjuvant chemotherapy was used only in one patient in this group. During the period corresponding to group II, 23 total gastrectomies were executed per year. In patients >70 years and in those with comorbidities (malnutrition, diabetes mellitus, moderate cardiac risk, etc.), 14 Fr feeding tube-enterostomy was fulfilled in order to start enteral feeding and discontinue intravenous infusion as earlier as possible.

All patients in group III underwent D2 lymph node dissection. Surgeries were performed on these patients when our surgical team had gained the highest level of experience on total gastrectomy. Neoadjuvant chemotherapy was employed in some patients (26 patients) of group III. Neoadjuvant chemotherapy was

conducted only in patients with locally advanced tumor based on CT scan. During the period corresponding to group III, 25 total gastrectomies were performed per year. 14 Fr feeding tube-enterostomy was created in all patients in this group.

Roux-en-Y gastrectomy with hand-sewn esophagojejunal anastomosis was performed in all cases. The peritoneal cavity was drained by 2 drains: the right one placed under the liver, the left one under the left hemidiaphragm. Right drain was removed on the 9th or 10th postoperative day (a day later after starting oral feeding) unless there were indirect clinical signs of esophagojejunal anastomotic leakage (mucus in the drainage, filling of drainage bag with air). The left drain has been kept longer (10-12 days) depending on the drainage volume.

Adequate water-electrolyte balance was maintained by intravenous infusions in the postoperative course. Postoperative energy support has not exceeded 1800 kcal /day prior to starting enteral feeding. Enteral feeding through tube-enterostomy started on the 4th or 5th postoperative day depending on the time for restoration of bowel peristalsis in uneventful cases. Oral feeding started on the 8th or 9th postoperative day unless the indirect signs of esophagojejunal anastomotic leakage were observed. Upper GI contrast

study has not been routinely performed before starting enteral feeding.

Complications following total gastrectomy were classified according to Clavien-Dindo classification [4]. Comparison of mortality rates was performed using the χ^2 test. A P-value <0.05 was considered statistically significant.

RESULTS

Esophagojejunal anastomotic leakage rate varied with periods and ranged from 1.1% to 3.3%, 1.7% in total. In our patients, the indirect clinical signs of esophagojejunal anastomotic leakage were discovered between postoperative 5-8 days (mean, 6 days).

12 patients underwent relaparotomy for various reasons, including one patient for esophagojejunal anastomotic leakage, and 7 patients for intraperitoneal bleeding. Postoperative death rate following relaparotomy for intraperitoneal bleeding was 43.0%.

When comparatively analyzing the complication and death rates following total gastrectomy based on the different periods, it was found that the differences were not significant despite the fact that the surgical procedures were performed at different levels of experience on this surgery. Differences were insignificant also in complication and death rates between the patients aged ≤ 70 years and > 70 years ($p>0.05$). Death rate within 90 days was 42% higher compared to that in standard 30-day follow-up period following total gastrectomy.

One out of the 27 patients (3.7%) who received neoadjuvant chemotherapy and underwent total gastrectomy (all patients were <70 years of age) died of intraperitoneal bleeding 7 days after surgery. Therefore, neoadjuvant chemotherapy was not found to be associated with an increased rate of 30-day postoperative mortality ($p>0.05$).

DISCUSSION

Total gastrectomy is a complex surgical procedure that is characterized by significant postoperative morbidity and mortality rates, and the patients may continue to experience adverse events beyond the standard 30-day follow-up period after surgery. Large studies from high-volume centers with detailed 90-day follow-up data are needed to provide benchmarks for high-quality care for the patients undergone this complex surgical procedure [5].

The risk for complications after total gastrectomy is substantial, ranging from 24% to 62% morbidity rate, including a 14-28% rate of serious morbidity (Clavien-Dindo classes III and IV) according to data from relevant studies [5-8]. Among our patients, the complication rate (Clavien-Dindo classes III and IV) was the highest in group I, and ranged from 7.3% to 18.0% (Table 2), depending on the period the patients underwent surgery ($p>0.05$).

Esophagojejunal anastomotic leakage following total gastrectomy for gastric cancer represents one of the most serious and life-threatening complications,

Table 2: Complications (Clavien-Dindo Classes III-V) and their Rates following Total Gastrectomy in Different Periods

	Group I (N=61)	Group II (N=163)	Group III (N=177)	Total (N=401)
Complications (n, %)	11 (18.0%)	12 (7.4%)	13 (7.3%)	36 (9.0%)
Surgical complications (n, %)	9 (14.8%)	8 (4.9%)	11 (6.2%)	28 (7.0%)
Non-surgical complications(n, %)	2 (3.2%)	4 (2.5%)	2 (1.1%)	8 (2.0%)
Leakage of esophagojejuno-anastomosis (n, %)	2 (3.3%)	3 (1.8%)	2 (1.1%)	7 (1.7%)
Relaparotomy (n, %)	-	4 (2.5%)	8 (4.5%)	12 (3.0%)
Death among patients ≤ 70 (%)				
within 30 days (n/N, %)	3/55 (5.5%)	5/146 (3.4%)	4/166 (2.4%)	12/367 (3.3%)
within 90 days (n/N, %)	4/55 (7.3%)	6/146 (4.1%)	7/166 (4.2%)	17/367 (4.6%)
received neoadjuvant chemotherapy (n/N, %)				1/27 (3.7%)
without neoadjuvant chemotherapy (n/N, %)				11/340 (3.2%)
Death among patients >70 (%)				
within 30 days (n/N, %)	1 /6 (16.7%)	1/17 (5.9%)	1/11 (9.1%)	3/34 (8.8%)
within 90 days (n/N, %)	1/6 (16.7%)	1/17 (5.9%)	1/11 (9.1%)	3/34 (8.8%)

with prolonged postoperative hospital stay and high mortality rate. Despite improvements in surgical techniques and perioperative management, esophagojejunal anastomotic leakage following total gastrectomy for gastric cancer varies from 4% to 19% [4, 7-9]. In single-institution studies, esophagojejunal anastomotic leakage rates were reported to be 5.4-14.7% [5, 7, 9]. In our series, leakage rate of esophagojejunal anastomosis was 1.7% in total, 1.1-3.3% in different periods. When analyzed closely, our lower esophagojejunal anastomotic leakage rate compared to those reported in series from other high-volume centers is likely not to be due to any one particular factor. One possible explanation about our relatively low anastomotic leakage rate, especially over the past 7 years, is that in our clinic, complex surgical gastrointestinal procedures, including total gastrectomy are performed by a single, specialized, high-volume team, that gained experiences in different specialized centers for this procedure. The other factor that may influence on the leakage rate is early enteral feeding through tube-enterostomy with late oral feeding. Early enteral feeding provides wholesome nutrition, eliminating needs for less-balanced parenteral nutrition, thereby may improve anastomotic wound healing and delays starting of oral feeding, which may otherwise cause tension at the esophagojejunal anastomosis the next few days following surgery. Maintenance of albumin level by adequate enteral feeding can also reduce the risk of edema at the site of anastomosis without albumin infusion.

Esophagojejunal anastomotic leakage is mainly discovered between post-operative days 4 and 7, and all patients become symptomatic [5]. Selby *et al.* noted that the majority (71%) of their anastomotic leaks were discovered during the inpatient stay, on the average of 7.5 days [7]. Li *et al.* (2019) report that they successfully managed most of the cases of esophagojejunal anastomotic leakage with conservative measures, including bowel rest, antibiotics, and percutaneous drainage. Half of the patients (4/8) required an invasive intervention and one case (12.5%) required surgical intervention. The 30- and 90-day mortality rates were 2.0% and 3.4%, respectively, in their study [5].

In our patients, the indirect clinical signs of esophagojejunal anastomotic leakage were discovered between postoperative 5-8 days (mean, 6 days). All cases suspicious of esophagojejunal anastomotic leakage were confirmed by upper GI contrast study or upper abdominal CT scan with oral contrasting. In

patients with esophagojejunal anastomotic leakage who didn't have clinical and radiological signs of intraperitoneal fluid collection, enteral feeding through tube-enterostomy started (or continued). Tube-enterostomy enteral feeding in those patients provided discontinuing parenteral feeding and intravenous fluid infusion. In 2 patients with intraperitoneal fluid collection due to anastomotic leakage the drain was changed (28.6%) and one patient (14.3%) underwent relaparotomy. All the remaining patients were managed conservatively. The patient undergone relaparotomy for leakage of esophagojejunal anastomosis died of multiorgan failure, and in the other patients, leakage was eliminated uneventfully.

Recent studies have demonstrated that 30-day mortality rates following total gastrectomy range from 3.7% to 12.8% among patients with gastric cancer [3, 6, 8]. According to the results of conducted investigations, ASA grade, neoadjuvant chemotherapy, albumin <3 g/dL, substantial weight loss before surgery, and associated pancreatectomy are associated with higher postoperative morbidity and mortality rates in patients with gastric cancer, irrespective of age [10, 11]. Although neoadjuvant chemotherapy was given to a small group of our patients (27 patients), this approach was not associated with higher mortality rate in patients aged <70 years (3.7% vs 3.2%, $p>0.05$).

In a Dutch nationwide study, the 30-day mortality rate following total gastrectomy was seen to be affected significantly by patients age. So patients aged over 75 years had a significantly higher risk of 30-day mortality, being 12.8%. It was suggested that mortality is influenced by the growing prevalence of comorbidities in older patients [12]. According to opinions of some authors, the overall population is ageing and comorbidity is increasing in the elderly people; hence careful selection of elderly patients for gastric surgery is of high importance. Nevertheless, results of some other studies suggest that the age alone is not the main predictive factor of postoperative outcome [10].

No higher complication and death rates were observed in our patients aged >70 years. A possible explanation for this may be our stricter selection criterion while selecting these patients for surgery. Another possible explanation can be the fact that we fulfilled tube-enterostomy in all elderly patients in order to start more wholesome enteral feeding earlier and to discontinue parenteral infusion as soon as possible, as

mentioned above. It facilitates delayed oral feeding on one hand and escape of overloading of cardiovascular system by infusion on the other hand. It is not excluded that the latter factor might contribute to higher complication rates in elderly patients undergone total gastrectomy.

Given the fact that total gastrectomy is a complex procedure and performance status of patients cannot be restored within 30 days, some authors report that 90-day outcome reflects the short-term outcome better. Li *et al.* (2019) declare the 90-day mortality rate to be higher by 70%, compared to that of the period of 30-day (3.4% versus 2.0% respectively) [5]. Shannon *et al.* (2021) report that 39.2% to 46.2% (in 2004 and 2015, respectively) of the deaths within 90 days after total gastrectomy for cancer occur beyond 30 days postoperative [13]. In our patients, postoperative 90-day mortality rate was higher by 42% compared to that within 30 day in patients aged ≤ 70 years (17 vs 12 cases of death, respectively). This result corresponds to the results of other studies, confirming that restoration of patients' performance status requires longer period than one month period following total gastrectomy. According to Shannon *et al.* (2021), high rates of 90-day mortality after total gastrectomy suggest the need for improved out-of-hospital postoperative care beyond 30 days [13].

In recent years, many studies have demonstrated the advantages of a minimally invasive approach over the conventional open gastrectomy, including lower complication and mortality rates [14-16]. On the contrary, other studies have shown no significant differences in morbidity and mortality rates between those two approaches [17-19]. Li *et al.* (2019) state that an open total gastrectomy is the most appropriate choice, since most of patients present with advanced gastric cancer, often with bulky regional nodal disease, and are treated with neoadjuvant chemo(radio)therapy [5]. Moreover, laparoscopic total gastrectomy for gastric cancer is a relatively complicated procedure that should be performed by well-trained and experienced laparoscopic surgeons, and the long-term oncologic outcomes have not yet been clarified [20, 21]. All our patients underwent open gastrectomy because our team have not gained experience on laparoscopic approach due to the fact that early-stage gastric carcinoma is very rare event in our patients.

CONCLUSIONS

Total gastrectomy for gastric cancer may be associated with minimal rates of esophagojejunal

anastomotic leakage and mortality when performed by specialized and experienced high-volume surgeons. 90-day mortality rate after total gastrectomy is higher by 42% compared with 30-day mortality, which warrants more intense monitoring of the relevant patients within 3 months after surgery. Total gastrectomy executed in properly selected patients aged >70 years or following neoadjuvant chemotherapy in patients aged <70 years is not associated with significantly higher mortality rates.

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